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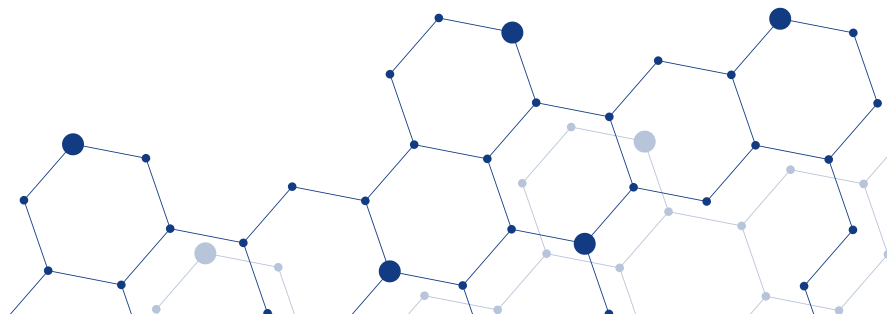
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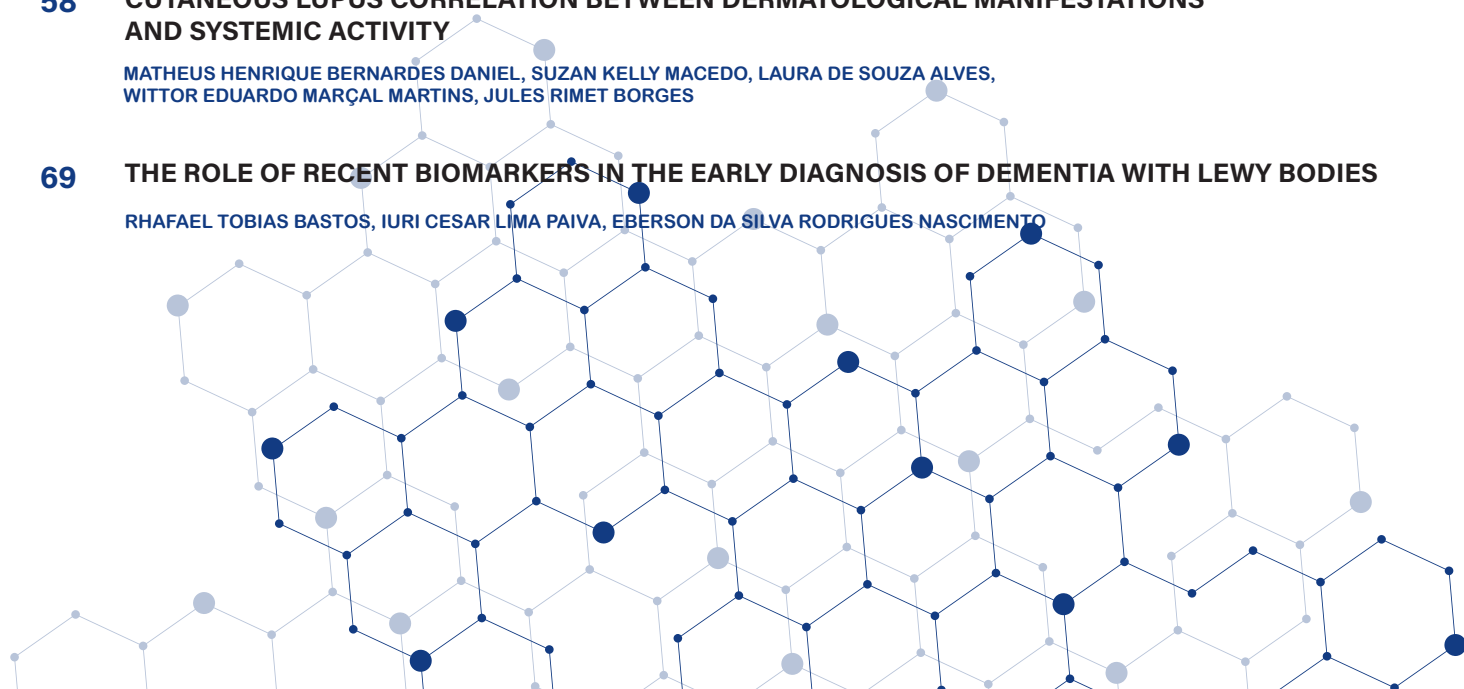
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INDEX

- 7** **ECOLOGICAL STUDY ON BREAST CANCER SCREENING IN THE CENTRAL-WEST REGION: AN EPIDEMIOLOGICAL ANALYSIS OF MAMMOGRAPHIES PERFORMED BY THE THE BRAZILIAN UNIFIED HEALTH SYSTEM**
HENRIQUE ALMEIDA DE BERREDO REIS, FELIPE RODRIGUES RESENDE, GUSTAVO MACHADO MAGALHÃES FILHO, HUNTER ALEIXO REZENDE, DIEGO VINÍCIUS GONÇALVES SANTANA
- 14** **ANALYSIS OF HOSPITAL MORBIDITY AND MORTALITY AND COSTS ASSOCIATED WITH SURGICAL ANESTHESIA PROCEDURES IN BRAZIL: A LITERATURE REVIEW BASED ON CROSS-SECTIONAL STUDIES**
ANA LUÍSA MIRANDA DE LIMA, GUILHERME AUGUSTO D'ASSUMPÇÃO ARANTES, THAÍS ROSA DOS SANTOS, VITOR DAVI FERREIRA, MARINA MATOS RAMOS, JOÃO BRUNO MACHADO UCHOA
- 20** **LATE COMPLICATIONS ASSOCIATED WITH THE USE OF HYALURONIC ACID DERMAL FILLERS IN FACIAL AESTHETIC PROCEDURES: AN INTEGRATIVE REVIEW**
BRUNA ZACHARIAS PAOLUCCI, HELOÍSA PACÍFICO GOMES, MILENA DE CAMPOS MIRANDA, GUSTAVO MACHADO MAGALHÃES FILHO, GUILHERME TOMAS LUCIANO
- 30** **EFFICACY AND SAFETY OF ANTI-AMYLOID ANTIBODIES IN EARLY ALZHEIMER'S DISEASE: A SYSTEMATIC REVIEW OF LECANEMAB AND DONANEMAB**
PAULO HENRIQUE LUIS DA SILVA JÚNIOR, YANLEY LÚCIO NOGUEIRA
- 41** **ATRIAL FIBRILLATION AND PREVENTION OF THROMBOEMBOLIC EVENTS: A REVIEW OF CURRENT STRATEGIES**
RAFAEL COSTA LIMA, VITOR DAVI FERREIRA, AIRTON SILVA DE SANTANA, MATEUS DE SOUZA ARRAES RIOS PINTO, HUMBERTO GRANER MOREIRA
- 50** **ARTIFICIAL INTELLIGENCE IN RISK STRATIFICATION OF ACUTE CORONARY SYNDROME: A COMPARATIVE REVIEW WITH TRADITIONAL CLINICAL RISK SCORES**
SUZAN KELLY MACEDO, BRUNA DE SOUZA FERREIRA, KAROLINE JOSÉ DE DEUS SOUZA GOMES, GUILHERME TOMAS LUCIANO, FABIANO INÁCIO DE SOUZA
- 58** **CUTANEOUS LUPUS CORRELATION BETWEEN DERMATOLOGICAL MANIFESTATIONS AND SYSTEMIC ACTIVITY**
MATEUS HENRIQUE BERNARDES DANIEL, SUZAN KELLY MACEDO, LAURA DE SOUZA ALVES, WITTOR EDUARDO MARÇAL MARTINS, JULES RIMET BORGES
- 69** **THE ROLE OF RECENT BIOMARKERS IN THE EARLY DIAGNOSIS OF DEMENTIA WITH LEWY BODIES**
RHAFEL TOBIAS BASTOS, IURI CESAR LIMA PAIVA, EBERSON DA SILVA RODRIGUES NASCIMENTO



- 76** **POLYLAMININ AND NERVOUS SYSTEM REGENERATION: A SYSTEMATIC REVIEW OF EXPERIMENTAL AND CLINICAL EVIDENCE**
GABRIELA BASTOS MESQUITA, MARIA LUISA GONÇALVES MARTINS, MARIANA DA ROCHA TELES, MARINA FUSO PRUDENTE, ROBERPAULO ANACLETO NEVES
- 84** **MULTIMODAL PREHABILITATION ASSOCIATED WITH THE ENHANCED RECOVERY AFTER SURGERY PROTOCOL IN COLORECTAL SURGERY: IMPACT ON POSTOPERATIVE OUTCOMES**
LARA MARÇAL MACHADO, GABRIEL FAGUNDES MOREIRA, JOÃO GABRIEL PEIXOTO SANTANA, NATHÁLIA GOULART FERREIRA, BRUNA DELL'ACQUA CASSÃO REZENDE
- 91** **ACUTE CORONARY SYNDROME: EARLY DIAGNOSIS AND PROGNOSTIC IMPACT**
GABRIEL FAGUNDES MOREIRA, PAULO VINÍCIUS DIAS, MATHEUS LÚCIO FERNANDES GOMES, IGOR DINIZ ALVES, AIRTON SILVA DE SANTANA
- 100** **USE OF INDOCYANINE GREEN IN THE PREVENTION OF ANASTOMOTIC LEAK IN COLORECTAL SURGERIES: A SYSTEMATIC REVIEW**
FANIELI PEREIRA BORGES, RAYSSA ANDRADE GALDINO DA SILVA, ALINE GUIMARÃES SANT'ANA
- 107** **VALIDATION OF AI ALGORITHMS IN OPHTHALMOLOGICAL POPULATION SCREENING**
GABRIEL RIBEIRO DE OLIVEIRA SILVA, ÍTALO BEZERRA ALVES, ISABELA LUIZA PACHECO RODRIGUES, DOUGLAS WALLACY DA SILVA AMÂNCIO, FABIANO INÁCIO DE SOUZA
- 117** **VITILIGO: NEW THERAPEUTIC APPROACHES BASED ON IMMUNE PATHOPHYSIOLOGY**
JÚLLIA AQUINO DA SILVA, WALDEMAR NUNES DA SILVA QUEIROZ NETO, DANIELLE DE OLIVEIRA TEIXEIRA, ANA CLARA DOS SANTOS SOUZA, GUILHERME HOLANDA BEZERRA

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AMG presents this special edition of its Scientific Journal, dedicated to the papers presented at the 38th edition of the Scientific Meeting of Medical Students (ECAM), organized by students from the Faculty of Medicine of the Federal University of Goiás.

In 2026, ECAM chose “Cutting-Edge Medicine: Innovation, Ethics, and Care” as its theme. The choice could not have been more relevant. The speed at which new technologies and discoveries reach medical practice expands possibilities, but also requires discernment. Incorporating what is new is only one part of the challenge. It is necessary to understand its limitations, assess its effects, and decide how to use it without losing sight of what sustains Medicine: responsibility toward life and people.

It is from this perspective that the scientific papers gathered in this edition take on special relevance. They represent a significant part of the academic production presented at the meeting. By being published, these studies reach other readers, broaden the debate, and become part of the record of the scientific education of a new generation of physicians.

As one of the sponsors of ECAM 2026, AMG reaffirms its commitment to medical education and to the advancement of science. Supporting an initiative such as this means recognizing that the development of Medicine also depends on creating conditions for future professionals to conduct research, question, and share knowledge.

AMG congratulates the students, professors, researchers, and other professionals who contributed to the organization of ECAM 2026 and to the production of the papers published in this edition.

Truly cutting-edge Medicine is not merely Medicine that keeps pace with the future. It is Medicine that prepares to build it with knowledge, awareness, and humanity.

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ECOLOGICAL STUDY ON BREAST CANCER SCREENING IN THE CENTRAL-WEST REGION: AN EPIDEMIOLOGICAL ANALYSIS OF MAMMOGRAPHIES PERFORMED BY THE THE BRAZILIAN UNIFIED HEALTH SYSTEM

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ABSTRACT

Breast cancer is a major public health concern, and mammography plays a fundamental role in its early detection. This study aimed to analyze the epidemiological profile of mammograms performed within the Brazilian Unified Health System in the Central-West Region of Brazil between 2017 and 2025, considering temporal, regional, and sociodemographic aspects. This ecological time-series study, with a descriptive and analytical design, was based on secondary data from the Cancer Information System (SISCAN/DATASUS) and included the states of Goiás, Mato Grosso, and Mato Grosso do Sul, as well as the Federal District. The variables analyzed were age group, race/skin color, screening interval, and BI-RADS classification, according to period and federative unit of residence. During the study period, 1,713,676 mammograms were recorded, with Goiás accounting for the highest absolute number. A marked decline in examinations occurred in 2020, followed by a recovery in subsequent years, reaching the highest volume in 2023. Women aged 50–59 and 40–49 years accounted for 38.02% and 32.35% of examinations, respectively. Differences were observed in the distribution of records according to race/skin color, while BI-RADS categories 2, 1, and 0 predominated. These findings demonstrate temporal, regional, and sociodemographic variations in mammography records within the Brazilian Unified Health System in the Central-West Region and reinforce the importance of improving data quality, expanding access to mammography, and ensuring appropriate follow-up of inconclusive or suspicious findings to strengthen the breast cancer care pathway.

Keywords: Ecological studies, Mammography, Breast neoplasms, Mass screening; Unified health system.

INTRODUCTION

According to the International Agency for Research on Cancer (IARC), breast cancer (BC) is the most prevalent neoplasm worldwide, excluding non-melanoma skin cancer, and this increasing trend has been observed since the end of the 20th century. This higher prevalence is associated with an increase in risk factors,

including population aging, obesity, greater use of hormone therapy with estrogen and progesterone, early menarche, late menopause, nulliparity, physical inactivity, and alcohol consumption.¹ In addition, BC is the leading cause of death from neoplastic diseases among the Brazilian female population, with mortality being proportional to age group². Due to its epidemiological and clinical importance, measures on a global scale have prioritized early detection and management of breast cancer, with emphasis on clinical and imaging examinations, particularly mammography². It is known that the Brazilian Society of Mastology recommends one mammogram per year for women aged 40 to 74 years, except in particular cases of hereditary cancer or genetic mutations detected through genetic testing.³

Despite its effectiveness in reducing mortality from BC, factors related to the socioeconomic conditions of individuals and of the country in which they live influence the quality of the structure and organization of healthcare systems in promoting screening and early detection of this disease, access to mammography, and awareness of its importance, and this applies to all countries, including Brazil.^{1,2} In addition, active case finding and the development of measures and public policies aimed at encouraging early detection have a global scope and, considering the particularities of each country's healthcare system, have proven effective in reducing costs associated with BC morbidity and mortality⁴.

The lack of studies addressing the relationship between the number of mammograms performed in a population and its comparison with specific socioeconomic factors indicates a gap that needs to be investigated and filled in order to understand whether this inequality has a significant impact and how it is expressed, with emphasis on social determinants.

OBJECTIVES

The study aimed to analyze the epidemiological profile of mammograms performed by the Brazilian Unified Health System in the Central-West region of Brazil from 2017 to 2025, based on records from the Cancer Information System. It sought to describe the temporal and regional distribution of examinations according to federative unit of residence, as well as to characterize the records according to age group, race/skin color, examination periodicity, and BI-RADS classification, in order to identify screening patterns, possible inequalities in access, and relevant aspects for the organization of the breast cancer care pathway in the region.

METHODS

This is an ecological time-series study with a descriptive and analytical design, using data from the Central-West region of Brazil from 2017 to 2025, separated by Federative Units (FUs), namely Goiás, Mato Grosso, Mato Grosso do Sul, and the Federal District. Data were extracted from the Cancer Information System (SISCAN) of the Department of Informatics of the Brazilian Unified Health System (DATASUS), through TabNet, together with the most recent sociodemographic data from the Brazilian Institute of Geography and Statistics (IBGE), including the estimated population for 2025.^{5,6}

All individuals who underwent mammography during the study period were included. The variables collected were age group, ethnicity, periodicity, and Breast Imaging Reporting and Data System (BI-RADS), all stratified by FU of residence and race/skin color.

The rate of examinations performed within a specific time period, generally 2025, was calculated and expressed per 100,000 inhabitants, using the ratio between the number of mammograms performed and the estimated resident population in the respective year, multiplied by 100,000.

As this study was based exclusively on secondary, aggregated, publicly available data, without nominal identification or risk of breach of participant confidentiality, submission to and prior approval by a Research Ethics Committee were not required, in accordance with the guidelines of Resolution No. 510/2016 of the National Health Council.

RESULTS AND DISCUSSION

The number of mammography examinations performed by the SUS and recorded in SISCAN/DATASUS was analyzed, totaling 1,713,676 examinations performed in the Central-West region between 2017 and 2025. As shown in Table 1, a higher proportion of mammograms was observed in the state of Goiás, considering that it has the largest absolute population, at 7.42 million in July 2025 (IBGE). Although Mato Grosso is the second most populous state, with 3.89 million inhabitants, it has fewer mammography examination records than Mato Grosso do Sul.

Table 1: Number of Mammograms per Year According to Federative Unit of Residence (2017–2025).

FU of residence	2017	2018	2019	2020	2021	2022	2023	2024	2025	Total
MS	33,860	43,244	59,989	26,908	51,431	57,117	58,753	61,959	52,334	445,595
MT	29,782	30,719	34,468	17,083	27,056	47,035	44,967	41,701	40,711	313,522
GO	79,369	80,268	94,483	50,100	81,037	100,631	113,855	107,963	102,887	810,593
DF	364	7,878	15,034	13,153	16,754	12,476	28,649	23,534	26,124	143,966
Total	143,375	162,109	203,974	107,244	176,278	217,259	246,224	235,157	222,056	1,713,676

Regarding age group, Table 2 shows a higher volume of examinations among individuals aged 50 to 59 years (38.02%) and 40 to 49 years (32.35%), consistent with the recommendations of Brazilian guidelines for mammographic screening of breast diseases. From the age of 60 years onward, there is a decrease in the number of examinations performed, since routine large-scale mammographic screening is no longer recommended from this age group onward, except in specific cases according to the patient's clinical condition.

Table 2: Number of Mammograms by Age Group According to Federative Unit of Residence (2017–2025).

FU of residence	Up to 9 years	10 to 19 years	20 to 29 years	30 to 39 years	40 to 49 years	50 to 59 years	60 to 69 years	70 to 79 years	Over 79 years	Unkn own	Total
MS	90	246	1,054	7,768	159,991	164,197	97,093	13,611	3,803	-	445,595
MT	113	122	912	8,775	98,128	121,535	68,496	14,114	1,324	3	313,522
GO	208	224	1,805	20,569	266,080	301,212	177,556	38,937	10,803	8	810,593
DF	26	28	388	3,468	30,179	64,610	37,655	6,886	1,850	-	143,966

Regarding distribution by race/ethnicity, there is a predominance of White and Asian individuals, with examination rates per thousand inhabitants of 12.76 and 1,330.46, respectively, as shown in Table 3. Despite this, according to the IBGE, there is a predominance of mixed-race individuals (9.033 million) in the region compared with White individuals (6.378 million) and Asian individuals (69,000), but the examination rate among mixed-race individuals is 4.00. This may be explained by greater access to mammography among certain populations, encompassing possible factors such as socioeconomic conditions and awareness of breast cancer, as well as by the higher frequency of examinations performed within the same year, with this latter factor explaining why the Asian population had more examinations despite its smaller absolute population, as shown in Table 4.

Table 3: Number of Mammograms by Race from 2017 to 2025.

Race/Skin colour	2017	2018	2019	2020	2021	2022	2023	2024	2025	Total
White	56,165	63,280	79,825	39,744	65,361	82,001	91,533	88,810	81,382	648,106
Black	7,784	9,029	11,006	5,739	9,512	11,380	13,525	12,496	12,280	92,751
Asian	42,984	50,315	66,776	37,863	64,461	80,561	97,781	94,833	91,802	627,376
Brown	30,422	32,190	38,058	19,634	30,941	37,805	41,840	38,598	36,137	305,628
Indigenous	208	192	388	239	208	265	459	415	453	2,827
No information	5,812	7,100	7,921	4,025	5,795	5,242	1,086	5	-	36,988

Table 4: Number of Mammograms by Screening Interval According to Race/Skin Color (2017–2025).

Race/Skin colour	Same year	1 year	2 years	3 years	4 years or more	Unknown	Total
White	22,024	152,877	139,248	68,058	117,880	148,019	648,106
Black	2,936	21,530	18,610	9,173	15,503	24,999	92,751
Asian	18,558	146,144	125,583	62,084	103,446	170,961	627,376
Brown	9,219	75,025	61,477	30,030	46,904	82,913	305,628
Indigenous	90	301	299	164	426	1,547	2,827
No information	1,297	8,476	7,558	3,779	4,195	11,683	36,988

Regarding the BI-RADS classification, based on mammograms performed through the SUS, there is a predominance of categories considered benign, in descending order, categories 2, 1, and 0. This indicates that most alterations observed on imaging examinations are benign or inconclusive, that is, they do not indicate signs of malignant neoplasia or require further investigation to rule out a diagnosis of breast cancer.

Table 5: Number of Mammograms by BI-RADS Category According to Federative Unit of Residence (2017–2025).

FU of residence	Category 0	Category 1	Category 2	Category 3	Category 4	Category 5	Category 6	Total
MS	43,519	114,570	268,457	11,733	5,951	1,026	339	445,595
MT	41,153	66,839	195,500	6,613	2,818	455	114	313,522
GO	93,188	343,413	348,787	17,737	6,241	883	344	810,593
DF	28,036	17,863	88,083	6,127	2,882	579	396	143,966

DISCUSSION

The Thus, 1,713,676 mammograms performed through the SUS were identified in the Central-West region between 2017 and 2025, with relevant temporal and regional variations. The number of examinations increased until 2019, followed by a marked decline in 2020 and progressive recovery in subsequent years, with the highest volume observed in 2023⁷. This pattern suggests an impact of the COVID-19 pandemic on the performance of screening and diagnostic examinations, a phenomenon also described in national studies reporting reductions in mammography during the pandemic period. Interruption or reduction of these actions may compromise early diagnosis and contribute to delays in the investigation of suspected cases^{8,9}. In addition, the distribution by federative unit showed the highest absolute number of examinations in Goiás, followed by Mato Grosso do Sul, Mato Grosso, and the Federal District. Although this finding is partly explained by the population size of Goiás, the fact that Mato Grosso do Sul had more records than Mato Grosso, despite having a smaller population, suggests possible differences in network organization, availability of services, access to mammography, regulation, and quality of data recording in SISCAN. Therefore, absolute analysis should be complemented by indicators standardized according to the eligible female population in order to better estimate actual screening coverage.

Regarding age group, the highest concentration of examinations occurred among women aged 50 to 59 years, a result consistent with Brazilian recommendations historically focused on biennial mammographic screening in the 50-to-69-year age group. However, the high number of examinations among women aged 40 to 49 years suggests the presence of opportunistic screening, spontaneous demand, diagnostic investigation, or requests outside the traditionally prioritized age group. In addition, the reduction in examinations among older age groups may indicate barriers to access, lower levels of active case finding, or difficulties in continuity of care among elderly women.

Analysis by race/skin color revealed a predominance of records among White and Asian women, with lower proportions among Brown, Black, and Indigenous women. This result should be interpreted cautiously because of the possibility of underreporting and inadequate completion of the race/skin color variable, but it may indicate inequalities in access to secondary prevention of breast cancer. Socioeconomic, territorial, cultural, and health service organization-related factors may influence mammography uptake, reinforcing the need for active case-finding policies and expansion of access among historically vulnerable groups.

Regarding BI-RADS, categories 2, 1, and 0 predominated, indicating a higher frequency of

benign findings, normal examinations, or inconclusive results. This pattern is expected in screening examinations, but the presence of BI-RADS 0 reinforces the need to ensure timely complementary diagnostic assessment. Categories 4, 5, and 6, although less frequent, require prompt referral for histopathological investigation and treatment. Thus, the effectiveness of screening depends not only on performing mammography but also on the system's capacity to ensure continuity of the care pathway.

The study has limitations because it uses secondary data from SISCAN/DATASUS, which are subject to underreporting, duplication, data-entry errors, and variations in record quality. In addition, the number of examinations does not necessarily correspond to the number of women screened, since the same individual may undergo more than one mammogram during the study period. As this is an ecological study, it is not possible to establish causality or assess individual factors such as income, education, family risk, presence of symptoms, and time to diagnosis. Despite these limitations, the findings contribute to understanding the regional pattern of mammography performed through the SUS in the Central-West and highlight relevant public health challenges. Heterogeneity among states, the decline during the pandemic, possible inequalities by race/skin color, and the need for follow-up of abnormal findings reinforce the importance of strengthening primary care, improving data quality, and organizing the breast cancer care pathway in order to expand equitable access to screening and early diagnosis.

CONCLUSION

The present study made it possible to characterize the epidemiological profile of mammograms performed through the SUS in the Central-West Region between 2017 and 2025, revealing relevant temporal, regional, and sociodemographic variations. A higher concentration of examinations was observed in Goiás, with a predominance among women aged 50 to 59 years and a higher frequency of BI-RADS categories 1, 2, and 0. A marked decline in the number of examinations was also identified in 2020, followed by recovery in subsequent years, suggesting an impact of the COVID-19 pandemic on mammographic screening.

The findings indicate the need to strengthen breast cancer screening actions within the SUS, with expanded equitable access, improved quality of SISCAN records, and assurance of appropriate follow-up for cases with inconclusive or suspicious findings. Thus, the study contributes to understanding the regional scenario and reinforces the importance of organizing the care pathway to promote early diagnosis and reduce health inequalities.

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ANALYSIS OF HOSPITAL MORBIDITY AND MORTALITY AND COSTS ASSOCIATED WITH SURGICAL ANESTHESIA PROCEDURES IN BRAZIL: A LITERATURE REVIEW BASED ON CROSS-SECTIONAL STUDIES

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ABSTRACT

Morbidity and mortality in emergency surgeries pose a challenge for anesthesiology and public health in Brazil, particularly in cases of vascular diseases, which often require high-cost interventions with adverse outcomes. This study aimed to assess the landscape of hospital morbidity and mortality and the economic impact of anesthetic-surgical procedures in the Unified Health System (SUS) between 2019 and 2025, correlating surgical volume, mortality rates, and hospitalization costs with regional distribution. A systematic review was conducted in PubMed using the search terms "Surgical Procedures, Operative," "Anesthesia," "Morbidity," "Mortality," "Costs and Cost Analysis," "Cross-Sectional Studies," and "Brazil." Of 14 articles, 7 original cross-sectional studies were selected for reporting morbidity, mortality, and cost outcomes in surgeries in Brazil. The results indicate that more than 69.5 million surgeries were performed between 2008 and 2019, with a projection of over 42 million for 2019–2025. Mortality in emergency surgeries was consistently higher than in elective surgeries, reaching 5.24% in open revascularizations compared to 1.56% in endovascular procedures. The North and Northeast regions have the highest mortality rates and the lowest reimbursement rates. Outpatient thermal ablation stood out for its safety and cost-effectiveness. Therefore, it can be concluded that the transition to less invasive techniques and the correction of regional disparities are essential measures for improving the quality of perioperative care and optimizing the allocation of public resources.

Keywords: Anesthesia, Brazil, Health care costs, Mortality, Surgical procedures.

INTRODUCTION

Morbidity and mortality associated with emergency surgical procedures represent a critical challenge for public health and contemporary anesthesiology in Brazil, since vascular diseases are frequently associated with high rates of adverse cardiovascular events.¹ In Brazil, the prevalence of conditions such as varicose vein disease reaches approximately 38% of the population, reinforcing the need to consider the transition to minimally invasive methods with rapid recovery, such as endovenous thermal ablation.² However, more

than half of high-complexity interventions are performed on an emergency basis, as in the case of peripheral aneurysm repair, accounting for 59.56% of cases recorded in the public health system.³

The analysis of mortality in emergency settings reveals important disparities depending on the technique employed and the patient's clinical severity. In revascularization procedures for the treatment of critical ischemia, the hospital mortality rate for open procedures reaches 5.24%, significantly higher than the 1.56% observed in endovascular interventions.¹ In addition to mortality, anesthetic-surgical management in conventional procedures results in longer hospital stays, with a mean of 10.2 days, whereas percutaneous approaches reduce this period to 5.3 days.¹ In specific cases of peripheral aneurysm repair, hospital mortality in emergency situations may range from 3.67% to 4.24%, highlighting the severity of patients admitted to the hospital system without prior scheduling³.

In addition to the clinical impact, morbidity and mortality in emergency settings impose a substantial economic burden on the Unified Health System (SUS), with hospitalization costs for revascularization procedures totaling more than R\$333 million between 2010 and 2020.¹ The mean government reimbursement cost for peripheral aneurysm repair is US\$1,170.05 for the open technique and US\$1,802.01 for the endovascular technique.³ Regarding safety, recent studies on saphenous vein thermal ablation demonstrate that the procedure can be performed without intraoperative or postoperative complications both in hospital settings and private clinics, with a favorable cost-benefit profile². Thus, the study of morbidity and mortality and costs during the period from 2019 to 2025 is justified by the need to update national epidemiological data for the development of safer anesthetic protocols and the efficient allocation of resources.³

OBJECTIVES

To assess the landscape of hospital morbidity and mortality and the economic impact of anesthetic-surgical procedures in Brazil, using cross-sectional data from the Hospital Information System (SIH/SUS) for the period from 2019 to 2025. The study sought to describe the total surgical volume, perioperative mortality rates, and associated healthcare costs, correlating these variables with the type of admission (emergency versus elective) and their distribution across Brazilian regions. In addition, it aimed to discuss temporal trends and the allocative efficiency of public resources expended, demonstrating the relevance of perioperative health indicators for supporting public policies on surveillance in anesthesiology.

METHODS

This An integrative literature review was conducted, with a structured search in the PubMed database covering publications from 2021 to 2026. The search strategy combined official terms and free-text expressions, using the terms "Surgical Procedures, Operative," "Anesthesia," "Morbidity," "Mortality," "Costs and Cost Analysis," "Cross-Sectional Studies," and "Brazil," both individually and in combination. A total of 104 articles were identified. After screening by title and abstract, 14 remained for full-text reading. Of these, 7 were selected for the final synthesis according to specific eligibility criteria: original cross-sectional studies available in Portuguese or English that reported in-hospital morbidity and mortality outcomes and the direct costs associated with anesthetic-surgical interventions in the Brazilian healthcare system were included. Articles with purely bibliometric analyses, publications containing global data not specific to Brazil, and studies that did not present patient data or surgical outcomes were

healthcare system without prior scheduling and already presenting with rupture or rapid aneurysm expansion. Complementarily, a study involving 13,506 abdominal aortic aneurysm repairs, 52% of which were performed on an emergency basis, found that the endovascular technique was associated with lower mortality, reinforcing the benefit of less invasive approaches also in high-complexity procedures.⁶

In clear contrast to major vascular interventions, endovenous thermal ablation of the saphenous veins, a minimally invasive procedure performed under tumescent local anesthesia and minimal sedation, showed a notable safety profile. Studies reported that, among 1,240 patients followed at three Brazilian centers, there were no serious intraoperative or postoperative complications, and return to usual activities occurred after a mean of 2.1 days. Considering that varicose vein disease affects approximately 38% of the Brazilian population, expansion of this technique, whose projected savings reach 40% compared with conventional phlebectomy when performed on an outpatient basis, has transformative potential for system efficiency. Similarly, endoscopic thoracic sympathectomy for the treatment of hyperhidrosis, another elective and minimally invasive procedure, reinforces this favorable profile: a study reported mortality of 0.045%, a mean hospital stay of 1.8 days, and a cost of US\$512.68 among the 13,201 interventions recorded.⁷ Thus, Table 1^{1,2,3} consolidates the outcome and cost indicators of the included vascular studies, allowing direct comparison among the different modalities.

Table 1^{1,2,3}: Hospital Mortality and Length of Stay by Anesthetic-Surgical Technique in Selected Vascular Procedures, SUS, Brazil, 2019–2025.

Procedure and technique	Mortality (%)	Hospital stay (days)
Open revascularization	5.24	10.2
Endovascular revascularization	1.56	5.3
Open peripheral aneurysm repair	3.67	8.7
Endovascular peripheral aneurysm repair	4.24	6.1
Saphenous vein thermal ablation (outpatient)	0.0	0
Conventional phlebectomy	0.12	2.5

Source: Adapted from 1, 2, and 3.

Note: As thermal ablation was performed on an outpatient basis, it did not involve hospital admission. No deaths were recorded in the analyzed sample.

Additionally, the overall financial burden of surgical hospitalizations within the SUS, which reached tens of billions of reais during the period covered by the studies, confirms that emergency surgeries account for a disproportionate share of expenditures, whether because of longer hospital stays or the intensive need for

both technological and pharmacological resources.^{2,4} Regional analysis shows that the North and Northeast regions, which already have higher mortality rates of 5% and 4.8%, respectively, also have the lowest reimbursement values per procedure, creating a scenario of chronic underfunding that limits the availability of technologies and restricts access to multiparameter monitors and capnography in up to 34% of small institutions.⁶ In this context, Table 2^{2,5} details the regional contrasts in volume, mortality, and costs. Thus, although the analyzed studies indicate that the lack of monitoring equipment and specialized professionals contributes to poorer outcomes in the North and Northeast regions¹, addressing these structural disparities remains one of the major challenges to achieving equity in perioperative healthcare in the country.

Table 2^{2,5}: Regional Indicators of Surgical Volume, Perioperative Mortality, and Mean Cost, SUS, Brazil, 2019–2025.

Region	Procedures (%)	Mortality (%)	Mean cost (R\$)
North	5.2	5.0	3,800.00
Northeast	20.1	4.8	4,000.00
Southeast	48.3	2.5	5,200.00
South	18.4	2.2	4,800.00
Central-West	8	2.9	4,500.00

Source:SIH/SUS, adapted from references 2 and 5.

From an epidemiological perspective, analysis of temporal trends reveals a continuous reduction in overall surgical mortality since 2015, largely attributed to the dissemination of minimally invasive techniques and the implementation of surgical safety checks. Costs, however, have continued to rise, driven by population aging and the incorporation of high-value technologies, such as endovascular devices.^{2,1} The COVID-19 pandemic temporarily altered this dynamic, as the postponement of elective surgeries created a backlog of cases that, when eventually treated at a later stage and under worse clinical conditions, led to a transient increase in perioperative mortality, a phenomenon clearly captured in the time series of emergency surgeries.

Thus, it is necessary to recognize that the findings discussed carry limitations inherent to the cross-sectional administrative nature of the primary SIH/SUS data, which are subject to underreporting of nonfatal complications and to biases in diagnostic and procedure coding. Methodological heterogeneity among the studies, although mitigated by the eligibility criteria adopted, prevents the performance of a formal meta-analysis, restricting this synthesis to a descriptive and critical approach. Projections for the 2022–2025 period, in particular, should be interpreted with caution, as they depend on pre-pandemic trends whose future stability cannot be guaranteed.

Therefore, despite these limitations, the consolidated results provide concrete support for anesthesiology practice and for the formulation of public policies. Persistently high mortality in emergency surgeries, particularly in the North and Northeast regions, indicates the need for institutional protocols for accelerated perioperative optimization and standardized intraoperative

monitoring, even in smaller hospitals. The safety and favorable cost-effectiveness of outpatient thermal ablation, as well as the lower morbidity associated with endovascular techniques, provide evidence for public healthcare managers to expand the availability of these alternatives, with the potential to simultaneously reduce waiting lists, costs, and complications. Finally, the persistence of regional inequalities in the density of specialists and surgical infrastructure reiterates that, without policies aimed at expanding services to underserved areas and targeted investment, equity in perioperative healthcare will remain a goal to be pursued rather than a reality for the Brazilian population.

CONCLUSION

The analysis of hospital morbidity and mortality and the costs associated with anesthetic-surgical procedures in Brazil shows that emergency surgeries remain associated with poorer clinical outcomes and greater use of healthcare resources when compared with elective procedures. It was observed that patients' clinical severity, combined with the limitations inherent to emergency settings, contributes significantly to increased perioperative mortality, longer hospital stays, and higher hospital costs.

Additionally, the incorporation of minimally invasive techniques has been shown to provide favorable outcomes, with reduced mortality, shorter hospital stays, and the potential for cost optimization in different surgical settings, particularly in vascular diseases. These findings reinforce the importance of expanding access to technologies and care strategies capable of promoting greater perioperative safety and more efficient use of public resources.

Important regional disparities were also identified, with higher mortality rates and lower availability of specialized resources in regions of the country that have historically been more vulnerable, highlighting the need for targeted investments in improving anesthetic-surgical care and reducing structural inequalities within the healthcare system.

Thus, it can be concluded that continuous monitoring of morbidity and mortality indicators and perioperative costs is an essential tool for healthcare planning, supporting public policies aimed at strengthening surgical safety, expanding cost-effective technologies, and promoting a more equitable allocation of resources within the Unified Health System.

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LATE COMPLICATIONS ASSOCIATED WITH THE USE OF HYALURONIC ACID DERMAL FILLERS IN FACIAL AESTHETIC PROCEDURES: AN INTEGRATIVE REVIEW

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ABSTRACT

The use of hyaluronic acid dermal fillers has become increasingly prominent in facial aesthetics due to their effectiveness and safety profile. However, late complications associated with these procedures have been increasingly reported in the scientific literature. This study aimed to analyze the scientific evidence regarding the main late complications related to facial hyaluronic acid fillers. An integrative review was conducted using PubMed/MEDLINE, SciELO, and BVS databases, including studies published between 2017 and 2026. The findings demonstrated that intermittent delayed edema, inflammatory nodules, granulomas, hypersensitivity reactions, and biofilm-associated complications are the most frequently reported adverse events, being associated with technical factors, biomaterial characteristics, and systemic patient conditions. It is concluded that preventing such complications requires careful clinical assessment, comprehensive anatomical knowledge, and early management strategies, contributing to greater patient safety and improved aesthetic outcomes.

Keywords: Adverse complications, Dermal fillers, Facial aesthetics, Hyaluronic Acid, Patient safety.

INTRODUCTION

Facial aging is a multifactorial process characterized by progressive loss of soft tissue volume, laxity of ligamentous structures, facial bone remodeling, and changes in adipose compartments. Among the most affected regions is the midface, particularly the anteromedial cheek, areas that are responsible for maintaining facial symmetry, harmony, and a youthful appearance. In this context, hyaluronic acid-based fillers have been widely used in facial aesthetics because of their ability to provide volumization, tissue support, and rejuvenation through a minimally invasive technique.¹ The use of hyaluronic acid has gained increasing prominence in recent years due to the high demand for nonsurgical aesthetic procedures, greater emphasis on physical appearance, the desire to achieve a more youthful appearance, and advances in facial harmonization techniques. In addition to its high biocompatibility and resorbable nature, hyaluronic acid has clinical safety, which favors its use in different anatomical regions of the face. However, despite its aesthetic and functional benefits, complications associated with facial fillers have been increasingly reported in the scientific literature.^{1,2}

Complications resulting from the use of hyaluronic acid-based fillers may range from mild and transient manifestations, such as edema, erythema, bruising, and local pain, to severe manifestations, including infections, nodule formation, granulomas, tissue necrosis, and vascular occlusion. Among these, vascular obstruction stands out because of the possibility of rapid progression to ischemia, skin necrosis, and even irreversible visual loss.^{2,3,4} The occurrence of these complications is related to factors such as inadequate technique, lack of anatomical knowledge, incorrect product selection, and performance of the procedure by unqualified professionals.² In this context, there is considerable concern among the scientific community and professionals working in aesthetics regarding the safety of injectable aesthetic procedures and the need for continuous professional updating. Recent studies have investigated the main pathophysiological mechanisms related to hyaluronic acid complications, as well as preventive strategies and therapeutic protocols for the early management of these adverse events. In addition, the marked increase in demand for facial harmonization reinforces the importance of adopting measures that ensure greater patient safety.²

Therefore, it is relevant to gather and analyze the available evidence in the literature regarding complications associated with facial filling using hyaluronic acid. Thus, through an integrative review, this study aims to identify the main complications related to the use of hyaluronic acid in facial aesthetics, their predisposing factors, clinical manifestations, prevention methods, and therapeutic possibilities based on the literature.

OBJECTIVES

To analyze, through an integrative literature review, the available scientific evidence regarding complications resulting from hyaluronic acid fillers in facial aesthetics. Specifically, the study aims to identify predisposing and risk factors, clinical manifestations and the frequency of these adverse events, preventive methods, and the therapeutic approaches described, with the purpose of supporting safer and more effective practices in facial harmonization.

METHODS

This integrative review followed Ganong's methodological framework, organized into six stages: selection of the topic and research question, establishment of inclusion and exclusion criteria, definition of the information to be extracted, evaluation of the studies, interpretation of the results, and presentation of the review. The guiding question, structured according to the PICO strategy, was: "What are the main late complications and safety outcomes associated with the use of hyaluronic acid fillers in facial procedures, according to the current literature?"

The data search was conducted in May 2026 in the PubMed/MEDLINE, SciELO, and VHL databases. The Medical Subject Headings (MeSH Terms) and Health Sciences Descriptors (DeCS) were used for vocabulary control and identification of corresponding terms. The search string combined the terms ("Hyaluronic acid" OR "Ácido Hialurônico") AND ("Dermal Fillers" OR "Preenchedores Dérmicos") AND ("Postoperative Complications" OR "Complicações Pós-Operatórias" OR "Delayed-onset edema") AND ("Face") using the Boolean operators OR and AND.

The inclusion criteria comprised original articles, case reports, and consensus statements published between 2017 and 2026 in Portuguese, English, or Spanish. Selection was performed by two independent researchers to avoid bias, resulting in a final corpus of 7 articles. Data analysis was performed narratively,

correlating complications such as inflammatory nodules and intermittent delayed edema with new clinical triggers, such as the use of GLP-1 analogues and innovations in hybrid fillers.

RESULTS

The integrative analysis of the seven included articles allowed a comprehensive characterization of late complications associated with the use of hyaluronic acid fillers in facial aesthetic procedures, as well as the identification of emerging predisposing factors and contemporary prevention and management strategies.

Table 1: Characteristics of the included studies.

Author and year	Methodologic Design	Population/ Sample	Main Focus	Main Findings	Level of Evidence
Piton et al. (2025)	Systematic Literature Review	Analysis of multiple studies on filler complications	Taxonomy and classification of late complications	Identification of 8 main categories of late complications; intermittent delayed edema and inflammatory nodules as the most frequent	II
Ciaramicolo et al. (2024)	Case Report	3 patients undergoing semaglutide (Ozempic®) therapy	Association between GLP-1 analogues and delayed facial edema after filler injection	Recurrent intermittent facial edema in patients using GLP-1; hypothesis of systemic inflammatory modulation as the mechanism; absence of technical or biomaterial failure	IV
Urdiales Galvez et al. (2017)	Expert Consensus	Panel of 15 specialists in facial aesthetics	Recommendations for the prevention of technical complications	Anatomical knowledge, safe injection technique, appropriate product selection, and injector experience as pillars of prevention; standardized technical safety protocols	III

Lee et al. (2026)	Prospective Controlled Study	120 patients; 24-week follow-up	Safety and efficacy of hybrid fillers (hyaluronic acid + polynucleotides)	Favorable tolerability profile; absence of serious adverse events; maintenance of volume and patient satisfaction; no stratification regarding systemic medications	II
Qiu et al. (2026)	Retrospective Study	85 patients receiving combined treatments	Efficacy of combined treatments (hyaluronic acid + other bioactive agents) for photoaging	Synergy between different bioactive agents; dynamic interaction between components determines final safety; importance of considering biomaterial-host compatibility	III
Bettiol et al. (2026)	Longitudinal Observational Study	60 patients; 12-month follow-up	Orofacial function and quality of life after facial filler treatment	Preservation of masticatory and phonatory function in most cases; impact on quality of life correlated with functional maintenance, not only with the absence of complications;	II
				delayed edema significantly affects function	

Shturman et al. (2026)	Review of Minimally Invasive Treatments	Analysis of 12 corrective protocols	Minimally invasive approaches for correction of aesthetic complications	Importance of individualized management; integration of energy-based technologies; consideration of the “corrective patient archetype”; psychosocial safety as a component of success	III
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Source: Prepared by the authors (2026).

The results of this integrative review demonstrate a clear evolution in the understanding of late complications associated with hyaluronic acid fillers. First, a spectrum of manifestations extending beyond mere local inflammation has become established, including intermittent delayed edema, inflammatory nodules, foreign-body granulomas, conditions suggestive of biofilm formation, and delayed hypersensitivity reactions. It is important to emphasize that these events affect not only morphological aspects but also orofacial function and psychosocial well-being, with a direct impact on the patient’s quality of life—a dimension intrinsic to the contemporary concept of safety.

At the same time, traditionally emphasized risk determinants—such as gaps in anatomical knowledge, inadequate technique, inappropriate product selection, and injector inexperience—remain relevant but do not fully explain the heterogeneity of outcomes. Recent literature introduces systemic risk modifiers, particularly the use of GLP-1 agonists and other drugs with the potential to modulate inflammation, which may alter the tissue response to the biomaterial and thereby predispose patients to complications with delayed onset and an intermittent course. Regarding biomaterials, studies involving hybrid formulations support a favorable safety profile in general populations but suggest individual variability that remains insufficiently characterized. This dissociation—positive overall safety versus idiosyncratic responses in subgroups—reinforces the need for prior risk stratification that considers not only the product and technique but also the patient’s systemic status and concomitant therapies.

DISCUSSION

The results of this study demonstrate that late complications associated with the use of hyaluronic acid fillers in facial aesthetic procedures represent a multifactorial phenomenon, whose understanding requires the integrated synthesis of technical, biomaterial, systemic, and psychosocial knowledge. While previous studies focused primarily on technical-procedural factors as the sole determinants of safety, contemporary literature reveals that the heterogeneity of clinical outcomes emerges from dynamic interactions among multiple levels of factors.

Overview of Late Complications in Facial Filling with Hyaluronic Acid

The analysis of the included studies allows the characterization of a broad spectrum of late

complications occurring weeks to months after the initial procedure. Unlike acute complications, such as vascular occlusion or necrosis, which manifest immediately and are primarily attributable to technical error, late complications exhibit a distinct phenomenological pattern. Intermittent delayed facial edema emerges as the most frequently reported complication, characterized by recurrent episodes of swelling that resolve spontaneously between events. Inflammatory nodules and foreign-body granulomas constitute the second most common category, frequently associated with delayed hypersensitivity reactions or bacterial biofilm formation. The clinical importance of this categorization lies in the fact that each type of complication involves a distinct pathophysiological mechanism and, consequently, a different therapeutic strategy. The temporal pattern of late complications suggests that they do not represent primary tissue injury, as expected in acute technical complications, but rather recurrent inflammatory decompensation or failure of biomaterial integration over time. This observation is fundamental for understanding the predisposing factors discussed in the following section.³

Predisposing Factors and New Clinical Triggers — The Influence of Systemic Conditions on the Safety of Facial Fillers

To adequately answer the guiding question of this review — “What are the main late complications and safety outcomes associated with the use of hyaluronic acid fillers in facial procedures?” — it is not sufficient merely to identify the complications; it is necessary to understand the predisposing mechanisms that explain why some patients develop these complications while others undergoing technically similar procedures do not. The expert consensus by Urdiales-Gálvez et al.² is based on the premise that complications of facial fillers arise primarily from insufficient anatomical knowledge, inadequate injection technique, inappropriate product selection, and lack of injector experience. This technically centered paradigm was, and remains, entirely valid for acute complications and many early complications. However, it has an important explanatory limitation when confronted with contemporary findings. The case report by Ciaramicolo et al.⁴ documents a remarkable finding: intermittent delayed facial edema after hyaluronic acid filler injection in patients receiving semaglutide (Ozempic®), a widely prescribed GLP-1 receptor agonist. What makes this case clinically significant is not the complication itself, but the context in which it occurred: a procedure performed by an experienced professional, with an appropriate injection technique and suitable product, and without vascular injury or technical failure. In other words, all the technical predisposing factors identified by Urdiales-Gálvez et al.² as causal were absent or optimized, yet the complication still occurred. This phenomenon suggests the existence of a new class of predisposing factors not contemplated by the technical paradigm of 2017.

Ciaramicolo et al.⁴ propose that the common factor among their patients — semaglutide therapy — acts as a systemic modifier of the inflammatory response. Although the report does not provide its own mechanistic data, the hypothesis is based on well-characterized properties of GLP-1 agonists: reduction of systemic inflammatory markers, modulation of the adaptive response, and effects on endothelial permeability. The integrated explanation is that the injected biomaterial, hyaluronic acid, triggers the expected local inflammatory response, which would normally be rapidly resolved by the host’s homeostatic systemic inflammatory state. However, in patients receiving GLP-1 analogue therapy, chronic modulation of the inflammatory response may result in a biphasic response: excessive reduction of local inflammation during the initial phase, causing fibrosis or entrapment of the biomaterial, followed by periodic decompensation when systemic inflammatory suppression fluctuates or when local stimuli reactivate inflammation. This mechanism explains why the edema is

intermittent and why it occurs in patients without technical failure.

Integrated analysis with subsequent studies reveals a crucial pattern. The prospective study by Lee et al.¹ evaluated hybrid fillers, hyaluronic acid plus polynucleotides, over 24 weeks and documented a favorable tolerability profile, with no serious adverse events. There is no contradiction with Ciaramicolo et al.⁴, but rather complementarity: Lee et al.¹ confirm that hyaluronic acid, even in new formulations, maintains a favorable safety profile when used in a prospectively monitored general population, whereas Ciaramicolo et al.⁴ demonstrate that biomaterial safety is not equivalent to universal safety across all patient subpopulations. The gap between the two studies is revealing: Lee et al.¹ did not stratify their population according to the use of GLP-1 analogues or other inflammation-modulating drugs. This lack of pharmacological stratification is particularly relevant considering that Lee et al.¹ was published in 2026, a period of increasing GLP-1 use, and that it is plausible that disaggregated data from Lee et al. would reveal safety differences between subgroups with and without GLP-1 use. The retrospective study by Qiu et al.⁵, which investigated combined treatments for photoaging, provides additional important context. Although Qiu et al.⁵ did not specifically investigate late complications, their findings regarding interactions among different bioactive agents reinforce the concept that the final safety of the procedure does not arise from a single isolated component, but from the dynamic interaction among multiple factors. Applying this reasoning to the findings of Ciaramicolo et al.⁴, the complication may be understood as the result of the interaction between hyaluronic acid, as a stimulus for a local inflammatory reaction, and an altered systemic inflammatory state, as a modifier induced by GLP-1. The biomaterial itself remains safe, as documented by Lee et al.¹; decompensation occurs at the interface between local and systemic factors.

Prevention Strategies and Therapeutic Protocols

The literature analyzed demonstrates a clear paradigm shift. The consensus by Urdiales-Gálvez et al.² establishes the fundamental basis for any preventive strategy: in-depth anatomical knowledge of facial vasculature, safe injection techniques, including prior aspiration, use of cannulas in high-risk areas, and slow injection of small volumes, product selection based on rheological properties compatible with the anatomical area, and appropriate patient preparation. These preventive measures centered on technical optimization remain entirely valid and necessary to avoid acute complications and many early complications. However, when technical prevention fails or when late complications occur, the literature points toward a more sophisticated hierarchy of intervention. Management of inflammatory nodules and delayed edema presents an important dichotomy: in cases of suspected bacterial biofilm, the classical approach involves long-term antibiotic protocols, such as macrolides including clarithromycin, although efficacy is often limited by the protective nature of the biofilm matrix. In immune-mediated reactions, including granulomas or inflammatory nodules, treatment involves the use of hyaluronidase to degrade the filler, with or without corticosteroids, either intralesional or systemic, and, in refractory cases, immunomodulatory agents.

The finding by Ciaramicolo et al.⁴ regarding delayed edema associated with the use of GLP-1 analogues adds an important layer of complexity. In patients receiving GLP-1 therapy, administration of hyaluronidase or corticosteroids may require adjustments based on the patient's systemic inflammatory status. Current literature still lacks specific guidelines for this subgroup, representing an important gap to be addressed. The study by Shturman et al.⁶ offers a different perspective by proposing a minimally invasive corrective approach. Rather than aggressive protocols based solely on

chemical degradation with hyaluronidase or systemic suppression with corticosteroids, Shturman et al.⁶ propose individualizing the therapeutic plan not only according to the complication, but also according to the patient profile, including age, previous history, and expectations. The authors suggest that the use of energy-based technologies, such as intense pulsed light, also mentioned by Qiu et al.⁵, may be integrated into complication management, acting on modulation of the local inflammatory response and improving skin quality, thereby assisting in the resolution of late inflammatory conditions. This convergence with the view that complication correction should be integrative marks an important evolution: while Urdiales-Gálvez et al.² focused on “how to inject,” Shturman et al.⁶ focus on “how to manage outcomes holistically.”

Functional Safety and Patient Quality of Life — Beyond the Absence of Complications

The integrative literature review reveals a fundamental paradigm shift that transcends previous technical discussions: the success of a facial filler procedure should not be measured solely by the absence of severe complications, but also by preservation of orofacial function and maintenance of long-term quality of life (QoL). The longitudinal observational study by Bettiol et al.⁷ is central to this discussion. By assessing orofacial function after mandibular angle contouring, the authors challenge the reductionist view that “safety = absence of adverse events.” Safety must include preservation of fundamental functions: mastication, speech, and facial expression. Bettiol et al.⁷ demonstrate that even in technically successful procedures without late inflammatory complications, changes in muscular and ligamentous dynamics may affect orofacial function. If a filler produces an apparently perfect aesthetic result but causes masticatory discomfort or speech alteration, the procedure has failed in one of its primary safety outcomes. This evidence integrates critically with the findings of Ciaramiccolo et al.⁴: intermittent delayed edema is not merely an isolated inflammatory problem; by definition, it is a factor causing recurrent functional impairment that reduces the patient’s quality of life over time. A patient experiencing recurrent episodes of facial edema lives in a constant state of vigilance, with a negative impact on confidence, self-image, and satisfaction with the outcome of the procedure.

The study by Shturman et al.⁶ further expands this discussion by introducing the concept of the “corrective patient archetype” and the psychosocial perspective of safety. Complications such as inflammatory nodules or intermittent edema are not neutral events. They generate anxiety and distress because of their recurrent and unpredictable nature, doubts regarding the choice of professional and product, with consequent loss of trust in the physician-patient relationship, and a direct impact on self-image, since the complication alters the face itself, undermining the very reason why the patient sought the procedure. Shturman et al.⁶ argue that the management of these complications should be holistic: patient safety involves not only clinical resolution but also restoration of confidence and self-image. The “corrective patient” is one who has already had a negative experience and whose safety in future procedures depends on an approach that takes this emotional burden into account.

CONCLUSION

Considering the results of the present integrative review, it can be concluded that late complications associated with the use of hyaluronic acid dermal fillers in facial aesthetic procedures are multifactorial events influenced by injection technique, biomaterial characteristics, individual inflammatory response, and the patient’s systemic conditions. The main adverse events described include intermittent delayed edema, inflammatory nodules, granulomas, delayed hypersensitivity

reactions, and conditions associated with biofilm formation.

Therefore, it is recommended that professionals responsible for injectable aesthetic procedures adopt individualized clinical assessment, in-depth anatomical knowledge, careful product selection, and protocols for the prevention and early management of complications. In addition, further prospective studies with larger numbers of patients and stratification of risk factors are needed in order to improve safety protocols and strengthen evidence-based clinical practice.

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EFFICACY AND SAFETY OF ANTI-AMYLOID ANTIBODIES IN EARLY ALZHEIMER'S DISEASE: A SYSTEMATIC REVIEW OF LECANEMAB AND DONANEMAB

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ABSTRACT

Alzheimer's disease has historically been treated with symptomatic drugs, without consistent modification of its biological course. The recent approval of anti-amyloid monoclonal antibodies has changed this landscape, especially for patients with mild cognitive impairment or mild dementia associated with amyloid pathology. This systematic review without meta-analysis assessed evidence on the efficacy and safety of lecanemab and donanemab in early Alzheimer's disease. Randomized, double-blind, placebo-controlled clinical trials evaluating these drugs in biomarker-confirmed Alzheimer's disease were included. The synthesis followed PRISMA 2020 and SWiM recommendations, grouping findings by drug, trial phase, cognitive-functional outcomes, biomarkers, and adverse events. Four clinical trials met eligibility criteria. Lecanemab and donanemab reduced amyloid burden and slowed cognitive-functional decline in phase 3 studies, although the absolute magnitude of benefit was moderate. The main adverse events were amyloid-related imaging abnormalities, infusion-related reactions, and rare hemorrhagic events, with higher risk among ApoE ϵ 4 carriers. The findings suggest a real but limited therapeutic advance, restricted to carefully selected patients and dependent on biomarker confirmation, serial magnetic resonance imaging, and healthcare infrastructure able to recognize and manage treatment-related adverse events.

Keywords: Alzheimer disease, Amyloid beta-Peptides, Antibodies monoclonal, Mild Cognitive impairment, Systematic review.

INTRODUCTION

Alzheimer's disease remains one of the neurological conditions with the greatest clinical and social impact. Its relevance is not limited to how frequently it occurs among dementias. The burden of the disease also lies in the way it progressively transforms memory, language, autonomy, family caregiving, and the organization of healthcare services. For decades, pharmacological treatment was restricted to symptomatic interventions, such as acetylcholinesterase inhibitors and memantine, which are useful in certain contexts but are unable to demonstrably modify the central neuropathological processes of the disease. This gap between clinical impact and therapeutic limitations has made the search for disease-modifying treatments one of the most persistent areas of research in neurology.

In recent years, the very definition of Alzheimer's disease has shifted. Diagnosis is no longer based solely on the syndromic recognition of an amnesic dementia and has increasingly incorporated amyloid, tau, and neurodegeneration biomarkers. The AT(N) model, proposed in the NIA-AA Research Framework, organized the disease according to measurable biological processes, separating the clinical syndrome from the neuropathological etiology.¹ More recent criteria from the Alzheimer's Association reinforced this direction by stating that core biomarkers, including amyloid PET, approved cerebrospinal fluid markers, and accurate plasma biomarkers, can establish the biological diagnosis of the disease in appropriate contexts.² This change is not merely conceptual. It has become a practical requirement for prescribing beta-amyloid-targeted therapies.

Lecanemab and donanemab have emerged in this context. Both are anti-amyloid monoclonal antibodies, but they are not identical. Lecanemab is a humanized IgG1 antibody with greater affinity for soluble beta-amyloid aggregates, particularly protofibrils.³ Donanemab recognizes an N-terminally truncated and pyroglutamylated form of beta-amyloid, found predominantly in established plaques.⁴ This distinction is relevant because the two drugs differ not only in epitope but also in clinical development design, biomarker selection, dosing regimen, and monitoring strategy.

Phase 3 clinical trials produced statistically favorable results. Clarity AD demonstrated that lecanemab reduced amyloid markers and resulted in less decline on the Clinical Dementia Rating Scale Sum of Boxes in patients with early Alzheimer's disease.⁵ TRAILBLAZER-ALZ 2 showed that donanemab slowed clinical progression in patients with early symptomatic Alzheimer's disease, positive amyloid status, and different levels of tau pathology.⁶ These findings represented a turning point compared with previous attempts at anti-amyloid therapies, many of which were marked by negative or controversial clinical results.

However, interpretation of these studies requires caution. Relative percentages of slowing, such as 27%, 29%, or 35%, may suggest a more substantial effect than that observed in absolute units on clinical scales. Contemporary discussion regarding clinically meaningful differences in Alzheimer's disease shows that statistical significance and clinical perception by the patient or caregiver are not equivalent.⁷ In addition, amyloid removal should not automatically be treated as synonymous with sufficient functional benefit. The field of anti-amyloid therapy itself has been built around the tension between biomarker improvement, mean clinical effect, and applicability outside the controlled environment of clinical trials.

Safety also occupies a central position. Lecanemab and donanemab are associated with amyloid-related imaging abnormalities, known by the acronym ARIA. These abnormalities include edema or effusion, classified as ARIA-E, and hemorrhagic changes, such as microhemorrhages and superficial siderosis, classified as ARIA-H. Most events in the trials were asymptomatic, but symptomatic, severe, and rarely fatal cases have been described.^{8,9} The risk is higher in ApoE ϵ 4 carriers, especially homozygotes, and is also related to pre-existing findings of cerebral amyloid angiopathy, microhemorrhages, anticoagulation, and the need for thrombolysis in situations of suspected stroke.

The arrival of these drugs in the Brazilian debate makes the issue even more complex. The position paper of the Scientific Department of Cognitive Neurology and Aging of the Brazilian Academy of Neurology states that anti-amyloid antibodies provide modest clinical benefits, relevant risks, and important challenges related to diagnostic access, cost-effectiveness, safety, and population representativeness.¹⁰ The Brazilian Health Regulatory Agency approved donanemab in 2025 and lecanemab in 2025 for adult patients in the early stage of the disease, with restriction to ApoE ϵ 4 non-carriers or heterozygotes.^{11,12} Even so, regulatory approval alone does not resolve clinical

implementation. Treatment depends on early diagnosis, biomarker confirmation, serial magnetic resonance imaging, an infusion center, and a team capable of managing ARIA.

Given this scenario, the relevant question is not merely whether anti-amyloid antibodies work. The more precise question is in which patients, with what magnitude of benefit, under what level of risk, and under what implementation conditions they may be considered. This systematic review analyzes the efficacy and safety of lecanemab and donanemab in early Alzheimer's disease, using a structured narrative synthesis without meta-analysis.

OBJECTIVES

The general objective of this study was to systematically analyze the available evidence on the efficacy and safety of lecanemab and donanemab in the treatment of early Alzheimer's disease.

The specific objectives were to describe the characteristics of the randomized clinical trials that evaluated these drugs; synthesize the main cognitive and functional outcomes, including the Clinical Dementia Rating Scale Sum of Boxes, Integrated Alzheimer's Disease Rating Scale, Alzheimer's Disease Assessment Scale Cognitive Subscale, and measures of activities of daily living; analyze the effects on amyloid and tau biomarkers, when available; identify the frequency and clinical relevance of adverse events, with emphasis on ARIA-E, ARIA-H, infusion-related reactions, serious adverse events, and treatment discontinuation; and discuss the clinical applicability of the findings in light of the need for biomarker-based selection, ApoE stratification, serial magnetic resonance imaging, and healthcare infrastructure.

METHODS

A systematic literature review without meta-analysis was conducted, using a structured narrative synthesis. The reporting followed the PRISMA 2020 recommendations for systematic reviews and incorporated SWiM principles for synthesis without meta-analysis, since the included studies differed substantially in terms of drug, development phase, primary scale, biomarker criteria, follow-up duration, and outcome reporting.^{13,14} The protocol was not prospectively registered.

The research question was formulated according to the PICO strategy. The population included adults with early Alzheimer's disease, defined as mild cognitive impairment or mild dementia associated with Alzheimer's disease, with biomarker confirmation of amyloid pathology. The interventions were lecanemab or donanemab. The comparator was placebo. Outcomes included cognitive-functional decline, biomarker changes, ARIA-E, ARIA-H, infusion-related reactions, serious adverse events, treatment-related deaths, and discontinuation.

Publications from January 2020 to June 2026 were considered, a period selected to encompass the consolidation of phase 2 and phase 3 clinical trials of the studied drugs, as well as regulatory publications and appropriate-use recommendations. The databases searched were PubMed/MEDLINE, the Virtual Health Library, Cochrane Library, SciELO, and Google Scholar as a complementary source. Reference lists of the included articles and regulatory or clinical guidance documents directly related to implementation of the drugs were also reviewed.

The search strategy combined terms in English and Portuguese related to early Alzheimer's disease, lecanemab, donanemab, anti-amyloid antibodies, efficacy, safety, and ARIA. In PubMed/MEDLINE, the main strategy was: ("Alzheimer Disease" OR "early Alzheimer's disease" OR "mild cognitive impairment" OR "mild dementia") AND (lecanemab OR donanemab OR "anti-amyloid monoclonal antibody") AND (efficacy

OR safety OR "amyloid-related imaging abnormalities" OR ARIA OR "CDR-SB" OR iADRS). In the VHL and SciELO, equivalent terms in Portuguese were used: ("Doença de Alzheimer" OR "comprometimento cognitivo leve" OR "demência leve") AND (lecanemabe OR donanemabe OR "anticorpos monoclonais anti-amiloide") AND (eficácia OR segurança OR ARIA OR "anormalidades de imagem relacionadas ao amiloide").

Randomized, double-blind, placebo-controlled clinical trials evaluating lecanemab or donanemab in patients with early Alzheimer's disease and biomarker confirmation of amyloid pathology were included. Phase 2 and phase 3 studies were eligible provided that they reported clinical efficacy and safety data. Preclinical studies, animal studies, case reports, editorials, commentaries, conference abstracts without full text, studies of other anti-amyloid antibodies without separate analysis of lecanemab or donanemab, studies in moderate or severe Alzheimer's disease, and publications without clinical outcomes, biomarkers, or safety data were excluded.

Records were initially screened by title and abstract. Potentially eligible full-text articles were then reviewed. Data extraction included author, year, drug, study phase, design, number of participants, age, clinical stage, biomarker criteria, intervention, comparator, duration, primary outcome, main secondary outcomes, biomarker changes, ARIA-E, ARIA-H, infusion-related reactions, serious adverse events, treatment-related deaths, and methodological limitations.

Risk of bias assessment for the clinical trials was planned according to the domains of the Cochrane RoB 2 tool, considering the randomization process, deviations from intended interventions, missing data, outcome measurement, and selection of reported results. As this was a literature review based on secondary data and public documents, submission to a Research Ethics Committee was not required.

Regulatory documents, appropriate-use recommendations, diagnostic guidelines, reviews on ARIA, national position statements, and health technology assessments were not treated as clinical trials included in the main synthesis. These texts were used as complementary references to interpret safety, eligibility, monitoring, and applicability. This separation was adopted to preserve the methodological coherence of the systematic review and to avoid synthesizing documents of different natures as if they represented the same level of evidence.

RESULTS AND DISCUSSION

The search and full-text review identified four randomized clinical trials eligible for the main synthesis: one phase 2b study of lecanemab, Clarity AD, TRAILBLAZER-ALZ phase 2, and TRAILBLAZER-ALZ 2.3-6. Complementary documents included appropriate-use recommendations for lecanemab and donanemab, the Brazilian position statement of the Brazilian Academy of Neurology, diagnostic guidelines, publications on ARIA, documents from the Brazilian Health Regulatory Agency, an assessment by the National Institute for Health and Care Excellence, and a recent Cochrane review on anti-amyloid antibodies.^{1,2,7-12,15-21}

Table 1: Main Characteristics of the Included Clinical Trials.

Study	Drug	Phase	Participants	Population	Entry Biomarkers	Primary Outcome	Duration
BAN2401-G 000-2013	Lecanemab	2b	854 treated	Early Alzheimer's disease	Amyloid positive	ADCOMS at 12 months	18 months
Clarity AD5	Lecanemab	3	1.795	Mild cognitive impairment or mild dementia due to Alzheimer's disease	Amyloid by PET or cerebrospinal fluid	CDR-SB at 18 months	18 months
TRAILBLAZER-ALZ4	Donanemab	2	257	Early symptomatic Alzheimer's disease	Amyloid and tau by PET	iADRS at 76 weeks	76 weeks
TRAILBLAZER-ALZ26	Donanemab	3	1.736	Mild cognitive impairment or mild dementia due to Alzheimer's disease	Amyloid and tau by PET	iADRS at 76 weeks	76 weeks

Source: Authors' own elaboration, 2026.

The development pathway of these drugs shows that the positive phase 3 results did not emerge in a linear manner. In the phase 2b study of lecanemab, the primary Bayesian objective at 12 months was not met. The 10 mg/kg dose administered every two weeks had a 64% probability of being superior to placebo by at least 25% on the Alzheimer's Disease Composite Score, below the prespecified threshold of 80%.³ At 18 months, however, the same dose showed amyloid reduction and favorable signals on the Alzheimer's Disease Composite Score, Alzheimer's Disease Assessment Scale Cognitive Subscale, and Clinical Dementia Rating Scale Sum of Boxes.³ This result should not be interpreted as either a simple failure or an unequivocal success. It shows that the clinical effect of these antibodies may depend on treatment duration, dose selection, choice of scale, and the relationship between biomarker and functional outcome.

Clarity AD was the confirmatory study of lecanemab. In this trial, 1,795 patients with early Alzheimer's disease received lecanemab 10 mg/kg every two weeks or placebo. The primary outcome was the change in the Clinical Dementia Rating Scale Sum of Boxes at 18 months. The lecanemab group worsened by 1.21 points, whereas the placebo group worsened by 1.66 points, a difference of -0.45 points, corresponding to a 27% relative slowing.⁵ Secondary outcomes also favored lecanemab, including the Alzheimer's Disease Assessment Scale Cognitive Subscale, Alzheimer's Disease Composite Score, and Alzheimer's Disease Cooperative Study Activities of Daily Living Scale for Mild Cognitive Impairment.⁵ Appropriate interpretation of this result requires clarity about what it represents. Lecanemab did not improve patients' cognition. It reduced the mean rate of decline in a selected population followed under clinical trial conditions.

The phase 2 study of donanemab, TRAILBLAZER-ALZ, included 257 patients with early symptomatic Alzheimer's disease and amyloid and tau positivity on PET. Donanemab was administered every four weeks, at 700 mg for the first three doses and 1,400 mg thereafter. The primary outcome was the change in the Integrated Alzheimer's Disease Rating Scale at 76 weeks. The change was -6.86 points with donanemab and -10.06 with placebo, a difference of 3.20 points.⁴ Although the primary endpoint favored the drug, most secondary outcomes did not show substantial differences.⁴ This finding is important because it prevents an overly homogeneous interpretation. Donanemab showed a clinical signal and

marked amyloid reduction, but clinical consistency still needed to be tested in a larger sample.

TRAILBLAZER-ALZ 2 expanded this evidence. The study included 1,736 participants with early symptomatic Alzheimer's disease, amyloid positivity, and low/medium or high tau pathology. Donanemab was compared with placebo for 76 weeks. In the low/medium tau population, the change in the Integrated Alzheimer's Disease Rating Scale was -6.02 in the donanemab group and -9.27 in the placebo group, a difference of 3.25 points. In the combined population, the difference was 2.92 points. On the Clinical Dementia Rating Scale Sum of Boxes, the difference was -0.67 in the low/medium tau population and -0.70 in the combined population.⁶ The study therefore demonstrated a statistically significant slowing of progression. At the same time, the need for stratification by tau and amyloid reinforces that the observed effect applies to a biologically selected population.

Table 2: Main Clinical Efficacy Results.

Study	Primary Scale	Main Result	Interpretation
Swanson, Zhang, Dhadda, Wang, Kaplow, Lai, Lannfelt, Bradley, Rabe, Koyama, Reyderman, Berry, Berry, Gordon, Kramer e Cummings ³	ADCOMS	Primary endpoint at 12 months not met; favorable signals at 18 months	Study provided the rationale for dose selection and phase 3, with an initially negative primary result
van Dyck, Swanson, Aisen, Bateman, Chen, Gee, Kanekiyo, Li, Reyderman, Cohen, Froelich, Katayama, Sabbagh, Vellas, Watson, Dhadda, Irlizarry, Kramer e Iwatsubo ⁷	CDR-SB	Difference of -0.45 points at 18 months	Statistically significant slowing, with modest absolute magnitude
Mintun, Lo, Evans, Wessels, Ardayfio, Andersen, Shcherbinin, Sparks, Sims, Brys, Apostolova, Salloway e Skovronsky ⁶	iADRS	Difference of 3.20 points at 76 weeks	Favorable primary outcome, with mixed secondary outcomes
Sims, Zimmer, Evans, Lu, Ardayfio, Sparks, Wessels, Shcherbinin, Wang, Monkul Nerv, Collins, Solomon, Salloway, Apostolova, Hansson, Ritchie, Brooks, Mintun e Skovronsky ⁶	iADRS	Difference of 3.25 points in the low/medium tau group and 2.92 in the combined population	Statistically significant slowing in a phase 3 study

Source: Authors' own elaboration, 2026.

The efficacy synthesis allows an initial conclusion: both drugs showed a favorable clinical effect in phase 3 studies. The question that remains concerns the clinical magnitude of this effect. The rapid review by Muir, Hill, Black, and Smith identified previously published thresholds for clinically important differences in scales used in Alzheimer's disease trials. For mild cognitive impairment, approximately +1 point on the Clinical Dementia Rating Scale Sum of Boxes, -5 points on the Integrated Alzheimer's Disease Rating Scale, +2 to +3 points on the Alzheimer's Disease Assessment Scale Cognitive Subscale, and -1 to -2 points on the Mini-Mental State Examination were considered meaningful. For mild Alzheimer's disease, the thresholds were even higher.⁷ The mean differences observed in the lecanemab and donanemab studies fall below some of these thresholds. This does not invalidate the trials, but it requires a distinction between mean population effect, clinically perceptible difference, and possible individual benefit.

The difficulty lies in translating a group mean into the life of an individual patient. In neurodegenerative diseases, slowing decline may be relevant even when the change on a scale is small. Preserving a few months of autonomy may have value for the patient and family. However, this argument does not justify overstating the result. The scientific text must hold both ideas together. There is statistical and biological benefit. There is also uncertainty regarding the clinical perception of its magnitude.

Biomarkers showed a more robust response than clinical scales. The phase 2b lecanemab study demonstrated amyloid reduction on PET with the 10 mg/kg every-two-weeks regimen.³ Clarity AD confirmed a reduction in amyloid burden and favorable changes in disease-related biomarkers.⁵ In the phase 2 donanemab study, there was a marked reduction in amyloid plaques, with a difference of 85.06 centiloids compared with placebo.⁴ TRAILBLAZER-ALZ 2 also demonstrated amyloid reduction and supported the strategy of discontinuing treatment when amyloid burden reached low levels, a particular feature of donanemab.⁶

This relative dissociation between biomarker effect and clinical magnitude is one of the central issues of the review. Lecanemab and donanemab alter the biological target they are intended to affect. The question is not whether they remove amyloid, but how much that removal translates into measurable and clinically valued functional benefit. The 2026 Cochrane review, evaluating anti-amyloid monoclonal antibodies as a class, concluded that mean effects on cognition and function were small or trivial, while events such as cerebral edema and microhemorrhages increased.²¹ This conclusion should be interpreted with caution because it groups older and newer drugs with distinct mechanisms and performance. Even so, it serves as a necessary methodological counterpoint to an excessively optimistic interpretation of amyloid removal.

Table 3: Safety in the Main Clinical Trials.

Study	Most Relevant Safety Event	Main Finding
Swanson, Zhang, Dhadda, Wang, Kaplow, Lai, Lannfelt, Bradley, Rabe, Koyama, Reyderman, Berry, Berry, Gordon, Kramer e Cummings ³	ARIA-E	Incidence of 9.9% with the 10 mg/kg every-two-weeks regimen
van Dyck, Swanson, Aisen, Bateman, Chen, Gee, Kanekiyo, Li, Reyderman, Cohen, Froelich, Katayama, Sabbagh, Vellas, Watson, Dhadda, Irizarry, Kramer e Iwatsubo ⁵	ARIA e reações infusionais	ARIA-E in 12.6% and infusion-related reactions in 26.4%
Mintun, Lo, Evans, Wessels, Ardayfio, Andersen, Shcherbinin, Sparks, Sims, Brys, Apostolova, Salloway e Skovronsky ⁴	ARIA-E e descontinuação	Amyloid-related edema or effusion occurred with donanemab and was generally asymptomatic
Sims, Zimmer, Evans, Lu, Ardayfio, Sparks, Wessels, Shcherbinin, Wang, Monkul Nery, Collins, Solomon, Salloway, Apostolova, Hansson, Ritchie, Brooks, Mintun e Skovronsky ⁶	ARIA-E e eventos graves	ARIA-E in 24.0%; 52 symptomatic cases; three deaths in the donanemab group and one in the placebo group considered treatment-related

Source: Authors' own elaboration, 2026.

Safety is the area in which clinical interpretation becomes most concrete. In Clarity AD, ARIA-E occurred in 12.6% of participants treated with lecanemab, and infusion-related reactions occurred in 26.4%.⁵ In TRAILBLAZER-ALZ 2, ARIA-E occurred in 24.0% of patients treated with donanemab, with 52 symptomatic cases.⁶ These events cannot be treated as footnotes. They reshape the way treatment must be prescribed, monitored, and discontinued.

The review by Jeong, Suh, Kim, Lemere, Lim, and Lee helps clarify the clinical and radiological nature of ARIA. The phenomenon is described as resulting from alterations in vascular integrity and permeability, leading to edema or effusion in ARIA-E and deposition of blood products in ARIA-H.⁸ The minimum recommended MRI sequences for evaluation are T2-FLAIR, T2* gradient

echo or susceptibility-weighted imaging, and diffusion-weighted imaging.⁸ FLAIR is essential for ARIA-E, T2* or susceptibility-weighted imaging for ARIA-H, and diffusion-weighted imaging helps differentiate ARIA from acute or subacute ischemia.⁸

The recommendations of the American Society of Neuroradiology reinforce this point in operational terms. ARIA occurs in approximately 10% to 30% of participants treated with anti-amyloid immunotherapies, and most cases are asymptomatic and detected on surveillance MRI.⁹ When symptomatic, it may present with headache, confusion, dizziness, visual disturbances, apraxia, or focal deficits.⁹ Its resemblance to stroke is a practical concern. Treating ARIA as acute ischemia and administering thrombolytic therapy may result in severe intracranial hemorrhage.⁹

Risk is not the same for all patients. Appropriate-use recommendations for lecanemab state that candidates should have mild cognitive impairment or mild dementia due to Alzheimer's disease, confirmation of amyloid pathology by PET or cerebrospinal fluid, a cognitive range compatible with early-stage disease, and no major risk factors for bleeding.¹⁵ They also recommend ApoE genotyping to inform ARIA risk and considerable caution in patients requiring anticoagulation.¹⁵ For donanemab, appropriate-use recommendations indicate patients in clinical stages 3 to 4, Mini-Mental State Examination scores between 20 and 30 or an equivalent assessment, confirmation of Alzheimer's disease pathology by PET or cerebrospinal fluid, and recent pretreatment MRI.¹⁶ Tau PET is not required for clinical eligibility, although it may help estimate individual benefit.¹⁶

This point highlights a difference between trials and practice. TRAILBLAZER-ALZ 2 used tau PET for stratification, whereas real-world use acknowledges that this examination may not be available.^{6,16} The transition from research to clinical practice requires simplification, but each simplification may alter the treated population. If eligibility becomes broader than in the trials, uncertainty regarding efficacy and safety increases. If it remains as restrictive as in the trials, treatment becomes accessible to only a small fraction of patients.

In Brazil, this tension is even more evident. The Brazilian position paper highlights four main concerns: the modest magnitude of benefit, real-world eligibility, high cost, and the risk of indiscriminate use in ineligible patients, such as asymptomatic individuals or people with moderate to severe dementia.¹⁰ The Brazilian Health Regulatory Agency approved donanemab for mild cognitive impairment and mild dementia associated with Alzheimer's disease in adults who are either ApoE $\epsilon 4$ heterozygotes or non-carriers.¹¹ Lecanemab was approved for early-stage Alzheimer's disease with confirmed amyloid pathology and the same restriction regarding ApoE $\epsilon 4$.¹² These regulatory indications already show that, in Brazil, treatment is introduced as a selective therapy.

The comparison between regulatory approval and health-system incorporation is also relevant. In 2025, the National Institute for Health and Care Excellence concluded that the benefits of lecanemab and donanemab remained too small to justify the additional costs to the National Health Service, including acquisition, administration, and monitoring.²⁰ This decision does not invalidate the clinical trials. It addresses a different question. While a regulatory agency asks whether a drug has an acceptable benefit-risk relationship for a given indication, a healthcare system must ask whether it can deliver that treatment safely, equitably, and at a justifiable cost.

The discussion of blood-based biomarkers fits into this context. The 2025 Alzheimer's Association guideline proposed that blood tests with sensitivity of at least 90% and specificity of at least 75% may be used for triage in specialized services, and that tests with both sensitivity and specificity of at least 90% may replace amyloid PET or cerebrospinal fluid testing in certain contexts.¹⁷ At the

same time, the guideline emphasizes that many available tests do not meet these thresholds and that blood biomarkers do not replace a complete clinical assessment.¹⁷ For Brazil, this suggests a possible pathway toward broader diagnostic access, but not an immediate solution.

The review also highlights methodological limitations of the included studies. The trials were randomized, double-blind, and placebo-controlled, strengthening internal validity. However, they were conducted in highly selected populations, with biomarker confirmation, strict MRI criteria, exclusion of patients at high hemorrhagic risk, and intensive follow-up.^{3,6} External validity is therefore limited. Real-world patients tend to be older, have more comorbidities, use more medications, and access less coordinated services than research-center populations.¹⁶

Another issue is funding. The main trials were sponsored by the companies developing the drugs, with sponsor involvement in study design, conduct, analysis, or interpretation of the data.⁶ This does not invalidate the findings, but it should be recognized as an element of critical appraisal. In a field marked by strong public expectations and commercial interest, independent real-world studies will be decisive in defining the place of these drugs in clinical practice.

The absence of meta-analysis in this review reflects a methodological choice. Lecanemab and donanemab have not been compared directly. The studies differ in primary scale, entry criteria, tau burden, dosing, discontinuation strategy, and outcome reporting. Pooling these findings into a single quantitative effect could create an appearance of precision beyond what the evidence supports. A structured narrative synthesis better preserves the differences between the drugs and avoids inappropriate indirect comparison.

An integrated reading of the studies supports an intermediate conclusion. Lecanemab and donanemab are not merely new versions of symptomatic treatments. They reduce amyloid and, on average, slow cognitive-functional decline in patients with early Alzheimer's disease. At the same time, they do not represent a cure, clinical reversal, or a broadly applicable intervention for anyone with dementia. Rational use requires biological diagnosis, stage selection, genetic and hemorrhagic risk assessment, serial MRI, and shared decision-making with the patient and caregiver.

This conclusion may appear less compelling than the idea of a therapeutic breakthrough. Even so, it is the interpretation most faithful to the data. The real advance represented by these antibodies may lie less in solving Alzheimer's disease and more in inaugurating a new way of treating it, in which prescribing depends on the convergence of biology, imaging, cognition, vascular risk, cost, and institutional capacity. This new model may open relevant avenues. It may also increase inequalities if implemented without planning.

CONCLUSION

Lecanemab and donanemab demonstrated reductions in amyloid burden and slowing of cognitive-functional decline in patients with early Alzheimer's disease, particularly in populations with biomarker confirmation and structured follow-up. Phase 3 trials support a statistically significant benefit, but the absolute magnitude of the effect was moderate, with no evidence of disease reversal or actual cognitive improvement.

Safety remains a central limitation. ARIA-E, ARIA-H, infusion-related reactions, and rare hemorrhagic events require rigorous patient selection, ApoE genotyping when available, baseline and serial magnetic resonance imaging, and a team prepared to recognize symptoms that may mimic stroke. Thus, the efficacy of these drugs cannot be separated from the practical conditions required for their safe use.

In Brazil, clinical implementation is likely to be particularly complex. Access to biomarker-based diagnosis, cognitive specialists, serial magnetic resonance imaging, infusion centers, and ARIA management is uneven. Therefore, lecanemab and donanemab should be understood as therapies representing genuine but

conditional progress. Their place in clinical practice will depend on long-term follow-up data, real-world studies, cost-effectiveness assessment, and the organization of care pathways capable of delivering treatment to the appropriate patients, with acceptable risk and realistic clinical expectations.

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ATRIAL FIBRILLATION AND PREVENTION OF THROMBOEMBOLIC EVENTS: A REVIEW OF CURRENT STRATEGIES

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ABSTRACT

Atrial fibrillation represents the most prevalent sustained supraventricular tachyarrhythmia in global clinical practice, configuring a serious public health problem due to its direct impact on cardiovascular morbidity and mortality and the risk of ischemic stroke. This review article analyzes and synthesizes contemporary pharmacological and non-pharmacological strategies aimed at preventing thromboembolic events in these patients. Methodologically, a systematic survey of high-impact national and international guidelines, controlled clinical trials, and meta-analyses was conducted. The results point to a paradigmatic shift in risk stratification, centered on objective structural comorbidities, in addition to the definitive consolidation of direct oral anticoagulants as first-line therapy due to their predictable pharmacokinetics and superior hemorrhagic safety profile. Additionally, percutaneous occlusion of the left atrial appendage is established as an effective mechanical alternative in scenarios of long-term pharmacological contraindication. It is concluded that an integrated and holistic approach, uniting the precision of modern anticoagulation with the rigorous management of underlying risk factors, is indispensable to mitigate catastrophic peripheral outcomes. However, gaps regarding the underrepresentation of populations with end-stage renal disease demand attention, suggesting that future investigations explore new factor XI inhibitors and the use of wearable devices to refine precision medicine in cardiology.

Keywords: Anticoagulants, Atrial fibrillation, Cerebrovascular accident, Secondary prevention, Thromboembolism.

INTRODUCTION

Atrial fibrillation (AF) is recognized as the most common sustained supraventricular tachyarrhythmia in global clinical practice, with a prevalence that progressively increases with age.¹ The clinical relevance of this arrhythmia lies in its direct association with increased cardiovascular morbidity and mortality, resulting in a fivefold higher risk of ischemic stroke, in addition to being associated with the development of heart failure.¹ Thromboembolic events associated with AF tend to be more severe, making the prevention of these outcomes the fundamental pillar of therapeutic management.¹

Historically, vitamin K antagonists (VKAs), such as warfarin, became the standard treatment for stroke prevention in AF.^{1,2} However, limitations such as a narrow therapeutic window, the need for frequent monitoring, and multiple drug interactions have driven the development of direct oral

anticoagulants (DOACs).^{1,2,3} Robust evidence indicates that drugs such as apixaban, dabigatran, edoxaban, and rivaroxaban provide efficacy equal to or greater than that of warfarin, with a favorable biological safety profile, particularly in reducing intracranial hemorrhage.³⁻⁶

Despite these advances, many gaps and uncertainties remain regarding the management of specific and highly vulnerable population subgroups. Very elderly patients, individuals with low body weight, or those with advanced chronic kidney disease have frequently been underrepresented in major clinical trials.⁷⁻¹⁰ In addition, the management of patients who survive spontaneous intracranial hemorrhage and require antithrombotic protection remains a complex therapeutic dilemma, in which the balance between ischemic benefit and the risk of new fatal bleeding events has not yet been fully established.¹¹

An updated synthesis of the evidence and improvement of stratification models are essential to guide personalized agent selection and the optimal timing of intervention.^{1,12,13} Addressing these nuances is essential to mitigate catastrophic outcomes and improve precision in cardiovascular health management. For patients with absolute contraindications to pharmacological anticoagulation, percutaneous left atrial appendage occlusion has emerged as an effective mechanical alternative, consisting of isolating the main thrombus-forming structure.^{14,15}

OBJECTIVES

To investigate current strategies for the prevention of thromboembolic events in patients with atrial fibrillation through an integrative literature review, evaluating risk stratification mechanisms, the efficacy and safety of direct oral anticoagulants, left atrial appendage occlusion therapies, and future perspectives related to factor XI inhibitors and continuous monitoring technologies.

METHODS

This is an integrative literature review with a qualitative approach and an analytical-descriptive design, conducted with the aim of analyzing the scientific evidence regarding the prevention of thromboembolic events in patients with atrial fibrillation. The search for studies was conducted in the PubMed, Virtual Health Library (VHL), and Scientific Electronic Library Online (SciELO) databases.

The descriptors indexed in the Health Sciences Descriptors (DeCS) and Medical Subject Headings (MeSH) were used: Atrial Fibrillation, Thromboembolism, Stroke Prevention, and Anticoagulants, combined using the Boolean operators AND and OR, with the following search strategy: ("Atrial Fibrillation") AND ("Thromboembolism" OR "Stroke Prevention") AND ("Anticoagulants").

Articles published between 2020 and 2026 in English, Portuguese, and Spanish were included. The inclusion criteria were: full-text articles available in full; studies related to the prevention of thromboembolic events in patients with atrial fibrillation; clinical trials, systematic reviews, meta-analyses, and clinical guidelines; as well as publications within the established time frame. Duplicate studies, case reports, letters to the editor, incomplete articles, and publications that did not directly address the proposed topic were excluded.

The study selection process occurred in three stages: identification, screening, and eligibility, following the principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Initially, 290 articles were identified in the selected databases. Subsequently, titles and abstracts were reviewed to apply the inclusion and exclusion criteria. Potentially eligible articles underwent full-text review, resulting in the final selection of 20 studies that fully met the previously established criteria.

The following variables were analyzed: year of publication, type of study, population profile, thromboembolic prevention strategies, therapeutic efficacy and safety, as well as the main clinical outcomes related to the occurrence of thromboembolic events. The data were organized in tables and analyzed descriptively through a narrative synthesis of the evidence found.

As this study was based on secondary data available in the scientific literature, submission to a Research Ethics Committee was not required.

RESULTS AND DISCUSSIONS

Ten Thromboembolic Risk Stratification Mechanisms and Therapeutic Thresholds

The contemporary approach to the prevention of thromboembolic events in atrial fibrillation is based on the accurate identification of predictive factors for vascular injury and blood stasis. Historically, tools such as the CHADS2 score served as an initial screening method; however, the international scientific literature has demonstrated significant limitations in its sensitivity, particularly in identifying patients classified as being at intermediate risk who, in fact, went on to experience catastrophic ischemic outcomes¹. The transition to the CHA2DS2-VASc score refined risk assessment by incorporating high-impact biological variables, such as peripheral vascular disease, sex, and more stratified age groups, allowing for more reliable calibration of the risk of ischemic stroke.¹

Data derived from the reviewed epidemiological studies confirm that the systematic application of CHA2DS2-VASc substantially modified the threshold for initiating oral anticoagulant therapy. Currently, the consensus recommendation establishes that a score equal to or greater than two points for men and equal to or greater than three points for women constitutes a class I indication for the introduction of antithrombotic agents.¹ However, the major debate in medical practice concerns management in the setting of borderline risk, represented by a score of one for men and two for women. In these scenarios, the individualized analysis of additional biomarkers and echocardiographic parameters, such as left atrial volume and left atrial appendage emptying velocity, serves as a highly precise clinical tiebreaker.¹ At the same time, bleeding risk assessment should not be used as an exclusion criterion for anticoagulation, but rather as a surveillance tool for the modification of risk factors amenable to intervention. The use of the HAS-BLED score has become established in clinical practice not to contraindicate protective therapy, but to alert the multidisciplinary team to the need for rigorous monitoring and strict control of variables such as uncontrolled arterial hypertension, concomitant use of nonsteroidal anti-inflammatory drugs, and labile international normalized ratio in warfarin users.¹ The compiled data demonstrate that patients with a high HAS-BLED score (greater than or equal to 3) paradoxically obtain the greatest net benefit in terms of mortality reduction when adequately anticoagulated with agents with a better safety profile.¹

Table 1¹: Thromboembolic Risk Stratification and Annual Stroke Rates According to the CHA2DS2-VASc.

Score	Risk Category	Annual Ischemic Stroke Rate (%)	Therapeutic Recommendation
0 (Men) / 1 (Women)	Low	0.0 - 0.2	No antithrombotic therapy
1 (Men) / 2 (Women)	Intermediate	0.6 - 1.3	Anticoagulation should be considered
Maiores ou iguais a 2 (Homens) / Maiores ou iguais a 3 (Mulheres)	High	2.2 - 9.6	Oral anticoagulation is mandatory

Source: Adapted from the Brazilian Guideline on Atrial Fibrillation – 2025.¹

Comparative Efficacy and Safety Profile of Direct Oral Anticoagulants

The introduction of direct oral anticoagulants (DOACs) has changed the paradigm of antithrombotic management in non-valvular atrial fibrillation. Combined data from major phase III randomized clinical trials — comparing rivaroxaban, apixaban, dabigatran, and edoxaban with traditional warfarin — have shown that the newer agents are at least non-inferior to vitamin K antagonists in the prevention of ischemic stroke and systemic embolism³⁻⁶. However, the major competitive advantage of DOACs lies in their biological safety profile, demonstrated by a consistent reduction of more than 50% in the occurrence of intracranial hemorrhage, which represents the most feared complication of traditional anticoagulant therapy.³⁻⁶

From a pharmacokinetic perspective, the direct inhibition of specific factors in the coagulation cascade — factor Xa by rivaroxaban, apixaban, and edoxaban, and factor IIa (thrombin) by dabigatran — eliminates the biological instability characteristic of warfarin, dispensing with routine laboratory monitoring and mitigating the risk of therapeutic fluctuations caused by dietary variations or antibiotic use.¹⁻² Additionally, subgroup analyses based on real-world data show that apixaban has the best gastrointestinal safety profile among factor Xa inhibitors, while dabigatran 150 mg demonstrated statistical superiority in reducing ischemic stroke when directly compared with the standard dose of warfarin.^{3,4,6,7}

A critical challenge discussed in the literature concerns the management of elderly patients and

those with varying degrees of chronic renal dysfunction, since all DOACs depend, to a greater or lesser extent, on renal clearance for elimination. Dabigatran has the highest rate of renal excretion (approximately 80%), which requires extreme caution or contraindication in patients with an estimated glomerular filtration rate below 30 mL/min^{1,8}. For the management of this complex patient population, factor Xa inhibitors, notably apixaban and rivaroxaban, adjusted according to strict dose-reduction criteria based on serum creatinine, age, and body weight, have been shown to be safer and more effective in preserving long-term renal function and preventing major bleeding.⁸

Advances in Interventional Therapy: Left Atrial Appendage Occlusion

For the subgroup of patients affected by atrial fibrillation who present formal and absolute contraindications to long-term anticoagulation — such as survivors of recurrent spontaneous intracranial hemorrhages, patients with inaccessible cerebral arteriovenous malformations, or individuals with severe gastrointestinal bleeding from a non-treatable source — cardiovascular medicine has developed strategies based on mechanical barriers. Since more than 90% of thrombi originating in the left atrium in patients with non-valvular atrial fibrillation develop within the left atrial appendage, the mechanical isolation of this anatomical structure has become a highly attractive and effective therapeutic target.^{14,15}

The clinical results of long-term randomized trials confirm that percutaneous left atrial appendage occlusion, using endovascular devices, provides protection against ischemic stroke that is non-inferior to that provided by warfarin.^{14,15} With regard to long-term safety outcomes, mechanical exclusion of the appendage resulted in a marked reduction in overall bleeding rates after the initial device endothelialization period, which typically requires short-term transient antithrombotic therapy with antiplatelet agents or low-dose anticoagulation.^{14,15}



Figure 1¹⁶: Schematic representation of the mechanism of percutaneous left atrial appendage occlusion.

Source: Montenegro et al.¹⁶ Image courtesy of St. Jude Medical Inc.

The selection of patients who are candidates for mechanical occlusion should be conducted by a multidisciplinary cardiology team, based on high-resolution imaging examinations. Two-dimensional and three-dimensional transesophageal echocardiography, together with cardiac computed tomography angiography, constitutes the gold standard for mapping the complex anatomy of the atrial appendage, which varies among the phenotypes known in the medical literature as chicken wing, windsock, broccoli,

or cactus.^{14,15} Studies indicate that successful implantation and the absence of significant residual peridevice leaks (less than or equal to 5 mm) are directly correlated with a sustained reduction in embolic events and with successful permanent discontinuation of systemic anticoagulant therapy.^{14,15}

New Frontiers and Future Perspectives: Factor XI Inhibitors and Wearable Devices

The ongoing pursuit of a definitive dissociation between antithrombotic efficacy and bleeding risk has driven translational science toward new targets within the coagulation cascade. Coagulation factor XI has emerged as an ideal biological component for this new generation of modulation. Genetic and epidemiological studies have observed that individuals with congenital factor XI deficiency have a significantly reduced risk of thromboembolic events and ischemic strokes, without showing a tendency toward spontaneous bleeding or major hemorrhage resulting from severe trauma.^{18,19}

Preliminary data from phase II clinical trials evaluating factor XI inhibitors — including parenterally administered monoclonal antibodies, small synthetic oral compounds, and antisense oligonucleotides — in patients with atrial fibrillation have shown extremely promising results. These new drugs demonstrated a dose-dependent reduction in factor XI activity, associated with bleeding event rates virtually identical to those observed in placebo-treated groups, while maintaining protective efficacy equivalent to that of conventional DOACs. This innovation opens a new treatment perspective for the population currently neglected because of high bleeding risk, introducing the concept of anticoagulation with near-zero hemorrhagic potential.^{18,19}

Alongside pharmacological innovations, the digital transformation in cardiology, driven by the use of wearable devices for continuous monitoring, has changed the detection and temporal management of atrial fibrillation. Smartwatches and portable sensors equipped with photoplethysmography and single-lead electrocardiography algorithms enable the early diagnosis of subclinical arrhythmia in asymptomatic individuals. Current discussion in the medical literature focuses on the concept of targeted or intermittent anticoagulation, popularly known as the “pill-in-the-pocket” approach, in which patients at intermediate risk initiate temporary antithrombotic therapy only when the wearable device detects an atrial fibrillation burden above a critical threshold of continuous hours, thereby avoiding unnecessary exposure to bleeding risks during prolonged periods of stable sinus rhythm.^{1,17}

CONCLUSION

The optimization of thromboembolic prevention strategies in atrial fibrillation has become established as one of the most effective pillars for reducing morbidity and prolonging overall survival in the population with cardiovascular disease. The evolution of scientific evidence clearly demonstrates that the management of this arrhythmia has moved beyond the restricted view of purely electrophysiological control of cardiac rhythm or heart rate. The contemporary approach requires an integrated and holistic perspective in which antithrombotic protection is prioritized and guided by more objective and simplified clinical risk stratification tools, which remove demographic variables of low specificity and focus decision-making on actual and modifiable cardiovascular comorbidities.

The establishment of direct oral anticoagulants as first-line therapy has transformed the safety profile and therapeutic adherence in clinical practice, overcoming the historical limitations and pharmacokinetic instabilities associated with older vitamin K modulators. It has been shown that the predictability of the biological response of these newer pharmacological classes has dramatically reduced the incidence of catastrophic hemorrhagic outcomes, particularly intracranial bleeding, without compromising efficacy in the prevention of ischemic stroke. At the same time, for the subgroup

of patients with formal contraindications or refractoriness to long-term anticoagulant management, advances in interventional techniques for percutaneous left atrial appendage occlusion have become established as a safe, mechanical, and biologically viable therapeutic alternative.

Despite conceptual and clinical advances, this review study has limitations inherent to the temporal transition of medical guidelines and to the heterogeneity of the patient profiles evaluated in the literature, since populations with end-stage renal dysfunction or severe rheumatic valvular disease remain frequently underrepresented in major clinical trials of direct anticoagulants. Additionally, variability in infrastructure and access to advanced imaging examinations and high-cost interventional therapies across different public healthcare settings limits the universal and immediate applicability of certain cutting-edge recommendations.

For future investigations and research, the development of randomized clinical trials focused on validating the safety and efficacy of new coagulation factor XI inhibitors is suggested, as these agents promise to further dissociate thrombotic risk from bleeding risk, ushering in an era of anticoagulation with near-zero bleeding potential. Longitudinal studies aimed at integrating artificial intelligence and wearable devices for continuous monitoring are also recommended, evaluating the clinical impact of intermittent anticoagulation or anticoagulation strictly guided by arrhythmia burden episodes detected in real time, thereby refining the principles of precision medicine in cardiology.

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ARTIFICIAL INTELLIGENCE IN RISK STRATIFICATION OF ACUTE CORONARY SYNDROME: A COMPARATIVE REVIEW WITH TRADITIONAL CLINICAL RISK SCORES

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ABSTRACT

Acute Coronary Syndrome (ACS) demands early and effective risk stratification to guide rapid clinical decisions in emergency settings. Given the limitations of traditional scores in capturing complex non-linear biological interactions, this study aimed to review the discriminatory and predictive performance of Artificial Intelligence (AI) models, such as Machine Learning and Deep Learning, compared to conventional tools (GRACE, TIMI, and HEART) in predicting Major Adverse Cardiovascular Events (MACE). For this purpose, an integrative literature review was conducted based on the PRISMA 2020 protocol, selecting nine original articles published in PubMed between 2021 and 2026. The results consistently demonstrate that AI algorithms outperform the accuracy of current clinical scores, achieving Areas Under the ROC Curve (AUROC) of up to 0.94. This prognostic refinement is rooted in the autonomous extraction of subtle morphological variables from raw electrocardiograms — drastically reducing false positives in the cath lab — and the synergistic integration of molecular and inflammatory biomarkers. Explainable tools such as SHAP validate mathematical findings by aligning them with medical guidelines. In conclusion, AI represents a disruptive advancement in ACS risk stratification. However, definitive bedside translation still depends on overcoming methodological challenges, requiring external validations with real-time live data streams to establish a safe and personalized clinical practice.

Keywords: Machine learning, Cardiology, Artificial intelligence, Risk assessment, Acute coronary syndrome.

INTRODUCTION

Acute Coronary Syndrome (ACS) remains one of the leading causes of cardiovascular morbidity and mortality worldwide, requiring rapid and accurate clinical decision-making in the emergency setting.¹ Successful treatment of ACS critically depends on early and effective risk stratification. This triage is essential to distinguish patients at high anatomical and clinical risk, who benefit

from immediate invasive interventions, from those at low to moderate risk, who may be managed conservatively or undergo subsequent outpatient investigation.²

Historically, risk stratification has been based on the integration of clinical parameters, electrocardiographic findings, and biomarkers of myocardial injury and has been operationalized through structured and widely validated scores, such as GRACE, TIMI, and HEART.³ However, the transition toward precision medicine has highlighted important limitations of these conventional tools. Because they are predominantly based on linear regression statistical models, traditional scores have difficulty capturing complex and nonlinear interactions among multiple biological variables.⁴ Consequently, they tend to underestimate risk in specific population subgroups and fail to integrate continuous temporal dynamics, such as the rigorous kinetics of high-sensitivity troponin and subtle morphological variations in the raw electrocardiogram (ECG) signal.^{2,5}

In this context, Artificial Intelligence (AI), driven by Machine Learning (ML) and Deep Learning (DL) algorithms, is becoming established as a disruptive strategy for cardiology practice. Unlike traditional methods, AI models have the intrinsic ability to process vast volumes of data (Big Data) simultaneously, identifying previously imperceptible multidimensional phenotypic patterns.^{4,6} Recent evidence demonstrates that machine learning algorithms consistently outperform current clinical scores in predictive and discriminatory accuracy for Major Adverse Cardiovascular Events (MACE).^{4,6} By processing data ranging from sociodemographic characteristics and electronic health records to the autonomous extraction of ECG data, AI enables highly individualized prognostic prediction, optimizing resource allocation and mitigating preventable adverse outcomes.^{1,5}

Therefore, the present study aims to synthesize contemporary scientific evidence regarding the performance of Artificial Intelligence models in risk stratification and outcome prediction in patients with Acute Coronary Syndrome, directly comparing them with conventional clinical scores. Additionally, it seeks to discuss the feasibility, methodological limitations, and perspectives for the safe translation and integration of these technologies into decision-making in real-world clinical settings.

OBJECTIVES

This study aims to review contemporary scientific evidence regarding the discriminatory and predictive performance of Artificial Intelligence models (Machine Learning and Deep Learning) integrated with traditional clinical scores (GRACE, TIMI, and HEART) for risk stratification and the prediction of Major Adverse Cardiovascular Events (MACE) in patients with Acute Coronary Syndrome.

METHODS

This is an integrative literature review, adapted to the recommendations of the PRISMA 2020 protocol.¹⁶ The search was conducted in the PubMed/MEDLINE database using controlled descriptors (MeSH). Free original articles published between 2021 and 2026 were included. The selection process resulted in 9 studies for the final analysis.

2.1 Guiding Question

The guiding question was developed using the PICO strategy (Population, Interest, Context/Outcome), defined as: "How can Artificial Intelligence be applied to risk stratification in individuals with Acute Coronary Syndrome in clinical practice to optimize prognosis and personalize the care of critically ill patients based on multiple records?"

2.2 Inclusion and Exclusion Criteria

The inclusion criteria were: original articles from the PubMed database, available in full text free of charge ("free full text"), with no language restrictions, published between 2021 and 2026, involving human samples, and addressing the research question. Regarding content, studies evaluating the use of AI applied to different data sources were included, including automated ECG analysis and chest pain stratification; studies integrating classical and modern biomarkers with machine learning to estimate cardiovascular risk; studies evaluating the reliability of multiple predictive models; and studies focused on the development and multicenter validation of new AI-based scores. The exclusion criteria were: articles not available in full text free of charge, studies that did not report clear performance metrics, and studies focused on chronic diseases without correlation with or inclusion of the acute event.

2.3 Information Sources and Search Strategy

The search was conducted in the PubMed/MEDLINE database using a combination of controlled descriptors (MeSH) and free-text terms to maximize search sensitivity. The search string used was: (("Acute Coronary Syndrome"[Mesh] OR "Myocardial Infarction"[Mesh]) AND ("Artificial Intelligence"[Mesh] OR "Machine Learning"[Mesh] OR "Gradient Boosting"[tw]) AND ("Risk Assessment"[Mesh] OR "Prognosis"[Mesh] OR "Risk Stratification"[tw])). In addition, filters were applied for time (last five years), human samples, and without language restrictions.

2.4 Study Selection Process (Following PRISMA)

The selection was conducted in two phases: screening and eligibility. In this process, of the 186 results obtained, titles and abstracts were analyzed to exclude studies irrelevant to the research objective, and 14 were selected for more in-depth review. Thus, during the eligibility stage, the 14 preselected articles were read in full to confirm the inclusion criteria, and 9 studies were ultimately selected for the integrative literature review. The search and selection process was documented in the PRISMA 2020 flow diagram (Figure 1).

2.5 Data Extraction and Analysis

For data extraction, a data collection instrument developed by the authors was used, containing the following information: authors, year, country, objective, methodological design, and main results. The analysis was performed descriptively, categorizing the studies thematically to synthesize the knowledge produced on the topic.

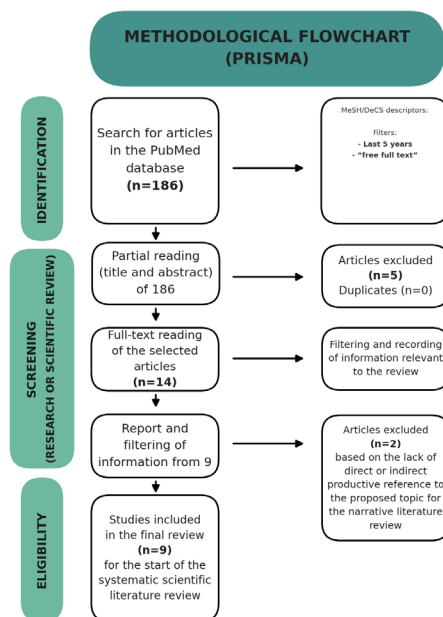


Figure 1: Flow Diagram of the Study Identification, Screening, and Inclusion Process.
Source: Prepared by the author (2026).

RESULTS AND DISCUSSIONS

1. Discriminatory Performance and Predictive Accuracy of AI Compared With Traditional Scores

The data synthesized in this integrative review consistently demonstrate that the incorporation of models based on Artificial Intelligence (AI), using Machine Learning (ML) and Deep Learning (DL) algorithms, significantly outperforms the discriminatory accuracy of conventional clinical scores, such as HEART, GRACE, QRisk3, and the Framingham Heart Risk Score (FHRS), in predicting Major Adverse Cardiovascular Events (MACE) and mortality.

In the setting of emergency chest pain triage and ST-Segment Elevation Myocardial Infarction (STEMI), the use of automated models for electrocardiographic analysis demonstrated a disruptive operational impact. In multicenter registry data, the AI-based ECG model outperformed standard triage by achieving a sensitivity of 92% compared with only 71% for the conventional method, in addition to increasing specificity from 29% to 81%.⁷ This substantial improvement in discriminatory performance, reflected by an Area Under the ROC Curve (AUROC) of 0.94, was accompanied by a marked reduction in false-positive rates in the cardiac catheterization laboratory (from 41.8% to 7.9%), remaining robust even in complex subgroups such as patients with bundle branch blocks and atrial fibrillation.⁷

This ability to extract complex nonlinear morphological patterns directly from the raw 12-lead ECG signal was also validated for the prediction of all-cause mortality. The Extra Survival Trees algorithm, based exclusively on electrocardiographic data, outperformed the HEART score by reducing the rate of undetected adverse events by more than 90%, demonstrating a Negative Predictive Value (NPV) of 93.4% and sensitivity of 85.9%.⁸

The superiority of AI also extends to models incorporating heterogeneous clinical data and long-term prediction scores. In large-scale cohorts of Indian and Dutch populations, the multilayer neural risk score AICVD outperformed FHRS and QRisk3 in predicting acute coronary events over 10 years, achieving an AUROC of up to 0.92 and an overall accuracy of 80.15%, compared with traditional epidemiological performance ranging from 51% to 59%.⁹ In the short-term predictive spectrum (7 days) for major cardiovascular outcomes in the emergency setting, the automated DPI-AI classifier outperformed models based solely on structured demographic data and biological positivity (AUROC of 0.82 and 0.79), demonstrating the robustness of integrating deep numerical ECG representations with admission biomarkers.¹⁰

Complementing the perspective of extended follow-up, analysis of the large multicenter COREA-AMI registry, which evaluated 10,172 patients undergoing percutaneous coronary intervention (PCI), revealed that the Random Forest (RF) model showed consistently superior predictive performance compared with four other ML techniques and traditional logistic regression in estimating MACE at 1 and 5 years.¹¹ At the 5-year time horizon—when the cumulative incidence of composite outcomes (cardiac death, myocardial infarction, or stroke) reached 30.5% of the sample—the RF model achieved an AUC of 0.822, accuracy of 0.804, and an F1-score of 0.870.¹¹

The relevance of the F1-score in this setting reinforces the need for more robust metrics in real-world and imbalanced datasets, where the prevalence of non-events significantly exceeds that of macrovascular events, protecting the analysis against statistical distortions commonly associated with the isolated assessment of overall accuracy or AUC.^{11,12}

2. Prognostic Optimization: Integration of ECG Signals and Inflammatory Biomarkers

The findings indicate that the prognostic success of AI in Acute Coronary Syndrome (ACS) lies in its intrinsic ability to process multimodal datasets and identify variables that usually go unnoticed by the human eye or by linear statistical models.¹² Historically, risk stratification has neglected subtle kinetics or synergistic interactions among new pathophysiological markers due to the limitations of classical logistic regression models.¹³ However, the understanding of the molecular complexity of myocardial infarction—which involves myocardial stress, necrosis, and remodeling—has found in artificial intelligence algorithms the ideal tool to enable strategies based on multiple biomarkers.¹³

A clear example of this evolution is the optimization of the traditional GRACE score through machine learning. The combination of the Random Forest classifier with contemporary inflammatory biomarkers increased the sensitivity of the GRACE score from 75% to 83%, while maintaining high levels of specificity in predicting death or reinfarction at six months.¹⁴ Therefore, the integration of computational intelligence and precision biology offers a concrete pathway for personalizing care for critically ill patients, refining the identification of individuals at high anatomical risk who were previously incorrectly categorized by conventional screening methods.

3. Methodological Challenges: Feasibility, Interpretability, and Clinical Translation

Despite the promising statistical results, the effective translation of these technological tools into daily bedside medical practice faces important methodological and conceptual barriers. A critical gap identified in the current literature concerns heterogeneity in model development, characterized by the absence of adequate control groups, the persistence of small, homogeneous, or single-center datasets, and the scarcity of real-time validations using live data streams in the emergency setting.¹² Dependence on static or simulated datasets restricts the generalizability of algorithms and may lead to distorted

performance metrics when they are applied to new populations or different ethnic contexts.^{11,12}

Furthermore, the common failure to report comprehensive metrics concurrently weakens evaluation in medical settings where the clinical costs of a false negative or false positive may be potentially fatal.¹² Similarly, selection biases inherent in observational registry studies and the latent risk of data leakage during complex data imputation steps require strict methodological caution to avoid overestimating the models' actual predictive capacity.¹¹

Another major obstacle lies in the "black-box" nature of deep neural networks, which limits the acceptance of algorithms due to the lack of transparency regarding how risk predictions were structured. Because clinical decisions have a direct impact on patient morbidity and mortality, AI-based decision support intrinsically depends on the performance-trust relationship.¹⁵ To mitigate this limitation, innovative agnostic approaches have proposed quantifying reliability through dimensions of robustness, confidence interval stability, and, fundamentally, interpretability—comparing the ranking of feature importance generated by the model with established clinical evidence.¹⁵

In this regard, the incorporation of innovative explanatory tools, such as Shapley Additive Explanations (SHAP) analysis, emerges as a transformative element for clinical validation. The application of SHAP values to robust models made it possible to decode the weight of individual long-term prognostic variables, isolating confounding factors arising from acute in-hospital complications that mimic predictive causes.¹¹ Through this methodology, non-modifiable parameters such as age, renal function, and left ventricular ejection fraction (LVEF) were determined to have the greatest predictive power for long-term post-infarction outcomes, even surpassing purely procedural variables such as the anatomical length of the implanted stent.¹¹

In parallel, SHAP distinguished the crucial protective impact of modifiable interventions related to secondary prevention at hospital discharge, mapping the protective role of dual antiplatelet therapy (DAPT), statins, and renin-angiotensin-aldosterone system inhibitors.¹¹ This direct alignment between the mathematical findings of explainable algorithms and the Class I recommendations established by international cardiology guidelines not only legitimizes the practical utility of the machine learning model but also fosters the confidence required for its integrated clinical adoption.¹¹

Additionally, the use of interpretable rule-based schemes demonstrated that it is possible to achieve an acceptable balance between predictive accuracy and diagnostic transparency, obtaining a sensitivity of 76.3% and specificity of 77.8% in predicting MACE in a manner that is completely clear to the attending physician.¹⁴ Finally, it should be emphasized that satisfactory average model performance does not eliminate the need for automated individual assessments; estimating the degree of uncertainty of each point prediction emerges as an essential line of research for consolidating the safe, ethical, and effective integration of artificial intelligence into routine emergency cardiology practice.¹⁵

CONCLUSION

This integrative review demonstrates that Artificial Intelligence, through Machine Learning and Deep Learning models, represents a disruptive and statistically superior advance in the risk stratification of patients with Acute Coronary Syndrome when compared with traditional clinical scores, such as GRACE, TIMI, and HEART. By processing complex nonlinear interactions in multimodal databases, these algorithms overcome the limitations of classical linear statistical methodologies, optimizing the predictive accuracy of Major Adverse Cardiovascular Events (MACE) and mortality both in the short-term emergency setting and during extended follow-up of up to five years.

The findings demonstrate that the prognostic refinement provided by AI is consolidated along two main fronts: the autonomous extraction of subtle morphological variables from the raw 12-lead electrocardiogram signal—drastically reducing false-positive rates in the cardiac catheterization laboratory and identifying atypical presentations—and the synergistic integration of new molecular and inflammatory biomarkers with patients' baseline clinical parameters.

However, the definitive and safe translation of these computational tools into bedside cardiology practice still depends on overcoming important methodological challenges. The future clinical applicability of AI in emergency cardiology requires real-time external validation using live data streams, mitigation of biases in imbalanced observational registries, and, fundamentally, the widespread adoption of explainable intelligence methods, such as SHAP analysis. The ability to decode the “black box” of algorithms, aligning their mathematical predictions with evidence-based medical guidelines, is the essential pillar for building the professional trust required to transform the predictive potential of Artificial Intelligence into a safe, personalized, and efficient clinical reality.

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CUTANEOUS LUPUS CORRELATION BETWEEN DERMATOLOGICAL MANIFESTATIONS AND SYSTEMIC ACTIVITY

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ABSTRACT

Morbidity Lupus erythematosus is an autoimmune pathology whose clinical spectrum ranges from isolated cutaneous manifestations to severe multivisceral systemic involvement. This study aimed to analyze the interdependence between specific and nonspecific dermatological phenotypes and systemic inflammatory activity in lupus. An integrative literature review was conducted, designed according to the PRISMA protocol guidelines, through a systematized search in the PubMed, Scopus, and SciELO databases. Following the application of rigorous eligibility criteria focused on original studies published in the last decade, nine articles were selected for qualitative synthesis. The evidence indicates that the skin acts as a sentinel organ in the disease course. A predictive risk hierarchy was observed: acute cutaneous lupus and nonspecific lesions, such as vasculitis and alopecia, are strongly associated with systemic exacerbation, reflected by high clinical scores (such as Mex-SLEDAI), anti-dsDNA positivity, and complement consumption. The subacute subtype denotes intermediate systemic activity, strongly correlated with anti-Ro/SSA antibodies and photosensitivity. Conversely, chronic presentations predominantly reflect accumulated, irreversible tissue damage, requiring clinical distinction from current inflammatory activity using validated indices like CLASI. It is concluded that the detailed characterization of the dermatological phenotype constitutes an essential clinical biomarker, indispensable for risk stratification, anticipating visceral involvement, and individualizing therapeutics in the management of lupus patients.

Keywords: Autoimmunity, Biomarkers, Cutaneous manifestations, Diagnosis, Systemic lupus erythematosus.

INTRODUCTION

Lupus erythematosus (LE) comprises a heterogeneous group of chronic inflammatory autoimmune diseases, with a spectrum ranging from strictly cutaneous manifestations to severe multivisceral systemic involvement.¹⁻³ The skin is the second most frequently affected system in systemic lupus erythematosus (SLE), occurring in 70% to 85% of patients and representing the initial symptom in up to 25% of cases.^{1,2,4} Fijałkowska, Kądziela, and Żebrowska¹ highlight that clinical diversity and similarity to other dermatoses may delay diagnosis, making the identification of cutaneous lesions a valuable diagnostic tool.¹

Although the mechanistic relationship between cutaneous lupus erythematosus (CLE) and the systemic form is not fully understood, Maz and Kahlenberg⁴ emphasize that both presentations share common pathways of immune activation, particularly those mediated by type I interferon (IFN) and autoreactive lymphocytes.^{2,4} Clinically, the Gilliam and Sontheimer classification subdivides lesions into LE-specific and LE-nonspecific lesions.^{1,2,5}

Specific manifestations are categorized as acute (ACLE), subacute (SCLE), and chronic (CCLE).^{1,2,5,6} Filotico and Mastrandrea⁵ note that this subdivision reflects a clinical and histological polarity, in which chronicity and greater cutaneous involvement often correspond to a lower immediate risk of progression to SLE.⁵ In contrast, nonspecific lesions, such as vasculitis, Raynaud phenomenon, and nonscarring alopecia, frequently correlate with periods of systemic disease activity and a higher risk of internal organ damage.^{3,5,7,8}

Elmgren and Nyberg⁶ reinforce that clinical surveillance during the first years after a diagnosis of CLE is crucial, given the higher risk of systemic progression during this period⁶. The pathogenesis of CLE is influenced by genetic and hormonal factors as well as environmental triggers, with ultraviolet (UV) radiation being the main inducer and exacerbating factor of lesions.^{1,2,4,6} Vale and Garcia² state that sun exposure induces keratinocyte apoptosis and the production of pro-inflammatory cytokines, triggering the recruitment of plasmacytoid dendritic cells (pDCs), which are major producers of IFN.^{2,4,9}

Brahmanti, Wahono, Pratama, Rahman, Suhendra, Rizky, and Mukti⁸ demonstrated that patients with cutaneous manifestations have significantly higher scores on the disease activity index (Mex-SLEDAI), suggesting that the skin acts as a reliable biomarker of systemic inflammation.^{7,8} The morbidity associated with cutaneous lupus is substantial, severely affecting quality of life because of the disfiguring potential of sequelae such as scarring and alopecia.^{1,3,6,7} Childs and Merola⁷ point out that, although antimalarials are the cornerstone of systemic therapy, the evolution toward biologic therapies and small molecules reflects the need for more precise and safer management.⁷

Ker, Teske, Feng, Chong, and Werth⁹ emphasize that the early identification of predictive factors, using validated instruments such as the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI), allows timely interventions to minimize irreversible sequelae.^{6,9} Given this complexity, the present article aims to analyze the interdependence between specific and nonspecific dermatological manifestations and systemic disease activity in lupus. It seeks to provide a theoretical and clinical basis to support the identification of cutaneous patterns that may precede or indicate worsening internal involvement, thereby optimizing patient management and prognosis.

OBJECTIVES

To General objective

To analyze the correlation between the dermatological manifestations of cutaneous lupus and systemic disease activity, considering the different clinical subtypes and their association with laboratory markers and systemic manifestations.

Specific Objectives

- Identify and describe the main dermatological manifestations of cutaneous lupus, including their clinical classifications (acute, subacute, and chronic).
- Evaluate the association between the different subtypes of cutaneous lupus and the levels of systemic disease activity.

- Correlate specific cutaneous manifestations, such as malar rash, discoid lesions, and photosensitivity, with laboratory markers of disease activity, including autoantibodies and complement levels.
- Investigate the relationship between dermatological manifestations and systemic organ involvement in systemic lupus erythematosus.
- Compare the prognostic potential of different cutaneous manifestations in predicting systemic disease activity.

METHODS

This is an integrative literature review with a descriptive design and qualitative approach, conducted with the aim of analyzing and synthesizing scientific knowledge regarding the correlation between dermatological manifestations and systemic activity in lupus erythematosus. To ensure methodological rigor and transparency, the study selection process was structured in accordance with the recommendations of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) protocol.

The literature search was conducted systematically in three electronic health databases: PubMed (via the National Library of Medicine), Scopus (Elsevier), and SciELO (Scientific Electronic Library Online). The search strategy was developed by combining controlled health descriptors (DeCS and MeSH) with Boolean operators. The search string was established using the terms “Lupus Erythematosus” AND “Cutaneous” AND “Disease Activity” AND “Systemic Skin Manifestations,” ensuring the simultaneous intersection of all concepts within the same publication. In the Scopus and SciELO databases, the syntax was adapted according to the filters and specific characteristics of each platform.

To define the sample, rigorous eligibility criteria aligned with the guiding research question were established. Original articles were included, comprising observational studies, cohort studies, case-control studies, and clinical trials that primarily investigated the clinical, laboratory, or prognostic correlation between cutaneous lesions and systemic disease involvement. Publications were also required to fall within the previous ten years, be available in full text free of charge, be written in Portuguese, English, or Spanish, and exclusively report research conducted in humans.

In contrast, exclusion criteria included articles duplicated across databases, as well as study designs with a low level of evidence or without clear methodological description, such as narrative reviews, case reports, and case series with small samples. Editorials, letters to the editor, preliminary reports, abstracts published in conference proceedings, in vitro studies or experimental animal studies, as well as studies focused strictly on topical treatment of cutaneous lupus without establishing a correlation with overall systemic activity, were also excluded.

The process of study identification, screening, and selection was conducted in consecutive and documented stages, as presented in Figure 1. The initial search of the databases identified 256 publications, of which 166 were retrieved from PubMed, 62 from Scopus, and 28 from SciELO. During the identification stage, 56 articles were immediately excluded as duplicates. The remaining 200 records underwent primary screening through independent and careful review of titles and abstracts, during which 165 manuscripts were excluded because they did not address the thematic scope or met the pre-established exclusion criteria.

Subsequently, the 35 articles considered potentially eligible were retrieved and assessed in full text. After this in-depth analysis, 26 studies were excluded for specific reasons, such as incompatible study design or absence of clear correlational data. Following rigorous application of all methodological criteria, the final sample consisted of nine articles.

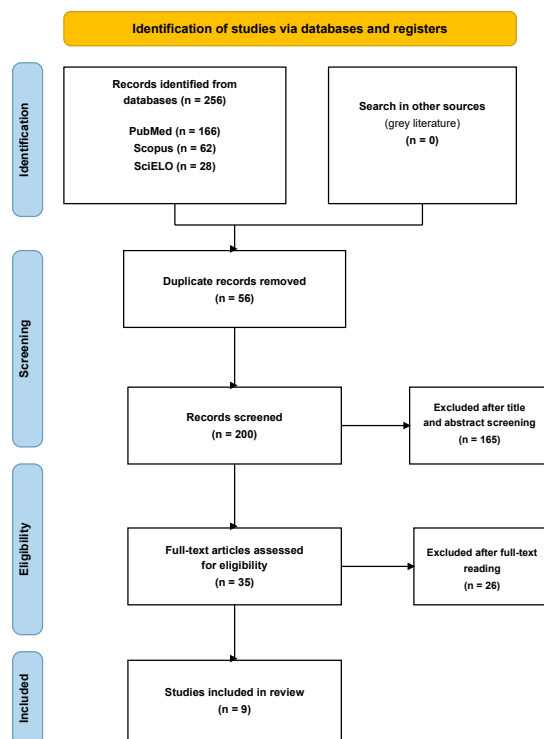


Figure 1: Flowchart of the Selection of Studies Included in the Integrative Review
Source: Prepared by the authors, 2026.

RESULTS AND DISCUSSIONS

The integrated analysis of the selected studies demonstrates that cutaneous lupus should not be understood merely as an isolated dermatological manifestation, but rather as the clinical expression of an immunoinflammatory spectrum that may range from disease restricted to the skin to forms associated with significant systemic activity. This interpretation is essential to the present study, since the correlation between dermatological manifestations and systemic activity depends not only on the presence or absence of cutaneous lesions, but also on the clinical subtype, extent of the lesions, association with nonspecific manifestations, serological profile, and coexistence of systemic signs.

The cutaneous manifestations of lupus erythematosus are generally classified as specific and nonspecific lesions. Specific lesions are those in which clinical and histopathological findings support the diagnosis of cutaneous lupus, including acute cutaneous lupus, subacute cutaneous lupus, and chronic cutaneous lupus. This classification, originally proposed by Gilliam and Sontheimer, remains the most widely used in clinical practice and in the literature, although it has limitations, particularly because of clinical overlap among subtypes and the absence of universally accepted diagnostic criteria for all forms of cutaneous lupus.¹⁻³ This classificatory limitation is relevant because different cutaneous subtypes show distinct patterns in relation to

systemic activity: while acute cutaneous lupus tends to accompany more evident systemic activity, localized discoid lupus frequently behaves as predominantly cutaneous disease.¹⁻⁵

Across the articles analyzed, there was convergence regarding the high frequency of cutaneous manifestations in systemic lupus erythematosus. Recent reviews indicate that dermatological changes occur in approximately 70% to 85% of patients with systemic lupus erythematosus during the course of the disease and may constitute the initial manifestation in up to one quarter of cases.^{2,5} This finding reinforces the concept that the skin functions as a sentinel organ in lupus, since it may signal systemic immune activity even before the development of severe organ manifestations. However, clinical interpretation requires caution: not every cutaneous lesion in a patient with lupus indicates severe systemic activity, and not every form of cutaneous lupus progresses to systemic lupus. The central contribution of the literature lies precisely in distinguishing which dermatological patterns have greater prognostic value.

Acute cutaneous lupus is the subtype most closely associated with active systemic lupus erythematosus. Its classic manifestation is the malar rash, characterized by symmetrical erythema over the malar region and bridge of the nose, usually sparing the nasolabial folds, with a predilection for photoexposed areas.^{1,2,5} This manifestation has diagnostic and prognostic importance because it is included in the classification criteria for systemic lupus and is associated with periods of inflammatory exacerbation. In the 2019 European Alliance of Associations for Rheumatology/American College of Rheumatology (EULAR/ACR) criteria, the mucocutaneous domain assigns different scores to cutaneous manifestations, with acute cutaneous lupus receiving a higher score than discoid or subacute lupus, reflecting its greater weight as an expression of systemic disease.^{2,5}

The association between malar rash and systemic activity was reinforced by the cross-sectional study by Brahmanti, Wahono, Pratama, Rahman, Suhendra, Rizky, and Mukti⁸, in which patients with malar rash had significantly higher Mex-SLEDAI scores than patients without this manifestation. In this study, malar rash was present in 20.4% of the evaluated patients and was associated with greater disease activity, with a median Mex-SLEDAI score of 8 in patients with malar rash versus 2 in those without this manifestation.⁸ This finding is particularly relevant because it provides quantitative evidence for an association frequently described clinically: malar rash is not merely an aesthetic or diagnostic finding, but may reflect a state of greater systemic activation.

From an immunological perspective, this association is biologically plausible. Acute cutaneous lupus is related to immune complex deposition, complement activation, increased keratinocyte apoptosis, and an exacerbated response to ultraviolet radiation.¹⁻³ Ultraviolet radiation promotes cellular damage, exposure of nuclear autoantigens, and alterations in inflammatory pathways, favoring autoantibody production and amplification of the immune response. Thus, the skin not only reflects systemic activity but may also participate in the immunopathogenic cycle that perpetuates the disease. This interpretation helps explain why photoinduced manifestations, such as malar rash and photosensitivity, frequently accompany periods of greater activity.

Subacute cutaneous lupus occupies an intermediate position in this correlation. Clinically, it presents with annular, polycyclic, or papulosquamous lesions, predominantly in photoexposed areas, with less tendency to scar than discoid lupus but with a strong association with photosensitivity and anti-Ro/SSA antibodies.^{1,2,7} The literature indicates that a significant proportion of patients with subacute cutaneous lupus may meet classification criteria for systemic lupus, although often with milder systemic manifestations, such as arthralgia, myalgia, and constitutional symptoms.¹ This distinction is crucial: SCLLE does not necessarily indicate severe systemic disease, but it suggests a greater likelihood of systemic autoimmunity compared with localized discoid lupus.

In the study by Brahmanti, Wahono, Pratama, Rahman, Suhendra, Rizky, and Mukti⁸, subacute cutaneous lupus was observed in 11.1% of patients and showed one of the strongest correlations with systemic activity, with a median Mex-SLEDAI score of 9 in patients with SCLE versus 2 in those without SCLE, with statistical significance.⁸ In addition, SCLE was associated with malar rash, vasculitis, and fatigue, suggesting that its presence may identify patients with a more inflammatory phenotype and a greater systemic burden.⁸ This association should not be interpreted as direct causality, since the cross-sectional design limits temporal inferences; nevertheless, the finding strengthens the hypothesis that SCLE, particularly when coexisting with nonspecific lesions or systemic symptoms, should prompt a broader clinical and laboratory investigation.

The strong relationship between SCLE and anti-Ro/SSA also has relevant implications. Vale and Garcia² highlight that anti-Ro/SSA is present in a large proportion of SCLE cases and is associated with the marked photosensitivity of this subtype, while anti-La/SSB may coexist less frequently². This information allows two distinct axes of correlation to be identified: in ACLE, systemic activity is often linked to anti-dsDNA, hypocomplementemia, and overall SLE activity; in SCLE, the correlation is more strongly related to anti-Ro/SSA, photosensitivity, and generally less aggressive systemic manifestations.² Therefore, the mere presence of a cutaneous lesion is not sufficient; the dermatological subtype must be interpreted together with the serological profile.

Chronic cutaneous lupus, particularly discoid lupus, behaves differently. Discoid lesions are chronic erythematous-squamous plaques, usually located on the face, scalp, and ears, with the potential to progress to atrophy, dyspigmentation, and scarring.^{2,5,7} This subtype is most strongly associated with permanent cutaneous damage, but not necessarily with greater systemic activity. Localized discoid lupus usually remains confined to the skin, whereas generalized, extensive, or progressive forms may carry a higher risk of association with SLE.⁵ This distinction is essential to avoid two clinical errors: underestimating patients with generalized discoid lupus while, at the same time, overestimating systemic risk in every patient with localized discoid lesions.

The review by Stull, Sprow, and Werth³ reinforces this prognostic gradation by indicating that patients with localized discoid lupus, tumid lupus, lupus profundus, and hypertrophic forms tend to have disease more limited to the skin, whereas patients with generalized discoid lupus, SCLE, ACLE, or nonspecific lesions are more likely to have associated systemic disease³. The same study highlights that progression from cutaneous lupus to systemic lupus occurs in a minority of patients, but in a clinically relevant proportion, with cumulative incidence increasing over the years.³ This supports an important practical conclusion: cutaneous lupus requires longitudinal follow-up, even when initially restricted to the skin.

This interpretation is consistent with the findings of Fijałkowska, Kądziela, and Żebrowska¹, who describe a risk of progression to SLE in the years following a diagnosis of cutaneous lupus and emphasize the need to assess internal organs before considering the condition exclusively dermatological¹. This recommendation has a direct impact on the present topic, since the correlation between the skin and systemic activity is not limited to the time of diagnosis. It may emerge during follow-up through changes in the dermatological pattern, the appearance of nonspecific lesions, laboratory abnormalities, or systemic symptoms.

Nonspecific lesions deserve particular attention because they often correlate more strongly with systemic activity than some specific lesions. Nonscarring alopecia, oral or nasal ulcers, cutaneous vasculitis, livedo reticularis, Raynaud phenomenon, and photosensitivity may occur in patients with active SLE and are not always exclusive to lupus^{2,5}. However, their presence in patients with established or suspected lupus increases the need for systemic evaluation. Stull, Sprow, and Werth³ highlight that SLE activity indices, such as the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and SLEDAI-2K, incorporate cutaneous and

mucosal manifestations, including alopecia, ulcers, vasculitis, and rash, demonstrating that dermatological activity formally contributes to the measurement of systemic activity.³

In the study by Brahmanti, Wahono, Pratama, Rahman, Suhendra, Rizky, and Mukti⁸, alopecia was the most frequent nonspecific cutaneous manifestation, present in 46.3% of patients, followed by photosensitivity in 44.4%. Both were associated with significantly higher Mex-SLEDAI scores⁸. This finding is important because it broadens the analysis beyond classic lesions. In many clinical settings, manifestations such as alopecia and photosensitivity are considered less “dramatic” than nephritis or neuropsychiatric manifestations; however, within the overall disease spectrum, they may signal ongoing inflammatory activity.

Photosensitivity has a dual role: it is both a clinical manifestation and a triggering factor. Ultraviolet radiation induces keratinocyte damage, exposure of nuclear autoantigens, activation of plasmacytoid dendritic cells, and amplification of the type I interferon pathway.^{1,3,6,7} Thus, photosensitive patients not only develop cutaneous lesions after sun exposure but may also experience systemic exacerbations related to environmental stimulation. This mechanism makes photoprotection a therapeutic intervention with the potential to reduce cutaneous activity and possibly modulate the risk of exacerbations.

Oral and nasal ulcers, although not statistically associated with Mex-SLEDAI in the study by Brahmanti, Wahono, Pratama, Rahman, Suhendra, Rizky, and Mukti⁸, are relevant manifestations in classification criteria and may accompany systemic activity.^{2,5,8} The fact that a specific study did not demonstrate a statistical association does not eliminate their clinical relevance, since the presence of ulcers may vary according to the population, sample size, ongoing treatment, and timing of assessment. This is one of the main limitations of the literature on cutaneous lupus: many studies are cross-sectional, with small samples, and may capture only a single time point in a fluctuating disease.

Cutaneous vasculitis represents a particularly relevant manifestation because of its association with systemic activity. Unlike specific lesions such as discoid lupus, vasculitis is a nonspecific lesion, but its presence may indicate more intense systemic inflammation, vascular involvement, and a greater risk of association with other organs. In the study by Brahmanti, Wahono, Pratama, Rahman, Suhendra, Rizky, and Mukti⁸, vasculitis was strongly associated with the presence of SCLE, and cutaneous infections were associated with vasculitis and nephritis.⁸ Although cutaneous infection is not a classic manifestation of lupus activity, its association with higher Mex-SLEDAI scores suggests that patients with more active disease, greater immunosuppression, or impaired skin barrier function may be more vulnerable to infections.

The correlation between cutaneous manifestations and renal involvement should be interpreted with caution. Cutaneous lupus, in isolation, does not predict nephritis in all patients. However, certain findings, such as ACLE, nonspecific lesions, vasculitis, active serology, elevated anti-dsDNA, and hypocomplementemia, increase the need for renal screening.^{1,2,5} In the cited cross-sectional study, the presence of cutaneous infection was associated with nephritis, but this finding should not be interpreted as a direct relationship between infection and renal damage⁸; more likely, it represents an indirect marker of greater disease activity, immunosuppressive treatment, or systemic vulnerability.

Laboratory markers help qualify the correlation between the skin and systemic involvement. Anti-dsDNA and anti-Sm are more specific for SLE, although anti-Sm has lower sensitivity. Anti-dsDNA also has value in monitoring, since its levels tend to parallel disease activity, particularly nephritis, especially when associated with complement consumption.² In contrast, anti-Ro/SSA and anti-La/SSB are not specific for SLE, but are strongly associated with SCLE and photosensitivity.² Thus, laboratory interpretation should be guided by the cutaneous phenotype: malar rash and suspected systemic activity require assessment of anti-dsDNA, complement, complete blood count, urinalysis, and renal function; SCLE requires particular attention to anti-

Ro/SSA; localized discoid lupus may show lower serological positivity, but still requires baseline evaluation.

The pathophysiology described in the articles supports the idea that dermatological manifestations and systemic activity share common immunological pathways. Maz and Kahlenberg³ discuss the role of B lymphocytes, BAFF signaling, T cells, neutrophils, NETs, and plasmacytoid dendritic cells at the interface between cutaneous and systemic lupus. This perspective shifts the skin from a passive role to an active position within the immunological network of lupus. The cutaneous lesion may represent the visible site of systemic processes, but it may also contribute to maintaining the autoimmune response through the release of autoantigens, local cytokine production, and recruitment of inflammatory cells.

The type I interferon pathway is particularly relevant. Recent reviews indicate that interferon participates in immune activation in both cutaneous and systemic lupus, promoting dendritic cell maturation, B-cell activation, autoantibody production, and perpetuation of tissue inflammation.^{1,2,3,7} The central role of this pathway also explains the growing interest in targeted therapies such as anifrolumab and other molecules under investigation.⁹ Thus, the clinical findings regarding the correlation between cutaneous lesions and systemic activity are not merely observational; they reflect overlapping immunopathological mechanisms.

Another relevant point is the distinction between activity and damage. Cutaneous activity includes erythema, scaling, infiltration, recent lesions, nonscarring alopecia, and mucosal involvement. Damage includes scarring, atrophy, persistent dyspigmentation, and scarring alopecia.^{5,8} This distinction is fundamental to the present topic because not every visible lesion indicates current systemic activity. A patient with longstanding, scarred discoid lupus may have substantial dermatological damage but low systemic activity at that time. In contrast, a patient with a recent malar rash, photosensitivity, diffuse alopecia, and laboratory abnormalities may have little scarring but high systemic activity.

CLASI is the main specific instrument for measuring activity and damage in cutaneous lupus. It separates the activity score, CLASI-A, from the damage score, CLASI-D, allowing assessment of erythema, scaling, hypertrophy, mucosal involvement, alopecia, dyspigmentation, and scarring.^{2,5,8} This distinction is more sensitive for cutaneous lupus than systemic indices such as SLEDAI, which include some cutaneous manifestations but do not accurately capture the extent and severity of dermatological involvement across different subtypes.^{2,5}

The longitudinal study by Ker, Teske, Feng, Chong, and Werth⁹ makes an important contribution to understanding the evolution of cutaneous activity and damage. In a cohort of 83 patients with cutaneous lupus assessed using CLASI over time, patients with an initial CLASI-A greater than 9 had a higher probability of improvement in cutaneous activity, while patients with greater baseline damage also showed specific patterns of progression.⁹ The study showed that 72.73% of patients with an initial CLASI-A greater than 9 improved, compared with 14% of those with a CLASI-A less than or equal to 9.⁹ This finding may appear paradoxical, but it suggests that patients with greater initial inflammatory activity have a larger measurable margin for response to treatment.

The longitudinal analysis also demonstrates that cutaneous damage should not be used in isolation as a marker of systemic activity. Scarring, dyspigmentation, and scarring alopecia may persist even after inflammatory control.⁹ Therefore, in an article aimed at correlating dermatological manifestations with systemic activity, it is essential not to conflate accumulated damage with current activity. This distinction improves the methodological quality of the discussion and prevents erroneous conclusions, such as assuming that every patient with extensive cutaneous lesions necessarily has active systemic disease.

The literature also demonstrates a relevant impact of cutaneous manifestations on quality of life. Lesions in visible areas, such as the face and scalp, are associated with stigma, psychosocial impairment, anxiety,

depressive symptoms, and reduced self-esteem^{2,5,7}. Even in the absence of severe systemic activity, permanent cutaneous damage may cause substantial morbidity. This point broadens the discussion beyond biological correlation: dermatological manifestations have diagnostic, prognostic, therapeutic, and psychosocial value. Therefore, their assessment should not be considered secondary in rheumatological or clinical practice.

From a therapeutic perspective, the correlation between the skin and systemic activity supports an integrated approach. General measures, such as strict photoprotection, smoking cessation, review of medications associated with drug-induced SCLE, and vitamin D replacement when indicated, form the basis of management^{2,7,9}. Localized lesions may be treated with topical corticosteroids or calcineurin inhibitors, whereas extensive, recurrent, or refractory disease often requires antimalarials, particularly hydroxychloroquine.^{2,7,9}

Therapeutic response may also provide information about disease activity. Patients with cutaneous manifestations associated with systemic activity may require immunosuppressive agents or biologic therapies according to the organ involved and disease severity. Recent reviews highlight emerging therapies such as belimumab, anifrolumab, litifilimab, deucravacitinib, and enpatoran, reflecting the transition toward approaches guided by specific immunological pathways⁹. This perspective is relevant to the discussion because it reinforces that the skin may serve as a measurable endpoint in clinical trials and as a practical marker of therapeutic response.

Comparative analysis of the articles allows a clinical hierarchy of systemic risk to be proposed. ACLE, particularly recent and photoinduced malar rash, appears to be the manifestation most strongly associated with systemic activity. SCLE occupies an intermediate position, with a strong serological association and photosensitivity, and may coexist with SLE, but often with a milder systemic course. Localized CCLE shows a lower immediate systemic correlation, but a greater risk of permanent cutaneous damage. Nonspecific lesions—particularly vasculitis, alopecia, ulcers, Raynaud phenomenon, and photosensitivity—should be interpreted as potential markers of systemic activity, especially when they arise newly or are associated with laboratory abnormalities.¹⁻⁹

This hierarchy, however, should not be applied rigidly. The coexistence of different cutaneous subtypes in the same patient is possible, and temporal evolution may modify risk. Stull, Sprow, and Werth⁵ report that a proportion of patients may present with more than one type of cutaneous lupus, which makes simplistic classifications difficult. Thus, the prognostic value of dermatological lesions depends on the overall clinical context: subtype, extent, timing, inflammatory activity, damage, systemic symptoms, serology, complement levels, urinalysis, and renal function.

It is also important to consider the limitations of the analyzed studies. Part of the evidence derives from narrative reviews or cross-sectional studies, which are useful for clinical synthesis but do not establish causality. The study by Brahmani, Wahono, Pratama, Rahman, Suhendra, Rizky, and Mukti⁸, although relevant for quantifying the association between cutaneous lesions and Mex-SLEDAI, included a limited sample and a specific population, which may restrict the generalizability of the findings.⁸ The study by Ker, Teske, Feng, Chong, and Werth⁹, in turn, contributes a longitudinal analysis using CLASI, but primarily evaluates the cutaneous course and not necessarily systemic activity across all outcomes.⁹ Therefore, the discussion should acknowledge that the correlation between cutaneous and systemic involvement is consistent but heterogeneous, dependent on subtype, and still lacking larger prospective studies.

Despite these limitations, the findings are clinically coherent and convergent. Dermatological manifestations of lupus function as accessible markers of immunological activity, with particular value in longitudinal follow-up. The presence of malar rash, SCLE, photosensitivity, alopecia, vasculitis, and ulcers should prompt

investigation of systemic activity through complete clinical examination, complete blood count, renal function, urinalysis, proteinuria assessment, complement levels, anti-dsDNA, and other autoantibodies according to the phenotype. In contrast, scarred discoid lesions should be evaluated with a focus on local activity, accumulated damage, risk of permanent alopecia, and the need to prevent sequelae.

In summary, the results indicate that there is a relevant correlation between dermatological manifestations and systemic activity in lupus, but this correlation is not uniform. The greatest systemic risk is concentrated in acute, subacute, and nonspecific manifestations associated with inflammatory activity, whereas localized chronic forms tend to reflect cutaneous damage more than systemic activity. This distinction is fundamental for guiding diagnosis, risk stratification, follow-up, and treatment. The skin should therefore be interpreted as a clinical interface between local inflammation and systemic disease and is indispensable for the early recognition of activity, prevention of damage, and individualization of care in lupus erythematosus.

CONCLUSION

The integrated analysis of this study allows us to conclude that the dermatological manifestations of lupus erythematosus function as a true “sentinel organ,” in which the morphology and chronology of lesions provide valuable information for predicting the systemic behavior of the disease. This correlation, however, is heterogeneous: while acute cutaneous lupus, such as malar rash, and nonspecific manifestations, such as vasculitis and alopecia, are strongly associated with systemic activity and higher Mex-SLEDAI scores, the chronic form tends to follow a course more limited to the skin, although with a greater potential for irreversible scarring damage.

The investigation demonstrated that laboratory and immunological markers—including the autoantibody profile (anti-dsDNA and anti-Ro/SSA) and complement consumption—help qualify this correlation, allowing clinicians to distinguish acute inflammatory activity from accumulated tissue damage. Thus, the early identification of these patterns and the use of validated instruments such as CLASI are essential for risk stratification and timely therapeutic management, while also helping to mitigate the disfiguring psychosocial impact of the lesions.

Finally, longitudinal follow-up is essential, since the patient’s clinical phenotype may shift between subtypes over time. The methodological limitations of the current literature highlight the need for further prospective studies to refine predictive factors for systemic progression. In summary, interdisciplinary integration between dermatology and rheumatology is established as a central pillar for anticipating internal organ involvement and optimizing the overall prognosis of patients with lupus.

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THE ROLE OF RECENT BIOMARKERS IN THE EARLY DIAGNOSIS OF DEMENTIA WITH LEWY BODIES

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ABSTRACT

Dementia with Lewy Bodies is one of the most challenging neurodegenerative conditions in older adults, frequently underdiagnosed due to its phenotypic overlap with Alzheimer's disease and Parkinson's disease. This study synthesizes the primary molecular, imaging, and neurophysiological biomarkers that enable the early detection and pathological differentiation of this condition during prodromal phases. Through a critical review of contemporary biological consensus criteria, the disruptive role of Alpha-Synuclein Seed Amplification Assays in cerebrospinal fluid and peripheral tissues is analyzed, showcasing high diagnostic specificity *in vivo*. Additionally, the contribution of iodine-123-metaiodobenzylguanidine myocardial scintigraphy in identifying postganglionic sympathetic denervation and dopamine transporter imaging in evaluating striatal neuronal loss is examined. In the neurophysiological spectrum, the value of quantitative electroencephalography in identifying the slowing of posterior background activity is highlighted, correlating with characteristic cognitive fluctuations. It is established that transitioning from a purely clinical diagnostic model to an integrated bio-clinical approach is essential for identifying the disease in its earliest stages. This advancement facilitates the timely enrollment of patients in clinical trials for disease-modifying therapies and optimizes early, targeted therapeutic management.

Keywords: Alpha-synuclein, Dementia with Lewy Bodies, Early diagnosis, Fluid biomarkers, Molecular imaging.

INTRODUCTION

Morbidity Dementia with Lewy bodies (DLB), also known as Lewy body dementia, is a progressive neurodegenerative disease and part of the spectrum of synucleinopathies, alongside Parkinson's disease and Parkinson's disease dementia.^{1,2} DLB is estimated to account for approximately 5–10% of all dementia cases and 15–20% of primary neurodegenerative dementias, making it the second most common cause after Alzheimer's disease.^{1,3} From a neuropathological perspective, the disease is characterized by the presence of intracellular aggregates of phosphorylated α -synuclein, Lewy bodies, distributed throughout the cerebral cortex, brainstem, limbic system, and subcortical structures, frequently in association with Alzheimer-type pathology.^{1,4,5} The pathophysiology of DLB involves conformational changes in α -synuclein, a protein encoded by the SNCA gene and normally involved in regulating neurotransmitter release

at presynaptic terminals.^{2,6} Under pathological conditions, α -synuclein undergoes phosphorylation, oxidation, and cleavage, forming insoluble oligomers and fibrils that accumulate in Lewy bodies and trigger mitochondrial dysfunction, oxidative stress, and neuronal death.^{1,4,6} Experimental evidence suggests a “prion-like” propagation mechanism, with trans-synaptic spread of pathogenic α -synuclein species between connected regions, which contributes to the progressive nature and anatomoclinical distribution of the disease.^{4,6,7} The co-occurrence of β -amyloid deposits and hyperphosphorylated tau, as well as vascular pathology, is frequent and influences the clinical phenotype and disease course.^{3,8,9}

Clinically, DLB presents a heterogeneous picture, but four core features are considered central: recurrent well-formed visual hallucinations, marked cognitive fluctuations, parkinsonism, and REM sleep behavior disorder.^{1,2} Clinical studies and international consensus statements also highlight the high prevalence of neuropsychiatric symptoms, autonomic dysfunction, neuroleptic hypersensitivity, and deficits in visuospatial functions, executive attention, and visuoperceptual processing.^{2,3,10} These manifestations partially overlap with those observed in Alzheimer’s disease and psychiatric disorders, making early recognition of DLB difficult, particularly in prodromal stages or atypical presentations.^{3,11,12}

The consensus diagnostic criteria for Dementia with Lewy Bodies (DLB), established in 2017, stratify cases as probable or possible through the combination of core clinical features, suggestive manifestations, and biomarkers.^{1,2} Probable DLB is diagnosed in the presence of two core features or, alternatively, one core feature associated with a suggestive biomarker—such as reduced dopaminergic uptake on FP-CIT SPECT, occipital hypometabolism on FDG-PET, or abnormalities on cardiac MIBG scintigraphy.^{1,4,13} In contrast, the category of possible DLB includes cases with only one core feature or combinations of suggestive findings in the absence of biomarker support, a scenario frequently observed in clinical practice in services with restricted access to advanced diagnostic technologies.^{3,10}

Epidemiological studies in different countries report prevalence rates ranging from 0.5 to 4.5% among patients with dementia in tertiary centers and from 0.02 to 0.34% in the general population, with an annual incidence of approximately 1.5–3.5 cases per 100,000 person-years.^{1,3} The mean age at onset is between the sixth and seventh decades of life, with a slight predominance in males, and survival after diagnosis is approximately 6–8 years, although there is considerable interindividual variability.^{1,3,12} The presence of co-pathologies, such as Alzheimer’s disease and vascular lesions, negatively influences prognosis and is associated with greater functional burden and a higher risk of institutionalization.^{3,4,9}

Despite advances in clinical criteria, the diagnosis of DLB remains challenging, with more than half of cases initially classified as Alzheimer’s disease, Parkinson’s disease, or psychiatric disorders.^{1,2,11} The reasons include symptomatic overlap with other dementias, phenotypic variability, limited availability of biomarkers, and still insufficient familiarity among healthcare professionals with DLB-specific criteria.^{3,10,11} In this context, fluid biomarkers, neuroimaging biomarkers, and biomarkers derived from Alzheimer-type pathology have emerged as promising tools for improving diagnostic accuracy, early detection, and prognostic stratification.^{1,4,6} α -Synuclein seed amplification assays in cerebrospinal fluid, analysis of phosphorylated α -synuclein in skin biopsies, plasma markers of neurodegeneration and neuroinflammation, as well as dopaminergic and metabolic functional neuroimaging techniques, constitute a growing panel of tests under evaluation.^{6,7,13,14}

OBJECTIVES

General objective:

Analyze the role of recent biomarkers in the early diagnosis of dementia with Lewy bodies,

highlighting their diagnostic accuracy, clinical applicability, and potential to differentiate it from other neurodegenerative dementias.

Specific Objectives:

- Identify the most promising fluid biomarkers (cerebrospinal fluid and blood) for the early diagnosis of DLB.
- Evaluate the diagnostic accuracy of neuroimaging biomarkers (FP-CIT SPECT, FDG-PET, MRI).
- Compare the sensitivity and specificity of biomarkers in differentiating DLB from Alzheimer's disease.
- Discuss the limitations and future perspectives for the clinical implementation of biomarkers.

METHODOLOGY

This is a narrative review of the literature aimed at analyzing the role of recent biomarkers in the early diagnosis of dementia with Lewy bodies. The literature search was conducted in the PubMed/MEDLINE database, as it is one of the main sources of information in the health sciences and provides broad coverage of studies in neurology and neurodegeneration.

English-language terms related to dementia with Lewy bodies and biomarkers were used, combining free-text descriptors and indexed terms. The strategy included expressions such as "dementia with Lewy bodies", "Lewy body dementia", "biomarkers", "alpha-synuclein", "neuroimaging", "cerebrospinal fluid", and "plasma biomarkers", combined with Boolean operators in order to retrieve studies evaluating fluid biomarkers (cerebrospinal fluid and blood) and neuroimaging biomarkers in individuals with suspected or diagnosed dementia with Lewy bodies.

Articles published between January 2005 and December 2025 in English, Portuguese, and French were included. The inclusion criteria comprised human studies addressing biomarkers applied to the diagnosis or differential diagnosis of dementia with Lewy bodies and presenting relevant quantitative data, such as sensitivity, specificity, diagnostic accuracy, or related measures. Observational studies (cross-sectional, case-control, and cohort studies) and systematic reviews or meta-analyses focusing on biomarkers were considered. Publications conducted exclusively in animal models or in vitro, studies without numerical data on diagnostic performance, studies dedicated only to Alzheimer's disease or other dementias without specific analysis of dementia with Lewy bodies, as well as isolated case reports and very small case series without structured statistical analysis, were excluded.

The initial search identified 844 records. After reviewing titles and abstracts, studies that did not meet the eligibility criteria were excluded, resulting in a subset of articles selected for full-text review. In this second stage, the inclusion and exclusion criteria were applied again, with detailed verification of the methodological design and outcomes of interest. At the end of the process, 41 articles were considered eligible and included in the narrative synthesis, and were organized into three analytical groups: fluid biomarkers, neuroimaging biomarkers, and systematic reviews/meta-analyses.

RESULTS AND DISCUSSION

The Fluid Biomarkers: Cerebrospinal Fluid and Blood

Fluid biomarkers have emerged as key tools in the evaluation of synucleinopathies, including DLB, because they directly reflect ongoing neuropathological processes.^{6,15} Traditional measurements of total α -synuclein in cerebrospinal fluid have shown limited ability to discriminate DLB from healthy controls, although reduced levels are associated with the presence of Lewy bodies and tissue deposition of the protein.^{1,6} In contrast, seed amplification assays, such as α -syn RT-QuIC and similar seed amplification

assay techniques, have demonstrated high sensitivity and specificity in detecting pathogenic α -synuclein and in differentiating DLB from Alzheimer's disease.^{6,14} Recent studies suggest that these methods may achieve diagnostic accuracy above 90%, including in prodromal stages, although interlaboratory standardization and automation are still required.^{4,6,14} The detection of phosphorylated α -synuclein in cutaneous nerve fibers obtained by skin biopsy has become established as a promising peripheral biomarker for synucleinopathies, including Parkinson's disease and DLB.^{4,6} Multicenter studies indicate high concordance between cutaneous α -synuclein deposits and the clinical diagnosis of DLB, with potential to complement cerebrospinal fluid assessment in settings in which lumbar puncture is contraindicated or refused.^{4,6,10} However, aspects such as technical standardization of the biopsy procedure, availability of specialized immunohistochemistry, and reproducibility across centers still limit routine use.^{4,6}

In the field of plasma biomarkers, increased levels of neurofilament light chain (NfL) indicate generalized axonal neurodegeneration and have been consistently associated with the severity and progression of dementias, including DLB.^{6,15} Although NfL has high sensitivity for detecting neurodegenerative processes, its specificity for DLB is limited, requiring interpretation together with other markers and clinical data.^{6,9,15} Glial fibrillary acidic protein (GFAP) is emerging as a marker of astrogliosis and inflammation, with studies reporting elevations in neurodegenerative dementias and suggesting possible complementary value in DLB.^{6,15}

Plasma biomarkers related to amyloid and tau pathology, such as p-tau181, p-tau217, and p-tau231, have shown excellent performance in identifying Alzheimer's disease and distinguishing it from other dementias.^{8,15,16} Although they are not specific to DLB, these markers are useful for identifying Alzheimer-type co-pathology in patients with synucleinopathies, which has diagnostic and prognostic implications.^{8,9,15} Recent reviews indicate that the combination of plasma phosphorylated tau biomarkers with NfL and GFAP may provide a robust panel for risk stratification in settings of mild cognitive impairment and suspected DLB.^{6,9,15}

In addition, cerebrospinal fluid studies have explored the activity of enzymes involved in neurotransmitter synthesis, such as DOPA decarboxylase, suggesting that its measurement may assist in distinguishing DLB from Parkinson's disease in multicenter cohorts^{4,6}. Although these findings are preliminary, they point to a possible role for enzymatic markers in the more refined characterization of the synucleinopathy spectrum.^{4,6,14} Overall, fluid biomarkers offer substantial potential for the early diagnosis of DLB, especially when integrated with neuroimaging markers and Alzheimer's disease biomarkers in the development of multimodal algorithms.^{1,6,15}

Neuroimaging Biomarkers

Neuroimaging biomarkers constitute a fundamental pillar in the diagnostic assessment of DLB, allowing in vivo visualization of dopaminergic, metabolic, and structural changes.^{1,13,17} Dopamine transporter scintigraphy using ¹²³I-FP-CIT (DaTSCAN) is the most established examination, demonstrating sensitivity of around 80–90% and specificity above 90% in differentiating DLB from Alzheimer's disease in studies and meta-analyses.^{1,13} These findings supported the inclusion of reduced striatal dopamine uptake as a suggestive biomarker in the consensus criteria for probable and possible DLB.^{1,2,13} However, the usefulness of DaTSCAN in the prodromal phase remains under investigation, with lower performance in very early stages or in presentations with mild parkinsonism.^{1,4,12}

Cardiac scintigraphy with metaiodobenzylguanidine (MIBG) evaluates myocardial sympathetic innervation, which is frequently impaired in synucleinopathies, and has shown good accuracy in distinguishing DLB and Parkinson's disease from Alzheimer's disease and other dementias.^{1,4,17} Studies indicate that the combination of MIBG with DaTSCAN may increase diagnostic confidence in uncertain cases, although issues related to

radiopharmaceutical availability and expertise in interpretation still limit its widespread use.^{1,4,10}

FDG-PET, in turn, demonstrates a characteristic metabolic pattern in DLB, with hypometabolism in occipital regions and relative preservation of the posterior cingulate compared with Alzheimer's disease^{1,17}. Meta-analyses indicate that this pattern may assist in differential diagnosis in mild stages, particularly when integrated with clinical data and other biomarkers.^{9,13,17} More recent PET techniques targeting amyloid and tau deposits have also been explored in DLB, mainly to assess the burden of Alzheimer-type co-pathology, although their specific role has not yet been fully established.^{4,8,9}

On magnetic resonance imaging, conventional measures of volume and cortical thickness show less marked changes compared with Alzheimer's disease, but group studies describe reduced volume in structures such as the insula and occipital lobe in prodromal DLB.^{1,17} Advances in diffusion imaging, particularly free-water diffusion MRI, have revealed a progressive increase in free water in multiple brain regions over 12 to 24 months in patients with DLB, associated with clinical progression and suggesting usefulness as a monitoring marker and possibly as a prodromal-phase marker.⁷ These findings point to the potential of advanced MRI techniques in longitudinal assessment and prognostic refinement.^{7,17}

In summary, neuroimaging biomarkers offer high accuracy for differentiating DLB from Alzheimer's disease and other dementias, particularly when dopaminergic, metabolic, and structural examinations are combined.^{1,13,17} However, barriers such as cost, unequal availability of PET and SPECT, and the need for protocol standardization remain relevant, especially in healthcare systems with limited resources.^{3,4,11}

Alzheimer's Disease Biomarkers in DLB

The coexistence of Alzheimer-type pathology in patients with DLB is common and has important clinical implications, as it may mask core features of DLB and make recognition of the synucleinopathy more difficult^{1,4}. Alzheimer's disease biomarkers, such as A β 42, A β 40, total tau (t-Tau), and phosphorylated tau (p-Tau) in cerebrospinal fluid, as well as their plasma counterparts, have proven to be relevant tools for identifying these mixed cases^{8,15,16}. Studies suggest that Alzheimer-compatible profiles in patients with a clinical picture suggestive of DLB are associated with greater cognitive impairment, poorer prognosis, and a higher likelihood of atypical presentation.^{4,9} Meta-analyses indicate that t-Tau and p-Tau181 have excellent discriminatory ability between Alzheimer's disease and DLB, while ratios involving A β 42 and A β 40 contribute to differential diagnosis in early stages.^{8,9,16} In individuals with mild cognitive impairment, the combination of Alzheimer's disease biomarkers with synucleinopathy markers, such as α -synuclein amplification assays, may increase accuracy in predicting future conversion to DLB or Alzheimer's disease.^{6,9,14} Thus, the systematic integration of these biomarkers into diagnostic algorithms allows better classification of patients with mixed or less typical phenotypes.^{1,4,9}

Diagnosis of the Prodromal Phase

In recent years, there has been growing interest in defining criteria for prodromal DLB, with a focus on risk syndromes such as isolated REM sleep behavior disorder, mild cognitive impairment with a visuospatial/attentional profile, and early forms of parkinsonism with subtle cognitive manifestations.^{1,2,12} The aim is to identify individuals in pre-dementia stages, in which clinical interventions and future disease-modifying therapies may have a greater impact.^{1,2}

Biomarkers play a central role in this phase, as certain findings may precede the onset of established dementia by several years.^{1,7,12} Cerebrospinal fluid α -synuclein amplification assays have shown positivity in individuals with idiopathic REM sleep behavior disorder, indicating a high

risk of conversion to DLB or Parkinson's disease.^{6,14} Likewise, abnormalities on DaTSCAN, reduced MIBG uptake, and free-water MRI changes have been described in prodromal cohorts, suggesting that a set of biomarkers may define distinct risk profiles.^{1,7,13}

Limitations and Challenges

Despite significant advances, several challenges limit the full incorporation of biomarkers into the routine diagnosis of DLB.^{3,4,11} First, many of the most promising tests, such as α -synuclein amplification assays and some plasma biomarkers, still lack widely standardized protocols, making it difficult to compare results across centers and establish universal cutoff values.^{4,6,14} Second, cost, the need for specialized infrastructure, and unequal availability of sophisticated examinations such as PET and SPECT restrict access in low- and middle-income countries and even in peripheral regions of high-income countries.^{3,11}

Another limitation concerns the clinical and neuropathological heterogeneity of DLB, which is frequently associated with Alzheimer's disease pathology, vascular disease, and other comorbidities, reducing the specificity of some biomarkers when considered in isolation.^{1,4,9} In addition, much of the evidence derives from studies conducted at tertiary centers and in selected cohorts, limiting the generalizability of the results to primary or secondary care settings.^{3,10,11} Finally, there is still no consensus regarding which minimum combinations of biomarkers should be recommended in different clinical scenarios, nor regarding the best way to integrate these results into diagnostic decision-making and risk stratification models.^{4,11}

CONCLUSION

Recent advances in biomarker research have significantly transformed the diagnostic approach to dementia with Lewy bodies. Fluid biomarkers, functional neuroimaging methods, and markers of Alzheimer-type co-pathology expand the capacity for early diagnosis and refine differential diagnosis. From a clinical perspective, the most promising trend is the combined use of these biomarkers in multimodal algorithms, rather than the isolated interpretation of each test. This integration may increase diagnostic confidence, especially in prodromal presentations, mixed phenotypes, or cases overlapping with Alzheimer's disease and Parkinson's disease. However, limitations related to laboratory standardization, cost, technological availability, and the need for validation in larger cohorts still restrict their universal adoption. Thus, the consolidation of these biomarkers in clinical practice will depend on the development of harmonized protocols, greater accessibility, and the definition of diagnostic strategies adapted to the realities of different healthcare systems.

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POLYLAMININ AND NERVOUS SYSTEM REGENERATION: A SYSTEMATIC REVIEW OF EXPERIMENTAL AND CLINICAL EVIDENCE

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ABSTRACT

Injuries to the central (CNS) and peripheral (PNS) nervous systems exhibit limited regenerative capacity, especially in the CNS, due to glial scar formation, persistent inflammation, and low neuronal plasticity. In this context, polylaminin (polyLM), a polymerized form of laminin with biomimetic organization of the extracellular matrix, emerges as a promising strategy in neural regenerative medicine. This systematic review evaluated the efficacy of polyLM in neural regeneration, functional recovery, and modulation of the tissue microenvironment after nervous system injuries. The review followed the PRISMA guidelines and the PICO strategy, with searches in the PubMed, Scopus, and SciELO databases. Experimental, observational, and clinical trials published in Portuguese or English, that investigated the use of polyLM in neural injuries were included. The outcomes analyzed included axonal regeneration, functional recovery, histological aspects, and modulation of the extracellular matrix. The results demonstrated high bioactivity of polyLM, promoting neuritogenesis, cell proliferation, and inflammatory modulation. In spinal cord injury models, axonal growth across the injury site, significant locomotor improvement, and a reduction in the early inflammatory response were observed. Translational evidence indicated functional improvement in dogs with chronic spinal cord injury and recovery of voluntary muscle contraction in patients with functionally complete spinal cord injury. Furthermore, its incorporation into biomaterials reduced fibrosis and macrophage activation, creating a microenvironment more favorable to regeneration. It is concluded that polylaminin is a bioactive biomaterial with potential in neural regeneration, acting on structural, cellular, and inflammatory mechanisms. However, its clinical consolidation requires controlled studies, therapeutic standardization, and long-term safety evaluation.

Keywords: Extracellular matrix, Laminin, Neurology, Nerve regeneration, Spinal cord injuries.

INTRODUCTION

Injuries to the central and peripheral nervous systems represent an important public health problem, affecting millions of people worldwide and being associated with permanent functional deficits and a significant impact on patients' quality of life. Neural regenerative capacity, particularly in the central nervous system, is extremely limited due to low intrinsic neuronal plasticity, the

presence of inhibitory molecules, and glial scar formation.^{1,2}

Poly laminin, the polymerized form of laminin, exhibits a biomimetic organization of the extracellular matrix and has been associated with positive effects on recovery from these injuries. Experimental studies have demonstrated its ability to promote axonal regeneration and functional improvement after spinal cord injury¹, as well as to modulate cellular pathways related to neuronal growth³. Recent evidence suggests potential translational applications, including functional improvement in animal models and preliminary results in humans.^{1,2}

Although experimental and translational studies have demonstrated promising results with poly laminin, the evidence remains scattered throughout the literature, and there is no consensus regarding its efficacy across different models of neural injury. In addition, the predominance of preclinical studies makes it difficult to extrapolate the findings to clinical practice. Therefore, a systematic analysis of the available evidence is needed to critically understand the effects of poly laminin on nervous system regeneration, identify its potential therapeutic applications, and highlight the main gaps that still limit its clinical applicability.

Given the limitations of current therapeutic approaches, increasing attention has been directed toward a deeper understanding of the role of the neural microenvironment in the regenerative process. In this context, the extracellular matrix emerges as a central element in the regulation of cell adhesion, axonal growth, and neuronal differentiation, with laminin being one of its main components and playing an important role in stimulating neuritogenesis.³

In this context, several strategies have been investigated with the aim of promoting axonal regeneration and functional recovery after nervous system injury, including cell therapies, growth factors, and biomaterials. However, the results remain limited and insufficient to promote significant recovery.

OBJECTIVES

The primary objective of this study is to evaluate, through a systematic literature review, the efficacy of poly laminin in axonal regeneration following nervous system injuries. As secondary objectives, it seeks to analyze the effects of poly laminin on functional recovery, investigate its role in modulating the extracellular matrix during the neural regeneration process, identify the main scientific evidence regarding its clinical applicability, and describe the existing gaps in the literature related to its therapeutic efficacy.

METHODS

This is a systematic review conducted in accordance with the PRISMA recommendations for systematic reviews.

The research question was structured according to the PICO strategy: P (Population): patients (humans or animal models) with central or peripheral nervous system injury; I (Intervention): treatment with poly laminin (or polymerized laminin); C (Comparison): no treatment, placebo, or other regenerative treatments; O (Outcome): axonal regeneration, functional recovery (motor/sensory), modulation of the extracellular matrix, and cytological/histological aspects.

The literature search was conducted in March 2026 in the PubMed, Scopus, and SciELO databases, considering publications in English or Portuguese available in full text for analysis. No eligible studies were identified in the SciELO database. Due to the scarcity of publications on poly laminin, a broad search strategy based on the terms “poly laminin” and “polymerized laminin” was used, followed by the

application of eligibility criteria. A total of 30 records were identified in the databases searched (15 in PubMed and 15 in Scopus). After removal of duplicates, 15 studies remained for screening. Of these, 5 were excluded after title and abstract screening because they did not address neural regeneration or did not meet the eligibility criteria. In the end, 10 studies were included in the systematic review.

Experimental *in vitro* studies, animal model studies, observational studies, and clinical trials investigating the use of polylaminin as the main intervention in central or peripheral nervous system injuries and reporting outcomes related to neural regeneration, functional recovery, histological changes, or modulation of the extracellular matrix were included. Duplicate studies, studies without full-text access, letters to the editor, editorials, literature reviews, as well as studies that did not use polylaminin as the main intervention or did not assess outcomes related to neural regeneration, were excluded.

Study screening was performed independently by two reviewers, with initial analysis of titles and abstracts followed by full-text reading of potentially eligible articles, without the use of automation tools. Data extraction was performed by four independent reviewers using a standardized form. Information was collected on the author, year of publication, country, study design, sample size, population characteristics, study objective, and main outcomes. Disagreements were resolved by consensus between the two editors in both cases.

Considering the heterogeneity of the designs of the included studies and the small number of available publications, a qualitative assessment of methodological quality was performed, considering study design, presence of a control group, sample size, and clarity of outcomes. The data were organized with the aid of the Mendeley platform.

RESULTS AND DISCUSSIONS

The analysis of the selected articles demonstrated a multifaceted role of polylaminin (polyLM) in nervous system regeneration, encompassing structural, cellular, and functional aspects. Consistently, the studies demonstrated its ability to promote neuritogenesis, modulate the extracellular matrix, attenuate inflammation, and favor functional recovery in different experimental models, including preliminary evidence in humans.

Ten studies were included in this systematic review, comprising biophysical analyses, *in vitro* studies, animal models of central and peripheral nervous system injury, translational studies in dogs, and one pilot study in humans. The studies evaluated different aspects of polylaminin, including its structural properties, ability to promote neuritogenesis, axonal regeneration, functional recovery, inflammatory modulation, and applications in biomaterials. The main characteristics of the included studies are summarized in Table 1.

Reference	Model	Main outcome
Franchi et al. (2014)	Biophysical analysis	Identification of fractal characteristics and increased surface area.
Menezes et al. (2010/2020)	Rats / In vitro	Axonal regeneration in SCI and organization of collagen IV.
Siqueira-Santos (2013)	Retinal cells	Significant increase in neuritogenesis and cell adhesion.
Spanevello et al. (2019)	Sciatic nerve (rats)	Improved regeneration in PCL filaments.
Gadelha et al. (2025)	Dogs (chronic SCI)	Clinical safety and efficacy in a large-animal model.
Menezes et al. (2024)	Humans (SCI)	Recovery of voluntary motor contraction in complete injuries.
Ullah et al. (2022)	iPSCs	Stem cell expansion with a low protein dose.
Jatuviriyapornchai (2019)	Microcapsules	Reduced inflammation and fibrosis in implants.

3.1. Structural Properties and Interaction with the Extracellular Matrix

Poly laminin is characterized by a unique structure, consisting of an acid-induced, non-covalent nano- and microstructured laminin polymer⁴. Morphologically, it appears as a loose, homogeneous, flocculated network, in contrast to the dense aggregates of conventional laminin. This supramolecular organization has a fractal nature, suggesting a relevant role in the organization of basement membranes in neurogenic niches of the central nervous system.¹

Additionally, polyLM demonstrates the ability to organize other components of the extracellular matrix. Type IV collagen has been observed to conform to its structure, indicating that polymerized laminin may guide basement membrane assembly⁵. This biomimetic behavior reinforces its role as a structural template for the formation of artificial basement membranes. Its chemical nature, based on the self-association of heterotrimeric laminin under specific electrostatic conditions, favors molecular recognition and anchoring of different cellular substrates.⁶

3.2. Effects on Neuritogenesis and Cell Proliferation

Poly laminin has consistently demonstrated the ability to stimulate neuritogenesis and cell proliferation. In *in vitro* studies, it promotes neuritogenesis at levels higher than those observed with non-polymerized laminin.⁴

Retinal cells distinguish polyLM from conventional laminin, showing greater adhesion and greater neurite extension when cultured on the polymerized form³. Thus, active polymerized laminin exerts a positive influence on both neuritogenesis and cell proliferation, demonstrating greater bioactivity and efficiency as a substrate for neuronal growth.³

In addition, poly laminin-521 has been shown to be a viable substrate for the expansion of human induced pluripotent stem cells, allowing large-scale expansion with high viability and maintenance of pluripotency even at low concentrations.⁷ Its organization mimics the native basement membrane, favoring more stable cell-matrix interactions and appropriate integrin recruitment.

3.3. Axonal Regeneration and Functional Recovery

The application of poly laminin has demonstrated promising results in axonal regeneration and functional recovery. In rat models of spinal cord injury, local administration resulted in axonal growth across the injury site, associated with significant functional improvement.¹ Increased locomotor scores and evidence of neural reconnection were observed, indicating regeneration of nerve fibers.

Furthermore, poly laminin exhibited an anti-inflammatory effect, contributing to the early onset of functional improvement, which was already observed during the first week after treatment.¹

On the other hand, in peripheral nerve injury models, the results were heterogeneous. Although poly laminin showed benefits at the cellular level, non-polymerized laminin associated with poly- ϵ -caprolactone (PCL) filaments demonstrated better motor functional recovery and a greater number of motor endplates, suggesting that its effects may vary according to the experimental context.⁸

3.4. Clinical Applications and Translational Evidence

Translational studies reinforce the therapeutic potential of poly laminin. In animal models, such as dogs with chronic spinal cord injury, the administration of polyLM associated with neurotrophic factors was shown to be safe and promoted significant improvement in motor function.²

In humans, a pilot study demonstrated the recovery of voluntary muscle contraction after functionally complete spinal cord injury, with recovery confirmed by clinical and electrophysiological methods⁹. Although preliminary, these findings indicate a potentially relevant regenerative effect of poly laminin.

3.5. Modulation of the Inflammatory Response and Biomaterials

Poly laminin also plays a relevant role in modulating the inflammatory response. Its incorporation into biomaterials, such as alginate microcapsules, resulted in reduced macrophage activation, decreased pericapsular fibrosis, and lower production of pro-inflammatory cytokines¹⁰.

In addition, improved integration with host tissue and preservation of the function of encapsulated cells were observed, indicating that polyLM contributes to the creation of a microenvironment more favorable to tissue regeneration.

The findings of this systematic review suggest a promising role for poly laminin (polyLM) as a bioactive biomaterial in nervous system regeneration, particularly because it acts simultaneously on multiple aspects of the regenerative process, including extracellular matrix organization, neuritogenesis, inflammatory

modulation, and functional recovery. This multifactorial action is particularly relevant given the complexity of neural injuries, especially in the central nervous system, where spontaneous regeneration is limited.

From a structural perspective, the supramolecular organization of polyaminin emerges as one of the main determinants of its bioactivity. Unlike conventional laminin, which tends to form irregular aggregates, polyLM exhibits a homogeneous three-dimensional network with fractal characteristics, capable of mimicking the architecture of the native basement membrane.³ This organization favors more efficient cell-matrix interactions, promoting greater cell adhesion, axonal guidance, and organization of the regenerative microenvironment. In addition, evidence indicates that this structure results from the non-covalent self-association of laminin under specific pH conditions and in the presence of Ca^{2+} , reinforcing its biomimetic and functional nature.⁶ In this context, polyaminin acts not only as structural support but also as an active modulator of tissue regeneration.

At the cellular level, the results demonstrate that polyaminin is consistently superior to non-polymerized laminin in inducing neuritogenesis and cell proliferation. In *in vitro* models, polyLM promotes greater neurite extension, increased cell adhesion and proliferation, as well as activation of intracellular pathways related to neuronal differentiation, such as PKA and PKC³. These effects are attributed to its spatial organization, which favors recognition by cellular receptors such as integrins, promoting more efficient intracellular signaling. Additionally, its use in pluripotent stem cell culture demonstrates the ability to maintain viability, genetic stability, and pluripotency even at low concentrations, reinforcing its translational potential in regenerative medicine.⁹

Regarding axonal regeneration and functional recovery, the data indicate that polyaminin has significant effects, particularly in spinal cord injury models. Experimental studies demonstrate functional improvement associated with axonal growth, with evidence of neural reconnection and increased locomotor scores after injury.⁸ These effects appear to be related not only to direct stimulation of axonal growth but also to modulation of the inflammatory response, with a reduction in secondary inflammation, a crucial factor in the progression of neural injury. In fact, inflammation is one of the main mechanisms of secondary degeneration after spinal cord injury, and its early modulation is a determining factor for functional prognosis.

However, the results are not uniform across all experimental contexts. In peripheral nerve injury models, although polyaminin demonstrates a greater ability to induce neuritogenesis *in vitro*, non-polymerized laminin associated with biomaterials, such as poly- ϵ -caprolactone filaments, showed better motor functional outcomes *in vivo*.⁴ This finding suggests that the efficacy of polyaminin may depend on the microenvironment and its interaction with other biomaterials, indicating that its isolated application may not be ideal in all settings. Thus, combined strategies may be more effective in enhancing its effects.

From a translational perspective, the available data are particularly relevant. Studies in large-animal models, such as dogs with chronic spinal cord injury, demonstrate significant improvement in locomotor function after the use of polyaminin associated with neurotrophic factors, without relevant adverse events.² In addition, preliminary evidence in humans indicates recovery of voluntary muscle contraction in patients with complete spinal cord injury, a notable finding considering the low rate of spontaneous recovery in these cases.⁹ These results suggest that polyaminin may overcome classical limitations of clinical translation by acting as a multitarget therapeutic strategy.

Another relevant aspect observed is the ability of polyaminin to modulate the inflammatory response and improve integration with biomaterials. Its incorporation into systems such as alginate microcapsules reduces macrophage activation and fibrosis formation, favoring a microenvironment more permissive to regeneration. This effect is particularly important because glial scar formation and exacerbated inflammation

represent critical barriers to regeneration in the central nervous system.

Despite the promising results, this review highlights important limitations. Most studies are based on experimental models, with substantial methodological heterogeneity, including variations in injury models, doses, routes of administration, and evaluated outcomes. In addition, clinical studies remain preliminary, with small samples and the absence of robust control groups, limiting the generalizability of the findings. Furthermore, there is a scarcity of investigations addressing long-term safety and potential adverse effects of polyaminin, which are essential aspects for its clinical validation.

CONCLUSION

Thus, although polyaminin appears to be a highly promising strategy for neural regeneration, its clinical application still requires validation through randomized controlled clinical trials, as well as the standardization of therapeutic protocols. Future studies should explore combined therapeutic approaches, including the use of growth factors, enzymes that modulate glial scarring, and biomaterials, in order to enhance its effects. Furthermore, a deeper understanding of the molecular mechanisms involved in the interaction between polyaminin and the neural microenvironment, particularly with regard to integrin-mediated signaling, inflammatory modulation, and extracellular matrix organization, will be essential to optimize its therapeutic application.

The findings of this review indicate that polyaminin acts not only as structural support but also as a bioactive biomaterial capable of integrating multiple regenerative processes, representing a potentially multitarget approach to the treatment of nervous system injuries. Despite methodological limitations and the predominance of preclinical evidence, the results point to a promising scenario in which polyaminin may represent an advance in neural regenerative medicine.

Therefore, it can be concluded that polyaminin has relevant potential for promoting axonal regeneration and functional recovery, particularly in central nervous system injuries. However, its consolidation in clinical practice will depend on the robustness of future evidence, the reproducibility of the results, and the establishment of safe, effective, and scalable therapeutic protocols.

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MULTIMODAL PREHABILITATION ASSOCIATED WITH THE ENHANCED RECOVERY AFTER SURGERY PROTOCOL IN COLORECTAL SURGERY: IMPACT ON POSTOPERATIVE OUTCOMES

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ABSTRACT

Recovery after colorectal surgery remains a significant challenge, particularly in patients with low functional capacity and a higher risk of complications. In this context, the combination of multimodal prehabilitation with the Enhanced Recovery After Surgery protocol has been proposed as a strategy to better prepare patients for surgical stress and enhance postoperative recovery. This review analyzed studies published between 2019 and 2026 to evaluate the impact of this approach on postoperative outcomes. The findings demonstrated consistent improvements in functional capacity, reflected by better performance in the Six-minute Walk Test, as well as evidence of faster recovery and greater adherence to Enhanced Recovery After Surgery components. Although the effects on postoperative complications and length of hospital stay were variable, the benefits were more pronounced in patients with lower physiological reserve. Therefore, multimodal prehabilitation stands out as a promising tool to optimize perioperative care, reinforcing the importance of an individualized approach focused on the patient's overall recovery.

Keywords: Colorectal surgery, Enhanced postoperative recovery, Postoperative complications, Preoperative exercise, Rehabilitation.

INTRODUCTION

Colorectal surgery is one of the most complex procedures in the elective surgical setting and is associated with relevant rates of postoperative morbidity, functional decline, and prolonged hospital stay.¹ Patients undergoing this type of surgery frequently present with comorbidities, malnutrition, and low aerobic capacity, factors that increase the risk of complications and delay recovery.^{2,3} The Enhanced Recovery After Surgery (ERAS) protocol represents the main paradigm shift in the perioperative management of this population, incorporating evidence-based multimodal interventions aimed at reducing surgical stress, accelerating

recovery, and decreasing postoperative complications.³ The ERAS® Society guidelines for elective colorectal surgery consolidate graded recommendations for perioperative optimization, ranging from nutritional preparation and anemia management to early mobilization and multimodal analgesia.³

Despite the advances achieved with the ERAS protocol, a significant proportion of patients still present insufficient physiological reserve in the preoperative period, limiting the potential benefits that can be achieved.⁴ In this context, multimodal prehabilitation—defined as a set of interventions performed between diagnosis and surgery, integrating structured physical exercise, nutritional support, and psychological support—emerges as a complementary strategy to increase functional capacity and patient resilience to surgical stress.^{4,5} Recent evidence indicates that prehabilitation programs may reduce postoperative complications, shorten hospital stay, and improve functional recovery, with potentially greater benefit in patients with lower baseline physical fitness.^{5,6} The association between multimodal prehabilitation and the ERAS protocol therefore represents a promising and complementary perioperative approach, although results in the literature remain heterogeneous, justifying the present integrative review.⁶

OBJECTIVES

The objective of this study is to conduct an integrative literature review to evaluate the impact of multimodal prehabilitation associated with the Enhanced Recovery After Surgery (ERAS) protocol on postoperative outcomes in patients undergoing elective colorectal surgery, based on evidence published between 2019 and 2026. The study seeks to identify the components of prehabilitation most frequently associated with improved clinical outcomes, as well as to analyze their effects on postoperative complications, length of hospital stay, mortality, and patients' functional recovery. In addition, it aims to discuss the clinical applicability of combining multimodal prehabilitation with the ERAS protocol in the perioperative setting of colorectal surgery.

METHODS

This is an integrative literature review conducted with the aim of synthesizing the available evidence on the effects of multimodal prehabilitation integrated with the Enhanced Recovery After Surgery (ERAS) protocol on postoperative outcomes in patients undergoing colorectal surgery. The process of study identification, screening, and selection was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.⁷

The literature search was performed in two electronic databases: MEDLINE/PubMed and Embase. Searches were conducted in [month/year], with no language restrictions and with publication dates limited to the period between 2019 and 2026. In PubMed, the following structured search strategy using Boolean operators was applied: ("prehabilitation" OR "multimodal prehabilitation") AND ("ERAS" OR "Enhanced Recovery After Surgery" OR "fast-track surgery") AND ("colorectal surgery" OR "colorectal cancer" OR "colectomy") AND ("postoperative outcomes" OR "postoperative complications" OR "length of stay" OR "functional recovery" OR "mortality"). In Embase, an equivalent search strategy was used, adapted to the database's controlled vocabulary (Emtree), with the same descriptors and logical operators.

Studies published between January 2019 and May 2026, with full text available free of charge, were included if they had one of the following designs: clinical trial, randomized clinical trial, observational study, systematic review, or meta-analysis. Studies were considered eligible if they specifically addressed multimodal prehabilitation in patients undergoing colorectal surgery and reported at least one postoperative outcome of

interest, including complications, length of hospital stay, functional recovery, or mortality. Duplicate studies identified in more than one database, studies addressing exclusively unimodal prehabilitation, as well as case reports, case series, letters to the editor, editorials, and conference abstracts without a direct relationship to the ERAS protocol or colorectal surgery were excluded.

Screening was conducted in three sequential stages: title assessment, abstract assessment, and full-text review. In PubMed, the search identified 10 records; after exclusion by title ($n = 2$) and abstract ($n = 1$), 7 articles were included. In Embase, the search identified 52 records; after exclusion by title ($n = 39$) and abstract ($n = 9$), 4 articles underwent full-text review, of which 3 were excluded as duplicates already identified in the PubMed search, resulting in the inclusion of 1 article unique to this database. At the end of the selection process, a total of 8 articles were included. The study selection flow is presented in the PRISMA diagram (Figure 1).

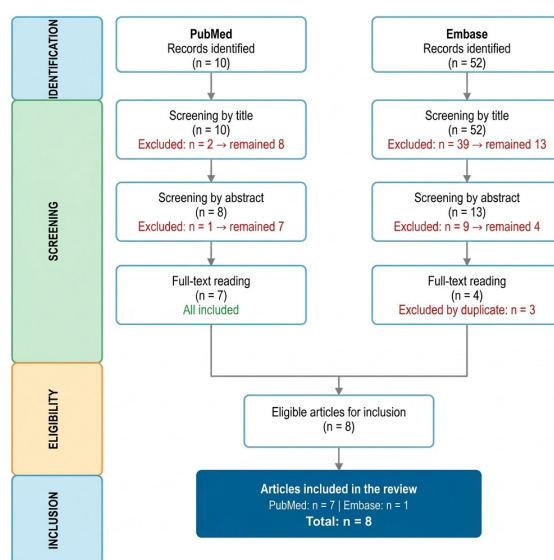


Figure 1: Flowchart of Article Selection
Source: Prepared by the authors (2026).

Data were extracted in a standardized manner, including authors, year of publication, country, study design, population, characteristics of the multimodal prehabilitation intervention, components of the ERAS protocol adopted, and outcomes assessed. The synthesis was conducted narratively due to the heterogeneity among the included studies regarding the type of intervention, population, and measured outcomes.

RESULTS AND DISCUSSIONS

Functional capacity, assessed using the 6-Minute Walk Test (6MWT), showed statistically significant improvements in the preoperative period. Of the 8 articles included in this review, 6 provided quantitative data eligible for comparison of functional performance between the analyzed groups, as summarized in Table 1. Overall evidence shows that multimodal prehabilitation increases the

distance walked before surgery by an average of 24.91 meters compared with the control group.^{1,table1} In a study conducted in China, the intervention group showed better performance both on the day before surgery (400.40 meters vs. 383.25 meters) and at 30 days postoperatively (375.40 meters vs. 336.85 meters).^{8,table1} These findings were also observed in recent meta-analyses, which identified a mean gain of 50.83 meters eight weeks after surgery, suggesting faster functional recovery.^{6,table1} In older adults, there was also a significant improvement of 18.38 meters in the 6MWT, although the impact on other clinical outcomes was less evident in this group.^{5,table1} In addition, some studies associated functional improvement with increased cardiorespiratory fitness and physiological reserve during the perioperative period.^{2,4}

Table 1: Comparison of Functional Performance Between the Multimodal Prehabilitation and Control.

Study (Ref.)	Population Evaluated	Time of Assessment	Functional Outcome (6MWT)	Prehabilitation Group	Control Group	Statistical Result
Molenaar et al. ¹	Patients undergoing abdominal surgery	Preoperative	Mean difference in distance walked (m)	+24.91 m	—	p < 0.001
Carli et al. ²	Patients undergoing abdominal surgery	4 weeks postoperatively	Distance walked (m)	336.40 m	286.10 m	p = 0.34
Gillis et al. ⁴	Patients in an ERAS protocol	6 weeks postoperatively	Distance walked (m)	554.00 m	537.00 m	p = 0.01
Srinivasan et al. ⁵	Older adults undergoing colorectal surgery	Postoperative	Change in distance walked (m)	+18.38 m	—	p = 0.04
Widanage et al. ⁶	Patients undergoing multimodal prehabilitation	8 weeks postoperatively	Mean gain in 6MWT (m)	+50.83 m	—	p < 0.001
Tai et al. ⁸	Patients with colorectal cancer	30 days postoperatively	Distance walked (m)	375.40 m	336.85 m	p = 0.03

Source: Prepared by the author (2026) based on the articles included in the review.

Regarding postoperative complications, the studies present divergent results, demonstrating the complexity of the clinical application of multimodal prehabilitation. Some analyses reported a significant reduction in the risk of overall postoperative morbidity, with an odds ratio of 0.60⁶. In addition, an international clinical trial showed a decrease in major complications from 29.7% to 17.1%, as well as a reduction in medical complications from 27.3% to 15.4%.^{1,6} On the other hand, studies conducted in centers with well-established Enhanced Recovery After Surgery (ERAS) protocols and greater use of minimally invasive surgery did not identify statistically significant differences in the severity of complications assessed by the Comprehensive Complication Index (CCI).^{2,9} In these settings, the additional benefits of prehabilitation on morbidity were considered

limited, possibly due to the already high quality of established perioperative care.^{1,2} Although improvement in functional capacity was consistent across the studies, this improvement did not always translate into a proportional reduction in postoperative complications, demonstrating that functional gain alone may not be sufficient to modify all clinical outcomes.^{2,6,9}

Regarding hospital efficiency, some studies observed a reduction in length of stay (LOS), particularly in supervised hospital-based programs.⁷ In these cases, an approximate reduction of 1.15 days in hospital stay was reported.⁷ However, most of the evidence, including meta-analyses involving older patients and studies conducted in routine clinical practice, did not demonstrate a significant reduction in total length of stay.^{2,4,5,9} Nevertheless, multimodal prehabilitation was found to contribute to greater readiness for hospital discharge and better adherence to essential components of the ERAS protocol, such as early ambulation and adequate postoperative oral intake.⁴ The studies also highlighted that higher adherence rates to the programs were associated with better functional outcomes and faster postoperative recovery.^{4,8}

Multimodal prehabilitation aims to increase the patient's physiological reserve in order to reduce the impact of surgical stress.³ One of the main points discussed in the literature is the effectiveness of this strategy in settings where ERAS protocols are already well established. Some authors suggest the existence of a "ceiling effect," in which the high quality of perioperative care, including multimodal analgesia and early mobilization, would reduce the additional benefits of prehabilitation.^{2,9} In this context, the strategy may have a greater impact on high-risk patients or those with low functional reserve, whereas the benefits may be more modest in highly specialized centers². Patients with sarcopenia, pre-existing functional limitations, and lower physical fitness appear to have greater potential for clinical benefit from the intervention.^{1,5}

The combination of physical exercise, nutritional support, and psychological support is considered fundamental to the observed outcomes. Adequate nutritional support plays an important role in increasing strength and muscle mass, since protein deficiency may limit the effects of exercise.⁴ In addition, inspiratory muscle training helps strengthen the diaphragm and reduce respiratory complications, acting as a complement to nutritional support.⁸ Psychological support also contributes to reducing anxiety related to the diagnosis and surgical procedure, favoring greater adherence to the program and better functional recovery, particularly in older adults.^{4,7} The integration of these components demonstrates that the benefits of prehabilitation depend not only on physical training alone, but also on the overall optimization of the patient's clinical and emotional condition during the preoperative period.^{1,4}

The included studies showed important differences regarding the duration, intensity, and degree of supervision of prehabilitation programs, involving variable combinations of aerobic exercise, resistance training, nutritional support, and psychological support.^{1,4,8} This methodological heterogeneity may directly influence the differences observed among the study results.^{1,5}

Despite the positive results, important limitations remain regarding the universal application of multimodal prehabilitation.^{1,5} The wide variety of protocols used makes comparisons between studies and standardization of the strategy difficult. In addition, short intervention periods may not be sufficient to reverse more advanced sarcopenia, which may require longer programs.² Another issue discussed is the risk of bias in non-blinded studies, as well as the possibility that patients in the control group may begin exercising on their own, which may interfere with the results.¹ The methodological heterogeneity observed among the studies, including differences in exercise intensity, duration of interventions, and criteria used for functional assessment, also limits direct comparison of the available findings.^{1,3,5} Thus, future studies are likely to direct prehabilitation

toward more individualized models, combined with the use of remote monitoring technologies to improve adherence and expand the application of this strategy within healthcare services.^{4,8} Overall, the findings suggest that multimodal prehabilitation has a greater clinical impact in patients with lower baseline functional reserve and higher surgical risk, particularly when combined with well-structured perioperative strategies.^{1,2,5}

CONCLUSION

Multimodal prehabilitation associated with the ERAS protocol proved to be a promising strategy for optimizing recovery in patients undergoing elective colorectal surgery, particularly by improving functional capacity during the perioperative period. The analyzed findings indicate that interventions combining structured physical exercise, nutritional support, psychological support, and, in some cases, inspiratory muscle training may increase patients' physiological reserve and promote faster postoperative recovery.

However, the effects on postoperative complications, length of hospital stay, and mortality remain inconsistent across studies. In centers with well-established ERAS protocols and extensive use of minimally invasive techniques, the additional benefit of prehabilitation appears to be more modest, possibly because of the quality of the perioperative care already in place. On the other hand, patients with higher surgical risk, low functional capacity, sarcopenia, advanced age, or multiple comorbidities appear to constitute the group with the greatest potential for clinical benefit.

The main limitations observed in the literature involve the heterogeneity of prehabilitation protocols, differences in the duration and intensity of interventions, variability in the outcomes assessed, and the difficulty of making direct comparisons between studies. Therefore, although the findings support the incorporation of multimodal prehabilitation as a complement to ERAS, further prospective, multicenter studies using more standardized protocols are still needed to determine which components are most effective, the optimal duration of the intervention, and which patient profiles should be prioritized.

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ACUTE CORONARY SYNDROME: EARLY DIAGNOSIS AND PROGNOSTIC IMPACT

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ABSTRACT

Acute coronary syndrome remains one of the leading causes of cardiovascular morbidity and mortality and requires early diagnosis, accurate risk stratification, and rapid therapeutic decision-making in emergency settings. This study aimed to analyze the available evidence on early diagnostic strategies and their prognostic implications in patients with suspected or confirmed acute coronary syndrome. This is an integrative literature review conducted in the PubMed/MEDLINE database, including five studies published between 2016 and 2026. The findings show that high-sensitivity cardiac troponin has expanded the ability to identify myocardial infarction and different categories of myocardial injury, although this diagnostic improvement has not consistently translated into better clinical outcomes. The HEART score showed superior performance compared with TIMI and GRACE in identifying low-risk patients, supporting safer hospital discharge strategies. Coronary computed tomography angiography demonstrated operational value by reducing unnecessary invasive procedures but without a proven impact on mortality or nonfatal myocardial infarction. It is concluded that prognosis in acute coronary syndrome depends not only on diagnostic accuracy, but also on the integration of biomarkers, clinical risk scores, imaging methods, and therapeutic protocols directed at the newly identified high-risk patient groups.

Keywords: Acute coronary syndrome, Biomarkers, Cardiac troponin, Early diagnosis, Prognosis.

INTRODUCTION

Acute coronary syndrome (ACS) represents one of the leading causes of morbidity and mortality worldwide and constitutes a daily challenge in emergency departments. The assessment of patients presenting with acute chest pain requires speed and accuracy, since early diagnosis and the immediate initiation of evidence-based therapies are decisive for preserving cardiac muscle and patient survival. Historically, the focus of initial care has been the rapid exclusion of acute myocardial infarction (AMI) and the identification of patients requiring immediate invasive intervention, balancing the safety of hospital discharge with the rational use of healthcare system resources.

In recent decades, the diagnostic paradigm of ACS has undergone a profound transformation with the introduction of high-sensitivity cardiac troponins (hs-cTn). The ability of these biomarkers to detect minute

concentrations of myocardial protein has not only accelerated algorithms for ruling out (rule-out) and confirming (rule-in) ischemia, but has also driven the reclassification of myocardial injury in accordance with the Fourth Universal Definition of Myocardial Infarction. In parallel with laboratory advances, the systematic application of validated clinical risk scores, such as History, ECG, Age, Risk factors, and Troponin (HEART), Thrombolysis in Myocardial Infarction (TIMI), and the Global Registry of Acute Coronary Events (GRACE), has become a cornerstone in structuring clinical reasoning. The combination of these tools aims to reduce medical subjectivity, optimizing predictive accuracy for short-term major adverse cardiac events (MACE).^{1,2}

In addition to laboratory and clinical approaches, the initial diagnostic armamentarium has been expanded by incorporating noninvasive imaging tests. Coronary computed tomography angiography (CTCA) has emerged as a complementary strategy for intermediate-risk patients, intended to function as an anatomical filter capable of confirming or ruling out the presence of obstructive coronary artery disease, with the aim of reducing the incidence of unnecessary diagnostic catheterizations.³ Additionally, recent evidence has broadened the prognostic spectrum of initial assessment, demonstrating that even detectable baseline concentrations of hs-cTn, although still within reference limits, are directly correlated with the future development of ventricular failure, suggesting the feasibility of risk prediction extending beyond the acute phase of the ischemic event.⁴

However, contemporary literature reveals a significant paradox between advances in diagnostic accuracy and actual modification of clinical prognosis (Knowledge Gap). Although the integration of hs-cTn with emergency-oriented clinical scores, such as HEART, has improved the safety of discharging very-low-risk patients, increased laboratory sensitivity has generated an epidemic of diagnoses of type 2 myocardial infarction and acute and chronic non-atherosclerotic myocardial injury.⁵ These subgroups, which currently account for a substantial proportion of troponin elevations, have cardiovascular and noncardiovascular mortality rates equivalent to or higher than those of type 1 myocardial infarction. However, the increased recognition of these etiologies has not been accompanied by a corresponding adaptation in secondary prevention and treatment protocols.⁵ These patients systematically receive fewer cardioprotective therapies and appropriate interventions, resulting in stagnant outcomes.

Likewise, the benefit of early anatomical screening with CTCA appears to be restricted to purely operational aspects of hospital workflow, lacking substantial evidence regarding reduction in hard outcomes (mortality or nonfatal myocardial infarction) among intermediate-risk populations.³

Therefore, there is a critical need to understand the limitations of the current application of stratification tools. Technological advances have provided an unprecedented level of diagnostic and anatomical detail; however, the absence of structured therapeutic pathways for the new risk categories identified by hs-cTn and the uncertainties regarding the isolated impact of imaging tests highlight fragmentation in patient care. It is imperative to critically analyze how highly precise diagnosis is, or is not, being translated into risk modification, in order to guide future therapeutic strategies aimed at reducing morbidity and mortality in this complex population.

OBJECTIVES

Analyze the evidence available in the literature on early diagnostic strategies and their prognostic consequences in patients with suspected or confirmed Acute Coronary Syndrome.

METHODS

This is an integrative literature review. The search was conducted in the PubMed/MEDLINE database using controlled MeSH descriptors and free-text terms: (“Acute Coronary Syndrome” OR “STEMI” OR “NSTEMI” OR “unstable angina”) AND (“early diagnosis” OR “troponin” OR “high-sensitivity troponin” OR “HEART score” OR “GRACE score” OR “cardiac biomarkers”) AND (“prognosis” OR “mortality” OR “outcomes” OR “MACE”). Filters were applied for studies published between 2016 and 2026. The search strategy yielded 68 articles, from which 5 studies with the greatest methodological relevance and suitability to the topic were selected.

RESULTS AND DISCUSSIONS

This integrative review selected five studies published between 2017 and 2023, with different methodological designs—including randomized clinical trials, multicenter prospective cohorts, and a systematic review—totaling more than 77,000 patients evaluated in emergency or inpatient settings for suspected acute coronary syndrome (ACS). The studies were conducted in the United Kingdom^{3,4,5} the Netherlands^{1,2} Canada¹, the United States¹, Israel¹, Switzerland¹, and Australia¹, covering different early diagnostic strategies: high-sensitivity cardiac troponin (hs-cTn), clinical risk scores, coronary computed tomography angiography (CTCA), and diagnostic classification based on the Universal Definition of Myocardial Infarction. The characteristics of the included studies are summarized in Table 1.

Table 1: Characteristics of the Included Studies.

Study	Design	N	Country	Primary outcome	Follow-up
Poldervaart et al., 2017 ²	Prospective multicenter cohort	1,748	Netherlands	MACE at 6 weeks	6 weeks
O’Rielly et al., 2023 ¹	Systematic review	20,959	Multicenter	MACE at 30 days	30 days
Chapman et al., 2020 ⁵	Stepped-wedge RCT (High-STEACS)	48,282	United Kingdom	IAM or CV death at 1 year	1 year
Stelzle et al., 2018 ⁴	Prospective cohort	4,748	United Kingdom	Hospitalization for IC	~5 months
Gray et al., 2021 ³ -CTCA	Multicenter RCT (RAPID)	1,748	United Kingdom	Death or MI at 1 year	1 year

Source: Prepared by the authors, 2026.

Clinical Risk Stratification Using Validated Scores

The direct comparison of clinical risk scores in patients presenting with chest pain in the emergency department was addressed in a complementary manner by Poldervaart et al.² and O’Rielly et al.¹, providing perspectives that converge on the superiority of the HEART score over the other available tools. Poldervaart et al.² conducted a multicenter prospective cohort study in 9 hospitals in the Netherlands, including 1,748 patients evaluated for chest pain, excluding cases of immediately recognized STEMI.

The primary outcome—MACE at 6 weeks, including unstable angina, NSTEMI, STEMI, coronary stenosis managed conservatively, revascularization, and cardiovascular death—occurred in approximately 19% of the sample (325–326 patients). The HEART score demonstrated superior discriminatory performance compared with TIMI and GRACE, with areas under the ROC curve (AUC) of 0.86 (95% CI 0.84–0.88), 0.80 (95% CI 0.78–0.83), and 0.73 (95% CI 0.70–0.76), respectively, with all paired differences being statistically significant ($p < 0.001$)². Using a minimum sensitivity criterion of 95%, the HEART score with a cutoff ≤ 3 classified 40.5% of patients as low risk, with a residual MACE rate of 2.0% and a negative predictive value (NPV) of 98% (95% CI 97–99%).² The TIMI score identified 25.1% of patients as low risk, and GRACE only 19.1%, with residual MACE rates of 3.2% and 3.6%, respectively.² In the more conservative scenario, with a minimum sensitivity of 98%, the HEART score with a cutoff ≤ 2 classified 21.8% of patients as low risk, with a residual MACE rate of only 0.8%, no deaths, and an NPV of 99% (95% CI 98–100%).² The TIMI score was unable to identify a low-risk group at this level of safety, and GRACE classified only 13.2% of patients, with a residual MACE rate of 2.2%.²

These findings are supported and complemented by the systematic review by O’Rielly et al.¹, which evaluated the prognostic performance of clinical scores specifically in patients in whom myocardial infarction had already been ruled out by hs-cTn, totaling 20,959 patients across six eligible studies. In this post-MI rule-out population, the HEART score with a cutoff ≤ 3 , combined with hs-cTnT, was the score that classified the largest proportion of patients as low risk—up to 62.5% in one study—with sensitivity for 30-day MACE ranging from 93.8% to 100% and NPV between 99.7% and 100%.¹ The TIMI score ≤ 1 classified similar proportions of patients as low risk in some studies, but with highly variable sensitivity across cohorts (66.7% to 98.9%), limiting its reliability as a universal triage tool.¹ The GRACE score with a cutoff < 73 demonstrated unsatisfactory performance in this population, achieving a sensitivity of only 75.4%¹—a finding that reflects the inadequacy of a tool originally developed for populations with established ACS when applied to patients who had already undergone hs-cTn algorithms. The performance hierarchy identified—HEART superior to TIMI and GRACE—was consistent across both studies, regardless of the populations and comparative methods used.^{1,2}

A finding of particular clinical relevance concerns the limited incremental value of the scores after exclusion of AMI by hs-cTn¹. The 30-day MACE rate in this population is already intrinsically low—below 1% in most studies—reducing the margin for additional gain from any extra score. This observation suggests that patients with negative hs-cTn results according to a validated algorithm may be candidates for safe discharge without the need for routine noninvasive testing, regardless of individual clinical characteristics¹.

Impact of High-Sensitivity Troponin on Diagnosis and Prognosis

Chapman et al.⁵ demonstrated, in a multicenter stepped-wedge randomized clinical trial involving 48,282 consecutive patients with suspected ACS across 10 hospitals in Scotland, that implementation of hs-cTnI significantly increased recognition of different categories of myocardial injury compared with conventional troponin. The increases were 11% for the diagnosis of type 1 myocardial infarction (510/4,471), 22% for type 2 MI (205/916), 36% for acute myocardial injury (443/1,233), and 43% for chronic myocardial injury (389/898)⁵. This pattern shows that the diagnostic gain provided by hs-cTn is disproportionately greater for non-atherosclerotic categories of myocardial injury, with direct implications for prognostic stratification in a subgroup of patients that is usually underdiagnosed.

Diagnostic classification according to the Fourth Universal Definition of Myocardial Infarction revealed that all identified categories of myocardial injury confer significantly increased cardiovascular

risk at 1 year, regardless of pathogenesis.⁵ The risk of myocardial infarction or cardiovascular death was highest in patients with type 1 AMI (csHR 5.64; 95% CI 5.12–6.22), but remained substantial in the other categories: type 2 AMI (csHR 3.50; 95% CI 2.94–4.15), acute myocardial injury (csHR 4.38; 95% CI 3.80–5.05), and chronic myocardial injury (csHR 3.88; 95% CI 3.31–4.55), all compared with patients without myocardial injury.⁵ The risk of noncardiovascular death was highest in patients with acute myocardial injury (csHR 2.65; 95% CI 2.33–3.01), a category in which more than one third of deaths occurred within the first 30 days due to pneumonia, exacerbation of chronic obstructive pulmonary disease, or sepsis—extracardiac causes whose management requires a multidisciplinary approach.

Despite the demonstrated diagnostic and prognostic capacity, implementation of hs-cTn did not translate into consistent improvement in clinical outcomes⁵. There was no reduction in the primary outcome in any of the diagnostic categories after the introduction of hs-cTnI, including type 1 AMI, in which modest increases in antiplatelet therapy (43% vs. 61%) and coronary revascularization (35% vs. 44%) were observed, without an impact on the composite event (csHR 1.00; 95% CI 0.82–1.21).⁵ For patients with type 2 AMI and myocardial injury, there was no change in investigation, treatment, or outcomes after implementation⁵, exposing a critical gap: the diagnostic advance provided by hs-cTn was not accompanied by appropriate therapeutic protocols for these populations. Patients with type 2 AMI underwent coronary angiography in only 10% of cases and percutaneous intervention in only 2%, compared with 59% and 41%, respectively, among patients with type 1 MI⁵, despite presenting a 1-year cardiovascular risk more than 3 times higher than that of patients without myocardial injury.

Prognostic Value of hs-cTnI Beyond the Diagnosis of Myocardial Infarction

Stelzle et al.⁴ broadened the prognostic scope of hs-cTnI by demonstrating, in a prospective cohort of 4,748 consecutive patients with suspected ACS, that hs-cTnI concentration independently predicts the risk of hospitalization for heart failure—even among patients with troponin levels within the normal reference range. The relationship between hs-cTnI concentration and the risk of hospitalization for heart failure was nonlinear: each doubling of hs-cTnI concentration below the upper reference limit (URL) was associated with a 2.80-fold increase in the risk of hospitalization for heart failure (HR 2.80; 95% CI 1.81–4.31), whereas above the URL, higher concentrations did not confer a significant additional risk (HR 1.03; 95% CI 0.96–1.12).⁴ Incidence rates of hospitalization for heart failure ranged from zero in the two lowest troponin quartiles to 118 per 1,000 person-years in the group with troponin levels above the URL, with progressively higher adjusted HRs of 3.0 (Group 3), 11.7 (Group 4), and 28.9 (Group 5) compared with the reference group⁴.

The discriminatory ability of hs-cTnI for predicting heart failure was comparable to that of a complete clinical model (C-statistic 0.80 for both), and its combination with clinical variables increased discrimination to 0.86 (95% CI 0.82–0.89; $p < 0.001$)⁴, a level indicating usefulness for individual event prediction. Patients in the two lowest troponin quartiles experienced no hospitalization for heart failure or cardiac death during follow-up, reinforcing the negative predictive value of hs-cTn and the safety of early discharge strategies for this subgroup⁴. These data are consistent with the findings of O’Rielly et al.¹ and Poldervaart et al.² regarding the excellent performance of negative hs-cTn results in identifying very-low-risk patients.

Role of Early Coronary Computed Tomography Angiography

Gray et al.³ evaluated, in the RAPID-CTCA trial, whether the early incorporation of CTCA into standard care could improve clinical outcomes in 1,748 patients with suspected ACS and at least one intermediate-

risk marker—elevated troponin (57%), abnormal ECG (61%), or previous coronary artery disease (34%)—with a mean GRACE score of 115. The primary outcome of all-cause death or nonfatal type 1 or 4b myocardial infarction at 1 year occurred in 5.8% of patients in the CTCA group and 6.1% in the control group (adjusted HR 0.91; 95% CI 0.62–1.35; $p=0.65$)³, indicating no significant clinical benefit of the strategy on hard outcomes. All secondary outcomes related to mortality and cardiovascular events were likewise neutral, with no significant heterogeneity in subgroup analyses by age, sex, GRACE score, history of coronary artery disease, or troponin³.

The benefit of CTCA was concentrated on the care process: there was a significant reduction in the rate of invasive coronary angiography (54.0% vs. 60.8%; adjusted HR 0.81; 95% CI 0.72–0.92; $p=0.001$) and in subsequent noninvasive testing for coronary artery disease or ischemia (19.4% vs. 26.2%; adjusted HR 0.66; 95% CI 0.54–0.81; $p<0.001$)³. There was no difference in revascularization (34.2% vs. 33.1%; $p=0.76$) or in pharmacological treatment for ACS (67.8% vs. 66.6%; $p=0.63$)³. The anatomical findings of CTCA provide a relevant interpretive perspective: 23% of patients had normal coronary arteries, 29% had nonobstructive disease, and 47% had obstructive disease³—showing that more than half of intermediate-risk patients, even with abnormal biomarkers or ECG findings, did not have significant coronary obstruction, which supports the role of CTCA as an anatomical triage tool to avoid unnecessary invasive angiography in selected subgroups. CTCA was, however, associated with a slight increase in length of stay (2.2 vs. 2.0 days; $p=0.009$)³, differing from studies in low-risk populations, in which the examination usually reduces hospital stay.

Integration of Findings and Clinical Implications

The integrative analysis of the five studies allows a coherent overview of early diagnosis and prognostic impact in ACS to be outlined. hs-cTn constitutes the central pillar of the contemporary diagnostic strategy^{4,5} with greater ability than previous generations of troponin to identify myocardial injury in its different forms.⁵ However, the diagnostic gain did not automatically translate into improved outcomes⁵, demonstrating that the clinical value of hs-cTn lies primarily in risk stratification—both to identify patients who require immediate intervention and to safely characterize those at very low risk who are eligible for early discharge.^{1,4}

In this context, the application of validated clinical scores represents an essential complementary step. The HEART score consistently demonstrated superiority over TIMI and GRACE both in event discrimination (AUC 0.86 vs. 0.80 vs. 0.73)² and in the efficient identification of low-risk patients after MI was ruled out by hs-cTn (up to 62.5% classified as low risk, with an NPV of 99.7% to 100%).¹ This superiority may be attributed to the alignment of the HEART score with the specific clinical setting of the emergency department—having been developed for patients with undifferentiated chest pain—unlike GRACE and TIMI, which are more strongly oriented toward prognostic stratification in patients with already confirmed ACS.² The integration of hs-cTn and structured clinical scores such as HEART therefore represents the most rational approach to risk stratification in ACS, combining the analytical precision of the biomarker with the multivariable clinical context of the score.^{1,2}

The prognostic impact of the different categories of myocardial injury identified by hs-cTn represents the most relevant clinical gap highlighted by this review. Type 2 AMI and acute and chronic myocardial injury—which account for nearly half of all troponin elevations⁵—present a 1-year cardiovascular risk comparable to that of type 1 AMI, yet they systematically receive less investigation and cardioprotective treatment.^{4,5} This disparity is aggravated by the absence of specific therapeutic protocols for these

categories and by the predominance of noncardiovascular deaths—particularly infections and pulmonary decompensations—among patients with acute myocardial injury⁵, requiring an integrated clinical approach that extends beyond conventional ACS management.

The finding by Stelzle et al.⁴ that hs-cTnI predicts heart failure even within the normal reference range further expands the prognostic dimension of the biomarker, suggesting that patients with detectable troponin—particularly those in the upper quartiles of the reference range—may benefit from additional structural cardiac investigation, such as echocardiography and NT-proBNP measurement, strategies that are not currently routine in this group.⁴

Early CTCA, in turn, should be interpreted within its actual clinical scope: it is a tool with predominantly operational value, capable of reducing unnecessary invasive procedures and increasing diagnostic certainty, but without demonstrated prognostic benefit in intermediate-risk patients³. Its selective use—in scenarios of diagnostic uncertainty, in hospitals with limited access to invasive angiography, or in patients with elevated troponin without clear evidence of coronary obstruction—appears to be the most rational approach based on the available evidence.³ Comparison with studies of stable chest pain, in which CTCA demonstrated a reduction in long-term events through intensification of preventive therapy, reinforces that the impact of the test is strongly dependent on the pretest risk profile, the prevalence of obstructive disease, and the quality of the available standard care.³

Finally, the findings of this review point to the urgent need for randomized clinical trials evaluating specific secondary prevention strategies for type 2 AMI and myocardial injury,^{4,5} as well as studies defining the role of additional biomarkers and imaging methods in the prognostic stratification of patients with elevated hs-cTn without criteria for type 1 AMI.⁴ The integration of validated clinical scores, high-sensitivity biomarkers, and, when indicated, coronary imaging methods into structured diagnostic algorithms represents the most promising path toward improving outcomes in ACS.^{1,2,3,4,5}

CONCLUSION

Based on this study, optimizing risk stratification for patients with suspected acute coronary syndrome in the emergency setting depends on the synergistic integration of high-sensitivity biomarkers and validated clinical scores. The analyzed data confirm the superiority of the HEART score over traditional tools such as TIMI and GRACE, showing significantly greater discriminatory ability for predicting short-term major adverse cardiac events. While the HEART score was able to safely identify approximately 40% of the sample as low risk—with sensitivity above 95%, a negative predictive value of up to 99%, and minimal residual event rates—the traditional scores proved less efficient or overly conservative, limiting their usefulness in initial triage. This superior performance results from the alignment of the HEART score with the clinical reality of undifferentiated chest pain, allowing early identification of candidates for safe hospital discharge and reducing reliance on routine noninvasive testing after myocardial infarction has been ruled out using high-sensitivity troponin algorithms.

At the same time, the implementation of high-sensitivity troponins revealed a scenario of diagnostic progress accompanied by persistent therapeutic challenges. A substantial increase was observed in the recognition of type 2 myocardial infarction and acute and chronic myocardial injury, categories that now account for nearly half of troponin elevations in clinical practice. However, the findings highlight a critical gap: this increase in diagnosis was not accompanied by improved clinical outcomes at one year, demonstrating the absence of specific treatment protocols for non-atherosclerotic causes.

Patients with myocardial injury have cardiovascular risks comparable to those with type 1 myocardial

infarction, but systematically receive fewer protective interventions, indicating that effective detection is only the first step toward reducing morbidity and mortality. In addition, the ability of troponin to predict the risk of heart failure even at levels considered normal expands its prognostic value beyond acute diagnosis, suggesting that detectable concentrations may indicate the need for structured preventive monitoring. Regarding the role of coronary computed tomography angiography, its usefulness is essentially operational, as it is effective in avoiding unnecessary invasive procedures in intermediate-risk patients, although without a direct impact on mortality. Therefore, the evolution of care in acute coronary syndrome requires not only analytical and clinical precision in triage, but also the urgent development of clinical trials to define effective secondary prevention strategies for the new high-risk populations identified through high-sensitivity testing.

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USE OF INDOCYANINE GREEN IN THE PREVENTION OF ANASTOMOTIC LEAK IN COLORECTAL SURGERIES: A SYSTEMATIC REVIEW

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ABSTRACT

Anastomotic leak is a serious complication in colorectal surgery, with an incidence of up to 19% and significant mortality. Indocyanine green (ICG) allows intraoperative assessment of bowel perfusion through fluorescence imaging, but its effectiveness in reducing leaks remains controversial. This systematic review aimed to evaluate whether ICG use reduces anastomotic leak rates in colorectal surgery compared to conventional visual inspection. The search was performed in PubMed using MeSH terms, identifying 198 articles. After applying inclusion and exclusion criteria, 7 randomized controlled trials were analyzed. Two studies demonstrated significant leak reduction with ICG (Alekseev et al., 2020: 16.3% vs 9.1%, $p=0.04$; Watanabe et al., 2023: 11.8% vs 7.6%, $p=0.041$), while five studies showed no statistically significant difference, although with a numerical trend favoring ICG. Subgroup analyses suggest ICG benefit in low anastomoses (rectal). No serious adverse events were reported. ICG is safe, but its clinical efficacy remains uncertain. Routine use for all colorectal surgeries is not recommended, although it may be promising in high-risk scenarios, such as low rectal surgery.

Keywords: Anastomotic leak, Colorectal surgery, Disease Management, Fluorescence, Indocyanine green.

INTRODUCTION

Anastomotic leak (AL) is one of the most feared complications following colorectal surgery with primary anastomosis. Its incidence ranges from 1% to 19%, depending on the level of the anastomosis and the patient's clinical condition, and it is associated with mortality rates that may reach 35%.¹ In addition to its clinical impact, AL significantly increases length of hospital stay, healthcare costs, and the need for surgical reinterventions, constituting an important public health problem.

Currently, the decision regarding the ideal site for anastomosis is based primarily on the surgeon's subjective visual inspection, assessing parameters such as serosal color, bleeding at the edges, and pulsation of the vascular arcades. However, this method has low sensitivity and specificity for detecting inadequate tissue perfusion² and is widely recognized as imprecise and dependent on the surgeon's experience.

Indocyanine green (ICG) has emerged as a promising alternative to overcome these limitations. It is a fluorescent tricarbo-cyanine dye administered intravenously that rapidly binds to plasma proteins. When

illuminated with near-infrared light, it emits fluorescence detectable by specific cameras, allowing the surgeon to assess perfusion of the bowel edge in real time before performing the anastomosis.³ Studies have shown that ICG identifies inadequate perfusion and changes the anastomotic site in approximately 10% of cases⁴, potentially preventing the occurrence of anastomotic leak.

Initial evidence regarding the effectiveness of ICG was promising. Meta-analyses published between 2023 and 2024 demonstrated a significant reduction in AL with the use of fluorescence angiography, with odds ratios ranging from 0.46 to 0.586 in colorectal and rectal surgery.^{5,6} However, more recent randomized controlled trials (RCTs) have yielded conflicting results, with some studies showing significant benefit^{7,8} and others finding no statistically significant differences.^{9,10} This heterogeneity of findings maintains the debate regarding the actual role of ICG in surgical practice.

Given this scenario of uncertainty and the recent publication of new RCTs, an updated systematic review is justified. The present study aims to evaluate whether the intraoperative use of indocyanine green for assessment of bowel perfusion reduces the rate of anastomotic leak in patients undergoing colorectal surgery compared with the conventional method based on subjective visual inspection.

OBJECTIVES

The general objective of this study is to evaluate whether the intraoperative use of indocyanine green (ICG) for assessment of bowel perfusion reduces the rate of anastomotic leak in patients undergoing colorectal surgery compared with the conventional method based on subjective visual inspection.

The specific objectives are to compare the incidence of anastomotic leak between the ICG and control groups; analyze the impact of ICG on surgical reintervention rates and length of hospital stay; and describe adverse effects related to the use of indocyanine green reported in the literature.

METHODS

This is a systematic literature review conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist guidelines.

Studies were included if they met the following criteria:

- (1) original studies designed as randomized clinical trials, non-randomized clinical trials, or cohort studies (prospective or retrospective);
- (2) adult patients undergoing colorectal surgery with primary anastomosis;
- (3) intraoperative use of indocyanine green (ICG) for assessment of bowel perfusion;
- (4) comparison with the conventional method based on subjective visual inspection;
- (5) primary outcome reporting the anastomotic leak rate;
- (6) articles published in English, Portuguese, or Spanish; and
- (7) publication between January 2015 and April 2026.

The following were excluded:

- (1) review studies (systematic, integrative, or narrative), meta-analyses, editorials, letters to the editor, case reports, and case series;
- (2) animal or cadaver studies;
- (3) studies without a control group;

- (4) studies without full-text access; and
- (5) duplicate articles.

The search was conducted in May 2026 in the PubMed/MEDLINE database. English-language descriptors based on MeSH (Medical Subject Headings) and Boolean operators were used according to the following PubMed search strategy: ("Indocyanine Green" [Mesh] OR "ICG" OR "indocyanine green") AND ("Colorectal Surgery" [Mesh] OR "colorectal resection" OR "colorectal anastomosis") AND ("Anastomotic Leak" [Mesh] OR "anastomotic leakage" OR "anastomotic leak").

The following filters were applied: randomized clinical trials, controlled clinical trials, observational studies, cohort studies, publications from the last 10 years, and articles in English, Portuguese, or Spanish.

Two reviewers independently screened the titles and abstracts. Disagreements were resolved by consensus or with the assistance of a third reviewer. Full texts of potentially eligible articles were retrieved and evaluated according to the inclusion criteria.

Data were extracted using a standardized form containing:

- (1) study identification (author, year, country);
- (2) study design;
- (3) sample size (ICG group and control group);
- (4) population characteristics (age, sex, type of surgery);
- (5) anastomotic leak rate in each group; and (6) secondary outcomes (reintervention, length of hospital stay, adverse effects).

The methodological quality of the included studies was assessed according to each study design: for randomized clinical trials, the Cochrane RoB 2 (Risk of Bias 2) tool was used; for cohort studies, the Newcastle-Ottawa Scale was used. Two reviewers performed the assessment independently.

The results were synthesized descriptively (narratively) and presented in tables. A meta-analysis was not performed due to methodological heterogeneity among the studies.

RESULTS AND DISCUSSIONS

The initial PubMed search identified 198 articles using the defined descriptors. After applying the publication date filter for the last 10 years (2015–2025), 192 articles were retrieved. Of these, 12 controlled clinical trials and 8 observational studies were selected for abstract review. After application of the inclusion and exclusion criteria, 7 randomized controlled trials (RCTs) were included in this systematic review. The flowchart of the study selection process is presented in Figure 1 (PRISMA).

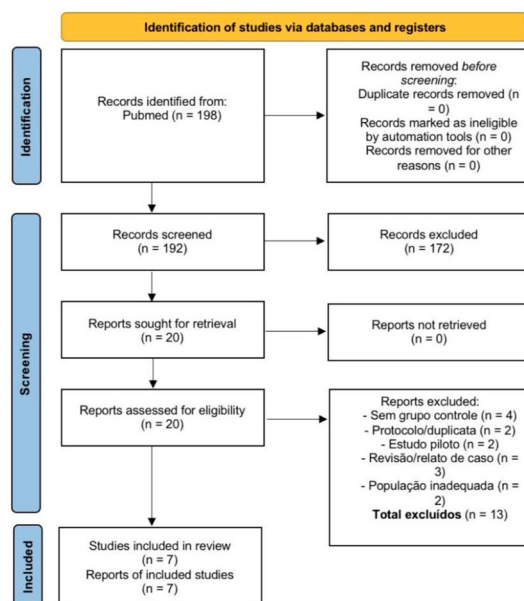


Figure 1: PRISMA Flowchart of the Study Selection Process.

Source: Prepared by the authors based on the PRISMA 2020 model.¹¹

Table 1 presents the characteristics and main findings of the 7 RCTs included. The studies were published between 2020 and 2025, with sample sizes ranging from 240 to 931 patients. All studies compared the intraoperative use of indocyanine green (ICG) for assessment of bowel perfusion with the conventional method based on subjective visual inspection. The primary outcome in all studies was the anastomotic leak rate. Six studies were multicenter, and one was conducted at a single center.

Table 1: Characteristics of the Included Studies.

	Author (year)	Typo	N (ICG)	N (control)	ICG leak (%)	Control leak (%)	p value	Sign ificant
1	Faber, 2024	RCT	463	468	6.9%	9.0%	0.04	No
2	Rinne, 2025	RCT	567	569	5.8%	7.9%	0.16	No
3	Watanabe, 2023	RCT	422	417	7.6%	11.8%	0.041	Yes
4	Jayne, 2025	RCT	343	355	10.5%	15.2%	0.087	No
5	Alekseev, 2020	RCT	187	190	9.1%	16.3%	0.04	Yes
6	De Nardi, 2020	RCT	118	122	5.1%	9.0%	n.s.	No
7	Jafari, 2021	RCT	178	169	9.0%	9.6%	0.37	No

Legend: RCT = randomized controlled trial; ICG = intraoperative indocyanine green.

Table 1: Prepared by the authors.

Of the 7 RCTs included, two studies (28.6%) demonstrated a statistically significant reduction in the anastomotic leak rate with the use of ICG. The study by Alekseev et al.⁷ reported a reduction from 16.3% to 9.1% ($p=0.04$), while the study by Watanabe et al.⁸ showed a reduction from 11.8% to 7.6% ($p=0.041$). The remaining five studies found no statistically significant difference between the ICG and control groups, although most demonstrated a numerical trend favoring ICG.^{2,9,10,12,13}

Two studies performed subgroup analyses suggesting a benefit of ICG in specific populations. Alekseev et al.⁷ observed that ICG significantly reduced anastomotic leak in low colorectal anastomoses (4–8 cm from the anal verge): 14.4% in the ICG group versus 25.7% in the control group ($p=0.04$), whereas no benefit was observed for high anastomoses ($p=0.37$). Rinne et al.¹² demonstrated a trend toward benefit in left-sided surgery (OR 0.55; 95% CI 0.29–1.05), although without statistical significance.

Watanabe et al.⁸ reported that the reoperation rate was significantly lower in the ICG group (0.5% vs. 2.4%; $p=0.021$). De Nardi et al.² observed that ICG angiography led to a change in surgical strategy (extended bowel resection) in 11% of patients due to the identification of inadequate perfusion. None of the studies reported serious adverse events related to the use of ICG.^{2,7-10,12,13}

This systematic review synthesized the available evidence on the use of indocyanine green (ICG) in the prevention of anastomotic leak in colorectal surgery, based on 7 randomized controlled trials totaling 3,195 patients. The results demonstrated that two studies (28.6%) found a significant reduction in the leak rate with the use of ICG^{7,8}, while five studies did not show a statistically significant benefit^{2,9,10,12,13}, although most showed a numerical trend favoring the intervention.

The heterogeneity of the results reflects the current state of knowledge regarding ICG in colorectal surgery. The positive studies share some characteristics: both predominantly included low rectal surgery, a procedure associated with a higher risk of anastomotic leak^{7,8}. In contrast, the negative studies included a mixture of right-sided colon, left-sided colon, and rectal surgeries, which may have diluted the effect of ICG.^{2,9,10,12,13} This observation is supported by the subgroup analyses: Alekseev et al.⁷ demonstrated that ICG significantly reduced anastomotic leak in low anastomoses (14.4% vs. 25.7%; $p=0.04$), but not in high anastomoses. Rinne et al.¹² also observed a trend toward benefit in left-sided surgery (OR 0.55; 95% CI 0.29–1.05). These findings suggest that ICG may be more useful in settings with a higher risk of anastomotic leak, where bowel perfusion is more critical.

Several factors may explain the variation in results among the studies: type of surgery (rectal versus colonic), differences in ICG administration protocols (dose, timing of injection, criteria for modifying the resection), experience of the surgical centers, and variations in the definition of anastomotic leak (grades A, B, and C). The largest study included, with 931 patients¹², was negative, whereas smaller studies with more selected populations were positive^{7,8}, suggesting that the benefit of ICG may be more evident in specific high-risk subgroups.

The largest study included, with 931 patients, was negative, whereas smaller studies with more selected populations were positive.⁹ This raises a critical question: could the benefit of ICG, when present, be a false-positive finding related to selection bias or insufficient sample size? Smaller studies have a greater risk of overestimating effects, and the lack of confirmation in a large multicenter RCT is a warning sign that cannot be ignored.

Despite the lack of statistical significance in some studies, secondary outcomes suggest a benefit of ICG. Watanabe et al.⁸ reported a significant reduction in the reoperation rate (0.5% vs. 2.4%; $p=0.021$). De Nardi et al.² observed that ICG led to a change in surgical strategy in 11% of cases, potentially avoiding anastomoses in poorly perfused areas. No study reported serious adverse events related to ICG^{2,7-10,12,13}, confirming its safety.

This review has limitations that should be considered. The search was restricted to PubMed, although it is the most comprehensive database in biomedical sciences. Methodological heterogeneity among the studies, including differences in ICG protocols and definitions of anastomotic leak, limited comparability and prevented the performance of a meta-analysis. In addition, most studies did not adequately describe blinding, and some are very recent^{9, 10, 12}, with no independent replication to date.

Based on the findings, routine use of ICG cannot be recommended for all colorectal surgeries. However, ICG appears promising in low rectal surgery (anastomoses less than 8 cm from the anal verge), where the risk of anastomotic leak is higher and subgroup analyses have shown significant benefit⁷. Future research should standardize ICG administration and interpretation protocols, focus specifically on low rectal surgery, and evaluate the cost-effectiveness of the technology, considering the potential reduction in reoperations and length of hospital stay.

Indocyanine green (ICG) is a safe tool for intraoperative assessment of bowel perfusion in colorectal surgery.^{2,7-10,12,13} Although most randomized controlled trials have not demonstrated a statistically significant reduction in anastomotic leak, there is a consistent numerical trend toward benefit and a significant benefit in higher-risk subgroups, such as low anastomoses.⁷ ICG may be more useful in low rectal surgery, where it modifies the surgical strategy in approximately 10% of cases.² Additional studies focused on high-risk populations are needed to establish its actual role in clinical practice.

CONCLUSION

This systematic review demonstrated that indocyanine green (ICG) is a safe tool for intraoperative assessment of bowel perfusion in colorectal surgery. Although most randomized controlled trials did not demonstrate a statistically significant reduction in anastomotic leak in general populations, there was a consistent numerical trend toward benefit, as well as significant benefit in higher-risk subgroups, particularly in low rectal anastomoses, where ICG modified the surgical strategy in approximately 10% of cases.

A major limitation was the methodological heterogeneity among the studies, which prevented the performance of a meta-analysis. Future research should standardize ICG administration and interpretation protocols, focus specifically on low rectal surgery, and evaluate the cost-effectiveness of the technology. Based on the findings, routine use of ICG cannot be recommended for all colorectal surgeries, but it appears promising in settings with a high risk of anastomotic leak.

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VALIDATION OF AI ALGORITHMS IN OPHTHALMOLOGICAL POPULATION SCREENING

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ABSTRACT

The application of artificial intelligence (AI) in ophthalmology has emerged as a promising strategy for the early diagnosis and population screening of visual diseases, mitigating the shortage of specialists and optimizing the management of health resources. The present study aims to analyze the clinical efficacy, robustness, and generalization capacity of AI algorithms applied to the screening and diagnostic support of ophthalmological pathologies. For this purpose, an integrative literature review was conducted through searches in the Google Scholar, PubMed, ResearchGate, and CAPES Periodicals Portal databases, culminating in the selection and analysis of ten studies published between 2018 and 2025. The synthesis of evidence demonstrated that deep learning models focused on the analysis of fundus images present high rates of sensitivity and specificity, especially in the detection of diabetic retinopathy, retinopathy of prematurity, glaucoma, and age-related macular degeneration. Furthermore, it was found that the integration of these technologies significantly expands clinical screening capacity. However, the performance of these algorithms can undergo significant variations when faced with distinct populations or different capture equipment, a technical challenge known as domain shift. Therefore, it is inferred that the safe clinical implementation of AI requires rigorous multicenter external validations and the development of clear ethical-regulatory guidelines, acting as a complement to medical judgment and democratizing access to visual care.

Keywords: Artificial Intelligence, Ophthalmology, Screening, Algorithms, External Validation.

INTRODUCTION

Ophthalmic diseases represent a substantial challenge to global public health, accounting for high rates of morbidity and preventable vision loss. In settings characterized by a shortage of medical specialists and geographical or socioeconomic barriers, timely access to diagnosis and early treatment becomes limited, overburdening healthcare systems and worsening patient prognosis.¹

In this context, the integration of new technologies has driven the development of innovative strategies for population screening. Artificial intelligence (AI), particularly through deep learning algorithms, has emerged as a transformative force in contemporary ophthalmology.² The use of these tools in combination with teleophthalmology has demonstrated a strong capacity to analyze fundus photographs and stratify risks with high accuracy, optimizing the care pathway for highly prevalent

conditions such as diabetic retinopathy, glaucoma, and age-related macular degeneration.^{3,4}

Despite the promising results achieved during the development phase in controlled environments, the scientific literature raises questions regarding the safety and effectiveness of these tools in real-world settings. Algorithm performance often declines when exposed to new populations, different image acquisition protocols, or variations in equipment, constituting a technical challenge known as domain shift.⁵

Therefore, understanding the limitations and accuracy of these technologies is particularly relevant. Assessing the robustness of AI models through external validation processes is essential to ensure that their incorporation into large-scale screening programs occurs safely, reliably, and equitably, without compromising the quality of care provided to patients.^{6,7}

OBJECTIVES

Perinatal hemolytic disease (PHD) is defined as an immunological condition resulting from incompatibility between antigens present on fetal red blood cells and specific maternal antibodies, leading to the destruction of these blood cells either during intrauterine life or in the early neonatal period. This incompatibility occurs predominantly when the mother is previously sensitized to erythrocyte antigens inherited by the fetus from the father.²

The maiGeneral Objective:

- To analyze the robustness, diagnostic performance, and generalizability of artificial intelligence algorithms designed for population screening of ophthalmic diseases, based on scientific evidence compiled from the literature.

Specific Objectives:

- To classify the deep learning models and the respective ocular diseases mapped in the included studies, outlining the current landscape of technological tools applied to visual health.
- To distinguish the variability in diagnostic accuracy indicators (sensitivity, specificity, and area under the ROC curve) of AI tools according to different diseases, such as diabetic retinopathy, glaucoma, retinopathy of prematurity, and age-related macular degeneration.
- To enumerate the main methodological limitations and ethical and technical challenges reported, with particular emphasis on the phenomenon of domain shift and technical dependence on the quality of the images acquired.
- To select perspectives for future clinical applicability and the public health impact resulting from the integration of these algorithms with primary care and teleophthalmology systems.

METHODS

The present article is characterized as an integrative literature review of a qualitative and exploratory nature, focused on the validation of Artificial Intelligence (AI) algorithms applied to population screening for ophthalmic diseases. Data collection was conducted in May 2026 through a systematic search of Google Scholar, PubMed, ResearchGate, and the CAPES Journal Portal databases, selected for their coverage of high-impact journals and access to recent scientific publications on diagnosis in visual health.

The search strategy employed controlled descriptors and technical terms in Portuguese and English, combined with basic Boolean operators ("Artificial Intelligence" AND "Ophthalmology", "AI algorithms" AND

“Screening” AND “Retina”), in order to ensure the intersection between technology and clinical practice, as well as the grouping of terminological variations such as deep neural networks and machine learning.

The inclusion criteria comprised original articles and reviews published between 2018 and 2025 that specifically addressed the accuracy, sensitivity, and specificity of AI tools in screening settings. After the initial search, titles and abstracts were analyzed to exclude duplicate studies or those without validated data on algorithmic performance. The selected texts were read in full, allowing the synthesis of the main external validation models and evidence regarding the feasibility of these technologies in public healthcare systems and mass screening programs.

RESULTS AND DISCUSSIONS

• Characterization of the Included Studies

Ten studies published between 2018 and 2025 were included, comprising original diagnostic validation studies, observational studies, and literature reviews. The main characteristics of the included studies are presented in Table 1. There was a predominance of research focused on the application and validation of artificial intelligence (AI) algorithms in retinal diseases, with other ophthalmic conditions addressed less frequently.

Table 1: Characterization of the Included Studies.

Author/year	Type of study	Did the study validate the algorithm?	Country/Setting
Pionório et al., 2024	Integrative review	N/A	N/A
Checon et al., 2025	Qualitative/exploratory research	N/A	N/A
Mamprin et al., 2025	Narrative review	N/A	Primary health care
Arenas-Cavalli et al., 2021	Observational clinical validation study	Yes	Chile; national health system
Han et al., 2022	Prospective validation study	Yes	China; hospital and community
Coyner et al., 2022	Diagnostic study with multicenter external validation	Yes	India, Nepal, and Mongolia; telemedicine program
Zapata et al., 2020	Retrospective study	Yes	Spain; teleophthalmology
Kuiava et al., 2021	Development/validation study	Yes	Brazil; teleophthalmology
Chen et al., 2025	Diagnostic study with workflow	Yes	USA and Singapore
Chen et al., 2021	Observational development/validation study	Yes	Taiwan

Source: Pionório et al., 2024; Checon et al., 2025; Mamprin et al., 2025; Arenas-Cavalli et al., 2021; Han et al., 2022; Coyner et al., 2022; Zapata et al., 2020; Kuiava et al., 2021; Chen et al., 2025; Chen et al., 2021.³⁻⁴⁻⁸⁻¹⁴

Table 2: Description and Results of the Studies.

Author/year	Disease/Application	AI Model	Main Contribution
Pionório et al., 2024	Focus on diabetic retinopathy and glaucoma	IDx-DR, Eyer, and other systems	Reinforces the role of AI in democratizing diagnosis and providing clinical support
Checon et al., 2025	Focus on diabetic retinopathy, glaucoma, and age-related macular degeneration	Synthesis of studies on deep learning	Highlights the low diversity of databases and the need for local validation
Mamprin et al., 2025	Diabetic retinopathy screening	Deep learning	High diagnostic performance and potential to reduce costs
Arenas-Cavalli et al., 2021	Diabetic retinopathy screening	DART system with convolutional networks	Sensitivity of 94.6%, specificity of 74.3%; feasibility of application in a heterogeneous public healthcare network
Han et al., 2022	Referable diabetic retinopathy, retinal macular disease, and suspected glaucoma	AI-100 (deep learning)	Robustness in real-world settings, but with domain shift across cameras and populations
Coyner et al., 2022	Retinopathy of prematurity screening	Based on gestational age and vascular severity score (VSS)	Sensitivity of 100% in all three settings and an estimated 38–51% reduction in examinations
Zapata et al., 2020	Identification of image quality, laterality, age-related macular degeneration, and suspected glaucoma	5 deep learning algorithms / convolutional neural network	High accuracy for multiple tasks; useful for the screening workflow
Kuiava et al., 2021	Glaucoma, diabetic retinopathy, ocular toxoplasmosis, papilledema, retinal detachment, normal retina	MobileNet and Inception	Sensitivity ~91% and specificity ~98%; useful as a screening support tool
Chen et al., 2025	Diagnosis/classification of age-related macular degeneration	DeepSeeNet and DeepSeeNet+	Increased accuracy for 23/24 clinicians; reduced diagnostic time; reinforces the need for accountability
Chen et al., 2021	Eyelid measurements for ptosis: MRD1, MRD2, and LF	MAIA software and convolutional networks	Demonstrates the application of AI via smartphone for objective and rapid measurement

Source: Pionório et al., 2024; Checon et al., 2025; Mamprin et al., 2025; Arenas-Cavalli et al., 2021; Han et al., 2022; Coyner et al., 2022; Zapata et al., 2020; Kuiava et al., 2021; Chen et al., 2025; Chen et al., 2021.³⁻⁴⁻⁸⁻¹⁴

Overall, there was a predominance of deep learning-based algorithms applied to the analysis of fundus photographs, with a primary focus on diabetic retinopathy, retinopathy of prematurity, age-related macular degeneration (AMD), and suspected glaucoma.⁸⁻¹⁴ Despite the methodological differences observed, the studies converged in assessing the potential of AI to support screening processes and expand access to ophthalmic care, frequently in teleophthalmology and large-scale screening settings.^{4,8-11} In parallel, the included reviews reinforced these general trends, particularly regarding the prospects for incorporating these tools into visual health programs.^{3,4}

• Performance of AI Algorithms

The studies analyzed demonstrated high overall performance for AI algorithms, as evidenced by high sensitivity, specificity, and area under the ROC curve values, reinforcing the potential of these

tools for use in screening programs and clinical decision support.⁹⁻¹⁴

Diabetic retinopathy (DR) was the condition for which this performance was most stable. In a primary care and population-based DR screening context,⁸ deep learning-based systems were described as having accuracy above 90%, accompanied by sensitivity and specificity of approximately 95%, as well as the potential to reduce the costs of manual screening.⁸ In the clinical validation conducted in Chile,⁹ the DART system showed a sensitivity of 94.6%, specificity of 74.3%, and AUC of 0.915 in 1,123 diabetic eye examinations, suggesting applicability within a heterogeneous national healthcare network.⁹ Meanwhile, in a real-world community and hospital setting in China,¹⁰ AI-100 also demonstrated robust performance for referable diabetic retinopathy, with a sensitivity of 95%, specificity of 96.3%, and AUC of 0.954.¹⁰ Thus, the findings demonstrate that AI has high potential for DR screening, particularly in population-based programs and teleophthalmology.

In retinopathy of prematurity, the ability to anticipate risk was particularly noteworthy. The model based on gestational age and vascular severity score¹¹ maintained consistent performance across the populations evaluated, with a sensitivity of 100% in all three cohorts, specificity of 63.3% in India, 77.8% in Nepal, and 45.8% in Mongolia, as well as an AUC of 0.919 in 5-fold cross-validation and 0.944 in the validation set. This performance allowed early identification of cases that would progress to require treatment, reinforcing the role of AI not only as a diagnostic tool but also as a predictive resource in a setting in which early detection has a direct impact on visual prognosis.¹¹

Studies evaluating AI for glaucoma or suspected glaucoma showed favorable performance, although it was more heterogeneous than that observed for retinal diseases.^{10,12,13} In a Spanish database containing more than 300,000 images,¹² deep learning models achieved an AUC of 0.863, accuracy of 80.2%, sensitivity of 76.8%, and specificity of 83.8% for suspected glaucomatous neuropathy, maintaining applicability for screening, although with lower performance than for other diseases analyzed in the same study. In contrast, the AI-100 algorithm¹⁰ showed superior performance in a real-world clinical setting, with a sensitivity of 95%, specificity of 94.6%, and AUC of 0.976 for suspected glaucoma, in a validation environment involving different cameras and healthcare settings. Similarly high results were observed with the Brazilian screening software,¹³ whose MobileNet and Inception models achieved sensitivities ranging from 93.33% to 96.55% and specificities above 99% for glaucoma. Taken together, these studies suggest that AI has significant potential for glaucoma screening, although performance varies according to image quality, population characteristics, and database composition.^{10,12,13}

For AMD, the results were also consistent, both for disease detection and for specialist support.^{12,14} In the study conducted in Spain,¹² deep learning models achieved an AUC of 0.936, accuracy of 86.3%, sensitivity of 90.2%, and specificity of 82.5%, indicating effective discrimination between affected and unaffected individuals. A multicenter study evaluated an AI-assisted workflow for the diagnosis and severity classification of AMD.¹⁴ In this study, AI assistance increased the clinicians' mean F1-score from 37.71 to 45.52 and reduced the estimated diagnostic time, although the lower performance observed in the external Singapore cohort suggests potential limitations in generalizability even for promising models. Thus, AMD appears to be a condition in which AI can support both detection and severity stratification, but further refinement is still required for broader use in more diverse populations.^{12,14}

In addition to applications targeting specific diseases, some studies demonstrated the potential of AI for use in a variety of ophthalmic settings.^{13,15} The Brazilian software developed for automated classification of fundus diseases¹³ demonstrated the ability to identify other ophthalmic conditions beyond glaucoma and diabetic retinopathy, including ocular toxoplasmosis, papilledema, retinal

detachment, and normal images, achieving an overall sensitivity above 91% and specificity close to 99% for the MobileNet and Inception architectures. Similarly, a system based on smartphone-acquired photographs for automated measurement of eyelid parameters¹⁵ showed high agreement with assessments performed by specialists, with high correlations for MRD1, MRD2, and levator muscle function. Taken together, these results suggest that AI can be used not only for retinal disease screening but also as a multimodal tool for diagnostic support, telemedicine, and objective standardization of clinical measurements in ophthalmology.^{13,15}

• External Validation and Model Generalizability

External validation emerged as one of the main criteria for assessing the clinical applicability of AI algorithms.^{4,14} The studies analyzed showed that high performance indicators obtained during development do not, by themselves, guarantee equivalent results when models are applied to different populations or exposed to factors such as epidemiological differences, image quality, acquisition protocols, and variations among equipment.^{9,10} In this context, even algorithms with high performance in their training datasets may show reduced performance in external settings, a phenomenon known as domain shift.⁵ Thus, robustness, reliability, and adaptability are as important as diagnostic performance itself,^{4,14} reinforcing the need for independent and multicenter validation before large-scale adoption, particularly in population-based screening programs and public healthcare systems.⁷

The included studies employed different external validation strategies, particularly multicenter validations in independent populations,^{11,14} analyses at different levels of healthcare,¹⁰ and tests performed using different image acquisition equipment.^{9,10} Less frequently, there were also evaluations focused on integrating the models into real-world clinical workflows, not only to assess diagnostic performance but also their practical utility.¹⁴ Taken together, these approaches made it possible to assess the ability of the algorithms to maintain performance and applicability outside the environment in which they were originally developed.^{10,11,14}

Among the strategies employed, multicenter validations provided the most robust evidence of generalizability, demonstrating maintenance of performance even in the presence of epidemiological, operational, and technological differences.^{10,11} However, the reduction in performance observed in some external cohorts indicates that generalizability remains a relevant challenge for some of the models evaluated.¹⁴ These findings reinforce that external validation should be understood as a fundamental requirement for the safe incorporation of AI into ophthalmic screening programs.^{4,14,16}

• Clinical Applicability and Public Health Impact

The included studies demonstrated that the main clinical contribution of AI to ophthalmology is related to expanding screening capacity and improving healthcare workflows.^{3,4,8} In practical terms, the algorithms showed potential for the early identification of individuals at higher risk of ocular disease, thereby facilitating timely referral and reducing the burden on referral services.⁹⁻¹¹ This potential was observed particularly in screening programs for highly prevalent diseases, in which AI was frequently proposed as a complementary tool for primary care and teleophthalmology.^{4,8,9,17}

Another recurring aspect was the rationalization of healthcare resources.^{4,8} The studies suggest that incorporating AI systems may contribute to reducing unnecessary examinations and improving the allocation of the specialized workforce.^{8,11} In some settings, a potential reduction in healthcare workload was observed without compromising diagnostic sensitivity, positioning these technologies as tools to support the management of screening programs.^{10,11,14,18,19}

The relevance to public health was particularly evident in settings characterized by a shortage of ophthalmologists and difficulties in accessing specialized services.^{3,4,11} In this regard, the integration of AI, teleophthalmology, and digital platforms was identified as a strategy capable of expanding diagnostic coverage and strengthening prevention programs, particularly in regions with geographical barriers to access.^{3,4,9} In vulnerable populations and healthcare systems with limited resources, these algorithms emerge as a concrete means of expanding ophthalmic care.^{1,4,8,11,17}

• Methodological Limitations and Ethical-Technical Challenges

Despite the promising results of the included studies, several methodological limitations were identified and should be considered when interpreting the findings. The main limitation was the heterogeneity among the studies, which differed in terms of the diseases evaluated, population characteristics, methodological structures, equipment used, and reported performance metrics.^{3,4} In addition, the algorithms were developed for different purposes, such as screening, severity classification, risk prediction, and clinical decision support, which makes direct comparisons difficult and limits the standardization of the available evidence.^{3,4,20}

Another critical issue was the dependence of the algorithms on the quality of the data used.^{9,10,11} The studies highlighted that factors such as image quality, differences among equipment, acquisition protocols, and specific characteristics of the populations evaluated can significantly influence model performance.^{9-11,14} This variability favors the occurrence of domain shift, demonstrating that the reliability of the algorithms remains directly related to the quality and representativeness of the data used in their training and application.^{10,14,21}

Regarding ethical and regulatory aspects, the studies raised concerns related to model interpretability, the limited diversity of certain training datasets, the risk of algorithmic bias, and the definition of clinical responsibilities in cases of diagnostic error.^{4,14} Issues related to data governance, system transparency, and the need for continuous professional oversight were also highlighted.^{4,14,22,23} Therefore, the safe implementation of these technologies depends not only on the technical performance of the algorithms but also on regulatory and monitoring mechanisms that ensure their safety, reliability, and equitable use across different clinical application settings.^{4,14,24}

• Perspectivas futuras

The future perspectives identified in the studies converge toward the consolidation of AI as a tool integrated into ophthalmic healthcare workflows,^{2-4,14} which requires advances related to algorithm robustness, generalizability, and validation.^{4,14} In this regard, priorities include conducting prospective, multicenter studies in more diverse populations, as well as increasing the representativeness of the datasets used for training and validation.^{4,11,14} These measures are essential to increase system reliability and reduce limitations related to domain shift and selection bias, particularly when these models are intended for incorporation into different healthcare settings.^{4,6,10,14}

Another recurring trend is the integration of artificial intelligence, teleophthalmology, and established clinical workflows.^{3,4,14} The studies suggest that the future of these technologies is less related to replacing specialists and more to developing tools capable of supporting decision-making, optimizing screening programs, and expanding access to ophthalmic care.^{4,8,14,25} Thus, aspects such as algorithm interpretability, continuous performance monitoring, and safe integration into healthcare systems are likely to play a central role in consolidating AI as a complementary strategy for the prevention, detection, and management of ophthalmic conditions.^{4,14,26,27}

CONCLUSION

The review showed that artificial intelligence algorithms, particularly those based on deep learning applied to the analysis of ophthalmic images, demonstrate high performance for the screening and diagnostic support of various ocular diseases. Studies conducted on diabetic retinopathy, retinopathy of prematurity, age-related macular degeneration, and glaucoma generally demonstrated high sensitivity, specificity, and area under the ROC curve values. Among these diseases, the population-based screening model and its application in primary care for the detection of diabetic retinopathy achieved the best results among the diseases analyzed, with high rates of accuracy, specificity, and sensitivity. This analysis reinforces the potential of these tools to expand screening capacity, optimize healthcare workflows, and facilitate the early detection of conditions associated with preventable vision loss.

However, the findings also demonstrate that performance obtained exclusively in development datasets does not guarantee the clinical applicability of the models, since limiting factors such as image quality, diversity, dataset size, and differences among the technological equipment used represent relevant challenges for the safe implementation of these technologies. In this regard, external validation proved to be a fundamental step in assessing the robustness, reliability, and generalizability of algorithms across different populations, epidemiological contexts, and operational conditions.

In addition to its high diagnostic potential, AI proved to be a tool with great potential to contribute to expanding access to ophthalmic care, particularly when integrated with ophthalmic teleconsultation and large-scale screening programs, potentially benefiting populations with limited access to specialists. However, its effective incorporation into healthcare systems requires addressing methodological, ethical, and regulatory issues related to model transparency, bias mitigation, clinical supervision, regulation, and data security.

Therefore, artificial intelligence represents a promising and potentially transformative tool for contemporary ophthalmology. However, the future of AI in the specialty does not point toward replacing clinical judgment, but rather toward its use as a tool to support greater diagnostic efficiency.

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VITILIGO: NEW THERAPEUTIC APPROACHES BASED ON IMMUNE PATHOPHYSIOLOGY

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ABSTRACT

Vitiligo is a chronic autoimmune skin disease characterized by the progressive destruction of melanocytes, resulting in a profound psychosocial impact. Historically challenging, therapeutic management has been revolutionized by recent discoveries in the field of immune pathophysiology, as the disease is mediated by autoreactive cytotoxic CD8+ T cells and the Janus Kinase/Signal Transducer and Activator of Transcription (JAK/STAT) signaling pathway, activated by interferon-gamma (IFN- γ). Therefore, the present literature review aimed to analyze new therapeutic approaches based on this immune pathophysiology, encompassing studies from 2016 to 2026 selected from the PubMed/MEDLINE, Embase, Cochrane, and Web of Science databases. The findings demonstrate that the recognition of the JAK/STAT pathway has enabled the development of targeted immunomodulators with highly promising results. Topical ruxolitinib stands out as the first JAK inhibitor drug approved for the treatment of vitiligo, showing consistent and clinically significant repigmentation, particularly in facial lesions. Concurrently, systemic JAK inhibitors, such as baricitinib, ritlecitinib, and upadacitinib, show promising clinical results, with even more notable synergistic effects when combined with phototherapy. Biological therapies and mesenchymal stem cells are also emerging as viable alternatives. It is concluded that the transition from empirical treatments to interventions targeted at the pathophysiology of the disease represents a transformative advancement in the treatment of vitiligo. However, gaps in clinical evidence persist, especially regarding long-term outcomes and pediatric populations, demanding the need for further and deeper research, primarily focused on identifying biomarkers and eliminating resident memory T cells, in order to prevent long-term relapses.

Keywords: Dermatology, Immunological factors, Immunomodulation, Janus kinase inhibitors, Vitiligo.

INTRODUCTION

Vitiligo is a chronic autoimmune skin disease characterized by the progressive destruction of melanocytes, resulting in visible depigmented patches on the skin. It affects approximately 0.5% to 2.0% of the global population, with a significant impact on patients' quality of life due to the associated psychosocial burden.¹

Although it does not affect life expectancy, vitiligo imposes a profound psychosocial impact, with more than half of patients presenting moderate to severe depressive symptoms and high rates of diagnosed anxiety.² The impairment in quality of life is particularly pronounced in patients with facial or

hand lesions, greater extent of affected body surface area, and darker skin phototypes.^{2,3}

Historically, the therapeutic management of vitiligo has been challenging. Conventional options include topical and systemic corticosteroids, calcineurin inhibitors, and narrowband ultraviolet B phototherapy (NB-UVB).⁴⁻⁶ However, many patients, particularly those with extensive or refractory disease, are unable to achieve satisfactory or lasting repigmentation.⁴ The clinical course is further complicated by high relapse rates and heterogeneous treatment responses at different anatomical sites.⁴

Over the past two decades, significant advances in the understanding of the immunological pathophysiology of vitiligo have transformed the therapeutic landscape.⁷⁻⁹

Studies have demonstrated that the disease is mediated by autoreactive cytotoxic CD8+ T lymphocytes that destroy melanocytes through the local production of interferon-gamma (IFN- γ), a central cytokine that activates the Janus kinase/signal transducer and activator of transcription (JAK/STAT) signaling pathway.⁸⁻¹⁰ In this regard, this pathway promotes the secretion of chemokines that recruit T cells to the skin, perpetuating a self-sustaining inflammatory cycle.^{8,10} Additionally, epidermal resident memory T cells are responsible for disease relapse after treatment discontinuation.⁸

In this context, recognition of the JAK/STAT pathway as a central mechanism in melanocyte destruction paved the way for the development of targeted therapies.^{4,5,9} JAK inhibitors have emerged as a promising therapeutic strategy, with topical ruxolitinib (a JAK1/JAK2 inhibitor) becoming the first medication approved specifically for repigmentation in vitiligo.^{4,10,11} Phase III clinical trials demonstrated clinically significant repigmentation, particularly in facial lesions.¹⁰ In turn, oral JAK inhibitors, including ritlecitinib, upadacitinib, and povorcitinib, are currently in phase II and III clinical trials, with promising results as monotherapy or in combination with phototherapy.^{1,4,5}

Given the recent advances in the understanding of the immunological pathophysiology of vitiligo, particularly the role of the JAK/STAT pathway, pro-inflammatory cytokines, and autoreactive T cells in melanocyte destruction, new targeted therapeutic strategies have been developed and incorporated into clinical practice. Despite the growing number of studies on these approaches, there is still a need to critically integrate the evidence related to the immunological mechanisms of the disease and the clinical outcomes of emerging therapies. In this context, the present review brings together and analyzes the most recent scientific evidence on new therapeutic approaches for vitiligo, with an emphasis on JAK inhibitors and other promising immunomodulatory strategies, discussing their perspectives, limitations, and potential applications in the contemporary management of the disease.

OBJECTIVES

• General objective:

Analyze the available scientific evidence on new therapeutic approaches for vitiligo based on the understanding of the immunological pathophysiology of the disease, with emphasis on Janus kinase (JAK) inhibitors and other emerging immunomodulatory strategies, based on studies published between 2016 and 2026.

• Specific objectives:

1. Describe the immunological mechanisms involved in the pathogenesis of vitiligo, with emphasis on the JAK/STAT pathway and the role of cytotoxic CD8+ T cells and IFN- γ .
2. Evaluate the efficacy and safety of topical and systemic JAK inhibitors in the treatment of vitiligo,

based on randomized controlled clinical trials.

3. Identify other emerging immunomodulatory therapies and their therapeutic potential in the management of vitiligo.
4. Discuss future perspectives and challenges in the development of targeted treatments for vitiligo.

METHODOLOGY

OR “tofacitinib” OR “upadacitinib” OR “ritlecitinib” OR “povorcitinib”) AND (“treatment” OR “therapy” OR “repigmentation”) AND (“immunopathogenesis” OR “interferon-gamma” OR “IFN-gamma” OR “JAK-STAT pathway” OR “CD8 T cells” OR “CXCL10” OR “autoimmune”). Additionally, the reference lists of the selected articles were consulted to identify relevant complementary studies.

The inclusion criteria were:

- (a) randomized clinical trials, systematic reviews, meta-analyses, clinical guidelines, and phase II and III studies published between 2016 and 2026;
- (b) publications in English and Portuguese;
- (c) studies addressing the immunological pathophysiology of vitiligo, with a focus on the JAK/STAT pathway and T-cell-mediated mechanisms;
- (d) studies on emerging immunomodulatory therapies;
- (e) systematic reviews and meta-analyses on vitiligo treatment;
- (f) international consensus guidelines for the management of vitiligo;
- (g) studies on biomarkers and mechanisms of relapse.

The exclusion criteria, in turn, included:

- (a) articles published before 2016;
- (b) isolated case reports without relevance to the understanding of therapeutic mechanisms;
- (c) studies in animal models without clinical correlation;
- (d) articles that did not specifically address the relationship between immunological pathophysiology and therapeutic approaches; (e) duplicate or retracted studies, or studies with inadequate methodology.

The initial selection was based on the reading of titles and abstracts. Potentially relevant articles were retrieved in full and assessed for eligibility. Phase II and III clinical trials, systematic reviews, meta-analyses, and international consensus guidelines were prioritized. Data extraction focused on: pathophysiological mechanisms, therapeutic agents investigated, study design, study population, efficacy outcomes (including repigmentation indices such as F-VASI, from the English Facial Vitiligo Area Scoring Index, or Facial Vitiligo Area Scoring Index, and T-VASI, from the English Total Body Vitiligo Area Scoring Index, or Total Vitiligo Area Scoring Index), safety and tolerability profile, and main conclusions.

RESULTS AND DISCUSSION

Immunological Pathophysiology of Vitiligo and the Jak/Stat Pathway

The modern understanding of the pathophysiology of vitiligo establishes the disease as an autoimmune disorder mediated by cytotoxic CD8⁺ T cells that destroy melanocytes.^{7,8,12} Genetic predisposition and increased melanocyte vulnerability to stressors lead to a specific immune response against these melanocytes, associated with an interferon-gamma-mediated immune signature.¹³

IFN- γ plays a central role in the pathogenesis of vitiligo, signaling through the JAK-STAT pathway. 10 This pathway is activated by key cytokines, including IFN- γ and interleukin 15 (IL-15), which sustain cytotoxic T-cell infiltration and melanocyte apoptosis.⁴ Keratinocytes detect IFN- γ in vitiligo lesions and are the main producers of Monokine Induced by Gamma Interferon (CXCL9) and Interferon Gamma-Induced Protein 10 (CXCL10), chemokines that promote T-cell recruitment. 14 This process creates a positive feedback loop: autoreactive CD8⁺ T cells engage melanocytes and promote disease progression through the local production of IFN- γ , and IFN- γ -induced chemokines are then secreted by surrounding keratinocytes to recruit even more T cells to the skin.⁸

In addition, JAK inhibitors target the pathway through which resident memory T cells become dependent on IL-15 for their survival as they establish residence in the epidermis. 1 These autoreactive cells are precisely those responsible for disease relapse after treatment discontinuation. In view of this, new therapeutic strategies focus specifically on eliminating these cells to promote lasting benefit.⁸

Furthermore, new studies suggest that the immune response in vitiligo is not restricted to IFN- γ , but may be associated with a type 2 immune response, evidenced by increased IL-13 production. 1 This immunological complexity highlights the need for therapeutic approaches capable of modulating multiple inflammatory pathways.

Topical Jak Inhibitors: Ruxolitinib

Topical ruxolitinib represents the first JAK inhibitor approved for the treatment of vitiligo. 4,10,13 As a JAK1 and JAK2 inhibitor, ruxolitinib cream has demonstrated consistent and clinically significant efficacy in phase 2 and 3 clinical trials.^{10,14}

Specifically, in the randomized controlled phase II study, ruxolitinib cream resulted in repigmentation over 52 weeks in adults with vitiligo. 14 Among patients who applied 1.5% ruxolitinib cream twice daily, 45% achieved at least a 50% improvement from baseline in the Facial Vitiligo Area Scoring Index (F-VASI) at week 24 (primary endpoint), and 30% achieved a reduction of at least 75%, with continued improvement through week 52.¹⁰

Additionally, 45% of patients with a baseline total body surface area of 20% or less (and who therefore could treat all depigmented skin) who received 1.5% ruxolitinib cream twice daily achieved a 50% or greater improvement from baseline in the Total Vitiligo Area Scoring Index (T-VASI50; total body assessment, including the face) at week 52.¹⁴

Two phase III clinical trials (Topical Ruxolitinib Evaluation in Vitiligo Study 1 and Study 2 - TRuE-V1 and TRuE-V2) were conducted in adolescents and adults with nonsegmental vitiligo. 10 These studies confirmed the efficacy of topical ruxolitinib, demonstrating consistent and clinically significant repigmentation, particularly in facial lesions.^{4,10}

The safety profile of topical ruxolitinib is favorable, with application-site reactions being rare during treatment.¹⁴ Topical agents are generally well tolerated with minimal systemic absorption, making them an attractive option for patients with localized disease, especially involving the face and less than 10% of body surface area.^{1,4}

In addition, topical ruxolitinib is approved in Europe through the European Medicines Agency (EMA) and in the United States through the Food and Drug Administration (FDA), for use in adolescents aged 12 years and older and adults with nonsegmental vitiligo and facial involvement.¹³ To date, the medication has not yet been approved by the Brazilian Health Regulatory Agency (ANVISA) for use in Brazil.

Systemic Jak Inhibitors

As systemic therapy, oral JAK inhibitors may have advantages over topical treatments for rapidly stabilizing the disease in patients with very active disease and when larger areas are involved. 1 The following stand out:

- **Baricitinib:** a recent randomized clinical trial evaluated the combination of baricitinib and phototherapy in adults with active vitiligo. 1 Baricitinib, a JAK1/JAK2 inhibitor, demonstrated clinical benefit in the management of vitiligo, particularly when combined with NB-UVB phototherapy. 1 This study highlights the potential of systemic therapies for patients with extensive or rapidly progressive disease.

- **Ritlecitinib:** ritlecitinib: a JAK3/TEC inhibitor (tyrosine kinase expressed in hepatocellular carcinoma), showed promising efficacy, either as monotherapy or in combination with NB-UVB phototherapy. 1,4 Ongoing phase III clinical trials should further define its role in clinical practice.⁴

- **Upadacitinib and Povorcitinib:** these JAK1 inhibitors have also demonstrated promising efficacy in clinical studies. 4,15 Upadacitinib has been described in previous reports as providing clinical benefit in the management of vitiligo, and povorcitinib is being evaluated in phase II and III clinical trials.^{1,15}

- **Other agents:** tofacitinib, abrocitinib, and other JAK inhibitors are currently under investigation or being used off-label in clinical practice. 1,4 Although JAK inhibitors demonstrate high rates of repigmentation, optimal results may take several months to years.⁹

JAK inhibitors exhibit variable safety profiles depending on selectivity, formulation, and dose. 4 While topical agents are generally well tolerated with minimal systemic absorption, oral JAK inhibitors require monitoring due to potential risks of infection, hematological abnormalities, and cardiovascular events.⁴

Combination of Jak Inhibitors With Phototherapy

The influence of environmental ultraviolet (UV) exposure on repigmentation in patients receiving immunomodulatory medications remains largely unexplored. 9 However, the combined effect of phototherapy with JAK inhibitors is striking and suggests that targeted immune treatment may still require additional melanocyte stimulation for repigmentation.⁹

Several studies have demonstrated that the combination of JAK inhibitors with NB-UVB phototherapy may produce superior results compared with monotherapy.^{1,4,9} This combined approach allows both suppression of the autoimmune response and stimulation of melanocyte proliferation and migration from follicular reservoirs.

Other Emerging Immunomodulatory Therapies

Considering recent advances in the understanding of the pathophysiology of vitiligo, a number of other immunomodulatory therapies have been developed and studied, including:

- **Biological Therapies:** monoclonal antibodies targeting specific cytokines are being investigated for the treatment of vitiligo.^{5,15} Anifrolumab, an anti-type I interferon monoclonal antibody, is being evaluated in phase II and III clinical trials.¹⁵ However, treatment results with biologics have been more variable compared with JAK inhibitors.⁵

- **Mesenchymal Stem Cells (MSCs):** MSCs regulate cytokine secretion and the balance of T-cell subsets, making them a promising cell-based treatment option for autoimmune diseases.¹² The induction of MSC-mediated immunomodulation is complex and occurs through contact-dependent mechanisms and soluble extracellular vesicle (EV) mediators containing various growth factors and cytokines with anti-inflammatory effects on the cutaneous immune response.¹² Although promising, these therapies

still require additional in vitro studies and extensive clinical research involving a larger population.⁵

- **Other Approaches:** minimally invasive procedures, such as fractional lasers or microneedling, may help achieve optimal treatment outcomes when appropriately used. In addition, identifying alternative melanocyte stimulants beyond UV light remains crucial for the future management of vitiligo.⁹

International Consensus Guidelines

The International Vitiligo Task Force, composed of 42 international vitiligo experts and four patient representatives, developed the most comprehensive and up-to-date consensus recommendations for the diagnosis and management of vitiligo in 2023.^{6,17} These guidelines represent a milestone in the standardization of global disease management, emphasizing the importance of shared decision-making between physician and patient, with detailed explanations regarding prognosis and expected therapeutic outcomes based on clinical examination.¹⁷

The guidelines establish that assessment of disease activity remains a cornerstone of the personalized approach to patients with vitiligo.¹⁷ Treatment should be discussed considering different goals: disease stabilization versus repigmentation, recognizing that vitiligo generally requires a long-term approach.¹⁷ Treatment choice is individualized based on disease extent, stability, cost, accessibility, and response to previous therapy.¹⁸

The recommendations summarize the most recent evidence on the use of topical corticosteroids (TCS), topical calcineurin inhibitors (TCI), and topical JAK inhibitors (tJAKi).⁶ Topical calcineurin inhibitors, particularly tacrolimus, are recommended as first-line therapy for vitiligo in children, adolescents, and young adults, with a robust level of evidence (A1-A2, level 1-2).¹⁹ Pimecrolimus is also supported as first-line therapy, although with a slightly lower level of evidence than tacrolimus (A2, level 2).¹⁹ In turn, 1.5% ruxolitinib cream, as previously discussed, emerges as an important tool for achieving consistent and clinically significant repigmentation, particularly in facial lesions.⁴

Guidelines from the European Dermatology Forum and the Vitiligo Japanese Task Force recommend combination therapies with phototherapy as first-line treatment for vitiligo.²⁰ The European Dermatology Forum recommends NB-UVB, excimer light combined with topical corticosteroids or topical immunomodulators, while the Japanese task force recommends NB-UVB, UV-A photochemotherapy combined with topical corticosteroids or topical vitamin D analogues. 20

Along these lines, the guidelines recommend, during the unstable phase of the disease, aggressive therapy aimed at halting progression, using low-dose oral minipulse therapy together with standard topical therapy with steroids, topical calcineurin inhibitors, or vitamin D3 analogues.¹⁸ Stabilization therapy in some patients may include other immunosuppressive agents such as low-dose methotrexate, azathioprine, cyclosporine, or mycophenolate mofetil. 18 JAK inhibitors may be used as stabilization therapy.¹⁸

Additionally, interventional approaches, including surgical therapies, are presented for specific indications, particularly for stable vitiligo lesions in which medical therapy fails to induce repigmentation.^{6,18}

Challenges and Future Perspectives

Despite significant advances, gaps in the clinical evidence remain, especially regarding long-term outcomes and pediatric populations.⁷ Bibliometric analysis of research on vitiligo treatment from 2005 to 2025 revealed a gradual transition from traditional therapies, such as corticosteroids and phototherapy, to targeted immune strategies.⁷ Annual scientific output increased at a compound growth rate of 7.27%, reflecting the growing interest in this area.⁷

Disease relapse after treatment discontinuation remains a significant challenge.^{4,8} New therapeutic strategies focus on eliminating autoreactive resident memory T cells to promote lasting benefit.⁸ In this context, identifying predictive biomarkers of patients who are responsive to treatment with JAK inhibitors would be of considerable value and warrants continued investigation.¹⁴

CONCLUSION

Advances in the understanding of the immunological pathophysiology of vitiligo, especially the role of the JAK/STAT pathway and IFN- γ -mediated cytotoxic CD8⁺ T cells, have transformed the understanding of the disease and enabled the development of targeted therapies. This progress represents a paradigm shift in the management of vitiligo, with the transition from empirical approaches to more specific immunomodulatory strategies.

JAK inhibitors, particularly topical ruxolitinib, stand out as the main recent therapeutic innovation, demonstrating consistent efficacy in repigmentation, especially in facial areas. Systemic formulations and therapies combined with NB-UVB phototherapy have also shown promising results, although they still depend on long-term evidence to consolidate their efficacy and safety.

Despite these advances, some important challenges remain, including the need for long-term data, the identification of predictive biomarkers of response, and strategies for relapse prevention. Further investigation of these issues will be essential to optimize therapeutic outcomes and consolidate the new approaches in the treatment of vitiligo.

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