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MARKERS OF SEVERITY IN CHRONIC SYSTEMIC DISEASES: A SYSTEMATIC REVIEW

MARCADORES DE GRAVIDADE EM DOENÇAS SISTÊMICAS CRÔNICAS: UMA REVISÃO SISTEMÁTICA

MARCADORES DE GRAVEDAD EN ENFERMEDADES SISTÉMICAS CRÓNICAS: UNA REVISIÓN SISTEMÁTICA

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ABSTRACT

Introduction: Chronic systemic diseases represent a major cause of morbidity and mortality worldwide, and the identification of reliable markers of disease severity is essential for risk stratification, prognosis, and individualized management.

Objective: The main objective of this systematic review was to identify and critically appraise validated clinical, laboratory, imaging, and composite markers of severity across major chronic systemic diseases, with secondary objectives focused on prognostic value, clinical applicability, and implications for multidisciplinary care.

Methods: A systematic search was conducted in PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov, and ICTRP, including studies published in the last five years that evaluated severity markers in chronic systemic diseases, followed by structured data extraction and qualitative synthesis.

Results and Discussion: A total of 20 studies met the inclusion criteria, encompassing cardiovascular, metabolic, inflammatory, renal, respiratory, and autoimmune diseases, and demonstrated heterogeneous but clinically relevant markers associated with disease progression, complications, and mortality.

Conclusion: The findings highlight the growing role of integrated severity markers in guiding clinical decision-making and emphasize the need for standardized, evidence-based approaches to severity assessment in chronic systemic diseases.

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Keywords: Chronic Disease. Severity of Illness Index. Biomarkers. Prognosis.

RESUMO

Introdução: As doenças sistêmicas crônicas representam uma das principais causas de morbidade e mortalidade em todo o mundo, e a identificação de marcadores confiáveis de gravidade é essencial para a estratificação de risco, o prognóstico e o manejo individualizado.

Objetivo: O objetivo principal desta revisão sistemática foi identificar e avaliar criticamente marcadores validados de gravidade — clínicos, laboratoriais, de imagem e compostos — nas principais doenças sistêmicas crônicas. Como objetivos secundários, buscou-se analisar o valor prognóstico, a aplicabilidade clínica e as implicações para o cuidado multidisciplinar.

Métodos: Foi realizada uma busca sistemática nas bases PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov e ICTRP, incluindo estudos publicados nos últimos cinco anos que avaliaram marcadores de gravidade em doenças sistêmicas crônicas, seguida de extração estruturada dos dados e síntese qualitativa.

Resultados e Discussão: Um total de 20 estudos atendeu aos critérios de inclusão, abrangendo doenças cardiovasculares, metabólicas, inflamatórias, renais, respiratórias e autoimunes, e demonstrou marcadores heterogêneos, porém clinicamente relevantes, associados à progressão da doença, ocorrência de complicações e mortalidade.

Conclusão: Os achados destacam o papel crescente de marcadores integrados de gravidade na orientação da tomada de decisão clínica e enfatizam a necessidade de abordagens padronizadas e baseadas em evidências para a avaliação da gravidade nas doenças sistêmicas crônicas.

Palavras-chave: Doença Crônica. Índice de Gravidade da Doença. Biomarcadores. Prognóstico.

RESUMEN

Introducción: Las enfermedades sistémicas crónicas representan una de las principales causas de morbilidad y mortalidad a nivel mundial, y la identificación de marcadores confiables de gravedad es esencial para la estratificación del riesgo, el pronóstico y el manejo individualizado.

Objetivo: El objetivo principal de esta revisión sistemática fue identificar y evaluar críticamente marcadores validados de gravedad —clínicos, de laboratorio, de imagen y compuestos— en las principales enfermedades sistémicas crónicas. Como objetivos secundarios, se analizaron el valor pronóstico, la aplicabilidad clínica y las implicaciones para la atención multidisciplinaria.

Métodos: Se realizó una búsqueda sistemática en PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov e ICTRP, incluyendo estudios publicados en los últimos cinco años que evaluaron marcadores de gravedad en enfermedades sistémicas crónicas, seguida de extracción estructurada de datos y síntesis cualitativa.

Resultados y Discusión: Un total de 20 estudios cumplió con los criterios de inclusión, abarcando enfermedades cardiovasculares, metabólicas, inflamatorias, renales, respiratorias y autoinmunes, y demostró marcadores heterogéneos pero clínicamente relevantes asociados con la progresión de la enfermedad, las complicaciones y la mortalidad.

Conclusión: Los hallazgos resaltan el papel creciente de los marcadores integrados de gravedad en la orientación de la toma de decisiones clínicas y enfatizan la necesidad de enfoques estandarizados y basados en la evidencia para la evaluación de la gravedad en las enfermedades sistémicas crónicas.

Palabras clave: Enfermedad Crónica. Índice de Gravedad de la Enfermedad. Biomarcadores. Pronóstico.

1 INTRODUCTION

Chronic systemic diseases are among the leading contributors to global disability, healthcare utilization, and long-term mortality, affecting diverse populations across socioeconomic and geographic contexts.[1] These conditions are typically characterized by prolonged disease courses, fluctuating activity, and cumulative organ damage that complicate clinical management.[1] Accurate assessment of disease severity is therefore a cornerstone of modern chronic disease care, influencing diagnostic strategies, therapeutic intensity, and follow-up planning.[1] The absence of standardized severity markers across different diseases has historically limited comparability between studies and hindered personalized treatment approaches.[2]

Severity in chronic systemic diseases is a multidimensional construct that extends beyond symptom burden to include functional impairment, biological activity, and risk of adverse outcomes.[2] Traditional clinical assessment alone is often insufficient to capture the complexity of disease progression, particularly in conditions with subclinical inflammation or silent organ involvement.[2] As a result, objective markers capable of reflecting underlying pathophysiology have gained increasing relevance in both research and clinical practice.[3] The integration of such markers into routine care has the potential to improve prognostic accuracy and optimize resource allocation.[3]

Biomarkers derived from laboratory testing have been extensively investigated as indicators of disease severity in chronic systemic disorders.[3] Inflammatory markers, metabolic parameters, and organ-specific laboratory indices have shown associations with disease activity, progression, and mortality in multiple conditions.[4] However, the interpretation of isolated biomarkers is often limited by interindividual variability, comorbidities, and external influencing factors.[4] This has driven interest in composite indices and multimodal assessment tools.[4]

Imaging-based markers have emerged as valuable tools for severity assessment, particularly in diseases with structural or functional organ involvement.[5] Advances in imaging technologies have enabled earlier detection of subclinical damage and more precise monitoring of disease evolution.[5] Quantitative imaging parameters are increasingly used as surrogate endpoints in clinical trials and as prognostic indicators in routine care.[5] Nevertheless, variability in imaging protocols and limited accessibility in some settings remain important challenges.[6]

Composite severity scores that combine clinical, laboratory, and imaging variables have been proposed to address the limitations of single-parameter assessments.[6] Such scores aim to provide a more holistic representation of disease burden and future risk.[6] In

several chronic systemic diseases, validated scoring systems have demonstrated superior prognostic performance compared with isolated markers.[7] Despite these advances, heterogeneity in score composition and validation methods complicates their widespread adoption.[7]

The identification of reliable severity markers is also critical for guiding therapeutic decision-making in chronic systemic diseases.[7] Escalation or de-escalation of treatment often depends on perceived disease severity and predicted risk of complications.[8] Inaccurate severity assessment may lead to overtreatment, undertreatment, or delayed intervention, all of which can negatively impact outcomes.[8] Therefore, evidence-based severity markers are essential to support precision medicine strategies.[8]

From a research perspective, severity markers play a central role in patient stratification, outcome prediction, and comparison across clinical studies.[9] Consistent use of validated markers enhances the interpretability and external validity of research findings.[9] Regulatory agencies and clinical guidelines increasingly emphasize the incorporation of standardized severity measures in trial design and reporting.[9] This trend underscores the growing recognition of severity assessment as a fundamental component of chronic disease research.[10]

Despite the expanding body of literature on severity markers, existing evidence remains fragmented across different diseases and methodological approaches.[10] Previous reviews have often focused on single conditions or specific types of markers, limiting their generalizability.[10] A comprehensive synthesis that spans multiple chronic systemic diseases is needed to identify common principles, gaps in knowledge, and opportunities for harmonization.[11] Such an approach may facilitate cross-disciplinary learning and inform integrated models of care.[11]

In addition, the rapid evolution of biomarkers and digital health technologies has introduced novel candidates for severity assessment that require critical appraisal.[11] Wearable devices, advanced analytics, and artificial intelligence–based tools are increasingly proposed as severity markers, yet their clinical validity remains under investigation.[12] Understanding how these emerging tools compare with established markers is essential for their responsible integration into practice.[12] This systematic review was therefore designed to synthesize contemporary evidence on markers of severity in chronic systemic diseases.[12]

2 OBJECTIVES

The main objective of this systematic review was to identify, synthesize, and critically evaluate validated markers of disease severity across major chronic systemic diseases,

focusing on their prognostic value, clinical applicability, and role in guiding management decisions. The secondary objectives were: first, to classify severity markers according to their nature as clinical, laboratory, imaging, or composite indices; second, to analyze the association between identified severity markers and hard clinical outcomes such as mortality, hospitalization, and organ failure; third, to assess the consistency and reproducibility of severity markers across different populations and disease contexts; fourth, to evaluate the level of evidence and certainty supporting the use of these markers in routine clinical practice; and fifth, to identify gaps in current knowledge and propose priorities for future research aimed at standardizing severity assessment in chronic systemic diseases.

3 METHODOLOGY

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, with a predefined protocol developed to ensure methodological rigor and transparency. A comprehensive literature search was performed using the PubMed, Scopus, Web of Science, Cochrane Library, LILACS, ClinicalTrials.gov, and International Clinical Trials Registry Platform (ICTRP) databases. The search strategy combined controlled vocabulary and free-text terms related to chronic systemic diseases, severity assessment, prognostic markers, and outcomes, and was adapted for each database to maximize sensitivity. The primary time window included studies published within the last five years, with an extension to ten years planned only if fewer than ten eligible studies were identified for a given disease category.

Eligible studies included randomized controlled trials, prospective and retrospective cohort studies, and case-control studies that evaluated markers of disease severity in adults with chronic systemic diseases. Studies involving human participants were prioritized, while animal or in vitro studies were included only when directly relevant to severity mechanisms and were analyzed separately. There were no restrictions on language, geographic location, or healthcare setting. Studies with small sample sizes were not excluded a priori but were explicitly identified as having a higher risk of imprecision and were considered a limitation during synthesis. Exclusion criteria comprised narrative reviews, editorials, conference abstracts without full data, studies lacking clear severity-related outcomes, and publications with insufficient methodological detail.

Study selection was performed independently by two reviewers in two stages, consisting of title and abstract screening followed by full-text assessment. Disagreements were resolved through discussion and, when necessary, consultation with a third reviewer. Data extraction was conducted independently and in duplicate using a standardized form that

included study design, population characteristics, disease type, severity markers evaluated, outcomes assessed, main findings, and limitations. A PRISMA flow diagram was used to document the selection process and reasons for exclusion at each stage.

The risk of bias was assessed according to study design, using the Cochrane Risk of Bias 2 tool for randomized controlled trials, the ROBINS-I tool for non-randomized studies of interventions, and the QUADAS-2 tool for diagnostic accuracy studies. The overall certainty of evidence for each severity marker was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework, considering risk of bias, inconsistency, indirectness, imprecision, and publication bias. The justification for conducting a systematic review was based on the heterogeneity and fragmentation of existing evidence across different chronic systemic diseases, and full compliance with PRISMA recommendations was maintained throughout all stages of the review.

4 RESULTS

A total of twenty studies fulfilled all inclusion criteria and were included in the final qualitative synthesis.

Table 1

Characteristics of studies evaluating markers of severity in chronic systemic diseases (ordered from oldest to newest)

Reference	Population / Intervention / Comparison	Outcomes	Main conclusions
Matsushita K et al., 2021	Adults with chronic kidney disease stratified by estimated glomerular filtration rate and albuminuria categories	All-cause mortality, cardiovascular events, progression to end-stage kidney disease	Combined evaluation of renal function and albuminuria provided superior prognostic stratification and more accurately reflected disease severity.
Rapsomaniki E et al., 2021	Patients with type 2 diabetes mellitus assessed according to glycemic variability compared with mean glycated hemoglobin	Microvascular complications, macrovascular complications, mortality	Glycemic variability emerged as an independent marker of disease severity beyond average glycemic control.
Ridker PM et al., 2021	Patients with stable atherosclerotic cardiovascular disease	Major adverse cardiovascular events, cardiovascular mortality	Residual inflammatory risk identified a subgroup with higher severity despite optimal lipid management.

Reference	Population / Intervention / Comparison	Outcomes	Main conclusions
	stratified by high-sensitivity C-reactive protein levels		
Agca R et al., 2021	Patients with rheumatoid arthritis evaluated using disease activity scores and imaging markers	Cardiovascular mortality, systemic complications	Higher inflammatory burden was associated with increased systemic severity and adverse cardiovascular outcomes.
Huang C et al., 2022	Patients with chronic obstructive pulmonary disease assessed using composite severity indices compared with spirometry alone	Hospitalization, all-cause mortality	Multidimensional indices outperformed isolated pulmonary function measures in predicting disease severity.
Matsue Y et al., 2022	Patients with chronic heart failure evaluated using natriuretic peptides and congestion markers	Heart failure hospitalization, mortality	Integrated biomarker assessment improved identification of patients with more severe clinical profiles.
D'Agostino RB et al., 2022	Individuals with metabolic syndrome assessed using composite metabolic severity scores	Incident cardiovascular disease	Composite scores demonstrated robust prognostic value and reflected cumulative disease severity.
Koppe L et al., 2022	Chronic kidney disease cohorts evaluated for inflammatory and mineral metabolism biomarkers	Progression to end-stage kidney disease, mortality	Combined biomarkers identified high-risk patients earlier in the disease course.
Marques CDL et al., 2022	Patients with systemic lupus erythematosus evaluated using organ damage indices	Organ damage accrual, long-term morbidity	Damage indices were strong indicators of cumulative disease severity.
Anand IS et al., 2023	Patients with heart failure with preserved ejection fraction assessed using multimarker panels	Mortality, hospitalization	Multimarker strategies improved discrimination of disease severity.
Pugliese G et al., 2023	Patients with type 2 diabetes mellitus evaluated using renal and cardiovascular biomarkers	Composite renal-cardiovascular outcomes	Integrated severity markers predicted adverse outcomes more accurately than isolated parameters.
Gheith O et al., 2023	Patients with chronic liver disease stratified by noninvasive fibrosis scores	Decompensation, mortality	Fibrosis scores reliably stratified disease severity and prognosis.

Reference	Population / Intervention / Comparison	Outcomes	Main conclusions
Sin DD et al., 2023	Patients with chronic obstructive pulmonary disease assessed by blood eosinophil counts	Exacerbation frequency, hospitalization	Elevated eosinophil levels identified subgroups with more severe disease trajectories.
Ponticelli C et al., 2023	Patients with chronic glomerulonephritis evaluated according to proteinuria-based severity grading	Renal survival, progression	Persistent proteinuria remained a central marker of disease severity.
Krittanawong C et al., 2024	Patients with chronic coronary syndrome assessed using combined inflammatory and imaging markers	Cardiovascular events, mortality	Integration of imaging and inflammatory markers enhanced severity stratification.
Yusuf S et al., 2024	Patients with chronic heart failure evaluated using simplified clinical risk scores	All-cause mortality	Simplified scores retained strong prognostic performance for severity assessment.
Li X et al., 2024	Patients with systemic sclerosis stratified according to extent of organ involvement	Survival, disease progression	Multisystem involvement emerged as the primary determinant of disease severity.
Fernandes A et al., 2024	Patients with chronic inflammatory bowel disease evaluated using fecal inflammatory biomarkers	Disease flares, hospitalization	Biomarker-guided stratification improved identification of patients with more severe disease.
Global Burden of Disease Collaborators, 2024	Multinational cohorts with chronic systemic diseases analyzed using composite severity metrics	Disability-adjusted life years, mortality	Severity indices correlated strongly with global disease burden and long-term outcomes.
Visseren FLJ et al., 2024	Patients with chronic cardiometabolic diseases evaluated using integrated risk models	Cardiovascular events, mortality	Integrated models provided superior assessment of systemic disease severity.

5 DISCUSSION

The earliest included study by Matsushita et al. demonstrated that combined assessment of estimated glomerular filtration rate and albuminuria provided a more accurate stratification of disease severity in chronic kidney disease than either marker alone.[13] This finding reinforced the concept that single-parameter evaluation underestimates systemic risk

in chronic multisystem disorders.[13] The study also showed a graded association between worsening marker categories and mortality outcomes.[13] Subsequent investigations in diabetic populations expanded this paradigm to metabolic disease contexts.[14]

Rapsomaniki et al. showed that glycemic variability represented a distinct marker of disease severity in type 2 diabetes mellitus, independent of mean glycated hemoglobin levels.[14] This observation suggested that dynamic metabolic instability contributes substantially to systemic damage progression.[14] The results challenged traditional reliance on static glycemic targets as sole indicators of disease control.[14] Similar principles were observed in cardiovascular cohorts evaluating inflammatory burden.[15]

Ridker et al. identified high-sensitivity C-reactive protein as a robust marker of residual inflammatory risk in patients with stable atherosclerotic disease.[15] Elevated inflammatory markers were consistently associated with higher rates of adverse cardiovascular events despite optimal lipid lowering.[15] This dissociation highlighted inflammation as a key dimension of disease severity beyond conventional risk factors.[15] Autoimmune disease studies further corroborated inflammation-driven severity pathways.[16]

Agca et al. demonstrated that higher rheumatoid arthritis disease activity scores correlated with increased cardiovascular mortality, supporting systemic inflammation as a cross-disease severity determinant.[16] These findings emphasized the need for integrated cardiovascular risk assessment in chronic inflammatory conditions.[16] Disease severity in this context reflected cumulative inflammatory exposure rather than joint-specific manifestations alone.[16] Comparable multidimensional approaches were evaluated in chronic respiratory diseases.[17]

Huang et al. reported that composite severity indices in chronic obstructive pulmonary disease outperformed spirometric measures alone in predicting hospitalization and mortality.[17] This reinforced the limitation of single-organ functional tests for estimating global disease severity.[17] Multidimensional indices incorporating symptoms, biomarkers, and functional status better captured systemic disease burden.[17] Heart failure studies yielded analogous conclusions.[18]

Matsue et al. demonstrated that integration of natriuretic peptides with congestion markers improved prediction of decompensation in chronic heart failure.[18] This multimarker approach reflected both hemodynamic stress and systemic involvement.[18] The findings supported severity stratification models that combine biochemical and clinical indicators.[18] Metabolic syndrome cohorts further validated composite severity constructs.[19]

D'Agostino et al. showed that metabolic severity scores integrating anthropometric, biochemical, and clinical variables predicted cardiovascular events more accurately than

isolated risk factors.[19] This reinforced the concept of cumulative burden as a core element of severity in chronic systemic diseases.[19] Similar composite strategies were validated in chronic kidney disease progression studies.[19] Renal-specific biomarkers provided additional prognostic refinement.[20]

Koppe et al. identified inflammatory and mineral metabolism biomarkers as early indicators of accelerated chronic kidney disease progression.[20] These markers captured systemic dysregulation beyond glomerular filtration decline.[20] The study highlighted the interconnectedness of metabolic, inflammatory, and renal pathways in determining severity.[20] Autoimmune disease damage indices further illustrated cumulative severity assessment.[21]

Marques et al. demonstrated that organ damage indices in systemic lupus erythematosus were strong predictors of long-term morbidity and mortality.[21] These indices reflected irreversible disease burden rather than transient activity.[21] Severity assessment based on accumulated damage proved more prognostically relevant than short-term inflammatory markers alone.[21] Cardiovascular and metabolic multimarker studies echoed this cumulative risk model.[22]

Anand et al. and Pugliese et al. showed that multimarker panels combining renal, cardiovascular, and inflammatory parameters improved risk discrimination in heart failure and diabetes mellitus.[22] These approaches consistently outperformed single-domain markers across heterogeneous populations.[22] The convergence of evidence supported integrated severity models as superior tools for prognosis.[22] Imaging-based and organ-specific indices further refined severity stratification.[23]

Gheith et al. and Ponticelli et al. confirmed that fibrosis scores and persistent proteinuria reliably stratified severity in chronic liver and glomerular diseases.[23] These markers reflected irreversible structural damage associated with worse outcomes.[23] Their consistency across cohorts supported external validity.[23] Recent studies integrating imaging, biomarkers, and clinical scores consolidated this evidence.[24]

Krittanawong et al. and Yusuf et al. demonstrated that combining imaging markers with simplified clinical scores enhanced prognostic accuracy in chronic coronary syndrome and heart failure.[24] These models balanced feasibility with predictive performance.[24] Importantly, they facilitated translation into routine clinical practice.[24] Systemic autoimmune and inflammatory bowel disease studies further emphasized multisystem involvement.[25]

Li et al. and Fernandes et al. showed that extent of organ involvement and fecal inflammatory biomarkers were strong determinants of disease severity in systemic sclerosis and inflammatory bowel disease.[25] These findings reinforced severity as a multisystem construct rather than organ-isolated dysfunction.[25] Global analyses using composite indices

confirmed these associations at a population level.[25] Overall, the certainty of evidence was moderate, with heterogeneity primarily driven by disease-specific marker selection.[26]

5 CONCLUSION

This systematic review synthesized contemporary evidence on markers of severity across a wide range of chronic systemic diseases and demonstrated that severity is best captured through integrated, multidimensional approaches rather than isolated parameters. Across cardiovascular, metabolic, renal, inflammatory, respiratory, hepatic, and autoimmune conditions, composite markers consistently showed superior prognostic performance for mortality, hospitalization, and disease progression. Laboratory biomarkers, imaging parameters, clinical scores, and cumulative damage indices each contributed complementary information to severity assessment. Together, these findings underscore the systemic and interconnected nature of chronic disease severity.

From a clinical perspective, accurate identification of disease severity has direct implications for risk stratification, treatment selection, and follow-up intensity. Integrated severity markers enable earlier identification of high-risk patients who may benefit from intensified therapy or closer monitoring. Conversely, they may help avoid overtreatment in patients with stable or low-risk disease profiles. The use of validated severity markers therefore supports more precise, individualized, and value-based care in chronic systemic diseases.

The existing literature is limited by substantial heterogeneity in study designs, populations, and marker definitions across different diseases. Many studies relied on observational data, which limits causal inference and increases susceptibility to residual confounding. In addition, variability in outcome definitions and follow-up duration complicates direct comparison between studies. Some severity markers were evaluated in single cohorts only, reducing external validity and generalizability.

Future research should prioritize prospective validation of integrated severity models across diverse populations and healthcare settings. Standardization of severity definitions and core outcome sets would enhance comparability and facilitate meta-analytic approaches. Emerging digital biomarkers, advanced imaging techniques, and artificial intelligence–driven models warrant rigorous evaluation against established markers. Importantly, future studies should also assess how severity-guided strategies influence clinical decision-making and patient-centered outcomes.

In conclusion, severity assessment in chronic systemic diseases represents a critical component of modern, evidence-based medicine. Multidisciplinary and individualized

strategies grounded in validated severity markers have the potential to improve prognostication, optimize resource utilization, and enhance long-term outcomes. Continued integration of clinical expertise with robust empirical evidence will be essential to advance severity-based care models across chronic diseases.

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