

The Role of Myeloid-Derived Suppressor Cells in the Immunopathogenesis of Hodgkin Lymphoma: Integrative Literature Review

<https://doi.org/10.32635/2176-9745.RBC.2026v72n4.5715>

O Papel das Células Supressoras Derivadas de Mieloides na Imunopatogênese do Linfoma de Hodgkin: Revisão Integrativa da Literatura

El Papel de las Células Supresoras Derivadas de Mieloides en la Inmunopatogénesis del Linfoma de Hodgkin: Revisión Integradora de la Literatura

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ABSTRACT

Introduction: Hodgkin lymphoma (HL) is a hematological malignancy characterized by Hodgkin and Reed-Sternberg cells embedded in a tumor microenvironment rich in inflammatory mediators and immune cells, which plays a central role in disease progression and immune evasion. Among these components, myeloid-derived suppressor cells (MDSCs) have emerged as key regulators of antitumor immunity. **Objective:** To review and synthesize current evidence on the role of MDSCs in the immunopathogenesis of HL, emphasizing their phenotypic subtypes, mechanisms of action, and clinical relevance. **Method:** This study consists of a literature review based on the critical analysis of experimental and clinical studies retrieved from national and international databases. Eligible studies addressed the interaction between MDSCs, tumor cells, and the tumor microenvironment in HL. **Results:** The analyzed studies indicate that MDSCs are increased in patients with HL and are associated with poor prognosis, higher tumor burden, and reduced response to conventional therapies. MDSCs exert immunosuppressive effects through the production of arginase, nitric oxide, reactive oxygen species, and anti-inflammatory cytokines, while promoting regulatory T-cell expansion and inhibiting cytotoxic T lymphocyte and natural killer cell activity. In addition, MDSCs interact with other myeloid populations within the tumor microenvironment, further amplifying immune evasion mechanisms. **Conclusion:** Overall, the evidence supports a central role for MDSCs in the immunopathogenesis of HL, influencing tumor microenvironment dynamics and therapeutic response. Improved understanding of these interactions may support the development of novel immunomodulatory strategies and the identification of prognostic and predictive biomarkers in HL.

Key words: Hematological Neoplasms; Myeloid-Derived Suppressor Cells; Hodgkin Disease; Tumor Microenvironment; Immunosuppression Therapy.

RESUMO

Introdução: O linfoma de Hodgkin (LH) é uma neoplasia hematológica caracterizada pela presença das células de Hodgkin e Reed-Sternberg, imersas em um microambiente tumoral rico em mediadores inflamatórios e células imunes, cuja composição desempenha papel central na progressão da doença e na evasão da resposta imune, destacando-se, nesse contexto, as células supressoras derivadas de mieloides (MDSC) como reguladoras da imunidade antitumoral. **Objetivo:** Sintetizar criticamente as evidências disponíveis sobre o papel das MDSC na imunopatogênese do LH, com ênfase em seus subtipos fenotípicos, mecanismos de ação e relevância clínica. **Método:** Revisão da literatura baseada na análise crítica de estudos experimentais e clínicos recuperados de bases de dados nacionais e internacionais que abordaram a interação entre MDSC, células tumorais e o microambiente tumoral no LH. **Resultados:** Os estudos analisados demonstram que as MDSC encontram-se aumentadas em pacientes com LH e associam-se a pior prognóstico, maior carga tumoral e menor resposta às terapias convencionais, exercendo efeitos imunossupressores por meio da produção de arginase, óxido nítrico, espécies reativas de oxigênio e citocinas anti-inflamatórias, além de favorecerem a expansão de células T reguladoras e inibirem a atividade citotóxica de linfócitos T e células *natural killer*, bem como interagirem com outras populações mieloides no microambiente tumoral. **Conclusão:** Em conjunto, as evidências sustentam um papel central das MDSC na imunopatogênese do LH, influenciando a dinâmica do microambiente tumoral e a resposta terapêutica, o que pode contribuir para o desenvolvimento de novas estratégias imunomodulatórias e para a identificação de biomarcadores prognósticos e preditivos.

Palavras-chave: Neoplasias Hematológicas; Células Supressoras Mieloides; Doença de Hodgkin; Microambiente Tumoral; Terapia de Imunossupressão.

RESUMEN

Introducción: El linfoma de Hodgkin (LH) es una neoplasia hematológica caracterizada por la presencia de células de Hodgkin y Reed-Sternberg inmersas en un microambiente tumoral rico en mediadores inflamatorios y células inmunes, cuya composición desempeña un papel central en la progresión de la enfermedad y en la evasión de la respuesta inmunitaria, destacándose las células supresoras derivadas de mieloides (MDSC) como reguladoras de la inmunidad antitumoral. **Objetivo:** Sintetizar de manera crítica las evidencias disponibles sobre el papel de las MDSC en la inmunopatogénesis del LH, con énfasis en sus subtipos fenotípicos, mecanismos de acción y relevancia clínica. **Método:** Revisión de la literatura basada en el análisis crítico de estudios experimentales y clínicos recuperados de bases de datos nacionales e internacionales que abordaron la interacción entre las MDSC, las células tumorales y el microambiente tumoral en el LH. **Resultados:** Los estudios analizados muestran que las MDSC se encuentran aumentadas en pacientes con LH y se asocian con peor pronóstico, mayor carga tumoral y menor respuesta a las terapias convencionales, ejerciendo efectos inmunosupresores mediante la producción de arginasa, óxido nítrico, especies reactivas de oxígeno y citocinas antiinflamatorias, además de favorecer la expansión de células T reguladoras, inhibir la actividad citotóxica de los linfocitos T y de las células *natural killer* e interactuar con otras poblaciones mieloides del microambiente tumoral. **Conclusión:** En conjunto, la evidencia respalda un papel central de las MDSC en la inmunopatogénesis del LH, influyendo tanto en la dinámica del microambiente tumoral como en la respuesta terapéutica, lo que puede contribuir al desarrollo de nuevas estrategias inmunomoduladoras y a la identificación de biomarcadores pronósticos y predictivos.

Palabras clave: Neoplasias Hematológicas; Células Supresoras de Origen Mielode; Enfermedad de Hodgkin; Microambiente Tumoral; Terapia de Imunosupresión.

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INTRODUCTION

Hodgkin lymphoma (HL) is a neoplasm of the hematopoietic system that predominantly affects lymph nodes and structures of the lymphatic system¹. Formerly known as Hodgkin disease, HL originates mainly from B lymphocytes, although a small fraction of cases (1-2%) is derived from T lymphocytes. The neoplastic cells characteristic of the disease are known as Hodgkin and Reed–Sternberg (HRS) cells, a term that encompasses both mononuclear Hodgkin cells and multinucleated HRS cells^{2,3}.

The diagnosis of HL is based on the integration of clinical data, physical examination — with emphasis on the identification of lymphadenopathy and hepatosplenomegaly —, routine laboratory tests, investigation of associated infections, and imaging studies. However, definitive diagnosis requires excisional biopsy of an affected lymph node, allowing histopathological analysis of HRS cells and the characteristic tumor microenvironment, in which a small number of malignant cells are embedded within an abundant inflammatory infiltrate. In specific situations, complementary examinations such as bone marrow biopsy and aspiration, as well as lumbar puncture, may be performed^{2,4}. HL is classified into two main subtypes: classical Hodgkin lymphoma (cHL) and nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL)¹. cHL is further subdivided into four histological variants — nodular sclerosis, mixed cellularity, lymphocyte-rich, and lymphocyte-depleted — which differ in their morphological, clinical, and prognostic characteristics^{2,5}.

From a pathophysiological standpoint, cHL represents the most extensively studied model of the disease. HRS cells originate from germinal center B lymphocytes but display a profoundly altered phenotype, characterized by the loss of typical B-cell markers such as CD19, CD20, CD79A, CD79B, CD22, and immunoglobulins. Concurrently, these cells may aberrantly express markers associated with T lymphocytes, myeloid cells, and dendritic cells, reflecting a deep process of cellular reprogramming³. Among the major molecular mechanisms involved in HRS cell survival, constitutive activation of the nuclear factor kappa B (NF- κ B) signaling pathway stands out as a central regulator of genes associated with cell survival, inflammation, and resistance to apoptosis. This activation may result from genetic mutations and dysregulation, including amplifications of *MAP3K14* and *BCL3* and inactivation of negative regulators such as *TNFAIP3*, *NFKBIA*, and *NFKBIE*. Additionally, stimuli derived from the tumor microenvironment and infection with Epstein–Barr virus (EBV) contribute to sustained

activation of this pathway^{3,4,6}. Another relevant signaling pathway include the Janus kinase–signal transducer and activator of transcription (JAK–STAT) pathway, which is frequently activated by mutations in genes such as *GNA12*, *XPO1*, *ITPKB*, and *STAT6*, leading to hyperphosphorylation of STAT proteins involved in cell proliferation, differentiation, and survival^{7,8}. Signaling through the PI3K–AKT pathway also contributes to the maintenance of the malignant phenotype of HRS cells and is partly driven by aberrant expression of tyrosine kinase receptors³.

Clinically, HL presents classical features, including frequent involvement of cervical lymph nodes, the presence of scattered HRS cells within a rich inflammatory infiltrate, higher incidence in young adults, and organization of T-lymphocyte infiltrates surrounding neoplastic cells⁵. Epidemiological data indicate a higher incidence in males, with age peaks between 15 and 39 years and above 75 years. In 2020, approximately 83,000 new cases were estimated worldwide, with the highest rates reported in Europe, Australia, and New Zealand. In Brazil, HL ranked 20th among the most common cancer types, with an estimated 3,070 new cases expected for each year of the 2026-2028 triennium, corresponding to an estimated risk of 1.41 cases per 100,000 inhabitants⁹⁻¹¹.

The term myeloid-derived suppressor cells (MDSCs) was proposed in 2007 to accurately reflect both the myeloid origin and the immunosuppressive function of this cellular population¹². Early studies in murine models of chronic inflammation demonstrated systemic expansion of myeloid cells expressing CD11b and Gr-1, markers associated with heterogeneous populations of immature cells exhibiting potent immunosuppressive activity. Given this heterogeneity, the term “MDSCs” was consolidated to emphasize both their origin and their relevance in pathological contexts, particularly in cancer¹³.

MDSCs comprise immature myeloid cells that can negatively modulate immune responses under various physiological and pathological conditions. In physiological settings, their role in pregnancy is noteworthy, as they promote maternal–fetal immune tolerance^{14,15}. In pathological conditions, these cells are involved in immune regulation in autoimmune diseases¹⁶, bacterial and viral infections^{17,18}, fungal diseases^{19,20}, trauma²¹, graft-versus-host disease²², and, most notably, chronic inflammatory states associated with cancer¹³.

Currently, MDSCs are classified into subpopulations based on phenotypic markers and functional characteristics. In mice, two major subsets are distinguished: monocytic MDSCs (M-MDSCs), characterized as CD11b⁺ Ly6C^{high} Ly6G[−], and polymorphonuclear or granulocytic MDSCs

(PMN-MDSCs or G-MDSCs), defined as CD11b⁺ Ly6C^{low} Ly6G⁺¹³. In humans, MDSCs include three main subtypes: monocytic MDSCs (HLA-DR^{7/low} CD33⁺ CD11b⁺ CD14⁺), granulocytic MDSCs (Lin⁻ HLA-DR^{7/low} CD33⁺ CD11b⁺ CD15⁺), and early-stage MDSCs (Lin⁻ HLA-DR^{7/low} CD33⁺), reflecting their phenotypic and functional diversity in inflammatory environments¹³.

Under normal conditions, activation of myeloid cells occurs through recognition of pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) by pattern recognition receptors (PRRs), resulting in rapid and effective inflammatory responses. However, in contexts of persistent and low-intensity stimuli — such as chronic inflammation, cancer, and autoimmune diseases — dysregulated hematopoiesis occurs, leading to the expansion of immature myeloid cells with reduced phagocytic activity and high immunosuppressive potential. These cells exhibit elevated expression of arginase, prostaglandin E2, reactive oxygen species, nitric oxide, and anti-inflammatory cytokines, constituting the functional phenotype of MDSCs²³⁻²⁵.

In cancer, the presence of circulating and tumor-infiltrating MDSCs is associated with poor prognosis, higher tumor burden, and reduced response to conventional therapies²⁵. In addition, these cells contribute to the formation of pre-metastatic niches and interact with other myeloid populations within the tumor microenvironment, such as tumor-associated macrophages (TAMs) and tumor-associated neutrophils (TANs), thereby amplifying mechanisms of immune evasion and tumor progression^{13,26}. The tumor microenvironment represents the primary functional context of MDSCs, in which these cells exert immunosuppressive effects on T and B lymphocytes and natural killer (NK) cells, while simultaneously promoting tumor growth through the induction of pro-tumorigenic cytokines and factors, including IL-6, IFN- γ , IL-1 β , GM-CSF, TNF- α , and VEGF. Additionally, MDSCs favor the expansion of regulatory T cells (Tregs) through contact-dependent mechanisms or by secreting mediators such as IL-10, TGF- β , ARG1, and IDO²⁷.

In this context, understanding the role of MDSCs in the immunopathogenesis of HL is essential, particularly concerning the modulation of the tumor microenvironment and the induction of resistance to conventional therapies. Therefore, this review aims to synthesize available evidence on the involvement of MDSCs in HL, discussing their potential as diagnostic and prognostic biomarkers, as well as therapeutic targets that may contribute to more personalized and effective treatment strategies.

METHOD

This study consists of an integrative literature review conducted with the aim of identifying, compiling, and critically analyzing the available scientific evidence regarding the relationship between MDSCs and HL. This methodological approach allows the synthesis of findings from primary studies with different designs, enabling a comprehensive understanding of the current state of knowledge on the subject.

The literature search was conducted between May and August 2025 in the PubMed, Virtual Health Library (BVS/LILACS), and Google Scholar databases, using controlled and non-controlled descriptors related to MDSCs and HL, as described in Chart 1. Search terms were combined using Boolean operators to increase the sensitivity of the search strategy. To improve the consistency and reliability of study selection, the authors were organized into three independent pairs, with each pair assigned to one database and responsible for conducting the search, screening, and classification of the retrieved articles.

As an initial exclusion criterion, review articles were excluded throughout all stages of the selection process, and only primary studies were considered eligible. Titles, abstracts, and keywords were screened to identify studies addressing MDSCs in the context of HL. Studies that did not address MDSCs or that did not present a direct association with HL were excluded. Potentially eligible articles were subsequently subjected to full-text reading and evaluated for thematic relevance and alignment with the objectives of the review. To reduce the risk of inappropriate exclusion of relevant studies, each article was independently evaluated by both members of the respective pair and classified according to its relevance to the research question. Studies that, even after full-text assessment, did not establish an association between MDSCs and HL were excluded.

The studies included in the review were analyzed descriptively and critically, considering aspects such as study design, study population, main findings, methodological limitations, and contributions to the understanding of the role of MDSCs in the immunopathogenesis of HL. Particular attention was given to the strengths and limitations of the available evidence, as well as to methodological differences among studies that could influence the interpretation and comparison of results.

RESULTS

The literature search conducted in the PubMed, Virtual Health Library (BVS/LILACS), and Google Scholar



Chart 1. Databases and search terms used for the literature search

PubMed	BVS/LILACS	Google Scholar
"((MDCSs) OR (Cells, Myeloid-Derived Suppressor) OR (Myeloid Derived Suppressor Cells) OR (Suppressor Cells, Myeloid-Derived)) AND ((Granuloma, Hodgkin) OR (Hodgkin Granuloma) OR (Granuloma, Hodgkin's) OR (Hodgkin's Granuloma) OR (Hodgkin Lymphoma) OR (Lymphoma, Hodgkin))"	"((Linfoma de Hodgkin) OR (Doença de Hodgkin)) AND ((Células Supressoras Mieloides) OR (MDSCS))"	"((MDCSs) OR (Cells, Myeloid-Derived Suppressor) OR (Myeloid Derived Suppressor Cells) OR (Suppressor Cells, Myeloid-Derived)) AND ((Granuloma, Hodgkin) OR (Hodgkin Granuloma) OR (Granuloma, Hodgkin's) OR (Hodgkin's Granuloma) OR (Hodgkin Lymphoma) OR (Lymphoma, Hodgkin))"

databases initially identified 219 articles, including 43 from PubMed, 17 from BVS/LILACS, and 159 from Google Scholar. After excluding studies without access to the full text, 213 articles remained for subsequent analysis. Next, duplicate records were removed, resulting in 196 studies distributed across PubMed (42), BVS/LILACS (1), and Google Scholar (153). These articles underwent screening based on title, abstract, and keywords, and those which did not clearly address HL and/or corresponded to review articles were excluded. After this step, 26 articles were considered potentially eligible and were subjected to full-text assessment, including 18 from PubMed and 8 from Google Scholar. Following full-text evaluation, studies that did not establish a direct association between MDSCs and HL or that were review articles were excluded.

At the end of the selection process, 13 articles met all inclusion criteria and formed the final study sample, all of which were retrieved from PubMed database. The flowchart detailing the stages of identification, screening, eligibility, and inclusion of studies is presented in Figure 1. The main characteristics of the included studies are summarized in Chart 2²⁸⁻⁴⁰, which provides information on study design, evaluated population, objectives, main findings, and contributions to understanding the role of MDSCs in the immunopathogenesis of HL.

DISCUSSION

The role of MDSCs in LH has not yet been fully elucidated. Nevertheless, the studies analyzed in this review converge in demonstrating that these cells play a central role in immunological modulation of the tumor microenvironment, contributing to immune evasion mediated by Hodgkin and HRS cells, in addition to exhibiting potential prognostic and therapeutic value.

The integrated analysis of the tumor microenvironment performed by Menéndez et al.³⁸, using gene expression profiling and cellular deconvolution tools, demonstrated that immunosuppressive myeloid populations, including MDSCs, constitute a functional axis associated with poor prognosis in cHL. In this context, increased levels of these cells correlated with enhanced expression of

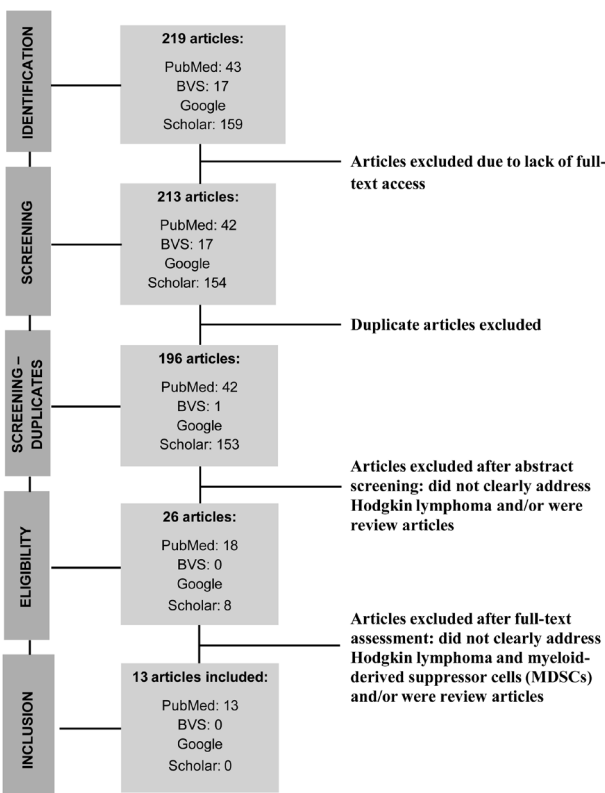


Figure 1. Flow diagram illustrating the process of identification, screening, eligibility assessment, and inclusion of studies in the integrative literature review evaluating the role of myeloid-derived suppressor cells (MDSCs) in Hodgkin lymphoma

immunoregulatory pathways such as IL-10, reduced antigen presentation via MHC class II, and T-cell exhaustion, reinforcing the role of MDSCs as key mediators of tumor-induced immunosuppression. Validation of these findings in independent cohorts strengthens their clinical relevance and supports the potential of MDSCs as prognostic markers and therapeutic targets³⁸. These findings are consistent with evidence indicating that the IL-10 pathway plays a central role in maintaining an immunosuppressive environment by inhibiting lymphocyte activation and reducing the expression of antigen-presenting molecules such as MHC class II⁴¹. Thus, the accumulation of MDSCs in HL integrates an unfavorable immunological landscape that supports tumor persistence.



Chart 2. Summary of articles evaluating the role of myeloid-derived suppressor cells in Hodgkin lymphoma

Study type and sample	Main findings
Experimental study (murine). CD99 ⁺ /GT, C57BL/6J, bm12, and CD45.1 mice ²⁸	CD99 inhibition altered immune responses and MDSC expansion. LMP-1 (EBV) activation was associated with the generation of Hodgkin cells
Prospective experimental study. 60 HL patients and 25 healthy controls ²⁹	CD34 ⁺ MDSCs showed potential as biomarkers of unfavorable outcomes and late therapeutic failure not detected by PET-2
Observational study. 31 HL patients, 93 B-cell non-Hodgkin lymphoma patients, and 48 controls ³⁰	Increased CD66b ⁺ CD33 ^{low} HLA-DR ⁺ cells compatible with G-MDSCs were observed in HL patients
Preclinical experimental study murine model of HL ³¹	MDSCs exerted immunosuppressive effects through high arginase-1 expression, which was associated with advanced disease stage and poorer progression-free survival
Clinical trial (phase II). 25 patients with relapsed or refractory HL ³²	Idelalisib (PI3K δ inhibitor) showed immunomodulatory potential, with evidence of MDSC and Treg inhibition
Preclinical and early clinical study (phase I). Human leukocytes ³³	Reduction of circulating MDSCs and chemokines was associated with induction of apoptosis in Hodgkin cells
Experimental study. Variable sampling ³⁴	Identification of secreted PD-L1 (secPD-L1) in approximately 70% of tumors, including HL, associated with MDSCs and immune evasion
Case-control study. 19 patients with classical HL and 24 with high-grade B-cell lymphoma ³⁵	Lymphoma patients showed increased G-MDSCs and reduced CD3 ⁺ T cells and regulatory NK cells. In classical HL, higher G-MDSC levels were associated with superior disease-free survival
Retrospective clinical study (single cohort). 15 patients with relapsed or refractory HL ³⁶	Brentuximab vedotin reduced MDSCs and serum arginase-1 levels, modulating immunosuppressive mediators and Tregs
Experimental and observational study. 22 tissue samples (lymphomas and controls) ³⁷	Increased MDSCs were observed in lymphomas, including HL, and were associated with poor prognosis and differentiation into tumor-associated macrophages
Retrospective observational study. 25 patients (main analysis) and 103 for validation ³⁸	A myeloid-rich signature with MDSCs, Tregs, and immature NK cells was associated with poor prognosis; the predictive model showed high accuracy
Retrospective observational study. 30 cases of classical HL ³⁹	MDSCs in the tumor microenvironment were associated with reduced therapeutic efficacy and functional modulation dependent on proximity to HRS cells
Mixed experimental study. HL patient samples and murine models ⁴⁰	PD-1 blockade reduced MDSC expansion, suggesting an immunomodulatory effect of immunotherapy

Captions: HL, Hodgkin lymphoma; cHL, classical Hodgkin lymphoma; MDSCs, myeloid-derived suppressor cells; G-MDSCs, granulocytic myeloid-derived suppressor cells; Tregs, regulatory T cells; NK, natural killer cells; TAMs, tumor-associated macrophages; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; secPD-L1, secreted PD-L1; EBV, Epstein-Barr virus; Arg-1, arginase-1; PI3K δ , phosphoinositide 3-kinase delta.

Similar observations were previously reported by Marini et al.³⁰, who identified a significant increase in granulocytic MDSCs (G-MDSCs) in the peripheral blood of HL patients at diagnosis. In that study, depletion of these cells restored T-lymphocyte proliferation, indicating that G-MDSCs directly contribute to tumor tolerance. Moreover, higher levels of these cells were associated with worse clinical outcomes, reinforcing their systemic immunosuppressive role and their relevance as potential targets for immunomodulatory interventions³⁰. However, not all studies have reported a uniformly detrimental role for granulocytic MDSCs in HL. While Marini et al.³⁰ observed an association between elevated G-MDSC levels and unfavorable clinical outcomes, subsequent

investigations have suggested that the prognostic significance of these cells may vary according to their phenotypic characterization, functional status, and spatial distribution within the tumor microenvironment. These observations indicate that MDSCs should not be considered a homogeneous population and highlight the complexity of interpreting their biological and clinical relevance in HL.

The tumor microenvironment of HL is characterized by high cellular complexity, including, in addition to MDSCs, TAMs, Tregs, exhausted T lymphocytes, and other immune populations that interact dynamically⁴². In this context, experimental and observational studies indicate that immunosuppression in HL results from the

coordinated activity of multiple cellular and molecular components. Supporting this myeloid interaction, Roussel et al.³⁷ demonstrated that, in HL, a subset of TAMs exhibits phenotypic and functional profiles similar to those of MDSCs, characterized by high expression of S100A9 and low expression of HLA-DR. These macrophages appear to derive from or maintain a close functional relationship with MDSCs, forming an MDSC–TAM axis associated with lymphocyte exhaustion and tumor progression. The specific distribution of these myeloid subtypes across different lymphomas further underscores the uniqueness of the HL immune microenvironment³⁷.

From a diagnostic and prognostic perspective, Romano et al.²⁹ demonstrated that MDSC subpopulations, particularly CD34⁺ cells, may serve as additional biomarkers to PET-2 by identifying patients at higher risk of therapeutic failure and relapse. However, the authors highlighted important limitations, as expansion of these cells may be influenced by chronic inflammation, hematopoietic growth factor use, and other non-tumor-related conditions, reinforcing the need for methodological standardization before routine clinical application²⁹.

From a therapeutic perspective, several approaches have investigated MDSC modulation as a strategy to potentiate antitumor immunity. The phase II clinical trial conducted by Gopal et al.³² evaluated idelalisib, a selective PI3K δ inhibitor, in patients with relapsed or refractory HL. Although clinical activity was modest, the study provided initial evidence that inhibition of this pathway may interfere with the immunosuppressive tumor microenvironment, paving the way for more effective therapeutic combinations³². Further advances were reported by Locatelli et al.³³ who demonstrated that dual PI3K δ / γ inhibition (RP6530) significantly reduces both the quantity and functional activity of MDSCs, in addition to reprogramming macrophages from an immunosuppressive M2 phenotype to a pro-inflammatory M1 phenotype. These findings reinforce the role of MDSCs not only as biomarkers but also as indicators of therapeutic response in HL³³.

Checkpoint blockade-based immunotherapy has also revealed direct effects on myelopoiesis. Boumpas et al.⁴⁰ demonstrated that PD-L1 blockade reprograms cancer-induced emergency myelopoiesis, reducing peripheral generation of MDSCs. This effect, observed in both murine models and HL patients treated with anti-PD-1 therapy, expands the understanding of the mechanisms of action of these treatments beyond simple reactivation of T lymphocytes⁴⁰. Complementarily, Mahoney et al.³⁴ identified a secreted PD-L1 splice variant (secPD-L1) capable of acting at a distance as a paracrine mediator of immunosuppression. In HL, this variant was associated

with MDSC expansion and pathological inflammatory signatures, adding a new dimension to immune evasion and suggesting that the PD-1/PD-L1 axis operates more broadly than previously recognized³⁴.

The therapeutic impact of MDSC modulation was also demonstrated with the use of brentuximab vedotin. Romano et al.³⁶ showed that this agent significantly reduces different MDSC subtypes and serum arginase-1 levels, while also modulating Treg populations, partially restoring antitumor immune competence. These off-target immunomodulatory effects may help explain, at least in part, the durability of clinical responses observed in treated patients according to these authors. The relevance of arginase-1 as a functional mediator of immunosuppression was further detailed by these same authors who demonstrated elevated levels of this enzyme in patients with cHL, correlating with advanced disease stages and therapeutic failure. The resulting depletion of L-arginine directly compromises T-cell function, consolidating arginase-1 as both a serum biomarker and a mechanistic link between MDSCs and immune evasion³⁶.

Finally, recent studies highlight the functional heterogeneity of MDSCs. Solórzano et al.³⁹ demonstrated that monocytic MDSCs are associated with worse prognosis and higher relapse risk in cHL, whereas G-MDSCs, when present at lower levels and in specific spatial contexts, may paradoxically associate with more favorable outcomes³⁹. A similar finding was reported by Amini et al.³⁵ who observed improved disease-free survival in patients with higher levels of G-MDSCs, contrasting with the findings of Marini et al.³⁰ and with the predominant view that MDSC expansion contributes to disease progression.

Several factors may explain these discrepancies. First, different studies have employed distinct phenotypic markers and gating strategies to identify MDSC subsets, which may result in the inclusion of biologically heterogeneous cell populations. Second, variations in patient characteristics, disease stage, treatment status, and sample source (peripheral blood versus tumor tissue) may influence both the frequency and functional properties of these cells. Finally, emerging evidence suggests that the biological impact of MDSCs may depend not only on their abundance but also on their activation state and interactions with other components of the tumor microenvironment. Taken together, these findings underscore the need for standardized methodologies and more refined characterization of MDSC subsets in future studies, thereby enabling a more accurate assessment of their prognostic and therapeutic significance in HL^{35,39}.

The clinical relevance of monitoring MDSCs extends beyond their role as biomarkers of disease progression. As discussed above, accumulating evidence indicates that

these cells actively contribute to tumor immune evasion by suppressing T-cell activation, promoting regulatory immune pathways, and fostering an immunosuppressive tumor microenvironment. In HL, increased frequencies of circulating and tumor-associated MDSCs have been associated with unfavorable clinical outcomes, treatment resistance, and reduced survival, suggesting that their assessment may provide valuable prognostic and predictive information. Therefore, monitoring MDSC levels may represent a useful strategy for patient stratification, therapeutic decision-making, and evaluation of treatment responses, particularly in the context of immunotherapeutic approaches.

This perspective is especially relevant considering the growing incorporation of immune-based therapies into the management of hematological malignancies. Immune checkpoint inhibitors targeting the PD-1/PD-L1 axis have become an important therapeutic option for relapsed or refractory cHL, demonstrating substantial clinical benefits. However, MDSCs are known to contribute to resistance against immunotherapy through multiple mechanisms, including the secretion of immunosuppressive cytokines such as TGF- β and IL-10, the upregulation of immune checkpoint molecules such as PD-L1, depletion of essential amino acids required for T-cell proliferation, and the production of reactive oxygen species that impair T-cell receptor signaling⁴³. Consequently, the monitoring of MDSC populations may help identify patients with a more immunosuppressive profile and potentially predict therapeutic responsiveness.

From a translational perspective, MDSCs may also play a critical role in the success of emerging cellular immunotherapies. Chimeric antigen receptor T-cell (CAR-T) therapy has shown promising results in relapsed and refractory cHL, particularly through targeting the CD30 antigen expressed by Hodgkin HRS cells⁴⁴. Nevertheless, accumulating evidence indicates that MDSCs can directly impair CAR-T cell efficacy by suppressing their activation and proliferation, promoting metabolic deprivation within the tumor microenvironment, generating oxidative stress, and even interfering with CAR-T cell manufacturing processes⁴³⁻⁴⁵. These observations reinforce the potential value of incorporating MDSC monitoring into future immunotherapy protocols and highlight these cells as potential therapeutic targets capable of enhancing treatment efficacy.

Within the Brazilian context, these considerations acquire particular importance. Recent advances in CAR-T cell development by public research institutions, especially the pioneering initiatives led by the “*Centro de Terapia Celular*” of the “*Universidade de São Paulo*” in Ribeirão Preto, demonstrate the growing national

capacity to develop advanced cellular therapies and expand access to innovative cancer treatments through the public healthcare system⁴⁵⁻⁴⁹. As immunotherapies become increasingly available and sophisticated, integrating immune biomarkers such as MDSCs into clinical practice may contribute to a more personalized and efficient management of HL within the Brazilian National Health System (SUS), while also supporting future strategies aimed at optimizing the effectiveness of high-cost immunological interventions.

Some limitations of this review should be acknowledged. First, the number of studies specifically investigating the role of MDSCs in HL remains limited, reflecting the relatively recent interest in this field and restricting the availability of high-quality evidence. In addition, most of the included studies consisted of observational investigations, retrospective analyses, or studies with relatively small sample sizes, which may limit the generalizability of the findings.

Another important limitation concerns the heterogeneity among the included studies regarding patient populations, methodological approaches, and criteria used to identify and characterize MDSC subpopulations. Variations in phenotypic markers, laboratory methodologies, and clinical endpoints may have influenced the comparability of results across studies. Furthermore, although efforts were made to minimize selection bias through independent article screening by paired reviewers, the possibility of publication bias and study selection bias cannot be completely excluded. Therefore, the findings presented in this review should be interpreted considering these limitations. Future studies employing standardized methodologies and larger prospective cohorts will be essential to strengthen the current evidence regarding the role of MDSCs in HL.

CONCLUSION

The evidence compiled in this review indicates that MDSCs play a central role in the immunopathogenesis of HL, acting as key mediators of tumor-induced immunosuppression and contributing to immune evasion, disease progression, and therapeutic resistance. The interaction of these cells with other components of the tumor microenvironment, such as TAMs, Tregs, and immunomodulatory molecules (IL-10, PD-L1, CD30L, and CD99), reinforces HL as a neoplastic model that is strongly dependent on immune regulation.

From a clinical perspective, MDSCs and their mediators, such as arginase-1, emerge as promising biomarkers for prognosis and therapeutic monitoring, with potential performance comparable, in specific



contexts, to PET-2. However, the biological variability of these cells and the influence of systemic inflammatory factors pose challenges to their standardization and clinical application. In the therapeutic field, strategies aimed at modulating MDSC expansion and function — including PI3K/Akt pathway inhibitors, immune checkpoint blockade, and agents such as brentuximab vedotin — appear promising for restoring antitumor immunity and enhancing the efficacy of established treatments.

In summary, regulation of MDSC activity represents a strategic axis in the management of HL. Future studies with robust methodological designs and integrated analyses of the tumor microenvironment will be essential to consolidate these cells as reliable therapeutic targets and biomarkers, thereby enabling progress toward more personalized and effective treatment strategies for patients with HL.

CONTRIBUTIONS

Beatriz Nascimento Fischer contributed to the conception and design of the study, data analysis and interpretation, drafting, and critical review. Maria Eduarda Anacleto Borborema Santos, Vitória Gabriela Porfírio Lemes, Mikaela Oliveira Moraes Lopes, Heloisa Bruna da Silva Rufino and Sofia de Vasconcelos Ramos Marinho contributed to the conception and design of the study, data acquisition, analysis and interpretation, drafting, and critical review. Valéria de Lima Kaminski contributed to the conception and design of the study, data analysis and interpretation, critical review and final supervision of the project. All the authors approved the final version for publication.

DECLARATION OF CONFLICT OF INTEREST

There is no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

All the content underlying the text of the article is included in the manuscript.

FUNDING SOURCES

None.

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Recebido em 10/2/2026

Aprovado em 26/8/2026

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