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Hematological complications in acute leukemia: a comparative analysis between tumor lysis syndrome and differentiation syndrome.

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Hematological complications in acute leukemia: comparative analysis between tumor lysis syndrome and differentiation syndrome

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ABSTRACT

Acute leukemias are hematological neoplasms characterized by the clonal proliferation of immature cells, with rapid progression and a high potential for complications arising from...

This study aimed to comparatively analyze these complications, emphasizing the pathophysiological mechanisms, risk factors, clinical manifestations, and management strategies. Methodology: This is an integrative literature review, conducted in the PubMed, SciELO, and ScienceDirect databases, encompassing studies published in the last five years. Twelve articles were selected after applying the eligibility criteria. Results: TLS is a metabolic emergency resulting from rapid cell destruction induced by therapies such as venetoclax, leading to electrolyte disturbances, hyperuricemia, hyperkalemia, and risk of renal failure. The study highlighted tumor lysis syndrome (TLS), mainly associated with acute myeloid leukemia (AML), and differentiation syndrome (DS), related to acute promyelocytic leukemia (APL). In contrast, SD presents a systemic inflammatory character, associated with cell differentiation induced by agents such as retinoic acid (ATRA) and arsenic trioxide (ATO), manifesting as fever, dyspnea, and organ dysfunction. Discussion: Both complications are multifactorial in nature, involving therapeutic, biological, and individual factors related to tumor burden and treatment response. It is evident that more effective therapies tend to intensify specific adverse events, reinforcing the need for rigorous monitoring, an individualized approach, and early interventions. Final considerations: Early recognition, risk stratification, and laboratory monitoring are fundamental for reducing morbidity and mortality.

Descriptors: Leukemia; Acute myeloid; Acute promyelocytic; Syndrome; and Tumor Lysis Syndrome.

INTRODUCTION

Acute leukemias constitute a group of hematological neoplasms characterized by

clonal proliferation of immature hematopoietic cells, called blasts, which exhibit

Loss of differentiation capacity and compromised normal hematopoiesis. These diseases have

They evolve rapidly and require specialized diagnosis and management, as they can trigger...

serious complications that directly impact patient morbidity and mortality.

(Schiavini et al., 2025; Whiteley et al., 2021).

An example of leukemia is acute myeloid leukemia (AML), the most common disease in

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Adults and elderly individuals, with a median age at diagnosis around 68 years, may be associated with genetic, environmental and pre-existing clinical conditions (Hu et al., 2023; Saiyin et al., 2025). From a molecular point of view, alterations such as the overexpression of the anti-apoptotic protein BCL-2 contribute to the survival of leukemia cells and to resistance to mechanisms of cell death, favoring the progression of the disease (Hu et al., 2023).

In recent years, therapeutic advances have significantly modified the management of AML. especially in patients ineligible for intensive chemotherapy. Among these approaches, The use of venetoclax, a selective inhibitor of the BCL-2 protein that restores apoptosis, stands out. in leukemic cells. The association of this drug with hypomethylating agents, such as azacitidine. or decitabine, has shown promising results in terms of therapeutic response and survival (Arora et al., 2022; Hu et al., 2023). However, the rapid induced cell destruction This regimen can trigger significant metabolic complications, such as syndrome Tumor lysis (TLS), characterized by the massive release of intracellular contents into the circulation, which results in potentially fatal electrolyte and metabolic disturbances (Calvache; Calvache; Weber, 2024).

Acute promyelocytic leukemia (APL), in turn, constitutes a specific variant of AML. characterized by the presence of the t(15;17) chromosomal translocation, which results in the formation of PML-RARÿ fusion gene. This molecular alteration promotes the blocking of differentiation of promyelocytes and the accumulation of these cells in the bone marrow and peripheral blood (de Figueiredo-(Pontes et al., 2024). Clinically, LPA is particularly relevant due to the association frequent with severe coagulation disorders, including hemorrhagic manifestations potentially fatal conditions, which are major causes of premature mortality in patients. affected (Mohammadzadeh et al., 2021).

The treatment of LPA has been significantly transformed with the introduction of trans-retinoic acid (ATRA) and arsenic trioxide (ATO), targeted therapies capable of inducing Differentiation of leukemic cells through the degradation of the oncoprotein PML-RARÿ. The combination of these agents allowed for high remission and survival rates, making LPA a among hematological neoplasms with better prognoses when diagnosed and treated early on (Albanesi et al., 2020; Luo et al., 2023). However, the use of these therapies may triggering differentiation syndrome (DS), a systemic inflammatory complication characterized by fever, dyspnea, weight gain, pleural effusions, and organ dysfunction, resulting from the rapid maturation and activation of leukemic cells (Mohammadzadeh et al., 2021; Wu et al., 2024).

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Therefore, early recognition and appropriate management of complications associated with Treatment of acute leukemias becomes fundamental for reducing mortality and... Optimization of clinical support. In this context, SLT stands out in AML and SD in APL, both associated with significant clinical and laboratory changes that require close monitoring. (Rowe et al., 2025; Saiyin et al., 2025). Thus, this study aims to analyze and compare hematological complications, focusing on SD in APL and SLT in AML, addressing their Pathophysiological mechanisms, risk factors, clinical manifestations, and management strategies.

METHODOLOGY

This study is characterized as an integrative literature review. The survey A bibliographic review was conducted between August 2025 and June 2026, through a search. structured in the PubMed, SciELO, and ScienceDirect databases. No further information was established. Language restrictions were applied; articles published in the last five years were selected.

For the search strategy, descriptors obtained from the Descriptors in were used. Health Sciences (DeCS), namely: “Acute Promyelocytic”, “Acute Myelocytic”, “Syndrome”, “Leukemia” and “Tumor Lysis Syndrome”, combined by means of the operators booleans “AND” and “OR”.

The inclusion criteria encompassed studies relevant to the proposed theme, available in complete and directly addressing the research. As exclusion criteria, the following were adopted Duplicate articles across the consulted databases, incomplete studies, and those that They strayed from the proposed topic, not directly addressing AML, LPA, or their complications. hematological disorders, such as SLT and SD.

RESULTS

Based on the structured search conducted in the databases, 554 studies were identified. Through reading titles and abstracts and applying inclusion and exclusion criteria, Twelve articles (Figure 1) were selected for the corpus of analysis.

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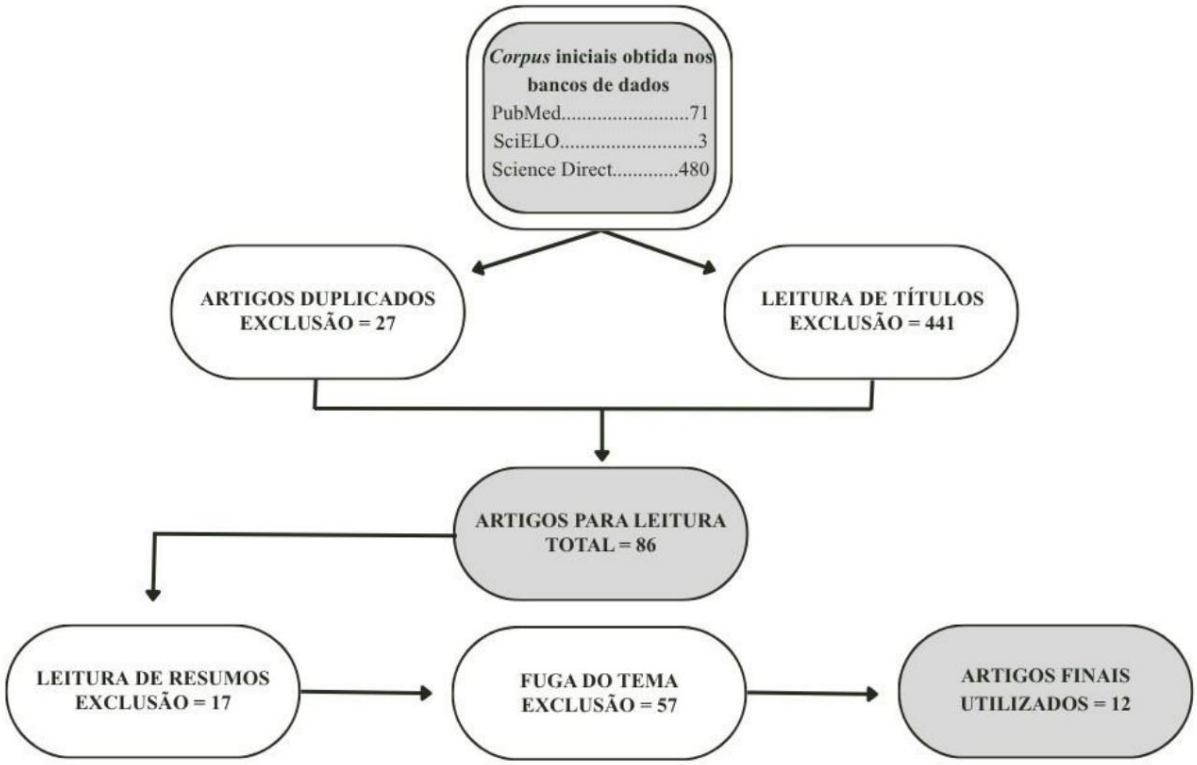
Figure 1. Article selection flowchart, 2026.



Source: Author's own work, 2026.

Among the 12 articles selected for review, studies that addressed the following were analyzed: Hematological complications associated with AML and LPA, with emphasis on TLS and SD. The studies The included studies primarily investigated the pathophysiological mechanisms and risk factors. clinical manifestations and therapeutic strategies related to these complications, such as the use venetoclax in AML and ATRA and ATO in APL. Details of the evaluated articles are available in Table 1.

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Table 1. Characteristics of the selected scientific articles, according to title, authors, year of publication, objective and results, 2026.

Title	Author	Year	Target	Results
Transcriptional and Metabolic Dissection of ATRA-Induced Granulocytic Differentiation in NB4 Acute Promyelocytic Leukemia Cells	Albanesi, J. et al	2020	Investigate transcriptional and metabolic changes during ATRA-induced differentiation.	ATRA promoted metabolic and gene expression changes associated with granulocytic differentiation, demonstrating that metabolic reprogramming is an essential part of the therapeutic response to LPA.
Leukemia: a model of metastatic disease	Whiteley, AE et al	2021	Discuss leukemia as a model of metastatic disease, exploring the mechanisms of cell dissemination and tissue invasion.	The authors demonstrated that leukemic cells have an intrinsic capacity for migration, survival in circulation, and tissue colonization, characteristics similar to those observed in metastases of solid tumors, highlighting the biological complexity of the disease.
The impact of ICAM-1, CCL2, and TGM2 gene polymorphisms on differentiation syndrome in acute promyelocytic leukemia	Mohamma dzadeh, Z. et al	2021	Investigate the association between inflammatory genetic polymorphisms and susceptibility to Down syndrome.	Polymorphisms in the inflammatory genes analyzed were associated with a higher risk of developing the syndrome, suggesting a genetic predisposition.
Tumor lysis syndrome and infectious complications during treatment with venetoclax combined with azacitidine or decitabine in patients with acute myeloid leukemia	Arora, S. et al	2022	Evaluate the incidence of TLS and infections in AML patients treated with venetoclax and hypomethylating agents.	A significant risk of SLT and infections was observed. In the initial phases of treatment, this reinforces the need for prophylaxis and intensive monitoring. SLT presented electrolyte disturbances such as hyperuricemia, hyperkalemia, and hyperphosphatemia, in addition to the risk of acute renal failure. Disorders Electrolyte imbalances, such as hyperuricemia, hyperkalemia, and hyperphosphatemia, and risk of acute renal failure.
Differentiation syndrome and coagulation disorder — comparison between treatment with oral and intravenous arsenics in pediatric acute promyelocytic leukemia	Luo, J. S. et al.	2023	Compare the incidence of SD and coagulopathies between oral (Realgar-Indigo naturalis formula [RIF]) and intravenous (ATO) forms of arsenic.	Both approaches were effective, however the incidence of SD varied according to the therapeutic regimen, demonstrating the need for specific monitoring. Clinical manifestations such as fever and dyspnea were observed, reinforcing the need for specific monitoring.

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Venetoclax in adult acute myeloid leukemia Hu, M. et	al.	2023	Review the efficacy, mechanisms, and adverse events of venetoclax in AML.	Venetoclax has demonstrated improved response and survival rates; however, it increases the risk of TLS, especially in patients with a high tumor burden.
Improved prevention and treatment strategies for differentiation syndrome contribute to reducing early mortality in patients with acute promyelocytic leukemia	Wu, Q. et al	2024	Evaluate strategies for prevention, early diagnosis and treatment of SD in LPA.	The implementation of standardized monitoring protocols, early use of corticosteroids, and rapid therapeutic interventions was associated with a significant reduction in early mortality and improved clinical outcomes in patients with APL. SD presented with manifestations such as fever, dyspnea, and organ dysfunction.
Tumor lysis syndrome in hematological Calvache, inpatients, experience from a university E.; hospital in Brazil: A retrospective cohort Tabares, study	HERE; Tabares Weber, S.	2024	Describe the incidence, risk factors and Outcomes of SLT in hematological patients hospitalized in a Brazilian tertiary hospital.	The incidence of TLS was 10.5%. The condition was associated with severe metabolic disorders, acute renal failure, and higher hospital mortality, demonstrating a significant clinical impact. A median survival of 13 months was also observed in affected patients.
Diagnosis and management of acute promyelocytic leukemia: Brazilian consensus guidelines 2024 on behalf of the Brazilian Association of Hematology, Hemotherapy and Cellular Therapy	of Figueiredo -Pontes, L. Lobo et al	2024	Review the Brazilian guidelines for the diagnosis and management of ALI (Acute Lipolytic Syndrome).	The use of ATRA and ATO has transformed the prognosis of ALI; however, complications such as SD remain relevant and require early intervention, with manifestations such as fever and dyspnea.
Prize en charge initiale d'une leucémie aiguë et de ses complications	Schiavini, Giulia et al	2025	Review initial guidelines The study acute complications in the management rapid diagnostic confirmation are clinical support and initiation of treatment.	highlights that clinical stabilization, prevention of metabolic and of adult patients with infectious leukemias, and key determinants in reducing early mortality.

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Incidence of Tumor Lysis Syndrome in Patients with Acute Myeloid Leukemia During Initiation of Therapy with Azacitidine and Venetoclax: A Retrospective Chart Review from a Canadian Single-Center Perspective	Saiyin, Tana et al.	2025	To evaluate the incidence and risk factors for TLS in AML patients treated with azacitidine in combination with venetoclax.	A significant incidence of tumor lysis syndrome was observed, associated with metabolic disorders, including hyperuricemia and electrolyte imbalances, which increases the risk of acute renal failure, especially in patients with a high tumor burden.
Tumor Lysis Syndrome in Acute Myeloid Leukemia Patients Treated With a Venetoclax-Based Regimen	Rowe, Margaret et al	2025	Investigate the occurrence of SLT in venetoclax-based therapeutic regimens in AML.	The use of venetoclax increased the risk of TLS in the early stages of treatment, but proper prophylactic management reduced serious complications and associated mortality.

Source: Author's own work, 2026.

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DISCUSSION

AML is a hematological neoplasm characterized by clonal proliferation.
uncontrolled proliferation of immature hematopoietic precursors in the bone marrow and peripheral blood,
resulting in suppression of normal hematopoiesis, progressive bone marrow failure, and impairment
Systemic. The biological heterogeneity of the disease, associated with the complex interaction between cells.
Leukemic conditions and the bone marrow microenvironment directly influence their clinical evolution and response to...
treatment and the occurrence of complications. In this scenario, understanding the mechanisms of
Cellular migration, survival, and adaptation become fundamental for the improvement of
therapeutic strategies. From this perspective, Whiteley et al. (2021) propose an interpretation
expanded by characterizing leukemia as a model of metastatic disease, highlighting the capacity
of leukemic cells to circulate, infiltrate tissues and establish new cellular niches, which
This contributes to the clinical complexity and challenges in managing the disease.
In a complementary approach, Albanesi et al. (2020) further explore the understanding of
molecular mechanisms, in demonstrating that ATRA-induced differentiation, is largely
Used in the treatment of LPA, it is associated with profound transcriptional and metabolic alterations.
Unlike the systemic perspective proposed by Whiteley et al., these authors demonstrate that
The therapeutic response involves significant intracellular metabolic reprogramming, which, although
essential for the maturation of myeloid cells, it can also contribute to the activation of
Inflammatory processes involved in SD.
Despite therapeutic advances, the treatment of acute leukemias remains associated with
potentially serious complications. With regard to SD, Luo et al. (2023) demonstrate that its
Incidence varies according to the therapeutic regimen when comparing different forms of administration of
arsenic, highlighting the influence of pharmacokinetics on the intensity of the inflammatory response.
Clinically, Down syndrome manifests with systemic signs such as fever, dyspnea, and organ dysfunction.
reflecting an exacerbated process resulting from rapid cell differentiation. In agreement, Wu
et al. (2024) highlight that early recognition of these clinical signs, combined with intervention
Immediate control is essential for managing the systemic inflammatory response.
Additionally, Mohammadzadeh et al. (2021) direct the analysis towards intrinsic factors to
patient, upon identifying genetic polymorphisms associated with increased susceptibility to the syndrome,
particularly in genes related to the inflammatory response, such as ICAM-1, CCL2, and TGM2.
form, while Luo et al. emphasize the role of treatment, Mohammadzadeh et al. highlight the
individual biological heterogeneity, reinforcing the multifactorial nature of Down syndrome.
From a clinical practice perspective, Wu et al. (2024) demonstrate that the implementation of strategies of

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Prevention, early diagnosis, and therapeutic intervention are associated with a significant reduction.
of mortality related to Down syndrome. Continuing this perspective, Wu et al. reinforce these
findings highlighting that early identification of clinical signs, combined with the immediate use of
Corticosteroids constitute a fundamental measure for controlling the inflammatory response.
systemic. However, upon critically analyzing these contributions, it is observed that, although the
Even if standardized protocols prove effective, their application may not fully encompass the...
individual variability described by Mohammadzadeh et al. (2021), which points to the need
more individualized approaches in managing the syndrome.

In parallel, SLT stands out as a metabolic emergency resulting from rapid destruction.
cell-induced by highly effective therapies. In this sense, Arora et al. (2022) show that the
The use of venetoclax in combination with hypomethylating agents significantly increases the risk of TLS.
especially in the early stages of treatment, characterized by a significant reduction in tumor burden.
This condition is characterized by significant metabolic disorders, including hyperuricemia.
Hyperkalemia and hyperphosphatemia, which can progress to acute renal failure. This corroborates...
These findings, Saiyin et al. (2025) identify as being directly related to
high tumor burden and rapid therapeutic response, which contributes to greater clinical severity and to
the need for intensive monitoring.

However, unlike these authors, who emphasize the inherent risk of the therapy, Rowe et al.
(2025) demonstrate that the adoption of appropriate prophylactic measures can significantly reduce
The occurrence of serious complications and mortality associated with SLT. This contrast highlights that the
The clinical impact of the syndrome depends not only on the treatment used, but also on...
The quality of clinical management highlights the importance of early intervention and monitoring.
intensive.

The clinical relevance of SLT is reinforced by Calvache et al. (2024), who, based on life data
In reality, studies demonstrate a significant association between SLT and the occurrence of acute renal failure.
and the increase in hospital mortality. In addition, Schiavini et al. (2025) emphasize that the
Initial clinical stabilization and prevention of metabolic and infectious complications are
determinants for reducing premature mortality, demonstrating that therapeutic success
It depends not only on the antineoplastic treatment, but also on the quality of clinical support and
laboratory.

Within the context of clinical guidelines, Figueiredo-Pontes et al. (2024) highlight that, despite the advances
Despite the combined use of ATRA and ATO, SD remains a significant complication.
and potentially fatal. Similarly, Hu et al. (2023) demonstrate that, although venetoclax
Although it has significantly improved response and survival rates in AML, its use is

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associated with an increased risk of TLS, highlighting a recurring pattern in the literature: therapies
More effective methods tend to intensify specific adverse events.

Thus, the integrated analysis of the studies shows that, although SD and SLT present
distinct pathophysiological mechanisms — the first being predominantly inflammatory and the
second metabolic —, Both are intrinsically related to therapeutic response and dynamics.
of the tumor burden. Furthermore, both can progress to serious systemic manifestations, including
Organic dysfunctions, especially when not recognized early. The presence of signs
clinical symptoms, such as fever and dyspnea, associated with laboratory abnormalities, such as electrolyte disturbances,
This reinforces the need for an integrated approach between clinical assessment and monitoring.
laboratory.

Finally, it can be inferred that the prognosis of patients with acute leukemias is directly related
not only to the effectiveness of antileukemic therapies, but also to the capacity of the team.
A multidisciplinary approach is needed to recognize and manage these complications early. In this context,
The strategic role of the biomedical professional stands out, especially in laboratory monitoring and in...
Early identification of metabolic and inflammatory changes. Thus, the integration between the
Scientific knowledge, clinical practice, and laboratory support constitute an element.
essential for reducing morbidity and mortality and consolidating a safer healthcare model
and effective in the treatment of acute leukemias.

FINAL CONSIDERATIONS

This literature review has allowed us to understand that acute leukemias, especially
AML and LPA remain diseases of high clinical severity, whose treatment, although
Although it has evolved significantly in recent decades, it is still associated with complications.
potentially fatal complications. Among these complications, SLT and SD stand out, events that can
occurring mainly in the initial phases of therapy and requiring clinical monitoring and
continuous laboratory work.

The studies analyzed demonstrated that SLT is directly related to rapid destruction.
Cellular changes induced by chemotherapeutic agents and targeted therapies, resulting in significant alterations.
Metabolic conditions, such as hyperuricemia, hyperkalemia, and acute renal failure. On the other hand, SD
It has been shown to be associated with the use of agents that induce cell maturation, such as ATRA and ATO, and
It is characterized by systemic inflammatory manifestations that can progress to severe conditions if...
not identified early.

In this context, the objectives proposed in this study were achieved, since it was possible

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to gather and analyze current scientific evidence on the pathophysiological mechanisms, risk factors, clinical manifestations, prevention strategies, and therapeutic approaches related to these complications. The analysis of the selected articles showed that early recognition of these syndromes, combined with the adoption of prophylactic measures and rigorous laboratory monitoring, is crucial for reducing mortality and improving the prognosis of patients with leukemia. acute.

Furthermore, the relevance of the biomedical professional's role in hospital and laboratory settings should be highlighted. especially in the monitoring of hematological and biochemical parameters, in the validation of Critical results and agile communication with the multidisciplinary team. This role is fundamental. for the early detection of changes consistent with SLT or SD, contributing directly to Patient safety and timely clinical decision-making.

Finally, the need to expand clinical and laboratory research focused on [topic] becomes evident. identification of new prognostic markers, standardization of monitoring protocols and to the development of increasingly specific and safe therapies. The continuation of studies in this area. This area is essential for improving the management of acute leukemias and reducing associated complications. to treatment, strengthening evidence-based practice and the quality of healthcare.

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