Ankyra Medical Journal
Review
DOI: 10.51271/ANKMJ-0066

Tumor lysis syndrome

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Cite this article: Balcı BH, Yalçın S. Tumor lysis syndrome. *Ank Med J.* 2026;5(2):50-55. doi: 10.51271/ANKMJ-0066

Received: 31/12/2025 ◆ Accepted: 25/01/2026 ◆ Published: 25/03/2026

ABSTRACT

Tumor lysis syndrome (TLS) is defined as the release of intracellular metabolites into the bloodstream, resulting from the breakdown of tumor cells due to various causes encountered in clinical practice. It has been observed that TLS, which occurs in patients with existing malignancy, further worsens the prognosis in the already poor condition and increases the risk of mortality in patients. Therefore, the diagnosis and follow-up of TLS by relevant clinicians is of great importance. This review examines overlooked aspects of TLS, including its etiology, pathophysiology, necessary investigations, diagnosis, treatment algorithms, and current clinical approach.

Keywords: Oncology, oncological emergency, tumor lysis syndrome

INTRODUCTION

Tumor lysis syndrome (TLS) is a condition characterized by the release of intracellular metabolites into the bloodstream, resulting from the breakdown of tumor cells. Its characteristic findings include hyperuricemia, hyperphosphatemia, hyperkalemia, and hypocalcemia. These electrolyte disturbances result in cardiac and renal effects, which can be life-threatening.[1]

TLS, which occurs in various malignancies, is associated with a poor prognosis because it occurs in patients who are currently undergoing chemotherapy and are in poor general condition. In addition to increasing mortality and morbidity in patients, it also creates extra costs for hospitals.[2]

ETIOLOGY AND RISK FACTORS

Furthermore, it has been determined that some solid tumors can also cause TLS. Among these, hepatoblastoma and neuroblastoma are more commonly seen. Although rare, cases of TLS occurring spontaneously before the start of chemotherapy have also been described in the literature.[3]

Based on studies, tumors that cause TLS have been classified by risk and summarized in Table 1.[4]

Although TLS is frequently associated with hematologic malignancies, it has also been observed to develop as a result of certain solid tumors. It primarily occurs in association with hepatoblastoma and neuroblastoma, while other related tumors are summarized in Table 2.[5]

Table 2. Solid tumors associated with tumor lysis syndrome

Solid tumors associated with tumor lysis syndrome
• Germ cell tumors • Neuro- and medulla blastomas • Small cell carcinoma and other lung tumors • Breast, ovarian, and vulvar neoplasms • Hepatoblastoma and hepatocellular carcinoma • Colorectal and gastric carcinoma • Melanoma • Sarcoma

Table 1. Classification of tumors according to their risk of developing tumor lysis syndrome

High-risk tumors	Intermediate-risk tumors	Low-risk tumors
Acute lymphocytic leukemia (5.2% to 23%) Acute myeloid leukemia with a WBC count greater than 75,000 (18%) B-cell acute lymphoblastic leukemia (26.4%) Burkitt lymphoma (14.9%)	Acute myeloid leukemia with a WBC count between 25,000 and 50,000 (6%) Diffuse large B-cell lymphoma (6%)	Acute myeloid leukemia with a WBC count less than 25,000 (1%) Chronic lymphocytic leukemia (0.33%) Chronic myelogenous leukemia (case reports) A solid tumor (case reports)

WBC: White blood cell

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In recent clinical studies on TLS, it has been determined that the chemotherapy regimen and biological agents administered also pose a risk for TLS. Chemotherapeutic and biological agents that are more frequently associated with TLS are summarized in Table 3.[4,6,7]

Table 3. Chemotherapeutic agents and biological agents that more frequently cause tumor lysis syndrome

Thalidomide	Venetoclax (BCL2 inhibitor)
Bortezomib	Obinutuzumab, rituximab (anti-CD20 monoclonal antibody)
Hydroxyurea	Nivolumab, pembrolizumab (anti-PD-1 monoclonal antibody)
Paclitaxel	Dinaciclib, alvocidib (cyclin-dependent kinase inhibitor)
Fludarabine	
Etoposide	
Zoledronic acid	

Studies on risk factors associated with the development of TLS have revealed that the increased risk is not solely related to tumor type but also to certain patient-specific factors. Accordingly, male gender, advanced age, underlying chronic kidney disease, and the presence of accompanying conditions have been found to increase the risk. The disease is generally classified into three risk categories. Accordingly, it is classified as high risk (TLS develops in more than 5% of patients), medium risk (TLS develops in 1-5% of patients), and low risk (TLS develops in less than 1% of patients). Risk factors associated with TLS are summarized in Table 4.[8-10]

Table 4. Tumor type and patient-related risk factors associated with tumor lysis syndrome

Tumor risk factors	Patient-related risk factors
• Type of tumor • Tumor volume (tumors >10 cm) • Metastatic disease • Tumor growth rate (LDH>2 times normal value) • Leukocytosis (>25,000/mm^3) • Sensitivity to chemotherapy (germ cell tumors, small cell lung cancer, etc)	• Male gender • Age >65 years • Pretreatment serum creatinine >1.4 mg/dl • Renal obstruction • Pretreatment serum uric acid >7.5 mg/dl • Associated conditions (hypotension, hypovolemia, nephrotoxic drugs, chronic kidney disease)

Spontaneous TLS is the spontaneous development of aggressive tumors due to an excessively rapid cell turnover, without any chemotherapy or radiotherapy support. This clinical picture is frequently observed in malignancies such as Burkitt lymphoma and acute lymphoblastic leukemia (ALL), and can sometimes appear as the first clinical sign of an as yet undiagnosed cancer case.[11] Statistical data show that this condition develops spontaneously in approximately 28% to 55.6% of childhood ALL cases.[12] Unlike treatment-induced TLS, hyperphosphatemia is generally milder in spontaneous cases because the viable tumor cells can metabolize the released phosphate for new cell production. However, since nucleic acid accumulation strains the body's detoxification capacity, uric acid concentrations can climb to risky levels. This condition, previously thought to be rare in solid tumors, is now reported more frequently thanks to improved monitoring methods and intensive treatment protocols. According to data, approximately 24% of TLS cases in solid tumors occur spontaneously. On the other hand, not only systemic drug therapies but also local interventions applied to liver tumors, such as TACE or radiofrequency ablation (RFA), carry a risk of triggering this syndrome.[13,14]

In modern oncology practice, TLS cases are being encountered more frequently as a result of the superior success of targeted and biological drugs in destroying cancer cells. Chronic lymphocytic leukemia (CLL) and multiple myeloma, which were previously considered low-risk, are now classified as high-risk diseases with the introduction of innovative methods such as venetoclax, obinutuzumab, rituximab, and CAR-T cellular therapies. Ironically, the rapid and intense destructive effect of these drugs on malignant cells can trigger serious metabolic disorders that endanger the patient's life.[15,16] Therefore, when assessing risk in current treatment protocols, not only the type of cancer should be focused on; the potency of the chosen therapeutic agent must also be considered as a vital criterion.

EPIDEMIOLOGY

Although the incidence of TLS has not been definitively established, clinical data have provided insight into which tumor types may be associated with secondary TLS. TLS is most commonly seen in hematological malignancies. The highest risk is observed in Burkitt lymphoma, ALL, and high-grade non-Hodgkin lymphoma (NHL). According to US data, 30% of patients discharged with a diagnosis of TLS are from NHL, 19% from acute myeloid leukemia (AML), and 13% from ALL. While this rate is not very high in solid tumors, small cell lung cancer, breast cancer, germ cell tumors, and hepatocellular carcinoma are the most common. Interestingly, TLS occurs spontaneously before treatment in 24% of these cases. Incidence data by tumor type are indicated in parentheses in Table 1.[4,17,18]

Pediatric patients are at higher risk because they are more affected by proliferative diseases. Burkitt lymphoma has the highest risk, at 30%, as in adults. In T-cell ALL and hyperviscosity cases, the risk of TLS increases to 20%. TLS is relatively rare in AML because the proliferation rate is lower.[11] Although TLS is rare in solid tumors, it has been reported in chemosensitive and bulky tumors such as hepatoblastoma, neuroblastoma, and germ cell tumors.[18] The risk is particularly significant in stage IV neuroblastoma.[11]

PATHOPHYSIOLOGY

The pathophysiology of TLS involves a complex combination of biochemical pathways. TLS is primarily based on an increase in products metabolized to uric acid and electrolyte imbalance. The DNA chain is composed of molecules called nucleotides. Nucleotides consist of a phosphate group, a sugar group, and a nitrogen base. The nitrogen bases are adenine, thymine, guanine, or cytosine. Adenine and guanine are called purines, while cytosine and thymine are called pyrimidines.[19] Purines are among the primary products metabolized into uric acid. Intermediate products are produced as a result of purine metabolism. These products can be listed as hypoxanthine and xanthine. Adenine is metabolized into hypoxanthine, while guanine is metabolized into xanthine. Xanthine is then converted into uric acid through a reaction catalyzed by xanthine oxidase. Under normal conditions, uric acid is excreted via the kidneys. Although many mammalian groups have the enzyme urate oxidase, which converts uric acid into its more soluble form, allantoin, humans do not. Figure 1 summarizes purine metabolism.[20]

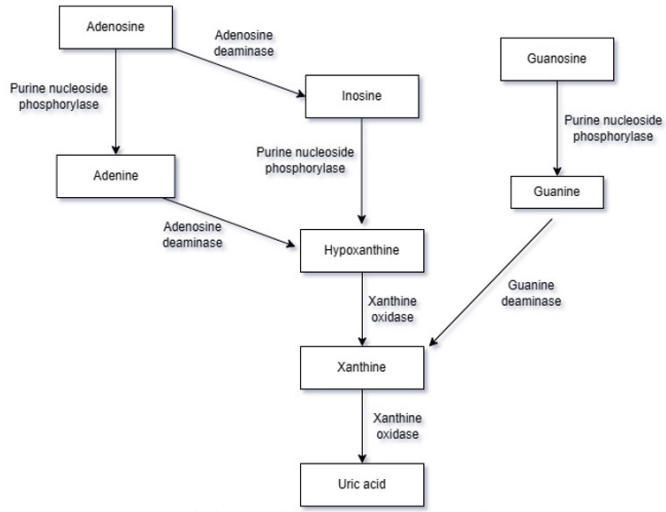

Figure 1. Purine metabolism and conversion to uric acid

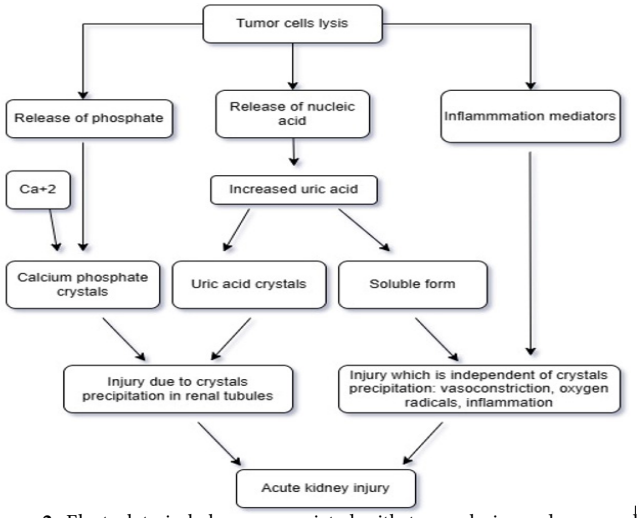

Figure 2. Electrolyte imbalances associated with tumor lysis syndrome and their relationship with kidney damage

Uric acid, which is produced as a result of purine metabolism, is normally excreted through the kidneys. However, in TLS, the release of large amounts of uric acid causes it to crystallize in the tubules and can lead to kidney damage. It has also been determined that uric acid crystals cause kidney damage by inducing the release of free oxygen radicals and stimulating vasoconstriction and inflammation.[21]

Many electrolytes are also released as a result of tumor cell destruction. The intracellular concentration of potassium is approximately 120-130 mEq/L. Potassium released from tumor cell breakdown is largely compensated for by the liver and skeletal muscle. However, in cases of excessive release, the compensation threshold is exceeded, serum potassium levels increase, and cardiac arrhythmias, particularly in the setting of hypokalemia, may occur.[22]

Another electrolyte imbalance associated with TLS is hyperphosphatemia. Intracellular phosphate enters the bloodstream as a result of cell breakdown. Under normal conditions, phosphate, which is excreted by the kidneys, precipitates with calcium and accumulates in the renal tubules, causing kidney damage.[23]

The precipitation of phosphate with calcium also lowers serum calcium levels. This is much more important than the clinical consequences of hyperphosphatemia. Due to the importance of calcium in cardiac rhythm, life-threatening situations may occur. In these patients, arrhythmias, tetany, and seizures may develop. Electrolyte imbalances and their effects associated with TLS are summarized in **Figure 2**.[24,25]

CLINICAL FINDINGS AND DIAGNOSTIC APPROACH

TLS does not present specific clinical findings. Clinical findings are mostly due to electrolyte and metabolite abnormalities caused by the syndrome. Therefore, patients may develop fatigue, weakness, and ECG abnormalities due to hyperkalemia. Due to hypocalcemia, spasms, tetany, positive Chvostek and Trousseau signs, and seizures may be observed. Due to hyperuricemia and obstructive uropathy, symptoms such as weakness, fatigue, irritability, nausea, vomiting, and itching may be observed.[26]

The diagnosis of TLS is based on the criteria developed by Cairo and Bishop. Although this classification is widely used, it has limitations in some areas. The most important disadvantage of the classification is that it is based on the development of the syndrome after patients have received chemotherapy. However, it is known that TLS can also develop in patients who have not yet started chemotherapy. Another disadvantage is that a serum creatinine level exceeding 1.5 times the normal level is one of the key criteria in the clinical diagnosis of TLS. This is because creatinine is considered a poor biomarker for detecting acute kidney injury, as it is heavily influenced by factors such as age, muscle mass, and hydration status. Furthermore, current criteria struggle to differentiate newly developed acute injury in chronic kidney disease patients who already have elevated baseline creatinine levels, as these patients may have creatinine values 1.5 times above the normal range even before developing acute kidney injury. On the other hand, impaired kidney function may not always be due to clinical TLS; conditions such as dehydration, use of nephrotoxic drugs (vancomycin, contrast agents, etc.), or direct infiltration of the kidneys by the tumor can mimic the criteria of TLS.[27]

The second disadvantage is the use of a 1.5-fold limit for serum creatinine levels. Conditions such as elevated baseline creatinine levels in patients with chronic kidney disease raise questions about the standardization of this criterion. Nevertheless, the Cairo and Bishop classification is the most clinically accepted and widely used classification and is summarized in **Table 5**.[28]

A staging system is used to evaluate treatment approaches for TLS. Although the staging system developed by Cairo and Bishop has been criticized by some authors for its definition of elevated creatinine, it is currently used clinically. The Cairo-Bishop TLS staging system is summarized in **Table 6**.[29] Although the Cairo-Bishop classification is a generally accepted classification, some of its limitations have been criticized in studies. The Cairo-Bishop definition limits TLS to the period between 3 days before and 7 days after the start of chemotherapy. However, in clinical practice, TLS can develop spontaneously before any treatment begins and this may initially be overlooked.[18] In addition, while a 25%

Table 5. Cairo and Bishop classification used in tumor lysis syndrome

Cairo-Bishop definition of tumor lysis syndrome (TLS)			
Laboratory TLS Defined by the modification of at least 2 parameters within 24 hours.	Uric acid ≥8 mg/dl Potassium ≥6 mg/dl Phosphate ≥4.5 mg/dl	or 25% increase	The condition typically occurs within 3 to 7 days after chemotherapy initiation
	Calcium ≤7 mg/dl	or 25% decrease	
Clinical TLS Defined as laboratory TLS plus one organ dysfunction or death.	Renal dysfunction (creatinine 1.5× normal values) Cardiac involvement (arrhythmias) Neurological involvement (seizures, tetany) Death		

Table 6. Cairo and Bishop staging system used in tumor lysis syndrome

	0	1	2	3	4	5
Creatinine	≤1.5xULN	>1.5xULN	1.5-3xULN	3-6xULN	>6xULN	Death
Arrhythmias	None	Intervention not indicated	Intervention indicated	Symptomatic, incompletely controlled	Life threatening	Death
Seizures	None	-	Single, easily controlled	Repeated, altered consciousness	Prolonged refractory	Death

ULN: Upper limit of normal

change from the baseline value is considered sufficient in laboratory TLS criteria, some clinicians argue that this 25% variation is not clinically significant and may increase the false positive rate, especially if the absolute values are within normal limits.[11,30] While the original criteria did not require the simultaneous occurrence of metabolic abnormalities, some researchers, such as Howard et al.,[29] have stated that individual abnormalities developing at different times may be unrelated to TLS, and therefore, the diagnosis should be based on the presence of at least two abnormalities within the same 24-hour period. Some experts argue that the "stage 0" definition in the Cairo-Bishop system is unnecessary and that more specific systems are needed for grading clinical complications (arrhythmia, seizures, etc.).[31] However, the shortcomings and difficulties related to the evaluation of renal function have also been mentioned above.

While the ASCO (2008), NCCN, and 2010 International Expert Panel Consensus (generally used as a basis by ESMO) guidelines on the management of TLS show significant similarities on a scientific basis, they have some shortcomings and differences in terms of risk assessment models and application details. Most guidelines accept the 2004 Cairo-Bishop criteria as the standard for diagnosis.[32] The biggest difference between the guidelines is on risk categorization and the effect of renal function on this risk. The 2010 International Consensus offers the most comprehensive and systematic model, classifying patients into "low, intermediate, high" risk groups. In contrast, the NCCN generally presents TLS risk by integrating it into disease-specific guidelines such as leukemia or lymphoma. The 2010 Consensus uses existing renal failure or dehydration as a "risk modulator"; that is, a low or intermediate-risk patient is automatically moved to a higher risk group if renal function is impaired.[32,33] ASCO (2008), however, focuses more on adult data and does not address renal function variables in the pediatric group in the same depth.[28]

TREATMENT APPROACH

First and foremost, prophylaxis should be prioritized in patients at high risk of developing TLS. The goal of adequate treatment is to prevent acute kidney injury and electrolyte imbalances that pose a major life-threatening risk. Therefore, in patients who have started cytoreductive therapy, renal function tests, serum electrolytes, and uric acid should be monitored at specific intervals based on risk category. The monitoring intervals for each group are summarized in Table 7.[29]

Table 7. Frequency of monitoring tests according to risk stages in tumor lysis syndrome

Patients at high risk	every 4 to 6 hours after antitumor therapy initiation
Patients at intermediate risk	every 8 to 12 hours after antitumor therapy initiation
Patients at low risk	daily

Intravenous hydration and ensuring adequate urine output are considered fundamental steps in the management of TLS. Guidelines recommend aggressive hydration, particularly in the moderate- and high-risk groups. As a result, glomerular filtration and urine output increase, reducing the likelihood of electrolyte and uric acid crystal precipitation in the renal tubules. Although there is no clear preference for intravenous fluid, Ringer's lactate should not be used due to its high potassium content.[34]

One of the key monitoring parameters following hydration is urine output. The recommended urine output is 80-100 ml/m² per hour. Diuretics may be preferred to achieve this output. Loop diuretics are the first-line diuretics. The reason for preferring loop diuretics is that they significantly increase potassium excretion.[35]

Hyperkalemia is a life-threatening electrolyte imbalance in TLS and requires acute intervention. In these patients, dietary potassium must be reduced, intravenous glucose-insulin solutions should be administered in cases of severe elevation, and loop diuretics should be preferred when necessary. Intravenous calcium gluconate should be administered to achieve cardiac stabilization in cases where cardiac risk is present.[29]

Hypocalcemia and hyperphosphatemia are also conditions that require prompt correction. Oral phosphate binders should be preferred for hyperphosphatemia when necessary,

and hypocalcemia should be managed with replacement therapy. Long-term phosphate stabilization has been shown to be beneficial in preventing the need for renal replacement therapy.[36]

In recent years, urinary alkalization has been actively used to increase the solubility of uric acid in urine. Sodium bicarbonate has been administered for urinary alkalization, aiming to reduce tubular precipitation of uric acid. However, recent studies have not shown that urine alkalization prevents uric acid precipitation; on the contrary, they have shown that it can cause calcium phosphate deposits in various organs. Therefore, the use of sodium bicarbonate for urine alkalization is not recommended today.[37]

Other methods for lowering uric acid involve directly suppressing uric acid synthesis and increasing uric acid breakdown. Currently, three hypouricemic agents are used with these methods. Allopurinol and febuxostat inhibit uric acid production, while rasburicase increases its breakdown. Hypouricemic agents and their mechanisms of action are summarized in **Table 8**.[32]

Table 8. Hypouricemic agents and mechanisms of action

Allopurinol	Xanthine oxidase inhibitors
Febuxostat	
Rasburicase	Recombinant urate oxidase

Allopurinol inhibits the formation of new uric acid by inhibiting xanthine oxidase. Because it affects the formation of new uric acid, it is administered prophylactically 24-48 hours before treatment. Studies have shown that it has no effect on pre-existing serum uric acid levels.[38] Its low cost and oral administration are its main advantages. However, as a result of inhibiting uric acid formation, serum levels of hypoxanthine and xanthine, which are precursors of uric acid, increase significantly. Therefore, it has been observed that it increases the risk of causing acute kidney injury by accumulating in the tubular lumen.[39]

Furthermore, allopurinol has been found to interact with various chemotherapeutic agents, particularly methotrexate.[40] In addition, the need for dose adjustment in renal function is another disadvantage.[41] Febuxostat is an agent that, like allopurinol, acts by inhibiting xanthine oxidase and is administered orally.

Febuxostat has been found to be superior to allopurinol in many ways. These include not requiring dose adjustment in mild to moderate renal impairment,[42] fewer drug interactions,[43] and greater uric acid-lowering effects.[44,45] On the other hand, its high cost is a factor that significantly limits its use.

Rasburicase is a recombinant form of urate oxidase that converts uric acid into allantoin, which is more soluble in water, has a lower toxicity risk, and is more easily excreted in urine. It has been shown to rapidly and effectively resolve TLS.

Rasburicase is often preferred in high-risk patients with TLS or in patient groups for whom xanthine oxidase inhibitors are contraindicated.[46] Renal replacement therapy should be considered without delay in patients who do not respond adequately to hypouricemic agents and who develop acute kidney injury and resistant electrolyte disturbances as a result.

While clinical guidelines align on the use of rasburicase for high-risk patients, the selection between allopurinol and rasburicase for moderate-risk individuals remains largely at the clinician's discretion due to a shortage of strong evidence-based findings.[31] Although most protocols advocate for weight-dependent dosing (0.15 - 0.2 mg/kg), recent studies suggest that fixed doses of 3 mg or 6 mg may be effective in adults, even though this methodology has not yet been integrated into all primary guidelines as a standard procedure.[15]

Currently preferred renal replacement therapies include daily hemodialysis, continuous venovenous hemofiltration, intermittent hemodialysis, and continuous hemofiltration. Renal replacement therapy should be continued until urine output and electrolytes return to normal.[47]

CONCLUSION

All these treatment methods should correct the kidney damage and electrolyte imbalances caused by TLS. Otherwise, it poses a life-threatening risk and leads to increased mortality.

ETHICAL DECLARATIONS

Peer Review Process

This review was externally peer-reviewed.

Conflict of Interest

The authors declare no conflicts of interest.

Financial Disclosure

No financial support was received for the preparation or publication of this article.

Author Contributions

Concept: BHB, SY; Design: BHB, SY; Control: BHB, SY; Data Collection and/or Processing: BHB, SY; Analysis and/or Interpretation: BHB, SY; Literature Review: BHB, SY; Article Writing: BHB, SY; Critical Review: All Authors.

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