REVIEW

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Tumor Lysis Syndrome in Lung Cancer Patients: A Review of the Literature

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Abstract

Background: Tumor lysis syndrome (TLS) in patients with lung cancer (LC) is poorly characterized, due to its predominance in hematologic malignancies, creating a gap in both recognition and management strategies. **Methods:** We reviewed the literature to identify features that distinguish patients with lung cancer (LC) at high risk for tumor lysis syndrome (TLS) and poor prognosis, and to evaluate treatment outcomes. The PubMed database was queried through February 2025 in accordance with PRISMA guidelines. Twenty-nine case reports, including clinical courses and biochemical data of LC patients who developed TLS, were analyzed and appraised. **Results:** Risk factors for tumor lysis syndrome (TLS) included elevated uric acid and lactate dehydrogenase (LDH) at baseline, along with dyspnea, oliguria, and lethargy. Factors associated with increased mortality included high baseline LDH, symptomatic TLS, the need for renal replacement therapy, liver metastasis, and widespread metastatic disease. Rasburicase was associated with improved survival in a limited subset. Mortality in patients with lung cancer (LC) and TLS rivaled that observed in hematologic malignancies. **Conclusion:** For patients with high-risk lung cancer (LC), proactive initiation of urate-lowering therapy and hydration along with rasburicase and continued hydration for those who develop tumor lysis syndrome (TLS) may reduce mortality. Further multicenter studies may influence diagnostic criteria, risk assessment, and prophylactic guidelines for TLS to better account for high-risk LC and other solid tumor patients.

Keywords: Tumor lysis syndrome- Prophylaxis- Lung cancer

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Introduction

Tumor lysis syndrome (TLS), a group of metabolic abnormalities, has widely been characterized as a rare but life-threatening oncologic emergency and is well described in aggressive leukemias and lymphomas, typically following chemotherapy initiation [1]. TLS is thought to occur as a result of intracellular release of components such as phosphate, potassium, and nucleic acids into the bloodstream, which leads to complications including arrhythmias, renal failure, and seizures, in addition to life-threatening acidosis [2, 3]. Unfortunately, despite significant inpatient treatment, one study of 28,000 patients with TLS cites a mortality rate as high as 21% [4].

Lung cancer (LC) is the second most common malignancy and the primary cause of cancer-related mortality in the United States [5]. In the United States, 240,000 new cases of LC emerge annually [6]. Cases of TLS following treatment for solid tumor malignancies, such as LC, are uncommon but have been reported and with significant mortality [7].

While there have been previous reviews on TLS across all malignancies, no review evaluating LC-specific patients currently exists. Clinicians with minimal concern for TLS within this population may overlook a potentially fatal complication that could manifest soon after presentation. Additionally, the efficacy of TLS treatment strategies has not been evaluated in the LC cohort.

The occurrence of TLS in LC remains underreported for several reasons. Hematologic malignancies demonstrate a high tumor turnover-rate in conjunction with greater sensitivity to chemotherapy [8]. Consequently, significant awareness of TLS is dedicated to these cancers, while it is less anticipated in solid malignancies. Additionally, advancements to cytotoxic chemotherapy regimens for solid tumors may explain why fewer cases were present in the past. LC patients frequently exhibit multiple comorbidities such as respiratory failure and multi-organ

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dysfunction, which can obscure recognition of TLS [9].

TLS, though rare in solid tumors, is a significant oncologic emergency with high mortality. Its occurrence in LC patients is underreported, creating a critical gap in diagnosis, prognostication, and management approaches. We aim to identify risk and prognostic factors and assess treatment efficacy of LC patients with TLS to enhance recognition and improve clinical outcomes.

Materials and Methods

Literature Search

This literature review was performed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) [10]. A completed PRISMA checklist is provided in Supplemental Figure 1. Two research team members (A.S., Z.S.) independently performed a search of the literature on the PubMed/MEDLINE database, most recently in February 24, 2025. Searches were filtered to only include English language, human species, and full text. Results included papers from all years up to 2025. Search queries were structured to correspond with primary and secondary search terms in sequence. The primary search term “tumor lysis syndrome” was searched with relevant secondary search terms including: “lung cancer”, “small cell lung cancer”, “combined small cell carcinoma of lung”, “bronchogenic adenocarcinoma”, “squamous cell carcinoma of lung”, “adenosquamous carcinoma of lung”, “large cell carcinoma of lung”, “pulmonary sarcomatoid carcinoma”, “lung carcinoid tumor”, “bronchioloalveolar carcinoma”, “adenoid cystic carcinoma of lung”, “pancoast tumor” and “non small cell lung cancer”.

Study Selection

Two independent reviewers (A.S., Z.S.) assessed the eligibility of relevant papers according to the inclusion and exclusion criteria. Inclusion criteria required detailed clinical and laboratory data for at least one confirmed TLS case in LC. Studies lacking specific patient-level data, reporting mixed malignancies, or written in non-English language were excluded. Five studies from the review portion of Dakhal et al. [11] were included outside of the PubMed searches [12–16] as they included primary patient data that met inclusion criteria. The process of study selection is depicted through a PRISMA flow diagram, shown in Figure 1.

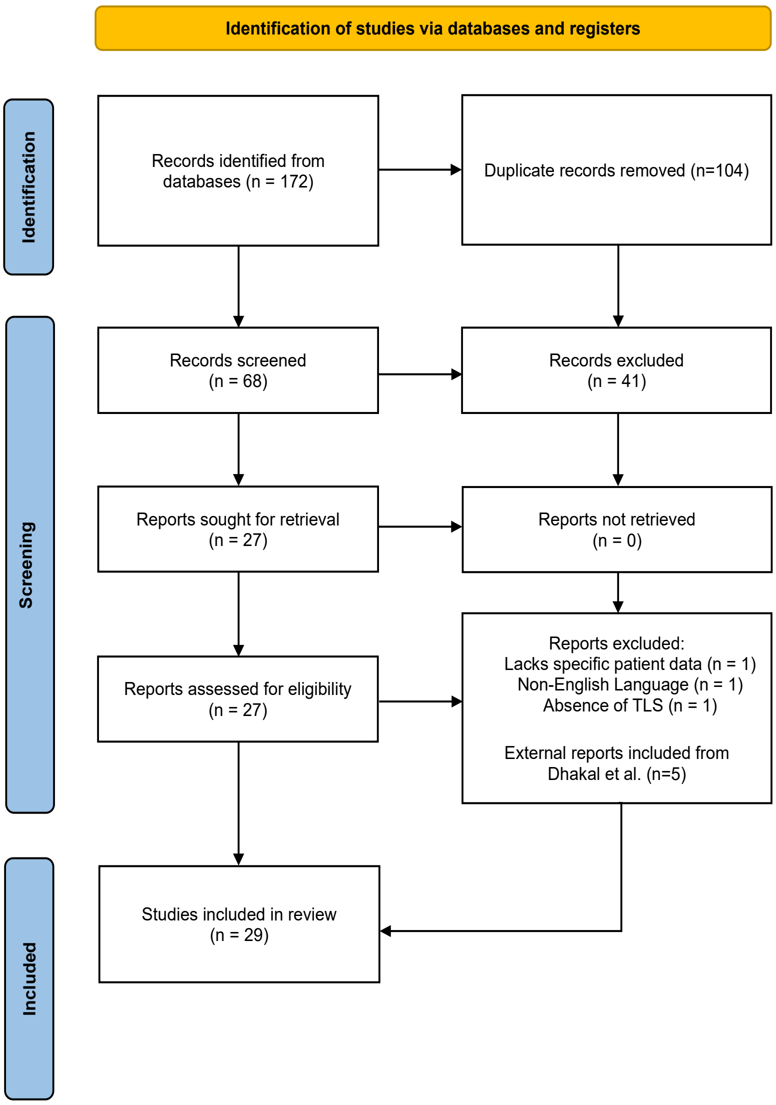

Figure 1. PRISMA 2020 Flow-Chart Diagram

Data Extraction & Analysis

Two coauthors (A.S., Z.S.) independently collected the following patient data from each study: patient age/gender, subtype of LC, primary tumor size, cancer stage, sites of metastases, cancer treatment, symptoms, designation of spontaneous or treatment-induced TLS etiology, specific TLS treatments, survival outcome, time to diagnosis, and time from diagnosis to death. Extracted lab values before, during, and after treatment of TLS included sodium, potassium, blood urea nitrogen (BUN), creatinine, calcium, phosphorus, uric acid, and LDH. These lab values were further assessed by calculating the mean and standard deviation for before, during, and after treatment of TLS. Mean electrolyte values were compared between the survival and deceased cohorts, and significance was determined using p-values derived from Welch's t-tests. Welch's t-test was chosen as it accounted for unequal variances between the survival and deceased cohorts, and is better suited for small sample sizes, making it appropriate for the heterogeneous data examined in this review. Mean time from diagnosis of TLS to death between survival and deceased cohorts was compared using 95% confidence intervals. Risk of bias was assessed by two independent reviewers (Z.S., A.A.) using relevant biases from the Cochrane Risk of Bias 2 Tool.

Data Synthesis

Due to the heterogeneity of the available information in the included studies, which consisted primarily of individual case reports with variable reporting on clinical and laboratory data, this review employs a narrative focus to best comprehensively integrate the given findings; this qualitative approach allows for meaningful interpretation, despite any reporting irregularities.

To supplement our qualitative synthesis, electrolyte and relevant lab values were extracted (when available) and aggregated in a data table. Welch's t-tests were utilized to assess significant differences between the mean lab values of the survival and deceased cohorts. However, this review's quantitative analysis remains limited, as the diversity of reporting formats and variation in study characteristics precluded any broader statistical pooling or meta-analysis.

Results

Description of Patients and Neoplasms

The findings of 29 case reports of patients with lung neoplasms with subsequent TLS are summarized in Supplementary Table 1 [11–39]. Of these patients, 21 were male (72.4%), and 8 were female (27.6%). Mean and median age was 62. The majority of studies did not report race. TLS was observed more frequently in small cell lung cancer (SCLC); 17 cases had small cell lung cancer (SCLC) (58.6%), and 12 cases had non-small-cell lung cancer (NSCLC) (41.4%). Adenocarcinoma was found in 7 cases (24.1%), 3 cases had squamous cell carcinoma (SCC) (10.3%), 1 case had typical carcinoid tumor (3.5%), and 1 case had mixed small cell and non-small cell (3.5%).

The overall mortality rate in patients with lung neoplasms who developed TLS was 48.3% (14/29). Death rates of LC patients with SCLC vs. NSCLC subtypes were similar (47%, n=17 vs. 50%, n=12). Patient factors and associated mortality are summarized in Figure 2.

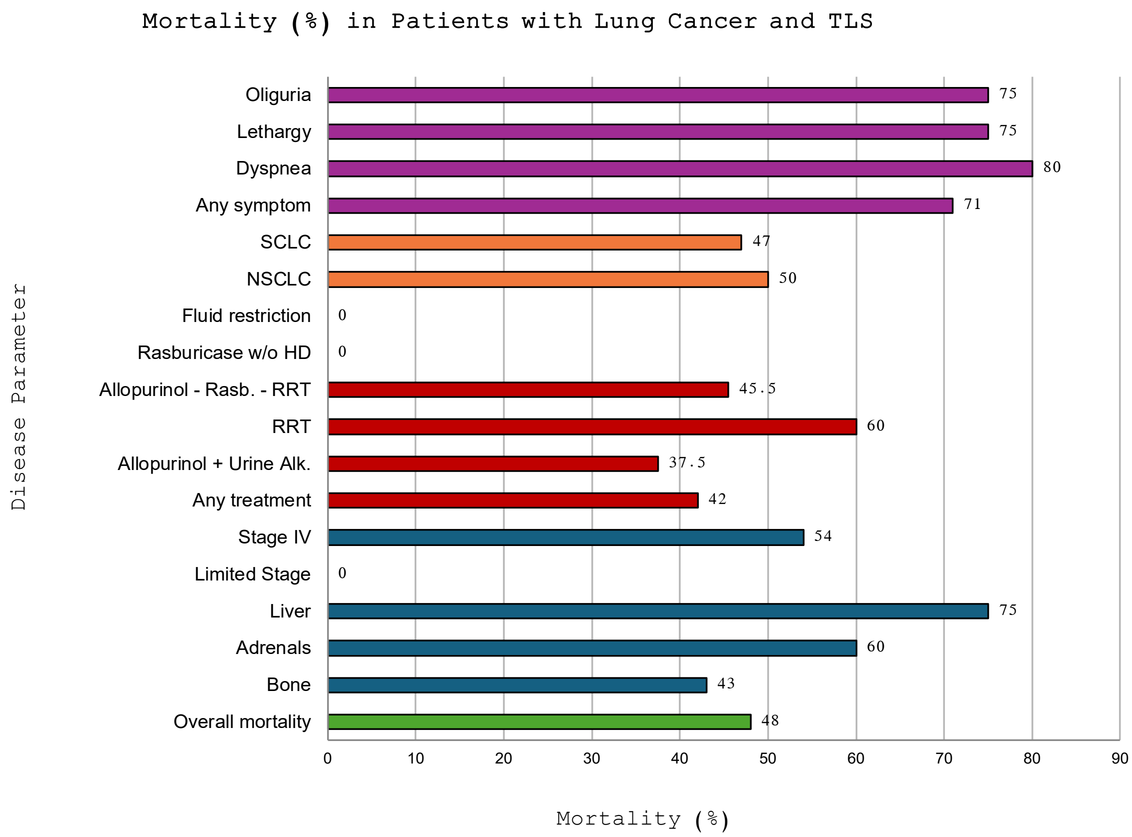

Figure 2. Breakdown of Mortality Differences Seen in LC Patients with TLS

Cancer treatments were reported in 21 out of 29 cases. There was no specific trend with the type of treatments used, which are detailed in Supplementary Table 1. Only 1 patient had a surgical resection (3.5%), and 1 patient received radiation therapy (3.5%), with the remaining patients receiving chemotherapy. Most commonly used chemotherapy agents included cisplatin, carboplatin, paclitaxel, etoposide, cyclophosphamide, doxorubicin, vincristine, and topotecan.

Tumor size was reported in 13 TLS cases (44.8%), with tumor mass sizes ranging from 3 cm or greater in maximum diameter.

Presenting Symptoms for TLS

The presenting symptoms for patients with lung neoplasm TLS varied greatly. The most reported symptoms patients experienced at time of diagnosis of TLS were dyspnea (34%, 10/29), oliguria (28%, 8/29), and lethargy (28%, 8/29). Dyspnea was attributed to acidosis mostly, with some cases reporting dyspnea secondary to tumor-induced obstruction of airways. Oliguria and lethargy were associated with 75% mortality, while dyspnea was associated with 80% mortality. In aggregate, LC patients with TLS who presented with any of these three symptoms had 71% mortality after accounting for overlap (n=17).

Biochemical Data

The mean and standard deviation of electrolyte values are given in Table 1. P-values from Welch's t-tests comparing survival and deceased cohort electrolytes are also included. Among the entire cohort, baseline uric acid and lactate dehydrogenase (LDH) values prior to the development of TLS were elevated (9.6, SD 5.9; 778, SD 521). At diagnosis of TLS, mean potassium (6.1, SD 1.2), blood urea nitrogen (71, SD 35), creatinine (3.3, SD 2.0),

Table 1. Mean Electrolyte Values[a]

	Total	Alive	Deceased	P-value
Sodium (mEq/L)				
Baseline	136.11 ± 2.52 (n = 9)	137.25 ± 1.5 (n =4)	135.2 ± 2.95 (n = 5)	0.22
Diagnosed	128.45 ± 10.06 (n = 11)	124.83 ± 11.65 (n = 6)	132.8 ± 6.34 (n = 5)	0.19
After Treatment	137.5 ± 0.71 (n = 2)	138 (n = 1)	137 (n = 1)	NA
Potassium (mEq/L)				
Baseline	4.47 ± 0.61 (n = 18)	4.68 ± 0.63 (n = 8)	4.31 ± 0.56 (n = 10)	0.22
Diagnosed	6.06 ± 1.21 (n = 26)	5.82 ± 1.21 (n =12)	6.26 ± 1.23 (n =14)	0.36
After Treatment	4.86 ± 1.24 (n = 7)	3.95 ± 0.92 (n = 2)	5.22 ± 1.23 (n = 5)	0.25
BUN (mg/dL)				
Baseline	24.82 ± 13.86 (n = 13)	25.12 ± 11.94 (n = 6)	24.57 ± 16.28 (n = 7)	0.95
Diagnosed	70.90 ± 35.83 (n = 14)	71.70 ± 41.57 (n = 5)	70.46 ± 34.95 (n = 9)	0.96
After Treatment	58.70 ± 29.34 (n = 5)	24 (n = 1)	67.37 ± 25.42 (n = 4)	NA
Creatinine (mg/dL)				
Baseline	1.14 ± 0.40 (n= 19)	1.18 ± 0.38 (n = 9)	1.10 ± 0.44 (n = 10)	0.68
Diagnosed	3.30 ± 1.98 (n = 25)	4.07 ± 1.81 (n = 12)	2.58 ± 1.91 (n = 13)	0.06
After Treatment	1.80 ± 0.84 (n = 8)	1 ± 0.44 (n = 3)	2.27 ± 0.63 (n = 5)	0.02*
Calcium (mg/dL)				
Baseline	9.06 ± 1.34 (n = 16)	8.71 ± 1.84 (n = 7)	9.33 ± 0.80 (n = 9)	0.43
Diagnosed	7.32 ± 1.83 (n = 21)	7.31 ± 1.63 (n = 9)	7.32 ± 2.04 (n = 12)	0.99
After Treatment	7.35 ± 0.93 (n = 3)	NA	7.35 ± 0.92 (n = 3)	NA
Phosphorus (mg/dL)				
Baseline	4.19 ± 2.22 (n = 13)	3.52 ± 0.90 (n = 5)	4.60 ± 2.73 (n = 8)	0.33
Diagnosed	7.45 ± 2.65 (n = 24)	6.78 ± 1.86 (n = 12)	8.12 ± 3.19 (n =12)	0.23
After Treatment	5.77 ± 1.74 (n = 5)	3.9 (n = 1)	6.23 ± 1.61 (n = 4)	NA
Uric Acid (mg/dL)				
Baseline	9.6 ± 5.87 (n = 13)	8.08 ± 2.85 (n = 6)	10.9 ± 7.61 (n = 7)	0.39
Diagnosed	14.32 ± 6.42 (n = 25)	15.15 ± 5.91 (n = 12)	13.56 ± 7.01 (n = 13)	0.55
After Treatment	7.72 ± 4.83 (n = 7)	3.05 ± 0.35 (n = 2)	9.59 ± 4.44 (n = 5)	0.03*
Lactate Dehydrogenase (U/L)				
Baseline	778 ± 520.8 (n = 14)	458 ± 236 (n = 7)	1098 ± 541 (n =7)	0.02*
Diagnosed	5645 ± 10567 (n = 16)	1335 ± 1138 (n = 5)	7603 ± 12389 (n = 11)	0.13
After Treatment	3018 ± 3466 (n = 4)	1229 ± 1173 (n = 2)	4807 ± 4676 (n = 2)	0.47

[a] BUN, blood urea nitrogen; LDH, lactate dehydrogenase; mEq/L, milliequivalents per litre; mg/dL, milligrams per decilitre; U/L units per litre; NA, not available; SD, standard deviation; * $p < 0.05$; statistical significance indicated by Welch t-test

phosphorus (7.5, SD 2.7), uric acid (14.3, SD 6.4), and LDH (5645, SD 10568) were elevated above the upper limit of normal.

Baseline LDH was significantly higher in the deceased cohort when compared to the surviving cohort (1098 vs. 458, p < .05, 95% CI 698-1498). Additionally, after treatment, deceased patients had significantly higher creatinine (2.27 vs. 1.00, SD 0.63 vs. 0.44, p < .05) and uric acid (9.59 vs. 3.05, SD 4.44 vs. 0.35, p < .05) when compared to the survival cohort. Baseline phosphorus, calcium, and uric acid were higher in the deceased cohort but not to statistical significance.

Spontaneous vs. Treatment-Induced

There were 21 cases of treatment-induced TLS and 8 cases of spontaneous TLS (72%, 18%). Treatment-induced TLS was secondary to mainly chemotherapy regimens outlined in Supplementary Table 1, with two studies mentioning targeted therapies (ceritinib, afatinib) [24, 37]. Death rates of LC patients with treatment-induced vs. spontaneous TLS were similar (50%, n=8 vs. 48%, n=21). Of the 8 spontaneous TLS cases, 4 (50%) involved SCLC, and 7 involved stage IV disease. All the deceased patients had liver metastases. Four cases among the treatment-induced TLS cohort involved atypical presentations, namely 2 cases of syndrome of inappropriate antidiuretic hormone secretion (SIADH), one case following radiation therapy, and one case following surgical resection of the tumor [31, 33, 36, 38]. All of these patients survived.

Metastasis

28 cases reported LC stage, and 24 (86%) were stage IV disease with 54% mortality. All limited-stage patients survived (100%, n=4). The most common metastasis site reported was the liver (n=16, 55%). Of all the cases with reported metastases, the cases with metastasis to the liver had the highest mortality rate of 75%. Mortality was 60% for patients with adrenal metastasis (n=5) and 43% for patients with metastasis to bone (n=7).

Prophylaxis vs. None

Out of 29 patient cases, prophylactic treatment was given only to 2 patients (6.9%). Allopurinol was given as prophylaxis for one patient [30], and allopurinol, intravenous fluids, and urine alkalization (sodium bicarbonate) were given as prophylaxis for the other patient [19]. Both TLS cases occurred after chemotherapy treatment and involved stage IV SCLC with liver metastasis. Both patients passed away from malignancy-related complications: disseminated intravascular coagulation (DIC) secondary to sepsis with multiorgan failure in the former case, and gastrointestinal bleeding secondary to tumor lysis of gastric wall metastasis in the latter. Four SCLC cases presented after May 2011, the date Howard et al. published their widely used TLS risk assessment/prophylaxis algorithm recommending allopurinol prophylaxis for SCLC patients with metastatic disease prior to treatment due to intermediate TLS risk [8]. The patients from Dhakal et al. and Jallad et al. had spontaneous TLS on presentation, while Boikos et al. and Kanchustambham et al. involved non-metastatic SCLC cases [11, 16, 20, 26]. The two cases that involved pre-chemotherapy urate lowering in our cohort predate Howard et al.'s guideline but acknowledge the role of elevated uric acid, renal dysfunction, and preceding case reports that may have influenced their decision to provide prophylaxis.

Treatment of TLS

Treatment type was only reported in 24 case reports. TLS treatment regimens included IV fluids with stepwise additions of allopurinol, rasburicase, and renal replacement therapy; treatment including urine alkalinization (with sodium bicarbonate), therapies to manage hyperkalemia, and fluid restriction (SIADH) differed case by case. The patient therapies and outcomes are listed in Table 2. No treatment was reported in 5 case reports. The mortality rate in those who sought treatment was 42% (n=24). The mortality rate was 37.5% for patients receiving allopurinol and urine alkalinization treatment (n=8). Patients receiving allopurinol therapy without rasburicase or dialysis had 45.5% mortality (n=11). All three non-dialysis patients that received rasburicase survived; two of the three concurrently received allopurinol. Only 5 patients received rasburicase, with the earliest case report dating back to 2013 [11, 16, 20, 21, 37]. Rasburicase received FDA approval for treatment of hyperuricemia in TLS for adults in October 2009 [40]. Review of the rest of the cohort mostly includes cases from prior to October 2009. Papers after this date either did not receive treatment for TLS [23, 26], did not specify which hyperuricemic agent was used [24], or had no contraindication [36]. All two patients who received fluid restriction for SIADH induced by tumor lysis survived. Patients who received renal replacement therapy had 60% mortality (n=5).

Summarization of Causes of Death

Fourteen studies specified the cause of death for LC patients experiencing TLS. Eight patients had deaths directly attributable to TLS, describing renal failure, cardiac arrest, and acidosis prior to their demise. The rest of the studies mention deaths due to multiorgan failure, sepsis, shock, hemorrhage, and other comorbidities, with TLS being a significant part of their decline. The causes of death reported for each case are summarized in Supplementary Table 1.

Time to Diagnosis/Death

Mean time to diagnosis of TLS was 2.44 days (SD 2.5, n=26). In the deceased cohort, mean time from TLS diagnosis to death was 2.8 days (SD 1.6, n=9). There was no significant difference between the time to diagnosis in the survival and deceased cohorts, respectively (2.86 days, n = 14, 95% CI 1.13-4.59; 2.0 days, n = 12, 95% CI 1.32-2.68).

Risk of bias

Due to reliance on heterogeneous case reports, reporting bias was present. Electrolyte values were not reported consistently across studies. Some studies would not report specific electrolyte values listed in the Cairo-

Table 2. Summary of TLS Treatment Strategies[a]

Paper	Therapy for TLS	Survival Status
Padhi and Singh [12]	IVF	Deceased
Sewani et al. [34]	IVF, Urine alkalinization	Deceased
Kalemkerian et al. [27]	IVF, Urine alkalinization, Forced diuresis	Alive
Kurt et al. [29]	IVF, Allopurinol, Urine alkalinization	Deceased
Ohnishi et al.[13]	Allopurinol, IVF, Urine alkalization	Alive
Baumann et al.[18]	IVF, Allopurinol, Urine alkalization	Alive
Hussein et al.[25]	Allopurinol, IVF, Urine alkalization	Alive
Marinella [30]	Allopurinol, IVF, Urine alkalinization	Deceased
Mott et al.[14]	Allopurinol, IVF, Urine alkalization	Alive
Pearsons et al.	Allopurinol, Urine alkalinization, IVF	Alive
Beriwal et al. [19]	Allopurinol, Phosphate binding resin, IVF, Urine alkalization	Deceased
Feld et al.[22]	Potassium and phosphate binders, Calcium gluconate, Allopurinol, IVF	Deceased
Shin et al. [36]	Insulin, Dextrose, Albuterol, Sodium polystyrene sulfonate (hyper-kalemia), Allopurinol, IVF	Alive
Vogelzang et al. [39]	Allopurinol, IVF	Deceased
Stuart and Auten [37]	Rasburicase and IVF	
Insulin, Dextrose, Urine alkalinization	Alive	
Kanchustambham et al. [16]	Allopurinol, Rasburicase, IVF	Alive
Boikos et al. [20]	Allopurinol, Rasburicase, IVF	Alive
Shenoy [35]	Allopurinol, Hemodialysis, IVF	Alive
Noh et al. [31]	IVF, Furosemide, Urine alkalinization, Hemodialysis	Deceased
Dhakal et al. [11]	Rasburicase, Allopurinol, IVF, Hemodialysis	Deceased
Hong [24]	IVF, Urine alkalinization, furosemide, 'specific interventions for hyper-uricemia and hyperkalemia'; continuous renal replacement therapy	Deceased
Causbie et al. [21]	Rasburicase, continuous renal replacement therapy	Alive
Vanhees et al. [38]	Fluid restriction (SIADH)	Alive
Saintigny et al. [33]	Fluid restriction (SIADH)	Alive
Ajzensztejn et al. [17]	None	Deceased
Honda et al. [23]	None	Deceased
Jallad et al.[26]	None	Deceased
Kallab and Jillella [28]	None	Deceased
Heching et al.[15]	None	Deceased

[a] IVF intravenous fluids; SIADH syndrome of inappropriate antidiuretic hormone secretion

Bishop criteria, likely due to them being normal as the other expected lab values were reported. Other studies would report electrolytes that were 'normal' but would not list values that would allow for further analysis in our review. Pretreatment/baseline and post-treatment labs were also not uniformly reported, often the focus was on reporting abnormal values if they were reported. Few studies did not specify treatments administered for TLS.

Discussion

Key Findings

Our cohort of LC patients with TLS experienced significant mortality, with overall mortality at 48%. SCLC and treatment-induced TLS occurred more frequently. Elevated baseline uric acid and LDH values, in addition to reported dyspnea, oliguria, and lethargy, were risk factors for TLS identified in our LC patient cohort. Poor outcomes seemed to reflect large tumor burden or greater illness severity. Specifically, elevated baseline LDH, liver metastasis, TLS-related symptoms, metastatic disease, and need for renal replacement therapy were associated with poor prognosis. Subgroups with increased survival tended to have limited-stage disease and atypical presentations of TLS stemming from radiation, surgery, or presenting as SIADH. Rasburicase conferred a survival benefit for a subset of LC patients presenting with TLS after its FDA approval.

Comparison to Literature

Uric acid greater than 7.5 (mg/dL) and LDH greater than two times the normal limit are identified risk factors for TLS in the general cancer population [41]. Patients reported dyspnea, oliguria, and lethargy at time of diagnosis of TLS, consistent with the pathophysiology and resulting electrolyte disturbances of TLS. These symptoms are consistent with the commonly reported presenting complaints in patients with TLS, which include nausea, lethargy, hypervolemia, oliguria, flank pain, muscle cramps, arrhythmia, and seizures [42]. Dyspnea, oliguria, and lethargy were also associated with increased mortality. Cho et al. report symptoms of TLS at the time of diagnosis of diffuse large B-cell lymphoma to be associated with increased mortality [43].

The overall mortality rate across all lung neoplasms with TLS was 48% (14/29). Durani et al. reported mortality to be 21% in a study of over 28,000 patients with TLS [4]. Alqurashi et al. reported a mortality rate of 54% among 101 patients with solid tumors who experienced TLS [7]. While the number of LC patients diagnosed with TLS may be small, they experience higher mortality than seen in TLS impacting hematological malignancies predominantly.

The majority of cases were stage IV LC; the four limited-stage LC patients featured in our study all survived. Our research suggests limited-stage LC confers improved prognosis. Bulky disease has demonstrated increased risk of TLS; similarly, metastatic disease for patients with solid tumors also increased risk of TLS, according to Alqurashi et al. [7].

Mortality was 75% for TLS patients with liver metastasis, in addition to 60% mortality (n=5) seen in patients with adrenal metastases. Patients with TLS and liver metastases represent a high-risk group. A study that focused on TLS in patients with solid tumors found a higher mortality rate in patients with liver metastasis [44]. They concluded that liver metastasis is an independent marker of poor outcomes in patients who develop TLS [44].

There were 17 cases of SCLC and 12 cases of NSCLC. Similarly, Alqurashi et al.'s review of 132 solid tumor patients with TLS reported 12 of 17 LC patients had SCLC [7]. SCLC, due to its neuroendocrine differentiation and high mitotic rate, responds well to chemotherapy, possibly explaining its predominance among LC patients who developed TLS in the literature [27, 45]. However, our study found no mortality difference from TLS between the two LC subtypes.

Our study found a predominance of treatment-induced TLS (72% vs. 18%), which was similar to Alqurashi et al. (76% vs. 24%) [7]. There was no mortality difference between treatment-induced TLS and spontaneous TLS cases. While there were no treatment-induced TLS cases secondary to immunotherapy in our study, there were two patients that developed TLS after receiving targeted therapy.

TLS was diagnosed within 2-3 days on average for LC patients. Some cases involved the diagnosis being made during hospital admission, while other cases involved patients being diagnosed with TLS upon presentation after relatively benign initial lab work days prior. There were no clear patterns to suggest mortality differences as the time to diagnosis of TLS increased. Our LC cohort demonstrates the rapid presentation of TLS reported in the literature [16, 37].

The mortality rate for patients who received treatment was 42% (n=24). Similar mortality was seen for patients receiving allopurinol and urine alkalinization. Despite urine alkalinization being historically recommended for its ability to reduce uric acid precipitation by increasing its solubility, recent recommendations caution against its routine use due to its role in exacerbating hypocalcemia and increasing the risk of xanthine crystal formation and calcium phosphate precipitation, limiting its indication to patients with existing metabolic acidosis [46]. Part of the pervasiveness of urine alkalinization could be explained by the age of some of the studies. Current practice favors rasburicase and volume resuscitation. All 3 patients who received rasburicase and did not require renal replacement therapy survived. Only 5 patients received rasburicase in total due to several papers predating FDA approval of rasburicase. Rasburicase has a more rapid onset of action than allopurinol [47] and has shown mortality benefit over allopurinol in smaller studies for management of TLS [48]. Prophylaxis with rasburicase and IV fluids is the standard of care for patients at high risk for TLS, while prophylactic allopurinol and hydration are indicated for intermediate-risk patients [49]. Given that stage IV SCLC confers intermediate risk for TLS, and only 2 patients (both with SCLC) received prophylactic allopurinol, a significant underutilization of prophylactic urate lowering therapy was present in our cohort. Both patients did not survive. Similar to rasburicase usage, the majority of studies predated the 2011 Howard et al. guidelines, and the studies that followed featured patients ineligible for prophylactic urate lowering therapy (low-risk per the guidelines) [8].

Clinical Implications

Both elevated uric acid and LDH were risk factors for TLS in LC patients. LDH may serve as a prognostic factor for worse outcomes of TLS. Lethargy and dyspnea are fairly nonspecific in LC and can be treatment-related or attributed to the disease itself or other complications. Oliguria may potentially be a more reliable risk factor. More research in this area is warranted. LC patients discussing these symptoms with their providers should undergo further evaluation for TLS, especially those undergoing treatment. SCLC and treatment-induced TLS were more prevalent in our cohort. While SCLC is a known risk factor for TLS in the literature, over 40% of our cohort had NSCLC, emphasizing the importance of assessing the full clinical picture to account for all risk factors. Interestingly, SCLC and treatment-induced TLS status did not affect prognosis in our study. TLS secondary to surgery, radiation, or associated with SIADH was associated with decreased mortality in addition to limited stage disease; these may serve as positive prognostic indicators after further research.

While TLS cases in LC patients are infrequent, mortality is possibly higher than seen in hematologic malignancies, and development time is marked by the same urgency, underscoring the importance of clinical vigilance and further study of this cohort. With the rise of immunotherapy and targeted agents for LC, their association with TLS warrants exploration, particularly given their potential to trigger tumor lysis in responders. While widespread T-cell mediated destruction of tumor cells as a consequence of immunotherapy may occur over a longer timeframe than conventional chemotherapy, there is an increasing number of case reports of TLS secondary to immunotherapy recently approved for solid malignancies [50].

Increased tumor burden may drive various risk and prognostic factors, including uric acid, LDH, metastatic disease, and liver metastasis. In our study, all primary lung masses had one dimension spanning at least 3 cm. Liver metastasis may serve as an independent poor prognostic indicator; mortality was 75% in our cohort, and similarly higher in the literature.

Current guidelines classify SCLC patients with large tumor burden as intermediate risk for TLS and recommend prophylactic hydration and allopurinol, while IV hydration and monitoring is recommended for NSCLC, deemed low risk along with other solid tumors [8]. In our cohort, prophylactic urate lowering therapy was underutilized. There is a need for large multicenter studies relating to TLS outcomes for lung cancer patients and solid tumor patients to further investigate the high mortality seen in our LC cohort. Retrospective studies could utilize aggregated patient databases (utilizing claims data linked to electronic medical records) to extract more cases of TLS in LC not reported in literature and provide access to more clinical data. Prospective registries could allow systematic collection of relevant clinical data and risk factors across multiple sites, while also encapsulating emerging therapies including immunotherapy (e.g., checkpoint inhibitors) and targeted agents against specific molecular mutations. Exploration of the prognostic utility of LDH and efficacy of prophylactic interventions for TLS would serve great benefit. Uric acid, LDH, metastatic disease, liver metastasis, and symptomatic TLS may help identify LC patients that would benefit from more aggressive prophylaxis and treatment. In the future, guidelines may adapt to account for high risk features present in solid tumor patients.

In light of the significant mortality seen in LC patients with TLS, we recommend prophylactic urate-lowering therapy and hydration for high risk LC patients: those with metastatic disease, liver metastasis, elevated LDH and uric acid, and presence of dyspnea, oliguria, or lethargy. Close monitoring of LDH and uric acid in high-risk LC patients may facilitate early TLS detection and management. With TLS manifesting in less than 3 days from baseline labs, early intervention is critical for this cohort, as the speed of decompensation and death seen in patients with poor outcomes was similar. LC patients with TLS should be managed with rasburicase based on uric acid levels and severity of disease in the same manner as patients with hematologic malignancies. The need for renal replacement therapy was another negative prognostic indicator in our study.

Limitations

While the findings provide insight, the small sample size limits statistical power and necessitates cautious interpretation. Furthermore, the use of case reports in much of the literature could indicate publication bias, since severe or unique TLS cases are more likely to be reported, while milder or uneventful cases may be less-frequently documented. This could lead to an imbalanced perception of outcomes. Electrolytes were not reported uniformly due to reporting bias, limiting the power of electrolyte analysis. Baseline or pretreatment electrolyte derangements with potential to predict TLS may not have manifested in our study as a result. Several studies predate approval of therapies for TLS such as rasburicase, likely explaining its lack of use across our LC cohort. Similarly, many studies predate guidelines recommending prophylactic urate lowering therapy for metastatic SCLC. The dearth of targeted therapies/immune therapies employed for LC patients in our cohort may be due to their recent approval or a potentially decreased risk of TLS; further study of this cohort may help shed light on this topic. The literature search was largely limited to the PubMed/MEDLINE database, consistent with the predefined scope of the project. While this approach ensured a focused and methodologically consistent review, a broader multi-database search could increase coverage and should be considered in future work. Multicenter registries and prospective studies may provide recent data at the statistical power needed to reliably stratify TLS risk-types in LC patients and assess outcomes after TLS prophylactic measures and treatments. The symptoms related to TLS found in our studies, specifically fatigue and dyspnea, are fairly nonspecific, especially in the context of LC. Oliguria may be a more reliable patient-reported risk factor, although more studies would allow further insight into this area. The LC patients who expired due to causes other than TLS (43%, n = 14) seemed to have significant comorbidities, including multiorgan failure, sepsis, and hemorrhage, with TLS being one of the factors contributing to their decline. This suggests that the illness severity of the deceased cohort was significant, complicating prognostication at its current statistical power.

Lung cancer patients who develop tumor lysis syndrome (TLS) face significant mortality, comparable to rates observed in hematologic malignancies. Given the rise of new immunotherapies and targeted agents, this cohort warrants further study. Clinical features such as elevated initial levels of uric acid and lactate dehydrogenase (LDH), along with the emergence of symptoms like dyspnea, reduced urine output, or fatigue, may aid in early identification of high-risk individuals. Adverse outcomes appear linked to extensive tumor burden or overall clinical severity. Elevated baseline LDH, liver metastasis, TLS-related symptoms, need for renal replacement therapy, and metastatic disease was associated with poor prognosis. Rasburicase is the preferred treatment for hyperuricemia and was associated with greater survival. We recommend prophylactic urate lowering therapy and hydration for patients with risk factors and poor prognostic factors identified in our review.

Author Contribution Statement

ZS: Conceptualization, Methodology, Investigation, Formal Analysis, Writing – Original Draft, Writing – Review & Editing, Visualization, Supervision, Project administration; AS: Investigation, Writing – Original Draft, Writing- Review & Editing, Visualization; AP: Conceptualization, Methodology, Writing – Original Draft, Writing – Review & Editing, Supervision, Project administration; AA: Investigation, Formal Analysis, Writing – Review & Editing, Visualization, Project administration; KR: Investigation, Formal Analysis, Writing – Original Draft, Writing – Review & Editing; MH: Investigation, Formal Analysis, Writing – Original Draft, Writing – Review & Editing, Visualization; MA: Investigation, Writing – Review & Editing, Visualization; MP: Conceptualization, Writing – Original Draft, Writing – Review & Editing, Project administration; UD: Investigation, Writing – Original Draft, Writing – Review & Editing; HN: Conceptualization, Methodology, Writing – Review & Editing; BA: Conceptualization, Writing – Original Draft, Writing – Review & Editing, Supervision, Project administration. All authors approved the final version and agree to be accountable for all aspects of the work.

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