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Review Paper

Clinical Significance of the Long Non-coding RNA Taurine Upregulated Gene 1 as a Predictive Biomarker in Neoplasms: A Systematic Review

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ABSTRACT

Background: Long non-coding RNAs (lncRNAs) are important regulators of cancer development and progression. Taurine upregulated gene 1 (*TUG1*) has been proposed as a prognostic biomarker in several malignancies, although its clinical significance remains inconsistent. This systematic review evaluated the available evidence on the association between *TUG1* expression and prognosis in patients with cancer.

Materials and Methods: A systematic literature search was conducted in Web of Science, PubMed, Scopus, ProQuest, ERIC, and ScienceDirect for studies published between January 2014 and December 2023. Original studies investigating the relationship between *TUG1* expression and cancer prognosis were included. Data on study characteristics, cancer type, sample size, *TUG1* detection method, follow-up, survival outcomes, and principal findings were extracted independently by two reviewers and synthesized qualitatively. Methodological quality was assessed using the Newcastle–Ottawa scale (NOS).

Results: Twenty studies were included. Most studies reported that elevated *TUG1* expression was associated with poor prognosis, including shorter overall survival, reduced disease-free survival, tumor progression, recurrence, metastasis, and chemoresistance. These findings were consistently observed in hepatocellular carcinoma, colorectal cancer, bladder cancer, renal cell carcinoma, esophageal squamous cell carcinoma, osteosarcoma, acute myeloid leukemia (AML), and Philadelphia chromosome-negative acute lymphoblastic leukemia. In contrast, inconsistent results were reported for lung cancer and glioma, where higher *TUG1* expression was associated with improved survival or showed no significant prognostic value in some studies. Study quality ranged from moderate to high (NOS scores: 6–8).

Conclusion: Current evidence suggests that *TUG1* is a promising prognostic biomarker in several malignancies. However, its prognostic significance appears to be cancer-specific, highlighting the need for large prospective studies to confirm its clinical utility.

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Introduction

As an increasingly recognized class of regulatory molecules, long non-coding RNAs (lncRNAs) have been shown to play crucial roles in a wide range of biological processes, including chromatin remodeling, transcriptional regulation, and post-transcriptional gene control; however, their functions are highly context-dependent [1]. In recent years, advances in next-generation sequencing technologies have significantly expanded our understanding of the non-coding transcriptome, revealing that numerous lncRNAs exhibit aberrant expression or mutations across different types of cancer [2, 3]. These findings suggest that lncRNAs may contribute to tumor initiation and progression, although the functional roles of many remain incompletely understood and require further investigation.

Among these regulatory molecules, increasing attention has been directed toward identifying lncRNAs that may serve as clinically relevant biomarkers in oncology. One such molecule is *TUG1* (taurine upregulated gene 1), a conserved lncRNA initially identified in retinal development. Emerging evidence indicates that *TUG1* is involved in tumor-related biological processes and may play a dual role in cancer depending on tumor type and cellular context [4]. This functional versatility has made *TUG1* a subject of considerable interest in cancer research.

In various malignancies, *TUG1* has been reported to be significantly upregulated and to act as a potential oncogene. Studies have demonstrated its overexpression in colorectal, bladder, esophageal squamous cell carcinoma, and osteosarcoma, where it is associated with enhanced tumor proliferation, invasion, and poor clinical outcomes [5-7]. In contrast, other studies have reported reduced expression of *TUG1* in certain cancers, including breast carcinoma, non-small cell lung cancer (NSCLC), and gliomas, where it may exert tumor-suppressive effects [8, 9]. This apparent functional heterogeneity suggests that the biological role of *TUG1* is highly context-dependent and may vary according to tumor type and molecular environment.

Given these conflicting findings, several studies and meta-analyses have attempted to clarify the clinical significance of *TUG1* in cancer prognosis. However, the results remain inconsistent, and no consensus has been reached regarding its overall prognostic value [10-12]. These discrepancies may be attributed to differences in sample size, tumor types, study design, and detection platforms used for *TUG1* quantification.

In recent years, a growing number of studies assessing *TUG1* expression have been conducted using high-throughput sequencing technologies and quantitative real-time polymerase chain reaction (qRT-PCR), resulting in an expanded body of evidence across multiple cancer types. Therefore, there is a need to integrate these updated findings to provide a more comprehensive and reliable assessment of its clinical relevance.

To address this gap, we conducted a systematic review to comprehensively evaluate the association between *TUG1* expression and prognostic outcomes in patients with cancer. By systematically summarizing the available evidence across different malignancies, this study aimed to provide more robust evidence regarding the prognostic significance of *TUG1* and its potential utility as a prognostic biomarker across different human malignancies.

Materials and Methods

Search strategy and study selection

This systematic review was conducted in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. A comprehensive literature search was performed in Web of Science, PubMed, Scopus, ProQuest, ERIC, and ScienceDirect to identify relevant studies published between January 1, 2014, and December 30, 2023. In addition, manual searches of reference lists of eligible articles and relevant journals were conducted to identify potentially relevant studies.

The search strategy combined the following keywords and Boolean operators: (“long non-coding RNA” OR “lncRNA”) AND (“taurine upregulated gene 1” OR “*TUG1*”) AND (“tumor” OR “cancer” OR “malignancy”) AND (“prognosis” OR “survival” OR “outcome”).

A total of 522 records were initially identified. After removing 198 duplicate records, 324 studies remained for title and abstract screening. Following screening, 160 articles were excluded because they were not relevant to the study objective. The full texts of the remaining 164 studies were assessed for eligibility. Studies were excluded if they (1) did not investigate *TUG1* expression in patients with malignant tumors, (2) reported irrelevant outcomes, (3) employed inappropriate study designs, (4) were not published in English, or (5) lacked sufficient clinical or prognostic information. Ultimately, 20 studies met the eligibility criteria and were included in this systematic review (Figure 1).

Eligibility criteria

Studies were included if they (1) investigated the expression of *TUG1* in patients with malignant neoplasms, (2) evaluated the association between *TUG1* expression and prognostic outcomes, including overall survival (OS), disease-free survival (DFS), recurrence, or other clinicopathological characteristics, (3) were original research articles conducted on human subjects, and (4) provided sufficient data on *TUG1* expression and clinical or prognostic outcomes for qualitative synthesis.

Studies were excluded if they were review articles, editorials, conference abstracts, case reports, letters, animal studies, in vitro studies, duplicate publications, or lacked relevant clinical outcome data.

Data extraction

Data extraction was independently performed by two reviewers using a standardized data extraction form. The following information was collected from each eligible study: first author, publication year, country, cancer type, sample size, method of *TUG1* assessment, follow-up duration, reported survival outcomes, hazard ratios (HRs) and corresponding 95% confidence intervals, when reported by the original studies, the Newcastle–Ottawa scale (NOS) scores, and the principal findings regarding the prognostic significance of *TUG1* expression. Any disagreements between the reviewers were resolved through discussion until consensus was reached.

Quality assessment

The methodological quality of the included studies was independently assessed by two reviewers using the NOS score, which evaluates study quality across three domains: selection of participants, comparability of study groups, and assessment of outcomes. Studies with NOS scores of 7 or higher were considered to be of high quality, whereas studies with a score of 6 were considered to be of moderate quality. Among the 20 included studies, NOS scores ranged from 6 to 8, with a mean score of 7.15. Overall, 16 studies (80%) were classified as being of high quality, and four studies (20%) were classified as being of moderate quality, indicating generally good methodological quality.

Data synthesis

A qualitative narrative synthesis was conducted because of the heterogeneity in cancer types, study populations, outcome measures, and reported prognostic indicators. The included studies were systematically summarized according to publication characteristics, cancer type, sample size, *TUG1* detection method, follow-up duration, survival outcomes, and the reported association between *TUG1* expression and prognosis. Particular emphasis was placed on the relationship between *TUG1* expression and OS, DFS, recurrence, tumor progression, and clinicopathological characteristics across different malignancies.

Results

Characteristics of the included studies

The literature search identified 522 records, of which 20 studies met the eligibility criteria and were included in this systematic review (Figure 1). The characteristics of the included studies are summarized in Table 1.

The included studies were published between 2014 and 2023 and were conducted predominantly in China (17/20), with the remaining studies originating from Egypt (n=2) and the Czech Republic (n=1). Sample sizes varied considerably, ranging from 33 participants to more than 370 clinical samples and publicly available datasets, depending on the study design. *TUG1* expression was primarily measured using quantitative real-time polymerase chain reaction (qRT-PCR) (n=12), whereas the remaining studies employed conventional PCR (n=8). When reported, follow-up durations ranged from 24 to 72 months, although several studies did not specify the follow-up period.

The included studies investigated a broad spectrum of malignancies, including acute myeloid leukemia (AML), hepatocellular carcinoma, Philadelphia chromosome-negative acute lymphoblastic leukemia, epithelial ovarian cancer, ovarian cancer, esophageal squamous cell carcinoma, lung cancer, bladder cancer, colorectal cancer, renal cell carcinoma, glioma, and osteosarcoma.

The majority of the included studies reported that elevated *TUG1* expression was associated with unfavorable clinical outcomes. Increased *TUG1* expression was frequently associated with shorter OS, reduced DFS, tumor progression, recurrence, and metastasis across several cancer types, including hepatocellular carcinoma, colorectal cancer, bladder cancer, esophageal squamous cell carcinoma, ovarian cancer, renal cell carcinoma, osteosarcoma, AML, and Philadelphia chromosome-negative acute lymphoblastic leukemia. In addition, one study reported an association between increased *TUG1* expression and chemoresistance in ovarian cancer.

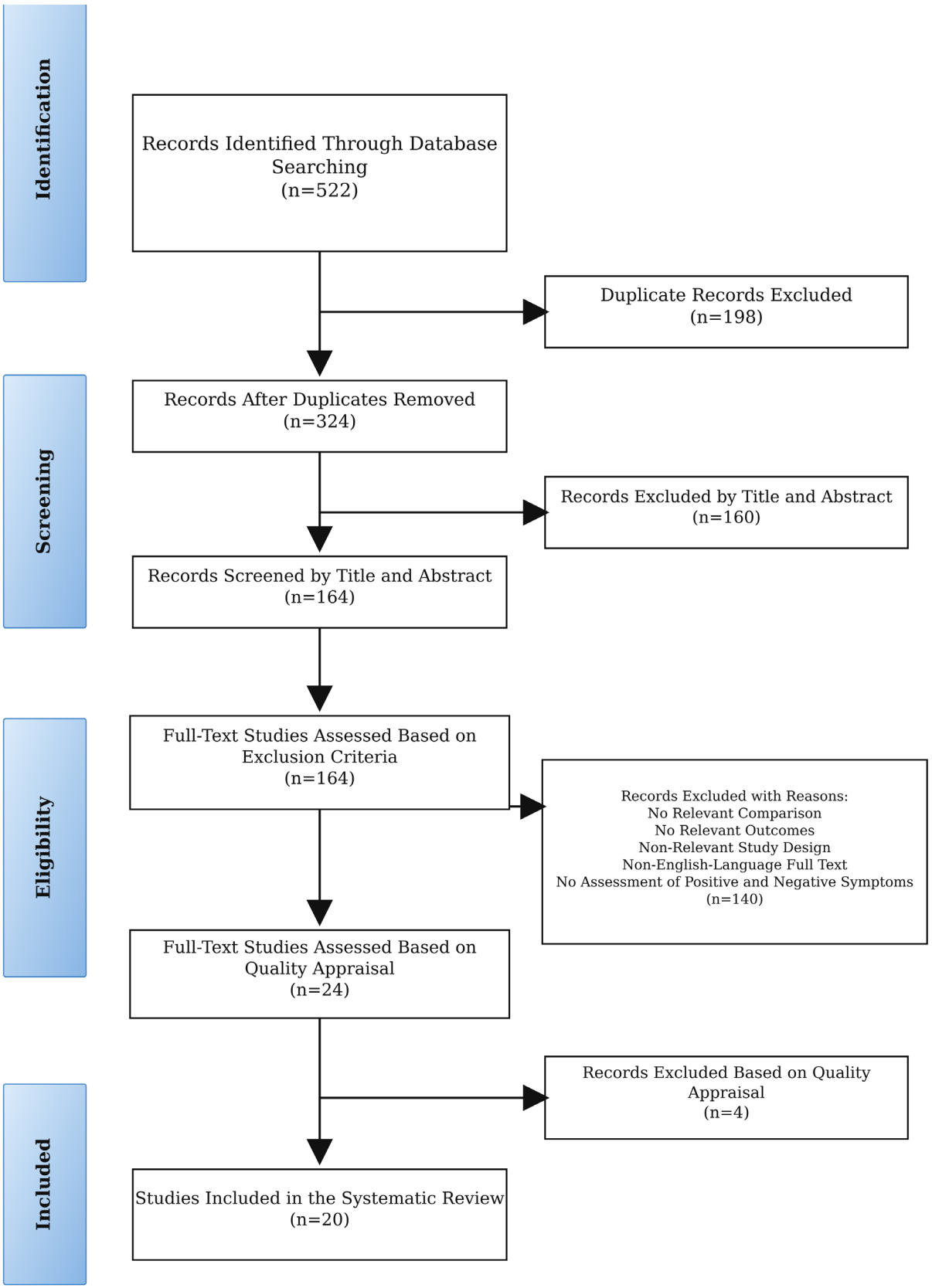


Figure 1. PRISMA 2009 flow diagram, adapted from Moher et al. [40]

Table 1. Summary of the characteristics of the 20 eligible studies included in the systematic review

Author(s), Year	Country	NOS	Sample Size	Cancer Type	TUG1 Assay	Follow-up (Month)	Outcome(s)	Survival analysis HR (95% CI)
Abdelrahman et al. 2023 [13]	Egypt	7	80 newly diagnosed with AML and 20 healthy subjects	AML	qRT-PCR	-	High expression of lncRNA *TUG1* is not a significant indicator of poor survival outcomes, serving instead as a diagnostic marker for AML	-
Li et al. 2022 [14]	China	6	371 hepatocellular carcinoma (HCC) samples from the TCGA cohort and 28 HCC patients from the GSE14323 dataset	HCC	qRT-PCR	-	High expression of lncRNA *TUG1* significantly predicts shorter survival time	1.843
Zeng et al. 2021 [15]	China	8	101 adult Ph– ALL patients and 40 healthy bone marrow donors (controls)	Philadelphia chromosome-negative acute lymphoblastic leukemia (Ph-ALL)	qRT-PCR	60	Higher lncRNA *TUG1* expression was associated with decreased DFS and overall survival (OD)	OS HR of 1.948 (95% CI, 1.211, 3.132) and DFS HR of 1.621 (95% CI, 1.083, 2.428)
El-Khazragy et al. 2020 [16]	Egypt	6	113	Epithelial ovarian cancer (EOC)	qRT-PCR	24	High expression of lncRNA *TUG1* significantly predicts shorter survival	-
Jin et al. 2020 [17]	China	7	50	Esophageal squamous cell carcinoma (ESCC)	qRT-PCR	-	High lncRNA *TUG1* expression was associated with lower survival rates	2.80 (1.26, 6.21)
Gu et al. 2020 [18]	China	6	41 ovarian cancer samples and 26 benign ovarian tumor samples	Ovarian cancer	qRT-PCR	60	Higher *TUG1* expression was associated with poorer prognosis and chemoresistance in ovarian cancer patients	3.07 (1.51, 6.25)
Guo et al. 2020 [19]	China	6	132	Lung cancer	qRT-PCR	60	Patients with a higher level of *TUG1* expression have a higher survival rate and a longer survival time than those with lower *TUG1* expression.	0.46 (0.29, 0.72)
Yu et al. 2019 [20]	China	8	87	Bladder cancer	qRT-PCR	36	*TUG1* levels were associated with shorter overall survival	3.25 (1.28, 8.24)
Wang et al. 2019 [21]	China	8	124	Colorectal cancer	qRT-PCR	60	*TUG1* levels were associated with shorter survival and cancer's recurrence	2.44 (1.57, 3.78)
Xiao et al. 2018 [22]	China	7	90	Colorectal cancer	qRT-PCR	72	*TUG1* upregulation was closely correlated with shorter survival	2.36 (1.14, 4.91)
Luo et al. 2018 [23]	China	8	73	AML	qRT-PCR	36	lncRNA *TUG1* high expression correlated with reduced survival	2.79 (1.55, 5.01)
Wang et al. 2017 [24]	China	8	203	Renal cell carcinoma	qRT-PCR	70	Higher *TUG1* expression levels were associated with a shorter overall survival	2.34 (1.45, 3.76)

Author(s), Year	Country	NOS	Sample Size	Cancer Type	TUG1 Assay	Follow-up (Month)	Outcome(s)	Survival analysis HR (95% CI)
Niu et al. 2017 [25]	China	7	33	Lung cancer	PCR	60	*TUG1* expression was correlated with the shorter survival	1.61 (0.52, 4.99)
Iliev et al. 2016 [26]	Czech	7	47	Bladder cancer	PCR	42	*TUG1* levels were significantly increased in metastatic tumors and were associated with shorter overall survival	2.54 (1.13, 5.74)
Zhang et al. 2016 [27]	China	8	218	Esophageal squamous cell carcinoma	PCR	54	Overexpression of *TUG1* predicts a poor prognosis	1.403 (1.012, 1.946)
Li et al. 2016 [28]	China	7	120	Glioma	PCR	60	*TUG1* expression was significantly correlated with Grade, tumor size, and overall survival	0.57 (0.34, 0.96)
Lin et al. 2016 [29]	China	7	89	Lung cancer	PCR	60	*TUG1* expression was significantly correlated with overall survival	0.77 (0.27, 2.22)
Sun et al. 2016 [4]	China	8	120	Colorectal cancer	PCR	36	*TUG1* upregulation was closely correlated with shorter overall survival	2.15 (1.29, 3.58)
Ma et al. 2016 [30]	China	8	76	Osteosarcoma	PCR	44	Upregulation of *TUG1* strongly correlated with poor prognosis and shorter overall survival	2.78 (1.29, 6.00)
Zhang et al. 2014 [31]	China	7	192	Lung cancer	PCR	60	Low *TUG1* expression in tumor tissues was associated with poor prognosis	0.46 (0.31, 0.68)

However, inconsistent findings were observed in a limited number of malignancies. Among studies involving lung cancer, two studies suggested that higher *TUG1* expression was associated with improved survival outcomes, whereas the remaining studies reported either no statistically significant association or inconsistent findings regarding the prognostic value of *TUG1*. Similarly, one study on glioma suggested that lower *TUG1* expression was associated with poorer prognosis, indicating that the biological and prognostic role of *TUG1* may differ according to tumor type.

Conflicting findings were also observed in AML. While one study reported that increased *TUG1* expression was associated with reduced survival, another study found that *TUG1* expression was not a significant predictor of prognosis and instead suggested its potential utility as a diagnostic biomarker.

Quality assessment

The methodological quality of the included studies was assessed using the NOS. Quality scores ranged from 6 to 8. Sixteen studies (80%) were classified as being of high quality (NOS ≥7), whereas four studies (20%) were classified as being of moderate quality (NOS=6). The mean NOS score was 7.15, indicating that the overall methodological quality of the included evidence was generally good (Table 2).

Quality classification: High quality (NOS ≥7); Moderate quality (NOS =6); Low quality (NOS <6).

Discussion

In this systematic review, which included 20 eligible studies published between 2014 and 2023, we comprehensively evaluated the prognostic significance of *TUG1* expression across multiple human malignancies. Overall, the available evidence indicates that elevated *TUG1* expression is frequently associated with unfavorable clinical outcomes, including reduced OS, disease progression, recurrence, metastatic potential, and, in one study, chemoresistance. These findings support the potential clinical relevance of *TUG1* as a prognostic biomarker in a broad range of cancers.

Previous systematic reviews and meta-analyses also suggested an association between dysregulated *TUG1* expression and poor prognosis; however, these studies were primarily based on evidence published before 2017

Table 2. Quality assessment of the included studies using the NOS

No.	Author(s), Year	Representa-tiveness	Selec-tion of Non-ex-posed	Ascertain-ment of Exposure	Outcome Absent at Baseline	Compara-bility	Outcome Assessment	Fol-low-up	Adequa-cy of Follow-up	Total NOS Score
1	Sun et al. 2016 [4]	★ (1)	★ (1)	★ (1)	(0)	★★ (2)	★ (1)	★ (1)	(0)	7 of 9
2	Abdelrahman et al. 2023 [13]	★ (1)	★ (1)	★ (1)	★ (1)	★★ (2)	★ (1)	★ (1)	(0)	8 of 9
3	Li et al. 2022 [14]	★ (1)	★ (1)	★ (1)	★ (1)	★★ (2)	★ (1)	★ (1)	(0)	8 of 9
4	Zeng et al. 2021 [15]	★ (1)	★ (1)	★ (1)	★ (1)	★★ (2)	★ (1)	★ (1)	(0)	8 of 9
5	El-Khazragy et al. 2020 [16]	★ (1)	★ (1)	★ (1)	(0)	★★ (2)	★ (1)	★ (1)	(0)	7 of 9
6	Jin et al. 2020 [17]	★ (1)	★ (1)	★ (1)	★ (1)	★★ (2)	★ (1)	★ (1)	(0)	8 of 9
7	Gu et al. 2020 [18]	★ (1)	★ (1)	★ (1)	★ (1)	★★ (2)	★ (1)	★ (1)	(0)	8 of 9
8	Guo et al. 2020 [19]	★ (1)	★ (1)	★ (1)	(0)	★★ (2)	★ (1)	★ (1)	(0)	7 of 9
9	Yu et al. 2019 [20]	★ (1)	★ (1)	★ (1)	★ (1)	★★ (2)	★ (1)	★ (1)	(0)	8 of 9
10	Wang et al. 2019 [21]	★ (1)	★ (1)	★ (1)	★ (1)	★★ (2)	★ (1)	★ (1)	(0)	8 of 9
11	Xiao et al. 2018 [22]	★ (1)	★ (1)	★ (1)	★ (1)	★★ (2)	★ (1)	★ (1)	(0)	8 of 9
12	Luo et al. 2018 [23]	★ (1)	★ (1)	★ (1)	(0)	★★ (2)	★ (1)	★ (1)	(0)	7 of 9
13	Wang et al. 2017 [24]	★ (1)	★ (1)	★ (1)	(0)	★★ (2)	★ (1)	★ (1)	(0)	7 of 9
14	Niu et al. 2017 [25]	★ (1)	★ (1)	★ (1)	★ (1)	★★ (2)	★ (1)	★ (1)	(0)	8 of 9
15	Iliev et al. 2016 [26]	★ (1)	★ (1)	★ (1)	★ (1)	★★ (2)	★ (1)	★ (1)	(0)	8 of 9
16	Zhang et al. 2016 [27]	★ (1)	★ (1)	★ (1)	★ (1)	★★ (2)	★ (1)	★ (1)	(0)	8 of 9
17	Li et al. 2016 [28]	★ (1)	★ (1)	★ (1)	★ (1)	★★ (2)	★ (1)	★ (1)	(0)	8 of 9
18	Lin et al. 2016 [29]	★ (1)	★ (1)	★ (1)	★ (1)	★★ (2)	★ (1)	★ (1)	(0)	8 of 9
19	Ma et al. 2016 [30]	★ (1)	★ (1)	★ (1)	(0)	★★ (2)	★ (1)	★ (1)	(0)	7 of 9
20	Zhang et al. 2014 [31]	★ (1)	★ (1)	★ (1)	(0)	★★ (2)	★ (1)	★ (1)	(0)	7 of 9

and therefore did not capture many of the more recent investigations [11, 12, 31, 32]. By incorporating studies published through 2023 and covering a wider spectrum of malignancies, the present review provides a more comprehensive and updated evaluation of the prognostic significance of *TUG1* and its potential utility as a pan-cancer biomarker for clinical risk stratification [33].

The majority of the included studies demonstrated that increased *TUG1* expression was significantly associated with poor clinical outcomes in several malignancies, including hepatocellular carcinoma, colorectal cancer, bladder cancer, esophageal squamous cell carcinoma, ovarian cancer, renal cell carcinoma, osteosarcoma, AML, and Philadelphia chromosome-negative acute lymphoblastic leukemia [18-23]. Across these tumor types, elevated *TUG1* expression consistently correlated with shorter OS, reduced DFS, tumor recurrence, advanced clinical stage, lymph node metastasis, distant metastasis, and other unfavorable clinicopathological characteristics, suggesting that *TUG1* contributes to tumor aggressiveness and disease progression.

The biological plausibility of these clinical findings is supported by numerous experimental studies demonstrating that *TUG1* regulates multiple oncogenic processes through diverse molecular mechanisms [34]. In most malignancies (Figure 2), *TUG1* functions as an oncogenic lncRNA by promoting cell proliferation, inhibiting apoptosis, enhancing migration and invasion,

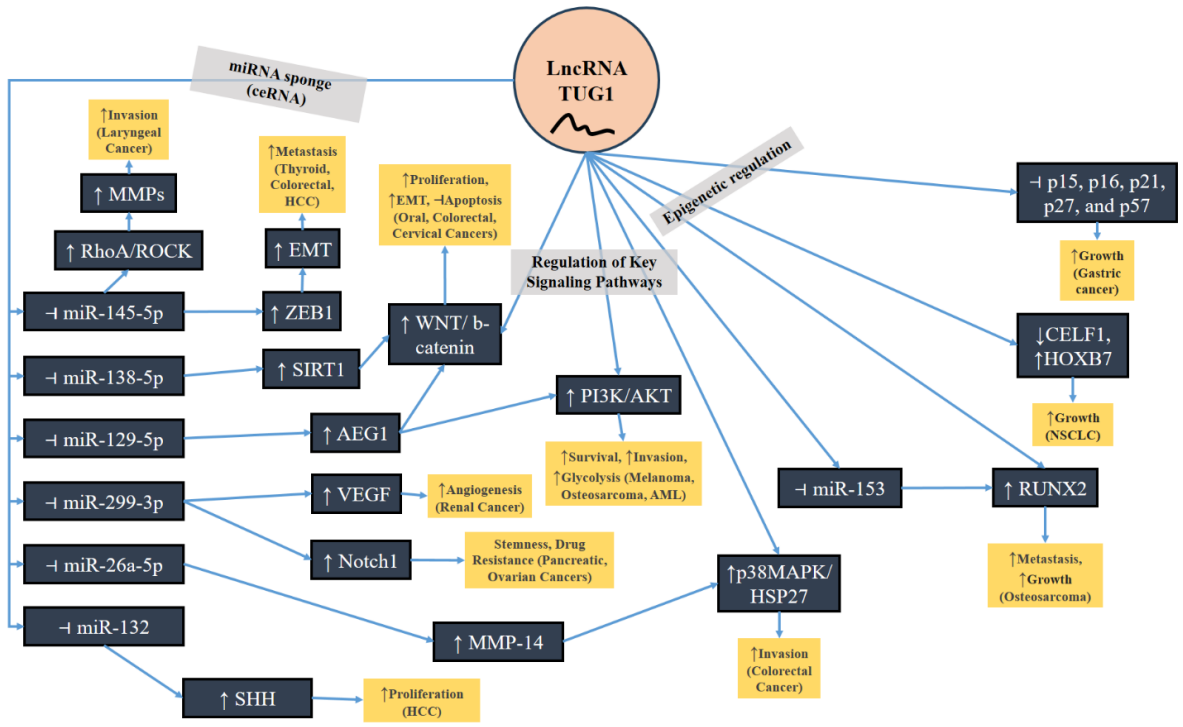


Figure 2. Comprehensive molecular mechanisms of lncRNA TUG1 in cancer: A regulatory network integrating miRNA sponging, epigenetic silencing, and signaling pathways (↑=activation, ↓=suppression, ⊣=inhibition, →=leads to)

stimulating angiogenesis, and reprogramming cellular metabolism. One of the principal mechanisms involves its function as a competing endogenous RNA (ceRNA), whereby *TUG1* acts as a molecular sponge for tumor-suppressive microRNAs, thereby preventing their inhibitory effects on downstream oncogenic targets. For example, in intrahepatic cholangiocarcinoma, *TUG1* sequesters miR-145, resulting in upregulation of Sirt3 and glutamate dehydrogenase (GDH), enhanced glutamine metabolism, and accelerated tumor growth. Likewise, in lung adenocarcinoma, *TUG1* promotes tumor progression by sponging miR-138-5p, leading to increased *HIF1A* expression, whereas in colorectal cancer, *TUG1* overexpression inversely correlates with p63 expression, thereby enhancing proliferation and migration while suppressing apoptosis [35].

In addition to miRNA-mediated regulation, *TUG1* has been shown to influence several critical oncogenic signaling pathways. Experimental evidence demonstrates activation of the Wnt/β-catenin pathway through SP1-mediated transcriptional regulation in colorectal cancer, enhancement of PI3K/AKT signaling in melanoma and osteosarcoma, and modulation of hypoxia-responsive signaling via the *miR-138-5p/HIF1A* axis in lung adenocarcinoma [36]. Furthermore, immunoprecipitation studies have demonstrated that *TUG1* directly interacts with the polycomb repressive complex 2 (PRC2), including EZH2 and SUZ12, facilitating histone methylation and epigenetic silencing of tumor suppressor genes. In gastric cancer, this interaction suppresses the cyclin-dependent kinase inhibitors p15 and p21, thereby promoting cell-cycle progression and tumor development [27]). Collectively, these molecular mechanisms provide a strong biological rationale for the observed association between elevated *TUG1* expression and poor clinical outcomes across many cancer types.

At the cellular level, functional studies further support the oncogenic role of *TUG1*. *TUG1* knockdown has been shown to reduce cell viability, inhibit proliferation, and induce apoptosis in colorectal cancer. In cholangiocarcinoma, however, *TUG1*-mediated suppression of miR-145 enhances glutamine metabolism, thereby sustaining tumor growth. Similarly, in lung adenocarcinoma, *TUG1* promotes metastatic behavior through HIF1A-dependent mechanisms [37]. Clinically, high *TUG1* expression has repeatedly been associated with advanced tumor stage, increased metastatic potential, and poor survival in cancers, such as cholangiocarcinoma, colorectal cancer, and lung adenocarcinoma, making *TUG1* an attractive candidate for therapeutic targeting through RNA interference or the restoration of tumor-suppressive miRNAs [19].

Nevertheless, the findings were not entirely consistent across all malignancies. Although *TUG1* is overexpressed and functions predominantly as an oncogene in most tumors, several studies have demonstrated tumor-suppressive properties in specific cancer types, particularly certain subtypes of breast cancer, non-small cell lung cancer (NSCLC), and glioma [38, 39]. In glioma, *TUG1* has been reported to induce apoptosis by activating caspase-3 and caspase-9 while simultaneously suppressing Bcl-2-mediated survival signaling, thereby shifting the balance toward programmed cell death. Consistent with these experimental findings, the glioma study included in this review demonstrated that lower *TUG1* expression was associated with poorer prognosis. Similarly, among the lung cancer studies, two reported that higher *TUG1* expression was associated with improved survival outcomes, whereas another found no statistically significant relationship between *TUG1* expression and OS. Conflicting findings were also observed in AML, where one study identified elevated *TUG1* expression as a predictor of poor survival, while another suggested no significant prognostic value and instead proposed its potential diagnostic utility. These observations collectively indicate that the biological and prognostic roles of *TUG1* are highly context-dependent and vary according to tumor type, cellular environment, and underlying molecular alterations.

The variability in the findings across the included studies may be attributed to several factors, including differences in tumor biology, disease stage, treatment strategies, patient characteristics, sample size, laboratory methods used to assess *TUG1* expression (qRT-PCR versus conventional PCR), and the cutoff values used to classify high and low *TUG1* expression. Furthermore, because nearly all included studies were conducted in China, the available evidence may not be fully generalizable to other ethnic or geographic populations. Additional well-designed multicenter studies involving more diverse populations are therefore needed to validate the prognostic significance of *TUG1* across different populations.

Several limitations of this systematic review should be acknowledged. First, the included studies varied considerably with respect to cancer type, patient characteristics, study design, follow-up duration, laboratory methods used for *TUG1* expression analysis, and reported clinical outcomes, making direct comparisons across studies challenging. Second, most of the included studies were retrospective observational studies, which may be subject to selection bias and residual confounding. Third, the majority of the available evidence originated from Asian populations, particularly China, limiting the generalizability of the findings to other ethnic and geographic populations. Fourth, differences in *TUG1* detection techniques, including qRT-PCR and conventional PCR, as well as variations in the cutoff values used to define high and low expression, may have influenced the reported associations between *TUG1* expression and clinical outcomes. Finally, publication bias cannot be completely excluded because studies reporting statistically significant findings are generally more likely to be published than those with negative or inconclusive results.

Conclusion

In conclusion, the evidence synthesized in this systematic review indicates that altered *TUG1* expression is significantly associated with prognosis across multiple human malignancies. In the majority of cancers, elevated *TUG1* expression correlates with unfavorable clinical outcomes through its involvement in miRNA sponging, epigenetic regulation via PRC2, and modulation of major oncogenic signaling pathways. However, conflicting findings in NSCLC, glioma, and AML highlight the context-dependent biological behavior of *TUG1* and indicate that its prognostic significance is not universal. Overall, the present review provides an updated and comprehensive overview of *TUG1* as a potential pan-cancer prognostic biomarker while emphasizing the need for well-designed, large-scale, prospective, and multi-ethnic studies to clarify its biological functions and validate its clinical utility (Table 3).

Table 3. TUG1's dual role in different cancers

Characteristics	Oncogene Role	Anti-tumor Role
Cancer type	Colorectal, bladder, esophageal squamous epithelium, bone, gastrointestinal, gynecological, hematological, urological	Breast carcinoma, NSCLC (non-small cell lung cancer), glial tumors
Expression level	Upregulated	Downregulated
Function	Promotes tumor progression, metastatic invasion, and angiogenesis	Triggers apoptosis and downregulates survival signals
Mechanism	Interacts with PRC2, sponges miRNAs, dysregulates signaling pathways	Activates caspase-3/9, downregulates Bcl2

Ethical Considerations

Compliance with ethical guidelines

This article is a review and does not involve human or animal samples.

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Author's contributions

Conceptualization and supervision: Hooman Zarei; Data collection and writing the original draft: Parisa Bahavar; investigation: Fatemeh Sadat Hosseini and Parisa Bahavar; Formal analysis and data interpretation: Mohammad Amin Rezaei; Methodology and statistical analysis: Mehrdad Payandeh; Data verification: Amirreza Rahimi; Review and editing: Amirreza Rahimi and Mohammad Amin Rezaei; Visualization: Hooman Zarei.

Conflict of interest

The authors declared no conflict of interest.

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