ORIGINAl ARTICLE

Clinicopathological and Prognostic Significance of Long Non-Coding RNA LINC00511 in Solid Tumors

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SUMMARY

Background: Although long non-coding RNA LINC00511 has emerged as an oncogene and was reported to be a poor prognosticator in cancer, the results remain uncharacterized. Hence, for the first time, we sought to clarify the association between LINC00511 and clinical outcomes in malignant tumors.

Methods: We conducted a detailed search of PubMed and Web of Science online databases for all eligible studies. A meta-analysis was performed using Stata 12.0 software. Based on TCGA datasets, the prognostic power of high LINC00511 expression in cancer was analyzed using Kaplan-Meier survival curves.

Results: Fifteen studies containing 1,356 individuals were eventually included in the current analysis. Compared with low LINC00511 expression, high LINC00511 expression was closely correlated with tumor size (OR = 2.46, 95% CI: 1.40 - 4.31, p = 0.001) tumor stage (OR = 2.52, 95% CI: 1.91 - 3.33, p = 0.000), lymph node metastasis (OR = 2.97, 95% CI: 2.22 - 3.97, p = 0.000), distant metastasis (OR = 2.09, 95% CI: 1.08 - 4.03, p = 0.028), and histological differentiation (OR = 1.29, 95% CI 1.00 - 1.66, p = 0.047) in cancer. TCGA data manifested that high LINC00511 expression was markedly associated with worse OS (HR = 1.9, p = 0.000) among tumor patients.

Conclusions: Thus, the increased expression level of LINC00511 was associated with more advanced clinicopathological features and poor prognosis as a novel predictive biomarker in various cancers.


KEY WORDS

long non-coding RNA, LINC00511, cancer

INTRODUCTION

Long non-coding RNAs (IncRNAs) are a group of RNA molecules with a length of more than 200 nucleotides that do not encode proteins [1]. High-throughput RNA sequencing (RNA-Seq) technology has driven genome-wide discovery and analysis of non-coding RNAs. Distinct from mRNAs, the expression and function of IncRNAs have specific features with cell, tissue, and temporal specificity [2]. There is growing evidence that IncRNAs exert crucial functions in biological processes that coordinate gene expression, particularly during tumor development [3]. Indeed, numerous studies have highlighted the importance of IncRNAs in regulating a wide range of tumor developmental processes, including apoptosis, proliferation, viability, motility, and me-
tastasis [4-7]. It has also been shown recently that several IncRNAs can play a role in prognosis for cancers, such as PVT1 for esophageal adenocarcinoma and CDR1as for melanoma [8,9]. Long intergenic noncoding RNA 00511 (LINC00511) is a newly identified IncRNA mapping to chromosome 17q24.3 which is transcribed as a 2.265 bp ncRNA [10]. LINC00511 plays a pivotal role in several human cancers and has been regarded as an oncogene. In recent years, LINC00511 has attracted considerable interest due to evidence indicating its up-regulation in multiple malignant tumors, including NSCLC, cervical cancer, breast cancer, glioblastoma, hepatocellular carcinoma, etc. [11-15]. Furthermore, the up-regulation of LINC00511 in tumor patients may contribute to poor prognosis. However, conclusions may not be highly reliable due to small sample sizes, methodological limitations, and few tumor types. Hence, it is essential to further explore the prognostic value of LINC00511 in various cancers on larger sample sizes and more tumor types. We gathered a larger set of eligible studies and conducted this quantitative meta-analysis to quantitatively review the clinicopathological significance of LINC00511 in cancer. Furthermore, the elevated expression of LINC00511 in cancer is significantly related to lymph node metastasis (LNM), distant metastasis, tumor size, tumor stage as well as histological differentiation. Based on The Cancer Genome Atlas (TCGA) database, high LINC00511 expression was positively correlated with a shorter OS time.

MATERIALS AND METHODS

Literature search
PubMed and Web of Science databases were comprehensively searched. The upper date of April 15, 2020 was applied. Search terms were used as follows: (“LINC00511” OR “IncRNA LINC00511”) AND (cancer OR carcinoma OR tumor). Only articles in English were included in this study.

Inclusion and exclusion criteria
The following selection criteria were utilized to set study eligibility: (1) patients were categorized into “high LINC00511” and “low LINC00511” groups based on expression levels of LINC00511 or (2) OR and 95%CI or relative data that could be used to calculate these clinical features were provided; (3) Case-control or cohort studies; (4) published in the English language. Exclusion criteria were used as follows: (1) retracted papers or duplicate articles; (2) data on the association between LINC00511 and clinical features were not provided; (3) sample cases fewer than 30; (4) case reports, reviews, expert opinions, letters, editorials, and commentaries.

Data extraction and methodological assessment
Two reviewers (Wu Y and Wang Q) independently determined study eligibility. Disagreements were resolved by consensus. Data from the enrolled articles were extracted: first author’s name, year of publication, country of origin, tumor type, LINC00511 expression detection method, sample size, the number of patients with larger tumor size, LNM and distant metastasis, higher tumor stage, poor histological differentiation, and reference gene.

Public data and tools
The Gene Expression Profiling Interactive Analysis (GEPIA) is a web tool based on the TCGA data, which are computed by a standard pipeline [16]. One-way ANOVA was used for differential expression analysis. For the patient survival analysis, the Kaplan-Meier method and a log-rank test were applied by GEPIA. The HR and 95% CI were also shown in the figure of Kaplan-Meier curves.

Statistical methods
This meta-analysis was performed with Stata SE 12.0 (Stata Corporation, College Station, TX, USA). Chi-squared (χ²)-based Q test was utilized to assess the heterogeneity among all the studies [17]. The Mantel-Haenszel fixed-effects model was adopted when p > 0.05 [18]. Otherwise, the random-effects model (Dersimonian-Laird method) was adopted (p ≤ 0.05, I² ≥ 50%) [19]. Begg’s test and Egger’s test were utilized for assessing the publication bias [20]. p < 0.05 was considered statistically significant.

RESULTS

Study selection and study characteristics
The process of literature search and selection was detailed in Figure 1. Ultimately, a total of fifteen articles involving 1,356 patients were enrolled in the current meta-analysis [11-13,15,21-31]. Fourteen studies came from China and one from Iran. All fifteen comprised nine different tumor types: non-small cell lung cancer (NSCLC), tongue squamous cell carcinoma (TSCC), pancreatic ductal adenocarcinoma (PDAC), breast cancer, cervical cancer, hepatocellular carcinoma (HCC), clear cell renal cell carcinoma (CCRC), papillary thyroid carcinoma and colorectal cancer (CRC). The main clinical characteristics of the patients from fifteen eligible studies were summarized in Table 1. qRT-PCR was used to detect LINC00511 expression levels in these included studies. All patients of each study were divided into high and low groups based on the expression of LINC00511.

Correlation of LINC00511 expression with tumor size
Twelve studies illustrated the correlation strength between the LINC00511 level and tumor size in cancer.
### Table 1. Characteristics of the studies included in the meta-analysis (n = 15).

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Country</th>
<th>Cancer type</th>
<th>Sample size</th>
<th>Gene</th>
<th>Expression</th>
<th>Total</th>
<th>LNM</th>
<th>High</th>
<th>Low</th>
<th>PD</th>
<th>HTS</th>
<th>LNM</th>
<th>ME</th>
<th>Total</th>
<th>LNM</th>
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<td>Sun CC</td>
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<td>124</td>
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<td>Low</td>
<td>93</td>
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<td>-</td>
<td>84</td>
<td>31</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td>Ding J</td>
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<td>China</td>
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<td>2</td>
<td>5</td>
<td>-</td>
<td>1</td>
<td>-</td>
<td>84</td>
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<td>15</td>
</tr>
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<td>41</td>
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<td>29</td>
<td>1</td>
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<td>-</td>
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<td>-</td>
<td>12</td>
<td>1</td>
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<td>China</td>
<td>PDAC</td>
<td>140</td>
<td>GAPDH</td>
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<td>102</td>
<td>-</td>
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<td>39</td>
<td>GAPDH</td>
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<td>23</td>
<td>4</td>
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<td>GAPDH</td>
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<td>49</td>
<td>24</td>
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<td>GAPDH</td>
<td>Low</td>
<td>49</td>
<td>11</td>
<td>14</td>
<td>7</td>
<td>16</td>
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<td>35</td>
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<tr>
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<td>GAPDH</td>
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<td>64</td>
<td>29</td>
<td>30</td>
<td>27</td>
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<td></td>
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<tr>
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<td>GAPDH</td>
<td>High</td>
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<tr>
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<td>GAPDH</td>
<td>Low</td>
<td>24</td>
<td>17</td>
<td>6</td>
<td>13</td>
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<td>-</td>
<td>4</td>
<td>46</td>
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<tr>
<td>Deng H</td>
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<td>China</td>
<td>CCRCC</td>
<td>49</td>
<td>GAPDH</td>
<td>Low</td>
<td>25</td>
<td>12</td>
<td>15</td>
<td>14</td>
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<tr>
<td>Zhu FY</td>
<td>2019</td>
<td>China</td>
<td>NSCLC</td>
<td>57</td>
<td>GAPDH</td>
<td>Low</td>
<td>29</td>
<td>18</td>
<td>-</td>
<td>20</td>
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<td>-</td>
<td>21</td>
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<tr>
<td>Hu WY</td>
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<td>China</td>
<td>HCC</td>
<td>334</td>
<td>GAPDH</td>
<td>Low</td>
<td>167</td>
<td>-</td>
<td>51</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>2</td>
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<td>Xiang J</td>
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<td>China</td>
<td>CRC</td>
<td>41</td>
<td>GAPDH</td>
<td>Low</td>
<td>14</td>
<td>6</td>
<td>-</td>
<td>0</td>
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<td>-</td>
<td>5</td>
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<tr>
<td>Sun S</td>
<td>2020</td>
<td>China</td>
<td>CRC</td>
<td>40</td>
<td>GAPDH</td>
<td>Low</td>
<td>20</td>
<td>-</td>
<td>15</td>
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<td>20</td>
<td></td>
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</tr>
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</table>

Figure 1. The flow diagram of search strategy.

Figure 2. Forest plot for the relationships between increased LINC00511 expression and tumor size.
Figure 3. Forest plot for the relationships between increased LINC00511 expression and tumor stage.

Figure 4. Forest plot for the relationships between increased LINC00511 expression and lymph node metastasis.
Figure 5. Forest plot for the relationships between increased LINC00511 expression and distant metastasis.

<table>
<thead>
<tr>
<th>Study</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lu G (2018)</td>
<td>1.88 (0.51, 6.90)</td>
</tr>
<tr>
<td>Mao BD (2019)</td>
<td>1.64 (0.61, 4.40)</td>
</tr>
<tr>
<td>Yu CL (2019)</td>
<td>17.66 (0.98, 318.99)</td>
</tr>
<tr>
<td>Hu WY (2020)</td>
<td>2.01 (0.18, 22.41)</td>
</tr>
<tr>
<td>Xiang J (2020)</td>
<td>0.35 (0.02, 7.84)</td>
</tr>
<tr>
<td>Overall (I-squared = 0.0%, p = 0.460)</td>
<td>2.09 (1.08, 4.03)</td>
</tr>
</tbody>
</table>

A random-effects effects model was applied to calculate the pooled effect size because heterogeneity was observed among the enrolled studies ($P_0 = 0.001$). The combined results indicated that elevated LINC00511 expression levels were significantly correlated with large tumor size in cancer patients (OR = 2.46, 95% CI: 1.40 - 4.31, p = 0.002) (Figure 2).

Figure 6. Forest plot for the relationships between increased LINC00511 expression and histological differentiation.

<table>
<thead>
<tr>
<th>Study</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sun CC (2016)</td>
<td>0.98 (0.44, 2.19)</td>
</tr>
<tr>
<td>Oskooei VK (2018)</td>
<td>0.23 (0.05, 0.95)</td>
</tr>
<tr>
<td>Zhao X (2018)</td>
<td>1.81 (0.79, 4.12)</td>
</tr>
<tr>
<td>Lu G (2018)</td>
<td>0.46 (0.10, 2.10)</td>
</tr>
<tr>
<td>Mao BD (2019)</td>
<td>1.60 (0.57, 4.50)</td>
</tr>
<tr>
<td>Wang RP (2019)</td>
<td>1.53 (0.75, 3.12)</td>
</tr>
<tr>
<td>Yu CL (2019)</td>
<td>1.72 (0.74, 3.97)</td>
</tr>
<tr>
<td>Zhang J (2019)</td>
<td>0.85 (0.27, 2.61)</td>
</tr>
<tr>
<td>Deng H (2019)</td>
<td>1.50 (0.48, 4.65)</td>
</tr>
<tr>
<td>Hu WY (2020)</td>
<td>1.47 (0.94, 2.29)</td>
</tr>
<tr>
<td>Sun S (2020)</td>
<td>1.00 (0.21, 4.71)</td>
</tr>
<tr>
<td>Overall (I-squared = 3.8%, p = 0.406)</td>
<td>1.29 (1.00, 1.66)</td>
</tr>
</tbody>
</table>
Figure 7. Publication bias test of the included studies for LINC00511 expression and tumor stage.

Correlation of LINC00511 expression with tumor stage
A correlation between LINC00511 expression and TNM stage was obtained from thirteen studies in different types of cancers, including NSCLC, breast cancer, cervical cancer, HCC, CCRCC, papillary thyroid carcinoma, and CRC. The pooled results also suggested that the high LINC00511 expression was related to the high tumor stage (OR = 2.52, 95% CI 1.91 - 3.33, p = 0.00) (Figure 3).

Figure 8. TCGA data manifested that high LINC00511 expression was markedly associated with worse OS in cancer.
Correlation of LINC00511 expression with lymph node metastasis (LNM)
Twelve studies with 295 patients were included in the meta-analysis of LNM. No significant heterogeneity was found among the studies ($p = 0.107$), and then the fixed-effects model was applied. As shown in Figure 4, the increased probability of LNM was observed in the patients with higher expression of LINC00511 ($OR = 2.97, 95\% CI 2.22 - 3.97, p = 0.000$).

Correlation of LINC00511 expression with distant metastasis
Five of the included studies were evaluated to determine the association between the LINC00511 expression with distal metastasis in cancer. We observed no significant heterogeneity among studies ($p = 0.46$). Then, a fixed-effects model was utilized. There was a connection between LINC00511 expression level and distal metastasis in cancer patients (pooled $OR = 2.09, 95\% CI: 1.08 - 4.03, p = 0.028$) (Figure 5).

Correlation of LINC00511 expression with tumor differentiation
Eleven studies focused on investigating the correlation strength between the LINC00511 level and histological differentiation. When no obvious heterogeneity among the studies ($p = 0.406$) was observed, the random-effects model was performed. The combined results indicated that elevated LINC00511 expression levels were significantly correlated with poor tumor differentiation ($OR = 1.29; 95\% CI: 1.00 - 1.66, p = 0.047$) (Figure 6).

Publication bias
As shown in Figure 7, Begg’s funnel plot and Egger’s test were performed to access publication bias in this meta-analysis. Visual inspection of the Begg’s funnel plot showed asymmetry (Figure 7) as well as Egger’s test and revealed that there was no publication bias in all groups ($p = 0.615$).

Validation of the results in TCGA dataset
Next, we explored the association of LINC00511 expression with OS in all the cancers using the data from the TCGA dataset. Data for 9,502 patients were extracted and then divided into high or low expression groups on the basis of median LINC00511 expression. As expected, patients in the high expression group denoted a worse OS than those in the low expression group (Figure 8 $HR = 1.9, p = 0$). These results confirmed that the expression of LINC00511 was significantly correlated with poor prognosis in these cancer patients.

DISCUSSION
Increasing studies have illustrated that a considerable number of lncRNAs are associated with cancer metastasis and tumorigenesis [6,32]. In recent studies, LINC00511 was showed abnormal expression in several types of cancers. Moreover, it was identified as a crucial modulator of cancer proliferation, migration, metastasis, and progression, including TSCC, NSCLC, PDAC, CRC, etc. Although LINC00511 was reported to be connected with clinicopathologic significance in cancer, inconsistencies exist for some clinical parameters across individual experiments. In this article, we selected all published articles in PubMed and Web of Science to clarify LINC00511 expression and cancer patient outcomes.

A total of fifteen published studies with 1,356 patients were ultimately included for this literature meta-analysis. We examined the clinicopathological significance of H19 expression levels in NSCLC, TSCC, PDAC, breast cancer, HCC, cervical cancer, CCRCC, PTC, and CRC. Furthermore, we evaluated the correlation between LINC00511 level, LNM, distant metastasis, advanced clinical stage, and histological differentiation. Our results demonstrated that increased LINC00511 expression may be associated with advanced features of cancer. Based on the TCGA data, a high level of LINC00511 indicated a shorter OS, suggesting that LINC00511 may shorten tumor survival and be an unfavorable predictor of survival for patients with malignant tumors.

The molecular pathways by which LINC00511 regulates cancer pathophysiology are not exactly clear. Several articles have suggested that LINC00511 is involved in tumorigenesis by regulating target gene expression by different mechanisms at transcriptional levels and post-transcriptional levels. LINC00511 has long been known to promote cell malignant behaviors by target protein, though the mechanism for this inhibition has not been fully elucidated. Xiang et al. provide a molecular basis that LINC00511 acting as an oncogene through cyclin-dependent kinases (CDKs) which can regulate the cell cycle of tumor cells in PTC [30]. LINC00511 was also identified as an oncogenic lncRNA partially through binding to EZH2 and suppressing p57 expression in NSCLC [21]. Also, Jiang showed LINC00511 promoted TGF-$\beta1$-induced migration and invasion by inducing the epithelial-mesenchymal transition (EMT) and MMPs in lung cancer [33]. Meanwhile, Zhu reported that LINC00511 promoted carcinogenesis via influencing LAT52 and KLF2 expression by binding to EZH2 and LSD1 in lung cancer [11]. Another oncogenic molecular mechanism known to be associated with lncRNAs is absorbing the tumor-suppressive microRNAs to effect on gene expressions. A study from Zhang showed that LINC00511 contributes to glioblastoma tumorigenesis and EMT through the LINC00511/miR-524-3p/YB1/ZEB1 positive feedback loop [14]. LINC00511 was also found to contribute to the cell malignant behaviors of hepatocellular carcinoma by modulating the miR-195/EYAI axis [15]. In tongue squamous cell carcinoma, LINC00511 promoted cancer cell progression via miR-765 [22]. LINC00511 could powerfully promote breast cancer stemness by acting as a ceRNA for miR-185-3p [25]. LINC00511 is also identi-
fied as a crucial modulator of another important signaling in cancer. For instance, most recently LINC00511 was found to promote EMT through the PTEN-AKT-FOXO1 signaling pathway in lung cancer [34]. This evidence indicates that LINC00511 may contribute to tumorigenesis through both the transcriptional and post-transcriptional pathways. This study has several limitations to be considered. First, since only 15 studies were included, the number of original research studies and the total sample size was relatively limited. Second, most of the studies enrolled were derived from China. Our results may best elucidate the relationship of LINC00511 with Asian patients. Third, the cutoff values are inconsistent between different literature reports, which would generate a region bias. In the future, multi-center, more well-designed studies with larger sample sizes are warranted to examine the results in this study.

CONCLUSION
In conclusion, our study indicates that LINC00511 expression is related to tumor size, LNM, metastasis, poor differentiation, and AJCC stage in human cancers. Besides, elevated LINC00511 expression was positively correlated with a shorter OS. Therefore, LINC00511 is promising to be used as a prognostic factor in cancer.

Declaration of Interest:
The authors declare no conflict of interest in this work.

References:


