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Clinicopathological and prognostic value of lncRNA TPT1-AS1 in cancer: a systematic review study and meta-analysis

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Abstract

Introduction. Aberrant expression of lncRNAs in cancer cells can impact their key phenotypes. We aimed to summarize available evidence on clinicopathological and prognostic value of lncRNA TPT1-AS1 in cancer.

Methods. A systematic search was performed on Medline and Embase databases using relevant key terms covering lncRNA TPT1-AS1, cancer, and clinical outcomes. The effect size estimates and their 95% confidence interval (CI) were pooled using random-effects models. Meta-analyses were conducted using STATA 16.0 software.

Results. Seventeen articles met our eligibility criteria. Tumor tissue compared to normal tissue showed increased level of lncRNA TPT1-AS1 expression (pooled standardized mean difference (95% CI): 0.65 (0.52 to 0.79)). Overexpression of this lncRNA was a significant predictor for poor prognosis (Pooled log-rank test P-value < 0.001); in patients with high-level of lncRNA TPT1-AS1, the risk of death at five years was 1.40 times greater than their counterparts. The pooled Odds ratios for association lncRNA TPT1-AS1 with tumor stage, tumor size, and lymph node metastasis were 1.94 (95% CI: 0.90 to 4.19, 8 studies, I^2= 79.6%), 2.33 (95% CI: 1.31 to 4.14, 5 studies, I^2= 40.0 %), and 1.89 (95% CI: 1.08 to 3.36, 5 studies, I^2= 61.7%), respectively. Regarding the identified potential mechanisms, lncRNA TPT1-AS1 plays a role in cancer growth mainly by sponging miRNAs and regulating their downstream targets or controlling the expression of key cell cycle regulators.

Conclusion. In cancer patients, elevated expression of lncRNA TPT1-AS1 might be associated with a shorter Overall Survival, advanced stages, larger tumor size, and lymph node metastasis.

Introduction

Cancer is primarily caused by genetic and epigenetic alterations leading to the aberrant expression of genes [1]. Cancer has remained a leading cause of mortality and morbidity worldwide despite the great advancement in therapeutic approaches [2, 3]. Understanding the molecular mechanisms underlying cancer development is vital to identify novel diagnostic/prognostic biomarkers and therapeutic targets for more efficient interventions in the fight against cancer [4].

The development of targeted therapy focusing on the regulation of cancer-related protein-coding genes was a breakthrough in cancer diagnosis, prognosis, and treatment [5-7]. Besides protein-coding genes, non-coding RNAs, such as microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), have been recognized to play a critical role in cancer biological processes, including cellular differentiation, proliferation, apoptosis, migration, and invasion[8-12]. Hence, they have the potential to be used as diagnostic and prognostic biomarkers and novel therapeutic targets in multiple cancers [13-15].

LncRNAs are exquisitely regulated. Based on growing evidence, the aberrant expression of certain lncRNAs drives various important phenotypes of cancer through regulating the expression of protein-coding genes in different ways, including transcriptional, posttranscriptional, post-translational, and epigenetic regulation [16-19]. However, the specific functions and clinical value of most lncRNAs have remained largely unknown in cancer.

Tumor protein translationally controlled 1 - antisense RNA 1 (TPT1-AS1) is the transcript of the TPT1 gene located at chromosome region 13q14.13. In recent years, increasing studies have attempted to identify the expression changes, clinical significance, and potential molecular mechanisms of lncRNA TPT1-AS1 in different cancers [20-36]. We aimed to summarize the

main findings reported in original studies on the clinical significance and functional roles of lncRNA TPT1-AS1 in different types of cancer.

Materials and Methods

The present systematic review was undertaken under the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. As a systematic review of published studies, it required no ethical approval.

All eligible studies assessing the functional roles, molecular mechanisms, and/or the clinical significance of lncRNA TPT1-AS1 in cancer were included in this systematic review.

Search

A comprehensive search was performed on two databases, Medline and Embase, on June 21^{th,} 2022, and updated on July 10th, 2022, using a combination of the key terms in three domains:

1- “long non-coding RNA TPT1-AS1”, “lncRNA TPT1-AS1", “TPT1-AS1”, “TPT1 Antisense RNA 1”,
2- "cancer", "carcinoma", "neoplasm", "tumor."
3- "tumorigenesis", "progression", "diagnostic", "prognostic", "prognosis", "survival", "recurrence", "metastasis", "invasion"

Key terms were combined by "OR" in each domain, and then domains were combined by "AND," tailored for each database.

We also manually screened reference lists of the included articles and the first 30 pages of the google scholar survey to identify any additional eligible studies. Citations from all retrieved articles were imported into the EndNote X9, and the duplicates were removed.

Study inclusion

According to predefined eligibility criteria, two researchers independently screened the retrieved articles by the title and abstracts, followed by reading the full-texts of potentially relevant publications. Any disagreements were resolved by consulting with a third researcher.

Studies were included in this review if they met the following criteria:

(1) Evaluating the functional roles, molecular mechanisms, and/or the clinical significance of lncRNA TPT1-AS1 in cancer

(2) Written in English

(3) Published in a peer-review journal

We excluded studies that had a non-original research design, lacked a clear description of utilized methods, and/or were not available as full-text.

Data extraction

From the final list of studies that fulfilled the study inclusion criteria, two researchers [MHM, SHS, and MS] independently extracted data on main study variables, including the first author's name, study year, country, study design, clinical information, including cancer type, stage of cancer, and sample size, expression changes and their clinical significance, and findings of functional study.

Statistical analysis

We used a standard meta-analysis model to pool effect measures (risk ratio or odds ratio) and their corresponding 95% Confidence Intervals (CI) for association between TPT1-AS1 expression level and outcomes including five-year mortality risk, cancer stage, tumor size, and

lymph node metastasis; results were presented in forest plots. I2 statistic was used to assess the inter-study heterogeneity. Based on the size of the observed heterogeneity, the pooled estimates derived either from the random or fixed effects model; an I^2 75% to 100% was considered as a substantial heterogeneity.[37]

The presence of publication bias checked objectively using Begg test and visually by the funnel plot. Using STATA's Metaninf command, the influence of each individual study was assessed by omitting each study in turn and re-estimating the summary estimate in the meta-analysis. We combined Log-rank p-values by Edgington's additive method using the Metap package; a P - value < 0.05 indicated significance. All statistical analyses were conducted using Stata/MP Version 16 (Stata Corp. LP, USA/ METAN package)

Bioinformatics analyses

We used StarBase v 2 [38] and MiRnet 2.0 [39] tools to predict the interacting miRNAs and target genes for lncRNA TPT1-AS1. A lncRNA-miRNA-mRNA interaction network was constructed using *TPT1-AS1* and all predicted miRNA-Target genes to discover more about related pathways.

Results

Study selection process

A total of 67 items were identified on the initial search from two databases, of which 23 were duplicates. A further 27 were excluded after screening by title/abstract (n=21) or full text (n=6) reviews. Hence, we included 17 studies meeting our eligibility criteria of which, including 11 studies on both human and in-vitro [20-22, 24-31] (animal experiments examined in 5 of them), 5 only on human [32-36], and one on in-vitro experiments [23]. (Suppl. Figure 1) shows the selection process in detail.

Evaluated cancers were breast (n=1) [22], ovarian (n=1) [21], cervical (n=1) [20], prostate (n=1) [36], brain (n=4) [23, 25, 33, 35], colorectal (n=4) [24, 28, 29, 34], gastric (n=2) [27, 32], pancreatic (n=1) [30], and hepatocellular cancer (n=2) [31]. (Table 1)

Human studies

Deregulated expression

Fourteen studies assessed lncRNA TPT1-AS1 expression changes in tumor tissue compared to non-tumor adjacent tissue [20-22, 24-32, 34, 36]. In breast cancer, Hu et al. identified the downregulation of lncRNA TPT1-AS1 [22]. The same pattern was observed in prostate cancer [36], but it failed to reach statistical significance. There was a controversy between studies in hepatocellular cancers, while Wei et al. [31] detected downregulation of lncRNA TPT1-AS1, Li et al. [26] observed a reverse pattern.

Of three studies in brain cancer, only Gao et al. [25] examined expression changes of lncRNA TPT1-AS1 in tumor tissue compared to non-tumor adjacent tissue. They found that lncRNA

TPT1-AS1 was upregulated in glioblastoma (GBM). However, the study of Wang et al. [33] compared different grades of the glioma and showed that the expression level of TPT1-AS1 was lower in tumor grade IV compared to grade II & III.

In other cancers, including colorectal [24, 28, 29, 34], cervical [20], ovarian [30], pancreatic [30], and gastric cancer [27, 32], lncRNA TPT1-AS1 expression was consistently upregulated. (Table 1)

The meta-analysis was conducted on nine studies; based on the pooled estimation of standardized mean differences (SMDs), expression level of lncRNA TPT1-AS1 was higher in tumor tissue compared to adjacent normal tissue (pooled SMD (95% CI): 0.65 (0.52 to 0.79)). (Suppl. Figure 2). However, sensitivity analysis showed that removing any study did not change the pooled OR. (Suppl. Figure 3).

Clinical significance of lncRNA TPT1-AS1 expression changes

- **Poor prognosis**

Nine studies evaluated prognosis of the disease in relation to the expression level of lncRNA TPT1-AS1 [follow-up duration: 60 to 120 months]. [21, 24, 26-30, 34] (Table 1) Most studies (n=8) found that upregulation of this LncRNA was associated with lower overall survival in cancer patients. [Pooled log-rank test P-value < 0.001]

Our meta- analysis of eight studies showed that patient with a high level of lncRNA TPT1-AS1 expression had a greater 5-year mortality risk compared to others (Pooled Crude Hazard Ratio (HR) (95% CI): 1.40 (1.10 to 1.78; I^2 = 75.6%) . (Figure 1) Sensitivity analysis revealed that the omission of any study would not modify the pooled effect size (Figure 2).

- **Other clinical outcomes**

Overall, included studies consistently reported a significant association between the aberrant expression of lncRNA TPT1-AS1 and adverse clinical outcomes, including the higher stages of the disease [20, 21, 24, 26-28, 30, 31], recurrence [24, 32], and lymph node metastasis [20, 24, 26, 27, 29]. (Table 1 and Figure 3)

Overexpression of LncRNA TPT1-AS1 was more frequently found in higher stages of ovarian [21], cervical [20], colorectal [24, 28], gastric [27], pancreatic [30], and hepatocellular [26] cancers; However, in contrary to Li et al study, [26] Wei et al. [31] observed that advanced stages of hepatocellular carcinoma had a lower level of lncRNA TPT1-AS1. (Table 1) The pooled Crude OR [95% CI] for all studies investigating association between expression of LncRNA TPT1-AS1 and advanced clinical stages of cancer was 1.94 (0.90 to 4.19), with heterogeneity of 79.6% (P value < 0.001). After excluding the Wei et al. study, association between lncRNA TPT1-AS1 and tumor-stage reached the statistical significance (pooled OR 2.71 (1.81 to 4.05) and the observed heterogeneity disappeared (I^2 = 18.9%). (Figure 3) The overall pooled estimate remained stable following sequential omission of each study in the sensitivity analysis. (Suppl. Figure 4)

Regarding the association of lncRNA TPT1-AS1 expression with the tumor size, a significant association was detected in colorectal [24], ovarian [21], and cervical [20] cancers. (Table 1) The pooled OR measuring this association was 2.33 (1.31 to 4.14) without a significant heterogeneity (N=5 studies; I2 =40.0 %). (Figure 3) In the sensitivity analysis, a greater pooled estimate without heterogeneity across the studies was obtained (2.97 (1.83 to 4.81); I^2 = 0.0%) by omitting Hu et al study[22].

High lncRNA TPT1-AS1 expression in colorectal [24, 29], gastric [27], hepatocellular[26], and cervical [20] cancers was significantly related to the presence of lymph node metastasis. Overall, the pooled OR for eight eligible studies evaluating association of lncRNA TPT1-AS1 expression and lymph node metastasis was 1.89 (1.08, 3.36) without substantial heterogeneity (I^2= 61.7%). During the sensitivity analysis, the omission of Hu et al study [22] showed notable changes in the pooled estimate (2.60 (1.82 to 3.72)) and heterogeneity was vanished completely (I^2 = 0.0%). (Supp. Figure 4)

Publication Bias

Overall, there was no evidence of substantial publication bias on both visual inspection of the funnel plot (Suppl. Figure 5) and the Egger's test (Suppl. Table 1).

More Findings

Besides, Zan et al. [35] identified lncRNA TPT1-AS1 as a potential biomarker to diagnose glioblastomas early and predict its prognosis through constructing a lncRNA-mediated ceRNA network. L Zhang et al. [28] by analysis of the GSE95423 dataset, found that lncRNA TPT1-AS1 is upregulated in colorectal tissue with liver metastasis compared to colorectal tissue without it. Further, their animal study showed that the knockdown of lncRNA TPT1-AS1 suppressed colorectal liver metastasis. In rectal cancer, Xing et al. [34] identified TPT1-AS as an immune-related differential expression lncRNA correlated with overall survival. (Table 1)

In breast cancer, Hu et al. found that deregulated expression of lncRNA TPT1-AS1 was directly associated with Her-2 negative status, but not with the status of estrogen and progesterone receptors [22]. In hepatocellular cancer, Wei et al. [31] detected a non-significant association between aberrant expression of lncRNA TPT1-AS1 and the status of HBs Ag, HCV Ag, and cirrhosis. (Table 1)

Cell line studies

The main subcellular location of lncRNA TPT1-AS1 was the cytoplasm in pancreatic[30], cervical [20], and glioma [40] cancer cells and the nucleus in ovarian [21] and colorectal [24, 29] cancer cells. (Table 2)

Regarding lncRNA TPT1-AS1 function, there was a controversy between studies; while most studies identified it as an oncogene, [20-30], Wei et al. [31] and Hu et al. [22] revealed that its "overexpression" reduced tumor cell proliferation and invasion.

In in-vivo studies, overexpression of lncRNA TPT1-AS1 increased tumor growth in colorectal [29], pancreatic[30], ovarian [21] and cervical [20] cancers but decreased it in hepatocellular carcinoma [31]. (Table 2)

Mechanisms

a) Acting as a sponge of miRNAs

Based on the functional studies, lncRNA TPT1-AS1 can play a role in the progression of breast, cervical, pancreatic, and brain cancers through sponging miRNAs and eliminating their suppressive effect on key downstream molecular targets (Table 2 and Supplementary figure 6)**.**

In breast cancer, Hu et al. [22] found that the lncRNA TPT1-AS1 sponges miR-330-3p and upregulates the expression of a tumor suppressor gene, QKI [40-42].

In cervical cancer, Jiang et al.[20] found that lncRNA TPT1-AS1 upregulates SP1[43, 44], an oncogene and an invasion-promoting factor, in tumor cells by sponging miR-324-5p.

In pancreatic cancer, Cheng et al. [30] uncovered that lncRNA TPT1-AS1 regulates cell proliferation and invasion by targeting ITGB3 via modulating miR-30a-5p.

In brain cancer, the study of Jia et al.[23] revealed that lncRNA TPT1-AS1 inhibits glioma cell autophagy and promotes cell proliferation through binding to the miR-770-5p and upregulating

expression of its downstream target, STMN1[45]. Gao et al.[25] found a different pathway in which overexpression of lncRNA TPT1-AS1 upregulates ECM1 by sponging miR-23a-5p, resulting in the increased cell proliferation rate of glioblastoma cells. (Table 2)

Regulation of key cell cycle regulators

In some cancers, lncRNA TPT1-AS was involved in cancer progression by regulating critical cell cycle regulators. In gastric cancer [27], lncRNA TPT1-AS1 knockdown induced cell cycle G0/G1 phase arrest via upregulating p21 and E-cadherin expression and downregulating cyclin-dependent kinase 4, cyclin D1, and vimentin expression and, accordingly, inhibited cell proliferation. In hepatocellular carcinoma, Wei et al.[31] showed that the "overexpression" of lncRNA TPT1-AS1 inhibits cell cycle progression by downregulating cyclin-dependent kinase 2. On the contrary, Li et al. [26] revealed that the "knockdown" of lncRNA TPT1-AS1 inhibits HCC cell proliferation, migration, and invasion by downregulating CDK4, N-cadherin, and Vimentin and upregulating p21 and E-cadherin expression levels. (Table 2 and Supplementary figure 6).

Regulation of mRNA expression

Based on in-vitro studies, lncRNA TPT1-AS1 is involved in the progression of ovarian and colorectal cancers via activating the TPT1 promoter and increasing its expression. Based on their findings, overexpression of the TPT1 gene leads to activation of FAK and JAK-STAT3 signaling pathways in colorectal cancer and phosphorylation of PI3K and AKT molecules in ovarian cancer [21, 28].

In colorectal cancer, other pathways were also identified; Chen et al. found that lncRNA TPT1-AS1 mediate the Wnt/β-catenin pathway, a major signaling pathway in cancer invasion, by regulating APC expression. Using RNA immunoprecipitation and mRNA stability assays, Yiyun

Zhang et al. found that lncRNA TPT1-AS1 promotes the association between NF90 and VEGFA mRNA, leading to the upregulation of VEGFA mRNA stability and colorectal cell angiogenesis [24]. (Table 2 and Supplementary figure 6)

Bioinformatics Results

A network of 19 miRNAs, 229 nodes and 846 edges (Figure 4) was created through the online StarBase v 2 [38] and MiRnet 2.0 [39] tools. KEGG pathway analysis on the whole network showed that the most significant related pathways amongst the considered target genes are Non-small cell lung cancer, Glioma and Chronic myeloid leukemia. GO functional enrichment analyses showed that the top GO-BP terms amongst the target genes are Negative regulation of transferase activity, Aging and Establishment of protein localization and Protein transport. As it is shown in Suppl. table 2 and 3, most of the target genes are incorporated in cancer related signaling pathways with significant adjusted p-values.

Discussion

Based on our meta-analysis results, the expression of TPT1-AS1 lncRNA is deregulated in cancer.

Its overexpression was a significant predictor for poor prognosis (Pooled log-rank test P-value < 0.001); high-level of lncRNA TPT1-AS1 was directly associated with tumor stage (Pooled Crude OR (95% CI): 1.94 (0.90 to 4.19)), tumor size (2.33 (1.31 to 4.14)) , and lymph node metastasis (1.89 (1.08, 3.36)). According to available evidence, aberrant expression of TPT1-AS1 lncRNA promotes tumor cell growth, invasion, and metastasis capacities through transcriptional and post-transcriptional regulation of cancer-related gene expression.

Previous studies have identified several deregulated lncRNAs in cancer cells [46-48]. Deregulation of lncRNAs in cancer cells may be explained by genetic, epigenetic, and transcriptional regulatory mechanisms [48].

Studies consistently found a direct association between lncRNA TPT1-AS1 misexpression in tumor tissue and unfavorable clinical outcomes. Similar to lncRNA TPT1-AS1, aberrant expression of a growing number of lncRNAs, such as HOTAIR [49], MALAT1 [50], and BANCR [37] lncRNAs, have been linked to poor cancer prognosis.

Overexpression of lncRNA TPT1-AS1 was found to inhibit cancer growth in breast cancer [22], but promote it in cervical [20], ovarian [21], colorectal [28, 29], brain [23, 25], pancreatic [30], and gastric cancer cells [27]. There was a controversy between the two studies in hepatocellular carcinoma [26, 31]. Deregulated expression of lncRNAs can impact tumor cell proliferation, resistance to apoptosis, and angiogenesis through diverse molecular mechanisms classified into four categories: signal, decoy, guide, and scaffold [51]. LncRNA TPT1-AS1 influences cancer growth by sponging miRNAs [20, 22, 23, 25, 29] and regulating their downstream targets or

controlling the expression of key cell cycle regulators [26, 27, 31]. In addition, lncRNA TPT1-AS1 affects angiogenesis by binding to NF90 and regulating VEGFA mRNA stability [24].

The process of cell metastasis [52-54], a leading cause of cancer mortality [55], has been extensively studied during the past decades. However, its underlying molecular and cellular mechanisms remain poorly understood. While myriads of metastasis-related protein-coding genes have been identified, the role of lncRNAs in cancer cell metastasis is in its infancy [17, 56]. Until now, a number of lncRNAs such as H19 [57], HOTTIP [58], MALAT1 [59], HOTAIR [60] are known to modulate key molecules in the main processes of metastasis, including epithelial-mesenchymal transition (EMT), intravascular transit, and metastatic colonization, in various cancers.

According to our included studies, lncRNA TPT1-AS1 can play a role in cancer metastasis via different ways. Their functional analyses suggest that lncRNA TPT1-AS1 controls the regulators of EMT, including Sp1 Transcription Factor [20], E-cadherin, and Vimentin [26, 27]. Besides, it activates the PI3K/AKT [21], STAT1/APC [29], and JAK/STAT3 [28] pathways, known regulatory pathways of EMT-related transcription factors.

Previous in vitro and in vivo studies revealed that the knockdown of certain oncogenic lncRNAs can diminish cancer cell growth in different cancer types [61]. In functional analysis, lncRNA TPT1-AS1 overexpression in breast cancer, and its knockdown in other cancers, inhibited cell proliferation. Also, an animal study showed that knockdown of lncRNA TPT1-AS1 suppressed colorectal liver metastasis [28]. Manipulating the expression level of lncRNAs such as lncRNA TPT1-AS1 could be a novel approach for cancer therapy. Advantages of lncRNAs compared to the routine gene targets, e.g., acting as a gene-specific epigenetic regulator and ability to become

directly functional right after delivery, might make them a better candidate for cancer therapy [62-64].

Conclusion

Studies have found that lncRNA TPT1-AS1 expression may be aberrantly expressed in different cancers. Misexpressed lncRNA TPT1-AS1 is involved in tumor cell growth, invasion, and metastasis by transcriptional and posttranscriptional regulation. Our included studies suggest that lncRNA TPT1-AS1 may be a promising therapeutic target. However, research on lncRNA TPT1-AS1 remains in the experimental phases.

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Author contribution:

MS and HR had the idea, designed the study, and prepared the manuscript. MM, HR, PS, and ZKH developed the search strategy and selection process. SHS, MHM, PS and MS extracted the data. All authors critically revised the manuscript for important intellectual content and gave final approval to publish the version.

Table 1. Expression and clinical significance of lncRNA TPT1-AS1 in various cancers.

ID	Author (Year)	Cancer type	Stage III–IV	Number of Tumor tissues (healthy adjacent tissues)		Expression changes and clinical outcome					More findings: Association of TPT1-AS1 expression level with other factors
				Study dataset	Online Dataset	Expression*	higher stage	Poor prognosis	Lower DFS/ Recurren	Lymph node metastasi	
1	Hu et al., (2020)	BC	33%	73 (45)	TCGA: 1109 (113) - GSE54002: 417 (16) GSE65194: 130 (11)	↓	NA	+	NA	NA	● Her- 2-negative status: + [directly] ● Age, grade, tumor size, ER status, and PR status: NS
2	Wu et al., (2019)	EOC	62% †	58 (20)	—	↑	+	NA	NA	NA	● Tumor size, Poor cell differentiation: +[directly]
3	Jiang et al., (2018)	CC	0% †	40 (40)	—	↑	+	+	NA	+	● Tumor size: + [directly]
4	Wan et al., (2016)	PC	NR	3 (3)	TCGA: 419 (52) - GSE73397: 3 (3) GSE55909: 2 (2)	NS	NA	NA	NA	NA	● TPT1-AS1 expression was "non-significantly "downregulated
5	Wang et al., (2016)	Glioma	NR	—	GSE16011 [(Grade II, III, IV)]: (22, 80, 142) CGGA: (120, 36, 126) REMBRANDT: (69, 67, 105)	NA	NA	NA	NA	NA	● Median of TPT1-AS1 exp. was lower in tumor grade IV compared to grade II & III.
6	Gao et al., (2020)	GBM	NR	60 (60)	—	↑	NA	NA	NA	NA	—
7	Zan et al., (2019)	GBM	NR	—	GSE9385: 26 (6)	NA	NA	NA	NA	NA	● TPT1-AS1 was identified as a relevant lncRNA biomarkers in GBM through establishing a functional lncRNA-mediated ceRNA network
8	L Zhang et al., (2021)	CRC	41%	72 (36)	GSE95423 [CRC tissues with liver Metastases (LM) (without LM)]: 7 (8)	↑	+	+	NA	NA	● ↑ TPT1-AS1 in CRC tissues with liver metastasis compared to CRC tissues without it .(GSE95423) ● tumor size: NS
9	Y Zhang et al., (2020)	CRC	66%	80 (80)	TCGA (N: NR)	↑	+	+	+	+	●Age, Sex, Cell differentiation: NS ● Tumor size: + [directly]
10	Xing et al., (2021)	READ	NR	—	TCGA: 166 (10)	↑	NA	+	NA	NA	● TPT1-AS1 was an immune-related differentially expressed lncRNAs
11	Tang et al., (2021)	GC	70%	76 (76)	—	↑	+	+	NA	+	●Age, Sex, Cell differentiation: NS
12	Tian et al., (2017)	GC	NR	—	GSE79973: 10 (10) - GSE62254: 300 (0) GSE15459: 191 (0)	↑	NA	NA	+	NA	—
13	Li et al., (2020)	HCC	48%	50 (50)	—	↑	+	+	NA	+	●Age, Sex, Cell differentiation: NS
14	Wei et al., (2021)	HCC	60%	62 (62)	—	↓	+	NA	NA	NA	● Age, Sex, HBs Ag, HCV Ag, Cirrhosis : NS
15	Chen et al., (2022)	CRC	NR	—	GSE146587: 6 (6)	↑	NA	+	NA	+	—
16	Cheng et al., (2022)	PDAC	42%	69(-)	GSE62452	↑	+	+	NA	NS	● Age, Sex: NS Poor cell differentiation: +[directly]

BC: Breast Cancer. CC: Cervical Cancer. CDK: Cyclin-Dependent Kinase. CGGA:Chinese Glioma Genome Atlas. CRC: Colorectal Cancer. CY: Cytoplasm. DFS: Disease Free Survival. EOC: Epithelial Ovarian Cancer. ER: Estrogen Receptor. GBM: Glioblastoma. GC: Gastric Cancer. GEO: Gene Expression Omnibus. HBsAg: Hepatitis B Surface Antigen. HCC: Hepatocellular Carcinoma. HCV Ag: hepatitis C virus Antigen. PC: Prostate Cancer. PDAC: Pancreatic ductal adenocarcinoma. PR: Progesterone Receptor READ: Rectum Adenocarcinoma. REMBRANDT: Repository for Molecular Brain Neoplasia Data TCGA: The Cancer Genome Atlas. NR: Not Reported. NA: Not Assessed. * In Tumor tissues compared to healthy adjacent tissues . † FIGO stage

Table 2. Molecular mechanisms of lncRNA TPT1-AS1 in various cancers.

ID	Author (Year)	Cancer type	Cell line type	Function	Mechanism	Targets or modulated molecules	Subcellular Location	Expression Manipulation	Functional changes			Findings
									Cell Prolif.	Invasion/ Migration	TG in vivo	
1	Hu et al., (2020)	BC	MDA-MB-231, BT-549, MDA-MB-468, Hs578 T HCC1937 - MCF-10A	Tumor Supp.	Decoy	miR-330-3p	NA	↑	↓	↓	NA	*TPT1-AS1 sponges miR-330-3p → ↑ QKI exp. → ↓ cell prolif., migration and invasion*
2	Wu et al., (2019)	OC	ES-2, SKOV3 HOSEpiC	Oncogene	Signal	PI3K/AKT	nucleus	↑	↑	↑	↑	- TPT1-AS1 upregulation is associated EOC cells invasion *TPT1-AS1 induces the transcriptional activity of the TPT1 promoter → ↑ TPT1 exp. → Phosphorylation of PI3K and AKT molecules → ↑ TG and metastasis*
3	Jiang et al., (2018)	CC	C33A, SiHa, HeLa, CaSki, ME-180 NC104	Oncogene	Decoy	miR-324-5p	CY	↑	↑	↑	↑	TPT1-AS1 sponges miR-324-5p → ↑ SP1 → ↑ cell prolif., migration, invasion and EMT progress
4	L Zhang et al., (2021)	CRC	HCT116, HT-29, SW620, LoVo NCM460	Oncogene	Signal	JAK/STAT3	nucleus	↑	↑	↑	NA	-TPT1-AS1 induced liver metastasis in vivo *↑ TPT1-AS1 → ↑ TPT1 expr. → Activation of the FAK and JAK-STAT3 → ↑ CRC progression*
5	Y Zhang et al., (2020)	CRC	SW480, HCT116	Oncogene	Decoy	NF90	NA	↑	NA	↑	NA	*TPT1-AS1 binds to NF90 → ↑ VEGFA mRNA stability → ↑ angiogenesis*
6	Jia et al., (2019)	Glioma	U87, U118, U251, U373, D247	Oncogene	Decoy	miR-770-5p	CY	↑	↑	NA	NA	*TPT1-AS1 sponges miR-770-5p → ↑ STMN1 exp. → inhibits autophagy & ↑ cell prolif.*
7	Gao et al., (2020)	GBM	U87	Oncogene	Decoy	miR-23a-5p	NA	↑	↑	NA	NA	*TPT1-AS1 sponges miR-23a-5p → ↑ ECM1 exp. → ↑ cell prolif.*
8	Tang et al., (2021)	GC	SGC-7901, AGS, BGC-823, MGC-803 , GES-1	Oncogene	Signal	*CDK 4, cyclin D1, vimentin, p21, E-cadherin*	NA	↓	↓	↓	NA	*↓ TPT1-AS1 → ↓ CDK 4, cyclin D1, and vimentin exp. & ↑ p21 and E-cadherin exp. → Induces G0/G1 phase arrest & Inhibits G1/S transition → ↓ cell prolif. & ↓ migration and invasion*
9	Wei et al., (2021)	HCC	SNU-398, SU.86.86	Tumor Supp.	Signal	*CDK2*	NA	↑	↓	NA	↓	*↑ TPT1-AS1 → ↓ CDK2 exp. → G1 arrest → ↓ cell prolif.* ● In vivo, ↑ TPT1-AS1 → ↓ Tumor volume and weight
10	Li ea al., (2020)	HCC	HepG2, SNU-182	Oncogene	Signal	*CDK4, N-cadherin, E-cadherin, Vimentin, p21,*	NA	↓	↓	↓	NA	*↓ TPT1-AS1 → ↓ CDK4, N-cadherin, and Vimentin exp. & ↑ p21 and E-cadherin exp. → Induces G0/G1 phase arrest & Inhibits G1/S transition → ↓ cell prolif. & ↓ migration and invasion*
11	Chen ea al., (2022)	CRC	HCT116, CACO2	Oncogene	Signal	*STAT1/APC*	nucleus	↓	↓	↓	↓	-TPT1-AS1 was significantly upregulated in CRC stem cells *↓ TPT1-AS1 → ↑ STAT1 → ↓ APC exp. → mediate the Wnt/β-catenin pathway. → ↓ cell proli, ↓ migration and invasion & ↓ stemness of CRC stem cells*
12	Cheng et al., (2022)	PDAC	BxPC-3, SW1990	Oncogene	Decoy	*miR-30a-5p*	*CY*	↑	↑	↑	↑	*↑ TPT1-AS1 → ↓ E-cadherin, ↑ Vimentin and N-cadherin exp → ↑ migration and invasion* *TPT1-AS1 sponges miR-30a-5p → ↑ ITGB3 → mediate enhanced STAT3 activation*

APC: Adenomatous Polyposis Coli. BC: Breast Cancer. CASP2: Caspase 2. CC: Cervical Cancer. CDK: Cyclin-Dependent Kinase. CRC: Colorectal Cancer. CY: Cytoplasm. ECM1: Extracellular Matrix Protein 1. EOC: Epithelial Ovarian Cancer. Exp.: Expression. GBM: Glioblastoma. GC: Gastric Cancer. HCC: Hepatocellular Carcinoma. ITGB3: Integrin Subunit Beta 3.

LC: liver Cancer. NA: Not Assessed. PDAC: Pancreatic ductal adenocarcinoma. Prolif.: Proliferation. STMN1: Stathmin 1. Supp.: Suppressor. TG: Tumor Growth. TPT1: Tumor Protein, Translationally-Controlled 1. TPT1-AS1: TPT1 Antisense RNA 1.

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Conflict of interests

Authors declare no conflict of interest.

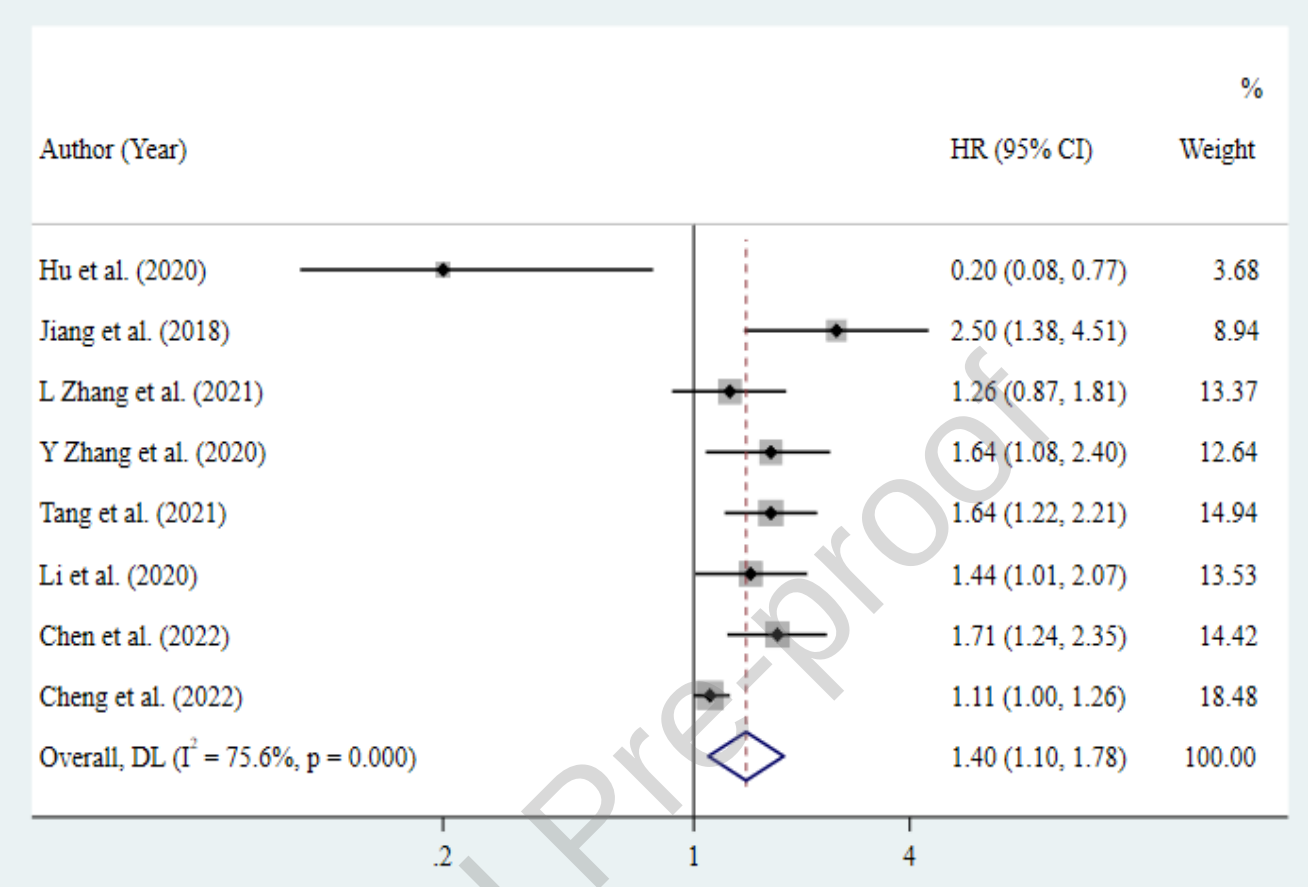

Figure 1. Forest plot showing the association between five-year risk of death and TPT1-AS1 expression in different cancer types (univariate model).

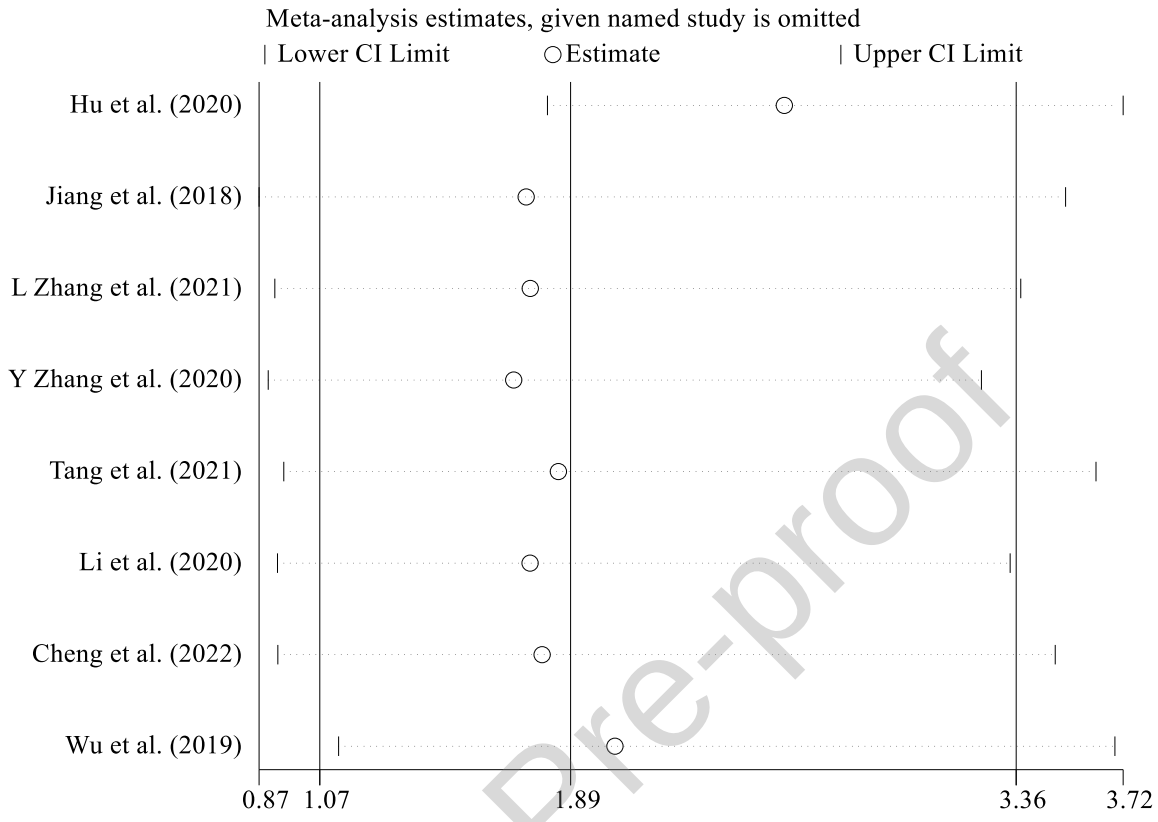

Figure 2. Sensitivity analysis for the meta-analysis of the association between TPT1-AS1 expression and five-year risk of death.

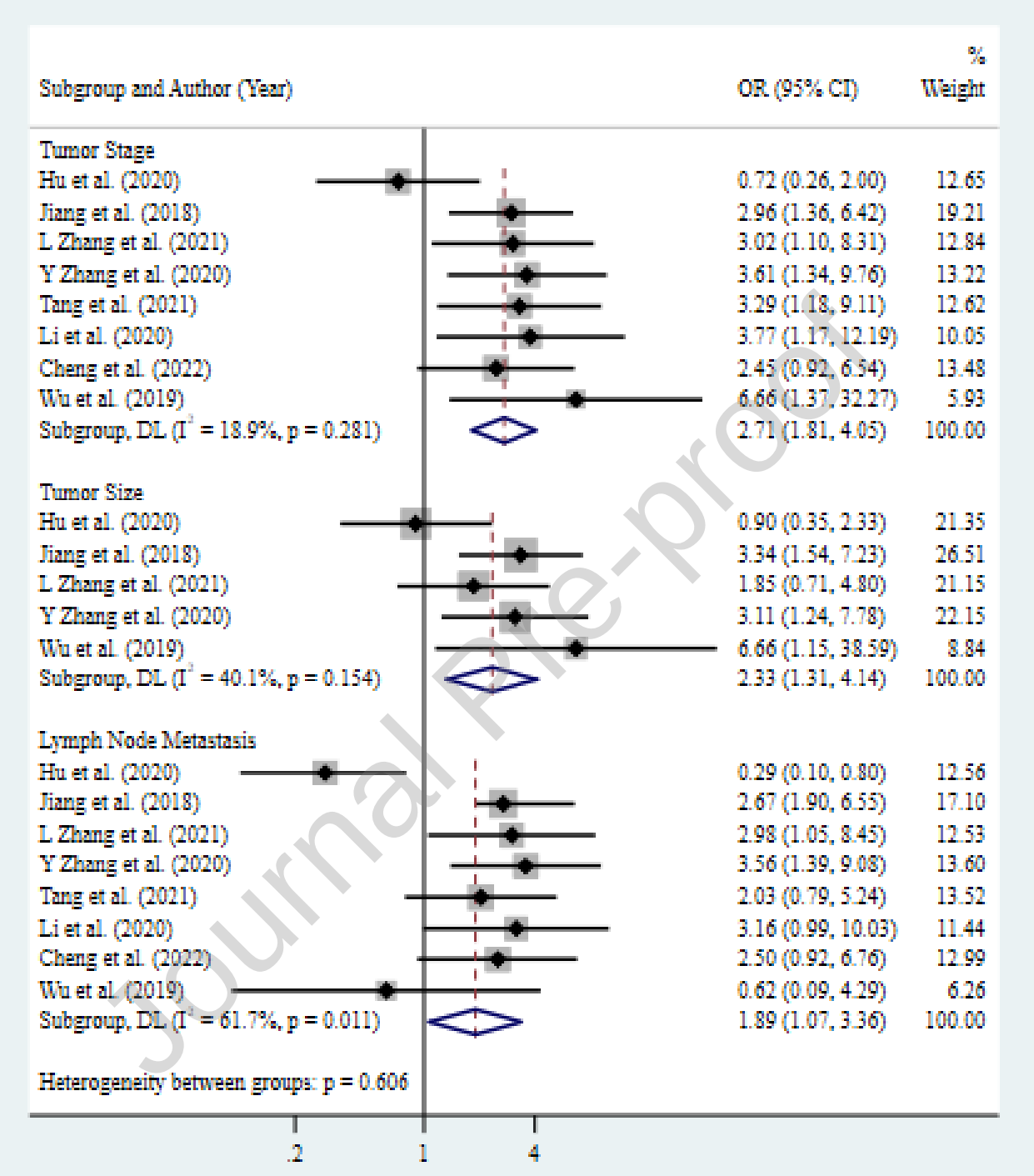

Figure 3. Forest plot showing the association between TPT1-AS1 expression and cancer stage, tumor size and lymph node metastasis in different cancer types (univariate model).

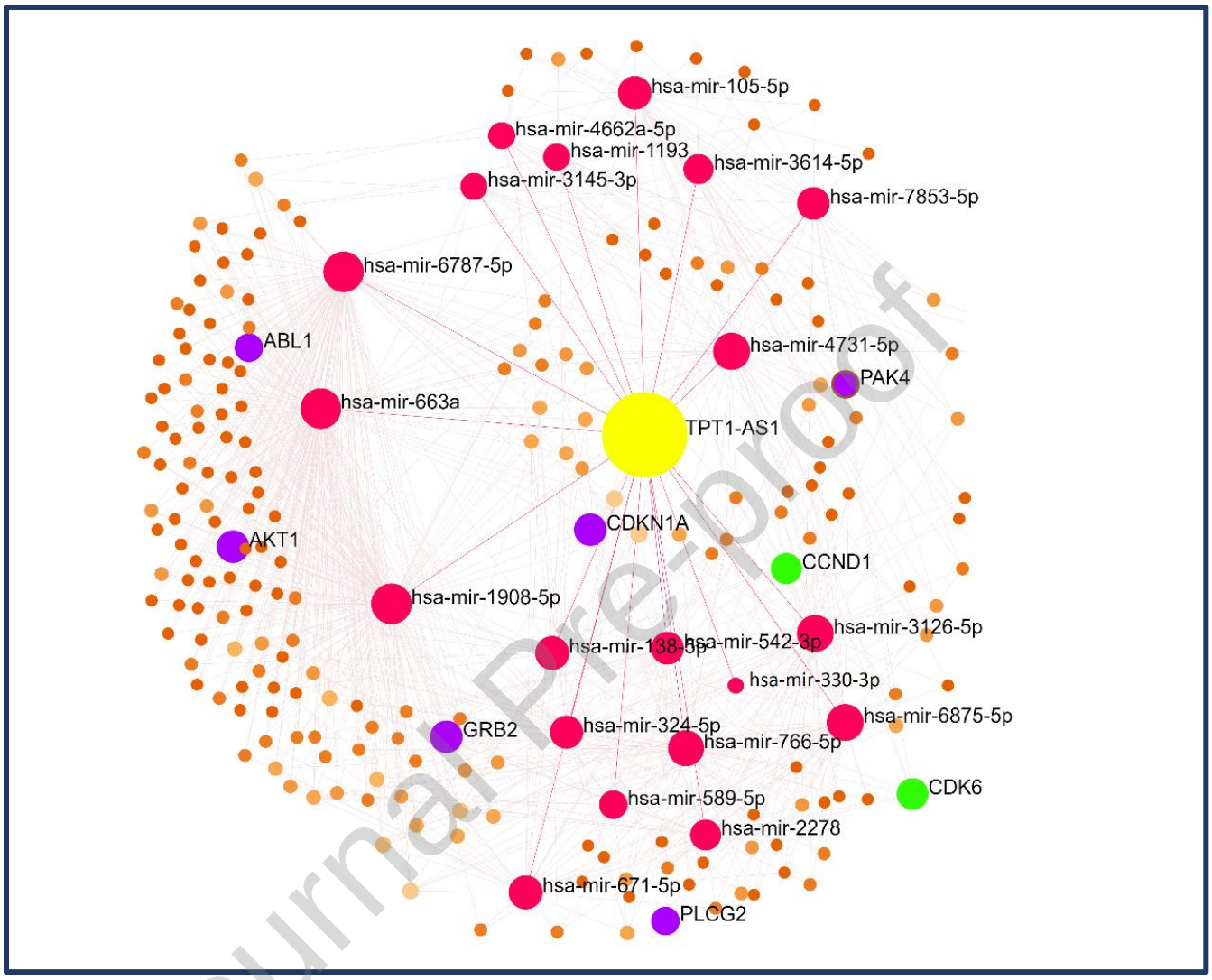

Figure 4: The LncRNA-miRNA-mRNA interaction network. TPT1-AS1 as the central node (Yellow), miRNA (Pink circles), Target mRNAs (Orange circles). The highlighted purple and green circles demonstrates genes correlated to cancer.