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LINC00657 exhibits oncogenic properties in prostate cancer and may serve as a prognostic biomarker in cancer

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Abstract

Background The prognostic significance of long non-coding RNA LINC00657 remains ambiguous, and its role in prostate cancer (PCa) is not well characterized. This study aims to conduct a meta-analysis to clarify the clinical implications of LINC00657 in various malignancies and to assess its impact on PCa.

Methods A systematic search was conducted across PubMed, Embase, and Web of Science to identify relevant studies. Hazard ratios (HR) with 95% confidence intervals (95% CI) and associated clinicopathological factors were extracted. Subgroup analyses were performed based on sample size and cancer type. The expression levels of LINC00657 in PCa tissues were analyzed using the GTEx and TCGA databases. Additionally, transwell, wound healing, and EdU assays were utilized to evaluate cell migration and proliferation. An in vivo xenograft model was also employed to investigate the role of LINC00657 in PCa.

Results The meta-analysis included 11 eligible studies comprising 1,226 patients. Our findings indicate that overexpression of LINC00657 is significantly correlated with poor overall survival (HR = 2.09, 95% CI: 1.26–2.91), distant metastasis (OR = 2.15, 95% CI: 1.34–3.46), and advanced TNM staging (OR = 3.07, 95% CI: 1.22–7.74) across malignancies. Analysis of the TCGA and GTEx databases, corroborated by experiments in cell lines, revealed that LINC00657 is overexpressed in PCa. Furthermore, knockdown of LINC00657 resulted in reduced migration and invasion of PCa cells in vitro, as well as inhibited cell growth both in vitro and in vivo.

Conclusion The findings suggest that LINC00657 plays an oncogenic role in PCa and could be a valuable indicator of poor prognosis in cancer.

Keywords LINC00657, Prostate cancer, Prognosis, Meta-analysis, Biomarker

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Introduction

Cancer remains the foremost cause of morbidity and mortality globally, posing a significant threat to human health. Prostate cancer (PCa) ranks as the second most prevalent cancer and the fifth leading cause of cancer-related deaths among males, with an estimated 1.46 million new cases and 396,792 deaths worldwide in 2022 [1]. The high mortality rate associated with PCa can be attributed to its poor prognosis and rapid progression, underscoring the urgent need to identify novel prognostic markers for this disease.

Long non-coding RNAs (lncRNAs), defined as RNA molecules exceeding 200 nucleotides in length that lack protein-coding reading frames, have historically been regarded as mere by-products of genomic transcription, often dismissed as "noise" generated by RNA polymerase II without any biological significance [2]. However, recent research has elucidated the critical regulatory roles that lncRNAs play in various cellular processes, including tumor cell proliferation, metastasis, apoptosis, gene transcription, chromatin modification, and nuclear transport [3, 4]. This emerging understanding highlights the potential clinical utility of lncRNAs as novel tumor markers, therapeutic targets, and prognostic indicators [2, 4]. One such lncRNA, long intergenic non-coding RNA 00657 (LINC00657, also named NORAD), is located on chromosome 20q11.23 in humans. It has been proposed to act as an oncogenic lncRNA by influencing the initiation and progression of various cancer types, including colorectal cancer [5, 6], lung adenocarcinoma, hepatocellular carcinoma [7], glioblastoma [8], gastric cancer [9], oral squamous cell carcinoma [10], cervical cancer [11–13], papillary thyroid carcinoma [14], pancreatic cancer [15]. Furthermore, the abnormal expression of LINC00657 in tumor tissue has been associated with clinicopathological characteristics and patient prognosis across various types of tumors. Nevertheless, numerous studies highlighting the clinical significance or prognostic implications of LINC00657 in human malignancies have been limited by sample size and inconsistent findings. Additionally, the specific role of LINC00657 in the progression of prostate cancer remains to be elucidated.

This study was carried out to perform a comprehensive meta-analysis of existing data to explore the relationship between LINC00657 and different clinicopathological factors, along with the prognosis of cancer patients. Furthermore, the expression levels of LINC00657 in PCa tissues and cell lines were analyzed. The impact of LINC00657 knockdown on the viability, migration, and invasion of PCa cell lines was also examined to evaluate its potential as a therapeutic target for treating PCa.

Materials and methods

Search strategy

Two researchers independently conducted a comprehensive literature search using the PubMed, Embase, and Web of Science databases, following the guidelines for meta-analysis [16]. The latest search was performed on June 30, 2024, using the keywords: ("LINC00657" OR "Long non-coding RNA NORAD") AND ("cancer" OR "tumor" OR "neoplasm" OR "carcinoma"). Additionally, the references of relevant articles were manually reviewed to find more eligible studies.

Inclusion criteria and exclusion criteria

The literature retrieved was assessed by two independent researchers to identify studies suitable for analysis. The inclusion criteria were as follows: (1) the study must analyze the correlation between LINC00657 expression and the clinicopathological characteristics or prognosis of patients with malignant tumors; (2) the expression levels of LINC00657 in human malignant tumor tissues must be documented; (3) the hazard ratios (HRs) and 95% confidence intervals (CIs) for survival rates must be provided or be calculable; (4) articles must be published in English; (5) the methodology for measuring LINC00657 expression must be clearly articulated. The exclusion criteria were: (1) duplicate publications (only the most recent and comprehensive studies were retained); (2) reviews, case reports, meeting abstracts, letters, and expert opinions; (3) studies lacking accessible clinical data; (4) meta-analyses; (5) studies involving patients with benign tumors; (6) studies that included patients who had undergone drug treatment.

Data extraction and quality assessment

Data extraction and quality assessment: Two researchers independently extracted data from the selected articles based on the inclusion and exclusion criteria. Any disagreements were resolved through discussion with a third researcher. The extracted data included variables such as the first author's name, publication year, patient count, cancer types, detection methods, HR, and 95% CI for overall survival (OS) or progression-free survival (PFS), along with relevant clinicopathological parameters. If only Kaplan-Meier survival curves were available, Engauge Digitizer version 4.1 and a spreadsheet were used to derive HR and 95% CI from the curves [17].

The quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS) by two independent researchers, with a score of 6 or higher indicating high quality. Any discrepancies in assessments were resolved through discussion among the researchers [18].

Bioinformatics analysis of LINC00657

We analyzed the differential expression of LINC00657 in prostate cancer (PCa) tissues compared to normal tissues using GEPIA2, which includes RNA sequencing data from 492 PCa samples and 152 normal samples from the TCGA and GTEx databases. We compared LINC00657 expression levels between PCa samples ($n = 52$) and their adjacent normal tissues ($n = 52$) from TCGA. The raw transcriptome data from TCGA were normalized to log2(FPKM + 1) values using R language version 4.0.2.

Cell cultures and transfection

The human prostate cancer cell lines PC-3 were acquired from the American Type Culture Collection (ATCC). All cell lines were cultured at 37 °C in a 5% CO2 environment, utilizing RPMI 1640 medium for RWPE-1, LNCap, PC-3, and 22Rv1 cells, while DU145 cells were grown in DMEM, both supplemented with 10% fetal bovine serum (FBS) (Gibco, Grand Island, NY, USA). Prostate cancer cells (PC-3) underwent transfection with specific small interfering RNA (siRNA) targeting LINC00657 or a scrambled negative control siRNA, both obtained from Invitrogen, using Lipofectamine 2000 (Invitrogen, USA). The efficacy of the transfection was assessed 48 h post-transfection through quantitative Real-time polymerase chain reaction (qRT-PCR).

RNA extraction and qRT-PCR assays

Total RNA was extracted from tissues and cultured cells using TRIzol reagent (Invitrogen), following the protocols provided by the manufacturer. The PrimeScript RT Reagent Kit (TaKaRa) was employed for the reverse transcription of RNA into complementary DNA (cDNA). Real-time polymerase chain reaction (PCR) was performed utilizing SYBR Premix Ex Taq (TaKaRa), adhering to the manufacturer's guidelines. The expression levels were normalized to that of glyceraldehyde-3-phosphate dehydrogenase (GAPDH).

Cell proliferation assay

Cell proliferation assays were conducted utilizing KFluor488 Click-it EdU imaging detection kits (KeyGen Biotech, Jiangsu, China) in accordance with the manufacturer's guidelines. In summary, prostate cancer cells were cultured in 24-well plates and subsequently treated with 50 μM EdU for a duration of 2 h. Following the treatment, the cells were fixed using 4% formaldehyde and then incubated with the Click-iT reaction mixture for the detection of EdU. The cell nuclei were stained with Hoechst 33,342. Ultimately, the cells were imaged using an inverted fluorescence microscope. The proliferation rate was calculated as the ratio of EdU-positive cells to the total number of Hoechst-stained cells (indicated by blue staining), with quantification performed using Image J software (National Institutes of Health).

Wound healing assay

To investigate cell migration, a wound healing assay was conducted. Prostate cancer cells were cultured in 6-well plates until they reached approximately 90% confluence. Subsequently, a linear scratch was made in the center of each well using a sterile pipette tip with a volume range of 20–200 μL. Detached cells were eliminated by rinsing the wells three times with phosphate-buffered saline (PBS). Following this, serum-free medium was introduced, and the cells were incubated for 48 h. The closure of the scratch was documented using a light microscope at both 0 h and 48 h. The wound healing rate was subsequently quantified utilizing ImageJ software.

Migration and invasion assays

Migration and invasion assays were conducted to assess cellular motility utilizing 24-well Transwell chambers featuring an 8-μm pore size polycarbonate membrane (BD Biosciences), in accordance with previously established protocols [19]. For the evaluation of invasion capability, the upper chambers were pre-coated with 0.33 mg/ml of Matrigel (Corning, Inc.) two hours prior to the experiment. In contrast, the migration assay did not require Matrigel. Prostate cancer (PCa) cells were introduced onto the upper surface of the membrane using serum-free medium, while the lower chambers were filled with complete medium. Following a 24-hour incubation period, cells adhering to the upper filter were removed, and those on the lower membrane surface were fixed using paraformaldehyde and subsequently stained with 0.1% crystal violet. The number of cells in each well was quantified by counting the nuclei in five randomly selected fields, which were photographed using a light microscope.

Xenograft assays and shRNA treatment

Four-week-old male BALB/c nude mice, weighing between 20 and 22 g, were acquired from the Experimental Animals Centre of Fujian Medical University in Fuzhou, China, and were housed under specific-pathogen-free conditions in accordance with institutional protocols. A stable knockdown of LINC00657 in prostate cancer cells was achieved through lentivirus-mediated transduction using sh-LINC00657 (Genepharma, Shanghai, China). The resulting LINC00657 knockdown PC-3 cells were utilized to establish a nude mouse xenograft model, as previously documented [19]. After a period of 25 days, the mice were euthanized via an overdose of pentobarbital (250 mg/kg administered via intraperitoneal injection). Following confirmation of death due to respiratory and cardiac failure, the tumors were excised

and weighed. All animal procedures were conducted in compliance with the approvals granted by the Institutional Animal Care and Use Committee of Fujian Medical University.

Statistical analysis

The analysis was conducted utilizing STATA Statistical Software (Version 12.0; StataCorp LP, TX, USA) to compute the pooled odds ratios (ORs) and hazard ratios (HRs) along with 95% confidence intervals (CIs), as well as to perform Begg's tests and sensitivity analyses as previously outlined. The heterogeneity of the pooled data was evaluated using the Cochran Q-test and the I-squared test. A threshold of $I^2 < 50\%$ or a p-value > 0.05 was indicative of low heterogeneity, warranting the application of a fixed-effects model. Conversely, a random-effects model was employed in cases of higher heterogeneity. The Student's t-test was utilized to assess differences between the two groups, while categorical data were analyzed using the Chi-square test. Additional statistical analyses were conducted using SPSS version 25.0. Results are presented as mean ± standard error of the mean (S.E.M.), with statistical significance established at $p < 0.05$.

Results

Literatures selection

The process for selecting literature is illustrated in Fig. 1. Initially, 111 articles were sourced from three databases, and 76 duplicates were removed. We then reviewed the titles and abstracts of the remaining 35 articles, eliminating 23 studies that did not meet the inclusion criteria. Afterward, we examined the full texts of the remaining 12 articles, excluding one that lacked available data. Ultimately, 11 articles were included in this meta-analysis.

Characteristics of included studies

The characteristics of the 11 studies included in the meta-analysis are detailed in Table 1. These studies, which involved 1,123 patients, were published between 2017 and 2024 and all provided Kaplan-Meier survival curves. The literature encompassed eight types of malignant tumors, including colorectal cancer, gastric cancer, hepatocellular carcinoma, oral squamous cell carcinoma, cervical cancer, pancreatic cancer, glioblastoma multiforme, and papillary thyroid carcinoma (Table 1).

Relationship between LINC00657 and prognosis

Out of the 11 eligible studies, 10 reported overall survival (OS) results related to LINC00657 expression, encompassing a total of 1,092 patients. OS was used as the outcome measure for patients with varying levels of LINC00657 expression. Due to significant heterogeneity among the studies ($I^2 = 81.9\%$, $p < 0.001$), a random-effects model was applied. The meta-analysis revealed that high LINC00657 expression was significantly linked to poor OS (HR = 2.09, 95% CI: 1.26–2.91, $p < 0.001$, Fig. 2).

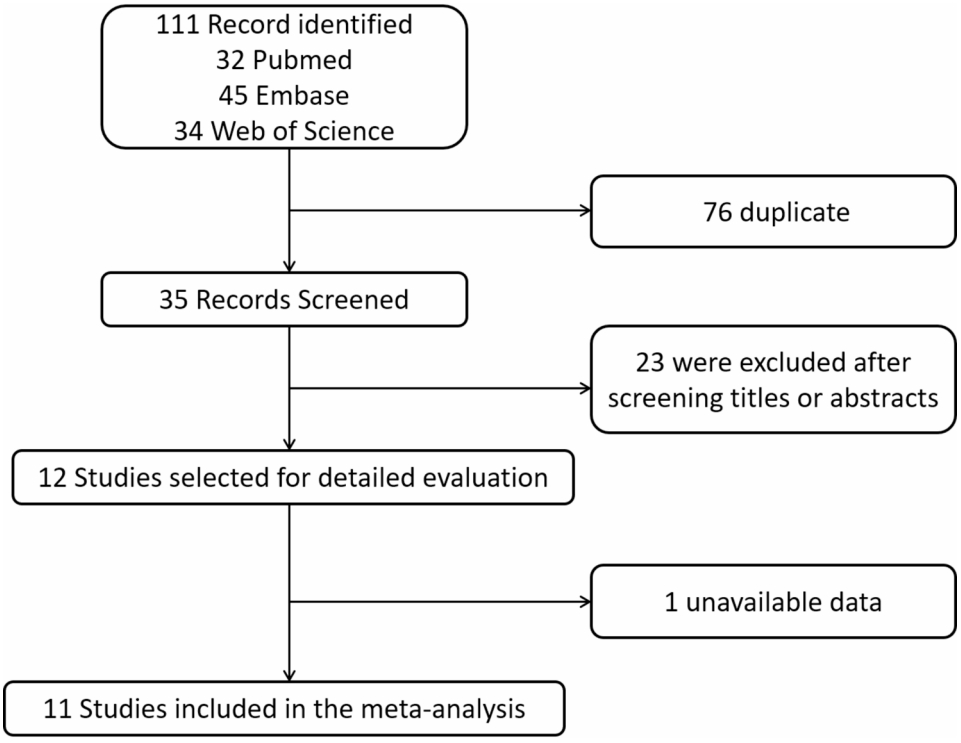

Fig. 1 Flow diagram of the literature search and selection

Table 1 Characteristic of included studies in this meta-analysis

First author, year	Samples	Types of cancer	Outcome	Stage	Analysis method	Long intergenic non-coding LINC00657 expression high	low	OS HR	95%CI
Cao 2020	60	HCC	OS	I-IV	Kaplan-Meier	34	26	2.23	1.1–4.51
Chu 2019	40	GBM	OS	I-IV	Kaplan-Meier	NA	NA	0.22	0.06–0.86
Hu 2017	49	HCC	OS	I-IV	Kaplan-Meier	24	25	0.39	0.16–0.96
Li 2021	60	PC	NA	I-IV	NA	30	30	NA	NA
Li 2024	501	PTC	OS	I-IV	Kaplan-Meier	250	251	2.35	1.21–4.56
Ma 2018	66	CC	OS	I-IV	Kaplan-Meier	33	33	2.27	1.11–4.64
Xu 2020	32	OSCC	OS	I-IV	Kaplan-Meier	16	16	1.19	2.31–16.85
Yu 2019	283	GC	OS	I-IV	Kaplan-Meier	121	162	1.59	1.09–2.3
Zhang 2024	26	CRC	OS	NA	Kaplan-Meier	NA	NA	3.34	6.39–11.98
Zhao 2020	181	CRC	OS	I-IV	Kaplan-Meier	92	89	1.82	2.33–4.89
Qin 2021	72	CC	OS	NA	Kaplan-Meier	32	40	0.75	0.38–1.46

Abbreviations: CRC, colorectal cancer; GC, gastric cancer; HCC, hepatocellular carcinoma; OSCC, Oral Squamous Cell Carcinoma; CC, Cervical Cancer; PC, pancreatic cancer; GBM, Glioblastoma Multiforme; PTC, Papillary Thyroid Carcinoma; OS, overall survival; NA, not available

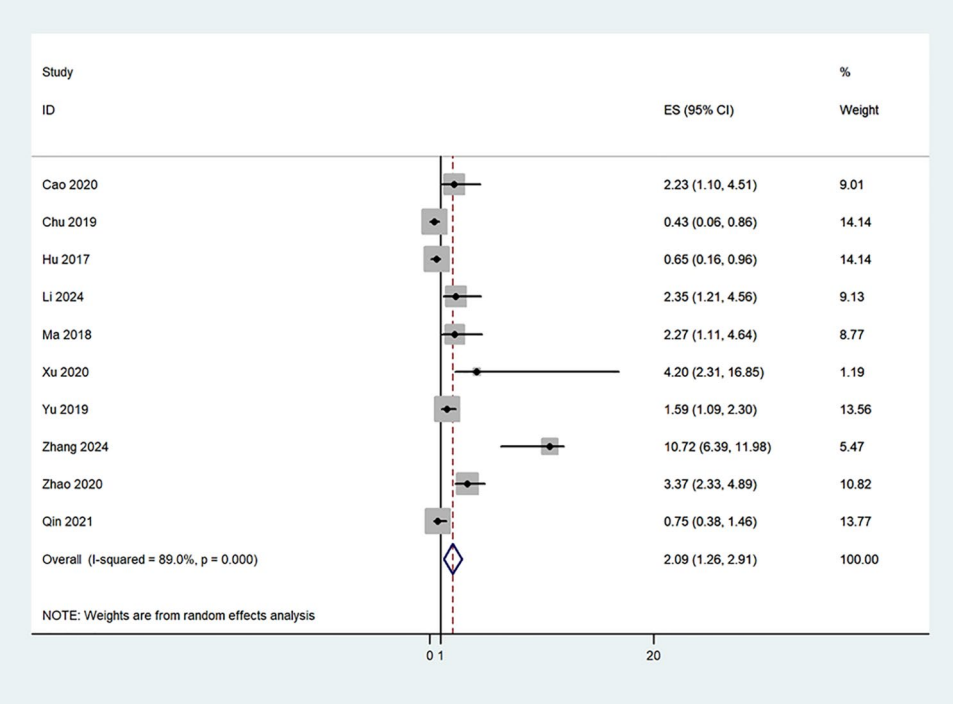

Fig. 2 Forest plot for the relationship between LINC00657 expression and OS. Squares represented HR in each trial. The horizontal line crossing the square indicated the 95% CI

To further investigate the heterogeneity and the relationship between abnormal LINC00657 expression and OS, subgroup analyses were conducted based on sample size and cancer type. In the analysis by cancer type, high LINC00657 expression was significantly associated with poor OS in patients with digestive system tumors (HR = 3.15, 95% CI: 1.50–4.79, $p < 0.001$), but not in those with non-digestive system tumors (HR = 1.02, 95% CI: 0.34–1.69, $p = 0.056$, Fig. 3A). Regarding sample size, high LINC00657 expression correlated with poor OS in both groups of 60 or fewer samples (HR = 2.55, 95% CI: 1.05–4.05, $p < 0.001$) and more than 60 samples (HR = 1.90, 95% CI: 1.00-2.80, $p < 0.001$, Fig. 3B).

Associations of LINC00657 expression with clinicopathological features

A pooled analysis based on various clinicopathological characteristics of the included patients (Table 2) indicated that higher LINC00657 expression was linked to worse TNM staging (OR = 3.07, 95% CI: 1.22–7.74, $p < 0.001$) and distant metastasis (OR = 2.15, 95% CI: 1.34–3.46, $p = 0.002$).

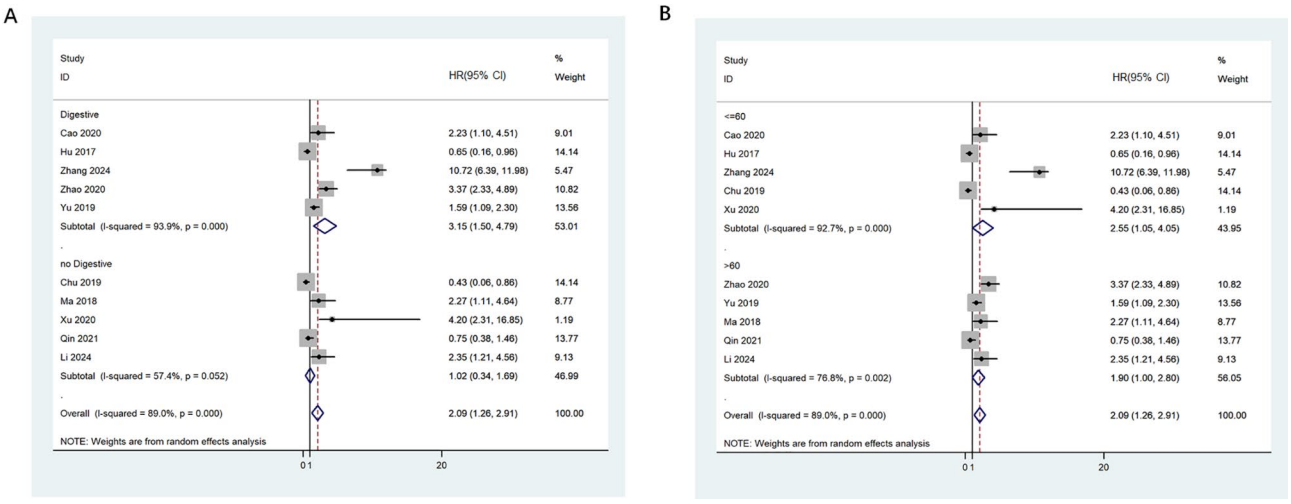

Fig. 3 Forest plots evaluating the stratified analyses of LINC00657 expression on OS in regard to subgroup including tumor type (**A**) and sample size (**B**)

Table 2 Characteristic of included studies in this meta-analysis

Clinicopathological parameters	Studies (n)	No. of patients	LINC00657 expression		OR(95%CI)	p-value	Heterogeneity		Model
			High	Low			I^2 (%)	P-value	
Histological grade (poorly /undifferentiated vs. well/moderately)	5	250	129	121	1.26(0.75,2.09)	0.382	53.3%	0.073	fixed
TNM stage (III-IV vs. I-II)	8	608	296	312	3.07(1.22,7.74)	0.018	78.1%	< 0.001	random
Distant metastasis (Yes vs. No)	6	477	239	238	2.15(1.34,3.46)	0.002	8.3%	0.363	fixed
Lymph node metastasis (Yes vs. No)	6	505	261	244	2.07(0.84,5.12)	0.115	77.9%	<0.001	random

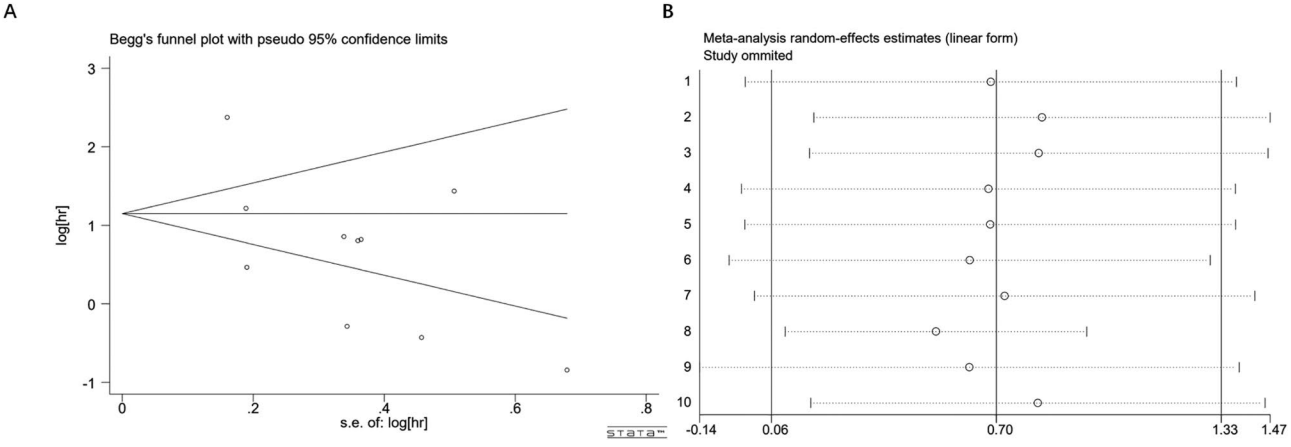

Fig. 4 Begg's funnel plot (**A**) of potential publication bias and sensitivity analysis (**B**) for the meta-analysis among those studies reporting OS

Publication bias and sensitivity analyses

The publication bias regarding LINC00657 expression and OS was evaluated using a Begg's funnel plot, which showed no significant bias (Pr >|z| = 0.47, z = 0.72) (Fig. 4A). Sensitivity analysis indicated that removing any single study did not significantly alter the pooled results (Fig. 4B), suggesting the robustness of the findings.

LINC00657 was upregulated in PCa tissues and cells

We first analyzed LINC00657 expression patterns in prostate cancer (PCa) samples using data from the TCGA and GTEx databases, which revealed that LINC00657 was significantly upregulated in PCa tissues compared to normal prostate tissues (Fig. 5A-B). Additionally, we assessed LINC00657 expression in various PCa cell lines (LNCap, 22Rv1, PC-3, and DU145) and the normal human prostate cell line RWPE-1 through qRT-PCR,

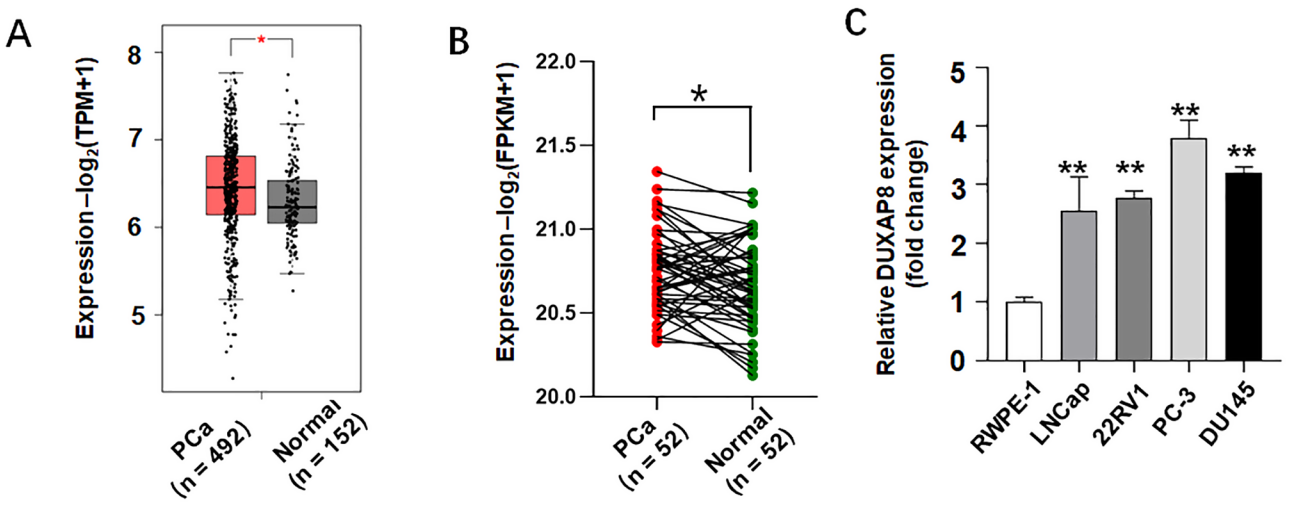

Fig. 5 LINC00657 showed a significant increase in expression in prostate cancer (PCa). (**A**) According to the GEPIA2 database, LINC00657 expression is elevated in PCa. (**B**) A paired Student's t-test was used to compare the expression levels of LINC00657 in PCa samples ($n = 52$) and corresponding adjacent normal tissues ($n = 52$) from TCGA. (**C**) The expression of LINC00657 was assessed in the normal human prostate cell line RWPE-1 and in PCa cell lines LNCap, 22Rv1, PC-3, and DU145. The RNA levels of LINC00657 were normalized to GAPDH expression. The values represent the mean ± SEM from three independent experiments. * $p < 0.05$, ** $p < 0.01$

finding a significant increase in LINC00657 levels in PCa cell lines compared to the normal line (Fig. 5C).

LINC00657 knockdown inhibited cell proliferation, invasion and migration of PCa cells

qRT-PCR analysis showed a significant reduction in LINC00657 levels, achieving about 70% knockdown efficiency (Fig. 6A). EdU staining assays indicated that LINC00657 knockdown reduced cell proliferation in DU145 and PC-3 cell lines compared to controls (Fig. 6B-C). The wound healing assay demonstrated a significant decrease in the wound healing rate in the LINC00657 knockdown group after injury (Fig. 6D-E). Furthermore, transwell assays confirmed that LINC00657 knockdown led to fewer invaded and migrated PCa cells (Fig. 6F-G).

To further investigate the impact of LINC00657 knockdown on tumor growth in vivo, we used a subcutaneous xenograft tumor model by injecting PCa cells with stable LINC00657 knockdown. qRT-PCR results showed a significant decrease in LINC00657 expression in the sh-LINC00657 group compared to the sh-NC group (Fig. 7A). As anticipated, the tumor volumes and weights in the sh-LINC00657 group were significantly smaller than those in the control group (Fig. 7B-D).

Discussion

Recent studies have increasingly emphasized the significant role of LINC00657 in tumor development, suggesting its potential as a novel biomarker and therapeutic target in cancer therapy [5–7, 13]. However, the clinical relevance of LINC00657 in cancer patients remains ambiguous and sometimes contradictory. For example, research by Hu et al. found a notable association between high LINC00657 expression and better prognosis in HCC patients [20], while Cao et al. reported that elevated LINC00657 levels correlated with poorer outcomes in the same group [7]. Ma et al.'s results indicated that cervical cancer patients with high LINC00657 expression had reduced overall survival compared to those with lower levels [12], but Qin et al. observed the opposite trend [11]. A potential contributing factor to the opposite trend may be the limited sample size of the studies. Regarding the connection between LINC00657 expression and clinical characteristics, Li, Ma, and Yu et al. found that high levels of LINC00657 were linked to metastasis and TNM staging in gastric, colorectal, and pancreatic cancer patients [9, 12, 15]. Conversely, Xu et al. noted that increased LINC00657 expression was only associated with T stage in oral squamous cell carcinoma patients [10]. To resolve these inconsistencies, we performed a meta-analysis to clarify the clinical significance of LINC00657.

To our knowledge, this is the first meta-analysis investigating the relationship between LINC00657 and cancer. Our results indicate that LINC00657 overexpression is closely related to poor outcomes in cancer patients. Subgroup analyses suggest that LINC00657 expression may act as an independent prognostic marker for overall survival. Furthermore, our meta-analysis revealed a significant association between elevated levels of LINC00657 and the presence of distant metastasis as well as TNM staging, potentially attributable to cancer-specific mechanisms. Overall, LINC00657 may play a role in tumor development and progression and could serve as

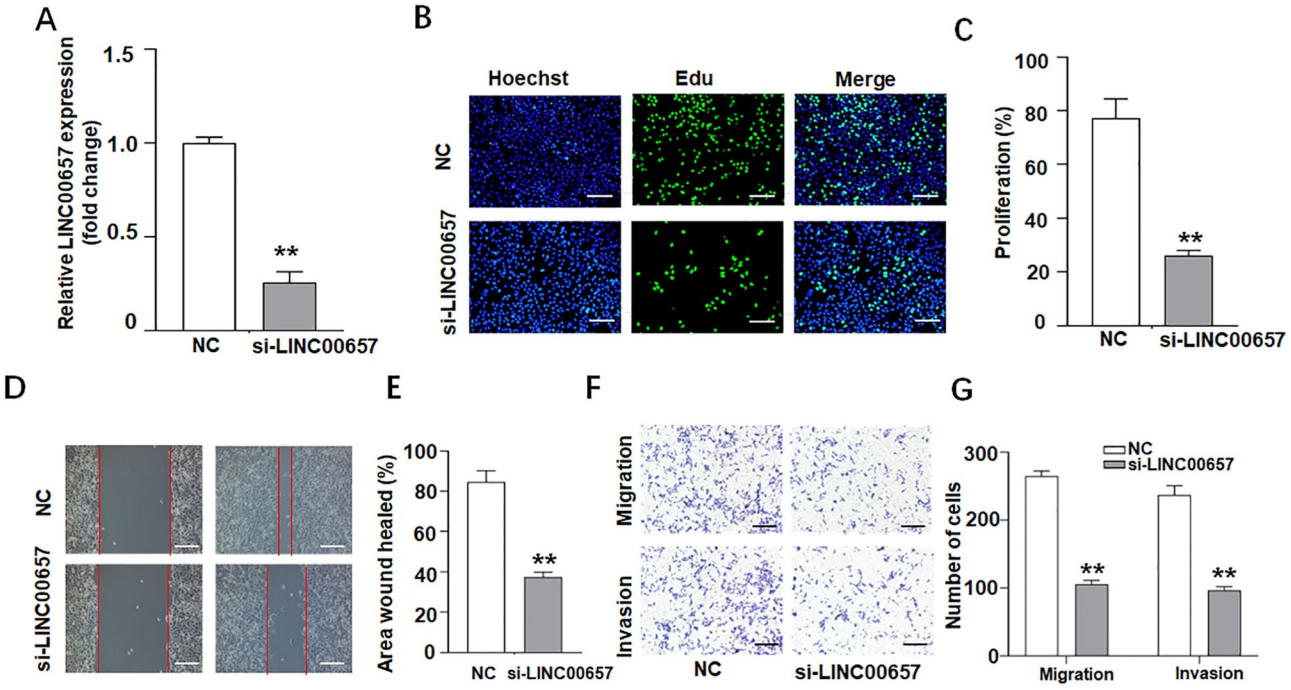

Fig. 6 The knockdown of LINC00657 reduced the proliferation, invasion, and migration of prostate cancer (PCa) cells in vitro. (**A**) LINC00657 was knocked down in PCa cells (PC-3) using si-LINC00657 transfection. (**B-C**) EdU assays were conducted to assess the proliferation of PC-3 cells following siRNA transfection targeting LINC00657. The green color indicates EdU staining for proliferating cells, while blue indicates Hoechst staining for the cell nucleus. (**D-E**) Wound healing assays were utilized to evaluate cell migration after LINC00657 knockdown. (**F-G**) Transwell assays were carried out to assess cell migration and invasion following LINC00657 knockdown. The values represent the mean ± SEM from three independent experiments. ** $p < 0.01$

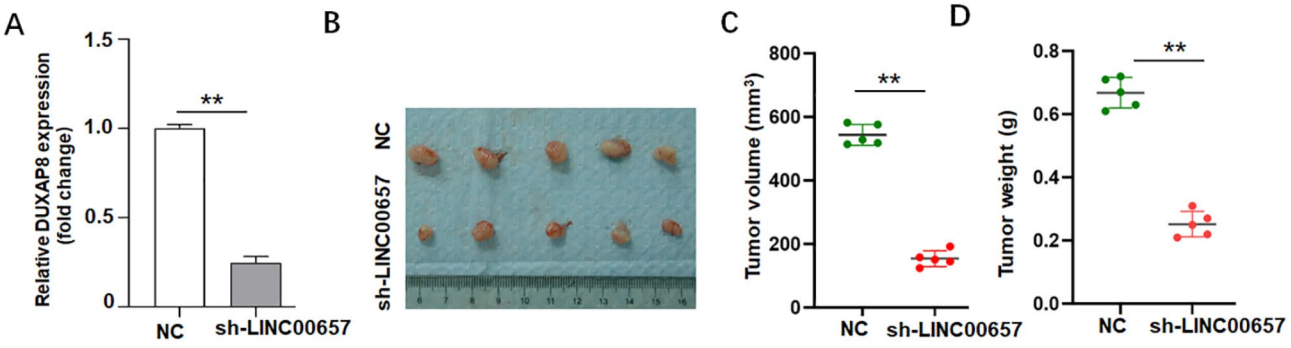

Fig. 7 The reduction of LINC00657 led to a decrease in the proliferation of prostate cancer (PCa) cells in vivo. (**A**) The creation of stable sh-LINC00657 PC-3 cell lines was confirmed through qRT-PCR. The results are shown as mean ± SEM from three separate experiments. (**B**) Tumors were collected six weeks post-inoculation. (**C-D**) The knockdown of DUXAP8 resulted in reduced tumor growth, affecting both tumor volume and weight. ** $p < 0.01$

a potential clinical prognostic biomarker. However, the expression levels and functions of LINC00657 in prostate cancer have not been thoroughly investigated.

By analyzing publicly available TCGA databases and validating our findings in cell lines, we found that LINC00657 is overexpressed in prostate cancer. To explore the functional role of LINC00657 in this context, we employed siRNA and shRNA techniques to reduce its expression. Our results are the first to demonstrate that knocking down LINC00657 reduces both the migration and invasion of prostate cancer cells in vitro, as well as inhibiting cell growth in both in vitro and in vivo models. These findings support previous research identifying LINC00657 as a key factor in tumor progression.

In this study, we initially conducted a meta-analysis to evaluate the clinical significance of LINC00657 in tumors. However, some limitations should be noted. All included studies were conducted in China, which may restrict the generalizability of our findings to other populations. Additionally, some studies only provided Kaplan-Meier curves without hazard ratios and confidence intervals, which could lead to inaccuracies. Lastly, the number of studies in certain subgroup analyses, particularly by cancer type, was relatively small. Our research is

the first to highlight the role of LINC00657 in prostate cancer, showing that it acts as a positive modulator in the disease's progression and aggressiveness. Nevertheless, the mechanisms by which LINC00657 influences prostate cancer progression remain unclear, warranting further molecular and functional studies to clarify these effects.

Conclusion

In summary, our findings show that the overexpression of LINC00657 is closely linked to more advanced stages of cancer and unfavorable outcomes for patients. Additionally, we observed that LINC00657 levels are elevated in prostate cancer, and reducing its expression leads to decreased cell growth, migration, and invasion. These outcomes imply that LINC00657 plays an oncogenic role in PCa and could be a valuable indicator of poor prognosis and a possible target for treatment in cancer.

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Author contributions
Conceptualization, Y.W., S.W. and S.Z.; methodology, Y.W., S.W., SY.Z. and L.Y.; software, S.W., S.Y. and SY.Z; formal analysis, SY.Z. L.Y. and S.Z.; writing-original draft preparation, Y.W., SY.Z and S.Y.; writing-review and editing, Y.W. and S.Z.; supervision, S.Z. and Y.W.; funding acquisition, Y.W. and S.Z. All authors have read and agreed to the published version of the manuscript.

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Data availability
The data presented in this study are available on request from the corresponding author.

Declarations

Ethics approval and consent to participate
The Institutional Animal Care and Use Committee of Fujian Medical University approved the animal study protocol.

Patient consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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