NON-CODING RNA HUBS IN BLADDER CANCER HIGHLIGHT POTENTIAL LIQUID BIOPSY CANDIDATES

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Abstract
Bladder cancer (BLCA) is a highly recurrent and heterogeneous malignancy, with current diagnostics such as cystoscopy and urine cytology being invasive or insufficiently sensitive. Non-coding RNAs (ncRNAs), particularly long non-coding RNAs (lncRNAs) and microRNAs (miRNAs), play key roles in tumor biology and hold promise as liquid biopsy biomarkers; however, most studies focus on individual ncRNAs, overlooking their coordinated regulation through competing endogenous RNA (ceRNA) networks. Here, we performed integrative bioinformatics analysis of TCGA-BLCA transcriptomes, identifying 1,248 mRNAs, 163 lncRNAs, and 72 miRNAs as differentially expressed. Using network modeling, correlation filtering, and functional enrichment, we reconstructed lncRNA–miRNA–mRNA ceRNA triplets, revealing oncogenic modules (e.g., LINC00460–miR-21–PTEN/PDCD4; LINC02884–miR-130b–RUNX3/PTEN) converging on PI3K/AKT, Wnt, and TGF-β pathways to promote proliferation and EMT, and tumor suppressor modules (e.g., ADAMTS9-AS1–miR-210–HIF3A/E2F3; CARMN–miR-145–SOX2/OCT4) reinforcing apoptosis, angiogenesis inhibition, and stemness suppression. Centrality analyses identified LINC00460, HAND2-AS1, ADAMTS9-AS1, and CARMN as master hubs, with recurrent mRNA targets including PTEN, VEGFA, and ZEB1 acting as network bottlenecks. By mapping redundant and convergent ceRNA architectures, this study highlights hub lncRNAs as system-level regulators rather than isolated candidates. These hubs represent strong candidates for liquid biopsy applications, enabling early detection, tumor subtype stratification, and real-time therapy monitoring. Overall, our integrative approach bridges molecular insight with translational relevance, providing a blueprint for developing ncRNA-based diagnostic and prognostic tools in bladder cancer.

Keywords:
Bladder Cancer, Non-Coding RNA, Liquid Biopsy, Biomarkers, ceRNA Network, Bioinformatics

INTRODUCTION
BLCA is a prevalent and aggressive malignancy, characterized by high recurrence rates, significant heterogeneity, and substantial clinical burden [1]. Traditional diagnostic methods, including cystoscopy and urine cytology, are widely used; however, they remain invasive, costly, and often insufficiently sensitive, particularly in detecting low-grade or early-stage tumors [2], [3], Cystoscopy, the clinical gold standard, involves insertion of a cystoscope through the urethra to visually inspect the bladder lining. Although it allows direct visualization of tumors, cystoscopy is associated with discomfort, potential complications, and significant costs. Furthermore, it may miss small or flat lesions, leading to false-negative results. Sensitivity ranges from 87% to 100%, while specificity ranges from 64% to 100% [4]. Urine cytology, examining exfoliated cells in urine, is particularly useful for high-grade tumors and carcinoma in situ; however, its sensitivity is approximately 40%, especially low for low-grade tumors, and may be influenced by inflammation or prior treatments[5]. These limitations highlight the need for alternative diagnostic approaches that are non-invasive, cost-effective, and capable of detecting BLCA earlier than traditional tissue biopsy

Non-coding RNAs (ncRNAs), including long non-coding RNAs (lncRNAs) and microRNAs (miRNAs), have emerged as pivotal regulators of gene expression and tumor biology. Unlike protein-coding genes, ncRNAs modulate transcriptional and post-transcriptional processes, influencing proliferation, apoptosis, differentiation, and metastasis [6]. In BLCA, several lncRNAs, such as UCA1 and TUG1, are upregulated in tissues and cell lines,

suggesting roles in tumorigenesis and potential as diagnostic markers[7], [8]. Similarly, miRNAs including miR-21 and miR-145 are differentially expressed and associated with tumor progression and prognosis[9], [10], [11]. Detection of ncRNAs in body fluids, such as urine and blood, has paved the way for non-invasive liquid biopsy approaches, which can complement or even outperform tissue biopsies for early detection, real-time disease monitoring, and prognostication in BLCA[12].

The ceRNA hypothesis proposes that RNA molecules, including lncRNAs, pseudogenes, and circular RNAs, can "sponge" miRNAs, regulating downstream mRNA targets. This network adds a layer of regulatory complexity influencing tumor growth, apoptosis, epithelial-mesenchymal transition (EMT), angiogenesis, and stemness[13],[14][15]. In BLCA, lncRNAs such as LINC00460 interact with miR-21 to regulate tumor suppressors PTEN and PDCD4, thereby promoting proliferation and EMT[16]. Mapping these ceRNA networks provides mechanistic insight into BLCA progression and identifies potential therapeutic targets and biomarkers that can be detected via liquid biopsy, offering a minimally invasive alternative to tissue analysis. Despite the potential of ncRNAs as biomarkers, most studies focus on individual molecules, overlooking their collective regulation within ceRNA networks. Reproducibility across cohorts and platforms is often limited due to sample heterogeneity, variations in detection methods, and lack of standardized analytical pipelines. Furthermore, the functional roles of many differentially expressed ncRNAs in BLCA remain poorly understood, hindering clinical translation. Liquid biopsy offers a promising alternative to traditional tissue-based diagnostics in BLCA due to its minimal invasiveness, systemic sampling capability, and high repeatability, enabling dynamic monitoring of tumor progression and treatment response over time. Table 1**.**

Unlike cystoscopy or tissue biopsy, liquid biopsy allows analysis of ncRNAs, including hub lncRNAs and miRNAs identified from ceRNA network analysis**,** from easily accessible body fluids such as urine and blood, providing a comprehensive snapshot of tumor biology across the patient rather than a single lesion. This approach also facilitates longitudinal sampling, making it possible to track disease evolution, therapeutic response, and recurrence with minimal patient discomfort. However, despite these advantages, challenges remain regarding sensitivity, standardization of detection methods, and reproducibility across platforms**,** which currently limit broad clinical adoption. By integrating ceRNA network modeling with systemic liquid biopsy analysis**,** our study aims to overcome these limitations, identifying central hub ncRNAs with translational potential as robust, minimally invasive biomarkers for early detection, prognosis, and therapy monitoring in BLCA figure 1.

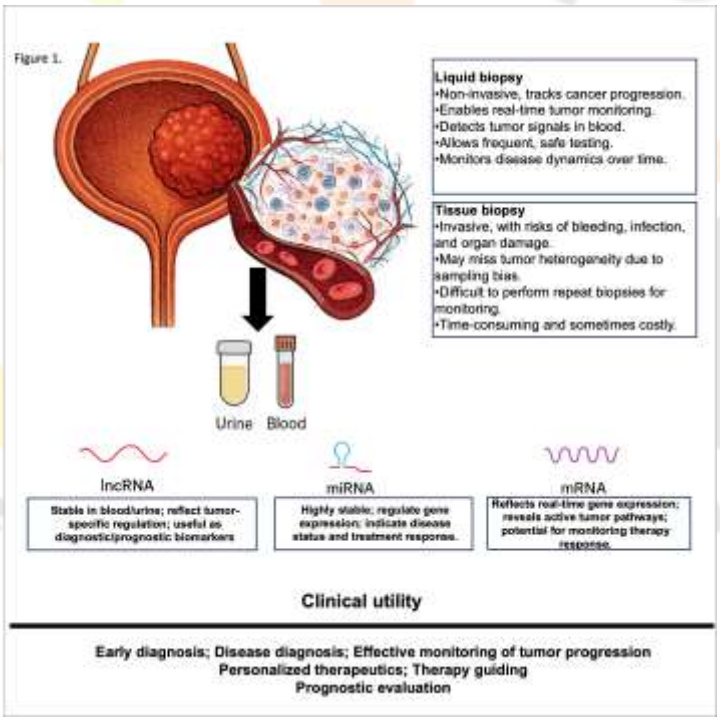

Figure 1. Early diagnosis; effective monitoring of tumor progression; personalized therapeutics; therapy guiding; prognostic evaluation.

2. METHODOLOGY

2.1. Data Acquisition and Pre-processing

2.1.1. Transcriptomic and Small RNA-Seq Data:

miRNA-seq and RNA-seq expression profiles of BLCA were downloaded from The Cancer Genome Atlas (TCGA) via using the TCGAbiolinks R package. The dataset contains 19 adjacent normal tissues and 81 primary tumor samples. Ensembl gene IDs were annotated using GENCODE v29, and transcripts were classified into lncRNAs, miRNAs, and protein-coding genes

2.1.2.Filtering and Normalization:

Genes and miRNAs with counts per million (CPM) <1 in more than 80% of samples were filtered out. Raw counts were normalised using the Trimmed Mean of M-values (TMM) method via edgeR. Batch effects were corrected using ComBat from the sva package if present.

2.2. Differential Expression Analysis

2.2.1. lncRNA and mRNA Analysis:

Differential expression analysis of mRNAs and lncRNAs between tumor and normal samples was performed using the limma-voom pipeline. Significant genes were defined based on adjusted p-value (FDR) < 0.05, (log2 Fold Change) > 1, Volcano plots and heatmaps were generated using ggplot2 and Complex Heatmap.

2.2.2. miRNA Analysis:

miRNA expression was analysed using DESeq2. Differentially expressed miRNAs were identified using FDR < 0.05 and (log2FC) > 1. Visualization was performed using ggplot2, pheatmap, and ggpubr.

2.3. Functional Enrichment Analysis

2.3.1. lncRNA Co-expression Network:

Pearson correlation coefficients were computed between DE lncRNAs and mRNAs to identify co-expression relationships ($|r| > 0.5$, $p < 0.05$). mRNAs co-expressed with lncRNAs were subjected to *Gene Ontology* (GO-Biological Process) and *KEGG pathway* enrichment using the clusterProfiler package. Enriched terms were visualized via bar plots, chord diagrams, and Sankey plots using GOplot, circlize, and ggalluvial.

2.3.2. miRNA Target Prediction and Pathway Analysis:

miRNA targets were predicted using validated interactions from **miRTarBase**, **miRDB**, and **TargetScan**. Enrichment of miRNA target genes in KEGG pathways was done using **clusterProfiler**. Bubble plots and chord diagrams were used to represent top miRNAs and their associated pathways.

2.4. Construction of lncRNA–miRNA–mRNA ceRNA Network

2.4.1. miRNA-lncRNA Interaction:

Potential miRNA-lncRNA binding pairs were predicted using **miRcode**, **starBase**, and **LncBase v3**. Only pairs with strong experimental support or high prediction confidence were retained.

2.4.2. ceRNA Triplet Construction:

For each lncRNA–miRNA–mRNA triplet,The lncRNA and mRNA must share a common miRNA. The expression of lncRNA and mRNA should be positively correlated ($r > 0.5$, $p < 0.05$). The miRNA should be negatively correlated with both lncRNA and mRNA ($r < -0.3$, $p < 0.05$).

2.5. Network Visualization

ceRNA networks were visualized using: **heatmaps** (for interaction strengths),**Sankey plots** (for modular relationships),and **circos plots** (for global ceRNA regulatory architecture).

2.6. Statistical Analysis

All statistical tests were two-sided. Benjamini-Hochberg correction was applied for multiple testing to control FDR. Analyses were performed in R (version 4.3.0) using Bioconductor packages.

3. RESULTS

Transcriptomic analysis of TCGA-BLCA datasets identified 1,248 differentially expressed mRNAs, 163 lncRNAs, and 72 miRNAs between bladder tumor tissues and adjacent normal controls (FDR < 0.05, |log2FC| > 1). Visualization using volcano plots and hierarchical clustering heatmaps clearly segregated tumor from normal samples, confirming the robustness of these transcriptomic signatures (Figure 2A–C). These findings reveal widespread ncRNA reprogramming in bladder cancer, consistent with earlier observations of non-coding RNA dysregulation in urothelial malignancies[17], [18].

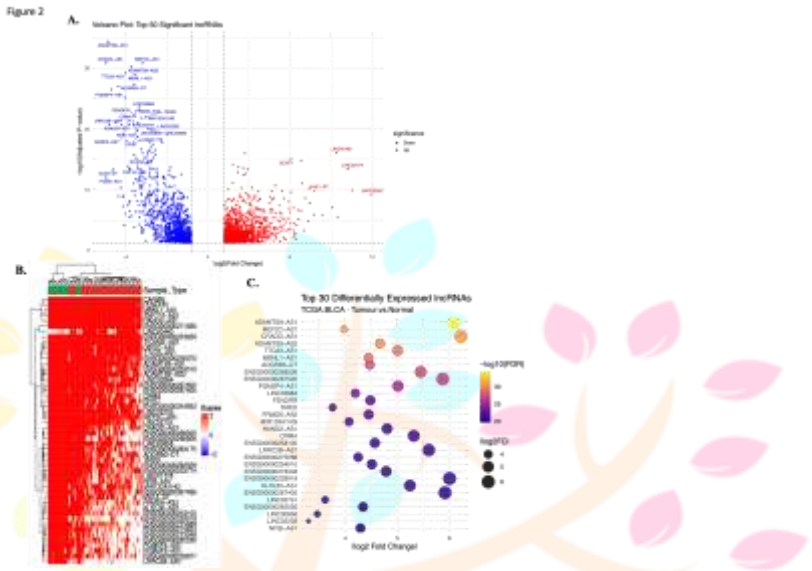

Figure 2. Differential expression of ncRNAs in BLCA. (A) Volcano plot showing significantly upregulated and downregulated mRNAs. (B) Volcano plot for differentially expressed lncRNAs. (C) Hierarchical clustering heatmap of differentially expressed miRNAs across tumor and normal samples. Distinct clustering patterns highlight clear transcriptomic separation between tumor and control tissues.

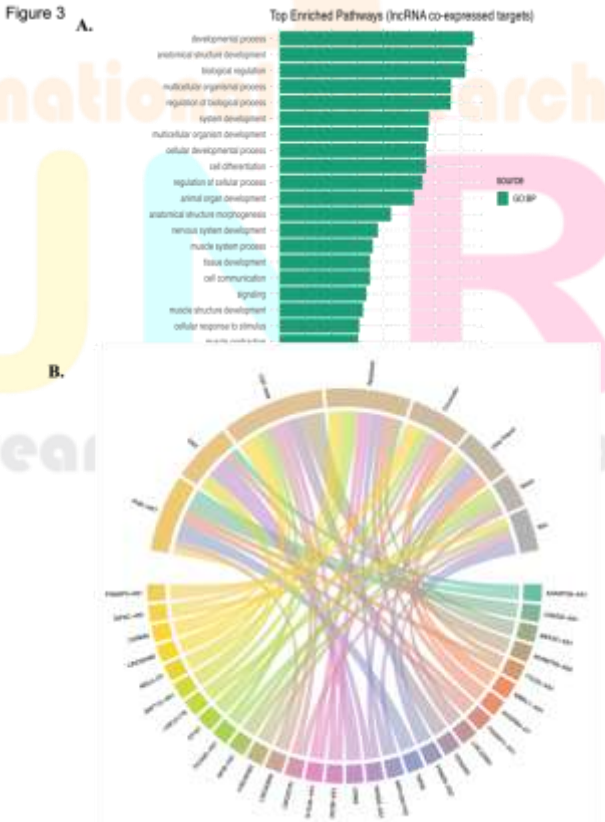

Figure 3. Representative ceRNA modules in BLCA. (A) Oncogenic triplets linking lncRNAs, miRNAs, and mRNAs enriched in PI3K/AKT, Wnt, and TGF-β signaling pathways. (B) Tumor-suppressive triplets involving lncRNAs and miRNAs that regulate apoptosis, angiogenesis, and cell cycle arrest.

Reconstruction of the ceRNA network revealed several oncogenic lncRNA–miRNA–mRNA triplets (Table 2). Among these, the LINC00460–miR-21–PTEN/PDCD4 axis emerged as a dominant oncogenic hub (Figure 3A). This triplet amplifies PI3K/AKT activation and represses tumor suppressor signals, consistent with prior recognition of miR-21 as a central oncomiR in bladder and other cancers[19], [20]. Other oncogenic circuits included LINC02884–miR-130b–RUNX3/PTEN/SMAD4 and CRADD-AS1–miR-96–FOXO1/PTPN9, both of which converge on PI3K/AKT, Wnt, and TGF-β pathways. These modules highlight the ability of lncRNAs to sponge oncogenic miRNAs and stabilize mRNA expression that promotes cell cycle progression, epithelial–mesenchymal transition (EMT), and invasion. Prior studies identified miR-130b and miR-96 as regulators of EMT and proliferation[21], [22], but the present analysis integrates these findings into network-level ceRNA modules that reinforce oncogenic signaling.

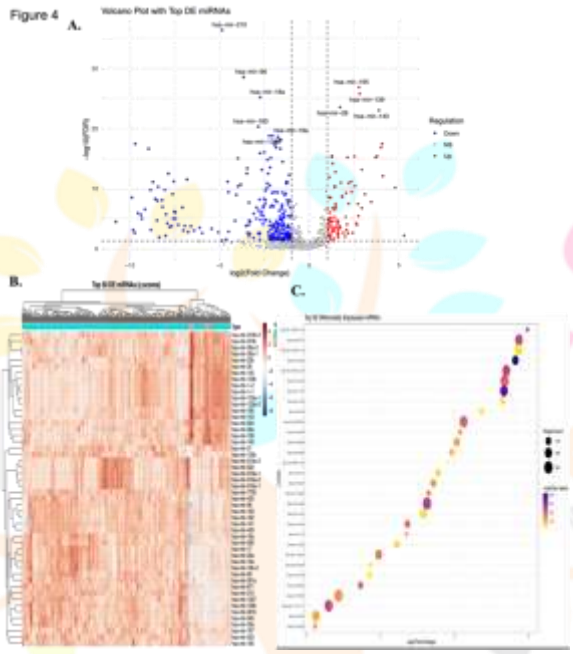

Figure 4. Detailed ceRNA triplet interactions. (A) Oncogenic modules illustrating ceRNA triplets such as LINC00460–miR-21–PTEN/PDCD4 and LINC02884–miR-130b–RUNX3/PTEN. (B) Tumor-suppressor triplets including ADAMTS9-AS1–miR-210–HIF3A/E2F3 and CARMN–miR-145–SOX2/OCT4, emphasizing regulatory diversity across pathways. (C) Integration of EMT- and angiogenesis-related ceRNA modules.

In contrast, tumor-suppressive ceRNA modules were centered around lncRNAs such as ADAMTS9-AS1, HAND2-AS1, CARMN, and PGM5P3-AS1 (Table 3; Figure 3B). These were paired with tumor-suppressive miRNAs including miR-195, miR-139, miR-145, and miR-143. The ADAMTS9-AS1–miR-210–HIF3A/E2F3 axis connected hypoxia signaling with angiogenesis inhibition, reflecting the dual role of miR-210 in tumor microenvironments[23], [24] Similarly, the CARMN–miR-145–SOX2/OCT4/FSCN1 module targeted stemness and invasion programs, echoing earlier findings of miR-145 as a bladder tumor suppressor[25], [26]These tumor-suppressive triplets function not in isolation but as stabilized ceRNA scaffolds, reinforcing apoptosis, angiogenesis inhibition, and suppression of stemness programs.

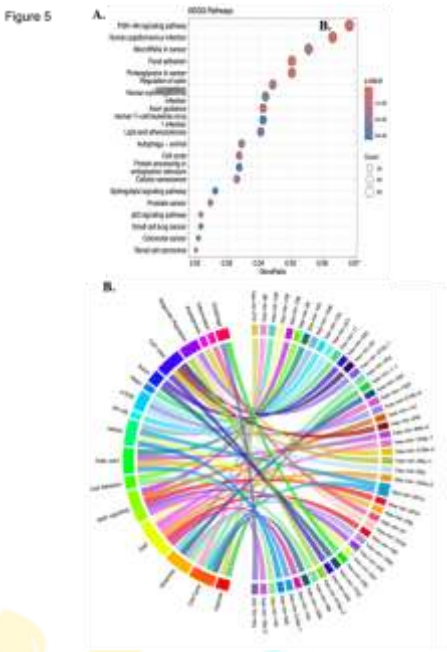

Figure 5. Functional enrichment analysis of ceRNA modules. (A) Pathway enrichment of oncogenic hubs showing alignment with cell cycle progression, PI3K/AKT activation, MAPK signaling, and EMT. (B) Pathway enrichment of suppressive hubs aligning with apoptosis, hypoxia response, and differentiation. The analysis underscores the push–pull dynamics between opposing ceRNA circuits.

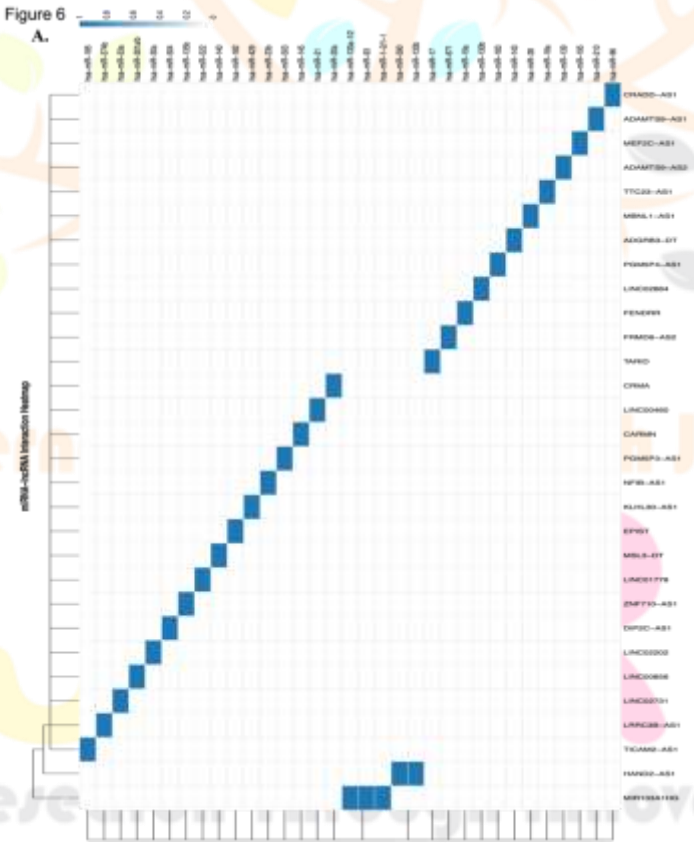

Figure 6. Integrated ceRNA network of BLCA. Highly connected lncRNAs (LINC00460, ADAMTS9-AS1, HAND2-AS1, CARMN) are positioned as master hubs, while recurrent mRNA targets such as PTEN, VEGFA, and ZEB1 act as network bottlenecks. The global architecture highlights redundant and convergent ceRNA circuits driving bladder cancer progression and identifies hub lncRNAs with biomarker potential for liquid biopsy applications.

Pathway enrichment of the ceRNA networks (Figure 5) revealed a duality in regulatory architecture. Oncogenic hubs were enriched in PI3K/AKT activation, MAPK signaling, EMT, and cell cycle progression, whereas suppressive hubs aligned with apoptosis induction, hypoxia response, cell cycle arrest, and differentiation programs. This "push–pull" dynamic between oncogenic and suppressive modules suggests that tumor behavior in bladder cancer arises from competition between antagonistic ceRNA circuits.

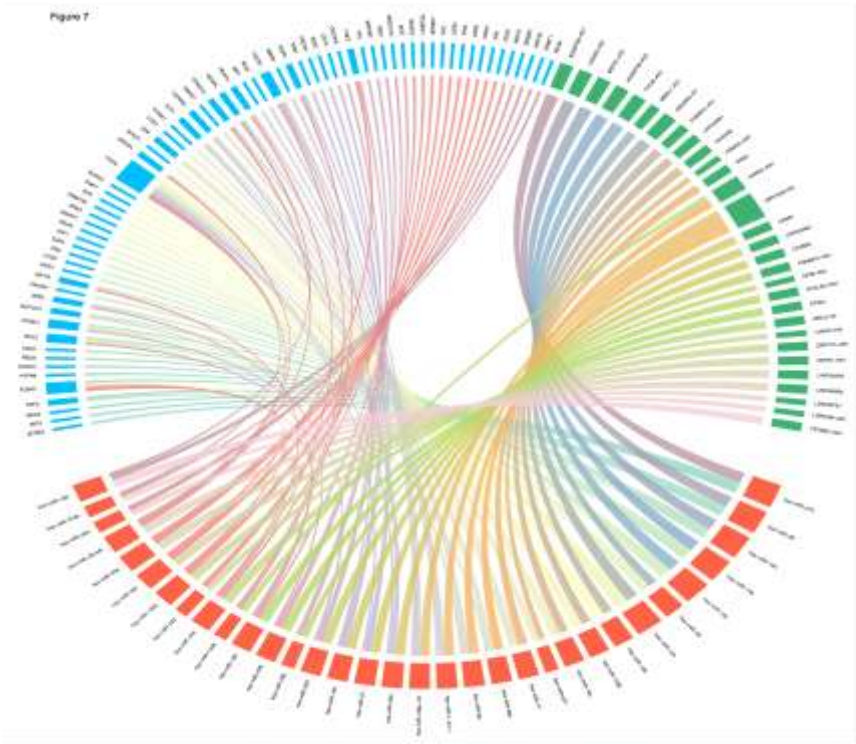

Figure 7. Proposed model summarizing the role of ncRNA-centered ceRNA networks in bladder cancer progression and their translational application as liquid biopsy biomarkers. Oncogenic lncRNA–miRNA–mRNA triplets activate PI3K/AKT, Wnt, and EMT pathways to promote proliferation, invasion, and angiogenesis, while tumor-suppressive triplets enforce apoptosis, cell cycle arrest, and inhibition of stemness. The integrated network highlights hub lncRNAs (LINC00460, HAND2-AS1, ADAMTS9-AS1, CARMN) as master regulators, detectable in urine or blood, providing a minimally invasive strategy for early detection, risk stratification, and therapy monitoring in BLCA.

The global ceRNA network (Figure 6) revealed high connectivity of LINC00460, ADAMTS9-AS1, HAND2-AS1, and CARMN, positioning them as master hubs. Key mRNAs such as PTEN, VEGFA, and ZEB1 appeared recurrently across modules, acting as bottlenecks of ceRNA regulation. Unlike prior single-gene studies[27], [28], these results underscore the importance of redundant and convergent ceRNA architectures in driving bladder cancer progression. Given their high centrality, hub ncRNAs were evaluated as potential liquid biopsy biomarkers. Circulating ncRNAs in blood and urine represent a minimally invasive and repeatable diagnostic modality (Figure 1; Table 1). Table 4 summarizes candidate hub ncRNAs (e.g., LINC00460, HAND2-AS1, ADAMTS9-AS1, CARMN) with validated targets and functional roles. Unlike tissue biopsy, liquid biopsy offers systemic sampling and repeatability, enabling early detection, subtype stratification, and therapy monitoring in bladder cancer patients.

Table 1. Comparison of tissue biopsy and liquid biopsy modalities across key parameters, including invasiveness, sampling bias, repeatability, sensitivity, spatial information, processing time, risk, standardization, and cost.

Feature	Tissue Biopsy	Liquid Biopsy	Reference
Invasiveness	High	Low	[33]
Sampling Bias	High (spatial heterogeneity)	Lower (systemic circulation)	[34]
Repeatability	Limited	Easy	[35]
Sensitivity (Early Cancer)	High at biopsy site	Low (ctDNA scarce)	[36]
Spatial Info	Yes	No	[37]
Processing Time	Longer	Faster	[38]
Risk	Infection, bleeding, tumor seeding	Minimal	[39]
Standardization	Established	Emerging	[32]
Cost	Moderate-High	low	[40]

Table 2. Summary of oncogenic ceRNA modules identified through integrative analysis. Each triplet includes lncRNAs, their interacting miRNAs, and validated/predicted mRNA targets. Functional roles are linked to proliferation, epithelial–mesenchymal transition (EMT), and activation of oncogenic signaling pathways such as PI3K/AKT, Wnt, and TGF-β.

miRNA	lncRNA Partner	Functional Role / Pathways	Validated/Predicted mRNA Targets	Reference
hsa-miR-96	CRADD-AS1	Cell proliferation, EMT	FOXO1, PTPN9, MTSS1, RECK	[22], [41]
hsa-miR-18a	TTC23-AS1	Cell proliferation, DNA damage response	ESR1, CTGF, ATM, BCL2	[42], [43]
hsa-miR-130b	LINC02884	EMT, Wnt, TGF-β	RUNX3, PTEN, SMAD4	[27], [44], [45]
hsa-miR-19a	FENDRR	OncomiR-1 cluster	PTEN, SOCS1, BIM	[46], [47]
hsa-miR-17	TARID	Cell proliferation, apoptosis	PTEN, BIM, E2F1	[48], [49], [50]
hsa-miR-21	LINC00460	Classic OncomiR, PI3K/AKT	PTEN, TPM1, PDCD4	[51], [52]
hsa-miR-20a	CRMA	Oncogenesis, cell cycle	E2F1, PTEN, TGFBR2	[53], [54], [55]
hsa-miR-301a/b	LINC00856	Oncogenic, EMT	PTEN, SMAD4, CDKN1A	[56], [57]
hsa-miR-425	--	Angiogenesis, inflammation, immune modulation	PTEN, Rb1, VEGFA	[58], [59], [60]
hsa-miR-1307	--	Drug resistance, cell survival	BCL2, RASSF1, HOXA1	[61], [62], [63]
hsa-miR-19b-2	--	OncomiR, PI3K/AKT	PTEN, BIM, SOCS1	[50], [64], [65]

Table 3. List of tumor suppressor ceRNA triplets detected in BLCA, highlighting their interactions and downstream mRNA targets. These modules are associated with induction of apoptosis, inhibition of angiogenesis, suppression of EMT, and regulation of stemness programs, collectively acting as checks against tumor progression.

miRNA	lncRNA Partner	Functional Role / Pathways	Validated/Predicted mRNA Targets	Reference
hsa-miR-210	ADAMTS9-AS1	Hypoxia, angiogenesis, cell cycle	EFNA3, ISCU, HIF3A, E2F3	[66], [67], [68]
hsa-miR-195	MEF2C-AS1	Cell cycle arrest, apoptosis	CDK1, BCL2, CCND1, E2F3	[69], [70]
hsa-miR-139	ADAMTS9-AS2	EMT, metastasis, PI3K/AKT	NOTCH1, ZEB1, CXCR4, IGF1R	[71], [72]
hsa-miR-28	MBNL1-AS1	Cell cycle regulation	CCND1, E2F6, IGF1	[72]
hsa-miR-143	ADGRB3-DT	Metabolism, MAPK signaling	KRAS, MAPK7, ERK5, DNMT3A	[73], [74]

hsa-miR-183	PGM5P4-AS1	Sensory organ development, cancer	FOXO1, EZR, EGR1	[75], [76], [77]
hsa-miR-671	FRMD6-AS2	Cell proliferation, stemness	CDR1, FOXM1	[78], [79], [80]
hsa-miR-590	HAND2-AS1	Cardiac development, cancer	TGFBR2, SMAD7, NOTCH1	[81], [82], [83]
hsa-miR-93	MIR133A1HG	Angiogenesis, proliferation	CDKN1A, VEGFA, PTEN	[84], [85], [86]
hsa-miR-1-2/1-1	MIR133A1HG	Muscle differentiation, metastasis	HDAC4, MET, PAX3	[87]
hsa-miR-133a-1/2	MIR133A1HG	Muscle, metastasis, cell migration	FSCN1, MMP9, EGFR	[88], [89]
hsa-miR-145	CARMN	Tumor suppressor, stemness	SOX2, OCT4, FSCN1	[10], [90], [91]
hsa-miR-503	PGM5P3-AS1	Cell cycle regulation	CCND1, CDC25A, FGF2	[92], [93], [94]
hsa-miR-23b	NFIB-AS1	EMT, apoptosis	VHL, MAP3K1	[94], [95], [96]
hsa-miR-429	KLHL30-AS1	EMT regulation	ZEB1, BMI1, ONECUT2	[97], [98], [99]
hsa-miR-182	EPIST	Metastasis, apoptosis	FOXO1, MITF, BCL2	[100], [101], [102]
hsa-miR-133b	HAND2-AS1	Muscle/cancer, migration	FSCN1, EGFR	[103], [104]
hsa-miR-140	MSL3-DT	Chondrogenesis, tumor suppression	HDAC4, IGF1R, SMAD3	[105], [106]
hsa-miR-522	LINC01778	Tumor progression, oxidative stress	TP53INP1, SPRED1	[107], [108], [109]
hsa-miR-135b	ZNF710-AS1	Wnt signaling, metastasis	APC, LATS2, FOXO1	[110], [111]
hsa-miR-504	DIP2C-AS1	p53 regulation, G1/S arrest	TP53, FGF2, CDK6	[112], [113]
hsa-miR-30a	LINC02202	EMT, autophagy	SNAI1, VIM, CDH2	[114]
hsa-miR-33a	LINC02731	Cholesterol metabolism	ABCA1, SREBF1	[115]
hsa-miR-374b	LRRC3B-AS1	EMT, stemness	WNT5A, PTEN	[116]
hsa-miR-185	TICAM2-AS1	Tumor suppression, angiogenesis	DNMT1, VEGFA, RHOA	[117]

Table 4. Key hub lncRNAs (LINC00460, HAND2-AS1, ADAMTS9-AS1, and CARMN) identified as highly connected regulators within the ceRNA network. Their corresponding miRNA partners, functional roles, and clinical applications are summarized. These ncRNAs represent promising minimally invasive biomarkers for early detection, risk stratification, and therapeutic monitoring in BLCA.

miRNA	Functional Role / Pathways	Validated/Predicted mRNA Targets	Reference
hsa-miR-519a-1/2	Proliferation, apoptosis, cell cycle	CDKN1A, CCNE1, MCL1	[118], [119]
hsa-miR-516a-1/2	Apoptosis, proliferation	CDKN1A, MCL1	[120], [121]
hsa-miR-141	EMT, metastasis, stemness	ZEB2, TGFBR2, PTEN	[71], [122]
hsa-miR-345	Hypoxia, apoptosis, p53 pathway	BCL2, HIF1A, TP53INP1	[123], [124], [125]
hsa-miR-767	Tumor progression, chromatin remodeling	TP53, HNRNPK, RASGRP1	[126]

Table 5. This table summarizes the top 10 hub lncRNAs and their key miRNA partners, ranked based on mechanistic evidence, pathway involvement, and clinical relevance in cancer. The Major Pathways Involved column highlights the primary biological processes regulated by each lncRNA–miRNA axis, including EMT, PI3K/AKT signaling, apoptosis, proliferation, angiogenesis, and stemness. Representative mRNA Targets are experimentally validated downstream effectors that mediate these functional roles. Clinical/Translational Utility indicates potential applications in prognosis, therapy response prediction, or monitoring tumor aggressiveness. The Biomarker Potential column combines qualitative assessment (High/Moderate) with a star rating system (★ = low, ★★★★★ = high) to facilitate rapid evaluation of each axis's translational relevance.

Rank	Hub lncRNA	Key miRNA Partner (s)	Major Pathways Involved	Representative mRNA Targets	Clinical/Translational Utility	Biomarker Potential
1	LINC00460	hsa-miR-21	PI3K/AKT, proliferation, apoptosis	PTEN, PDCD4, TPM1	Prognostic marker for tumor aggressiveness; therapeutic target in PI3K/AKT-driven cancers	High ★★★★★
2	FENDRR	hsa-miR-19a	OncomiR-1 cluster, apoptosis, proliferation	PTEN, SOCS1, BIM	Predicts proliferation status and response to targeted therapies	High ★★★★★
3	TARID	hsa-miR-17	Cell cycle regulation, apoptosis	PTEN, BIM, E2F1	Potential marker for tumor growth and chemoresistance	Moderate ★★★★
4	LINC02884	hsa-miR-130b	EMT, Wnt, TGF-β	PTEN, SMAD4, RUNX3	Indicator of metastatic potential; EMT-targeted therapy	High ★★★★★
5	ADAMTS9-AS2	hsa-miR-139	EMT, metastasis, PI3K/AKT	NOTCH1, ZEB1, CXCR4, IGF1R	Predicts metastasis and invasion; therapeutic monitoring	High ★★★★★

6	ADAMTS9-AS1	hsa-miR-210	Hypoxia, angiogenesis, cell cycle	EFNA3, ISCU, HIF3A, E2F3	Tumor microenvironment biomarker; angiogenesis-targeted therapy	Moderate ★★★★
7	MIR133A1HG	hsa-miR-93, hsa-miR-1-2/1-1, hsa-miR-133a-1/2	Angiogenesis, proliferation, metastasis	CDKN1A, VEGFA, PTEN, MET, FSCN1, MMP9	Multi-functional biomarker; potential predictor of tumor aggressiveness	High ★★★★★
8	ZNF710-AS1	hsa-miR-135b	Wnt signaling, metastasis	APC, LATS2, FOXO1	Marker for metastasis and Wnt pathway activation	Moderate ★★★★
9	CARMN	hsa-miR-145	Tumor suppression, stemness	SOX2, OCT4, FSCN1	Stemness and tumor-suppressive marker; prognosis indicator	High ★★★★★
10	LINC02202	hsa-miR-30a	EMT, autophagy	SNAI1, VIM, CDH2	Potential biomarker for EMT and therapy resistance	Moderate ★★★★

4. DISCUSSION

The analysis of bladder cancer transcriptomes revealed that ncRNAs function not as isolated molecules but as integrated components of ceRNA triplets that coordinate signaling regulation. Within this framework, oncogenic effects become amplified when miRNAs are embedded in ceRNA circuits. For instance, the role of miR-21 is reinforced through its interaction in the LINC00460–miR-21–PTEN/PDCD4 module, which stabilizes PI3K/AKT activation and promotes tumor progression. Such observations highlight the need to view ncRNA regulation as a network-level phenomenon rather than a collection of individual biomarkers. The ceRNA networks reconstructed in this study also demonstrate a dynamic push–pull balance between oncogenic and tumor-suppressive modules (Figure 5). Oncogenic hubs converge on PI3K/AKT and EMT signaling to promote proliferation, invasion, and dedifferentiation, while suppressor hubs stabilize checkpoints by inducing apoptosis, arresting the cell cycle, and inhibiting angiogenesis. This antagonistic interplay provides a mechanistic explanation for the heterogeneity of bladder tumors, where aggressive subtypes may be driven by dominant oncogenic hubs, whereas indolent subtypes are supported by the persistence of suppressive scaffolds.

These findings carry clear translational implications. Liquid biopsy emerges as an attractive approach for capturing hub ncRNAs (Table 1; Figure 1). Unlike cystoscopy, which though sensitive is invasive, costly, and prone to sampling bias[29], analysis of circulating ncRNAs in urine and plasma offers a minimally invasive and repeatable strategy. This systemic sampling reflects the broader tumor landscape rather than a single lesion. Previous studies have already reported urinary lncRNAs such as UCA1 and MALAT1, and plasma miRNAs including miR-141 and members of the miR-200 family, as promising markers[30], [31]. The integrative approach here expands upon those findings by identifying multi-hub ceRNA signatures, which may provide greater robustness and diagnostic accuracy than reliance on single transcripts.Another key insight is the redundancy observed across ceRNA modules, with multiple triplets converging on bottleneck regulators such as PTEN, VEGFA, and ZEB1. This suggests that bladder tumors maintain parallel ceRNA architectures to ensure robustness of oncogenic signaling. While such redundancy presents a challenge for therapies aimed at single targets, it simultaneously exposes

vulnerabilities. Targeting hub lncRNAs such as LINC00460 or ADAMTS9-AS1 has the potential to destabilize several oncogenic circuits at once. This network-based therapeutic strategy may therefore be more effective than approaches limited to individual genes or pathways. By mapping oncogenic and suppressive modules within a unified ceRNA network, the study provides a framework that connects molecular insight with clinical application. Hub ncRNAs such as LINC00460, HAND2-AS1, ADAMTS9-AS1, and CARMN emerge not only as regulators of bladder cancer biology but also as minimally invasive candidates for liquid biopsy detection (Table 4). Their centrality and recurrence across modules underscore their potential to serve as biomarkers for early detection, subtype stratification, and longitudinal monitoring of therapy response. In contrast to previous studies that focused on single ncRNAs, this work uniquely demonstrates how redundant and convergent ceRNA architectures define bladder cancer progression and can be harnessed for precision liquid biopsy applications. By shifting the perspective from individual molecules to network-level regulation, our study offers a novel and clinically actionable blueprint for ncRNA-based diagnostics and therapeutics in bladder cancer.

5. LIMITATIONS AND FUTURE DIRECTIONS

While our integrative ceRNA network reconstruction offers valuable insights into BLCA regulatory mechanisms, certain considerations remain for future exploration. The study leverages TCGA datasets (81 tumors, 19 normals) to identify hub ncRNAs, providing a robust foundation for biomarker discovery; however, validation in independent cohorts will strengthen generalizability. Likewise, translating these findings to liquid biopsy applications will benefit from standardized detection platforms to ensure reproducibility across patient samples[32]. Functional validation through in vitro and in vivo models is an important next step to confirm the causal roles of ceRNA interactions in BLCA progression. Moving forward, prospective clinical studies combining urine and plasma profiling with multi-omics integration have the potential to refine and implement hub ncRNAs as precise, non-invasive biomarkers for BLCA diagnosis and monitoring.

6. CONCLUSION

This study provides a blueprint for ncRNA-based biomarker development in bladder cancer**.** By moving beyond single-transcript approaches and mapping system-level ceRNA architecture**s**, we identify hub lncRNAs **table 5** (LINC00460, HAND2-AS1, ADAMTS9-AS1, CARMN) as master regulators of BLCA progression. These hubs, detectable via liquid biopsy, hold promise for early detection, subtype stratification, real-time therapy monitoring, and potentially therapeutic intervention**.**

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