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Predictive value of microRNA-133a-3p for early urinary incontinence after radical prostatectomy for prostate cancer and its correlation with rehabilitation effects

Fan Yang[1], Qiuxia Qin[1] and Juan Liu[1*]

Abstract

Aim The present study was conducted with the objective ascertaining the clinical implication of microRNA-133a-3p (miR-133a-3p) for urinary incontinence (UI) and rehabilitation effects in prostate cancer after radical prostatectomy.

Methods The measurements of miR-133a-3p in urethral tissue samples from prostate cancer patients after radical prostatectomy were carried out via quantitative real-time polymerase chain reaction (qRT-PCR) detection. Receiver operation characteristic (ROC) curve and logistic regression analysis were employed for evaluating the predictive significance of miR-133a-3p for the early UI of prostate cancer patients with radical prostatectomy. Bioinformatics tools were employed for mining the miR-133a-3p possible genes.

Results An obvious reduction of miR-133a-3p was detected in patients with UI compared with those with urinary continence (UC) ($P < 0.001$), demonstrating a high diagnostic capacity for patients with UI. Moreover, miR-133a-3p could be an independent predictive index for the early UI in patients with prostate cancer after radical prostatectomy ($P < 0.001$). Additionally, urine miR-133a-3p was notably increased in the UI patients after rehabilitation ($P < 0.001$). MiR-133a-3p largely concentered on the muscle-related diseases pathways using bioinformatics tools.

Conclusion MiR-133a-3p was a promising indicator for predicting early UI in patients with prostate cancer after radical prostatectomy.

Clinical trial number Not applicable.

Keywords MiR-133a-3p, Urinary incontinence, Rehabilitation, Predictive value

*Correspondence:
Juan Liu
tj32133213@163.com
[1]Nursing Department, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, No. 1095 Jiefang Avenue, Wuhan 430030, Hubei, China

Introduction

Urinary incontinence (UI) is a prevalent and distressing complication following radical prostatectomy in patients with prostate cancer [1]. It significantly impacts patients' quality of life, causing emotional distress and affecting their social interactions and daily activities [2, 3]. UI occurs when there is an involuntary leakage of urine or a lack of bladder control, leading to urinary accidents. The predominant forms of UI following racial prostatectomy in patients with prostate cancer are categorized as follows: stress, filling and urge UI, with most patients having stress UI caused by external sphincter injury [4]. Despite advancements in surgical techniques and postoperative care, UI remains a challenging issue that requires comprehensive management strategies [5]. Identifying risk factors for post-operative UI in prostate cancer patients is of great clinical importance in preventing its occurrence and improving its clinical outcome.

MicroRNAs (miRNAs) are short non-coding RNA molecules that significantly contribute to the post-transcriptional modulation of gene expression. Their primary function involves modulating the stability and translation of mRNA, thereby influencing protein synthesis in a variety of biological contexts [6]. Emerging evidence highlights the involvement of miRNAs in a broad spectrum of essential cellular events, such as cell differentiation, cellular proliferation, and the programmed cell death [7]. Recently, research has revealed that miRNAs act a critical role in bladder fibrosis and pelvic floor dysfunction [8, 9, 10]. As a promising miRNA, microRNA-133a-3p (miR-133a-3p) has been identified as a promising miRNA, with evidence suggesting its involvement in the initiation and formation of prostate cancer and muscle-related diseases [11]. For example, in diabetic cardiomyopathy, increased miR-133a-3p expression could improve myocardial injury and apoptosis [12]. Moreover, an obvious decrease of miR-133a-3p was found in scalded mice, and its overexpression could suppress scar formation and scar-derived fibroblasts cell growth [13]. Nonetheless, there is limited understanding of the function that miR-133a-3p plays in UI following radical prostatectomy in prostate cancer patients.

Transforming Growth Factor Beta 1 (TGF-β1) has been identified as a highly versatile protein that modulates a number of processes, including cell growth, differentiation, and programmed cell death. It has been proved to be the most important pro-fibrotic cytokine in a variety of diseases [14]. Collagen III, which is a pivotal component of the extracellular matrix, serves an essential function by providing structural support to various tissues throughout the body. Beyond its role in maintaining structural integrity, collagen III is instrumental in the processes of tissue repair and remodeling. Its presence is vital to facilitate healing and restore normal tissue architecture following injury or disease, highlighting its importance in health and pathological conditions [15]. In the urinary system, alterations in TGF-β1 and Collagen III expression may contribute to the pathophysiology of UI by affecting bladder structure and function.

Although previous studies have explored the role of miRNA in prostate cancer progression and muscle-related diseases, the predictive value of miR-133a-3p in UI after radical prostatectomy and its association with rehabilitation effects have not been systematically explored. The study is the first to propose miR-133a-3p as a potential biomarker for UI, and by combining the analysis of the molecular mechanism of TGF-β1 and collagen III, it fills the research gap of miRNA in the prediction and rehabilitation management of postoperative UI.

The current research aims to ascertain the clinical implication of a specific miRNA, miR-133a-3p, in UI following radical prostatectomy for prostate cancer. It was hypothesized that miR-133a-3p may serve as an indicator for early UI and that its expression is associated with the effectiveness of rehabilitation strategies. By examining the relative amounts of miR-133a-3p in urethral tissue samples and its correlation with TGF-β1 and Collagen III, we seek to uncover potential molecular mechanisms underlying the occurrence of UI and to explore novel targets for therapeutic intervention.

Methods and materials

Clinical samples

The approval of the present research was obtained by the Ethic Committee of Tongji Hospital. All the research subjects have provided written informed content before sample collections.

A total of 120 prostate cancer patients subjected to radical prostatectomy were recruited in Tongji Hospital. Based on the presence or absence of UI of patients, all the subjects were split into two groups: the urinary continence (UC) group ($n = 80$) and the UI group ($n = 40$). Urethral tissues were collected from each participant. Inclusion criteria between the UI and UC groups were as followed: (1) preoperative diagnosis of local prostate cancer (Stage T1-T2) confirmed by imaging and pathology; (2) local prostate cancer, without distant metastasis; (3) all underwent radical prostatectomy; (4) no preoperative history of UI (UI diagnosed postoperatively in the UI group and no UI postoperatively in the UC group). Exclusion criteria: (1) incomplete clinical data; (2) combined neurogenic bladder or urethral stenosis or other conditions affecting urinary function; (3) postoperative adjuvant therapies (e.g., radiotherapy), which may confound rehabilitation outcome; (4) patients exhibiting substandard compliance and noncompliance with treatment regimens. When all participants were grouped into the UI and UC groups, in addition to adhering to the

inclusion-exclusion criteria, we also considered several clinical differences. The occurrence of postoperative UI may be associated with the extent of urethral sphincter loss, as well as the involvement of pelvic floor nerves, and other structures resulting from the surgical maneuver.

Under the conditions of $\alpha = 0.05$ and power $(1-\beta) = 0.8$, the minimum total sample size was calculated to be 102 through the G*Power software. Our study included 120 participants, among whom 40 were in the study group and 80 were in the control group. The basic information of all patients was recorded, such as age (years), body mass index (BMI), smoking status, drinking history, history of urinary track infection (UTI), prostate volume, International Prostate Symptom Score (IPSS), Gleason score, serum prostate specific antigen (PSA), bladder neck management (Table 1).

The diagnostic criteria of UI were as followed: the presence of two or more urine pads/day is regarded as UI, while the use of one or fewer pads/day was considered to be UC. The basic characteristics, including age, BMI, smoking status, drinking history, UTI, prostate volume, IPSS score, Gleason score, PSA, and bladder neck management, were compared between the UI and UC groups.

Urine samples of patients with UI were collected postoperative and post-rehabilitation (6-month). Participants provided first-morning midstream urine (10 mL) in sterile containers. Samples were centrifuged at 3,000 rpm for 10 min to remove cellular debris, and supernatants were aliquoted into cryovials. These aliquots were stored at -80 °C until RNA extraction.

Table 1 Baseline information of prostate cancer patients undergoing radical prostatectomy

Factors	UI group($n=40$)	UC group ($n=80$)	*P* value
Age (years)	62.80±5.96	63.20±5.93	0.729
BMI (kg/m^2)	22.72±22.94	22.94±0.92	0.234
Smoking status (n, %)			
No	23 (57.5%)	47 (58.75%)	0.896
Yes	17 (42.5%)	33 (41.25%)	
Drinking history (n, %)			
No	28 (70%)	58 (72.5%)	0.774
Yes	12 (30%)	22 (27.5%)	
UTI (n, %)			**0.003**
No	19 (47.5%)	60 (75%)	
Yes	21 (52.5%)	20 (25%)	
Prostate volume (cm^3)	45.35±4.64	43.60±4.87	0.062
IPSS scores	22.08±2.69	20.55±2.31	**0.002**
Gleason scores	6.98±0.97	6.93±0.79	0.764
Serum PSA (μg/L)	15.13±1.67	15.07±1.38	0.854
Bladder neck status (n, %)			**0.002**
Preservation	12 (30%)	48 (60%)	
Resection	28 (70%)	32 (40%)	

Abbreviations: UI = urinary incontinence; UC = urinary continence; UTI = history of urinary tract infection; PSA = prostate specific antigen; IPSS = International Prostate Symptom Score; Data are expressed as n or mean ± standard deviation (SD). $P < 0.05$ means significant difference

Enzyme linked immunosorbent assay (ELISA)

The levels of TGF-β1 and collagen III were detected with ELISA kits (human TGF-β1 Quantikine ELISA Kit, USA; human collagen III ELISA Kits, Cusabio Biotech Co., China). The ELISAs were carried out at least three times based on the manufacturer's directions. Readings of absorbances were done at the wavelength of 450 nm using a spectrophotometer.

Rehabilitation approaches

Patients diagnosed with UI were administered pelvic floor muscle functional training as an intervention, on the basis of standard nursing protocols. The standard nursing approaches include patient education and counseling, post-operative nursing care, coordinating the patient's dietary plan etc. The primary sequence of pelvic floor muscle functional training involved the relaxation of the lower limbs and the abdominal buttock muscles. Subsequently, the muscles surrounding the pubic bone and tailbone were targeted for contraction and elevation for a duration of 5 to 20 s. This was followed by a period of relaxation and rest for a duration of 10 s, constituting a complete movement. The intervention was administered in 30 group sessions, with each session occurring three times daily, for a total duration of six months. After 6 months following rehabilitation training, 28 cases in the UI group had regained control of their urine, and were selected as the effective group, while 12 cases with no improvement was selected for the ineffective group, based on the diagnostic criteria of UI.

At the end of rehabilitation, several indicators, such as urinary control function, frequency of urination, urine leakages frequency, urination volume, IPSS score, international consultation on incontinence questionnaire urinary incontinence short form (ICI-Q-SF) score (0–35), and incontinence quality of life questionnaire (I-QOL) were statistically analyzed and assessed.

Quantitative real-time polymerase chain reaction assay (qRT-PCR) detection

Total RNA was isolated from urethral tissues of all patients using Trizol kit (Beijing, China), and then the purity of total RNA was detected with UV spectrophotometry. The OD260/OD280 ratio was detected to be between 1.8 and 2.0, indicating a high degree of concentrations, as would be required for next experimentation. To synthesize cDNA, the TaqMan miRNA Reverse Transcription Kit was utilized. qPCR was carried out using SYBR Premix DimerErase (Takara) based on the guidelines provided by the manufacturer. RNU6B was utilized for the normalization. The relative abundances

of miR-133a-3p were determined using $2^{-\Delta\Delta ct}$ equation. Each reaction was performed a minimum of three times.

Bioinformatics analysis

Three databases, including miRPathDB, miRTarBase and miRWalk, were utilized for predicting miR-133a-3p possible genes. Gene ontology (GO) analysis was executed in terms of biological process (BP), cellular component (CC), and molecular function (MF). The key signaling pathways were mined using the Kyoto Encyclopedia of Genes and Genomes (KEGG) functional enrichment. Protein-protein interaction (PPI) networks of the overlaps of miR-133a-3p-reglated genes were generated with the STRING database.

Statistical analysis

The data collected and recorded continuously were expressed by mean and standard deviation (SD) while the classified data were displayed as n and %. Independent Student's t test and Chi-square test were utilized for comparing the difference among groups. Receiver operating characteristics (ROC) curve was established to evaluate the diagnostic accuracy of miR-133a-3p, as well as logistic regression analysis for its predictive value. SPSS 23.0 version was conducted for the statistically data analysis and GraphPad prism 9.0 (GraphPad) was utilized to plot graphs in respective order. The statistical difference was identified at a *P* value with less than 0.05.

Results

Comparisons of basic data from all the participants

Table 1 indicated the baseline characteristics of the UI and UC groups. An obvious difference was observed in the history of UTI between two groups (UI vs. UC = 52.5% vs. 25%, $P = 0.003$), with a higher prevalence in the UI group. Prostate volume was measured preoperatively via transrectal ultrasound, reflecting baseline gland size prior to radical prostatectomy. No significant differences were observed between UI and UC groups (45.35±4.64 vs. 43.60±4.87, $P = 0.062$), suggesting that baseline prostate size may not independently predict UI development in this cohort. IPSS was notably increased in the UI group (22.08 ± 2.69) relative to the UC group (20.55 ± 2.31, $P = 0.002$), indicating more severe urinary symptoms in the UI group. There was a distinct difference in bladder neck preservation versus resection between two groups ($P = 0.002$), with more resections in the UI group. The UI group exhibited a notably higher prevalence of UTI history, higher IPSS scores, and more bladder neck resections against the UC group. Nevertheless, no statistical associations in two groups were found in other factors, such age, BMI, smoking status, drinking history, Gleason scores, and serum PSA levels (all $P > 0.05$).

Relative amounts of miR-133a-3p and its diagnostic value

To ascertain the role of miR-133a-3p in patients with UI, qRT-PCR assay and ROC curve were conducted. MiR-133a-3p expression in urethral tissues was obviously decreased in the UI group against the UC group ($P < 0.001$, Fig. 1A). ROC curve showed that the arear under the curve (AUC) was 0.910, with the sensitivity of 82.50% and the specificity of 86.25%, demonstrating a considerable diagnostic accuracy for the UI patients (Fig. 1B). The significant downregulation of miR-133a-3p in UI patients was consistent with the findings of Duan et al. in bladder fibrosis, suggesting a conserved role in the regulation of TGF-β1 pathway [16]. Similarly, Hirman et al. demonstrated miR-133a-3p's anti-fibrotic effects in scar formation, supporting its potential therapeutic relevance in tissue repair pathways [13].

Predicative value of miR-133a-3p for UI of prostate cancer patients

Logistic regression analysis in Table 2 identified several risk factors for the occurrence of UI in prostate cancer patients following radical prostatectomy. In the univariate analysis, several factors were evaluated, including age, BMI, smoking status, drinking history, history of UTI, prostate volume, IPSS scores, Gleason scores, serum PSA levels, bladder neck management and miR-133a-3p expression status.

Notably, miR-133a-3p levels were inversely associated with UI (OR: 0.042, 95%CI: 0.013–0.132, $P < 0.001$). Moreover, a history of UTI was closely associated with the occurrence of UI, with an OR of 3.316 (95% CI: 1.489–7.385, $P = 0.003$), as well as IPSS scores (OR: 2.508, 95%CI: 1.104-5.699, $P = 0.028$). Similarly, bladder neck resection was identified to be an important risk indicator, with an OR of 3.500 (95% CI: 1.556–7.874, $P = 0.002$).

In the multivariate analysis, miR-133a-3p expression (OR: 0.036; 95%CI: 0.010–0.126, $P < 0.001$) was still an important indicator of UI, as well as UTI history (OR: 3.357, 95%CI: 1.142–9.869, $P = 0.028$) and bladder neck resection (OR: 3.431, 95%CI: 1.176–10.004, $P = 0.024$), while the association with IPSS scores became non-significant (OR: 2.537, 95%CI: 0.853–7.543, $P = 0.094$). Other clinicopathological indicators, such as age, BMI, smoking status, drinking history, prostate volume, Gleason scores, and serum PSA levels did not reach statistical significance in either the univariate or multivariate analyses. This suggests that miR-133a-3p expression, UTI history, and bladder neck management are the primary predictors of UI in this cohort, suggesting their importance in the clinical assessment and management of post-prostatectomy incontinence.

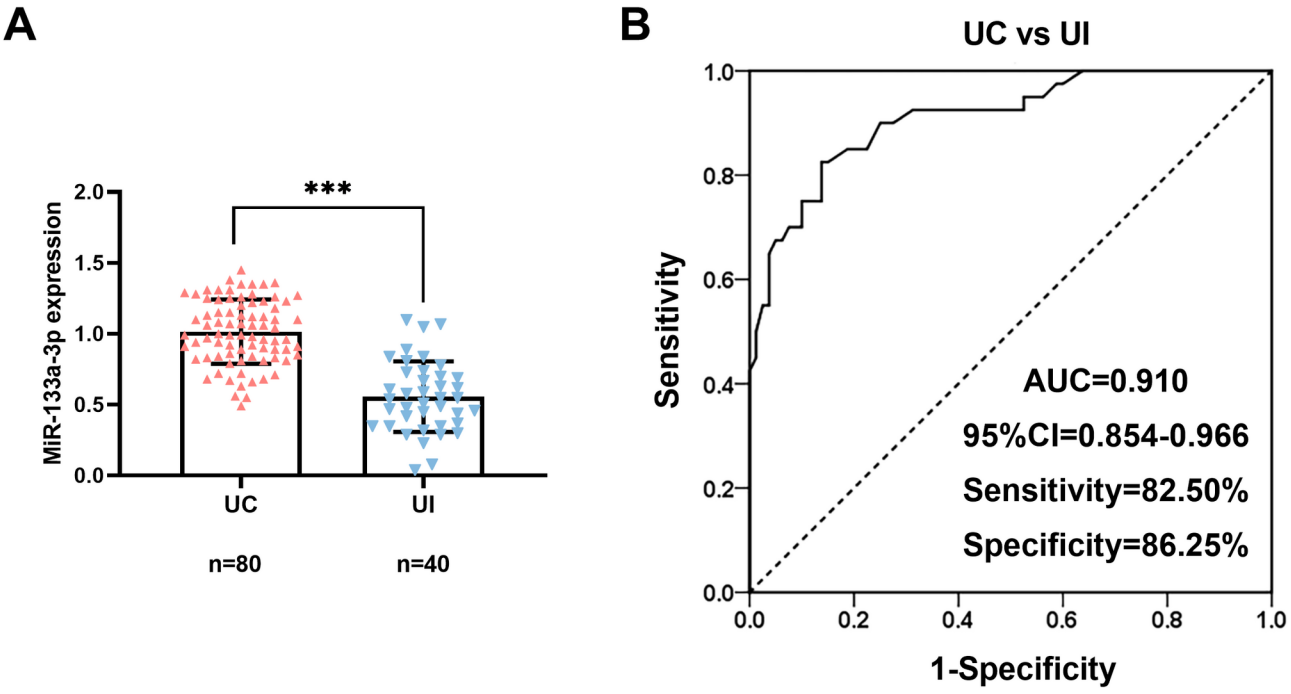

Fig. 1 MiR-133a-3p expression in urethral tissues was detected in patients with UI and UC (**A**), as well as its diagnostic value (**B**). (UI = urinary incontinence; UC = urinary continence; ***$P < 0.001$)

Table 2 Logistics analysis of risk factors for the occurrence of UI

Factors	Univariate		Multivariate	
	OR (95% CI)	*P*	OR (95% CI)	*P*
Age (years)	1.267(0.235–6.835)	0.783	/	/
BMI (kg/m^2)	0.571(0.263–1.240)	0.157	/	/
Smoking status	1.053(0.488–2.271)	0.896	/	/
Drinking history	1.130(0.490–2.606)	0.775	/	/
UTI	**3.316(1.489–7.385)**	**0.003**	**3.357(1.142–9.869)**	**0.028**
Prostate volume (cm^3)	2.037(0.937–4.431)	0.073	/	/
IPSS scores	**2.508 (1.104–5.699)**	**0.028**	2.537(0.853–7.543)	0.094
Gleason scores	1.138 (0.482–2.686)	0.768	/	/
Serum PSA (μg/L)	1.222(0.571–2.618)	0.606	/	/
Bladder neck status	**3.500 (1.556–7.874)**	**0.002**	**3.431(1.176–10.004)**	**0.024**
MiR-133a-3p	**0.042 (0.013–0.132)**	**< 0.001**	**0.036(0.010–0.126)**	**< 0.001**

Abbreviations: UI = urinary incontinence; UC = urinary continence; UTI = urinary tract infection; PSA = prostate specific antigen; IPSS = International Prostate Symptom Score; Data are expressed as n or mean ± standard deviation (SD). $P < 0.05$ means significant difference

Correlation of miR-133a-3p with TGF-β1 and collagen III levels

To appraise the relevance of miR-133a-3p with TGF-β1 and collagen III protein levels in urethral tissues from all enrolled prostate cancer patients, ELISA assay and Pearson's correlation were conducted. TGF-β1 protein levels were dramatically augmented in patients with UI group against those with UC ($P < 0.001$, Fig. 2A). Similarly, Collagen III protein levels in patients with UI are distinctly decreased against those with UC ($P < 0.05$, Fig. 2B). These findings suggested that both TGF-β1 and Collagen III may act a role in the pathophysiology of UI following radical prostatectomy.

Furthermore, an obvious negative correlation was found of miR-133a-3p with TGF-β1 (r=-0.6318, $P < 0.001$, Fig. 2C), indicating higher miR-133a-3p expression is in relation to lower TGF-β1 protein levels. Conversely, an obviously positive correlation was disclosed between miR-133a-3p and collagen III protein levels ($r = 0.6466$, $P < 0.001$, Fig. 2D), demonstrating higher miR-133a-3p is in relation to increased collagen III protein levels. These correlations highlighted the underlying regulatory function of miR-133a-3p in expression of TGF-β1 and collagen III, which may contribute to the occurrence of UI in prostate cancer patients following radical prostatectomy.

Association of urine miR-133a-3p and rehabilitation effects

Additionally, we further investigated the correlation of miR-133a-3p on rehabilitation effects in the UI group,

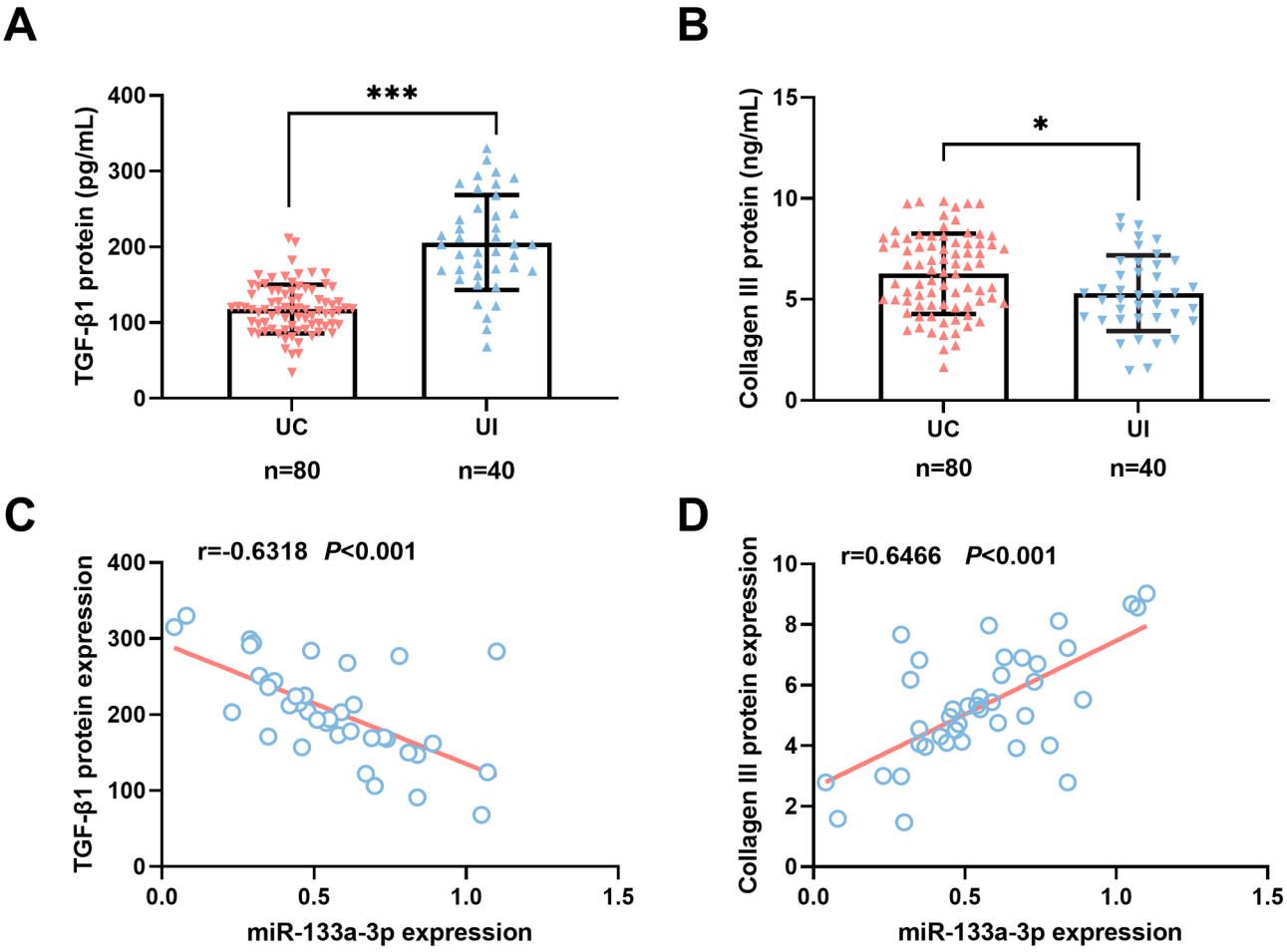

Fig. 2 Protein levels of TGF-β1 and collagen III in urethral tissues from patients in UI and UC groups. **A**. An enforced level of TGF-β1 was observed in patients with UI against those with UC. **B**. Collagen III protein levels were distinctly declined in patients with UI compared with those with UC. **C**. A negative correlation was found of miR-133a-3p with TGF-1 levels in patient with UI (r=-0.6318, $P<0.001$). **D**. MiR-133a-3p was positively in relation to collagen III protein levels ($r=0.6466$, $P<0.001$). (UI = urinary incontinence; UC = urinary continence; TGF-β1 = transforming growth factor-β1; *$P<0.05$; ***$P<0.001$)

Table 3 Analysis of UI effects between pre-rehabilitation and post-rehabilitation of the UI group

Effects	Pre-rehabilitation ($n=40$)	Post-rehabilitation ($n=40$)	P values
Frequency of urination (times/day)	20.35±1.72	13.00±1.40	< 0.001
Urine leakages frequency (times/day)	10.28±0.82	6.05±0.99	< 0.001
Urination volume (mL/day)	1439.08±117.60	1286.13±86.33	< 0.001
IPSS score (0–35)	22.08±2.69	8.35±3.09	< 0.001
ICI-Q-SF score (0–21)	13.85±1.92	6.03±1.23	< 0.001
I-QOL (0-100)	63.78±3.16	84.55±5.35	< 0.001

Abbreviations: ICI-Q-SF = international consultation on incontinence questionnaire urinary incontinence short form; I-QOL = incontinence quality of life questionnaire; IPSS = International Prostate Symptom Score; Data are expressed as n or mean ± standard deviation (SD)

and compared pre-rehabilitation and post-rehabilitation outcomes. The results demonstrated significant improvements in urinary control function following rehabilitation. Specifically, 28 patients achieved effective urinary control in a group of 40 UI patients. In addition to the binary effectiveness measure, several quantitative metrics, including frequency of urination and urine leakages, and daily urination volume, also showed obvious improvements. Furthermore, both IPSS score and ICI-Q-SF score, which assess lower urinary tract symptoms and UI severity, respectively, showed significant reductions ($P<0.001$). The I-QOL score, which measured the influence of UI on quality of life, improved significantly from 63.78 ± 3.16 to 84.55 ± 5.35 ($P<0.001$) (Table 3).

Furthermore, miR-133a-3p expression levels were statistically analyzed in urethral tissues between the effective and ineffective groups. Results showed that patients with effective rehabilitation exhibited a higher miR-133a-3p expression than those with ineffective

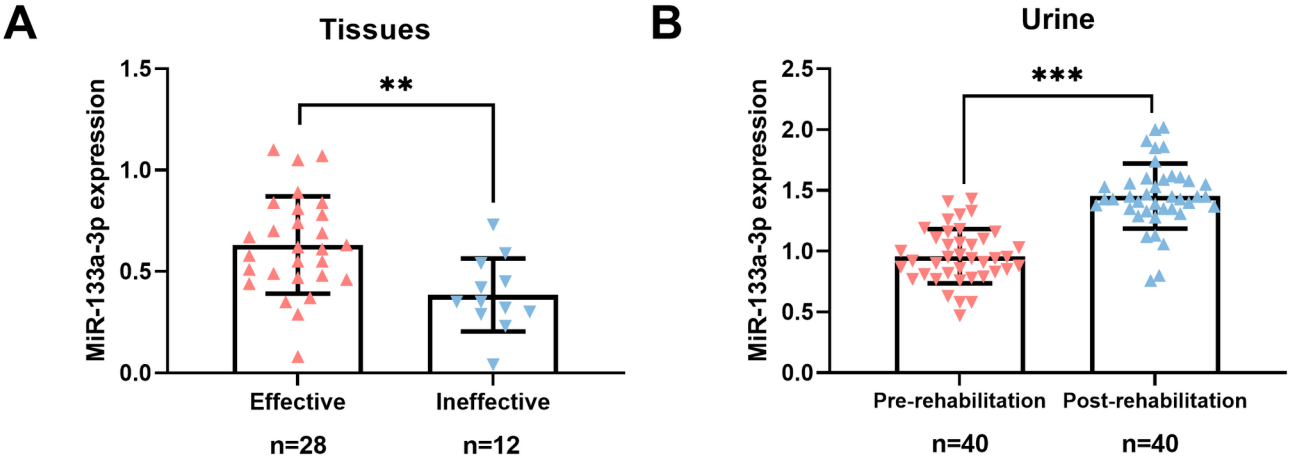

Fig. 3 MiR-133a-3p affected rehabilitation. **A**. MiR-133a-3p expression in urethral tissue specimens was obviously down-regulated in the ineffective group against the effective group. **B**. Following rehabilitation, urine miR-133a-3p were notably elevated in comparison to pre-rehabilitation. (**$P < 0.01$; ***$P < 0.001$)

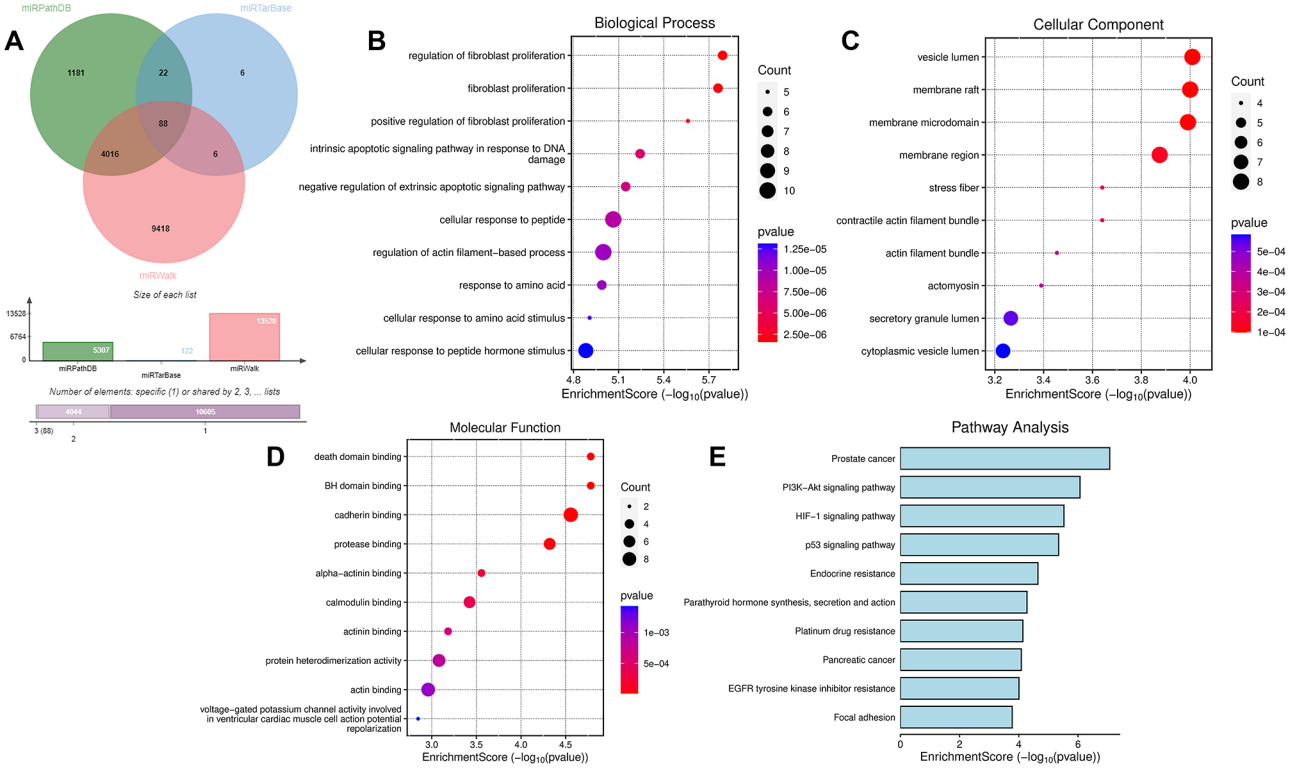

Fig. 4 MiR-133a-3p-regualted genes were predicted using bioinformatics tools. **A**. A Venn diagram was plotted for the overlapping genes from miRPathDB, miRTarBase and miRWalk databases. **B-D**. GO functional gene analysis was performed. **E.** The KEGG enrichment analysis was carried out.

rehabilitation ($P < 0.01$, Fig. 3A). Notably, urine miR-133a-3p expression status was compared in the pre- and post-rehabilitation, indicating an enforced expression in the post-rehabilitation group ($P < 0.001$, Fig. 3B). It was illustrated that miR-133a-3p may be a helpful factor for rehabilitation effects.

Bioinformatics analysis for predicting miR-133a-3p targets

The underlying miR-133a-3p-related genes were mined with three databases, and the intersection genes were displayed using a Venn diagram in Fig. 4A. Via GO and KEGG functional enrichment analysis, The enriched BP included fibroblast proliferation, apoptotic signaling pathways, and cellular responses to peptides and amino acids (Fig. 4B), suggesting roles in tissue repair, cell death,

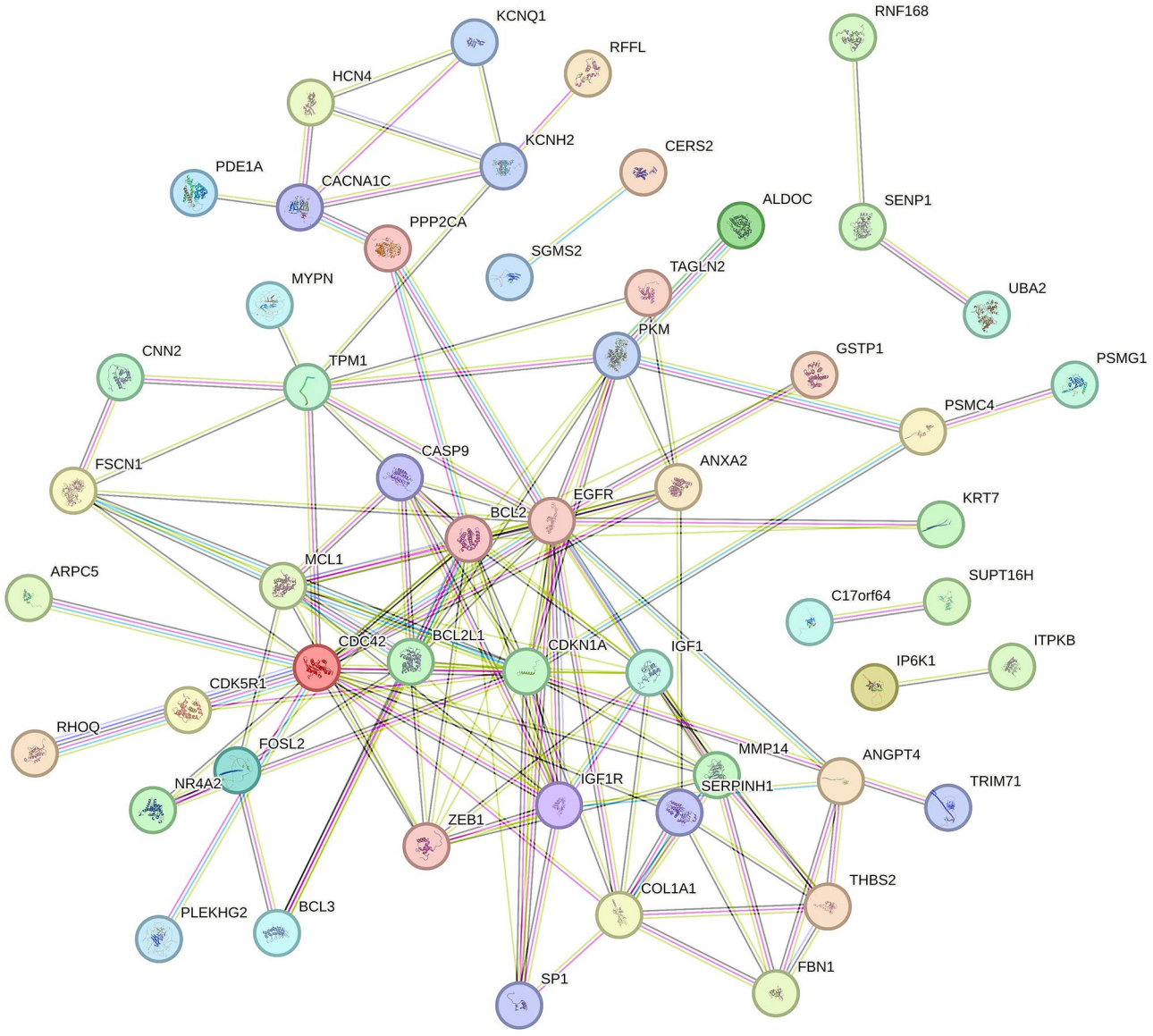

Fig. 5 A PPI network was generated using the overlapping genes of miR-133a-3p targets.

Table 4 The top 7 nodes of urinary incontinence-related PPI network

Node	Description	Degree
EGFR	*Epidermal growth factor receptor*	20
BCL2	*Apoptosis regulator Bcl-2*	18
CDKN1A	*Cyclin-dependent kinase inhibitor 1*	18
CDC42	*Cell division control protein 42 homolog*	15
IGF1	*Insulin-like growth factor I*	12
BCL2L1	*Bcl-2-like protein 1*	11
IGF1R	*Insulin-like growth factor 1 receptor alpha chain*	11

and metabolic regulation. The CC highlighted involvement in vesicles, membrane regions, and actin-related structures (Fig. 4C), indicating functions in intracellular transport and cytoskeletal organization. MF such as protein binding and ion channel activity further underscore roles in signaling and cellular regulation (Fig. 4D). KEGG pathway analysis identified critical pathways like Akt signaling, HIF-1 signaling, p53 signaling, and cancer-related pathways, linking the genes to cell survival, stress responses, and cancer progression (Fig. 4E).

PPI network was established with the overlapping genes of miR-133a-3p targets, with nodes representing proteins and lines indicating interactions between them (Fig. 5). Table 4 highlighted the top 7 nodes in the PPI network related to UI, ranked by their degree of connectivity, which indicates their centrality and importance in the network. The most prominent node is EGFR (epidermal growth factor receptor) with a degree of 20, suggesting its critical role in cell growth and signaling pathways

associated with UI. Together, these findings provide a comprehensive view of miR-133a-3p on UI and rehabilitation by modulating multiple biological pathways and molecular functions.

Discussion

A substantial body of research has identified miRNAs exhibit differential expression in tissues among various disorders, suggesting a potential involvement of miRNAs in the initiation and formation of numerous diseases, including muscle-related disorders [17, 18]. The current research investigated the clinical implications of miR-133a-3p in UI following radical prostatectomy for prostate cancer. Our findings demonstrated that miR-133a-3p is dramatically declined in with UI patients against those with UC, suggesting its potential role as an index for predicting UI at an early stage. Furthermore, dysregulation of miR-133a-3p was associated with the effectiveness of rehabilitation, highlighting its potential utility in guiding postoperative management strategies.

The dysregulation of miR-133a-3p in UI patients aligns with previous studies that have implicated miRNAs in pelvic floor dysfunction and bladder fibrosis [16, 19]. Enforced miR-133a-3p expression was involved in the reduction of fibrosis in the treatment of acute myocardial infarction [20]. Zhu and others also claimed that miR-133a-3p could attenuate cardiomyocyte hypertrophy, as a promising approach for cardiac hypertrophy treatment [21]. MiR-133a-3p has been documented as an important index in the pathophysiology of muscle-related diseases and tissue repair, which may explain its involvement in the pathophysiology of UI following radical prostatectomy. In chronic rotator cuff repair, miR-133a-3p might be an underlying predictor for muscle regeneration [22]. The findings demonstrated that miR-133a-3p yields a considerable diagnostic capacity for UI. This indicates that miR-133a-3p could be regarded to be a reliable predictor for predicting patients developing into UI after radical prostatectomy.

The analysis through logistic regression analysis further established that miR-133a-3p serves as an independent predictor UI, where its reduced expression levels were notably linked to an increased risk of UI. Moreover, having a history of UTI and undergoing bladder neck resection were recognized as significant risk contributors for UI. These results emphasize the critical importance of integrating both molecular markers and clinical history in the evaluation and management of UI following prostatectomy. This comprehensive approach can enhance the understanding of the underlying mechanisms of UI and contribute to more effective treatment strategies for affected individuals.

The relevance analysis of miR-133a-3p with TGF-β1 and collagen III levels provides insights into the molecular mechanisms underlying UI. TGF-β1, a key pro-fibrotic cytokine, was significantly elevated in UI patients, while collagen III levels were reduced. The negative association of miR-133a-3p with TGF-β1 suggests that miR-133a-3p may regulate TGF-β1 expression, potentially influencing bladder fibrosis and tissue remodeling [23, 24]. Conversely, the positive association of miR-133a-3p with collagen III indicates that miR-133a-3p may promote collagen synthesis, which is essential for tissue repair and structural integrity [25]. Our outcomes demonstrate miR-133a-3p as a dual function in regulating both fibrotic and reparative processes in the urinary system.

The rehabilitation outcomes further support the clinical relevance of miR-133a-3p. Patients with higher miR-133a-3p levels showed significant improvements in urinary control function, frequency of urination, and quality of life following pelvic floor muscle training. This suggests miR-133a-3p as a predictive index and an underlying therapeutic target for enhancing rehabilitation efficacy. The increase in urine miR-133a-3p levels post-rehabilitation further highlights its dynamic role in the recovery process.

To further support our findings and provide additional insights into the molecular mechanisms underlying the role of miR-133a-3p in UI, an in-depth bioinformatics analysis was conducted. Three databases were used to predict potential target genes of miR-133a-3p. The sequence of miR-133a-3p is 5'-UUUGGUCCCCUUCAACCAGCUG-3', and its interaction with specific gene sites was analyze using these databases. The analysis revealed that miR-133a-3p interacts with several genes involved in fibrotic processes and tissue repair, such as TGF-β1 and collagen III. These interactions are mediated through complementary base pairing between miRNA and 3'-untranslated regions (3'UTRs) of the target mRNA, potentially inhibiting its translation and expression. For instance, miR-133a-3p was predicted to bind to the 3'UTR of TGF-β1 mRNA, potential inhibiting its translation and expression [26]. This regulatory mechanism aligns with our experimental findings, where lower miR-133a-3p expression was associated with higher TGF-β1 protein levels in UI patients. Additionally, the analysis identified miR-133a-3p as regulator of genes implicated in critical pathways such as Akt signaling, HIF-1 signaling, and p53 signaling, which are associated with cell survival, stress responses, and tissue repair [27, 28], further supporting the role of miR-133a-3p in the pathophysiology of UI. The PPI network identified EGFR as a central node, suggesting its potential role in the molecular pathways underlying UI. These findings provide a comprehensive view of the molecular landscape regulated by miR-133a-3p and its potential impact on UI and rehabilitation.

Despite providing valuable insights, the present study is not without its limitations. Firstly, the relatively small sample size, coupled with the fact that all participants were recruited from a single institution, which may result in findings that are not readily generalizable to other populations. Future multi-center studies with larger cohorts are necessary to validate these results across diverse populations. Secondly, while the research focused on correlation between miR-133a-3p, TGF-β1, and collagen III, the lack of functional experiments (e.g., miR-133a-3p knockdown/overexpression models) precludes definitive conclusions about causality. Additional function research is essential to clarify the specific mechanism through which miR-133a-3p affects UI. Additionally, the 6-month follow-up period for rehabilitation outcomes is relatively short; long-term follow-up investigations are needed to assess the durability of miR-133a-3p as a predictive index and its impact on long-term rehabilitation outcomes. Addressing these limitations in future research will strengthen the clinical applicability of our findings.

In conclusion, our study demonstrates that miR-133a-3p is a promising biomarker for predicting early UI in prostate cancer patients following radical prostatectomy. Its expression is closely associated with TGF-β1 and collagen III levels, suggesting a regulatory role in bladder fibrosis and tissue repair. Furthermore, miR-133a-3p levels correlate with rehabilitation outcomes, indicating its potential utility in guiding postoperative management. Our findings position miR-133a-3p as a novel biomarker for early identification of high-risk UI patients. By integrating nursing care with miR-133a-3p detection and understanding of UI post-radical prostatectomy, nurses can provide more personalized, effective care that supports both the physical and psychological needs of patients, enhancing their recovery and quality of life. Combined with the dynamic changes of miR-133a-3p in rehabilitation training, individualized rehabilitation programs may be developed in the future to improve the quality of life of patients. Future studies should explore the therapeutic modulation of miR-133a-3p to enhance rehabilitation efficacy.

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Author contributions
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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Tongji Hospital before the study began. The written informed consent has been obtained from the participants involved.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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