REVIEW

# The MicroRNAs (miRNAs) Expression in Benign Urological Diseases: A Systematic Review

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**Purpose:** The exact molecular and cellular processes that cause benign urological diseases in the stromal and epithelial components of the urinary tract are yet unknown. Reviewing and analyzing the data linking microRNAs (miRNAs) expression in the pathophysiology of benign urological conditions, including overactive bladder (OAB), bladder outlet obstruction (BOO), bladder pain syndrome/interstitial cystitis (BPS/IC), and Lower urinary tract dysfunction (LUTD) is the objective of the current systematic review.

**Materials and Methods:** Evidence including all case-control, cohort, and cross-sectional studies that measure participants' MicroRNA as a biomarker for benign urological diseases has been gathered in January 2024, through searching MEDLINE via PubMed, Scopus, Web of Science, Embase, and ProQuest databases. Studies considered eligible that present information on the reference Gene, profile type, and serum levels of microRNA from patients diagnosed with benign urological disease including benign prostate hyperplasia (BPH) or benign prostate enlargement (BPE), overactive bladder (OAB), and bladder outlet obstruction (BOO). These studies were appraised by the quality assessment checklist of Joanna Briggs Institute (JBI).

**Results:** A total of 4,587 records related to miRNAs in urological diseases were retrieved. Of these, we identified 28 records for our systematic study. The most frequently associated miRNA was 92a-3p identified which was found upregulated in OAB diagnosis. In BOO, miR-146a-5p was identified to be upregulated. miR-146a-5p was upregulated in BO, and for other benign conditions, different miRNAs were reported. 491-5p miRNAs were found deregulated in OAB-related studies. We expected other miRNAs to have the same trend in the OAB studies. InSUI miR-93 was the most frequent downregulated miRNA. The other reported miRNAs had similar frequencies.

**Conclusion:** When it comes to the early detection and treatment of benign urological conditions, 92a-3p, miR-21, miR-199a-5p, and miR-146a-5p, and 491-5p have the potential to be employed as both a biomarker and a therapeutic target. The creation of pre-RNA or anti-RNA molecules within carrier vehicles that may be safely administered to patients should be made possible by technological advancements.

**Keywords:** miRNA; Benign, urology, overactive bladder, Diagnosis, Therapy, systematic review

## INTRODUCTION

Seventy-five percent of the human genome is transcribed into RNA, even as only three percent is transcribed into protein-coding mRNAs[(1)]. Based on their length, form, and location, non-coding RNAs (ncRNAs) have been divided into one-of-a-kind classes such as microRNAs (miRNAs)[(2)]which are small non-coding oligonucleotides that play a role in post-transcriptional regulation of gene expression[(3)]. Since their discovery, the presence of miRNAs in various organisms has been confirmed[(4,5)]. It is estimated that there are about 2,300 true human mature miRNAs[(6)]. miRNAs are important gene regulators that can direct entire cellular pathways through interaction with a wide range of target genes [(7)]. In most cases, miRNAs specifically align and bind to the 3' untranslated region of their target transcripts and cause mRNA degradation or translational repression by the RNA-induced silencing complex (RISC), thereby reducing protein levels. However, under certain conditions, miRNAs can also activate translation or regulate transcription[(2,8)]. Evidence shows that miRNAs regulate many basic cellular functions such as growth, differentiation, cell division, apoptosis, and metabolism through the control of biological processes, for this reason, disruption of miRNA function can lead to human diseases[(9,10)]. Many miRNAs can function as oncogenes or tumor suppressors, i.e., loss of function mutation and deletion of "suppressor-miRs" as well as genetic amplification, overexpression and gain of function mutation of "onco-miRs" are related to most cancers[(11-13)]. The same importance of miRNAs has also been seen in many human disorders.[(14)]. Many studies indicate the role of miRNAs in urological malignancies[(15,16)]. In addition to the tumor tissue itself, microRNA can be found in blood, saliva, and urine, which is a popular biological fluid for urological disease diagnosis and re-

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**Table 1.** miRNA expression and other features of the included studies

| MICRORNA | TYPE OF DISEASE | EXPRESSION | DETECTING METHOD | SENSITIVITY | SPECIFICITY | SPECIMEN | MRNA TARGET | PATHWAY | REFFERENCE |
|---|---|---|---|---|---|---|---|---|---|
| miR-92a-3p | OAB | Up | qRT-PCR | NM | NM | Urine | TrkA | NGF processing and signaling | P. G. Cammisotto 2022 |
| miR-98-5p | OAB | Up | qRT-PCR | AUC: 0.799 (CI: 0.710-0.889) 94.3% | 62.3% | Blood and Plasma | ADRB3 | Muscarinic pathway | E. Firat 2019 |
| let-7b-5p | OAB | Up | qRT-PCR | AUC: 0.625 (CI: 0.520-0.729) 78.6% | 50.8% | Blood and Plasma | ADRB3 | Muscarinic pathway | E. Firat 2019 |
| miR-92a-3p | OAB | Up | qRT-PCR | AUC: 0.615 (CI: 0.504-0.725) 92% | 38.5% | Blood and Plasma | ARHGEF10 | Muscarinic pathway | E. Firat 2019 |
| miR-142-3p | OAB | Up | qRT-PCR | AUC: 0.637 (CI: 0.536-0.738) 71.4% | 55.9% | Blood and Plasma | ROCK2 | Muscarinic pathway | E. Firat 2019 |
| miR-200c-3p | OAB | Up | qRT-PCR | AUC: 0.625 (CI: 0.520-0.729) 86.4% | 45.1% | Blood and Plasma | ROCK2 | Muscarinic pathway | E. Firat 2019 |
| miR-182 | NM | Up | NM | NM | NM | Tissue | NM | TGF-beta signaling | A. H. Gheinani 2014 [a] |
| miR-34c | NM | Up | NM | NM | NM | Tissue | NM | TGF-beta signaling | A. H. Gheinani 2014 [a] |
| has-miR-10a-5p | NM | Up | qRT-PCR | AUC: 0.81 | NM | Tissue | NM | NM | A. H. Gheinani 2017 |
| has-miR-212/132 | NM | Up | qRT-PCR | NM | NM | Tissue | NFAT | NM | A. H. Gheinani 2017 |
| has-miR-192 | NM | Up | qRT-PCR | NM | NM | Tissue | NM | NM | A. H. Gheinani 2017 |
| has-miR-34c | NM | Up | qRT-PCR | NM | NM | Tissue | NM | NM | A. H. Gheinani 2017 |
| has-miR-21 | NM | Up | qRT-PCR | NM | NM | Tissue | NM | NM | A. H. Gheinani 2017 |
| miR-212/132 | NM | Up | mRNA sequencing (mRNA-seq) | NM | NM | Tissue | TGF, WNT and cytoskeletal remodeling | TGF-beta and WNT-dependent signaling | A. Hashemi Gheinani 2014 [a] |
| miR-182 | NM | Up | mRNA sequencing (mRNA-seq) | NM | NM | Tissue | TGF, WNT and cytoskeletal remodeling | TGF-beta and WNT-dependent signaling | A. Hashemi Gheinani 2014 [a] |
| miR-34c | NM | Up | mRNA sequencing (mRNA-seq) | NM | NM | Tissue | TGF, WNT and cytoskeletal remodeling | TGF-beta and WNT-dependent signaling | A. Hashemi Gheinani 2014 [a] |
| has-miR-146a-5p | BO | Up | qRT-PCR | NM | NM | Tissue | NFkB | signaling molecules, including JUN, FOS, MAP3K14, and MYC | A. H. Gheinani 2017 |
| has-miR-146b-5p | BO | Up | qRT-PCR | NM | NM | Tissue | NFkB | signaling molecules, including JUN, FOS, MAP3K14, and MYC | A. H. Gheinani 2017 |
| has-miR-486-5p | BO | Up | qRT-PCR | NM | NM | Tissue | NFkB | signaling molecules, including JUN, FOS, MAP3K14, and MYC | A. H. Gheinani 2017 |
| miR-199a-5p | BPS/IC | Up | qRT-PCR | NM | NM | Tissue | MAP3K11, TGFB2, WNT2, ETS1, and | TGF-beta signaling | A. H. Gheinani 2019 [a] |

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|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | HGF | | |
| miR-1-3p | BPS/IC | Up | qRT-PCR | NM | NM | Tissue | NM | TGF-beta signaling | A. H. Gheinani 2019 [a] |
| miR-133a-3p | BPS/IC | Up | qRT-PCR | NM | NM | Tissue | NM | TGF-beta signaling | A. H. Gheinani 2019 [a] |
| has-miR-486-3p | BPS/IC | Up | qRT-PCR | NM | NM | Tissue | DDR1 | AMPK signaling pathway | S. Q. Yang 2023 |
| has-miR-20b-5p | BPS/IC | Up | qRT-PCR | NM | NM | Tissue | CCND1 | AMPK signaling pathway | S. Q. Yang 2023 |
| miR-21 | BPS/IC | Up | qRT-PCR | NM | NM | Tissue | RASGRP1, KLF5 and SC5D | lipopolysaccharide, IFNG, TNF, IL10, and IL4 | S. Liu 2019 |
| miR-4435-2HG | BPS/IC | Up | qRT-PCR | NM | NM | Tissue | AQP1 and TNFRSF13C | lipopolysaccharide, IFNG, TNF, IL10, and IL4 | S. Liu 2019 |
| miR-155HG | BPS/IC | Up | qRT-PCR | NM | NM | Tissue | FGF7, TDO2, ZNF385D, AKR1C1, WEE1, WWC1, VAV3, and CHST9 | lipopolysaccharide, IFNG, TNF, IL10, and IL4 | S. Liu 2019 |
| miR-199a | BPS/IC | Up | Taqman RT-PCR | NM | NM | Tissue | NK1R | NK1R and NK2R expression | V. Sanchez-Freire 2009 [a] |
| miR-320 | BPS/IC | Up | Taqman RT-PCR | NM | NM | Tissue | NK1R | NK1R and NK2R expression | V. Sanchez-Freire 2009 [a] |
| miR-192 | BPS/IC | Up | Taqman RT-PCR | NM | NM | Tissue | NK1R | NK1R and NK2R expression | V. Sanchez-Freire 2009 [a] |
| miR-328 | BPS/IC | Up | Taqman RT-PCR | NM | NM | Tissue | NK1R | NK1R and NK2R expression | V. Sanchez-Freire 2009 [a] |
| miR-212/132 | BOO | Up | NM | NM | NM | Tissue | NFAT | TGF-beta signaling | A. H. Gheinani 2014 [a] |
| miR-199a-5p | BOO | Up | qRT-PCR | NM | NM | Tissue | NM | TNF-a signaling | I. Koeck 2018 |
| miR-146a-5p | BOO | Up | qRT-PCR | NM | NM | Tissue | NM | TNF-a signaling | I. Koeck 2018 |
| miR-222-3p | BOO | Up | qRT-PCR | NM | NM | Tissue | NM | TNF-a signaling | I. Koeck 2018 |
| miR-30a-5p | BOO | Up | qRT-PCR | NM | NM | Tissue | NM | TNF-a signaling | I. Koeck 2018 |
| miR-7-5p | BOO | Up | qRT-PCR | NM | NM | Tissue | NM | TNF-a signaling | I. Koeck 2018 |
| miR-30e-5p | BOO | Up | qRT-PCR | NM | NM | Tissue | NM | TNF-a signaling | I. Koeck 2018 |
| miR-31-5p | BOO | Up | qRT-PCR | NM | NM | Tissue | NM | TNF-a signaling | I. Koeck 2018 |
| miR-1260a | BOO | Up | qRT-PCR | NM | NM | Tissue | NM | TNF-a signaling | I. Koeck 2018 |
| miR-7f-5p | BOO | Up | qRT-PCR | NM | NM | Tissue | NM | TNF-a signaling | I. Koeck 2018 |
| miR-146a-5p | BOO | Up | qRT-PCR | NM | NM | Tissue | NM | TNF-a signaling | I. Koeck 2018 |
| miR-146b-5p | BOO | Up | qRT-PCR | NM | NM | Tissue | NM | TNF-a signaling | I. Koeck 2018 |
| miR-21-5p | BOO | Up | qRT-PCR | NM | NM | Tissue | NM | TNF-a signaling | I. Koeck 2018 |
| miR-183-5p | BOO | Up | qRT-PCR | NM | NM | Tissue | NM | TNF-a signaling | I. Koeck 2018 |
| miR-22-3p | BOO | Up | qRT-PCR | NM | NM | Tissue | NM | TNF-a signaling | I. Koeck 2018 |
| miR-21 | BOO | Up | qRT-PCR | NM | NM | Tissue | NM | TNF-a signaling | I. Koeck 2018 |
| miR-146a/b | BOO | Up | qRT-PCR | NM | NM | Tissue | NM | TNF-a signaling | I. Koeck 2018 |
| let-7a | SUI | Up | qRT-PCR | NM | NM | Tissue | NM | apolipoprotein E, GRB2, Golgi SNAP receptor complex member 1, and glucosidase A acid | S. Liu 2014 |
| miR-101 | SUI | Up | qRT-PCR | NM | NM | Tissue | NM | apolipoprotein E, GRB2, Golgi SNAP receptor complex member 1, and glucosidase A acid | S. Liu 2014 |
| miR-125b-2 | SUI | Up | qRT-PCR | NM | NM | Tissue | NM | apolipoprotein E, GRB2, Golgi SNAP receptor | S. Liu 2014 |

| MICRORNA | TYPE OF DISEASE | EXPRESSION | DETECTING METHOD | SENSITIVITY | SPECIFICITY | SPECIMEN | MRNA TARGET | PATHWAY | REFFERENCE |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | complex member 1, and glucosidase A acid | |
| miR-190b | SUI | Up | qRT-PCR | NM | NM | Tissue | NM | apolipoprotein E, GRB2, Golgi SNAP receptor complex member 1, and glucosidase A acid | S. Liu 2014 |
| miR-892b | SUI | Up | qRT-PCR | NM | NM | Tissue | NM | apolipoprotein E, GRB2, Golgi SNAP receptor complex member 1, and glucosidase A acid | S. Liu 2014 |
| miR-376a-3p | BPO | Up | NM | NM | NM | Urine | NM | NM | M. Schneider 2019 [a] |
| miR-196a-5p | BPO | Up | NM | NM | NM | Urine | NM | NM | M. Schneider 2019 [a] |
| miR-363-3p | BPO | Up | NM | NM | NM | Urine | NM | NM | M. Schneider 2019 [a] |
| miR-21-5p | BPH | Up | qRT-PCR | AUC: 0.85 (CI: 0.75–0.95) 78.8% | 78.9% | Urine | PDE5 | NO/cGMP signaling | T. Tanaka 2018 |
| miR-301b-3p | BLUTD | Up | qRT-PCR | NM | NM | Urine | NM | NM | M. von Siebenthal 2021 |
| miR-10a-5p | NLUTD | Up | qRT-PCR | NM | NM | Urine | NM | NM | M. von Siebenthal 2021 |
| miR-363-3p | NLUTD | Up | qRT-PCR | NM | NM | Urine | NM | NM | M. von Siebenthal 2021 |
| miR-301b-3p | NLUTD | Up | qRT-PCR | NM | NM | Urine | NM | NM | M. von Siebenthal 2021 |
| miR-491-5p | OAB | Down | qRT-PCR | AUC: 0.763 (CI: 0.607- | NM | Urine | MMP-9 | NGF processing and signaling | P. G. Cammisotto |
| MICRORNA | TYPE OF DISEASE | EXPRESSION | DETECTING METHOD | SENSITIVITY | SPECIFICITY | SPECIMEN | MRNA TARGET | PATHWAY | REFFERENCE |
| | | | | 0.920) | | | | | 2022 |
| miR-592 | OAB | Down | qRT-PCR | AUC: 0.744 (CI: 0.586-0.903) | NM | Urine | P75NTR | NGF processing and signaling | P. G. Cammisotto 2022 |
| miR-139-5p | OAB | Down | qRT-PCR | AUC: 0.614 (CI: 0.508-0.719) 62.3% | 63.9% | Blood and Plasma | ROCK2 | Muscarinic pathway | E. Firat 2019 |
| miR-491-5p | OAB | Down | qRT-PCR | NM | NM | Urine and Blood | MMP9 | NGF synthesis | A. H. Mossa 2021 [a] |
| miR-592 | OAB | Down | qRT-PCR | NM | NM | Urine and Blood | p75NTR | p75NTR receptor synthesis | A. H. Mossa 2021 [a] |
| hsa-miR-199a-3p/hsamiR-3120-3p | DU | Down | NM | NM | NM | Tissue | NM | NM | A. H. Gheinani 2017 [a] |
| hsa-miR-429/hsa-miR-200b-3p | DU | Down | NM | NM | NM | Tissue | NM | NM | A. H. Gheinani 2017 [a] |
| has-miR-145 | DU | Down | qRT-PCR | NM | NM | Tissue | NM | phosphoinositide 3-kinase family | A. H. Gheinani 2017 |
| has-miR-143 | BO and DU | Down | qRT-PCR | NM | NM | Tissue | NM | signaling molecules, including JUN, FOS, MAP3K14, and MYC<br><br>phosphoinositide 3-kinase family | A. H. Gheinani 2017 |
| has-miR-497-5p | NM | Down | qRT-PCR | NM | NM | Tissue | SMAD3, JUN, FOSL1, TNFSF9, | NM | A. H. Gheinani 2017 |

| MICRORNA | TYPE OF DISEASE | EXPRESSION | DETECTING METHOD | SENSITIVITY | SPECIFICITY | SPECIMEN | MRNA TARGET | PATHWAY | REFFERENCE |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | CCND1 | | |
| has-miR-26-5p | NM | Down | qRT-PCR | NM | NM | Tissue | NM | NM | A. H. Gheinani 2017 |
| has-miR-29c-3p | NM | Down | qRT-PCR | NM | NM | Tissue | NM | NM | A. H. Gheinani 2017 |
| has-miR-1 | BOO | Down | qRT-PCR | NM | NM | Tissue | NM | HMGB1 signaling | A. H. Gheinani 2017 |
| has-miR-133 | BOO | Down | qRT-PCR | NM | NM | Tissue | NM | HMGB1 signaling | A. H. Gheinani 2017 |
| has-miR143/145 | BOO | Down | qRT-PCR | NM | NM | Tissue | NM | HMGB1 signaling | A. H. Gheinani 2017 |
| miR-199a-5p | BOO | Down | qRT-PCR | NM | NM | Tissue | NFkB | TNF-a signaling | A. Hashemi Gheinani 2018 [a] |
| miR-424-5p | BOO | Down | qRT-PCR | NM | NM | Tissue | NFkB | TNF-a signaling | A. Hashemi Gheinani 2018 [a] |
| miR-149-5p | BOO | Down | qRT-PCR | NM | NM | Tissue | NFkB | TNF-a signaling | A. Hashemi Gheinani 2018 [a] |
| miR-1180 | BOO | Down | qRT-PCR | NM | NM | Tissue | NM | TNF-a signaling | I. Koeck 2018 |
| miR-199a-3p | BOO | Down | qRT-PCR | NM | NM | Tissue | NM | TNF-a signaling | I. Koeck 2018 |
| miR-199a-5p | BOO | Down | qRT-PCR | NM | NM | Tissue | NM | TNF-a signaling | I. Koeck 2018 |
| miR-199b-3p | BOO | Down | qRT-PCR | NM | NM | Tissue | NM | TNF-a signaling | I. Koeck 2018 |
| miR-7-5p | BOO | Down | qRT-PCR | NM | NM | Tissue | NM | TNF-a signaling | I. Koeck 2018 |
| miR-26b | BOO | Down | qRT-PCR | NM | NM | Tissue | NM | TNF-a signaling | I. Koeck 2017 [a] |
| miR-205HG | BPS/IC | Down | qRT-PCR | NM | NM | Tissue | SCNN1A, DST, and FUT9 | CBX5, beta-estradiol, ESR2, ZEB1, and WISP2 | S. Liu 2019 |
| miR-328 | BPS/IC | Down | Taqman RT-PCR | NM | NM | Tissue | NK1R | NK1R and NK2R expression | V. Sanchez-Freire 2009 [a] |
| miR-320 | BPS/IC | Down | Taqman RT-PCR | NM | NM | Tissue | NK1R | NK1R and NK2R expression | V. Sanchez-Freire 2009 [a] |
| miR-124 | SUI | Down | qRT-PCR | NM | NM | Tissue | GRB2 | apolipoprotein E, | S. Liu 2014 |
| MICRORNA | TYPE OF DISEASE | EXPRESSION | DETECTING METHOD | SENSITIVITY | SPECIFICITY | SPECIMEN | MRNA TARGET | PATHWAY | REFFERENCE |
| | | | | | | | | GRB2, Golgi SNAP receptor complex member 1, and glucosidase A acid | |
| miR-330-3p | SUI | Down | qRT-PCR | NM | NM | Tissue | BICD2 | apolipoprotein E, GRB2, Golgi SNAP receptor complex member 1, and glucosidase A acid | S. Liu 2014 |
| miR-485-3p | SUI | Down | qRT-PCR | NM | NM | Tissue | NM | apolipoprotein E, GRB2, Golgi SNAP receptor complex member 1, and glucosidase A acid | S. Liu 2014 |
| miR-517b | SUI | Down | qRT-PCR | NM | NM | Tissue | NM | apolipoprotein E, GRB2, Golgi SNAP receptor complex member 1, and glucosidase A acid | S. Liu 2014 |
| miR-523 | SUI | Down | qRT-PCR | NM | NM | Tissue | NM | apolipoprotein E, GRB2, Golgi SNAP receptor complex member 1, and glucosidase A acid | S. Liu 2014 |
| miR-589 | SUI | Down | qRT-PCR | NM | NM | Tissue | NM | apolipoprotein E, GRB2, Golgi SNAP receptor complex member 1, and glucosidase | S. Liu 2014 |

| MICRORNA | TYPE OF DISEASE | EXPRESSION | DETECTING METHOD | SENSITIVITY | SPECIFICITY | SPECIMEN | MRNA TARGET | PATHWAY | REFFERENCE |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | A acid | |
| miR-93 | SUI | Down | qRT-PCR | NM | NM | Tissue | STAT3 | apolipoprotein E, GRB2, Golgi SNAP receptor complex member 1, and glucosidase A acid | S. Liu 2014 |
| miR-93 | SUI | Down | qRT-PCR | NM | NM | Tissue | CAPN2 | Calpain-2 expression | S. H. Yang 2018 |
| miR-10a-5p | BLUTD | Down | qRT-PCR | NM | NM | Urine | NM | NM | M. von Siebenthal 2021 |
| miR-30 | UTI | Down | qRT-PCR | NM | NM | Urine and Blood | NM | NM | J. Al fatleh 2023 |

**Abbreviations:** BOO, Bladder outlet obstruction; LUTS, Lower urinary tract symptoms; DO, Detrusor overactivity; DU, Detrusor underactivity; OAB, Overactive bladder; BO, Bladder outlet obstruction Without detrusor overactivity; BPS/IC, Bladder pain syndrome/interstitial cystitis; SUI, Stress urinary incontinence; BPO, Benign prostatic obstruction; BPH, Benign prostatic hyperplasia; BLUTD, Benign prostatic obstruction-induced LUTD; NLUTD, Neurogenic lower urinary tract dysfunction; VUAS, Vesicourethral anastomotic stricture; NM, Not-Mentioned.
[a] Abstract

search, due to its ease of collection and non-invasive nature[17,18]. The expression levels of miRNAs maybe useful as diagnostic markers[19,20] But few studies have focused on the expression of miRNA types in benign urologic diseases. The aim of this systematic review is to provide information about the expression of microRNAs and their role in benign urologic diseases.

## MATERIALS AND METHODS

The systematic review was conducted in accordance with the PRISMA guidelines (21), and is registered in PROSPRO (CRD42022382507).

### *Methodology for systematic review*

#### *Search strategy*

A methodological search of the electronic databases PubMed, Scopus, Web of Science, Embase, and ProQuest was performed on the 7th of January 2024 for relevant studies. This search included both plain words and MeSH terms, ensuring all publications with the keywords and related terms in their title or body were included in the search result. The MeSH terms associated with the keywords were: ((((((bladder[Title/Abstract]) OR (urinary[Title/Abstract])) NOT ((((("neoplasms"[MeSH Terms]) OR (neoplasm*[Title/Abstract])) OR (cancer*[Title/Abstract])) OR (tumor*[Title/Abstract]))) OR (neurogenic[Title/Abstract])) OR ((("lower urinary tract symptoms"[MeSH Terms]) OR ("urinary incontinence"[MeSH Terms])) OR ((lower urinary tract [Title/Abstract]) OR (lower urinary tract symptom[Title/Abstract]) OR (urinary incontinence[Title/Abstract]) OR (LUTS[Title/Abstract])))) OR ((((detrusor[Title/Abstract])) OR (("urinary bladder, overactive"[MeSH Terms]))) OR (overactive bladder[Title/Abstract]))) AND ((((("micrornas"[MeSH Terms]) OR (microRNA[Title])) OR (miRNA[Title])) OR (miR[Title])).

#### *Study eligibility*

The search results were tabulated, and duplicates were removed. Two authors independently reviewed the articles for eligibility from the titles and abstracts. Then, the full text of each article was retrieved and assessed for final eligibility independently by any authors. Any discrepancies between the authors concerning eligibility were resolved by consensus among authors. The articles that met the following inclusion criteria were considered: the study measured the expression of miRNA in tissues or circulation of patients with benign urological diseases, including benign prostate hyperplasia (BPH) or benign prostate enlargement (BPE), overactive bladder (OAB), bladder outlet obstruction (BOO), and other benign states (not xenograft or other animal models); the study performed analysis to examine the association of miRNA with the outcome.

Studies were excluded if tested the prognostic role of miRNA on malignancies of the urinary tract or host genes or target genes instead of the miRNA itself; or if the study tested the prognostic role of miRNA in combination with non-miRNA markers such as clinical factors, genes, or proteins; and if they were meta-analysis, review, commentary, letter or duplicate publication.

#### *Data extraction*

After selecting all collected records, two investigators summarized data that met the inclusion criteria into a customized Excel spreadsheet. A third author checked the extracted data for completeness and accuracy. Any disagreements were resolved by consensus among the authors. Data extraction from the selected publications was done using a standardized table by authors independently. For each study, the extracted data are reported in **Table 1** as follows: Reference, Publication Year, Other biospecimen, Urine Specimen, Centrifuge Protocol, Study Cohort, Method, Reference Gene, miRNAs, Multiple-miRNAs Signature, and Diagnostic Power

**Table 2.** up and down regulated miRNA in evaluated studies.

| Disease | Upregulated | Downregulated |
|---|---|---|
| OAB | miR-92a-3p | miR-491-5p |
| | miR-98-5p | miR-592 |
| | miR(92a)3p | miR(139)5p |
| | miR(142)3p | miR(491)5p |
| | miR(200c)3p | miR-592 |
| BOO | miR-212/132 | has-miR-1 |
| | miR-199a-5p | has-miR-133 |
| | miR-146a-5p | has-miR143/145 |
| | miR-199a-5p | miR-199a-5p |
| | miR-146a-5p | miR-424-5p |
| | miR-222-3p | miR-149-5p |
| | miR-30a-5p | miR-1180 |
| | miR-7-5p | miR-199a-3p |
| | miR-30e-5p | miR-199a-5p |
| | miR-31-5p | miR-199b-3p |
| | miR-1260a | miR-7-5p |
| | miR-7f-5p | miR-26b |
| | miR-146a-5p | |
| | miR-146b-5p | |
| | miR-21-5p | |
| | miR-183-5p | |
| | miR-22-3p | |
| | miR-21 | |
| | miR-146a/b | |
| BO | has-miR-146a-5p | miR-199a-5p |
| | has-miR-146b-5p | miR-133a-3p |
| | has-miR-486-5p | miR-133a-3p |
| BPS/IC | miR-4435-2HG | miR-205HG |
| | miR-21 | miR-328 |
| | miR-155HG | miR-320 |
| | miR-199a | |
| | miR-320 | |
| | miR-192 | |
| | miR-328 | |
| | has-miR-486-3p | |
| | has-miR-20b-5p | |
| SUI | let-7a | miR-124 |
| | miR-101# | miR-485-3p |
| | miR-125b-2 | miR-330-3p |
| | miR-190b | miR-517b |
| | miR-892b | miR-523 |
| | | miR-589 |
| | | miR-93# |
| | | miR-93 |
| BPO | miR-376a-3p | |
| | miR-196a-5p | |
| | miR-363-3p | |
| UTI | | miR-30 |
| BPH | miR-21-5p | |
| BLUTD | miR-301b-3p | miR-10a-5p |
| NLUTD | miR-10a-5p | |
| | miR-363-3p | |
| | miR-301b-3p | |
| DU | | hsa-miR-199a-3p/hsamiR-3120-3p |
| | | hsa-miR-429/hsa-miR-200b-3p |
| | | has-miR-145 |
| BO, DU | | has-miR-143 |

(Area under the ROC Curve).

Methodological quality of the included studies

The quality of each article was evaluated by the quality assessment checklists of the Joanna Briggs Institute (JBI). All disagreements about the collected data were adequately debated by the investigators, and they arrived at a final consensus.

## RESULTS

### *Study Selection*

A flowchart of the literature search and the detailed selection process of the articles are reported in **Figure 1**. A total of 3,224 records related to miRNAs and their diagnostic significance in urological diseases were retrieved from public databases. Of these, 1095 reports were excluded as duplicates. Next, the remaining 2,129 records were screened based on their titles and abstracts. A total of 2,016 records were excluded because they were ineligible after reading the titles and 71 were omitted after reading the abstracts. Thus, a total of 42 records were selected for full-text reading. Of these, we further excluded 16 studies due to their methodological/comparative/methylation/on malignant conditions. Finally, we identified 28 records for our systematic study.

### *General Findings*

The main features of each selected study are shown in **Table 1**. The eligible 28 articles were published between 2009 and 2024 About 55% of the studies were

**Table 3.** The reported outcomes in the included studies

| Authors | Outcome |
|---|---|
| J. Al fatleh | Downregulation of sRNA (As1974) in resistance suggested that As1974 could be potential marker to transform the bacteria from resistance to sensitive and downregulate Micro-30 in urine and blood samples compared to healthy subjects.<br>The host immune response to uropathogenic P. aeruginosa has been shown to be significantly influenced by miRNA. |
| P. G. Cammisotto | The article found that patients with OAB had specific demographic and symptom characteristics compared to a control group. The downregulation of miR-491-5p and miR-592 correlated with the severity of OAB symptoms. The study also identified potential mechanisms for the involvement of these miRNAs in OAB through their regulation of proteins related to OAB |
| E. Firat | No significant correlation was determined between the OAB symptom score and miRNA expression levels |
| A. H. Gheinani | Compared to the Hunner's ulcerative type IC, activation of the immune pathways was modest in non-ulcerative BPS, limited to neutrophil chemotaxis and IFN-γ-mediated signaling. EIF2 Signaling and Regulation of eIF4 and p70S6K Signaling, activated in response to cellular stress, were among the most significantly regulated processes during BPS. Leukotriene Biosynthesis nociceptive pathway, important in inflammatory diseases and neuropathic pain, was also significantly activated. |
| A. H. Gheinani | The article identified co-expressed miRNA sub-networks associated with BOO-induced bladder dysfunction and their functional associations. The down-regulation of hsa-miR-199a-3p/ hsamiR-3120-3p and hsa-miR-429/hsa-miR-200b-3p miRNA clusters were found to be necessary and sufficient to determine the functions of all miRNA regulated pathways in the UA group. Elucidating the down-regulation mechanisms of these miRNA clusters may help determine the "point of no return" for the loss of bladder function during BOO. |
| A. H. Gheinani these | This article revealed miRNAs that discriminated between the urodynamically-defined states of BOO-induced LUTD with high sensitivity and specificity. ROC analysis showed that miRNAs have promising diagnostic performances in DO, BO and UA patients and can be potentially used as a tool to evaluate disease progression. |
| A. H. Gheinani | MiRNAs play a key role in lower urinary tract dysfunction through their ability to regulate fundamental pathways such as TGF-beta, WNT, cytoskeletal remodeling and cell adhesion. The results define miRNA expression signatures that characterize different states of LUT dysfunction during BOO. |
| A. H. Gheinani | highly regulated miRNAs:<br>in BOO patients: miR-1, miR-146b-5p, miR-21-3p, miR-146a-5p, miR-486-5p<br>in DO patients: miR-132-3p, miR-335-5p, miR-374a-5p, miR-182-5p, miR-26b-5p<br>in BO patients: miR-146b-5p, miR-21-3p, miR-486-5p, miR-486-3p, miR-146a-5p<br>in UA patients: miR-146b-5p, miR-146a-5p, miR-21-3p, miR-155-5p, miR-142-5p<br>19 upregulated and 17 downregulated BOO miRNAs (221 and 215 mRNA targets, respectively)<br>Only 25 targets (11%) of upregulated miRNAs were downregulated, whereas 194 targets (90%) of downregulated miRNAs were upregulated.<br>Muscle-specific miRNAs, including miR-1, miR-133, and miR-143/145, were downregulated in BOO, BO and UA groups but increased in DO group. |
| A. Hashemi Gheinani | Multiple co-expressed miRNAs may cooperatively influence biological processes and a contractile urodynamic phenotype in the underactive bladder. Elucidating the down-regulation mechanisms of these miRNA clusters may help determine the "point of no return" for the loss of bladder function during BOO.<br>(The appropriately regulated targets of hsa-miR-199a-3p/hsa-miR-3120-3p and hsa-miR-429/hsa-miR-200b-3p clusters constituted the majority of miRNA-regulated pathway elements in the UA state.) |
| A. Hashemi Gheinani | Bladder biopsies of BPS patients have specific miRNA and mRNA profiles, clearly different from controls and BOO-induced LUTD.<br>(Pathway analysis in BPS revealed dysregulation of neuroinflammation, chemokines, Wnt, GDNF, ILK, cdc-42, production and activation of TGF-beta pathways.) |
| A. Hashemi Gheinani | Different states of bladder outlet obstruction have specific miRNA and mRNA profiles |
| A. Hashemi Gheinani | Specific miRNAs allow discrimination between urodynamically-defined states of BOO-induced LUTD with high sensitivity and specificity.<br>These miRNAs have promising diagnostic performances in DO, BO and UA. |
| A. Hashemi Gheinani | MiRNAs play a key role in lower urinary tract dysfunction through their ability to regulate fundamental pathways such as TGF-beta, WNT, cytoskeletal remodeling and cell adhesion. The results define miRNA expression signatures that characterize different states of LUT dysfunction during BOO. |
| A. Hashemi Gheinani | Compensatory up-regulation of miR-199a-5p and other miRNAs, inhibited by TNF-a might have a beneficial effect reducing the proliferative and fibrotic changes in bladder outlet obstruction bladders.<br>(629 targets of 15 down-regulated miRNAs were up-regulated, whereas only 352 targets of 13 elevated miRNAs were decreased)<br>(269 elevated mRNA targets of down-regulated miRNAs are implicated in regulation of 80% of all TNF-induced pathways) |
| J. M. Hotaling | An intergenic region on chromosome 10 between a microRNA and SH2D4B: (P = 1.7x10-7, OR=2.0 (1.8-5.0), MAF=5.9%, and on chromosome 2 in an intron of GPR39: P = 1.9x10-7, OR=2.2 (1.6 2.9), MAF=25.3%. GPRs) are involved in signaling.<br>Preliminary data demonstrates a potential role for a genetic contribution to LUTS in men with T1D. |
| I. Koeck | Five miRNAs (miR-361-5p, miR-582-5p, miR-424-5p, miR-27a-3p, and miR-503-5p) were increased in UE cells and decreased in SMCs.<br>Three miRNAs (miR-141-3p, miR-135b-5p, and miR-220b-3p) were significantly (up to 10-fold read number differences) more abundant in UE cells (Figure 2C), whereas 14 were en riched in SMCs |
| I. Koeck | TNF-a is important in the regulation of BOO-specific miRNAs.<br>miRNAs linking TNF-a signaling and fibrosis identified.<br>Modulation of expression levels of TNF-α-regulated miRNAs in cell-based models of human bladder using miRNA-overexpression and inhibition will elucidate their role in organ remodeling and lead to novel therapeutic approaches for BOO induced LUTD. |
| S. Liu | The present study identified PNOC, SSTR1, and FPR3 as key genes.<br>Upregulated microRNAs such as miR-21, miR-4435-2HG, and miR-155HG and downregulated miR-205HG were identified as key microRNAs in IC/PBS.<br>The top upstream regulators of upregulated genes were lipopolysaccharide, IFNG, TNF, IL10, and IL4, while CBX5, beta-estradiol, ESR2, ZEB1, and WISP2 were the top upstream regulators of downregulated genes. |
| X. Liu | All three predicated target genes, are associated with neurodegenerative conditions, indicating the significant role of neurodegenerative mechanisms in the etiology of SUI |
| bb | The detection ofmiR-491-5p and miR-592 in urine could be a useful and non-invasive tool for the diagnosis of OAB syndrome. |
| T. Overholt | There are significant molecular differences in IC/BPS associated with low vs non-low bladder capacity phenotype, and additional molecular findings that further define the phenotype of the patients with Hunners lesion. |
| V. Sanchez-Freire | In contrast to acute inflammatory states, continuous exposure to mediators of neurogenic inflammation in patients with IC/PBS induces re-modelling of the receptor signaling complex. MicroRNAs may play a role in the pathogenesis of IC/ PBS, demonstrated by a direct correlation between expression of miR-328 and down-regulation of NK1R in a cell-based model. |
| M. Schneider | Based on this study, a small panel of representative miRNAs, which can be further explored to develop a non-invasive diagnostic test for BOO, is available. |
| T. Tanaka | Urine expression patterns of miRNAs associated with endothelial function possibly correlate with effectiveness of tadalafil treatment in mLUTS/BPH patients. Particularly, the baseline urine levels of miR-21-5p could be a promising biomarker predictive for its response. (There are no significant differences between responders and non-responders in alterations of either urine miR-126-5p or miR-155-5p due to tadalafil administration) |
| M. von Siebenthal | There were no significant age-related differences in the total amount of proteins and RNA, there was a slight increase in RNA packaged in uEVs in the young patients (there was a significant increase in miR-374a-5p and miR-424-5p in the total RNA of the young).<br>A three urinary miRNA signature (miR-10a-5p, miR-301b-3p and miR-363-3p) could discriminate between controls and patients with LUTD (BLUTD and NLUTD). |
| T. S. Worst | The far most deregulated miRNA in WNT2B knockdown cells was miR-1246.<br>Upon WNT2B knockdown, the expression of miR-1246 was elevated 2.11-fold.<br>The data presented here shows a consecutive overexpression of miR-1246 after WNT2B knockdown.<br>9 deregulated miRNAs upon WNT2B knockdown: miR-1246, miR-199b-5p, miR-376b-3p, miR-299-5p, miR-299-3p, miR-337-5p, miR-3151-5p, miR-376a-3p, miR-553 |
| S. Q. Yang | This study successfully established a circRNA-miRNA-mRNA network, identified IFIT3 and RSAD2 as hub genes, and found that circ.5863 can reduce inflammation damage in IC/BPS. |
| S. H. Yang | miR-93 mediated collagen expression in stress urinary incontinence via calpain-2 |

**Table 4.** Quality assessment of the included studies based on JBI critical appraisal tool.

| Study | Q1 | Q2 | Q3 | Q4 | Q5 | Q6 | Q7 | Q8 | Q9 | Q10 | Overall |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Case-Control | | | | | | | | | | | |
| S. H. Yang | Yes | Yes | Yes | Yes | Yes | Yes | Unclear | Yes | Yes | Yes | Included |
| S. Q. Yang | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Included |
| M. von Siebenthal | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Included |
| F. Urabe (letter to editor) | Yes | Yes | Yes | Yes | Yes | Yes | Unclear | Yes | Unclear | Yes | Included |
| M. Schneider (ABSTRACT) | Yes | Yes | Yes | Yes | Yes | Unclear | Unclear | Unclear | Unclear | Yes | Included |
| V. Sanchez-Freire (ABSTRACT) | Yes | Yes | Yes | Yes | Yes | Unclear | Unclear | Yes | Unclear | Yes | Included |
| X. Liu | Yes | Yes | Yes | Yes | Yes | Yes | Unclear | Yes | Unclear | Yes | Included |
| S. Liu | Yes | Yes | Yes | Yes | Yes | Yes | Unclear | Yes | Unclear | Yes | Included |
| J. M. Hotaling (ABSTRACT) | Yes | Yes | Yes | Yes | Yes | No | No | Unclear | Unclear | Unclear | Included |
| A. Hashemi Gheinani 2014 (ABSTRACT) | Yes | Unclear | Yes | Yes | Yes | Unclear | Unclear | Yes | Unclear | Yes | Included |
| A. Hashemi Gheinani 2016 (ABSTRACT) | Yes | Unclear | Yes | Yes | Yes | Unclear | Unclear | Yes | Unclear | Yes | Included |
| A. Hashemi Gheinani 2015 (ABSTRACT) | Yes | Unclear | Yes | Yes | Yes | Unclear | Unclear | Yes | Unclear | Unclear | Included |
| A. Hashemi Gheinani 2019 (ABSTRACT) | Yes | Unclear | Yes | Yes | Yes | Unclear | Unclear | Yes | Unclear | Unclear | Included |
| A. Hashemi Gheinani 2017 (ABSTRACT) | Yes | Unclear | Yes | Yes | Yes | Unclear | Unclear | Yes | Unclear | Yes | Included |
| A. H. Gheinani 2017 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Unclear | Yes | Included |
| A. H. Gheinani 2014 (abstract) | Yes | Unclear | Yes | Yes | Yes | Unclear | Unclear | Yes | Unclear | Yes | Included |
| A. H. Gheinani 2016 (abstract) | Yes | Unclear | Yes | Yes | Yes | Unclear | Unclear | Yes | Unclear | Yes | Included |
| A. H. Gheinani 2021 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Unclear | Yes | Included |
| A. H. Mossa (abstract) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Unclear | Yes | Included |
| Cohort | | | | | | | | | | | |
| T. Overholt (abstract) | Yes | Yes | Yes | Unclear | Unclear | Yes | Unclear | Yes | Unclear | Yes | Included |
| I. Koeck 2018 | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Included |
| A. Hashemi Gheinani 2018 (abstract) | Unclear | Yes | Yes | Unclear | Unclear | Yes | Yes | Yes | Unclear | Unclear | Included |
| A. Hashemi Gheinani 2017 (abstract) | Yes | Yes | Yes | Unclear | Unclear | Yes | Unclear | No | Unclear | Unclear | Included |
| Cross-Sectional | | | | | | | | | | | |
| T. S. Worst | Yes | Yes | Yes | Yes | Unclear | Unclear | Yes | Yes | | | Included |
| T. Tanaka | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | | | Included |
| E. Firat Yes | Yes | Yes | Yes | Unclear | Unclear | Yes | Yes | | | Included | |
| J. Al fatlah | Yes | Yes | Yes | Yes | Yes | Unclear | Unclear | Yes | | | Included |

performed in Switzerland, 10% in China, 7% in Japan, Canada, and Germany, and 3% in Turkey, the UK, the USA, and Iraq, with a total population of N = 1530 enrolled subjects (609 participants in case group, and 721 in control in 21 studies; in 9 (this should be 6 + 1) studies, sample size did not mention). Of the reviewed articles, the largest cohorts were enrolled in one study, with a total of 630 subjects.

The included studies were on BOO/DO/DU in eight eligible studies, IC/ BPS in five, OAB, and BPO/LUTS in three studies, SUI, BOO/LUTS in two studies, and UTI, LUTS, IC/ BPS /BOO, BOO, IC/ BPS/SUI, POP, and Vesicourethral anastomotic stricture (VUAS) in one study.

Most of the studies validated by reverse transcription polymerase chain reaction (RT-qPCR) and a priori signature of miRNAs to find the best miRNAs for diagnostic purposes. Fluorescence Staining was mentioned only in one study, where the overall high levels of the relative fluorescence of miRNA 15a were detectable immediately before the operation, which decreased significantly (ie, decreased to nearly 0 at hospital release) [22]. Other characteristics of the included studies, including Housekeeping Gene, Sample Collecting Time, Ethnicity, Sensitivity, and Specificity are mentioned in **Tables 1-3**. About 32% of the studies screened urine, while in the remained studies other biological samples such as blood, or tissue were assessed.

### *Quality of the Selected Articles*

JBI appraisal checklists (APPENDIX) based on the study design (Cohort, Case-control, and cross-sectional), were used to assess the diagnostic accuracy of the eligible studies. The risk of bias for the included articles is shown in Table 4. We found that all 28 reports met the criteria for a high-quality score. Specifically, they were well described and adequately answered the quality questions. Regarding the risk of bias, more studies had a representative spectrum of patients, including clear selection criteria.

miRNAs Identified as Diagnostic Markers in benign urological diseases

Different markers were associated with urological disease (**Tables 1-3**): most of them were found to be upregulated. As reported in **Tables 1 and 2**, these miRNAs were clustered based on the frequency of their finding in the manuscripts. The most frequently associated miRNA was 92a-3p identified which was found upregulated in OAB diagnosis. In BOO, miR-146a-5p was identified to be the most upregulated miRNA. has-miR-146a-5p was the most upregulated in BO. For other benign conditions, different miRNAs were reported. 491-5p miRNAs, were recognized as the most deregulated in OAB-related studies (**Tables 1 and 2**). We expected other miRNAs to have the same trend in the OAB studies. In SUI miR-93 was the most frequent downregulated miRNA. The other reported miRNAs had similar frequencies (**Tables 1-3**).

## DISCUSSION

Different markers are associated with urological disease. In our systematic review, the linking of miRNAs in the pathophysiology of benign urological conditions, including OAB, BOO, BPS/IC, LUTD, or other conditions was evaluated. Most of the miRNAs were found to be upregulated. These miRNAs were clustered based on the frequency of their finding in the manuscripts. The most frequently associated miRNA was 92a-3p identified which was found upregulated in OAB diagnosis. In BOOmiR-146a-5p was identified to be upregulated and in BO, has-miR-146a-5p was upregulated. For other benign conditions, different miRNAs were reported. In contrast, 491-5p and 592 miRNAs, were found deregu-

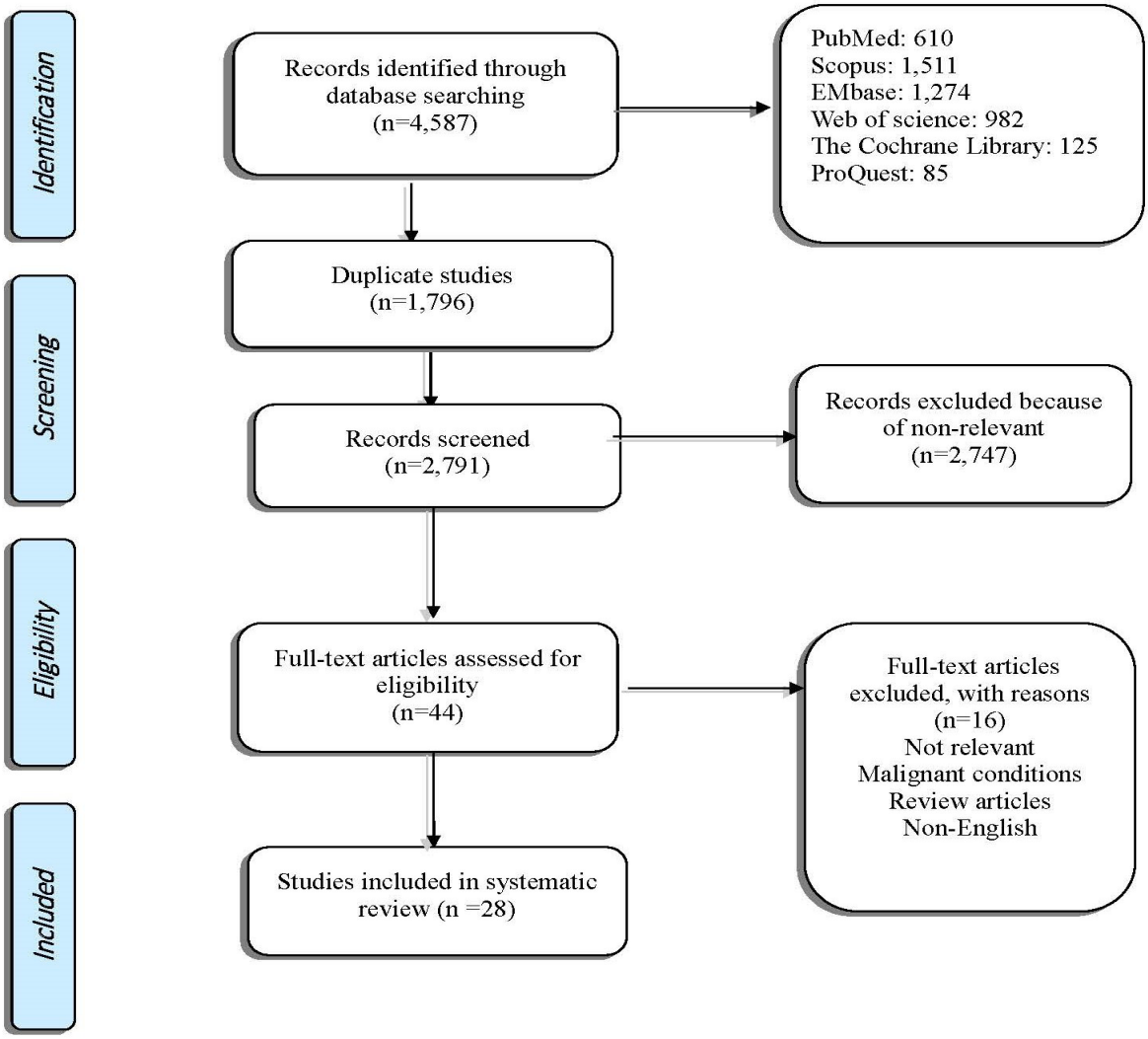


**Figure 1.** PRISMA flow diagram

lated in OAB related studies. We expected other miRNAs to have the same trend in the OAB studies. SUI miR-93 was the most frequent downregulated miRNA. The other reported miRNAs had similar frequencies.

OAB is a common urological condition characterized by urinary urgency, frequency, and nocturia, often accompanied by urinary incontinence. It significantly affects the quality of life of affected individuals. The pathophysiology of OAB involves alterations in the detrusor smooth muscle contractility, urothelial dysfunction, and neurogenic factors. However, the underlying molecular mechanisms are not fully understood. Recent studies have investigated the role of miRNAs in OAB and have identified several dysregulated miRNAs in OAB patients compared to healthy controls. These dysregulated miRNAs have been found to target genes involved in bladder smooth muscle contraction, inflammation, and nerve signalling pathways. Furthermore, miRNAs are differentially expressed in the urine of OAB patients, suggesting their potential as non-invasive biomarkers for OAB diagnosis and monitoring. Several studies have reported specific miRNA signatures that can distinguish OAB patients from healthy controls or differentiate between different subtypes of OAB. These findings hold promise for the development of miRNA-based diagnostic tests for OAB. In addition to their diagnostic potential, miRNAs also represent attractive therapeutic targets for OAB. Modulating the expression of dysregulated miRNAs may help restore normal bladder function and alleviate OAB symptoms. Despite the progress made in understanding the role of miRNAs in OAB, several challenges remain. First of all, the functional significance of dysregulated miRNAs in OAB pathogenesis needs to be further elucidated. It is crucial to determine the specific target genes regulated by these miRNAs and their impact on bladder physiology. Additionally, large-scale clinical studies are needed to validate the diagnostic and prognostic value of miRNAs in OAB patients[23,24].

The most prevalent benign urological disease in aging men, Benign Prostatic Hyperplasia (BPH) affects up to 90% of men by their ninth decade of life. It affects more or less 8% of men in their fourth decade of life[25]. BPH can be defined as epithelial glandular elements and the proliferation of fibroblasts near the urethra causes a change in the size of prostate gland so-called Benign Prostatic Enlargement (BPE)[26,27]. Men with BPH may have no symptoms, show improvement with dietary or

lifestyle modifications, or need medication and probably surgical therapy. As men mature, symptoms become more frequent. Obstructive symptoms, irritative symptoms, or both could be seen in men with symptomatic BPH[27]. BPE, which can contribute to lower urinary tract symptoms (LUTS) that comprise a wide spectrum of symptoms and etiologies, develops in 50% of men with BPH[26]. BPH may cause LUTS typified by continual urination, delay, and a puny flow, mostly in those over 40 years old[28,29]. Men with LUTS frequently have less physical and mental health, as well as lower quality of life[30]. In studies, it has been stated that BOO may lead to LUTS in 24% of men, and its symptoms could be caused by Benign Prostate Obstruction (BPO) due to BPH[31]. Benign prostate growth is ineffective until it leads to compression of the urethra and interruption of urine flow[32]. Bladder Outlet Obstruction (BOO) is a condition that causes growth and fibrosis of the bladder and about one-third of all men over the age of 60 are affected by it. In animal studies about BOO, it has been demonstrated that rat model showed a six-fold growth of the bladder during six weeks[33]. BOO in fetus, which can lead to atypical renal development, lung hypoplasia, thickening of the bladder wall, megacystis, and bilateral hydronephrosis with or without cystic dysplasia of the renal parenchyma, mainly due to the congenital absence or narrowing of the posterior valves of the urethra, has both a high prevalence and a high perinatal mortality rate[34] Reports in retrospective studies conducted on BOO in women indicate that women with LUTS have an obstruction rate between 2.7 and 8%. While BOO in women is largely undiagnosed and the reason could be the lack of regulatory parameters to diagnose this disease[35]. The codification of miRNAs to create treatments for urological disorders has drawn more attention in recent years. It is not surprising that miRNAs are involved in nearly every important cellular process, including proliferation, differentiation, migration, apoptosis, and stemness maintenance[36], given that each miRNA can modulate the expression of multiple messenger RNAs (mRNAs) and that each mRNA may be targeted by several different miRNAs. There is a growing body of research on the potential application of miRNAs as biomarkers for cancer diagnosis, prognosis, and therapy[37], including in prostate cancer[38]. It has been shown that miRNA expression levels are correlated with clinicopathologic factors[39-41]. Specific miRNAs' expression levels in clinical samples of prostate tissue may be employed as markers for medication selection and response, as well as for the detection, prognosis, and monitoring of cancer[36]. There is growing evidence that BPH is a risk factor for several prostate malignancies. Fast-growing BPH is associated with a higher chance of developing prostate cancer and an increased likelihood that such cancer will be of a high stage or grade, two factors that are both predictive and prognostic for prostate cancer[42]. We predicted that patients with BPH might also have miRNAs expressed in prostate cancer given the pathophysiological connections between BPH and prostate cancer. All studies examining the role of miRNAs in prostate cancer that used BPH patients as a control group were taken into account in a systematic review of the literature[43]. The RRA approach was used to assess the ranked lists of miRNAs generated for each study and revealed that miR-221 was the only miRNA significantly linked to BPH ($p$ = 0.013). For miR-221, only seven research provided data. By using a funnel plot and Egger's test, the seven included papers' publication bias was evaluated. In the total analysis of the seven included papers, publication bias was found ($p$ < 0.01). Egger's test, however, could not find any proof of publication bias after trim and fill technique[44] ($p$ = 0.76). The five miRNAs miR-32, miR-148a, miR-99a, miR21, and miR-221 that are controlled by dihydrotestosterone—which is advantageous for the prostate's development[45]—were discovered by Jalava et al. In castration-resistant prostate cancer, miR-32, miR-590-5p, miR-148a, and miR-21 were significantly overexpressed, while miR-99a, miR-99b, and miR-221 were significantly under-expressed. In contrast to BPH, Liu et al.[46] found that miR-182 expression was dramatically elevated in prostate cancer tissues and four cell lines, while miR-345, miR145, miR-221, miR-27b, and miR-378 were downregulated. Furthermore, miRNA-221 was downregulated in individuals with higher Gleason scores, advanced-stage tumors, and positive lymph nodes in all studies examining the relationship between miRNA-221 and prostate cancer[46-52]. mRNA and miRNA transcriptome sequencing of bladder samples from human patients with various urodynamically characterized states of bladder outlet obstruction (BOO) was recently described by Gheinani et al[53]. Out of 19 mRNA targets, only 221 and 215, respectively, upregulated and 17 of them downregulated BOO miRNAs, were found in the BOO mRNA data set. Important regulators of gene expression are miRNAs. They play a significant role in the etiology of BPH and are frequently changed in urologic malignancies. When it comes to the early detection and treatment of BPH, miR-221 has the potential to be employed as both biomarker and therapeutic target. The creation of preRNA or anti-RNA molecules within carrier vehicles that may be safely administered to patients should be made possible by technological advancements. For universal cell targeting, these compounds could be applied topically or continuously. To lessen the significant economic burden associated with this condition, the development of such innovative pharmacologic medicines should be looked into as a potential treatment for one of the most prevalent urologic diseases among elderly men with a significant impact on QoL. One limitation of the current systematic review is the inclusion of studies only focusing on benign cases of urological complications. By excluding studies on other urinary tract carcinomas, such as bladder cancer or renal cell carcinoma, the review may not capture the full spectrum of miRNA expression patterns in different types of urinary tract conditions. This limitation could potentially limit the generalizability of the findings and their applicability to a broader range of urological diseases. Additionally, by not including studies comparing the expression of different types of miRNAs with healthy or benign conditions, the review may lack a comprehensive understanding of the specific dysregulated miRNAs that are unique to overactive bladder (OAB) compared to other non-malignant urological conditions. This limitation may hinder the ability to accurately identify miRNA biomarkers or therapeutic targets that are specific to OAB and differentiate it from other urinary tract disorders. Furthermore, the exclusion of certain studies may introduce selection bias and affect the overall quality and reliabil-

ity of the systematic review. The findings may be skewed towards a particular subset of urological complications, potentially leading to an incomplete or biased understanding of the role of miRNAs in OAB. To overcome these limitations, future systematic reviews should aim to include a wider range of studies that encompass different types of urinary tract conditions, including both benign and malignant cases. This would provide a more comprehensive analysis of miRNA expression patterns across various urological diseases, allowing for a better understanding of the specific miRNAs involved in OAB pathogenesis. Additionally, conducting larger-scale clinical studies that incorporate diverse patient populations would help validate the diagnostic and prognostic value of miRNAs in OAB and improve the generalizability of the findings. Despite the promising findings in our systematic study of miRNAs in urological diseases potential sources of heterogeneity or bias that need to be considered may affect our findings. The variability in the reporting and measurement of miRNA expression levels across different studies could also contribute to heterogeneity in the data. Furthermore, the identification of specific miRNAs as biomarkers in different urological conditions may be influenced by factors such as sample size, patient characteristics, disease severity, and treatment history. Variability in experimental techniques and platforms used for miRNA profiling could also introduce bias and affect the reproducibility of our findings. It is important to acknowledge that the deregulation of miRNAs in urological diseases is a complex and multifactorial process, and our study may not capture the full spectrum of miRNA involvement in these conditions. Future research efforts should aim to address these limitations by conducting larger, more comprehensive studies that account for potential confounders and sources of bias. Overall, while miRNAs such as 92a-3p, miR-21, miR-199a-5p, and miR-146a-5p show promise as biomarkers and therapeutic targets in benign urological conditions, further research is needed to validate their clinical utility and address the limitations inherent in miRNA studies. Technological advancements in RNA-based therapeutics hold potential for the development of novel treatment strategies, but rigorous evaluation and validation are essential before their widespread clinical implementation.

## CONCLUSIONS

When it comes to the early detection and treatment of benign urological conditions, 92a-3p, miR-21, miR-199a-5p, and miR-146a-5p, and 491-5p have the potential to be employed as both a biomarker and a therapeutic target. The creation of pre-RNA or anti-RNA molecules within carrier vehicles that may be safely administered to patients should be made possible by technological advancements.

## ACKNOWLEDGEMENT

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## CONFLICT OF INTEREST

The authors report no conflict of interest.

## APPENDIX

https://journals.sbmu.ac.ir/urolj/index.php/uj/libraryFiles/downloadPublic/64

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