narra j

Short Communication

Long non-coding RNAs as prognostic biomarkers in non-muscle invasive bladder cancer: A systematic review

Ahmad Z. Hendri[1,2*], Sri Suryawati[3,4], Didik S. Heriyanto[5,6], Mardiah S. Hardianti[7,8], Narpati W. Pikatan[1,2], Sabillal Shaleh[1,2], Robert Robert[1,2], Toni Febriyanto[1,2], Belinda Liliana[1,2], Angga DM. Pratama[1,2]

[1]Division of Urology, Department of Surgery, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia; [2]Division of Urology, Department of Surgery, Dr. Sardjito General Hospital, Yogyakarta, Indonesia; [3]Department of Pharmacology and Therapy, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia; [4]Department of Pharmacology and Therapy, Dr. Sardjito General Hospital, Yogyakarta, Indonesia; [5]Department of Anatomical Pathology, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia; [6]Department of Anatomical Pathology, Dr. Sardjito General Hospital, Yogyakarta, Indonesia; [7]Division of Hematology and Medical Oncology, Department of Internal Medicine, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia; [8]Division of Hematology and Medical Oncology, Department of Internal Medicine, Dr. Sardjito General Hospital, Yogyakarta, Indonesia

*Corresponding author: zulfan.hendri@ugm.ac.id

Abstract

Traditional prognostic tools for non-muscle invasive bladder cancer (NMIBC) often overestimate progression and recurrence risks, underscoring the need for more precise biomarkers. While long non-coding ribonucleic acids (lncRNAs) have been reviewed in bladder cancer, no review has focused on NMIBC. The aim of this study was to address this gap by investigating the role of lncRNAs in predicting NMIBC survival and progression. A systematic review was conducted using PubMed, Scopus, and Cochrane databases as of July 31, 2024. Prognostic studies investigating the association between lncRNA expression and survival outcomes, such as cancer-specific survival, disease-free survival, recurrence-free survival, or overall survival, using Kaplan-Meier curves or hazard ratios, were included. A total of three studies were analyzed, involving 279 NMIBC patients and focusing on three lncRNAs: urothelial cancer associated 1 (UCA1), growth arrest-specific 5 (GAS5), and up-regulated in non-muscle invasive bladder cancer (UNMIBC). Increased UCA1 expression was strongly associated with poor disease-free survival (hazard ratio (HR): 1.974; 95%CI: 1.061–3.673; p=0.032) and progression-free survival (HR: 3.476; 95%CI: 1.187–10.18; p=0.023). Reduced GAS5 expression was significantly associated with poor disease-free survival (HR: 2.659; 95%CI: 1.348–5.576; p=0.005) and progression-free survival (HR: 6.628; 95%CI: 1.494–29.40; p=0.013). Higher level of UNMIBC was strongly associated with poor recurrence-free survival (HR: 2.362; 95%CI: 1.504–4.837; p=0.007). In conclusion, lncRNAs have potential as prognostic biomarkers in NMIBC, with UCA1 and UNMIBC overexpression and GAS5 underexpression being significant in predicting disease recurrence and progression, highlighting the clinical relevance of monitoring these lncRNAs to improve prognosis and guide treatment decisions.

Keywords: Bladder cancer, NMIBC, biomarker, long non-coding RNA, prognosis

Introduction

Non-muscle invasive bladder cancer (NMIBC) accounts for 70–80% of bladder cancer cases [1]. Despite its lower invasiveness, NMIBC presents significant clinical challenges, including a high

https://narraj.org/

Received: August 8, 2024 - Accepted: October 8, 2024 - Published online: November 1, 2024

rate of recurrence (50–70% within five years) and a 10–20% risk of progression to muscle-invasive disease [2]. This high recurrence rate necessitates frequent invasive and costly cystoscopic surveillance, highlighting the need for improved prognostic strategies [3].

NMIBC management is complicated by variability in individual recurrence risk; thus, complicating accurate disease outcome prediction [4]. Traditional prognostic tools, including the NMIBC risk scale [5], European Organization for Research and Treatment of Cancer (EORTC) risk tables [6], and European Association of Urology (EAU) risk groups [7], often overestimate progression and recurrence risk in patients receiving intravesical therapy, underscoring the need for more precise prognostic biomarkers to enhance therapeutic decision-making and surveillance [5-8].

Long non-coding ribonucleic acids (lncRNAs) play a pivotal role in gene regulation, cell cycle checkpoints, and migration [9]. LncRNAs influence chromatin architecture, gene expression, and cellular differentiation, thereby contributing significantly to cellular development [10,11]. Additionally, lncRNAs are pivotal in cancer proliferation and progression, acting as both tumor promoters and suppressors [12]. In bladder cancer, lncRNAs such as urothelial cancer associated 1 (UCA1), growth arrest-specific 5 (GAS5), and up-regulated in non-muscle invasive bladder cancer (UNMIBC) are implicated, with upregulation of UCA1 and UNMIBC and downregulation of GAS5 associated with disease outcomes [13,14].

Previous systematic review addressed the role of lncRNAs in bladder cancer generally; however, the study primarily focused on bladder cancer without exploring the potential therapeutic benefits of lncRNAs in NMIBC [14]. The aim of this study was to address this gap by investigating the role of lncRNAs in predicting NMIBC survival and progression, thereby offering insights for improved prognosis and patient management.

Methods

Study design and setting

A systematic review was conducted as of July 31, 2024. Protocols for the present systematic review followed Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines and were registered with PROSPERO under registration number CRD42024563505. This systematic review aimed to ascertain the role of lncRNAs as a prognostic factor in NMIBC patients.

Eligibility criteria

Studies included in the systematic review met the following criteria: (1) patients were diagnosed with NMIBC through histopathology; (2) the study assessed the association between lncRNA expression and NMIBC, including clinicopathological characteristics; (3) lncRNA expression level was categorized as high or low; (4) prognostic study assessing the role of lncRNAs on survival outcomes such as cancer-specific survival, disease-free survival, recurrence-free survival, or overall survival, using Kaplan-Meier curves or original data for hazard ratios (HR). Duplicate data, insufficient or low-quality studies, inappropriate article types (e.g., meeting reports, reviews, non-human studies) and unavailable full-text publications were all excluded.

Search strategy

A systematic search was conducted in PubMed, Scopus, and Cochrane databases up to July 31, 2024, to identify research on lncRNAs as prognostic indicators for NMIBC. The search utilized keywords including “long non-coding RNA”, “non-muscle invasive bladder cancer”, and “biomarker,” with their MeSH synonyms. The search process involved two steps: initially using broad keywords such as “lncRNA” and “bladder cancer,” followed by more specific terms such as (“lncRNA”, “long non-coding RNA”) AND (“NMIBC”, “non-muscle invasive bladder cancer”). Details of the keywords employed in the search strategy are provided in **Supplementary data**.

Screening and selection of the articles

Articles identified from the search were collected according to predetermined criteria for inclusion and evaluated by two authors (ADMP and BL). The authors independently screened the search results by considering the titles and abstracts. Afterwards, full-text articles of potentially

eligible studies were obtained and assessed for final inclusion or exclusion. In cases of discrepancies between the reviewers, a discussion with a third reviewer (AZH) was done to resolve the disagreement.

Data extraction

Data collected from the literature included the first author's details, publication year, country, study design, sample size, tumor-node-metastasis (TNM) stage, treatment, lncRNA levels, sample tissue, detection methods, cut-off values of lncRNA level used, follow-up duration and survival rate in hazard ratio (HR) for high vs low gene expression with 95%CI.

Quality assessment

The quality assessment of cohort studies was performed utilizing the Newcastle-Ottawa Scale (NOS) [15]. The three primary categories of bias in NOS are selection, comparability, and outcome. “Good” quality was defined as a score of 7 points or higher, “Fair” quality as 2 to 6 points, and “Poor” quality as ≤1 point. Two authors (TF and RB) independently assessed each study’s risk of bias, with any conflicts resolved through discussion.

Results

Characteristics of the included studies

Using the search keywords, 72 publication titles were retrieved. Of these, 56 were excluded for duplication, and 11 were excluded based on their abstracts and titles. Five full-text articles remained [16-20], from which one was excluded for lacking prognostic relevance [16], and one for focusing solely on bladder cancer rather than NMIBC [17]. Finally, three studies met the inclusion criteria [18-20]. The study selection process is depicted in **Figure 1**. The majority of included studies were conducted in Greek populations (60%) [18,19]. A total of 279 NMIBC patients were analyzed, focusing on three lncRNAs: UCA [18], GAS5 [19], and UNMIBC [20]. Two studies explored the association between aberrant lncRNA expression and disease-free survival and progression-free survival [18,19], while one study examined lncRNA and recurrence-free survival [20] (**Table 1**). The risk of bias assessment using the NOS is presented in **Table 2**.

Prognostic significance of lncRNA levels in survival outcomes

Increased UCA1 expression was strongly associated with poor disease-free survival (HR: 1.974; 95%CI: 1.061–3.673; p=0.032) and progression-free survival (HR: 3.476; 95%CI: 1.187–10.18; p=0.023) [18]. Reduced GAS5 expression was significantly associated with poor disease-free survival (HR: 2.659; 95%CI: 1.348–5.576; p=0.005) and progression-free survival (HR: 6.628; 95%CI: 1.494–29.40; p=0.013) [19]. Higher levels of UNMIBC were strongly associated with worse recurrence-free survival (HR: 2.362; 95%CI: 1.504–4.837; p=0.007) [20].

Discussion

The present study found that elevated UCA1 expression and reduced GAS5 expression were associated with poor disease-free survival (DFS) and progression-free survival (PFS). Additionally, increased UNMIBC expression was associated with unfavorable recurrence-free survival (RFS). Avgeris *et al.* conducted a retrospective cohort study of 176 bladder cancer patients, evaluating the prognostic utility of UCA1 [18]. The study found significant UCA1 upregulation in bladder tumors compared to normal urothelium [18]. Decreased UCA1 expression correlated with muscle-invasive disease, higher tumor stage, and grade [18]. Reduced UCA1 levels were significantly associated with an increased risk of immediate recurrence and progression to invasive stages in NMIBC [21].

UCA1, an oncogenic lncRNA from the endogenous H retrovirus, plays a significant role in NMIBC [18]. UCA1 regulates key biological processes involved in cancer progression, such as cancer cell proliferation, invasion, migration, metastasis, and angiogenesis [22]. Mechanistically, UCA1 upregulates high mobility group box 1 (HMGB1) and acts as a competitive endogenous RNA against miR-143, a tumor suppressor that inhibits epithelial-mesenchymal transition (EMT) [21]. The inverse correlation between UCA1 and microRNA 143 (miR-143), alongside the positive

correlation between UCA1 and HMGB1, emphasizes the UCA1/miR-143/HMGB1 axis's importance in NMIBC pathology [22,23]. UCA1's role in promoting EMT and invasion suggests its potential as a therapeutic target and prognostic marker in NMIBC [21]. UCA1 upregulates the expression of zinc finger e-box binding homeobox 2 (ZEB2), a transcription factor associated with tumor metastasis, by targeting microRNA 203 (miR-203) [23]. In various cancers, the association of high UCA1 expression with high-grade tumors and poor patient survival rates has been confirmed [22].

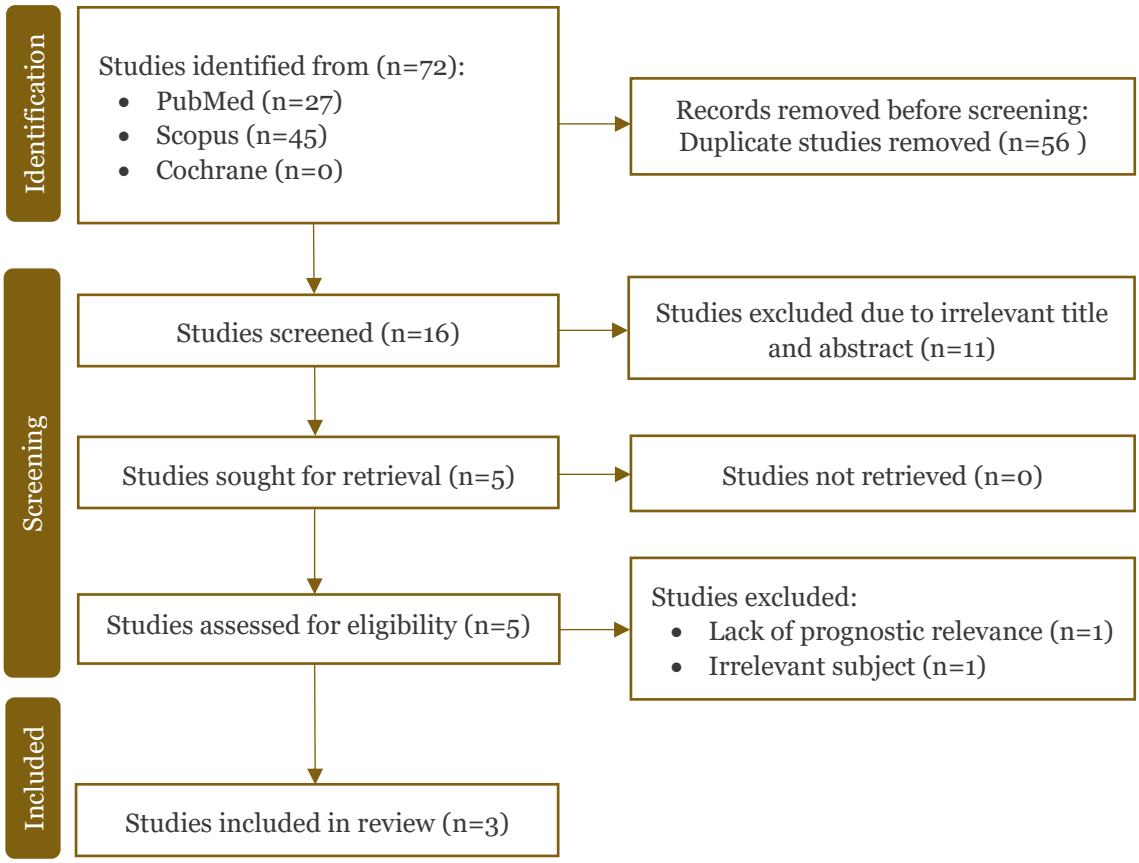

Figure 1. PRISMA flowchart of the included studies.

A retrospective cohort study of 176 bladder cancer patients by Avgeris *et al.* showed that UCA1 expression was significantly higher in T1-2 bladder tumors compared to T3-4 tumors and elevated in low-grade versus high-grade tumors without lymph node or distant metastases [18]. Due to its carcinogenic effects, including involvement in multiple molecular pathways, UCA1 is considered a potential therapeutic target [24]. Targeted elimination of UCA1 may inhibit cancer spread, increase tumor cell sensitivity to radiation, reduce tumor growth, induce apoptosis, and overcome drug resistance [25]. Furthermore, in NMIBC, lower UCA1 levels were correlated with increased tumor recurrence and progression [18]. This finding contradicted the expected oncogenic role of UCA1 [18]. To further validate these findings, Avgeris *et al.* conducted a validation cohort analysis using data from The Cancer Genome Atlas (TCGA), which was consistent with low UCA1 levels associated with worse outcome [18]. Lebrun *et al.* also showed that bladder cancer patients with elevated UCA1 levels exhibited a lower Ki-67 proliferative index and a p53 'wild-type' immunoprofile, leading to less aggressive behavior compared to urothelial bladder cancer (UBC) without UCA1 overexpression [17]. Further analysis by decision marker models alongside factors such as stage, grade, and EORTC risk led to an improvement of over 5% in clinical net benefit for predicting disease progression [18].

Table 1. Characteristics of included studies (n=3)

Author, year	Country	Study design	Treatment of patient	LncRNA type	LncRNA levels	Sample size, n			Sample tissue	Detected method	Cut-off value for low vs high expression	Follow-up duration	Survival rate in HR (high vs low) with HR 95%CI
						Total	Male	Female					
Avgeris *et al.*, 2019 [18]	Greece	Cohort	TURBT or radical cystectomy	UCA1	Up (p<0.001)	102	62	40	Bladder tissue sample	RT-qPCR	Median (0.151)	31 months	DFS Univariate: 1.974 (1.061–3.673) PFS Univariate: 3.476 (1.187–10.180)
Avgeris *et al.*, 2018 [19]	Greece	Cohort	TURBT	GAS5	Down (p=0.002)	102	48	54	Bladder tissue sample	RT-qPCR	Median (50th percentile)	31 months	DFS Univariate: 2.659 (1.348–5.576) Multivariate: 2.680 (1.248–5.753) PFS Univariate: 6.628 (1.494–29.400) Multivariate: 6.362 (1.144–35.390)
Zhang *et al.*, 2016 [20]	China	Cohort	NA	UNMIBC	Up (p=0.007)	75	45	30	Bladder tissue sample	RT-qPCR	Fold change of >1.5 was considered high expression	36 months	RFS Multivariate: 2.362 (1.504–4.837)

CI: confidence interval; DFS: disease-free survival; GAS5: growth arrest-specific 5; HR: hazard ratio; NA: not available; PFS: progression-free survival; RFS: recurrence-free survival; RT-qPCR: reverse transcription-quantitative polymerase chain reaction; TURBT: trans urethral removal of bladder tumor; UCA1: urothelial cancer associated 1; UNMIBC: up-regulated in non-muscle invasive bladder cancer.

Table 2. Risk of bias assessment results

Cohort study	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Total (0–9)
Avgeris *et al.*, 2019 [18]	*	*	*	*	*	*	*	*	8
Avgeris *et al.*, 2018 [19]	*	*	*	*	*	*	*	*	8
Zhang *et al.*, 2016 [20]	*		*	*	*	*	*		6

Zhang *et al.* found that lncRNA-UNMIBC was upregulated in 45 primary NMIBC tissues compared to healthy tissues, and was strongly associated with recurrence [20]. LncRNA-UNMIBC plays a critical role in G0/G1 cell cycle arrest and interacts with enhancer zeste homolog 2 (EZH2) and suppressor of zeste 12 homolog (SUZ12), affecting histone H3 lysine 27 methylation of target genes [20]. This suggests that lncRNA-UNMIBC may be a predictor of poor recurrence and a stimulator of tumor growth [20].

UNMIBC is associated with poor prognosis in NMIBC [20]. UNMIBC promotes tumor formation by enhancing histone H3 on lysine 27 (H3K27) methylation and polycomb repressive complex 2 (PRC2) complex restriction, which affects cell cycle regulatory genes [20]. Small interfering RNA (siRNA)-mediated reduction of lncRNA-UNMIBC increased the expression of potential PRC2 target genes, indicating that UNMIBC interacts with the PRC2 complex to regulate these targets [20]. Chromatin immunoprecipitation analysis showed that UNMIBC knockdown reduced histone 3 lysine 27 trimethylation (H3K27me3) levels in promoter regions of target genes, explaining the decreased expression observed after silencing lncRNA-UNMIBC or PRC2 [20].

GAS5 expression was significantly reduced in bladder cancer and correlated with aggressive high-grade tumors, particularly in high-risk NMIBC patients per European Organization Research and Treatment of Cancer (EORTC) criteria [19]. Reduced GAS5 level was associated with an increased risk of early relapse (HR: 2.680; 95%CI: 1.248–5.753; p=0.011) and progression (HR: 6.362; 95%CI: 1.144–35.390; p=0.035) [19]. Lower GAS5 levels predicted shorter disease-free survival and progression-free survival in NMIBC, highlighting GAS5 reduction as a key prognostic marker that enhances the predictive value of existing clinical markers [19].

GAS5 is a lncRNA that exhibits elevated expression during cellular quiescence and arrest phases, but its levels are diminished in cells undergoing active proliferation [19]. A negative correlation has been noted between GAS5 levels and both cyclin D1, which forms a complex with CDK4/CDK6 to activate these kinases, and the transcription factor E2F1, which regulates key genes involved in cell cycle control. In contrast, GAS5 levels show a positive correlation with the cyclin-dependent kinase inhibitor p21 [26]. GAS5 can interact with microRNAs, including microRNA 21 (miR-21) and microRNA-532-5p (miR-532-5p), to modulate the Akt signaling pathway, thereby influencing cell survival and apoptosis [27]. Akt, also known as protein kinase B, is a serine/threonine kinase that plays a crucial role in cell survival, growth, and metabolism [28]. GAS5 has been identified as being significantly downregulated in multiple cancer types [27]. GAS5 expression is significantly reduced in bladder cancer, likely serving as a miRNA sponge for miRNA-18a-5p [29]. Elevated miR-18a-5p promotes bladder cancer cell proliferation and migration by interacting with axis inhibition protein 2 (AXIN2) and glycogen synthase kinase 3 beta (GSK3β) in the Wnt/β-catenin pathway [29]. Downregulation of GAS5 disrupts this regulatory axis, facilitating bladder cancer progression [29]. Avgeris *et al.* reported significantly lower GAS5 levels in NMIBC compared to normal tissues (p=0.001) [19]. GAS5 downregulation was associated with increased cellular proliferation, higher S/G2 phase cell percentages, and elevated cyclin-dependent kinase 6 (CDK6) and chemokine (C-C motif) ligand 1 (CCL1) expression, while abnormal GAS5 expression interrupted the cell cycle at the G0/G1 stages [30].

Therefore, studies investigating the role of lncRNA as prognostic predictors for NMIBC are crucial to prevent progression from NMIBC to MIBC, thereby reducing the risk of metastasis and disease-specific mortality [31]. There is already existing utilization of lncRNA models for prognostic prediction and chemotherapeutic response [32]. Nevertheless, the application of the lncRNA models has been limited to bladder cancer as a whole and its effectiveness still needs to be confirmed through further validation.

While the present study highlighted the potential of lncRNAs as prognostic biomarkers in NMIBC, several limitations require further investigation. The present study was preliminary, with small sample sizes and single-center studies, necessitating large-scale, multicenter trials to confirm the clinical utility of lncRNAs. The molecular mechanisms underlying lncRNA influence on bladder cancer progression are not fully understood, emphasizing the need for research into their origins, regulatory pathways, and interactions. Comprehensive characterization and functional analysis of lncRNAs are essential for uncovering their roles in bladder cancer

progression and their potential as therapeutic targets. Additionally, exploring a broader range of lncRNAs across various bladder cancer stages may identify novel biomarkers and therapeutic strategies. Addressing these issues is crucial for integrating lncRNA-based biomarkers into NMIBC management, thereby enhancing prognosis and treatment outcomes. Large-scale, multicenter trials are crucial to validate their clinical utility. Future studies should focus on comprehensive characterization and functional analysis of lncRNAs to enhance understanding and applications, potentially transforming NMIBC prognosis and treatment.

Conclusion

LncRNAs have potential as prognostic biomarkers in NMIBC, with UCA1 and UNMIBC overexpression and GAS5 underexpression being significant in predicting disease recurrence and progression, highlighting the clinical relevance of monitoring these lncRNAs to improve prognosis and guide treatment decisions.

Ethics approval

Not required.

Acknowledgments

Authors have nothing to declare.

Competing interests

All the authors declare that there are no conflicts of interest.

Funding

The present study was supported by Final Project Recognition Grant from Universitas Gadjah Mada, Yogyakarta, Indonesia (Grant number: 5075/UN1.P.II/DitLit/PT.01.01/2023).

Underlying data

Details of the keywords employed in the search strategy are available at: https://doi.org/10.6084/m9.figshare.27152412.v1.

How to cite

Hendri AZ, Suryawati S, Heriyanto DS, *et al*. Long non-coding RNAs as prognostic biomarkers in non-muscle invasive bladder cancer: A systematic review. Narra J 2024; 4 (3): e1233 - http://doi.org/10.52225/narra.v4i3.1233.

References

1. Miyake M, Kitamura H, Nishimura N, *et al*. Validation of non-muscle-invasive bladder cancer risk stratification updated in the 2021 European Association of Urology guidelines. BJUI Compass 2023;5(2):269-280.
2. Jin YH, Zeng XT, Liu TZ, *et al*. Treatment and surveillance for non-muscle-invasive bladder cancer: A clinical practice guideline (2021 edition). Mil Med Res 2022;9(1):44.
3. Lee LJ, Kwon CS, Forsythe A, *et al*. Humanistic and economic burden of non-muscle invasive bladder cancer: Results of two systematic literature reviews. Clinicoecon Outcomes Res 2020;12:693-709.
4. Kwong JCC, Wu J, Malik S, *et al*. Predicting non-muscle invasive bladder cancer outcomes using artificial intelligence: A systematic review using APPRAISE-AI. NPJ Digit Med 2024;7(1):98.
5. Bedke J, Black PC, Szabados B, *et al*. Optimizing outcomes for high-risk, non-muscle-invasive bladder cancer: The evolving role of PD-(L)1 inhibition. Urol Oncol 2023;41(12):461-475.
6. Borkowska EM, Jedrzejczyk A, Marks P, *et al*. EORTC risk tables - their usefulness in the assessment of recurrence and progression risk in non-muscle-invasive bladder cancer in Polish patients. Cent European J Urol 2013;66(1):14-20.
7. Lobo N, Hensley PJ, Bree KK, *et al*. Updated European Association of Urology (EAU) prognostic factor risk groups overestimate the risk of progression in patients with non-muscle-invasive bladder cancer treated with *Bacillus Calmette-Guérin*. Eur Urol Oncol 2022;5(1):84-91.

8. Matulewicz RS, Steinberg GD. Non-muscle-invasive bladder cancer: Overview and contemporary treatment landscape of neoadjuvant chemoablative therapies. Rev Urol 2020;22(2):43-51.
9. Statello L, Guo CJ, Chen LL, Huarte M. Gene regulation by long non-coding RNAs and its biological functions. Nat Rev Mol Cell Biol 2021;22(2):159.
10. Beylerli O, Gareev I, Sufianov A, *et al*. Long noncoding RNAs as promising biomarkers in cancer: Long non-coding RNAs and cancer. Noncoding RNA Res 2022;7(2):66-70.
11. Wang J, Gao Y, Wang X, *et al*. Circulating lncRNAs as noninvasive biomarkers in bladder cancer: A diagnostic meta-analysis based on 15 published articles. Int J Biol Markers 2020;35(2):40-48.
12. Guzel E, Okyay TM, Yalcinkaya B, *et al*. Tumor Suppressor and Oncogenic Role of Long Non-Coding RNAs in Cancer. North Clin Istanb 2019;7(1):81-86.
13. Quan J, Pan X, Zhao L, *et al*. LncRNA as a diagnostic and prognostic biomarker in bladder cancer: A systematic review and meta-analysis. Onco Targets Ther 2018;11:6415-6424.
14. Su G, He Q, Wang J. Clinical values of long non-coding RNAs in bladder cancer: A systematic review. Front Physiol 2018;9:652.
15. The Ottawa Hospital Research Institute. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available from: https://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed: 10 April 2024.
16. Milowich D, Le Mercier M, De Neve N, *et al*. Diagnostic value of the UCA1 test for bladder cancer detection: A clinical study. Springerplus 2015;4:349.
17. Lebrun L, Milowich D, Le Mercier M, *et al*. UCA1 overexpression is associated with less aggressive subtypes of bladder cancer. Oncol Rep 2018;40(5):2497-2506.
18. Avgeris M, Tsilimantou A, Levis PK, *et al*. Unraveling UCA1 lncRNA prognostic utility in urothelial bladder cancer. Carcinogenesis 2019;40(8):965-974.
19. Avgeris M, Tsilimantou A, Levis PK, *et al*. Loss of GAS5 tumour suppressor lncRNA: An independent molecular cancer biomarker for short-term relapse and progression in bladder cancer patients. Br J Cancer 2018;119(12):1477-1486.
20. Zhang S, Zhong G, He W, *et al*. LncRNA up-regulated in nonmuscle invasive bladder cancer facilitates tumor growth and acts as a negative prognostic factor of recurrence. J Urol 2016;196(4):1270-1278.
21. Luo J, Chen J, Li H, *et al*. LncRNA UCA1 promotes the invasion and EMT of bladder cancer cells by regulating the miR-143/HMGB1 pathway. Oncol Lett 2017;14(5):5556-5562.
22. Hosseini NF, Manoochehri H, Khoei SG, Sheykhhasan M. The functional role of long non-coding RNA UCA1 in human multiple cancers: A review study. Curr Mol Med 2020;21(2):96-110.
23. Yao F, Wang Q, Wu Q. The prognostic value and mechanisms of lncRNA UCA1 in human cancer. Cancer Manag Res 2019;11:7685-7696.
24. Gong P, Qiao F, Wu H, *et al*. LncRNA UCA1 promotes tumor metastasis by inducing miR-203/ZEB2 axis in gastric cancer. Cell Death Dis. 2018;9(12):1158.
25. Aboelkhair NT, Mashal SS, El-Hefnawy SM, *et al*. The role of long non-coding RNA UCA1 and MALAT1 in bladder cancer patients. Hum Gene 2023;36:201164.
26. Lin G, Wu T, Gao X, *et al*. Research progress of long non-coding RNA GAS5 in malignant tumors. Front Oncol 2022;12:846497.
27. Lambrou GI, Hatziagapiou K, Zaravinos A. The non-coding RNA GAS5 and its role in tumor therapy-induced resistance. Int J Mol Sci 2020;21(20):7633.
28. Manning BD, Cantley LC. AKT/PKB signaling: Navigating downstream. Cell 2007;129(7):1261-1274.
29. Zhang Z, Liu T, Cheng C, *et al*. LncRNA GAS5 regulates the Wnt/β-catenin pathway through the miR-18a-5p/AXIN2/GSK3β axis to inhibit the proliferation and migration of bladder cancer cells. Carcinogenesis 2022;43(12):1176-1189.
30. Cao Q, Wang N, Qi J, *et al*. Long non-coding RNA-GAS5 acts as a tumor suppressor in bladder transitional cell carcinoma via regulation of chemokine (C-C motif) ligand 1 expression. Mol Med Rep 2016;13(1):27-34.
31. Hald OC, Phan YC, Carter CJM, Klatte T. Bladder tumor resection weight as a prognostic factor for recurrence and progression in patients with high-risk non-muscle invasive bladder treated with BCG. Clin Genitourin Cancer 2023;21(2):e70-e77.
32. Zhang YY, Li XW, Li XD, *et al*. Comprehensive analysis of anoikis-related long non-coding RNA immune infiltration in patients with bladder cancer and immunotherapy. Front Immunol 2022;13:1055304.