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MicroRNA As Prognostic And Diagnostic Biomarker In Upper Tract Urothelial Carcinoma: A Systematic Review and Meta-Analysis

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Introduction. Upper tract urothelial carcinoma (UTUC) is a relatively rare but aggressive form of cancer that affects the urinary system. Early detection and accurate prognosis are critical for improving patient outcomes. Recent studies suggest that microRNAs, small non-coding RNA molecules, may serve as potential biomarkers for various cancers, including UTUC. This systematic review and meta-analysis aim to evaluate the effectiveness of microRNAs as prognostic and diagnostic tools in UTUC.
Methods. We searched PubMed and EuropePMC for studies published until December 2024 and performed a meta-analysis using RevMan 5.4 and MetaDisc.
Results. The review included a total of 6 studies, encompassing data from over 300 sample patients. Our analysis confirmed that specific microRNAs are significantly associated with both the presence and progression of UTUC. MicroRNAs demonstrated significant prognostic outcomes, such as progression-free survival (3.72; 95% CI: 2.46-5.62; $p < 0.00001$) and cancer-specific survival (3.46; 95% CI: 1.68-7.15; $p = 0.0008$). These biomarkers showed high sensitivity (0.75; 95% CI: 0.72-0.78; $p = 0.0000$) and specificity (0.82; 95% CI: 0.79-0.85; $p = 0.0000$), with the following diagnostic indices Positive Likelihood Ratio (PLR) (4.45, 95% CI: 3.22-6.14), Negative Likelihood Ratio (NLR) (0.31, 95% CI: 0.24-0.39), Diagnostic Odds Ratio (DOR) (18.04, 95% CI: 10.46-31.14), and Area Under Curve (AUC) 0.86 in the diagnosis of UTUC. Subgroup analysis of diagnostic studies based on countries revealed higher results in Asian countries. MicroRNAs showed significant associations with UTUC progression and survival, with high diagnostic accuracy (AUC 0.86).
Conclusion. MicroRNA could be used as potential diagnostic and prognostic biomarkers in UTUC.

Keywords: biomarker, diagnostic, microRNA, prognostic, upper tract urothelial carcinoma

Introduction

Upper tract urothelial carcinoma (UTUC) is a relatively rare form of urothelial cancer that affects the lining of the upper urinary tract, including the renal pelvis and ureters, although it accounts for only 5-10% of all urothelial cancers. UTUC is often diagnosed at a more advanced stage compared to bladder cancer and has a poorer prognosis [1]. The incidence of UTUC varies geographically and is influenced by factors such as age, smoking, and exposure to certain chemicals. The aggressive nature of UTUC and its propensity for early metastasis underscore the need for improved diagnostic and prognostic methods to enhance patient management and outcomes [2].

Biomarkers are used to monitor how well the body responds to treatment for a disease or condition. In the context of cancer, biomarkers play crucial roles in screening, diagnosing, prognosticating, and monitoring response to therapy. Effective biomarkers can lead to earlier detection and more tailored treatment strategies, potentially improving survival rates [3].

MicroRNAs (miRNAs) are small, non-coding RNA molecules involved in the regulation of gene expression. In cancer, miRNAs can function as oncogenes or tumor suppressors. Due to their stability in body fluids and their role in cancer

pathology, miRNAs have emerged as promising biomarkers for cancer detection and prognosis [4].

In the more common bladder cancer, a substantial body of research has firmly established the significant role of specific microRNAs as non-invasive prognostic and diagnostic biomarkers, capable of predicting tumor aggressiveness and patient survival [5]. However, despite this established utility in bladder cancer, the potential of microRNAs as biomarkers specifically for UTUC remains significantly less explored. This gap in knowledge limits the development of tailored diagnostic and management strategies for UTUC patients. Therefore, the present systematic review and meta-analysis aims to synthesize the current evidence to evaluate the specific role of microRNAs as diagnostic and prognostic biomarkers in UTUC, thereby addressing a critical unmet need in the field.

Materials and Method

Study selection

This work is reported following the PRISMA 2020 statement for systematic reviews and meta-analyses. We systematically searched PubMed and Europe PMC with the last search conducted in December 2024. The majority of relevant articles were identified in PubMed and Europe PMC, and due to resource limitations, the search was restricted to these two major databases. Free-text keywords were employed in the search process: microRNA AND biomarker OR diagnostic OR prognostic AND upper tract urothelial carcinoma OR UTUC.

Inclusion and exclusion criteria

Studies were considered eligible for inclusion if they met the following criteria: (1) patients diagnosed with upper tract urothelial carcinoma; (2) Micro RNA as prognostic or diagnostic factor; (3) Studies with a control group; (4) Studies reporting at least one of the following prognostic or diagnostic outcomes: Cancer Specific Survival (CSS), Progression Free Survival (PFS), Sensitivity, Specificity, Positive Likelihood Ratio (PLR), Negative Likelihood Ratio (NLR), and Diagnostic Odd Ratio (DOR). Cancer-specific survival (CSS) refers to the proportion of patients alive without dying from a particular type of cancer over a defined time period, while Progression-free survival (PFS) refers to the duration from the time of randomization until either the disease worsens or the patient dies from any cause [6]. Sensitivity reflects how well a test detects true positives, while specificity shows how accurately it identifies true negatives. The Positive Likelihood Ratio (PLR) indicates how much a positive result increases the likelihood of disease, and the Negative Likelihood Ratio (NLR) shows how much a negative result reduces it. The Diagnostic Odds Ratio (DOR) summarizes overall test accuracy by comparing the odds of a positive result in diseased versus non-diseased individuals [7].

The exclusion criteria were as follows: (1) Patients with other cancers, (2) Non-human studies (3) Review studies, (4) Studies not published in English.

Quality evaluation and risk of bias (ROB)

Three studies use QUADAS-2 assessment tools to evaluate diagnostic studies. QUADAS-2 is designed to analyze four domains: patient selection, index test, reference standard, and flow and timing. For prognostic studies, the QUAPAS tool was used in three studies. QUAPAS, an adaptation of QUADAS-2 for prognostic accuracy tests, evaluates five domains: participants, index test, outcome, flow and timing, and analysis [5].

Data extraction

Data from the screened studies were extracted for evaluation as prognostic and diagnostic biomarkers. The extracted data included the following: author name, publication year, microRNA name, sample group, sample size, sample mean age, country, patient inclusion criteria, and outcomes.

Statistical analysis

Data were analyzed quantitatively using Revman version 5.4 for prognostic and MetaDisc for diagnostic analysis. The p-value and I^2 were used to assess heterogeneity. Data were considered heterogenous if I^2 was greater than or equal to 50%. A p-value of less than 0.05 was considered statistically significant. Subgroup analysis was performed on studies with high heterogeneity, and a random-effects model was employed to consolidate the results [8]. A funnel plot was used to assess publication bias. Outcomes were interpreted using forest plots for hazard ratios of CSS and PFS, as well as forest plots for sensitivity, specificity, NLR, PLR, DOR, and receiver operating characteristic (ROC) curves.

Result

Searching Strategy and Study Characteristics

Based on the database search, a total of 377 studies were identified. After duplicate articles were removed, 317 studies were evaluated based on the inclusion criteria. Six studies met the inclusion criteria. Figure 1 shows the PRISMA flowchart illustrating the article selection process.

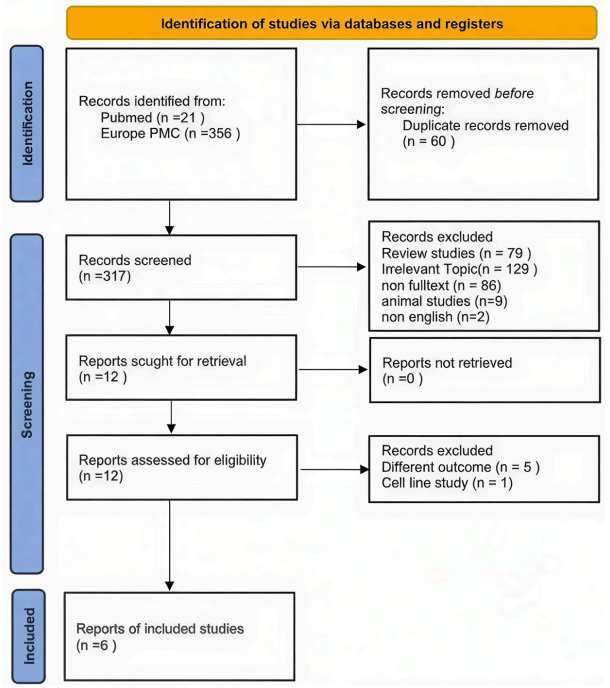

Figure 1. Flow diagram of meta-analysis for inclusion and exclusion studies

A summary of the characteristics of the included studies is shown in Table 1. Four studies were conducted in Europe, and two studies were conducted in Asia, with a total of 300 patient samples. Three studies reported prognostic outcomes, while three others reported diagnostic outcomes.

Risk Of Bias and Quality

QUADAS-2 and QUAPAS were used to evaluate the quality of three diagnostic and three prognostic studies (Figure 2). These studies were assessed as having a low risk of bias based on the tools.

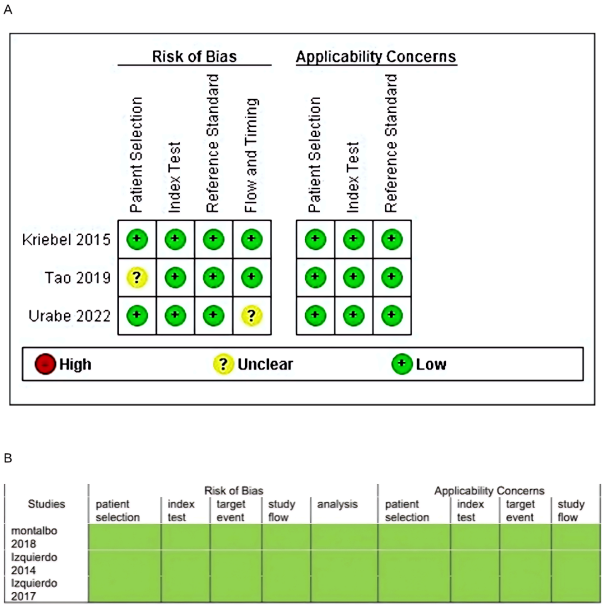

Figure 2. Risk of bias analysis: (A) QUADAS-2 in diagnostic study, (B) QUAPAS in prognostic study. Studies show low risk bias from QUADAS-2 and QUAPAS tools.

Prognostic and Diagnostic Outcomes

Based on the forest plot analysis in Figure 3, the studies demonstrate significant Cancer-Specific Survival (CSS) with a pooled hazard ratio of 3.46 (95% CI: 1.68, 7.15; I^2 = 19%; p = 0.0008) and Progression-Free Survival (PFS) with a pooled hazard ratio of 3.72 (95% CI: 2.46, 5.62; I^2 = 0%; p < 0.00001) . The pooled hazard ratio (HR) for Cancer-Specific Survival (CSS) of 3.46 (95% CI: 1.68–7.15) indicates that patients with high-risk microRNA expression have approximately a 3.5-fold higher risk of death from upper tract urothelial carcinoma (UTUC) compared to those with low-risk expression profiles. This substantial elevation in risk demonstrates that dysregulated miRNA expression is strongly associated with tumor aggressiveness and poor oncologic outcomes. Similarly, the pooled HR for Progression-Free Survival (PFS) of 3.72 (95% CI: 2.46–5.62) signifies that high-risk miRNA expression correlates with a 3.72-fold increased likelihood of disease progression or recurrence. These findings collectively highlight that abnormality of miRNA profiles not only predicts cancer-specific mortality but also serves as a reliable indicator of tumor progression dynamics.

The low heterogeneity values (I^2 = 19% for CSS and 0% for PFS) demonstrate the consistency of this effect across studies, reinforcing the

Table 1. Study characteristics

Author and year	miR	Sample Group	No. of Patients	Mean Age (year)	Country	Patients Inclusion	Outcomes
Montalbo 2018 [9]	miR-151b	high risk (down-regulated)	13	70	Spain	Prospective study of UTUC patients who underwent radical RNU at the Hospital Clinic of Barcelona from January 2008 to August 2014. Consecutive patients with a minimum of 36 months of follow-up were enrolled. Exclusion criteria were the presence of another active neoplasm or the absence of UTUC confirmation.	Cancer-specific survival, Progression-free survival survival
		low risk (up-regulated)	20				
Izquierdo 2014 [10]	miR-31, miR-149	high risk (up-regulated)	41	70	Spain, France	Retrospective study UTUC who underwent nephroureterectomy in three different centers (Hospital Clinic of Barcelona-Spain, Pitié Salpétrière Hôspital of Paris France, and Claude Huriez Hôspital of Lille-France) between 1990 and 2004 between 1990 and 2004	Cancer-specific survival, Progression-free survival survival
		low risk (down regulated)	91				
Izquierdo 2017 [11]	miR-31-5p, miR-149-5p	high risk (up-regulated)	52	67	Spain, Netherland	A retrospective study with UTUC who underwent nephroureterectomy in 4 different centers (Radboud University Medical Centre Nijmegen, Netherlands, Instituto Valenciano de Oncología-Spain, Hospital Universitario Reina Sofía of Córdoba-Spain, Hospital Clínic of Barcelona-Spain) between 1990 and 2012 of Barcelona-Spain) between 1990 and 2012	Progression-free survival
		low risk (down regulated)	51				
Urabe 2022 [12]	miR-1343-5p, miR-6778-5p, miR-4732-5p, miR-6087, miR-6768-5p, miR-4433a-3p, miR-4454, miR-1260a	UTUC patients	7	76	Japan	Serum samples were obtained from UTUC patients admitted or referred to the Kanagawa Cancer Center or National Hospital Organization Yokohama Medical Center between October 2016 and December 2018. Patients previously diagnosed with other cancer were excluded, and control samples were collected from the National Hospital Organization Yokohama Medical Center. For inclusion as a control sample, the participant must have had no history of cancer. Medical Center. For inclusion as a control sample, the participant must have had no history of cancer.	Sensitivity, Specificity, and AUC
		non-cancer patients	25	76			

Author and year	miR	Sample Group	No. of Patients	Mean Age (year)	Country	Patients Inclusion	Outcomes
Tao 2015 [13]	miR-16-5p, miR-191-5p, miR-22-3p, miR-26a-5p, miR-33b-3p, miR-423-3p, miR-431-5p, miR-664a-3p, let-7b-5p, let-7c	UTUC patients	46	68	China	Serum samples from UTUC patients undergoing radical nephroureterectomy at the First Affiliated Hospital of Nanjing Medical University (Nanjing, China), from 2007 to 2013. Matched cancer-free controls were also included. These controls were patients with hematuria who were further diagnosed with urinary tract infection, benign prostate hyperplasia, and urinary tract calculi at the First Affiliated Hospital of Nanjing Medical University (Nanjing, China). diagnosed with urinary tract infection, benign prostate hyperplasia and urinary tract calculi at the First Affiliated Hospital of Nanjing Medical University (Nanjing, China).	Sensitivity, Specificity, and AUC
		non cancer patients	30	67.9			
Kriebel 2015 [14]	miR-96, miR-135, miR-141, miR-182, miR-205, miR-429	UTUC patients	44	67.9	Germany	Serum collection was conducted from 2008 to 2013 at the urological departments at the University Hospitals Bonn and Münster. As a control individuals with non-malignant diseases (benign prostate hyperplasia, urethral stricture, incontinence, urinary stones) undergoing minor urological operations were used. urinary stones) undergoing minor urological operations were used.	Sensitivity, Specificity, and AUC
		non-cancer patients	34	63.5			

Table 2. Subgroup analysis of diagnostic studies

Country	Analysis				
	Sensitivity (95% CI)	Specificity (95%CI)	PLR (95% CI)	NLR (95% CI)	DOR (95% CI)
Europe	0.642 (0.563-0.715)	0.68 (0.589-0.759)	2.008 (1.569-2.571)	0.526 (0.43-0.643)	3.818 (2.551-5.714)
Asian	0.815 (0.769-0.853)	0.886 (0.849-0.914)	7.122 (5.394-9.405)	0.209 (0.167-0.261)	34.067 (23.302-49.807)

robustness of the prognostic significance of miRNAs in UTUC. Despite variability in effect sizes, the low heterogeneity among the studies suggests that the effect estimates are not widely disparate, supporting the reliability of the pooled result. The statistical significance of the overall effect underscores the robustness of the intervention's impact as analyzed in this meta-analysis. From a clinical perspective, these results imply that miRNA profiles can be used to identify patients at higher risk of cancer recurrence or death, enabling more targeted follow-up strategies and potentially guiding decisions regarding adjuvant therapy or intensive surveillance. Overall, these hazard ratios highlight the prognostic value of miRNA expression patterns as molecular markers of disease aggressiveness and survival outcomes in UTUC.

The combined diagnostic accuracy forest plot (Figure 3) shows that circulating microRNAs (miRNAs) exhibit strong diagnostic performance in detecting upper tract urothelial carcinoma (UTUC), with a combined sensitivity of 0.75 (95% CI: 0.72–0.78) and specificity of 0.82 (95% CI: 0.79–0.85). These results indicate that approximately 75% of true-positive UTUC cases were correctly identified, while 82% of non-UTUC cases were accurately excluded. The corresponding positive likelihood ratio (PLR = 4.45) indicated that patients with high levels of oncogenic miRNAs were more than four times more likely to have UTUC compared with samples with negative test results, while the negative likelihood ratio (NLR = 0.31) indicated a substantial decrease in the probability of disease when the test result was negative. The Diagnostic Odds Ratio (DOR) of 18.04 indicates a significant difference, suggesting that the odds of a positive miRNA test were 18 times higher in affected individuals compared to unaffected individuals. Overall, these values reflect the strong diagnostic capacity of circulating miRNAs in distinguishing between malignant and non-malignant urinary tract pathology.

The area under the ROC curve (AUC = 0.86) indicates excellent overall test accuracy, positioning miRNAs as a clinically relevant biomarker class. This finding is consistent with recent meta-analyses reporting comparable AUC values, ranging from 0.83 to 0.90, for circulating miRNA panels in UTUC and bladder carcinoma [13,16]. These results indicate that miRNAs exhibit superior biostability in serum and urine, are readily sampled non-invasively, and may reflect the presence and aggressiveness of disease.

Subgroup analysis was performed to identify potential heterogeneity (Table 2). Based on country, studies from Europe had a sensitivity of 0.642 and a specificity of 0.68, while studies from Asian countries had relatively higher sensitivity (0.815) and specificity (0.886). The subgroup analysis suggests that country or ethnic population has a significant influence on the diagnostic outcomes.

Publication Bias

The funnel plots of CSS and PFS (Figures 4A and 4B) do not show asymmetry. More studies are needed to confirm the absence of publication bias. The PFS Egger's test does not support the presence of funnel plot asymmetry (intercept: 1.44, 95% CI: 0.83-2.05, t = 4.626, p-value = 0.136). The funnel plot of DOR (Figure 4C) suggests potential publication bias. The Egger's test supports the presence of funnel plot asymmetry (intercept: 3.65, 95% CI: 2.58-4.72, t = 6.666, p-value = 0).

Discussion

According to EAU Guideline, CT Urography (CT-U) has the highest diagnostic accuracy of the available techniques with a sensitivity rate of 92% and a specificity rate of about 95%.15,16 Magnetic Resonance (MR) Urography is recommended for patients who cannot undergo CT Urography, particularly those with contraindications to radiation exposure. The sensitivity of MR Urography is 75% for detecting tumors smaller than 2 cm after contrast injection [17]. Flexible ureteroscopy (URS) allows for direct visualization of the ureter, renal pelvis, and collecting system, and enables the biopsy of suspicious lesions. Furthermore, ureteroscopic biopsies can successfully diagnose tumors in more than 90% of cases, maintaining a low false-negative rate, regardless of the size of the sample taken [15].

Recent research has shifted from imaging to the investigation of molecular biomarkers and inflammation to improve the diagnostic accuracy of upper tract urothelial carcinoma (UTUC). Among commonly used blood biomarkers, C-reactive protein (CRP) and interleukin-6 (IL-6) have been extensively studied. Elevated CRP levels indicate systemic inflammation and are associated with tumor progression, reduced survival, and advanced disease stages in urothelial carcinoma. A recent 2023 study by Egger, V., et al. found that fibrinogen and C-Reactive Protein (FC) scores significantly predicted worse survival outcomes in UTUC patients undergoing radical surgery [18]. However, these biomarkers; fibrinogen or CRP lacks specificity for organ involvement and is frequently

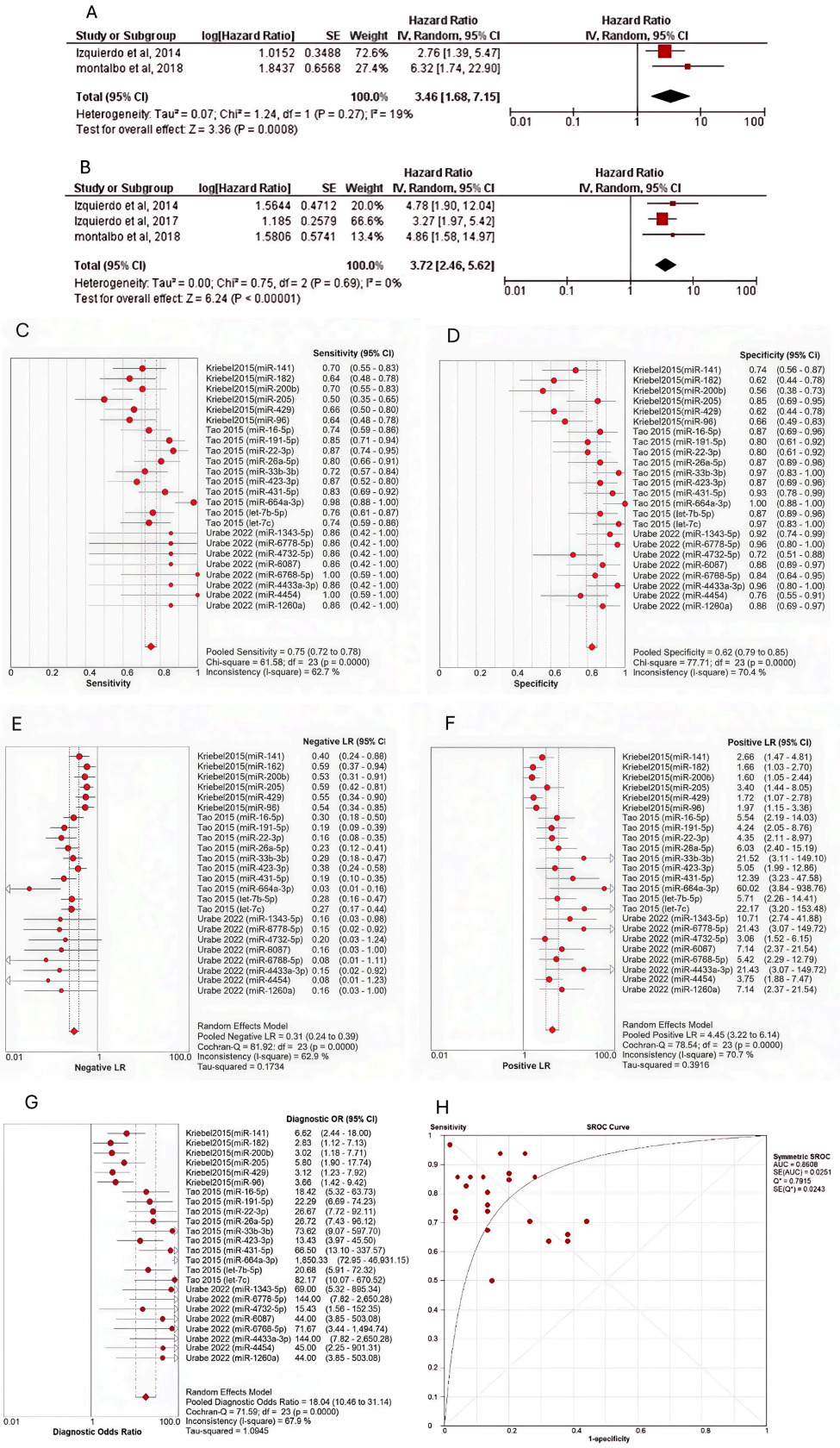

Figure 3. Forest plot of (A) CSS, (B) PFS, (C) Sensitivity, (D) Specificity, (E) Negative Likelihood Ratio, (F) Positive Likelihood Ratio, (G) Diagnostic Odd Ratio, and (H) Summary Receiver Operating Characteristic (SROC) of MicroRNAs as diagnostic biomarker in UTUC. Heterogeneity is expressed as I-square score.

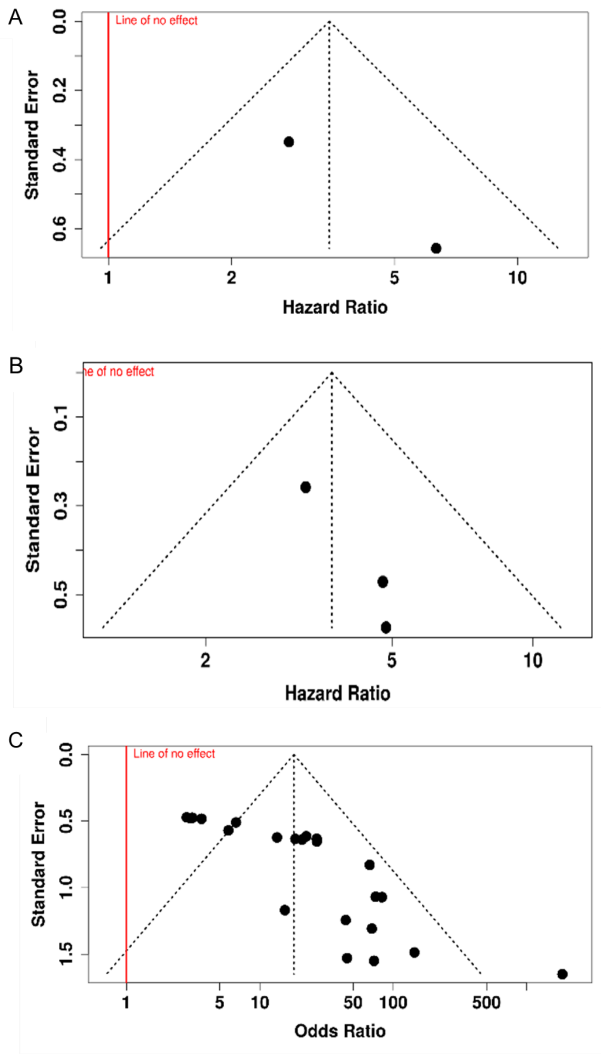

Figure 4. Funnel plot of (A) CSS (B) PFS and (C) DOR of MicroRNAs as diagnostic biomarkers in UTUC.

influenced by non-malignant inflammatory conditions. While IL-6, is mechanistically linked to tumor proliferation, angiogenesis, and immune modulation, elevated plasma/serum IL-6 (and its soluble receptor IL-6sR) correlates with adverse pathologic features and poorer survival in urothelial carcinoma [19]. In some studies, serum IL-6 has moderate discriminatory ability for advanced disease (AUC in the mid-range), but elevated IL-6 is not specific for UTUC and can occur in other inflammatory or malignant conditions [19]. In addition, its usefulness in detecting early stage disease is still limited.

In contrast, microRNAs (miRNAs) have emerged as promising molecular biomarkers that outperform conventional inflammatory and serologic indicators in the diagnosis and prognosis of upper tract urothelial carcinoma (UTUC). miRNAs provide direct markers of molecular dysregulation underlying oncogenesis. Several studies also showed that circulating and urinary miRNAs can accurately differentiate UTUC from benign conditions and predict patient outcomes. In a study conducted by Tao, J., et al. (2015), found that let-7b, miR-22, and miR-431 in serum were effective in distinguishing UTUC cases from controls, with AUCs of 85.6%, 83.6%, and 93.3%, respectively. These miRNAs have also been linked to the pathogenesis of other cancers, further strengthening their potential as biomarkers for cancer detection, including UTUC. Several miRNAs can be used as markers in UTUC prognosis. For example, a study by Montalbo, R., et al. (2018), found that miRNA-151b expression in serum samples significantly predicted cancer-specific progression and survival in UTUC patients, suggesting that miRNA-151b may be a potential minimally invasive biomarker for UTUC patient prognosis [9]. Another study by Izquerdo, L., et al. (2018), showed that miRNA miR-31-5p and miR-149-5p could be a useful prognostic marker of UTUC progression [11].

miRNA expression has been linked to the development and progression of cancer, as well as to many other pathological conditions [16]. Research has shown that certain miRNAs, such as miR-21 and miR-145, are frequently upregulated in UTUC tissues and can be detected in urine samples [20]. Overexpression of miR-222 in tumor tissues has been associated with a higher grade of cancer and a worse overall survival rate. These findings inline with meta-analysis result that UTUC samples with a high-risk expression of microRNAs have higher CSS (3.46x) and higher PFS (3.72x) than low-risk expression.

In our study, we demonstrated miR-6768-5p and miR-4454, achieving highest accuracy of 1.00 (95% CI: 0.59-1.00) although with limited studies. The average pooled sensitivity we observed from multiple microRNAs was 0.75. Another significant microRNA was miR-664a-3p, which demonstrated an accuracy of 1.00 (95% confidence interval: 0.88-1.00). Notably, the average pooled specificity was 0.82. PLR (4.45) imply a strong likelihood, On the other hand, NLR (0.31) suggests that the test was quite effective. The DOR value in this study was 18 times more likely to be found in individuals with the disease and had excellent ability to distinguish the disease, as indicated by the AUC result (0.86). These findings provided compelling evidence that this microRNA profile could serve as a valuable diagnostic tool for UTUC.

Asian patients have higher micro RNA expression compared to Western patients [21]. However, the incidence and disease patterns of

UTUC in Asia vary from those in Western countries. UTUC is far more prevalent among Asian populations, accounting for more than 10% of all UCs in Asia [22]. Other factors such as differences in sample size and the variety of microRNA types can also affect the prognostic and diagnostic results [23]. Future studies should aim to standardize detection methods, validate findings in diverse populations, and explore the therapeutic implications of miRNAs in the management of UTUC.

Limitation

The limitations of this systematic review and meta-analysis include the still limited number of studies and the lack of specific microRNA variation studies. This will certainly affect the accuracy of the data.

Conclusion

MicroRNA could be used as a potential diagnostic and prognostic biomarker in UTUC. More specific studies are needed to consolidate these results.

Conflict of Interest

The authors declare no conflict of interest.

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