Urine Biomarkers for the Diagnosis of Bladder Cancer: A Network Meta-Analysis

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Purpose: To identify effective urine biomarkers for bladder cancer diagnosis.

Materials and Methods: This meta-analysis was conducted following the guidelines of the Meta-Analyses (PRISMA) statement. Relevant studies were searched from the PubMed, Embase, and Cochrane Library databases. Heterogeneity tests were performed using Q statistics and I2 tests to determine the use of the random or fixed effects model. A direct comparison meta-analysis and network meta-analysis were conducted. The effect values are presented as odds ratios and 95% confidence intervals. Sensitivity analysis and consistency tests were performed.

Results: Fifty-eight studies with 12,038 participants were included. Direct comparison meta-analysis showed statistically significant differences in bladder cancer antigen (BTA) trak vs. nuclear matrix protein 22 (NMP22), BTA stat vs. urine cytology (UC), and fluorescence in situ hybridization (FISH) vs. UC, among the sensitivity indicators. Among the specificity indicators, there were statistically significant differences in BTA trak vs. UC, ImmunoCyt (immunocyte) vs. NMP22, and BTA stat vs. FISH. Among the positive predictive indicators, NMP22 vs. UC, BTA stat vs. UC, and FISH vs. NMP22 showed statistically significant differences. Among the negative predictive indicators, the differences in FISH vs. UC, FISH vs. NMP22, and hyaluronidase 1 (HYAL-1) vs. UC were statistically significant. Among the accuracy indicators, FISH vs. NMP22, FISH vs. UC, and HYAL-1 vs. UC showed statistically significant differences. Network meta-analysis showed that HYAL-1, urothelial carcinoma associated 1 (UCA1) and survivin had the highest sensitivity, while UC had the lowest sensitivity. The specificity of UC, FISH, and HYAL-1 was the highest, while that of UCA1 was the lowest. In terms of positive predictive indicators, UC, FISH, and HYAL-1 had the highest positive predictive value, while the BTA group had the lowest positive predictive value. In terms of negative predictive indicators, HYAL-1, UCA1, and survivin had the highest negative predictive value, while UC had the lowest negative predictive value. In terms of accuracy indicators, HYAL-1, UCA1, and survivin had the highest accuracy, while UC had the lowest accuracy.

Conclusion: HYAL-1 and survivin are suitable urine biomarkers for bladder cancer diagnosis.

Keywords: bladder cancer; urine biomarker; network meta-analysis; diagnostic value

INTRODUCTION

Bladder cancer (BC) is a common malignancy of the genitourinary system, which is characterized by urine occult blood, lower back pain, and painful urination[1]. BC is generally induced by family history, bladder infection, smoking, radiotherapy, and chemical exposure [2,3]. The main BC types include transitional cell carcinoma, adenocarcinoma, and squamous cell carcinoma [4]. BC patients in different stages may be treated with surgery, immunotherapy, chemotherapy, or radiotherapy, with five-year survival rates of 77% in the United States[5]. BC is more likely to occur in males than in females, and often occurs in people between the ages of 65–85 years[6]. In 2015, BC affected approximately 3.4 million people and was responsible for 188,000 deaths globally[7]. Therefore, BC should be further studied to improve its diagnosis and treatment. With the development of molecular biology techniques, new BC detection methods have arisen in recent years. Bladder tumor antigen (BTA) and fluorescence in situ hybridization (FISH) are the primary urine biomarkers for noninvasive screening and monitoring of BC in clinical research[8], however, the sensitivity and specificity of urine biomarkers for BC diagnosis vary widely among different studies. For example, nuclear matrix protein-22 (NMP22) and fibronectin have greater sensitivity than voided urine cytology (UC) and urinary BTA, while voided UC and NMP22 have superior specificities[9]. Urinary BTA has higher sensitivity and specificity for screening low- grade and low-stage BC, and thus, may be more valuable for BC diagnosis than the BTA stat test and NMP22[10]. UC is highly specific but poorly sensitive for detecting BC, and FISH combined with UC has good sensitivity and specificity in evaluating BC[11]. Moreover, direct comparison meta-analyses have explored the diagnostic value of urine biomarkers

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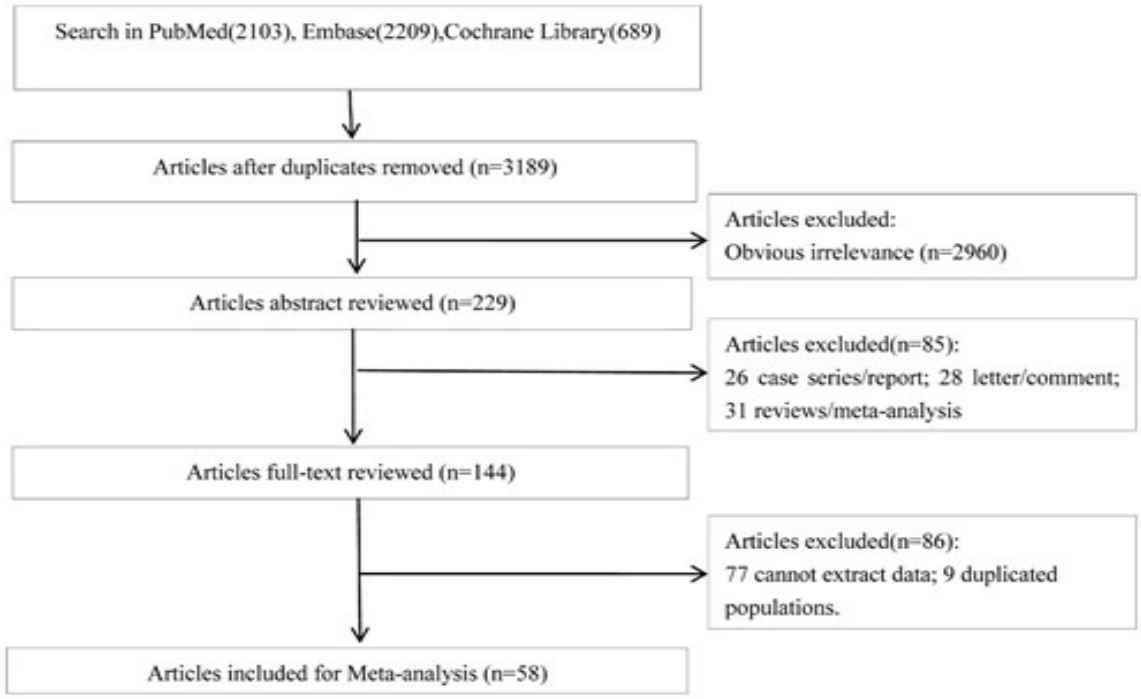

Figure 1. The literature screening processes.

in BC[12,13]. Chou et al. found that urine biomarkers miss a considerable fraction of BC patients, and their accuracies are low for low-grade and low-stage tumors[12]. Guo et al. revealed that the UC test may have a higher Q index, specificity, negative likelihood ratio (LR), positive LR, area under the curve, and diagnostic odds ratio in comparison to the BTA stat test, while the sensitivity of the BTA stat test is superior to that of the UC test[13]. However, no relevant network meta-analyses have been published to date. Therefore, it is necessary to carry out

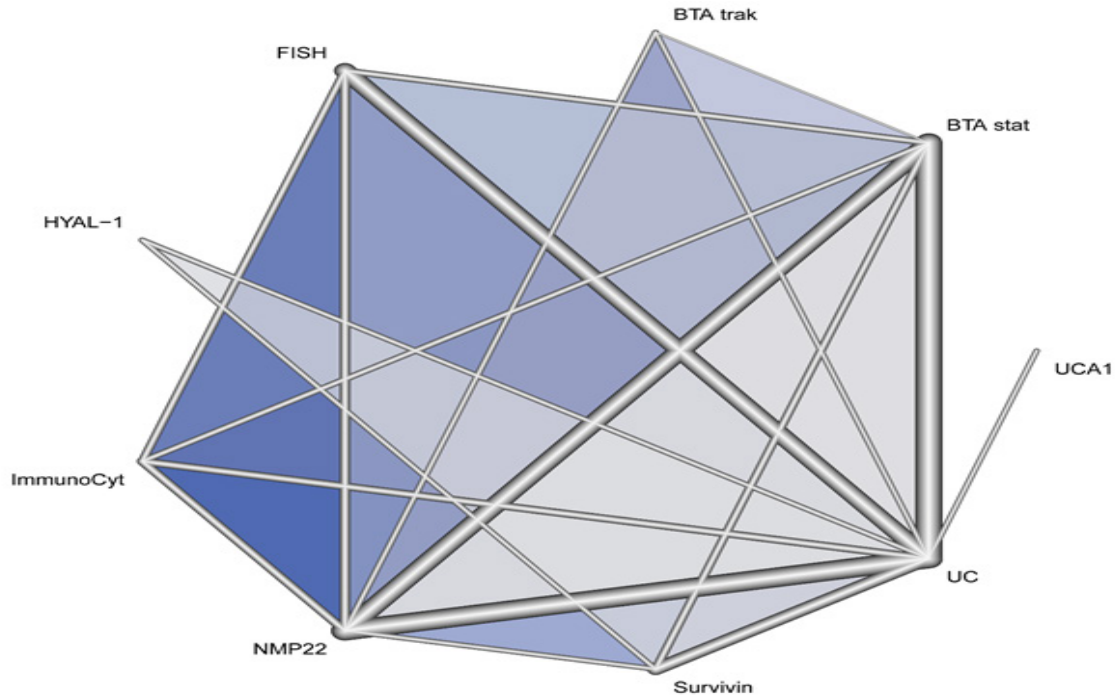

Figure 2. The network diagram. UC: urine cytology; FISH: fluorescence in situ hybridization; NMP-22: nuclear matrix protein 22; UCA1:urothelial carcinoma associated-1; HYAL-1: hyaluronidase 1; UC: urine cytology; ImmunoCyt: immunocyte; BTA: bladder cancer antigen.

Table 1. The comprehensive comparison of sensitivity

BTA stat							
0.84[0.30;2.38]	**BTA trak**						
1.08[0.67;1.74]	1.28[0.44;3.73]	**FISH**					.
0.23[0.07;0.71]	0.27[0.06;1.19]	0.21[0.07;0.66]	**HYAL-1**				.
0.80[0.38;1.69]	0.95[0.28;3.22]	0.74[0.35;1.57]	3.54[0.97;12.92]	**ImmunoCyt**			.
1.10[0.75;1.62]	1.31[0.47;3.60]	1.02[0.65;1.61]	4.84[1.56;15.02]	1.37[0.66;2.83]	**NMP22**		.
0.60[0.31;1.14]	0.71[0.22;2.26]	0.55[0.28;1.09]	2.62[0.88;7.81]	0.74[0.30;1.83]	0.54[0.28;1.04]	**Survivin**	.
2.69[1.90;3.81]	3.19[1.16;8.79]	2.49[1.72;3.59]	11.82[3.98;35.14]	3.34[1.65;6.77]	2.44[1.76;3.39]	4.52[2.52;8.10]	**UC**]
0.47[0.13;1.72]	0.55[0.11;2.78]	0.43[0.12;1.60]	2.05[0.39;10.82]	0.58[0.14;2.45]	0.42[0.12;1.55]	0.78[0.20;3.13]	0.17[0.05;0.61]
UCA1							

Abbreviations: UC, urine cytology; FISH, fluorescence in situ hybridization; NMP-22, nuclear matrix protein 22; UCA1:urothelial carcinoma associated-1; HYAL-1, hyaluronidase 1; UC, urine cytology; ImmunoCyt, immunocyte; BTA, bladder cancer antigen.

a network meta-analysis of the literature related to the accuracy of urine biomarkers in BC diagnosis using cystoscopy or pathological examination as the gold standards. This study may clarify the diagnostic values of several urine biomarkers for BC and provide a scientific basis for future clinical treatment, including hyaluronidase 1 (HYAL-1), urothelial carcinoma associated 1 (UCA1), survivin, immunocyte (ImmunoCyt), BTA stat, NMP22, BTA trak, UC, and FISH..

MATERIALS AND METHODS

This meta-analysis was conducted following the guidelines of the Meta-Analyses (PRISMA) statement [14].

Search strategy

From PubMed (http://www.ncbi.nlm.nih.gov/pubmed), Embase (http://www.embase.com), and Cochrane Library (http://www.cochranelibrary.com) electronic literature databases, the English literature on urine biomarkers in BC diagnosis (published before September 30, 2020) were systematically retrieved. The searching words were "bladder urothelial cell carcinoma" OR "carcinoma of urinary bladder" OR "bladder cancer" OR “carcinoma of bladder" OR "bladder carcinoma" OR "bladder tumor" AND "bladder cancer antigen" OR “BTA” OR "BTA stat" OR "BTA trak", “FISH” OR "fluorescence in situ hybridization", “cytology” OR “cytological”, “ImmunoCyt” OR “immunocyte”, "Nuclear Matrix Protein 22" OR “NMP22”, “HYAL1”, OR “hyaluronidase”, “survivin”, “urothelial carcinoma associated 1” OR “UCA1” AND “diagnostic” OR “diagnosis” OR “sensitiveness” OR “susceptibility” OR “sensitivity” OR “specificity” OR “ROC”. Furthermore, the reference lists of reviews and retrieved articles were manually searched for additional records.

Inclusion and exclusion criteria

Strict inclusion criteria were established, and the included literature were selected based on the following criteria: (1) the study was a published English literature on the diagnostic value of urinary biomarkers in patients with suspected bladder cancer (including primary bladder cancer, and recurrent or metastatic bladder cancer); (2) the cases were pathologically confirmed by cystoscopy or surgically proven bladder cancer patients; (3) the control group included healthy controls and other benign tumor participants; (4) the study involved at least two BTA, FISH, UC, ImmunoCyt, NMP22, HYAL-1, survivin, and UCA1, and the true positive (TP) number, false positive (FP) number, false negative (FN) number, and true negative (TN) number of diagnostic tests could be provided or obtained according to the relevant known indicators.

The exclusion criteria were as follows: (1) the study contained incomplete data and could not be used for statistical analysis; (2) the study was comment, review, letter, etc.; (3) for repeatly published studies or studies involving the same population data, only the most recent study or the study with the most complete information would be included; (4) studies with fewer than 10 patients were excluded in order to reduce the bias caused by chance.

Data extraction

Two investigators independently extracted relevant data from the included literature, and the extracted contents included: the first author of the literature, publication year, study year, study country, total number of included people, age of the subjects, number of men, diagnostic methods of bladder cancer, and number of TP, FP, FN, and TN.

The Quality Assessment of Diagnostic Accuracy Studies (QUADAS) tool was used to evaluate literature quality, and 14 items were evaluated according to three criteria: "yes" (meeting this standard), "no" (not meeting or not mentioned), and "unclear" (partially meeting or not getting information obtained from the literature) [15]. In case of any dispute in the data extraction and quality evaluation processes, a group discussion would be held, and a consistent result would be obtained after communicating with the third investigator.

Statistical analysis

The Meta package (version 3.4.3, http://cran.r-project.org/webpackages/meta/index.html) in R[16] was used for direct comparison. Sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV), and accuracy were used to evaluate the efficacies of the two diagnostic methods, and the odds ratio (OR) and 95% confidence interval (CI) were used as the effect values of the results. Before data consolidation, the research data were tested for heterogeneity, and the I^2 statistic was used for the heterogeneity test. If the heterogeneity test showed a statistical difference ($I^2 > 50\%$), the random effects model was used to calculate the combined effect value. Alternatively, the fixed effects model was selected to merge data ($I^2 \leq 50\%$) [17]. Egger’s test was used to evaluate whether there was publication bias among the included studies.

Network meta-analysis was conducted using the netmeta package (version 3.4.3, https://cran.r-project.org/web/packages/netmeta/index.html) in R[18]. The heterogeneity of the whole network meta-analysis was

Table 2. Comprehensive comparison of specificity.

BTA stat								
1.16[0.44;3.03]	**BTA trak**							
0.34[0.20;0.58]	0.30[0.11;0.82]	**FISH**						
0.26[0.02;2.81]	0.22[0.02;2.85]	0.76[0.07;8.37]	**HYAL-1**					
0.59[0.27;1.30]	0.51[0.16;1.66]	1.73[0.80;3.75]	2.29[0.19;27.17]	**ImmunoCyt**				
0.84[0.57;1.23]	0.72[0.28;1.84]	2.44[1.49;4.01]	3.23[0.30;34.91]	1.41[0.66;3.02]	**NMP22**			
1.29[0.53;3.14]	1.11[0.32;3.92]	3.76[1.45;9.73]	4.96[0.52;47.49]	2.17[0.71;6.67]	1.54[0.63;3.75]	**Survivin**		
0.21[0.14;0.31]	0.18[0.07;0.47]	0.62[0.40;0.94]	0.81[0.08;8.69]	0.36[0.17;0.75]	0.25[0.18;0.36]	0.16[0.07;0.39]UC		
2.01[0.31;13.20]	1.74[0.22;13.76]	5.87[0.89;38.75]	7.75[0.39;155.69]	3.39[0.47;24.64]	2.40[0.37;15.63]	1.56[0.20;11.94]	9.54 [1.52;60.04]	**UCA1**

UC, urine cytology; FISH, fluorescence in situ hybridization; NMP-22, nuclear matrix protein 22; UCA1:urothelial carcinoma associated-1; HYAL-1, hyaluronidase 1; UC, urine cytology; ImmunoCyt, immunocyte; BTA, bladder cancer antigen.

calculated using Cochran's Q statistic, and the model was selected based on the degree of heterogeneity (fixed effect model was used for the combination if the P-values of the Q statistic were all > 0.05. Otherwise, a random-effect model was used for the combination) [19]. The Mantel-Haenszel method was used for the fixed effect model, and the DerSimonian-Laird method was utilized for the random effect model. The good and bad order of each intervention was ranked according to the P-score[20]. The higher the P-score, the better the diagnostic effect. Sensitivity analysis of the P-score was performed using random effect and fixed effect models. In the test of consistency, all the P-values of the node-splitting analysis were used to judge the results of indirect and direct comparisons. If $P > 0.05$, it was considered consistent with the consistency hypothesis.

RESULTS

Eligible studies

The literature retrieval results and literature screening processes are presented in **Figure 1**. A total of 5,001 English articles were retrieved from PubMed (2103), Embase (2209), and Cochrane Library (689) databases using previously developed retrieval strategies. After 1812 duplicates were removed, 3189 studies remained. Then, 2960 articles were filtered out by browsing the title and abstract. From the remaining 229 studies, 171 studies (26 case series/reports, 28 letters/comments, 31 article reviews/meta-analysis, 9 repeated articles, and 77 researches with only a diagnostic method) were screened out after reading the full text. Finally, 58 studies were included in this meta-analysis[21-78].

Study characteristics

The 58 literatures were published from 1998 to 2020. The research locations include the United States, China, Germany, Spain, Italy, and others. A total of 12,038 participants were enrolled in this study. In terms of the age index, the participants were predominantly middle-aged and elderly. In terms of gender, there were more male participants than female participants. Biomarkers mainly included BTA, FISH, UC, ImmunoCyt, NMP22, HYAL-1, survivin, and UCA1. In the BTA trak group, the TP, FP, FN, and TN numbers were 98, 68, 53, and 188, respectively. In the BTA stat group, the TP, FP, FN, and TN numbers were 1177, 573, 571, and 1631, respectively. In the ImmunoCyt group, the TP, FP, FN, and TN numbers were 226, 69, 90, and 171, respectively. In the FISH group, the TP, FP, FN, and TN numbers were 964, 368, 421, and 2878, respectively. In the NMP 22 group, the TP, FP, FN, and TN numbers were 1551, 731, 616, and 3612, respectively. In the UC group, the TP, FP, FN, and TN numbers were 2034, 935, 1592, and 6412, respectively. In the HYAL-1 group, the TP, FP, FN, and TN numbers were 205, 21, 13, and 1239, respectively. In the survivin group, the TP, FP, FN, and TN numbers were 616, 152, 48, and 509, respectively. In the UCA1 group, the TP, FP, FN, and TN numbers were 153, 16, 20, and 110, respectively. (**Supplementary Table 1**).

Quality evaluation of the results showed that the overall quality of the literature was relatively high (**Supplementary Table 2**). However, part of the literatures did not mention "Did the spectrum of patients represent the patients who will receive the test in practice," and all the literatures did not mention "Were uninterruptable/intermediate test results reported." In other projects, most studies showed a low risk of bias.

Direct comparison meta-analysis

First, the heterogeneity test of sensitivity, specificity, positive predictive indicators, negative predictive indicators, and accuracy were performed, and suitable effect models were utilized (**Supplementary Table 3 and Supplementary Figures 1–5**). For instance, in the direct comparison meta-analysis, the sensitivity of BTA

Table 3. The comprehensive comparison of positive predictive.

BTA stat								
1.28[0.59;2.77]	**BTA trak**							
0.48[0.31;0.73]	0.37[0.16;0.85]	**FISH**						
0.26[0.03;2.13]	0.20[0.02;1.88]	0.55[0.07;4.52]	**HYAL-1**					
0.58[0.31;1.05]	0.45[0.18;1.14]	1.20[0.66;2.20]	2.20[0.25;19.13]	**ImmunoCyt**				
0.94[0.70;1.26]	0.74[0.35;1.55]	1.96[1.32;2.92]	3.60[0.44;29.31]	1.63[0.91;2.93]	**NMP22**			
1.30[0.64;2.62]	1.02[0.37;2.78]	2.71[1.27;5.79]	4.97[0.67;36.75]	2.26[0.94;5.43]	1.38[0.68;2.79]	**Survivin**		
0.45[0.33;0.62]	0.36[0.17;0.76]	0.95[0.68;1.33]	1.74[0.22;14.11]	0.79[0.45;1.40]	0.48[0.37;0.64]	0.35[0.18;0.70]	**UC**	
2.36[0.43;13.07]	1.85[0.29;11.71]	4.93[0.89;27.42]	9.04[0.62;132.43]	4.10[0.69;24.26]	2.51[0.46;13.82]	1.82[0.29;11.22]	5.19 [0.96;27.92]	**UCA1**

UC, urine cytology; FISH, fluorescence in situ hybridization; NMP-22, nuclear matrix protein 22; UCA1: urothelial carcinoma associated-1; HYAL-1, hyaluronidase 1; UC, urine cytology; ImmunoCyt, immunocyte; BTA, bladder cancer antigen.

Table 4. Comprehensive comparison of negative predictive.

BTA stat								
0.95[0.46;1.95]	**BTA trak**							
0.85[0.62;1.18]	0.90[0.43;1.88]	**FISH**						
0.25[0.11;0.54]	0.26[0.09;0.73]	0.29[0.13;0.64]	**HYAL-1**					
0.81[0.48;1.35]	0.85[0.36;1.98]	0.95[0.57;1.58]	3.27[1.32;8.10]	**ImmunoCyt**				
1.00[0.77;1.29]	1.05[0.52;2.12]	1.17[0.86;1.59]	4.05[1.84;8.93]	1.24[0.75;2.05]	**NMP22**			
0.62[0.39;0.97]	0.65[0.29;1.46]	0.72[0.45;1.17]	2.51[1.16;5.44]	0.77[0.41;1.44]	0.62[0.39;0.97]	**Survivin**		
1.31[1.04;1.66]	1.39[0.69;2.80]	1.54[1.20;1.98]	5.34[2.49;11.45]	1.63[1.00;2.66]	1.32[1.06;1.64]	2.13[1.42;3.20]	**UC**	
0.39[0.15;0.99]	0.41[0.13;1.28]	0.46[0.18;1.16]	1.58[0.49;5.15]	0.48[0.17;1.35]	0.39[0.15;0.99]	0.63[0.24;1.69]	0.30 [0.12;0.73]	**UCA1**

UC, urine cytology; FISH, fluorescence in situ hybridization; NMP-22, nuclear matrix protein 22; UCA1: urothelial carcinoma associated-1; HYAL-1, hyaluronidase 1; UC, urine cytology; ImmunoCyt, immunocyte; BTA, bladder cancer antigen.

stat vs. FISH, BTA stat vs. NMP22, BTA trak vs. UC, BTA stat vs. UC, and FISH vs. ImmunoCyt showed significant heterogeneity ($I^2 > 50\%$); thus, the random effect model was adopted. There were no significant differences in the sensitivity of BTA stat vs. ImmunoCyt, BTA trak vs. NMP22 ($I^2 < 50\%$); therefore, a fixed-effect model was used.

The results of the meta-analysis showed that there were statistically significant differences between BTA training and NMP22 (NMP22 was superior to BTA trak), BTA stat vs. UC (BTA stat was superior to UC), FISH vs. UC (FISH was superior to UC), NMP22 vs. UC (NMP22 was superior to UC), HYAL-1 vs. UC (HYAL-1 was superior to UC), survivin vs. HYAL-1 (HYAL-1 was superior to survivin), survivin vs. UC (survivin was superior to UC), and UCA1 vs. UC (UCA1 was superior to UC) among the sensitivity indicators ($P < 0.05$). Among the specificity indicators, there were statistically significant differences in BTA training vs. UC (UC was superior to BTA trak), ImmunoCyt vs. NMP22 (ImmunoCyt was superior to NMP22), BTA stat vs. FISH (FISH was superior to BTA stat), BTA stat vs. BTA trak (BTA group was superior to BTA stat), BTA stat vs. UC (UC was superior to BTA stat), NMP22 vs. UC (UC was superior to NMP22), HYAL-1 vs. UC (UC was superior to HYAL-1), survivin vs. UC (UC was superior to survivin), and UCA1 vs. UC (UC was superior to UCA1) ($P < 0.05$). Among the positive predictive indicators, NMP22 vs. UC (UC was superior to NMP22), BTA stat vs. UC (UC was superior to BTA stat), FISH vs. NMP22 (FISH was superior to NMP22), ImmunoCyt vs. NMP22 (ImmunoCyt was superior to NMP22), BTA trak vs. UC (UC was superior to BTA track), UCA1 vs. UC (UC was superior to UCA1), and survivin vs. UC (UC was superior to survivin) showed statistically significant differences ($P < 0.05$). Among the negative predictive indicators, FISH vs. UC (FISH was superior to UC), FISH vs. NMP22 (FISH was superior to NMP22), HYAL-1 vs. UC (HYAL-1 was superior to UC), survivin vs. HYAL-1 (HYAL-1 was superior to survivin), and survivin vs. UC (survivin was superior to UC) were statistically significant ($P < 0.05$). Among the accuracy indicators, FISH vs. NMP22 (FISH was superior to NMP22), FISH vs. UC (FISH was superior to UC), HYAL-1 vs. UC (HYAL-1 was superior to UC), survivin vs. HYAL-1 (HYAL-1 was superior to survivin), and survivin vs. UC (survivin was superior to UC) showed statistically significant differences ($P < 0.05$). There are no significant differences between the other groups (**Supplementary Table 3**). Egger's test showed that there was no significant publication bias among the groups.

Network meta-analysis

Network meta-analysis was performed using the netmeta package, and a network diagram was constructed (**Figure 2**); a total of nine biomarkers are included in this network meta-analysis: HYAL-1, UCA1, survivin, ImmunoCyt, BTA stat, NMP22, BTA trak, UC, and FISH. Among all the indicators, the heterogeneity of the network meta-analysis was calculated using Q statistics. Based on the results, a random effects model was used for meta-analysis consolidation.

The results of the network meta-analysis are listed in **Tables 1–6**. In terms of sensitivity, HYAL-1, UCA1, and survivin were the most sensitive groups in terms of P-score, and UC was the least sensitive group. Moreover, HYAL-1, UCA1, survivin, ImmunoCyt, BTA stat, NMP22, and FISH were statistically different from UC, and BTA stat was statistically different from HYAL-1. In terms of specificity, UC, FISH, and HYAL-1 were the highest, and that of UCA1 was the lowest. UC and FISH were statistically different from BTA stat. BTA, ImmunoCyt , NMP22, and FISH were statistically dif-

Table 5. Comprehensive comparison of accuracy.

BTA stat								
0.91[0.45;1.82]	**BTA trak**							
0.74[0.52;1.06]	0.82[0.40;1.69]	**FISH**						
0.22[0.09;0.53]	0.24[0.08;0.72]	0.30[0.12;0.72]	**HYAL-1**					
0.77[0.44;1.35]	0.85[0.37;1.98]	1.04[0.60;1.80]	3.49[1.29;9.43]	**ImmunoCyt**				
1.01[0.76;1.35]	1.12[0.57;2.21]	1.36[0.97;1.90]	4.57[1.91;10.96]	1.31[0.76;2.26]	**NMP22**			
0.46[0.28;0.76]	0.51[0.23;1.15]	0.62[0.37;1.05]	2.09[0.90;4.89]	0.60[0.30;1.20]	0.46[0.28;0.75]	**Survivin**		
1.03[0.79;1.34]	1.14[0.58;2.23]	1.38[1.05;1.81]	4.65[2.00;10.82]	1.33[0.79;2.26]	1.02[0.80;1.29]	2.22[1.41;3.50]	**UC**	
0.56[0.21;1.50]	0.62[0.19;1.98]	0.75[0.28;2.02]	2.53[0.71;9.02]	0.73[0.24;2.15]	0.55[0.21;1.47]	1.21[0.42;3.47]	0.54 [0.21;1.41]	**UCA1**

UC, urine cytology; FISH, fluorescence in situ hybridization; NMP-22, nuclear matrix protein 22; UCA1: urothelial carcinoma associated-1; HYAL-1, hyaluronidase 1; UC, urine cytology; ImmunoCyt, immunocyte; BTA, bladder cancer antigen.

Table 6. Ranking results of network meta-analysis (P-score).

Sensitivity			Specificity			Positive predictive			Negative predictive			Accuracy	
Group	Fixed	Random	Group	Fixed	Random	Group	Fixed	Random	Group	Fixed	Random	Group	Fixed	Random
HYAL-1	0.9775	0.9596	UC	0.9230	0.9431	HYAL-1	0.8882	0.8452	HYAL-1	0.9712	0.9694	HYAL-1	0.9930	0.9829
UCA1	0.8960	0.7546	FISH	0.7687	0.7867	UC	0.7763	0.8345	UCA1	0.9011	0.8496	Survivin	0.7678	0.8146
Survivin	0.7410	0.7170	HYAL-1	0.8543	0.7709	FISH	0.8247	0.7929	Survivin	0.7329	0.7136	UCA1	0.8624	0.6642
ImmunoCyt	0.5176	0.5429	ImmunoCyt	0.6575	0.5907	ImmunoCyt	0.7222	0.6872	ImmunoCyt	0.5630	0.5105	FISH	0.5032	0.5607
BTAtrak	0.2217	0.5019	NMP22	0.4001	0.4462	NMP22	0.4461	0.4107	FISH	0.5034	0.4800	ImmunoCyt	0.5868	0.4957
BTAstat	0.4666	0.3948	BTAstat	0.2559	0.3137	BTAstat	0.3413	0.3524	BTAtrak	0.2268	0.3612	BTAtrak	0.2430	0.3499
FISH	0.2716	0.3252	BTAtrak	0.4230	0.2703	BTAtrak	0.1931	0.2338	NMP22	0.2986	0.2945	BTAstat	0.1389	0.2332
NMP22	0.4078	0.3020	Survivin	0.1699	0.2168	Survivin	0.2236	0.2182	BTAstat	0.2754	0.2926	NMP22	0.1496	0.2145
UC	0.0002	0.0020	UCA1	0.0477	0.1615	UCA1	0.0846	0.1251	UC	0.0276	0.0286	UC	0.2554	0.1843

UC, urine cytology; FISH, fluorescence in situ hybridization; NMP-22, nuclear matrix protein 22; UCA1: urothelial carcinoma associated-1; HYAL-1, hyaluronidase 1; UC, urine cytology; ImmunoCyt, immunocyte; BTA, bladder cancer antigen.

ferent from UC. In terms of positive predictive indicators, UC, FISH, and HYAL-1 had the highest positive predictive value, while the BTA group had the lowest positive predictive value. HYAL-1 and UC were statistically different from FISH results. Furthermore, the differences in BTA stat/FISH and UC, FISH and NMP22, NMP22 and UC comparison groups were statistically significant. In terms of negative predictive indicators, HYAL-1, UCA1, and survivin had the highest negative predictive value, while UC had the lowest negative predictive value. There was a significant difference between FISH and UC groups. In terms of accuracy indicators, HYAL-1, UCA1, and survivin had the highest accuracy, while UC had the lowest accuracy. The differences between FISH and BTA stat were statistically significant. Additionally, the differences between FISH/NMP22 and UC were statistically significant. There were no statistically significant differences among the groups for the other indicators.

Sensitivity analysis

In the sensitivity analysis, the random effect model and fixed effect model of the P-score were calculated. The results show that the order is basically identical, proving that the results are relatively stable (**Table 6**).

Consistency test

Combined with the P-values of the node-splitting analysis, the results of indirect and direct comparisons were determined. The results showed that most results were > 0.05. These findings suggest that the results are relatively stable (**Supplementary Tables 4–8**).

DISCUSSION

In this meta-analysis, 58 eligible studies were selected. Quality evaluation showed that the overall quality of the included studies was relatively high. Network meta-analysis revealed that HYAL-1, UCA1, and survivin were the most sensitive groups, and UC was the least sensitive group. In terms of specificity, the specificity of UC, FISH, and HYAL-1 was the highest, and that of UCA1 was the lowest. UC, FISH, and ImmunoCyt had the highest positive predictive value, while the BTA trak had the lowest positive predictive value. Moreover, HYAL-1, UCA1, and survivin had the highest negative predictive value, whereas UC had the lowest negative predictive value. Additionally, HYAL-1, UCA1, and survivin had the highest accuracy, while UC had the lowest accuracy. Sensitivity analysis and consistency tests suggest that the results are relatively stable.

HYAL-1 has been reported to play an important role in tumor growth and progression. Kramer et al. found that HYAL-1 expression predicted BC metastasis disease-specific survival[79]. HYAL-1 and -2 are presumed to constitute the major hyaluronidases involved in the catabolism of hyaluronic acid (HA) in somatic tissues. A previous study indicated that HAase mRNA exhibited superior sensitivity (86.67%) over UC (38.33%) with specificities of 97.5% and 100%, respectively, in BC detection[68]. Moreover, survival had a slightly lower sensitivity of survivin (78.33%) than HAase (86.67%) for BC detection[68]. These results indicate that HYAL-1 is useful for BC diagnosis. However, inconsistent findings have been reported in other studies. For example, Eissa et al. showed that UCA1 (91.5% and 96.5%) had a greater sensitivity and specificity than HYAL-1 (89.4 and 91.2%) for distinguishing BC patients from non-BC patients[80]. These controversial results of the above studies might be due to different study countries and different total numbers of included people. Therefore, this network meta-analysis was important for providing a quantitative evaluation of the differences in the 58 included studies.

Survivin is expressed in urine, and its expression is associated with several adverse prognostic signs. Survivin can be reliably and quantitatively measured in the urine of BC patients, improving the sensitivity and specificity of urine cytology for BC diagnosis[68]. A previous study showed that UC had lower sensitivity, accuracy, and negative predictive values than survivin for BC diagnosis[70], which is consistent with our results. Moreover, Chang et al. found that 73% of low-grade BC cases were diagnosed by positive survivin, while only 57.5% were diagnosed with positive UC[81]. The survivin level is a more accurate test than the NMP22 test and the UC for the detection of lower grade and superficial BC [81], which further illustrates that survivin is suitable for BC diagnosis.

HYAL-1 using real-time polymerase chain reaction (RT-PCR) is considered the best individual test, while enzyme-linked immunosorbent assay (ELISA) is the best test for survivin[68]. Despite the lower sensitivity, specificity, and positive predictive value of survivin compared to HYAL-1, survivin detection has the advantage of being a quantitative test measured through ELISA, which is lower cost and more easily performed than RT-PCR.

In this study, the diagnostic results of urine biomarkers (including BTA, FISH, UC, ImmunoCyt, NMP22,

HYAL-1, UCA1, and survivin) for BC were analyzed for the first time using network meta-analysis, providing certain clues and basis for further clinical diagnosis of BC. However, this study also had certain non-negligible shortcomings. First, heterogeneity test showed that heterogeneity was statistically significant, which might be due to different study subjects (primary, recurrent, and metastatic) and different control groups (healthy and benign controls). As a potential confounding factor, heterogeneity might affect the results of the meta-analysis. Second, sponsorship bias may exist in this study. Third, sensitivity analysis of the P-score was performed using the random effect and fixed effect models, while the ranking results were not completely consistent. Furthermore, the consistency test showed that the *P*-values of sensitivity and negative predictive value in BTA trak and NMP22 were < 0.05, which was inconsistent with the consistency test and proved unstable results. The inconsistency might be caused by insufficient literature and other biases (e.g., sponsor bias, selection bias, etc.). Finally, this study only focused on studies on subjects with suspected BC; thus, we will pay attention to this research direction of noninvasive detection tests for BC patients with hematuria in the future, and continue to conduct a meta-analysis.

CONCLUSIONS

In conclusion, HYAL-1 and survivin were found to be the two most suitable urine biomarkers for BC diagnosis. However, more high-quality and rigorous studies are required to support our findings.

CONFLICT OF INTEREST

The authors declare that they have no competing financial interests.

APPENDIX

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