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Review Article

The Possible Relationship of Bladder Microbiota in Urinary Diseases and Cytokine Production: A Systematic Review and Meta-Analysis

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Abstract

Purpose: *The literature examining the relationship between bladder microbiota and urinary diseases and their effect on cytokine production was evaluated through a systematic review and meta-analysis.*
Methods: *The study was designed according to PRISMA criteria. Google Scholar and PubMed electronic databases were searched, and potential studies were selected according to inclusion/exclusion criteria. Studies were included in the meta-analysis using a random effects model. The Newcastle–Ottawa Scale (NOS) was used for bias assessment.*
Results: *Of the 46 studies included, 12 case-control studies covering the years 2019-2025 were deemed suitable for analysis. Most studies were conducted in China and the USA. In the meta-analysis evaluating the relationship between microbiota and disease, the combined effect size was found to be MD = 1.30 (95% CI: -2.18 – 4.78) and was not statistically significant (Z = 0.73; p = 0.46). Heterogeneity is at a very high level. In the meta-analysis regarding cytokine production, the combined analysis result was found to be MD= 21.05 (95% CI: -9.67–51.77), and this difference was not statistically significant (Z = 1.34, p = 0.18). A very high level of heterogeneity was detected among the studies.*
Conclusion: *The included studies have moderate to high methodological quality, and the reliability of the findings is at an acceptable level. The current data are insufficient to draw a definitive conclusion about the effectiveness of the approach evaluated. To obtain stronger evidence, advanced studies with larger sample sizes, using standardized methods, and reporting data suitable for meta-analysis are needed.*

Key Words: *Cytokines, Meta-analysis, Microbiota, Urinary bladder*

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Introduction

Nutrition is a Bladder cancer is common cancer type around the people in the world, with 573,278 new cases and an estimated 212,536 deaths. In the U.S. alone, approximately 84,530 new cases and 17,870 deaths are reported by 2026 (1, 2). Approximately 75% of patients have non-muscle invasive bladder cancer (NMIBC), where the disease is limited to the mucosa or submucosa, while 25% have muscle invasive bladder cancer (MIBC) (3).

Chronic inflammation is a significant risk factor today. Chronic inflammation associated with bladder cancer can arise from a host defense response to microbial infections or from cellular damage caused by stressors. Schistosomiasis, in particular, is an important parasitic infection associated with the development of bladder cancer (4).

Although urine was previously considered sterile, advanced molecular and microbiological methods, particularly 16S ribosomal RNA (16S rRNA) sequencing, have revealed the presence of a rich and diverse microbiome in urine (5, 6). The urinary microbiome can be influenced by many factors, including gender, presence of infection, smoking, dietary habits, and antibiotic use. While much of the research in this area has focused on bacteria, it is thought that different types of microorganisms may also be present in the urinary system (7-9). It also differs between healthy individuals and bladder cancer patients (10, 11). Commensal microorganisms in the bladder have critical role in maintaining physiological balance and preventing unnecessary inflammatory responses. Conversely, disruption of the balance in the urinary microbiota can initiate pro-inflammatory processes by triggering the migration of immune cells to the area (12). By creating a persistent inflammatory environment, this can provide condition for development of bladder cancer over time (12, 13). 16S rRNA gene amplification and sequencing techniques have enabled the characterization of the male urinary microbial community in healthy individuals and the elucidation of disease-related microbial imbalances. As with other components of the human microbiota, the urinary microbiome is thought to influence local immune and inflammatory responses in various urological diseases (14, 15). The possibility of bladder cancer increases with age and has approximately 4 times more effect in men than in women (16). Recently, the role of the urinary microbiome in urothelial carcinogenesis, particularly in relation to gender differences in bladder cancer, has been increasingly investigated (17).

The connection between microorganisms and carcinogenesis is well established for many types of cancer. For example, Helicobacter pylori is associated with stomach cancer, Human Papilloma Virus (HPV) with cervical and penis cancer, Epstein-Barr virus with Burkitt lymphoma, and Escherichia coli with colorectal cancer (18, 19). It has been shown that qualitative or quantitative changes in the composition of the human microbiome can disrupt the body's homeostasis and contribute to the carcinogenesis process (20). However, the exact definition of the urinary microbiome is still not definitively established. But the microbiome is generally described using the concepts of alpha diversity, beta diversity, and relative abundance, and this may be important in understanding the biological mechanisms of bladder cancer (21). The potential for a specific carcinogenic effect in the urinary microbiota makes it a promising biomarker candidate for bladder cancer (22). Furthermore, targeted regulation of the microbiota may offer a novel therapeutic approach that can be considered in addition to standard treatments (23, 24). In this study, we aimed to clarify the possible relationship between bladder microbiota and urinary diseases, and their effect on cytokine production, through a systematic review and meta-analysis.

Methods

This Protocol

This systematic review and meta-analysis was conducted in accordance with the PRISMA guidelines (25).

Study eligibility criteria

This study reviews research investigating the effects of bladder microbiota and microorganisms on urinary diseases and inflammatory response. Case-control, cohort, and cross-sectional studies examining microorganisms in the bladder or urinary tract microbiota and their association with inflammatory processes such as bladder diseases, urinary infections, or cytokine production were included in the study. Animal experiments and in vitro studies, review articles, studies that did not provide sufficient data, and single case reports were excluded from the evaluation.

Identification and selection of studies

Relevant studies were systematically searched in the Google Scholar and PubMed electronic databases within the framework of a predefined search strategy. Appropriate keywords and relevant medical subject headings were used in the search process. The obtained records were initially evaluated based on their titles and abstracts, and potentially suitable studies were identified. The full texts of the studies that

passed this stage were accessed and subjected to detailed review according to predetermined inclusion and exclusion criteria.

Data collection and assessing risk

Data were extracted from studies that met the defined criteria. In this context, data from control and comparison groups were obtained to evaluate the relationship between bladder microbiome and urinary diseases and cytokine production. Bladder microbiome–urinary diseases and bladder microbiome–cytokine production comparisons were analyzed separately using the RevMan program. The validated Newcastle–Ottawa Scale (NOS) was used to assess the risk of bias in non-randomized clinical trials (26). This scale uses a star rating system to evaluate three main categories: sample selection (maximum 4 points), comparability of groups (maximum 2 points), and reliability of exposure or outcome measurement (maximum 3 points). A higher total score indicates higher methodological quality and a lower risk of bias in the study.

Data synthesis

In this study, Review Manager (RevMan 5.4) software was used for meta-analysis of continuous data. For each study included in the analysis, mean, standard deviation (SD), and sample size (n) values for the experimental (patient) and control groups were obtained regularly. In the data extraction process, only quantitative data that were fully reported and suitable for analysis were considered.

Results

Study selection

Selection was made using Google Scholar and PubMed databases. In the first stage, a total of 46 studies that exceeded 18,500 publication evaluations between 2010-2026 were accessed and reviewed. A total of 34 studies were excluded due to not meeting the predefined eligibility criteria. As a result, 12 studies met the eligibility criteria and were considered for quantitative synthesis. Details of the 12 full-text articles that met the eligibility criteria are shown in Table 1.

Table 1: Included studies presented in chronological order by publication year.

Study details	Country	Study design	Case population	Control population	Selection (max 4)	Comparability (max 2)	Exposure (max 3)	Total
(27)	China	Case–control	Bladder cancer tissue	Adjacent normal tissue	3	2	2	7
(28)	USA	Case–control	Hematuria / possible BC	Non-cancer controls	2	1	2	5
(29)	UK	Case–control	rUTI / ASB patients	Healthy controls	4	2	3	9
(30)	USA	Case–control	Bladder cancer patients	Healthy controls	3	2	3	8
(31)	Iran	Case–control	UTI patients	Healthy controls	4	1	3	8
(32)	Italy	Case–control	Bladder cancer patients	Controls	3	2	2	7
(33)	China	Case–control	T2DM patients	Healthy controls	3	1	2	6
(34)	Spain	Case–control	Bladder tumor tissue	Non-tumor tissue	4	2	3	9
(35)	Iraq	Case–control	UTI patients (*E. coli*)	Healthy controls	3	1	3	7
(36)	Czech Republic	Case–control	Bladder cancer patients	Non-cancer controls	4	2	3	9
(37)	China	Case–control	Bladder cancer patients	Healthy controls	3	2	2	7
(38)	China	Case–control	Bladder cancer patients	Healthy controls	4	2	3	9

Although the meta-analysis evaluating the relationship between microbiota and disease included a total of 8 studies, only two studies (36, 37) could be quantitatively included in the analysis. Guo (2023) observed a significant increase in the case group (Mean Difference (MD) = 3.07; 95% Confidence Interval (CI): 2.92–3.22; weight 50.2%), while Hrbáček (2023) found a significant decrease (MD = -0.48; 95% CI: -0.91–-0.05; weight 49.8%). The combined effect size of the analysis, which included a total of 292 cases and 243 control individuals, was found to be MD = 1.30 (95% CI: -2.18 – 4.78), which is not statistically significant (Z = 0.73; p = 0.46). Heterogeneity is very high (I^2 = 100%; Tau^2 = 6.27), indicating significant methodological and clinical differences between studies. Therefore, the current findings do not reveal a clear and consistent relationship between microbiota and disease (Figure 1).

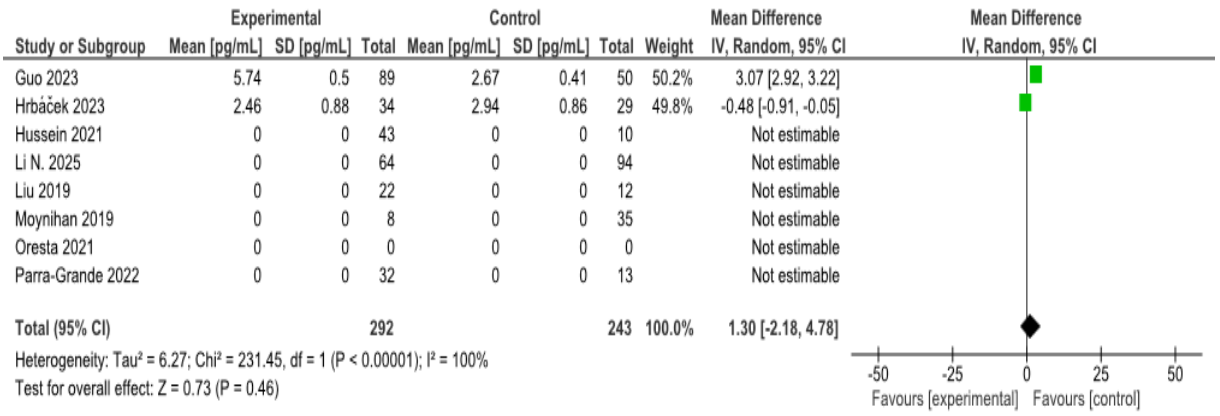

Figure 1. Meta-analysis of studies reporting the association between bladder microbiota and urinary diseases.

The meta-analysis regarding cytokine production included 4 studies (a total of 191 experiments, 135 controls), and one study, Sun (2021) was excluded from the analysis due to missing data. The mean difference (MD) of the combined analysis was found to be 21.05 (95% CI: -9.67–51.77), and this difference is not statistically significant (Z = 1.34, p = 0.18). A very high level of heterogeneity was detected among the studies ($Tau^2 = 725.91$; $Chi^2 = 197.75$, df = 2, $p < 0.00001$; $I^2 = 99\%$), indicating that the results differed significantly between studies. When individual studies were examined, Abbas (2022) (MD = 49.89, 95% CI: 45.29–54.49) and Pirdel (2021) (MD = 8.75, 95% CI: 4.88–12.62) showed significant results in favor of the experimental group, while Drage (2019) found no significant difference (MD = 4.10, 95% CI: -5.57–13.77) (Figure 2).

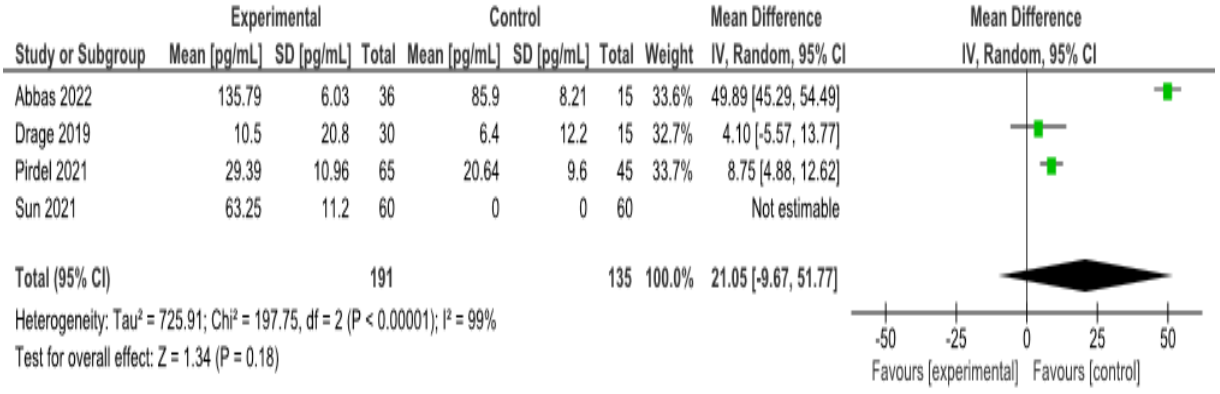

Figure 2. Meta-analysis of studies reporting the relationship between microorganisms and cytokine production.

Overall, although some studies showed significant results in favor of the experimental group, the total effect was not statistically significant due to high heterogeneity and wide confidence intervals. Based on the literature, microorganisms associated with bladder cancer and urinary tract microbiota have been identified. While a significant portion of these microorganisms consist of bacteria, some belong to viral and fungal groups. The analyzed studies show that the urinary microbiota has different compositions in both healthy individuals and bladder cancer patients. In studies on the microbiota associated with bladder cancer, it has been observed that certain bacterial phyla play significant role.

In the study, when the literature data analyzed one by one, reveal a strong association between urinary microbiota and bladder cancer. In particular, changes in bacterial diversity, the enrichment or decrease of specific microorganisms, and the relationship of microbial composition with treatment response suggest that urinary microbiota may play an important role in bladder cancer pathogenesis (Table 2).

Table 2: Composition of Urinary Microbiota (B: Bacteria, V: Virus, H: Healthy, P: Patient, F: Fungal, BC: Bladder Cancer).

Microorganisms	**Group**	**Case**	**Illness Title**	**Referans**
Firmicutes	B	H	–	(37)
Lactobacillus	B	H	–	(37)
Bifidobacterium	B	H	–	(37)
Proteobacteria	B	H	–	(37)
Pasteurella	B	H	–	(36)
Corynebacterium	B	H	–	(36)
Acinetobacter	B	H	–	(36)
Jonquetella	B	H	–	(11)
Parvimonas	B	H	–	(11)
Proteiniphilum	B	H	–	(11)
Saccharofermentans	B	H	–	(11)
Ruminococcus	B	H	–	(32)
Escherichia-Shigella	B	H	–	(39)
Helococcus	B	H	–	(39)
Prevotella	B	H	–	(40)
Gardnerella	B	H	–	(40)
Veillonella	B	P	BC	(36)
Varibaculum	B	P	BC	(36)
(Methylobacterium / Methylorubrum)	B	P	BC	(36)

Actinomyces	B	P	BC	(30)
Achromobacter	B	P	BC	(30)
Brevibacterium	B	P	BC	(30)
Brucella	B	P	BC	(30)
Cupriavidus	B	P	BC	(30)
Anoxybacillus	B	P	BC	(27)
Geobacillus	B	P	BC	(27)
Pelomonas	B	P	BC	(27)
Ralstonia	B	P	BC	(27)
Sphingomonas	B	P	BC	(27)
Stenotrophomonas	B	P	BC	(38)
Propionibacterium	B	P	BC	(38)
Acinetobacter	B	P	BC	(38)
Peptoniphilus	B	P	BC	(38)
Burkholderia	B	P	BC	(17)
Klebsiella	B	P	BC	(17)
Enterococcus	B	P	BC	(32)
Fusobacterium	B	P	BC	(32)
Acinetobacter	B	P	BC	(41)
Corynebacterium	B	P	BC	(41)
Escherichia-Shigella	B	P	BC	(41)
Streptococcus	B	P	BC	(41)
Prevotella	B	P	BC	(41)
Anaerococcus	B	P	BC	(41)
Staphylococcus	B	P	BC	(41)
Pseudomonas	B	P	BC	(41)
Streptococcus	B	P	BC	(42)
(Clostridium sensu stricto)	B	P	BC	(43)
Escherichia	B	P	Pyuria / urinary infection	(44)
Gardnerella	B	P	Pyuria / urinary infection	(44)
Polyomavirus	V	P	Pyuria	(44)
Aerococcus	B	P	Urgency urinary incontinence	(8)
Actinobaculum	B	P	Urgency urinary incontinence	(8)
Oligella	B	P	Urgency urinary incontinence	(8)
Serratia	B	P	BC	(30)
Brochothrix	B	P	BC	(30)
Negativicoccus	B	P	BC	(30)
Pseudomonas	B	P	BC	(30)
Saccharomycetales spp.	F	H	–	(45)
Hypocreales spp.	F	P	BC	(45)
Tremellales spp.	F	P	BC	(45)
Sporidiobolales spp.	F	P	BC	(45)

Studies examining cytokine production show that microorganisms in the bladder and urinary system have significant effects on the host immune response, leading to changes in the expression of various cytokines.

Overall, current studies show that the urinary tract microbiota or bacterial infections regulate the host inflammatory response by affecting the production of cytokines such as IL-1β, IL-6, IL-8, IL-10, IFN-γ, and IL-17A. These findings suggest that bladder microbiota may play a significant role in the pathogenesis of urinary tract infections and the regulation of inflammatory processes (Table 3).

Table 3: The Effect of Microorganisms on Cytokine Production.

Microorganisms	Cytokines	Reference
UTI bacteria	IFN-γ, IL-6, IL-10, IL-17A, TNF-α	(31)
E. coli, *Proteus*, *Klebsiella, Staphylococcus, Enterococcus*	IL-1β	(46)
E. Coli	IL-6, IL-8	(35)
urinary microbiota (multi-species)	IL-6	(33)
E. coli	IL-1, IL-5, IL-8, IL-10	(29)
Lactobacillus spp.	CXCL8 (IL-8)	(47)

Discussion

Studies examining the relationship between urinary microbiota and bladder cancer show differences in microbial composition between healthy individuals and patients. In particular, changes in certain bacterial groups and increases or decreases in specific species are related to the occurence and progression of the disease (32, 36, 37).

The relationships between microbiota, treatment response, and cytokine production are also noteworthy. The association of specific bacteria with response to BCG treatment and changes in cytokines such as IL-1β, IL-6, IL-8, and IL-10 suggest that the microbiota can regulate inflammatory processes and immune responses (30, 31).

The relationship between urinary microbiota and bladder cancer does not seem to be limited to changes in microbial diversity, but may also be related to the tumor microenvironment and immune response. In particular, the relationship between the response to BCG treatment and certain bacteria indicates that the microbiota may be a potential determinant in the course of the disease and treatment response.

Changes in cytokines suggest that this relationship may occur through inflammatory and immunological mechanisms. Therefore, urinary microbiota is a noteworthy research area in bladder cancer in the future, both in terms of understanding disease mechanisms and developing new biomarkers and treatment approaches.

In this meta-analysis, when the results regarding the relationship between bladder microbiota and both cytokine levels and urinary diseases are evaluated together, it is seen that although significant findings were obtained in some individual studies, the overall effect is not statistically significant. One of the most important reasons for this is the very high level of heterogeneity observed in both analyses (I^2=99%; I^2=100%, respectively). Such high heterogeneity suggests that there are significant methodological and clinical differences between the studies. Although some studies (31, 35) showed strong and significant effects in favor of the experimental group in cytokine analysis, the fact that the study (29) did not support this effect reduced the significance of the combined effect. These differences may stem from variations in sample sizes, characteristics of patient populations, measurement methods, and evaluation times. In particular, the fact that cytokine levels are biologically quite dynamic and easily affected by environmental/clinical factors may have increased the inconsistency between the results. In the analysis of the relationship between bladder microbiota and urinary diseases, the inclusion of only two studies in the meta-analysis is a significant limitation. The opposing results of these two studies (37) in favor of the experimental group, (36) in favor of the control group led to the combined effect being found insignificant. Furthermore, the fact that other studies were deemed "not estimable" indicates that data reporting deficiencies are common in the literature and significantly limits the power of the meta-analysis.

Furthermore, the fact that a significant portion of the studies have been conducted in specific geographical areas such as China and the USA may limit the generalizability of the obtained microbiota findings to different geographical and cultural populations. Indeed, significant differences in microbiota composition are reported depending on factors such as geographical location, lifestyle, and diet, and it has been shown that diet and lifestyle are among the determinants of microbial diversity (48). In terms of urinary microbiota, it has also been reported that factors such as age, gender, diet, and study location can affect microbial composition (49, 50). Furthermore,

regarding the possible effect of cultural factors on the microbiota, there is a study reporting that the Islamic fasting practice alters the abundance of certain bacteria in the gut microbiota (51). In this context, the possibility that Muslim countries may have different microbiomes from others in terms of culture, diet, and hygiene can be considered as a subject of future research.

Another important point that stands out in both analyses is the limited sample sizes and the fact that most studies have retrospective or heterogeneous designs. This reduces the generalizability of the results obtained. In addition, the differences in measurement standards between studies make it difficult to compare the results.

In the study, when the literature data analyzed one by one, reveal a strong association between urinary microbiota and bladder cancer. In particular, changes in bacterial diversity, the enrichment or decrease of specific microorganisms, and the relationship of microbial composition with treatment response suggest that urinary microbiota may play an important role in bladder cancer pathogenesis. But when looking total perspective for meta-analyse, when the results of the relationship between bladder microbiota, cytokine levels, and urinary diseases were evaluated together, “due to high heterogeneity, different patient groups, different analyse methods”, no statistically significant difference was found overall between the experimental and control groups. Although some individual studies showed significant results in favor of the experimental group, these effects were not consistent across studies. Six studies (2 microbiota and 4 cytokine) were included in the meta-analysis out of twelve. Although all twelve studies met the inclusion criteria specified in the text in terms of quality, only six were deemed suitable for the meta-analysis based on their (mean, SD, and n) values.

The use of PubMed and Google Scholar in this study was deemed appropriate due to PubMed's comprehensive structure in the biomedical literature and Google Scholar's broad access to publications. However, the use of only these two databases is a limitation of the study; some studies in databases such as Embase, Scopus, and Web of Science may have been overlooked. Nevertheless, the combined use of these two databases allowed access to a significant portion of the relevant literature and supported the main findings of the study. The use of more databases in the future could expand the scope of the literature.

Conclusion

In this meta-analysis, when the results of the relationship between bladder microbiota, cytokine levels, and urinary diseases were evaluated together, no statistically

significant difference was found overall between the experimental and control groups. Although some individual studies showed significant results in favor of the experimental group, these effects were not consistent across studies. The very high heterogeneity observed in both analyses (I^2=99–100%) limits the reliability of the findings and indicates significant methodological differences between studies. Furthermore, the exclusion of many studies from the meta-analysis, particularly in the analysis of the relationship between bladder microbiota and urinary diseases, reveals the limited available evidence. In conclusion, the current data are insufficient to draw a definitive conclusion about the effectiveness of the approach evaluated. To obtain stronger evidence, advanced studies with large-scale sample sizes, using standardized methods, and reporting data suitable for meta-analysis (mean, SD, n) are needed.

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Conflict of Interest

None.

Author Contributions

M.A.: Study hypothesis, design, management, data collection / processing / analysis / interpretation, literature review, writing; D.Y.: Data collection / processing / analysis / interpretation, literature review; O.C.: Study hypothesis, design, management, information / equipment procurement, review.

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