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Original Article

Preoperative risk factors associated with urosepsis following percutaneous nephrolithotomy: a meta-analysis

Zhiqiang Hao*, Jingshen Wang*, Qinzhang Wang, Guangchao Luan, Biao Qian

*Department of Urology Surgery, The First Affiliated Hospital of Medical College in Shihezi University, Shihezi 832000, Xinjiang, China. *Equal contributors and co-first authors.*

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Abstract: Objective: The aim of this meta-analysis was to identify the preoperative risk factors associated with urosepsis after percutaneous nephrolithotomy. Methods: A systematic search using electronic databases was performed to analyze the preoperative risk factors associated with urosepsis following percutaneous nephrolithotomy. The search period was from January 2006 to December 2016. Results: Totally, 18 studies were included in the analysis. Nine factors were identified as significant risk factors ($P<0.05$). These factors as well as their OR and 95% CI were listed as follows: female gender OR=3.89 (95% CI [2.07, 7.31], age (≥ 60 years) OR=1.71 (95% CI [1.23, 2.39]), diabetes mellitus OR=3.15 (95% CI [2.10, 4.72]), blood routine (White blood cells ≥ 10×10^9/L) OR=2.86 (95% CI [1.66, 4.92]), urinalysis (White blood cells ≥ +) OR=2.43 (95% CI [1.35, 4.37]), urine culture (positive) OR=1.60 (95% CI [1.12, 2.29]), stone size (≥ 2 cm) OR=1.94 (95% CI [1.49, 2.54]), staghorn stone OR=3.07 (95% CI [1.78, 5.31]), and, hydronephrosis (moderate-severe) OR=1.57 (95% CI [1.02, 2.43]). No significant difference was observed in terms of blood pressure, use of antibiotics before surgery and history of surgery. Conclusions: In summary, female gender, age (≥ 60 years), diabetes mellitus or history of preoperative infection, larger stones (≥ 2 cm), staghorn stone and severe hydronephrosis are identified as the possible risk factors of urosepsis after percutaneous nephrolithotomy. Recognition of these factors can be useful in early diagnosis and management of urosepsis. Thus, clinicians should pay attention to high risk patients to reduce the incidence of postoperative urosepsis.

Keywords: Percutaneous nephrolithotomy, urosepsis, risk factors, meta-analysis

Introduction

Renal stone is one of the common urological conditions. In current practice, percutaneous nephrolithotomy (PCNL) is the main treatment for renal stone. Urosepsis is the devastating complication following PCNL and the reported incidence of urosepsis after PCNL is 0.3-4.7% [1-3]. The preoperative risk factors associated with urosepsis following PCNL are widely studied, however, the results are not conclusive. For example, previous studies have reported that positive-urine culture, stone diameter, staghorn calculus, operation time, and blood transfusion are associated with systemic inflammatory response syndrome after PCNL [4, 5].

The aim of this review is to analyze risk factors of urosepsis and provide a theoretical basis for clinicians to assess high risk patients undergoing PCNL.

Materials and methods

Search strategy

The databases of CNKI, WANFANG, VIP Paper Check System, PubMed, EMBASE were searched. The search period was from January 2006 to December 2016. Articles that included risk factor associated with urosepsis following PCNL were retrieved. The search terms included "percutaneous nephrolithotomy" AND ("septic shock" OR "urosepsis") AND "risk factors". Articles in Chinese and English were both searched.

Inclusion and exclusion criteria

Inclusion criteria: 1) The original literatures on risk factor for urosepsis following PCNL; 2) Literatures with the definitions and quantitative indicators of risk factors; 3) Literatures with risk

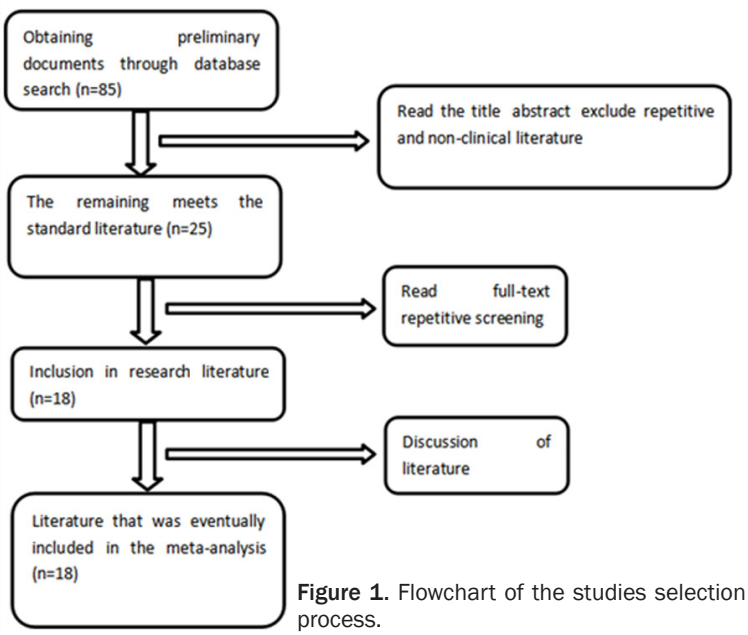

Figure 1. Flowchart of the studies selection process.

factor that could be accurately extracted (OR value and 95% confidence interval, 95% CI) or the OR and 95% CI could be calculated from the original data.

Exclusion criteria: 1) The literature with incomplete data or duplicate publication; 2) The original literature without accessible full text.

Quality assessment

Quality assessment of the included literature was performed according to Newcastle-Ottawa Scale.

Data extraction

Two authors independently extracted full texts of potentially eligible articles. The extracted data included basic information, research period, and type of research design.

Statistical analysis

The data was statistically analyzed using review manager 5.3, SPSS 22.0, and State 12.0 software. The standardized mean difference (SMD) was used to compare and analyze the numerical data with large differences in mean. Heterogeneity was tested by testing I^2. The heterogeneity was considered low when I^2<50% and high when I^2 > 50%. The random effect model was used when P<0.05 and I^2 > 50%. The fixed effect model was used when P > 0.05 and $I^2 \leq 50\%$. Subgroup analyses were used to detect heterogeneity sources included in the literature, and subgroups were grouped primarily based on characteristics such as gender, underlying disease, and stone size. The normal measurement data are expressed as the mean ± standard deviation. The median and quartiles are used to represent the data that do not meet normal distribution. The count data is expressed as the percentage and the comparison between the two groups was performed with the Chi-square test. Univariate analysis and logistic regression analysis were used to analyze the risk factors associated with urinary sepsis after PCNL. Pooled results were expressed in SMD and 95% CI. All statistical analyses used a two-sided test and were considered statistically different when P<0.05.

Results

Article retrieval

The flow chart for article enrollment was shown in **Figure 1**. A total of 85 (60 articles in Chinese and 25 articles in English) potential publications were identified. According to the inclusion and exclusion criteria, 67 studies were excluded and finally 18 case-control studies (14 articles in Chinese and 4 articles in English) were included in the final review. The characteristics of included studies were listed in **Table 1**.

Meta analysis outcomes

Among the 12 preoperative risk factors included in the study, 9 factors were identified to be associated with urosepsis and were statically significant (P<0.05) (**Table 2**) (**Figures 2-13**). Heterogeneity was measured and was present in the following five factors: female, age (≥ 60 years), diabetes mellitus, urinalysis (white blood cell (WBC) ≥ +), and urine culture (positive) (I^2 > 0%). Further sensitivity analysis in these five factors was performed. Sensitivity analysis and heterogeneity test outcomes are shown in **Table 3**.

Table 1. Demographics of individual studies

First author	Research type	Publication time (y)	Number of cases	Risk factors for research*	Literature quality evaluation (fraction)
Shiqiang Zhang [7]	Case-control study	2017	926	A, B, D, H	8
Jianbo Zhang [22]	Case-control study	2016	328	A, F, I	8
Zhenglong Zhang [23]	Case-control study	2017	724	A, B, D, F, H, I, L	8
Yuan Li [8]	Case-control study	2016	350	A, B, C, D, F, G, H,	7
Zesong Yang [9]	Case-control study	2016	412	A, B, D, J	8
Zhong Tu [24]	Case-control study	2013	209	A, B, C, D, F, G, H, J	8
Jiantao Xiao [6]	Case-control study	2015	1022	A, B, C, D, E, F, G, H, J, K	8
Weijun Ge [25]	Case-control study	2014	1260	A, B, E, H, I,	8
Xumin Xie [10]	Case-control study	2015	204	A, B, G, H, I,	8
Yueyun Deng [2]	Case-control study	2016	456	A, E, H, J, L	8
Guang Chen [26]	Case-control study	2015	358	A, D, F, G, H	8
Shulian Chen [27]	Case-control study	2014	386	A, B, D, F, G, H, J, K, L	8
Zikun Gao [28]	Case-control study	2014	682	A, B, C, D, F, G, H,	7
Xuanchen Zhou [29]	Case-control study	2012	266	G	7
Yanbo Wang [30]	Case-control study	2012	420	L	8
Omer Koras [11]	Case-control study	2015	303	J, L	8
Aso Omer Rashid [31]	Case-control study	2016	60	A, D, G, I, L	8
Chunlai Liu [32]	Case-control study	2013	834	A, B, C, D, F, G, H, J	8

Note: *A: female; B: age ≥ 60 years; C: hypertension; D: Diabetes; E: blood routine (white blood cells ≥ 10×10^9/L); F: urine routine (leukocyte +); G: urine culture (positive); H: stone size (≥ 2 cm); I: stag-horn stones; J: history of stone surgery; K: preoperative use of antibiotics; L: hydronephrosis (moderately severe).

Gender (female)

A total of 15 studies focused on female gender, including 13 Chinese articles and 2 English articles. These articles reported 8220 cases, including 305 cases of urosepsis and 7915 cases of non-urological cause of sepsis. A random-effect model was used as the heterogeneity was high (P<0.10, I^2=76%) with Z=4.22 and P<0.05. Heterogeneity was substantial in further sensitivity analysis, suggesting female gender as an independent risk factor of urosepsis. Female gender was statistically significant in both the urosepsis and the non-urological cause of sepsis group (OR=3.89, 95% CI [2.07, 7.31], P<0.01) (**Figure 2**).

Age

A total of 11 studies were related to age, including 10 Chinese and 1 English articles. These articles reported 7070 cases with 250 cases of urosepsis and 6820 cases of non-urological cause of sepsis. Statistical analysis showed heterogeneity (P<0.10, I^2=74%). In sensitivity analysis, the study by Xiao et al [6] did not meet the criteria and was excluded from the analysis. Further random-effect model analysis showed homogeneity (P=0.52, I^2=0%) with Z=3.17 and P=0.002. Age ≥ 60 was statistically significant in both the urosepsis and the non-urological cause of sepsis group (OR=1.71, 95% CI [1.23, 2.39], P=0.002) (**Figure 3**).

Hypertension

A total of 5 studies reported hypertension, including 4 Chinese and 1 English articles. Totally, 3106 cases were reported, including 107 cases of urosepsis and 2999 cases of non-urological cause of sepsis. Statistical analysis showed homogeneity (P=0.86, I^2=0%). Further random-effect model showed Z=0.88 and P=0.38. Thus, hypertension was not a significant risk factor in both groups (OR=1.22, 95% CI [0.78, 1.92], P=0.38) (**Figure 4**).

Diabetes mellitus

A total of 11 articles were related to DM, including 9 Chinese and 2 English articles. These articles reported 6016 cases with 228 cases of urosepsis and 5789 cases of non-urological cause of sepsis. Statistical analysis showed heterogeneity (P=0.06, I^2=44%). In sensitivity analysis, the studies by Zhang et al [7], Li et al

Table 2. Meta-analysis of 12 risk factors associated with Urosepsis after PCNL

Research factors	Number of documents	Number of cases	Control number	Heterogeneity test		Adopted model	OR (95% CI)	Z	*P*
				P	I^2				
Gender (Female)	15	305	7915	*P*<0.10	76%	Random Effect Model	3.89 [2.07, 7.31]	4.22	*P*<0.05
Age (≥ 60 years old)	11	188	5860	*P*<0.10	74%	Random Effect Model	2.08 [1.13, 3.82]	2.36	*P*=0.02
Hypertension	5	107	2999	*P*=0.86	0%	Random Effect Model	1.22 [0.78, 1.92]	0.88	*P*=0.38
Diabetes	11	228	5789	*P*=0.06	44%	Random Effect Model	3.70 [2.33, 5.90]	5.52	*P*<0.05
Blood routine (white blood cells ≥ 10×10^9/L)	3	114	2624	*P*=0.72	0%	Random Effect Model	2.86 [1.66, 4.92]	3.78	*P*<0.05
Urine routine (white blood cell ≥ +)	9	179	4723	*P*=0.02	57%	Random Effect Model	1.99 [1.06, 3.75]	2.14	*P*=0.03
Urine culture (positive)	9	168	4152	*P*=0.02	55%	Random Effect Model	2.04 [1.12, 3.69]	2.34	*P*=0.02
Stone size (≥ 2 cm)	12	278	7196	*P*=0.98	0%	Random Effect Model	1.94 [1.49, 2.54]	4.85	*P*<0.05
Stag-horn stones	5	65	2511	*P*=0.68	0%	Random Effect Model	3.07 [1.78, 5.31]	4.02	*P*<0.05
Hydronephrosis (moderate to severe)	5	102	1827	*P*=0.64	0%	Random Effect Model	1.57 [1.02, 2.43]	2.03	*P*=0.04
History of stone surgery	7	181	3441	*P*=0.04	55%	Random Effect Model	1.39 [0.83, 2.32]	1.26	*P*=0.21
Preoperative use of antibiotics	2	97	1311	*P*=0.01	83%	Random Effect Model	0.77 [0.24, 2.53]	0.43	*P*=0.67

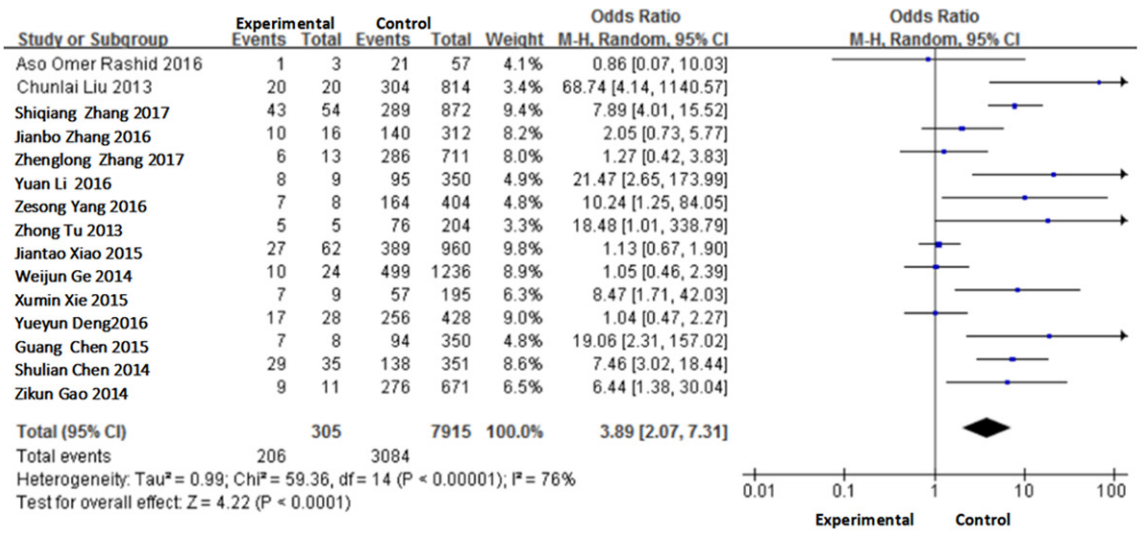

Figure 2. Meta-analysis of female factors in urosepsis and non-urological cause of sepsis.

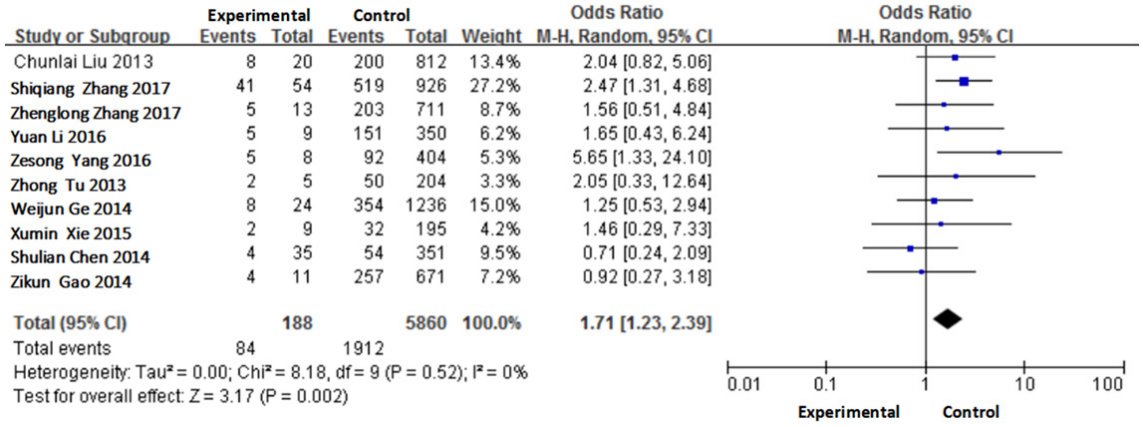

Figure 3. Meta-analysis of age ≥ 60 years in urosepsis non urological cause of sepsis.

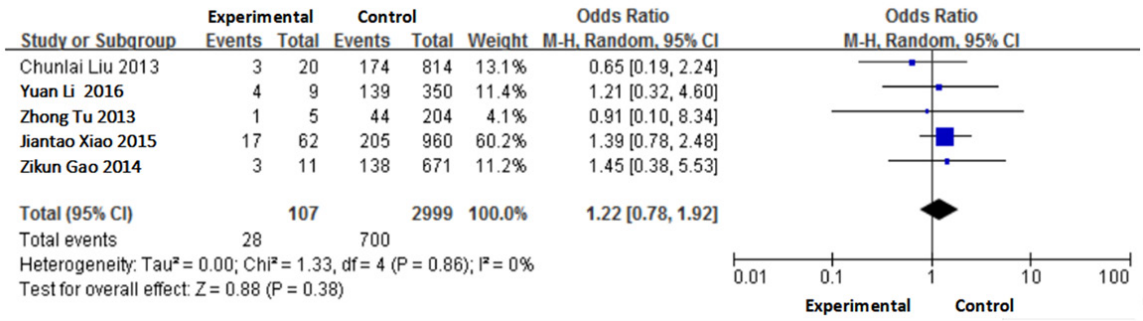

Figure 4. Meta-analysis of hypertension in urosepsis non urological cause of sepsis.

[8], and Yang et al [9] did not meet the criteria and were excluded. Further random-effect model analysis showed homogeneity (P=0.61, I^2=0%) with Z=5.57 and P<0.01. Thus, diabetes was a significant factor in both groups (**Figure 5**).

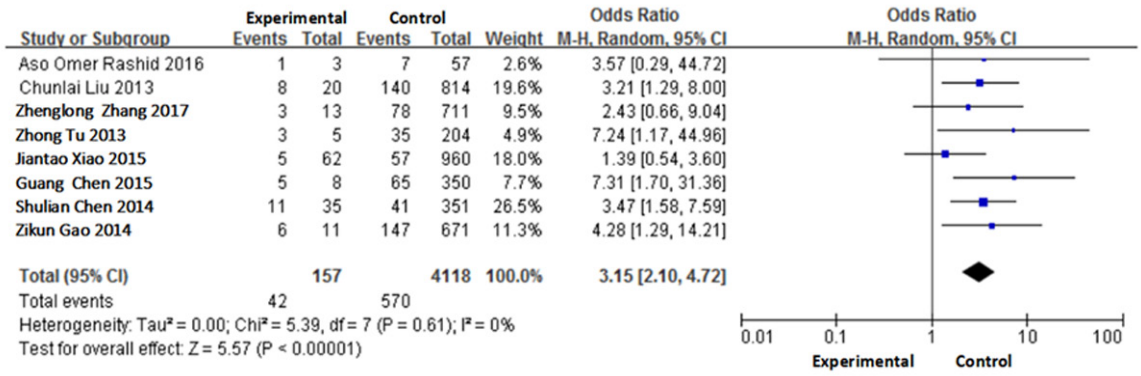

Figure 5. Meta-analysis of diabetes in urosepsis non urological cause of sepsis.

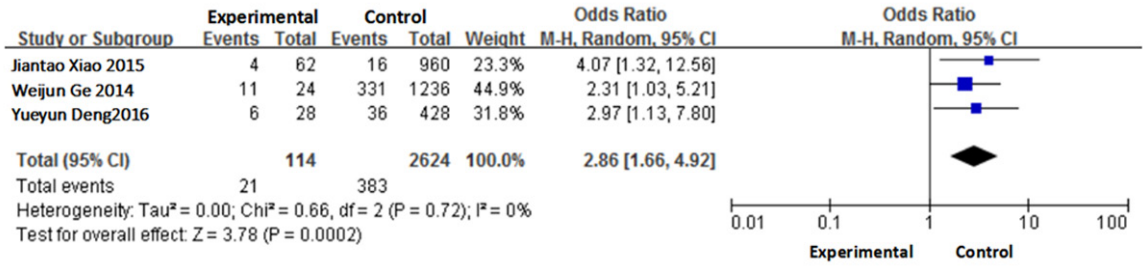

Figure 6. Meta-analysis of blood routine (WBC > 10×10^9/L) urosepsis non urological cause of sepsis.

Blood routine (WBC > 10×10^9/L)

Three Chinese studies reported the blood routine (WBC > 10×10^9/L), which included 114 cases of urosepsis and 2624 cases of non-urological cause of sepsis. Meta analysis showed homogeneity (P=0.72, I^2=0%) with Z=3.78 and P<0.01. Thus, blood routine (WBC > 10×10^9/L) was a significant factor in both groups (OR=2.86, 95% CI [1.66, 4.92], P<0.01) (**Figure 6**).

Urinalysis (WBC ≥ +)

Urinalysis (WBC ≥ +) was analyzed in 8 articles, including 7 Chinese and 1 English articles. Totally, 7726 cases with 317 cases of urosepsis and 7409 cases of non-urological cause of sepsis were reported. Statistical analysis showed heterogeneity (P=0.02, I^2=57%). In sensitivity analysis, the report by Li et al [8] did not meet the criteria and was excluded. The random-effect model analysis showed homogeneity (P=0.08, I^2=45%) with Z=2.96 and P<0.01. Further sensitivity analysis showed no significant difference. Therefore, urinalysis (WBC ≥ +) was a significant contributing factor in both groups (OR=2.43, 95% CI [1.35, 4.37], P<0.01) (**Figure 7**).

Urine culture positive

Nine studies, including 8 Chinese and 1 English articles, were related to positive urine culture. These studies reported 5214 cases with 225 cases of urosepsis and 4989 cases of non-urological cause of sepsis. Statistical analysis showed heterogeneity (P=0.02, I^2=5%). The article by Xie et al [10] did not meet the criteria and was excluded from the sensitivity analysis. The random-effect model analysis showed homogeneity (P=0.43, I^2=40%) with Z=2.58, P=0.01. No significant difference was found in further sensitivity analysis. Thus, positive urine culture was a significant contributing factoring in both groups (OR=1.60, 95% CI [1.12, 2.29], P<0.01) (**Figure 8**).

Stone size

Twelve studies reported stone size. These studies included 11 Chinese and 1 English articles and reported 11480 case, including 469 case of urosepsis and 11011 cases of non-urological cause of sepsis. Statistical analysis showed homogeneity (P=0.98, I^2=0%), with Z=4.85, P<0.01. Thus, stone size was a significant factor in both groups (OR=1.94, 95% CI [1.49, 2.54], P<0.01) (**Figure 9**).

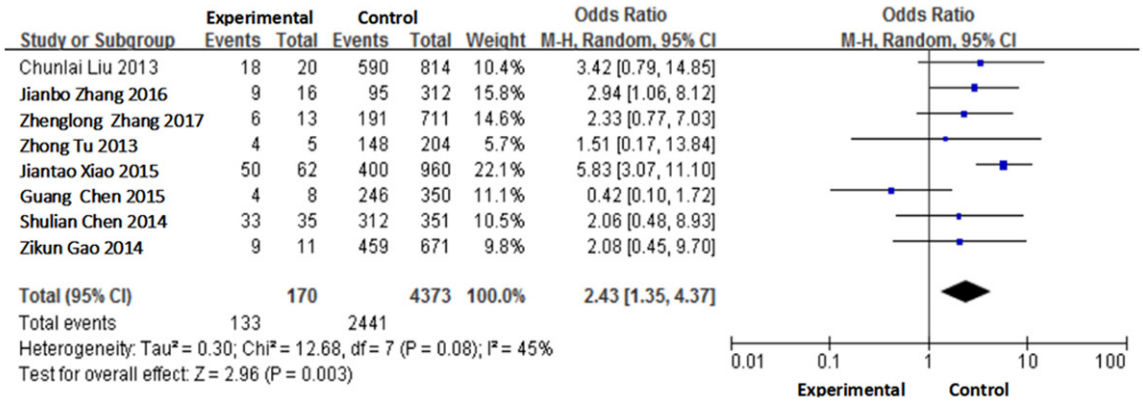

Figure 7. Meta-analysis of urine routine (white blood cell ≥ +) in urosepsis and non-urological cause of sepsis.

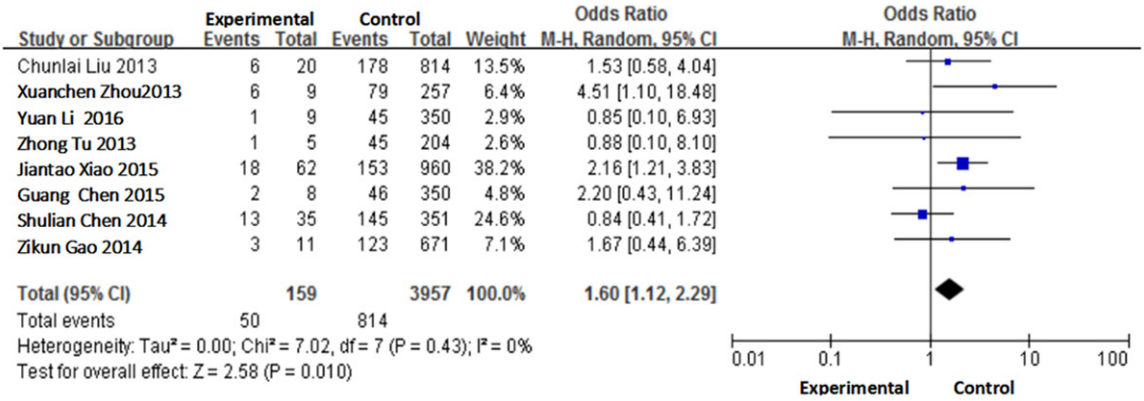

Figure 8. Meta-analysis of urine culture (positive) in urosepsis and non-urological cause of sepsis.

Staghorn stone

Staghorn stone were reported in 5 studies, including 4 Chinese and 1 English articles. Totally, 2979 cases with 89 cases of urosepsis and 2890 cases of non-urological cause of sepsis were reported. Statistical analysis showed homogeneity (P=0.68, I^2=0%), with Z=4.85, P<0.01. Thus, staghorn stone was a significant factor in both groups (OR=3.07, 95% CI [1.78, 5.31], P<0.01) (**Figure 10**).

Degree of hydronephrosis (moderate-severe)

A total of 6 studies focused on the degree of hydronephrosis (moderate-severe), including 3 Chinese and 3 English articles, which reported 3781 cases with 184 cases of urosepsis and 3597 cases of non-urological cause of sepsis. Statistical analysis showed heterogeneity (P=0.24, I^2=26%). The study by Wang et al [11] did not meet the criteria and was excluded from the sensitivity analysis. The random-effect model analysis showed homogeneity (P=0.64, I^2=0%) with Z=2.03 and P=0.04. The sensitivity analysis was not significant. Thus, degree of hydronephrosis (moderate-severe) was a significant contributing factor in both groups (OR=1.57, 95% CI [1.02, 2.43], P<0.05) (**Figure 11**).

Past history of surgery for stone

A total of 7 studies included information on past history of surgery for stone. These articles included 5 Chinese and 2 English articles, reporting 2165 cases with 270 cases of urosepsis and 5004 cases of non-urological cause of sepsis. Statistical analysis showed heterogeneity (P=0.04, I^2=55%). The random-effect model analysis showed Z=1.26 and P=0.21. Further sensitivity analysis showed persistence of heterogeneity. Thus, past surgical history for stone was not significant in both the groups (**Figure 12**).

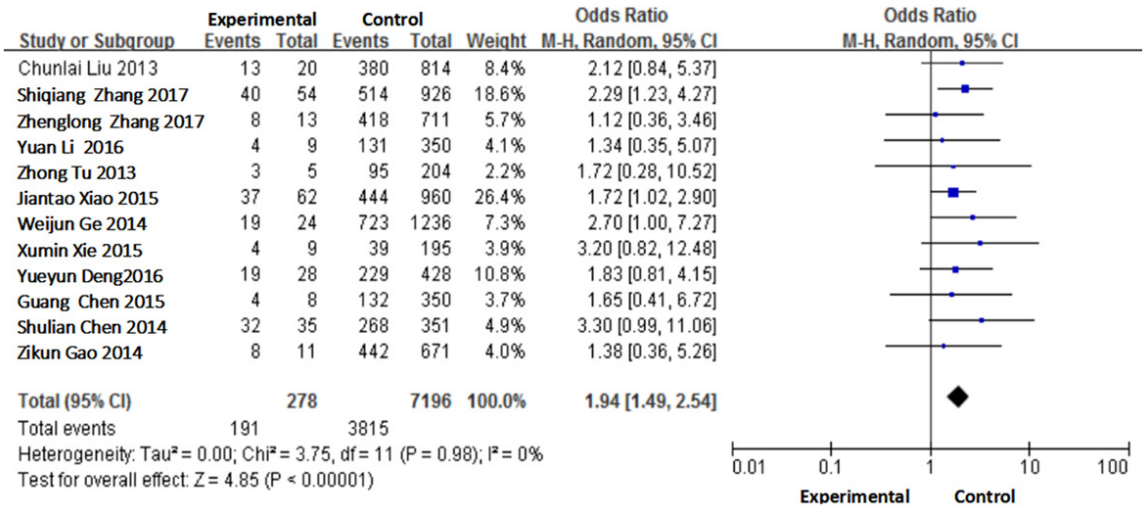

Figure 9. Meta-analysis of the size of stones in urosepsis and non-urological cause of sepsis.

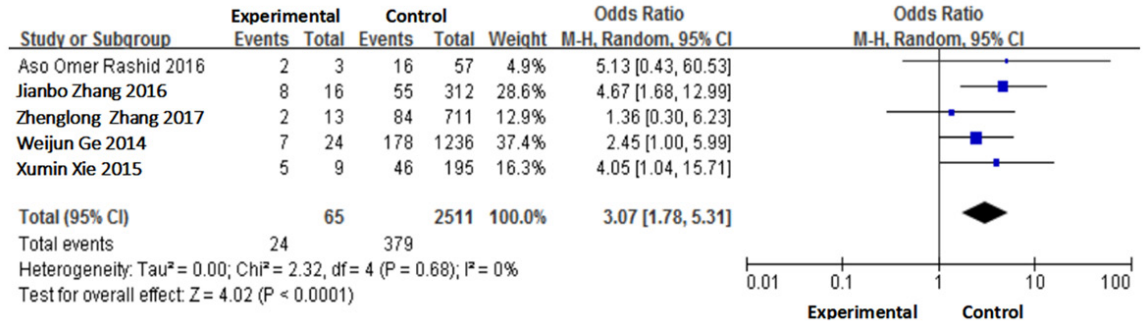

Figure 10. Meta-analysis of antler calculus in urosepsis and non-urological cause of sepsis.

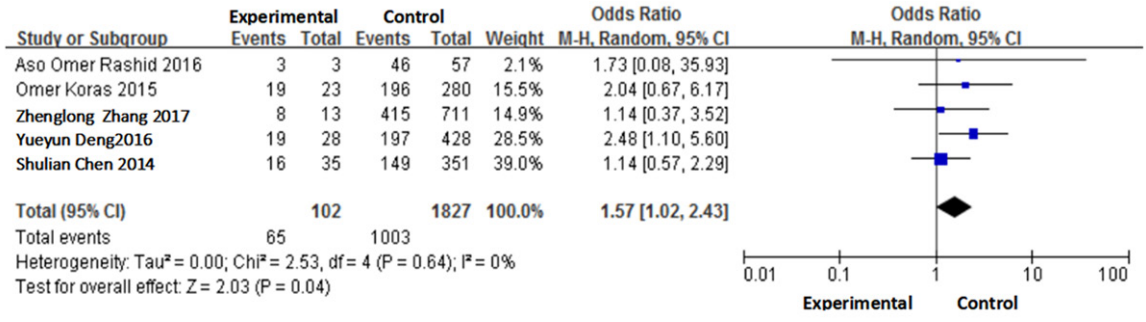

Figure 11. Meta-analysis of hydronephrosis (moderate to severe) in urosepsis and non-urological cause of sepsis.

Use of antibiotics before surgery

A total of 2 Chinese articles reported 2165 cases of use of antibiotics before surgery, including 153 cases of urosepsis and 2012 case of non-urological cause of sepsis. Statistical analysis showed heterogeneity (P= 001, I^2=83%). Random-effect model analysis showed Z=0.43 and P=0.67. Sensitivity analysis showed persistence of heterogeneity. Thus, use of antibiotics before surgery was not significant in both groups (**Figure 13**).

Publication bias

Represented by the risk factor of stone size, the publication bias of the article is analyzed. From **Figure 14**, it can be seen that the literature

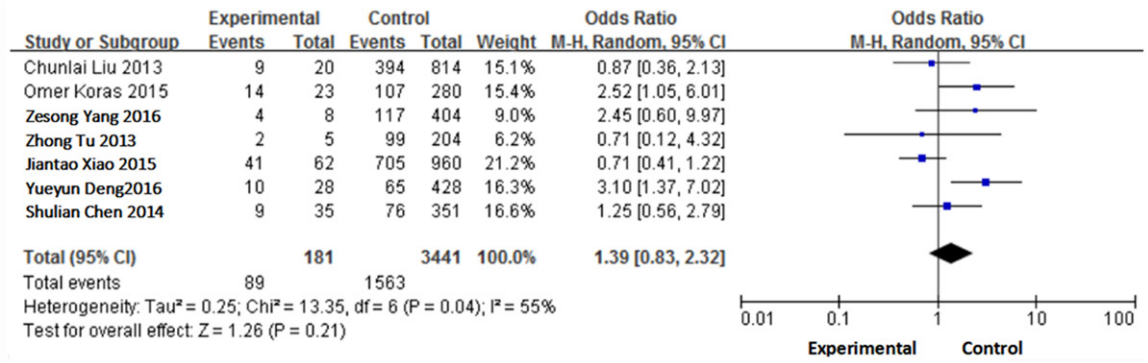

Figure 12. Meta-analysis of history of past surgery in urosepsis and non-urological cause of sepsis.

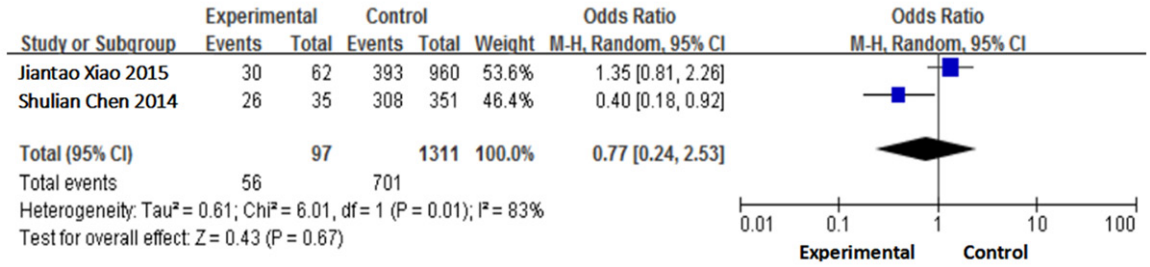

Figure 13. Meta-analysis of hydronephrosis (moderate to severe) in urosepsis and non-urological cause of sepsis.

data are evenly distributed on both sides of the invalid line, indicating that the publication bias is not obvious, and the included data is robust. The data included are true and reliable.

Discussion

PCNL has become the treatment of choice for large renal stones. However, postoperative urosepsis, although not common, is a catastrophic complication of PCNL. Therefore, identification of risk factors for urosepsis is warranted for its early diagnosis and prevention. Many studies have suggested that gender, age, hypertension, diabetes, positive-urine culture, stone diameter, staghorn calculus, previous surgical history for stone, and use of antibiotics, are factors associated with urosepsis after PCNL. However, there is controversy among these studies. Thus, in this review, we analyzed the most commonly reported 12 risk factors in the past 10 years.

The overall quality of evidence was assessed taking into account the risk of bias, consistency of results across the studies, precision of the results, and, likelihood of publication bias. We found that 9 different factors were associated with postoperative urosepsis. Here, we analyzed these factors under four different headings: demographic factors (age, gender), past medical history (diabetes mellitus), laboratory test (blood routine, urinalysis, and urine culture), and radiological factors (stone size and staghorn calculus).

Demographic factors

Aging is characterized by systemic inflammatory changes and organ dysfunction. In female, the ovarian activity decreases and eventually stops with aging [12, 13]. Estrogen has been shown to act as regulator of the immune function in females. Loss of estrogen makes these changes more intense and makes females prone to severe infection [14, 15]. The factors of poor perineal hygiene, menopause, and atrophic vaginitis increase the incidence of urosepsis in females by two fold compared to their male counterparts. Consistently, we found that female gender was statistically significant in both the urosepsis and in the non-urological cause of sepsis (OR=3.89, 95% CI [2.07, 7.31], P<0.01), thus increasing the likelihood of urosepsis. Age-related impairments in immune system after 60 years have been reported [16].

Table 3. Heterogeneity and sensitivity analysis of risk factors associated with urosepsis

Research factors	Remove documents	Before removing				After removing				Has the result changed
		I^2	Model	OR (95% *CI*)	*P*	I^2	Model	OR (95% *CI*)	*P*	
Gender (Female)	-	76%	Random Effect Model	3.89 [2.07, 7.31]	P<0.05	76%	Random Effect Model	3.89 [2.07, 7.31]	P<0.05	No
Age (≥ 60 years old)	Xiao Jiantao 2015	74%	Random Effect Model	2.08 [1.13, 3.82]	P=0.02	0%	Random Effect Model	1.71 [1.23, 2.39]	P=0.002	No
Diabetes	Zhang Shiqiang 2017	44%	Random Effect Model	3.70 [2.33, 5.90]	P<0.05	0%	Random Effect Model	3.15 [2.10, 4.72]	P<0.05	No
Urine routine (white blood cell ≥ +)	Li Yuan 2016	57%	Random Effect Model	1.99 [1.06, 3.75]	P=0.03	45%	Random Effect Model	2.43 [1.35, 4.37]	P=0.003	No
Urine culture (positive)	Yang Zesong 2016	55%	Random Effect Model	2.04 [1.12, 3.69]	P=0.02	0%	Random Effect Model	1.60 [1.12, 2.29]	P=0.01	No

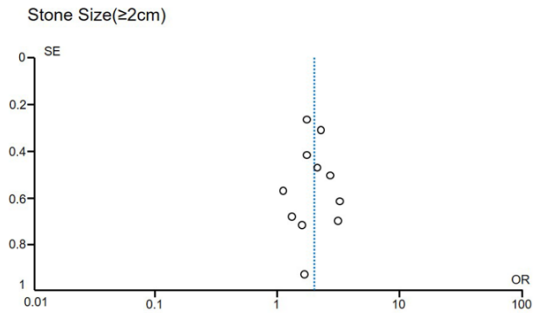

Figure 14. Bias analysis results of risk factors related to urinary sepsis.

In this study, age ≥ 60 was statistically significant in both the urosepsis and the non-urological cause of sepsis group (OR=1.71, 95% CI [1.23, 2.39], P=0.002). The high glucose status in diabetic patients serves as a suitable medium for bacterial growth, leading to frequent episodes of urinary tract infections [17, 18]. Microvasular changes in diabetic patients may cause circulatory dysfunction and poor immune response, which may make these population immuno-compromised and susceptible to urosepsis. This analysis also showed similar results, indicating diabetes as a possible risk factor. Therefore, factors of age, female gender and diabetes can increase the risk of postoperative urosepsis.

Laboratory test

Urine routine test and culture are effective measures to identify commonly seen pathogens. Preoperative history of urinary tract infection is a strong indicator of urosepsis after PCNL and different studies have indicated the significance of perioperative urine culture for infection after PCNL [4, 5, 19]. Abnormal blood results indicate infection with increased inflammatory mediators and hemodynamic changes, which may be aggravated by the surgical intervention, resulting in urosepsis. In this study, preoperative indicators of infection included blood test, urinalysis, and urine culture. Urinalysis (OR=2.43, 95% CI [1.35, 4.37], P<0.01) and positive urine culture was significant in both the groups (OR=1.60, 95% CI [1.12, 2.29], P<0.01), indicating increased risk of infection in these population.

Radiological factors

Studies have shown that patients with larger stone size have higher infection rate (6-10%). Moreover, stone type of the staghorn calculus is strongly associated with urosepsis [20, 21]. The loss of polysaccharide layer of the urinary tract due to urea-splitting organisms during PCNL in culture positive cases causes bacterial attachment and invasion, resulting in sepsis. Additionally, after fragmentation of infected stones, bacteria and large amounts of endotoxins are released, which enter into the circulation and increase the risk of endotoxemia and urosepsis. In contrast to previous study by Bag et al [3], which suggests stone size greater than 2.5 cm as a potential risk factor of urosepsis, we found that the risk of urosepsis was significantly higher in patients with stone size greater than 2 cm (OR=1.94, 95% CI [1.49, 2.54], P<0.01). Also, a significant correlation between staghorn stones and urosepsis was found in both groups (OR=3.07, 95% CI [1.78, 5.31], P<0.01).

The study has some limitations. For example, only 12 commonly reported preoperative factors were included in our meta analysis. The intraoperative factors were not taken in consideration in this meta analysis. Moreover, the size and number of tract, amount of bleeding, operative time, intraoperative irrigation volume and renal pelvis perfusion pressure, individual experience and skill, and postoperative fistula management are other important factors associated with urosepsis after PCNL, which need further investigation to formulate a precise and effective assessment system. Therefore, further study is needed.

In summary, our study suggests that female gender, age ≥ 60, associated conditions like diabetes or history of preoperative infection, large stone size, hydronephrosis, and staghorn calculus are risk factors for urosepsis. Thus, careful evaluation should be performed in patients who have the identified risk factors to prevent urosepsis.

Address correspondence to: Biao Qian, Associate Professor of Medicine, Department of Urology, The First Affiliated Hospital of Medical College in Shihezi University, Shihezi 832000, Xinjiang, China. Tel: +86-0993-2858894; Fax: +86-0993-2858894; E-mail: qb2003_2000@163.com

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