# Can we identify the risk factors for SIRS/sepsis after percutaneous nephrolithotomy? A meta-analysis and literature review

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**Abstract.** With the increase in percutaneous interventions such as percutaneous nephrolithotomy (PCNL) for renal lithiasis, infectious complications are becoming more frequent. The present study performed a systematic Medline and Embase databases search, using the following words: 'PCNL' [MeSH Terms] AND ['sepsis' (All Fields) OR 'PCNL' (All Fields)] AND ['septic shock' (All Fields)] AND ['urosepsis' (MeSH Terms) OR 'Systemic inflammatory response syndrome (SIRS)' (All Fields)]. Because of the technological advances in endourology, articles published between 2012 and 2022 were searched. Of the 1,403 results of the search, only 18 articles, representing 7,507 patients in which PCNL was performed, met the criteria to be included in the analysis. All authors applied antibiotic prophylaxis to all patients and, in some cases, the infection was treated preoperatively in those with positive urine cultures. According to the analysis of the present study, the operative time has been significantly longer in patients who developed SIRS/sepsis post-operatively (P=0.0001) with the highest heterogeneity ($I^2$=91%) compared with other factors. Patients with a positive preoperative urine culture had a significantly higher risk of developing SIRS/sepsis following PCNL (P=0.00001), OD=2.92 (1.82, 4.68) and there was also a high degree of heterogeneity ($I^2$=80%). Performing a multi-tract PCNL also increased the incidence of postoperative SIRS/sepsis (P=0.00001), OD=2.64 (1.78, 3.93) and the heterogeneity was a little smaller ($I^2$=67%). Diabetes mellitus (P=0.004), OD=1.50 (1.14, 1.98), $I^2$=27% and preoperative pyuria (P=0.002), OD=1.75 (1.23, 2.49), $I^2$=20%, were other factors that significantly influenced postoperative evolution. A total of two factors analyzed, body mass index and patient's age, did not influence the outcome, P=0.45, $I^2$=58% and P=0.98, $I^2$=63%.

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*Key words:* percutaneous nephrolithotomy, pyuria, risk factor, sepsis, urine culture

## Introduction

As the prevalence of kidney stone disease rises, a number of patients will need a minimally invasive procedure to remove kidney stones. In the 1970s, percutaneous nephrolithotomy (PCNL) was introduced as a less invasive option for kidney stone removal and it underwent additional development in the following years (1). However, extracorporeal shock wave lithotripsy was introduced in the early 1980s, decreasing PCNL frequency. Recent years have seen a redefining of the function of PCNL for treating urolithiasis, as clinical experience with ESWL has highlighted its limits (1). Nowadays, PCNL is a ubiquitous technique. In a recent survey by Jiang *et al* (2), ~80.5% of urologists in China practice PCNL and 96.2% said they like to perform it. According to the European Association of Urology, PCNL is recommended as the first-line treatment for kidney stones >2 cm and/or staghorn stones (3).

Technical advances have led to a significant reduction in the morbidity and mortality of this surgical technique. However, PCNL is not a risk-free intervention. According to Sharma *et al* (4), the rate of complications varies considerably, being between 3-83%. The most common are bleeding, pneumothorax, hydro/hemothorax, urinary fistula, pleural effusion and urosepsis. Although postoperative fever can be encountered in ≤30% of patients who undergo PCNL, urosepsis is diagnosed, according to Michel *et al* (5), in 0.9-4.7%. A number of authors have studied the factors that could favor the appearance of sepsis following PCNL, but the results are inconclusive. Postoperative infection is a common complication that, if untreated, can result in septic shock. According to Yang *et al* (6), the fatality rate for urinary septic shock can range from 25-60%, advances rapidly and is challenging to treat. There is currently no standard recommendation for the risk factors connected to postoperative infection. Preoperative urine culture positivity, stone bacterial culture positivity, stone

burden, female gender, elderly gender, diabetes mellitus and urinary tract obstruction are the key factors that lead to post-operative infection (6). The purpose of the present study was to analyze the data from the literature to date to help clinicians manage the risks of PCNL so that they become minimal.

## Materials and methods

The present study performed this meta-analysis using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 reporting guidelines (7). A systematic Medline (https://pubmed.ncbi.nlm.nih.gov/) and Embase (https://www.embase.com/) databases search was performed, using the following words: 'PCNL' [MeSH Terms] AND ['sepsis' (All Fields) OR 'PCNL' (All Fields)] AND ['septic shock' (All Fields)] AND ['urosepsis' (MeSH Terms) OR 'Systemic inflammatory response syndrome (SIRS)' (All Fields)].

*Inclusion criteria*. Due to the technological advances in endourology, the present study searched articles published between 2012 and 2022. Non-English language articles and those for which the full text was unavailable were excluded. The leading search, as well as screening for eligibility of titles, abstracts and full-text articles, was completed independently by two authors and any discrepancies were solved by consensus.

The present study selected studies with a control group (non-SIRS/sepsis) and analyzed elements that favored the appearance of sepsis after urological maneuvers. These have been patients' age, diabetes mellitus, preoperative pyuria, positive preoperative urine culture, operative time-minutes, multitract and body mass index (BMI).

*Statistical analysis*. Heterogeneity in PCNL's infectious complications outcome rate was assessed using $I^2$ statistics. Review Manager (RevMan), Version 5.4.1, and The Cochrane Collaboration, 2020, (both Cochrane) were used to calculate the individual odds ratios (OR), P-value and personal and pooled mean differences with corresponding 95% confidence interval (CI). A P-value <0.05 has been considered statistically significant. The mean difference was used to compare the outcomes following PCNL from the infectious complications point of view. While random-effect models are considered less statistically powerful, they may produce more logical estimates if absolute heterogeneity exists. Furthermore, random-effects models may overestimate the extent of error variance, whereas fixed-effects models may underestimate it. Due to the heterogeneity of the included studies, a fixed effect size would be very implausible. Therefore, a standard random effect model was applied. Considering that all of the included studies were observational, the risk of bias was assessed using the Newcastle-Ottawa quality assessment scale.

## Results

Of the 1,403 results of the search, only 18 articles were selected. The flowchart of selection is shown in Fig. 1. The chosen studies, published between 2014 and 2022, included a total of 7,507 patients on which PCNL was performed. Details of the included studies are shown in Table I.

All authors applied antibiotic prophylaxis to all patients and in some cases, the infection was treated preoperatively in those with positive urine cultures. According to the analysis of the present study, the operative time has been significantly longer in patients who developed SIRS/sepsis post-operatively (P=0.0001) with the highest heterogeneity ($I^2$=91%) compared with other factors. Patients with a positive preoperative urine culture have a significantly higher risk of developing SIRS/sepsis following PCNL (P=0.00001), OD=2.92 (1.82, 4.68) and there is also a high degree of heterogeneity ($I^2$=80%). Performing a multi-tract PCNL also increases the incidence of postoperative SIRS/sepsis (P=0.00001), OD=2.64 (1.78, 3.93) and the heterogeneity was a little smaller ($I^2$=67%). Diabetes mellitus (P=0.004), OD=1.50 (1.14, 1.98), $I^2$=27% and preoperative pyuria (P=0.002), OD=1.75 [1.23, 2.49], $I^2$=20%, as shown in Fig. 2, were other factors that significantly influenced postoperative evolution. However, BMI and patient's age did not influence the outcome; P=0.45, $I^2$=58% and P=0.98, $I^2$=63%, as shown in Fig. 3. Non-randomized study quality evaluation is an essential key part of a comprehensive meta-analysis of non-randomized research. Poor research might have a negative effect on the estimation of the overall effect. As the present meta-analysis included non-randomized studies, the Newcastle-Ottawa scale was used to assess the risk of bias. The Newcastle-Ottawa scale consists of eight criteria divided into three categories: Selection, comparability and outcome and exposure. Several answer alternatives are offered for each issue. A star system is employed to provide a semi-quantitative evaluation of study quality, the only exception being the comparability item, which permits the allocation of two stars, with the highest quality papers receiving a maximum of one star for each item. The risk of bias total score, assessed by the Newcastle-Ottawa scale, varied between five and eight, the mean risk of bias being 6.16, resulting in an average level of study quality, as seen in Table II.

## Discussions

PCNL is an increasingly widespread intervention that increases the incidence of complications. According to Ghani *et al* (26), sepsis following PCNL rose from 1.2% in 1999 to 2.4% in 2009 in the United States. Although not very common, post-operative urosepsis can be a life-threatening complication of PCNL.

Aging brings changes that can influence patients' immunity. A low-grade inflammatory condition characterizes elderly patients. According to Aiello *et al* (27), this situation is responsible for increased oxidative stressors and pro-inflammatory cytokines. Furthermore, in these patients, a decrease in peripheral naive T and B cells is found (28). According to Bajaj *et al* (28), neutrophils are involved in the immune response to bacterial aggression. They present an alteration of neutrophil extracellular traps, one of the mechanisms involved in the fight against pathogens. In addition, there is a reduction in phagocytosis and a lowered intracellular killing activity (28). In an animal model, an impairment of the migration of neutrophils was observed, despite a high level of chemokines (29). Other authors have

Table I. Characteristics of included studies.

| Author, year | Factor studied | Number of patients | Analyzed outcome | (Refs.) |
|---|---|---|---|---|
| Amier *et al*, 2022 | B,D,E,F | 171 | Sepsis | (8) |
| Chen *et al*, 2019 | A,B,C,D,E,F | 802 | Sepsis | (9) |
| Chhetri *et al*, 2018 | A,C,D,E,F | 97 | Sepsis | (10) |
| He *et al*, 2018 | A,B,C,D,E,G | 1,030 | SIRS | (11) |
| Koras *et al*, 2015 | A,D,E,F,G | 303 | SIRS | (12) |
| Kumar *et al*, 2021 | B,D,E,F | 320 | SIRS | (13) |
| Liu *et al*, 2020 | A,B,D,E,F | 303 | SIRS | (14) |
| Liu *et al*, 2021 | A,C,D,F,G | 241 | Sepsis | (15) |
| Lorenzo Soriano *et al*, 2019 | A,B,D,E,F,G | 203 | SIRS | (16) |
| Rashid and Fakhulddin, 2016 | A,D,E, | 60 | Sepsis | (17) |
| Tabei *et al*, 2016 | A,B,C,D,E,F,G | 370 | SIRS | (18) |
| Tang *et al*, 2021 | A,B,C,D,E,F,G | 758 | SIRS + Sepsis | (19) |
| Teh and Tham, 2021 | B,C,D,F | 425 | Sepsis | (20) |
| Wang *et al*, 2020 | A,D,E,F,G | 843 | Sepsis | (21) |
| Wei *et al*, 2015 | A,B,E,F,G | 411 | SIRS | (22) |
| Xu *et al*, 2022 | A,B,C,D,E,F,G | 220 | SIRS | (23) |
| Yang *et al*, 2017 | A,B,E | 164 | SIRS | (24) |
| Zhu *et al*, 2020 | A,B,C,D,E,F,G | 786 | Sepsis | (25) |

A, age; B, diabetes mellitus; C, pyuria; D, positive preoperative urine culture; E, operative time-minutes; F, multitract; G, body mass index.

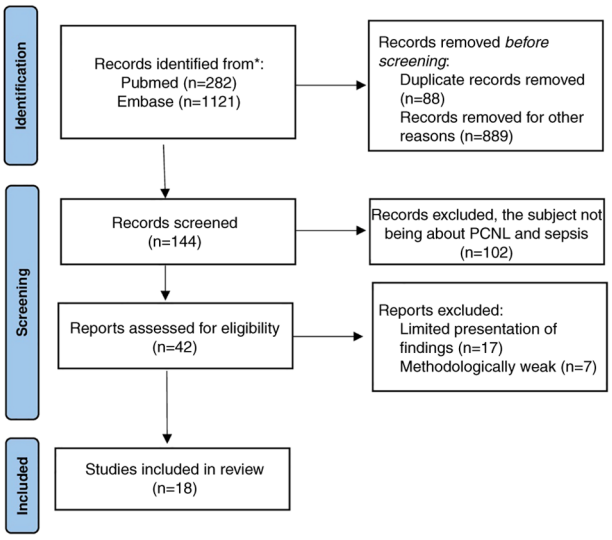


Figure 1. PRISMA flowchart of the study selection. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PCNL, percutaneous nephrolithotomy.

suggested that age-related alteration of hormonal status could be responsible. According to Hao *et al* (30), lower estrogen levels in women predispose them to infections, adding other factors such as poor perineal hygiene and menopause, making the incidence of urosepsis double in women. Understanding the surgical risk of PCNL in elderly patients is necessary, given the rise in life expectancy and the number of elderly individuals undergoing surgery. The results from the present study showed that, when conducted by a skilled surgeon and with compensated comorbidities, PCNL can be reasonably safe and efficiently performed on elderly patients.

A positive bladder urine culture before surgery will lead to better antibiotic prophylaxis, although a complete obstruction of the collecting system can lead to a sterile bladder urine culture. For this reason, some authors suggested that the renal pelvis urine culture could be more reliable for making preoperative prophylaxis. In a cohort of 138 patients, Dogan *et al* (31) noted that 10.1% of patients with previous sterile bladder urine cultures had positive renal pelvis urine cultures. Also, in a group of 122 patients, Walton-Diaz *et al* (32), bladder urine cultures were negative in all patients who developed infectious complications following PCNL. Of these, 57.1% had positive renal pelvis urine culture. For this reason, the authors recommend pelvic urine culture, especially in high-risk patients, because bladder urine culture is a poor predictor of the infectious complications outcome. However, the analysis results of the present study told a different story.

On the other hand, to get the renal pelvis urine culture, placing a needle in the collecting system is necessary. After obtaining the urine, the urologist can perform the intervention simultaneously or place a drainage tube until the result is available after ~48 h. The presence of a nephrostomy tube before PCNL is a debatable factor. In a cohort of 217 patients, Aghdas *et al* (33) noticed a higher incidence of postoperative fever in those who had a nephrostomy placed preoperatively. However, according to Benson *et al* (34), it has a protective role. There is no clear explanation for this situation. Although the tube will drain the infected urine, it would act as a foreign

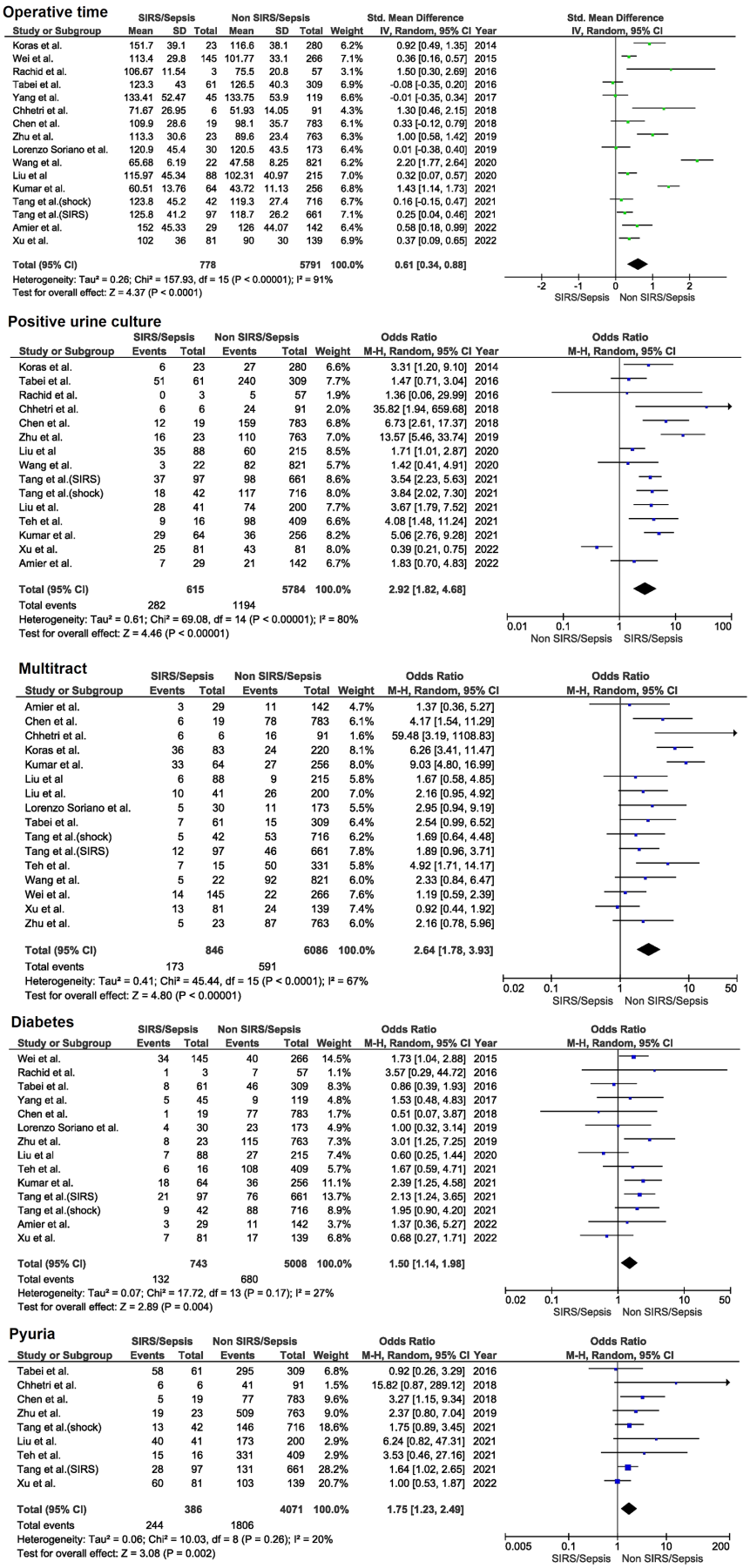


Figure 2. Forest plot showing factors influencing the PCNL outcome (Diabetes mellitus, multitract PCNL, preoperative pyuria, operative time and positive preoperative urine culture). Black diamonds indicate study weight. Green squares indicate the overall result. Horizontal lines indicate the 95% confidence interval. CI, confidence interval; df, degrees of freedom; Random, random effects model; SD, standard deviation; PCNL, percutaneous nephrolithotomy; SIRS, Systemic inflammatory response syndrome.

Table II. Newcastle-Ottawa scale of included studies.

| Author, year | Selection | Comparability | Exposure | Total score | (Refs.) |
|---|---|---|---|---|---|
| Amier *et al*, 2022 | **** | | *** | 7 | (8) |
| Chen *et al*, 2019 | *** | * | ** | 6 | (9) |
| Chhetri *et al*, 2018 | ** | * | *** | 6 | (10) |
| He *et al*, 2018 | **** | | ** | 6 | (11) |
| Koras *et al*, 2015 | *** | * | * | 5 | (12) |
| Kumar *et al*, 2021 | *** | | ** | 5 | (13) |
| Liu *et al*, 2020 | *** | * | ** | 6 | (14) |
| Liu *et al*, 2021 | *** | * | * | 5 | (15) |
| Lorenzo Soriano *et al*, 2019 | *** | * | *** | 7 | (16) |
| Rashid and Fakhulddin, 2016 | **** | | ** | 6 | (17) |
| Tabei *et al*, 2016 | *** | * | ** | 6 | (18) |
| Tang *et al*, 2021 | *** | | *** | 6 | (19) |
| Teh and Tham, 2021 | *** | * | **** | 8 | (20) |
| Wang *et al*, 2020 | **** | * | ** | 7 | (21) |
| Wei *et al*, 2015 | *** | * | *** | 7 | (22) |
| Xu *et al*, 2022 | *** | | ** | 5 | (23) |
| Yang *et al*, 2017 | *** | * | *** | 7 | (24) |
| Zhu *et al*, 2020 | **** | | *** | 7 | (25) |

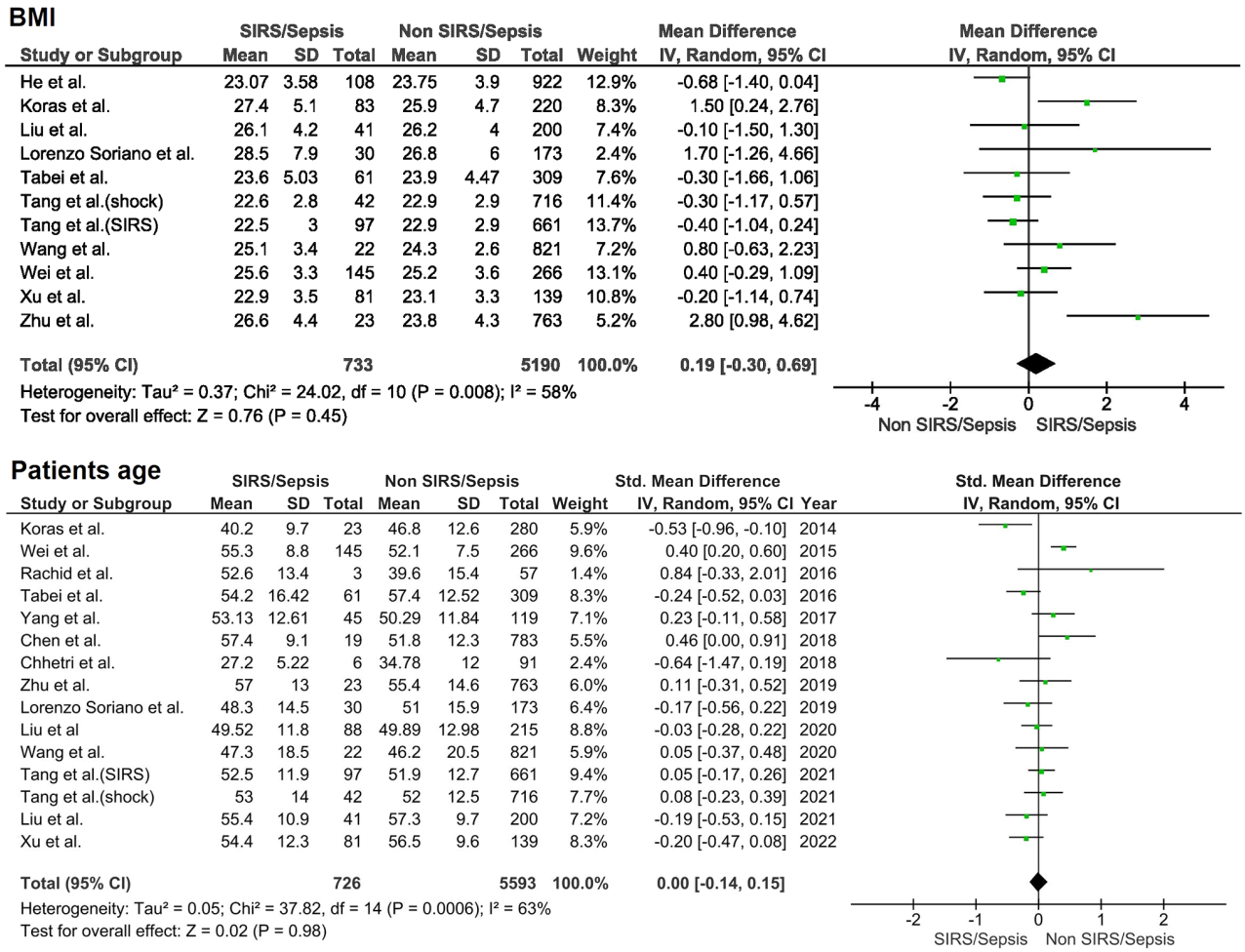


Figure 3. Forest plot showing factors that did not influence the PCNL outcome (BMI and patient's age). Black diamonds indicate study weight. Green squares indicate the overall result. Horizontal lines indicate the 95% confidence interval. PCNL, percutaneous nephrolithotomy; BMI, body mass index; CI, confidence interval; df, degrees of freedom; Random, random effects model; SD, standard deviation; SIRS, Systemic inflammatory response syndrome.

body, and the fast colonization of any urinary stent is well known. According to Verma *et al* (35), 43% of bladder catheters will be colonized after only five days and 20% will be with biofilm-forming bacteria.

A complex relationship exists between elevated BMI, kidney stones and urinary tract infections (UTIs). We are witnessing a concomitant increase in the prevalence of kidney stone disease and obesity. According to Poore *et al* (36), obesity in adults increased by 27.5% from 1980 to 2013. In women with an elevated BMI, there is a 1.30-fold increased risk for kidney stone development compared with those with a normal BMI. The explanation may be that obesity is associated with metabolic changes that favor stone formation. According to Taylor *et al* (37), urinary pH is more acidic in patients with greater BMI and urinary oxalate, sodium, uric acid and phosphate concentrations are higher. Similar findings were also reported by Ekeruo *et al* (38); the authors noticed that hyperoxaluria, hypercalciuria and hyperuricosuria are more commonly found in obese stone formers compared with a non-obese cohort. Although the present study analyzed the impact of BMI on infectious complications following PCNL, according to Poore *et al* (36), it seems that visceral obesity is the more predictive of kidney stone risk. However, it is more difficult to quantify because it requires imaging studies. In the present study, the BMI did not influence the infectious outcomes of PCNL, although some authors link obesity to a higher chance of developing UTI. In a cohort of 95,598 subjects, Semins *et al* (39) noticed that males with a BMI between 30.0-34.9 have a higher chance of developing UTI compared with patients with a BMI>50 (OR 1.59 vs. 2.35). A higher BMI does not influence PCNL outcome, not from the infection's point of view but overall. According to Ortiz *et al* (40), there is no significant difference in the stone-free rate, postoperative complication incidence, hemoglobin loss, or hospital stay.

Diabetes mellitus, obesity and arterial hypertension are essential elements of metabolic syndrome. Urinary abnormalities indicate a definite association between metabolic syndrome and kidney stones. According to Domingos *et al* (41), these patients have excessively acidic urine, high urinary calcium and oxalate levels and low urinary citrate. As in the case of patients with elevated BMI, there is a link between diabetes and UTI. According to Chiu *et al* (42), a UTI in a diabetic patient is 10 times more likely to progress to pyelonephritis. According to Murtha *et al* (43), one explanation is that the immunity to bacteria in the urinary tract is insulin-dependent. The authors proved in an animal model that insulin resistance leads to a suppression of urinary antimicrobial peptides suggesting that urinary sugar is not the essential element behind UTIs in these patients. In addition, elevated blood sugar influences resistance to UTIs. In diabetic patients, some immune alterations have been observed, such as an elevation in CD4+CD28null T-lymphocytes count, lower levels of serum complement factor 4 concentration and plasma zinc levels and also significantly lower PMNs chemotaxis (44,45). The results of the present study show that diabetes is a predisposing factor for postoperative infections. Considering that PCNL is an elective operation, it is assuming that the patient's blood sugar was within normal limits at the time of the intervention. However, an unbalanced history of diabetes may contribute to the unfavorable evolution. Future studies would help identify the relationship between hemoglobin A1c and SIRS/sepsis following PCNL.

In patients with staghorn stones, surgical management can be complex. Performing multiple tracts, PCNL can increase the rate of complications and the period of hospitalization. In a cohort of 27 patients where multiple tract PCNL was performed, Liang *et al* (46) obtained a stone-free rate within three sessions in 88.9% of cases. The authors did not report significant blood loss, while postoperative fever was encountered in only 22.22% of cases. A group of 65 patients evaluated by Rashid *et al* (47), who underwent multiple tract PCNL, had a significant decrease in hemoglobin level, while serum creatinine remained relatively unchanged. In their cohort, 11% had a postoperative fever, while only 3% presented an infection that required additional antibiotics. In a much larger cohort of 773 patients with staghorn calculi in which PCNL was performed, of which 514 with multiple tracts, Desai *et al* (48) reported postoperative fever in up to 28.2% of patients.

Given the risk of infectious complications, a logical strategy would be to use antibiotic prophylaxis. However, it remains a debatable topic related to the categories of patients who would benefit the most and the treatment regimen, a single preoperative dose or treatment for several days. In a meta-analysis by Yu *et al* (1), which included 13 studies with a total of 1,549 patients, the results indicated that for those receiving prophylactic treatment for a few days compared with those receiving a single dose, the symptoms of sepsis were significantly lower as well as positive cultures in the renal pelvis. Moreover, according to Xu *et al* (23), optimal antibiotic prophylaxis in those with preoperative positive urine cultures should last at least seven days. Schnabel *et al* (49) compared 98 patients who received antibiotics one day preoperatively with 76 patients who did not receive prophylaxis. The authors found no significant differences in fever, grade 1-3 complications, or hospitalization. The authors considered that antibiotic prophylaxis might not be necessary in selected cases, such as those with negative urine culture, non-staghorn stones and no history of urinary tract infections. Some authors have tried to evaluate the role of the urine dipstick test before the PCNL. In a group of 806 patients, Xu *et al* (50) reported that positive urine dipstick infection prior to surgery strongly predicted SIRS. Paradoxically, extensive preoperative antibiotic use was linked to a greater risk of SIRS.

According to European Association of Urology recommendations, 2022 edition, the probability of infection during PCNL is high and antibiotic prophylaxis has been demonstrated to minimize the risk for infectious complications significantly with a single dosage being adequate (51). Antibiotic prophylaxis should be given even with a negative urine culture, according to American Urological Association Guidelines, which are regarded as a clinical principle (52). In this part, the American Urological Association panel makes the case that there is insufficient evidence to suggest giving patients with a negative urine culture one week of preventive antibiotics. In a recent survey that included over 3,000 Chinese urologists, Zhang *et al* (53) reported that antibiotic prophylaxis for 1-3 days before surgery was most often used regardless of whether the urine culture was positive or negative (54.5 vs. 65.5%). Cephalosporins are the most used antibiotic type, followed by quinolones. Considering that urine cultures are

not specific for the colonization status, He *et al* (54) compared two types of antibiotic regimens with the presence of white blood cells (WBC) and nitrites in urine. The authors showed that one 1.5 g dose of cefuroxime before PCNL compared with 3-day treatment statistically lowered the incidence of SIRS in patients with positive nitrites in urine but did not influence the outcome in patients with absent nitrites in urine. In the cohort studied by Xu *et al* (23), the urine culture result was unavailable before the procedure in some patients. In these cases, they received an empirical antibiotic prophylaxis 30 before the surgery and postoperatively, the antibiotic therapy was adjusted after obtaining the result. The authors evaluated the effects of antibiotic prophylaxis schemes. Although a more extended antibiotic prophylaxis was significantly associated with a better outcome, the administration of sensitive antibiotics did not prove a significant advantage over non-sensitive antibiotics.

From the data of the present study, between 2017-2021, of the 463 cases in which PCNL was performed, 5.18% (n=24) developed postoperative sepsis/SIRS. Of these, 54.2% (n=13) were men and 45.8% (n=11) were women. The stone-free rate was 75% and the overall stone-free rate was 69.11%. The bladder preoperative urine culture was positive in 58.33% (n=14) of patients compared with 25.20% in the non-sepsis group. Also, the preoperative presence of urinary stents was noted more frequently in the sepsis/SIRS group (62.5% vs. 17.71%). The majority (93.33%) had JJ ureteral stents. In all cases, developing sepsis/SIRS symptoms led to a change in the postoperative antibiotic regimen (55).

The present meta-analysis has some limitations: First, the studies are somewhat heterogenous; the authors came from different continents, the number of patients varied from 60 to 1,030 and renal pelvic urine culture was not available in all cases. Also, the dilatation technique, balloon compared with telescopic/serial dilation, was not known in all studies. Another drawback of the meta-analysis is the need to evaluate the type of kidney stones according to the various scoring systems. Only one of the included studies reported that a higher STONE (Stone size, Tract length, Obstruction, Number of involved calices and Essence or stone density) score correlates significantly with sepsis/SIRS (19). From the present study authors' experience with the Guy stone score, it was also found that patients with the highest grade (IV) have significantly more preoperative positive urine culture and complications according to the Clavien scale and the lowest stone-free rate (56).

Despite this, the present meta-analysis has some strong points. All patients in the included studies underwent the same type of intervention. The outcomes are well defined, SIRS respectively sepsis, or quantified such as WBC, preoperative urine culture, or BMI. Thus, some elements are easy to compare, such as the operative time, which depends on several factors. According to Akman *et al* (56), some of these factors are the previous presence of hydronephrosis, stone characteristics and surgeon experience, which could not be evaluated in the present analysis. Further studies should evaluate supplemental sepsis indicators such as C-reactive protein, hemoglobin A1c or procalcitonin. Also, the type of PCNL technique (standard or miniPCNL) could be an influencing factor considering as, according to Jiao *et al* (57), there is no difference regarding postoperative fever between standard compared with miniPCNL. However, the operative time was significantly shorter in patients in which minPCNL and, according to the data of the present analysis, a longer operative time favors the development of SIRS/sepsis.

The present analysis showed that diabetes mellitus, multitract PCNL, pyuria, operative time and positive urine culture are factors that, if not controlled, favor the appearance of SIRS or urosepsis. In some high-risk patients, such as those with diabetes, a history of urinary tract infections, or positive urine cultures, antibiotic prophylaxis should be mandatory and performed for at least one week before surgery.

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**Availability of data and materials**

Data sharing is not applicable to this article, as no data sets were generated or analyzed during the current study.

**Authors' contributions**

DP and CP were responsible for conceiving the study and DP was responsible for the methodology, formal analysis and software. Validation was performed by DP, CP and SG and investigation by GR and SG. Data curation was by SG, GR and VJ. DP, GR and SG wrote the original draft of the manuscript, which was reviewed and edited by VJ and CP. CP and VJ were responsible for visualization and supervision. Data authentication is not applicable. All authors read and approved the final manuscript.

**Ethics approval and consent to participate**

Not applicable.

**Patient consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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