Research Square

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Application of gene chip technology in prediction of postoperative urosepsis in patients with upper urinary tract stones

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Abstract

Purpose

To find a more efficient and accurate pathogenic detection than midstream urine culture.

Methods

357 cases were included from 565 patients with upper urinary tract stones. We conducted gene chip technology and conventional midstream urine culture on the same urine samples obtained from patients. Statistical analysis of the comparison between the clinical diagnosis and the results of these two pathogenic detection techniques was conducted to assess the clinical value of gene chip technology.

Results

The overall compliance rate of the midstream urine culture in relation to the clinical diagnosis within the high-risk group was 79.2% ($\chi^2 = 10.402$, $P < 0.05$), with a sensitivity of 42.9%, specificity of 85.2%, positive predictive value of 32.4%, negative predictive value of 90.0%, positive likelihood ratio of 2.90, and negative likelihood ratio of 0.67. Under identical conditions, the overall compliance rate of gene chip test compared with the clinical diagnosis was 82.2% ($\chi^2 = 23.211$, $P < 0.05$), with a sensitivity of 50.0%, specificity of 87.6%, positive predictive value of 40.0%, negative predictive value of 91.4%, positive likelihood ratio of 4.03, and negative likelihood ratio of 0.57.

Conclusion

In clinical practice, when treating patients with urolithiasis at high risk for postoperative infection, gene chip test has a higher overall compliance (82.2% vs. 79.2%), sensitivity (50.0% vs. 42.9%), and specificity (87.6% vs. 85.2%) compared with midstream urine culture for the detection of E. coli and KP commonly found in urinary tract infections.

1. Introduction

Complications of urinary stones can significantly impact the patient's treatment outcome and potentially result in severe consequences such as infectious shock [1]. Studies have indicated that upper urinary tract obstruction caused by stones is a significant contributor to urogenital sepsis [2]. Furthermore, the increasing utilization of ureteral hard and soft lithotripsy in recent years has led to a gradual rise in postoperative sepsis and infective shock associated with stone removal procedures. The mortality rate for acute infective shock can be as high as 25% to 67% [3]. However, traditional clinical pathogenic

testing techniques, such as midstream urinary culture, have often proven inadequate due to their slow turnaround time (usually 3–5 days) and low positive detection rate in providing timely feedback on preoperative urinary tract infections [4].

Nowadays gene chip technology, comprising solid-phase and liquid-phase microarrays, is currently employed in clinical pathogenesis. This technology utilizes the principle of molecular hybridization of nucleic acids, where target sequences are hybridized with probes to detect the presence of corresponding pathogen gene sequences in the sample. It enables the simultaneous detection and identification of multiple pathogens, providing rapid and comprehensive information about the infection status [5–8]. In this study, we utilized gene chip technology to assess its clinical application by conducting pathogenic testing on the same urine samples. The results were then compared with those of urine culture methods.

2. Patients and methods

2.1 Study participants

This study included 565 patients with upper urinary tract stones admitted to Shanghai Sixth People's Hospital from January 2021 to August 2023. These patients were screened and underwent gene chip testing and midstream urine culture, resulting in 383 cases that met the inclusion criteria and were included in the data analysis. The criteria for data inclusion were as follows: (1) Preoperative diagnosis of upper urinary tract stones confirmed by urological ultrasound and urological CT plain scan. (2) Inadequate pain relief with medication. (3) Ineligibility for or poor results from ultrasound lithotripsy. (4) Indication for surgical treatment. The data exclusion criteria for inappropriateness of surgical treatment were as follows: (1) Patients receiving anticoagulation therapy or coagulation disorders. (2) Uncontrolled urinary tract infection. (3) Presence of a tumor along the predetermined surgical pathway. (4) Presence of an underlying malignant renal tumor. The above criteria are following the guidelines outlined in the "EAU Guidelines On Urolithiasis" [9].

2.2 Experimental method

Gene chip technology: Nucleic acid extraction from the patient's urine specimen was performed by transferring it to a 1.5 ml sterile centrifuge tube, followed by centrifugation at 12,000 rpm for 5 minutes and removing the supernatant. The nucleic acid extraction procedure was carried out according to the instructions provided by the equipment manufacturer. Once the nucleic acid extracts were successfully obtained, the isothermal amplification reaction solution was thawed at room temperature and briefly centrifuged to collect the contents at the bottom. A preprepared 200 μl centrifuge tube was filled with 26 μl of the reaction solution and transferred to the specimen preparation area. 26 μl of nucleic acid extract was added to each of the centrifuge tubes and gently mixed. The mixture was then briefly centrifuged, allowing any visible sediment to settle at the bottom of the centrifuge tube. The resulting product was added to the predetermined gene chip, sealed, and placed in an isothermal nucleic acid amplification

microfluidic microarray analyzer. Analysis was performed once the results were available. (For specific amplification methods and interpretation of results, please refer to the device's documentation [4, 10–12].) The gene chip assay used here is a probe-based nucleic acid hybridization method targeting predefined pathogen-specific sequences and does not involve whole-genome sequencing.

2.3 Research design

The study protocol was approved by the institutional ethics committee, and the requirement for informed consent was waived (see Declarations). The requirement for informed consent was waived by the ethics committee owing to the retrospective nature of the study and the use of de-identified residual clinical samples and data.According to the criteria outlined in Section 1.1, data from 383 patients with upper urinary tract stones were recorded. Additionally, two midstream urine specimens were retained for gene chip testing and midstream urine culture and identification. The raw data results included all cases involved in this study. The common pathogens associated with urinary system infections included *Escherichia coli* (*E. coli*), *Klebsiella pneumoniae* (*KP*), *Staphylococcus putrefaciens* (*SP*), *Enterococcus* (*Ent*), *Group B Streptococcus* (*GBS*), *Bacillus deformans* (*BD*), and *Pseudomonas aeruginosa* (*PA*) [13]. The gene chip used in this study was capable of detecting 12 pathogens: *Streptococcus pneumoniae* (*S.pneumoniae*), *Staphylococcus aureus* (*SA*), *Methicillin-resistant Staphylococcus* (*MS*), *Klebsiella pneumoniae* (*KP*), *Pseudomonas aeruginosa* (*PA*), *Acinetobacter baumannii* (*AB*), *Acinetobacter maltophilia* (*AM*), *Haemophilus influenzae* (*HI*), *Legionella pneumophila* (*LP*), *Escherichia coli* (*E. coli*), *Mycoplasma pneumoniae* (*MP*), and *Chlamydia pneumoniae* (*CP*). Therefore, we specifically selected cases involving *E. coli* and *KP*, as well as those with negative test results, resulting in a total of 357 cases for the study. The gene chip test results and midstream urine culture results were compared statistically with the clinical diagnostic results. This statistical analysis provided insights into the feasibility of predicting perioperative urogenital sepsis using gene chip technology for upper urinary tract stones. The full procedure is described in Fig. 1 for reference.

2.4 Statistical analysis

Statistical methods SPSS 26. 0 statistical software was used. The measurement data are herein expressed as (x ± s), and the count data are expressed as cases (%). Comparisons between groups were performed using the chi-square test and P < 0. 05 indicated statistical significance.

3. Results

3.1 Demographic and baseline characteristics

A total of 357 cases were included in the study, with a mean age of 52.9 ± 14.2 years. These cases were selected based on the availability of gene chip test results for *E. coli* and *KP*, with negative results. The patients' perioperative urinary tract infection with sepsis criteria were determined according to the EAU Guidelines on Urolithiasis and relevant literature [14–15]. The criteria included the following: (1) positive

urinary leukocyte esterase (LEU); (2) urine protein quantification > 100 mg/24 h; (3) microscopic examination of urine sediment showing leukocytes ≥ 10/HP; (4) positive urine nitrite; (5) presence of obvious clinical symptoms such as difficult urination, urinary urgency, urinary frequency, lateral abdominal pain, pressure pain at the angle of the cribriform vertebrae, suprapubic pain, and fever; and (6) sepsis diagnostic cutoff level: calcitoninogen > 0.5 ng/ml. Any patient meeting one or more of criteria (1) to (5) along with condition (6) was considered a positive case in the clinical diagnosis. The perioperative laboratory test results are presented in Table 1. Notably, the number of individuals testing positive for all items, except nitrite (urine), was significantly higher postoperatively. Conversely, the number of individuals testing positive for nitrite (urine) was significantly lower postoperatively. By conducting a paired t-test on the data from the table, a t value of -5.748 and a p value of 0.001 were obtained, indicating a p value < 0.05 at the chosen significance level. These findings provide compelling evidence of a significant disparity in laboratory test results before and after surgery, indicating that upper urinary tract stone surgery predisposes patients to urinary tract infections.

Table 1
Number of individuals with positive perioperative laboratory test results

Test items	Number of positive preoperative patients	Number of positive postoperative patients
Leukocytes>10.0×10^9/L	18	70
C-reactive protein>5 mg/l	42	164
Neutrophils>70%	28	132
calcitoninogen>0.5 ng/ml	4	39
Positive white blood cells (urine)	300	351
Positive red blood cells (urine)	248	352
Positive leukocyte esterase (urine)	226	338
Positive urine protein	176	350
Positive for nitrite (urine)	26	4

3.2 Gene chip test results

Out of the 383 patients, a total of 79 individuals tested positive for gene chip analysis. The predominant bacteria detected were *E. coli* (45 cases) and *MS* (30 cases). Importantly, there was no statistically significant difference in the results between patients with ureteral stones and those with renal stones ($\chi^2 = 0.042$, $P > 0.05$). Similarly, when considering only *E. coli* (45 cases) and *KP* (8 cases), there was still no statistically significant difference in the results between patients with ureteral stones and those with renal stones ($\chi^2 = 3.016$, $P > 0.05$). Regarding the urine culture results, out of the 383 patients, 49 had positive findings. The primary bacteria identified were *E. coli* (26 cases) and *Enterococcus faecalis* (8

cases). Interestingly, the proportion of positive results was lower in patients with ureteral stones than in those with renal stones, and this difference was statistically significant ($\chi^2 = 6.35$, $P < 0.05$). The results are presented in Table 2.

Table 2
Results of each pathogenic test

Testing Method	Pathogenic bacteria	Ureteral calculus	kidney stone	Total
Genetic test results	*E. coli*	13	28	41
	E. coli, MP	0	1	1
	E. coli, MS	3	0	3
	KP	2	3	5
	MS	18	7	25
	MS, KP	1	0	1
	MS, AB	0	0	0
	MS, AB, HI	1	0	1
	KP, AB	1	1	2
	Negative	154	150	304
Middle urine culture results	*E. coli*	8	18	26
	KP	0	2	2
	Ent	3	5	8
	Staphylococcus epidermidis	0	1	1
	Acid-producing Klebsiella	0	1	1
	Aspergillus singularis	0	4	4
	Streptococcus lactis	1	0	1
	Corynebacterium striatum	0	2	2
	Lactococcus-free	0	1	1
	Streptococcus pharyngitis	0	1	1
	Candida albicans	1	1	2
	Negative	180	154	334

3.3 Comparison of the results

Due to the significant variation in the gene chip test range used in this study compared to common urogenital pathogens, a new subgroup was created for comparison. This subgroup consisted of 357 patients with available gene chip test results for *E. coli* and *KP* and those with negative results. After adjustment the overall compliance rate of the midstream urine culture was 86.6% ($\chi^2 = 48.409$, $P < 0.05$), with a sensitivity of 48.7%, specificity of 91.2%, positive predictive value of 40.4%, negative predictive value of 93.5%, positive likelihood ratio of 5.53, and negative likelihood ratio of 0.56. Meanwhile the overall compliance rate of gene chip test was 84.3% ($\chi^2 = 33.947$, $P < 0.05$), with a sensitivity of 46.2%, specificity of 89.0%, positive predictive value of 34.0%, negative predictive value of 93.1%, positive likelihood ratio of 4.20, and negative likelihood ratio of 0.60.

Patients categorized as contaminated surgical environment (Grade IIIA surgery) according to the EAU Guideline[14], and those with high risk factors such as patients with large stone burden (stone diameter ≥ 2 cm) or moderate to severe hydronephrosis, lower urinary tract obstruction, long-term indwelling urinary drainage catheter, diabetic patients, and immunocompromised patients can also suffer from postoperative infection even with a negative urine culture result [16–17]. A high-risk group (H group) of 197 patients were found using the criteria above. The overall compliance rate of the midstream urine culture within the H group was 79.2% ($\chi^2 = 10.402$, $P < 0.05$), with a sensitivity of 42.9%, specificity of 85.2%, positive predictive value of 32.4%, negative predictive value of 90.0%, positive likelihood ratio of 2.90, and negative likelihood ratio of 0.67. Under identical conditions, the overall compliance rate of gene chip test was 82.2% ($\chi^2 = 23.211$, $P < 0.05$), with a sensitivity of 50.0%, specificity of 87.6%, positive predictive value of 40.0%, negative predictive value of 91.4%, positive likelihood ratio of 4.03, and negative likelihood ratio of 0.57. The results are presented in Table 3.

Table 3
Comparison of the consistency of pathogenic test results

Testing Method		**Midstream urine culture**[1]		**Gene chips**[1]		
		+	**-**	**+**	**-**	**Total**
Clinical Diagnosis	+	19	20	18	21	39
	-	28	290	35	283	318
Total		47	310	53	304	357
χ^2		48.409		33.947		-
P		<0.05		<0.05		-
Total compliance ratio		86.6%		84.3%		-
Sensitivity		48.7%		46.2%		-
Specificity		91.2%		89.0%		-
Positive predictive value		40.4%		34.0%		-
Negative predictive value		93.5%		93.1%		-
Positive likelihood ratio		5.53		4.20		-
Negative likelihood ratio		0.56		0.60		-
Testing Method			Midstream urine culture[2]		Gene chips[2]	
			+	-	+	-	Total
Clinical Diagnosis		+	12	16	14	14	28
		-	25	144	21	148	169
Total			37	160	35	162	197
χ^2			10.402		23.211		-
P			<0.05		<0.05		-

[1]: The grouping contains data of gene chip test results for *E. coli*, gene chip test results for *KP* and negative gene chip test results, for a total of 357 cases.

[2]: The grouping contains data of patients with high-risk factors such as large stone burden, moderate to severe hydronephrosis, lower urinary tract obstruction, etc.

Testing Method	Midstream urine culture[1]		Gene chips[1]		
	+	-	+	-	Total
Total compliance ratio		79.2%		82.2%	-
Sensitivity		42.9%		50.0%	-
Specificity		85.2%		87.6%	-
Positive predictive value		32.4%		40.0%	-
Negative predictive value		90.0%		91.4%	-
Positive likelihood ratio		2.90		4.03	-
Negative likelihood ratio		0.67		0.57	-

[1]: The grouping contains data of gene chip test results for *E. coli*, gene chip test results for *KP* and negative gene chip test results, for a total of 357 cases.

[2]: The grouping contains data of patients with high-risk factors such as large stone burden, moderate to severe hydronephrosis, lower urinary tract obstruction, etc.

4. Discussion

Midstream urine culture is mainly used as the primary basis for perioperative anti-infection treatment which costs 3–5 days. Some studies have shown that each 1-hour delay can result in an 8% decrease in mean survival [18]. Meanwhile, the traditional threshold for routine culture testing is 105 cfu/ml [19–20]. However, it has also been shown that culture results as low as 102 cfu/ml may still indicate an acute urinary tract infection [21]. In addition, routine urine culture results are dominated by *E. coli* and *Ent* [22–23]. In contrast, caustic bacteria, represented by anaerobic bacteria, are challenging to grow on conventional media. Therefore, a method that is less time-consuming and easier to operate is expected to fill the gap in rapid urological pathogen detection. In this study, we compared the results of gene chip with those of conventional midstream urine culture and found that the former had a shorter detection time (as fast as 2 h [24] vs. 3–5 d), similar overall compliance (86.6% vs. 84.3%), sensitivity (48.7% vs. 46.2%), and specificity (91.2% vs. 89.0%) for the detection of *E. coli* and *KP*.

As detailed in Section 3.3, patients with negative urine culture results may experience postoperative infection due to high-risk factors such as large stone burden, moderate to severe hydronephrosis, lower urinary tract obstruction, etc. Within the H group, the detection efficiency of gene chip test is significantly superior to that of midstream urine culture with a higher overall compliance (82.2% vs. 79.2%), sensitivity (50.0% vs. 42.9%), and specificity (87.6% vs. 85.2%).

The lack of urological-specific gene chips for pathogen detection was a limitation of this study. The microarray used in this research covered only 12 species of pathogens. Consequently, it was impossible

to detect all common pathogens in urinary tract infections. Additionally, current gene chip has relatively low specificity when not adjusted for the detection range.

In conclusion, gene chip test possesses a comparable detection efficiency to that of midstream urine culture with a rapid result turnaround. When treating patients with urolithiasis at high risk for postoperative infection, gene chip test has a higher overall compliance (82.2% vs. 79.2%), sensitivity (50.0% vs. 42.9%), and specificity (87.6% vs. 85.2%) compared with midstream urine culture. Given the ongoing advancements in gene chip design, future treatment of high-risk patients may involve utilizing gene chip test to guide antibiotic therapy and reduce the risk of postoperative infections and minimize hospital stay for patients.

Abbreviations

E. coli
Escherichia coli
KP
Klebsiella pneumoniae
SP
Staphylococcus putrefaciens
Ent
Enterococcus
GBS
Group B Streptococcus
BD
Bacillus deformans
PA
Pseudomonas aeruginosa
SA
Staphylococcus aureus
MS
Methicillin-resistant Staphylococcus
AB
Acinetobacter baumannii
AM
Acinetobacter maltophilia
HI
Haemophilus influenzae
LP
Legionella pneumophila
MP
Mycoplasma pneumoniae

CP
Chlamydia pneumoniae
LEU
leukocyte esterase
PCT
procalcitonin
EAU
European Association of Urology
IRB
institutional review board.

Declarations

Ethics approval and consent to participate

This study was submitted to and approved by the Ethics Committee of Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine (Approval No. V1.0/20251208). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The requirement for informed consent to participate was waived by the Ethics Committee of Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University School of Medicine, because the study was retrospective in nature and used de-identified residual clinical urine samples and anonymized clinical data.

Consent for publication

Not applicable.

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Author Contribution

Ranxing Yang and Yi Shao conceived and designed the study. Yanduo Lin and Wang Li collected the clinical data and performed the gene chip testing and midstream urine culture experiments. Hong Xie and Rong Chen conducted the statistical analysis and interpreted the data. Yanduo Lin and Wang Li drafted the manuscript. Yi Shao and Ranxing Yang critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Not applicable.

Data Availability

The gene chip technology used in this study is a probe-based nucleic acid hybridization assay targeting predefined pathogen-specific sequences; it does not rely on whole-genome sequencing and does not generate raw sequencing or microarray datasets requiring deposition. The datasets generated and/or analysed during the current study are not publicly available due to patient privacy and institutional restrictions but are available from the corresponding author on reasonable request.

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Figures

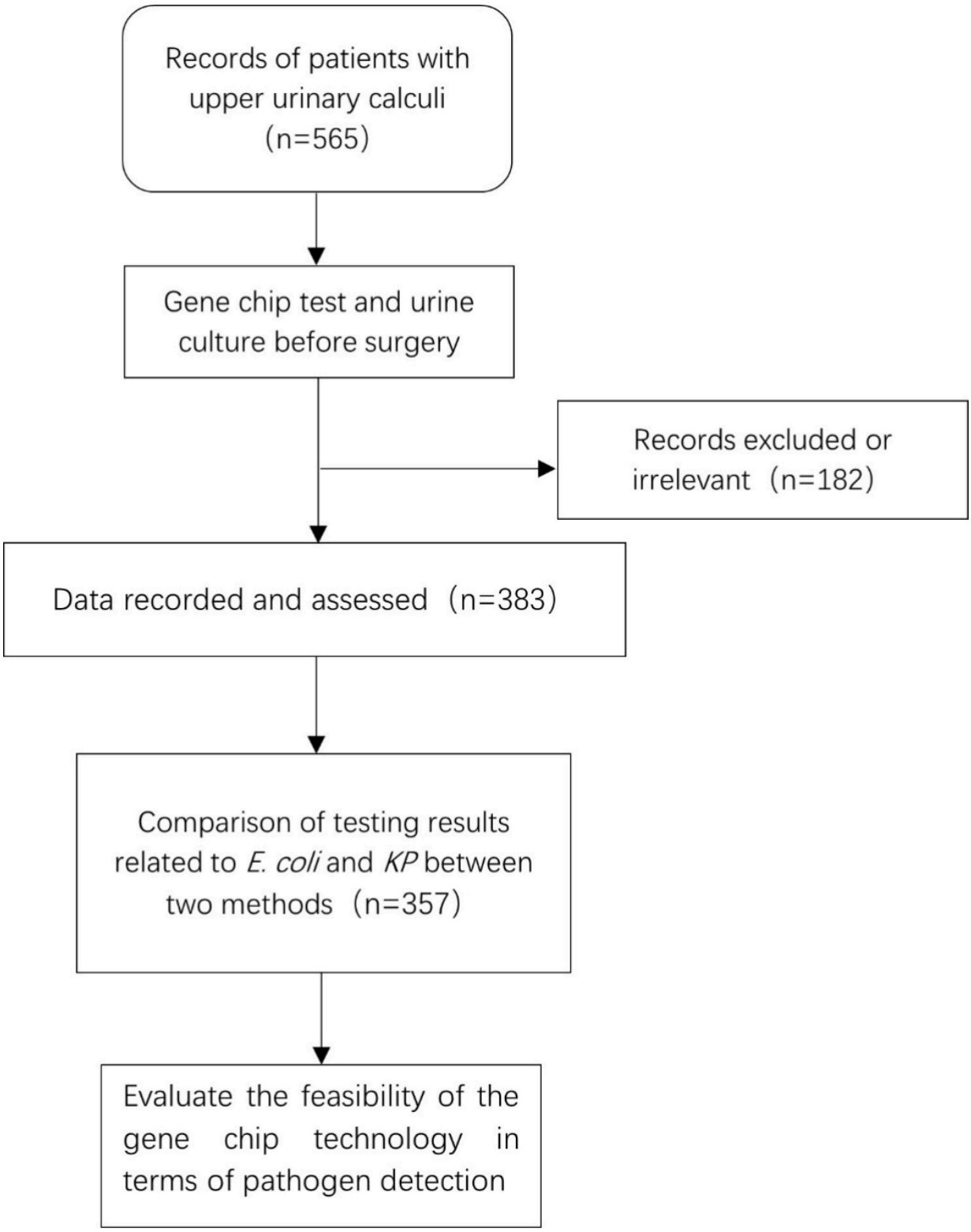


Figure 1

Statistical range of data and screening of results