

Incidence of Percutaneous Nephrostomy Tube-Associated Urinary Tract Infections in Vajira Hospital

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ABSTRACT

OBJECTIVE: To study the incidence of percutaneous nephrostomy tube-associated urinary tract infection (PCNI), changes in urinary characteristics, and factors associated with PCNI.

METHODS: A chart review was performed to retrospectively collect data on patients who underwent percutaneous nephrostomy (PCN) insertion for the first time. The eligibility criteria were met by 103 patients. PCNI incidence and correlation, changes in urinary characteristics and infectious events following insertion, bacterial characteristics, and the relationship between the type of bacteria and the presence of symptoms were all investigated.

RESULTS: The incidences of PCNI, sepsis, pyuria, and bacteriuria after insertion were 25.2%, 14.5%, 61.1%, and 48.5% within 76, 67, 25, and 46 days, respectively. The most common bacteria were multi-drug-resistant *Escherichia coli* (MDR *E. coli*) (16.2%), *Pseudomonas aeruginosa* (*P. aeruginosa*) (11.7%), *Escherichia coli* (*E. coli*) (10.3%), and *Enterococcus faecalis* (*E. faecalis*) (10.3%), which were susceptible to carbapenem, piperacillin/tazobactam, and amikacin. The bacterial type and PCNI demonstrated no correlation. However, the frequency of PCN change, indwelling period, pyuria, and bacteriuria in chronic kidney disease was significantly correlated with PCNI ($p < 0.05$).

CONCLUSION: Quarter of patients with a PCN catheter develops PCNI. More than half of patients with PCN indwellers had pyuria or bacteriuria. *E. coli* has the most significant ratio. Carbapenem, piperacillin/tazobactam, and amikacin all had benefits but should be adjusted in terms of culture results, especially in the multi-drug resistance group. The incidence of PCNI may decrease with early diagnosis, drainage, and the shortest period before specific treatment in the future.

KEYWORDS:

bacteriuria, percutaneous nephrostomy, pyuria, upper urinary tract obstruction, urinary tract infection

INTRODUCTION

Upper urinary tract obstruction is an obstruction from the renal pelvis to the distal ureter. Permanent renal failure or infection may occur if no immediate action is taken, which can be fatal. Goodwin et al.¹ invented percutaneous nephrostomy (PCN) that can address urinary obstruction, hydronephrosis, and

infection in the upper urinary tract², and renal function is renormalized³. However, a risk of complications exists from tube insertion to long-term use.

Urinary tract infection (UTI) is a common and serious complication of indwelling drainage tubes⁴, including PCN. Severe infections, such as sepsis, may require more complicated treatment,

with an increased risk of patient death⁵. The current standard treatment guidelines for catheter-associated UTI are clear⁶, but these guidelines exclude PCN patients whose definition varies among studies⁷⁻⁸. Previous studies have reported the incidence of percutaneous nephrostomy tube-associated urinary tract infection (PCNI) to be between 14-38%.^{4,8-11}. Among cancer patients, there is an increased risk of PCNI associated with a history of UTI or neutropenia. However, for other patient groups, the risk factors for PCNI remain unclear. Academically strong clinical evidence still needs to be improved, and developing clear diagnosis and treatment guidelines because of the differences in patient characteristics in each area and common microorganisms is impossible despite numerous studies on these populations⁸. We believed that studying the incidence of infection and microbiological characteristics would help us plan treatment and improve the quality of patient management while providing reference data for future studies.

METHODS

Data collection

This retrospective cohort study collected data via outpatient and inpatient department chart reviews of patients in Vajira Hospital. The first PCN insertion occurred from January 2016 to June 2022, with 154 patients. The types of tubes used in the study included a suction tube (10 Fr) or a pigtail catheter (10 Fr) with ultrasound-guided insertion. Routine changing of the tubes in the study was performed using the under-guidewire lead technique with changing times of 30 days and 90 days, respectively. Patients with PCNs inserted at other hospitals and those with a follow-up time of < 60 days were excluded. 103 patients met the eligibility criteria.

The collected patient data included sex, age, comorbidity, indication for insertion, and urinalysis profiles specifically collected from PCN, which diagnosed pyuria as having > 5 white blood

cells per high-power field in urine. The type of bacteria found in culture was recorded if bacteriuria ($\geq 10^5$ CFUs/ml) was present, along with antibiotic susceptibility. The duration from PCN insertion to changes in urine characteristics and the presence of signs of infection were also noted. Bacteriuria, together with symptoms such as fever of > 37.8°C or costovertebral angle tenderness, was identified as a UTI (PCNI in this study) or sepsis if positive hemoculture was also present. Patients who had their first PCN catheter inserted due to infection were not counted as having PCNI, and changes in urine output and infection status were recorded after successful treatment and negative urine culture results. The hospital length of stay in the PCNI population, number of sides of tube insertion, and frequency of tube change until September 2022 or tube removal were also recorded.

The Institutional Review Board approved this study, Faculty of Medicine Vajira Hospital, Navamindradhiraj University (COA 214/2565).

Statistical analysis

Qualitative data were reported as frequency distributions and percentages. Quantitative data were reported as mean and standard deviation, or median and interquartile range, regarding data appropriation. The frequency distribution and percentage with a 95% confidence interval were used to report the incidence and prevalence rates of pyuria, bacteriuria, PCNI and sepsis. Frequency distribution, percentage analysis, crude analysis, and the chi-squared test were used to report the correlation between the type of microorganism and PCNI. Frequency distribution, percentages, Spearman rank-order correlation, and pairwise correlation coefficients were used in the correlation analysis for patients with PCNI. SPSS for Windows, version 28.0 (IBM Corp., Armonk, NY, USA), was used for analysis. All statistical tests were considered statistically significant at a p-value of < 0.05.

RESULTS

This study involved 103 patients, primarily female (66%), with a mean age of 59.1 years and cancer as the main comorbidity (89.3%). Chronic kidney disease was also common among these patients (44.6%). The main indication for insertion was acute kidney injury (85.4%), and the leading cause was urinary tract obstruction due to cancer (80.5%). Unilateral insertion (68.9%) was more common than bilateral insertion, and the median number of tube changes was four with a 143-day indwelling period (table 1).

The prevalence of pyuria was 61.1% (n = 63), and the incidence of bacteriuria was 48.5% (n = 50) during the entire period of PCN indwelling, with 23.3% being asymptomatic (n = 24), 25.2% being PCNI (n = 26), and 14.5% having sepsis (n = 15)

(table 2). The median duration from PCN insertion to the presence of pyuria and bacteriuria was 25 and 46 days, respectively. The mean duration from PCN insertion to the presence of PCNI and sepsis was 76 and 67 days, respectively. The median length of stay for UTI treatment was 17 days. (table 3).

During the entire period of PCN indwelling in 51 patients with positive urine cultures, we analyzed 68 specimens. We found gram-negative bacteria in 59 specimens (86.7%), and 61% of the gram-negative bacteria were drug-resistant. Gram-positive bacteria were present in 8 specimens (10.2%), and only 1 (12.5%) was drug-resistant. The most common microorganisms detected were multi-drug-resistant *Escherichia coli* (MDR *E. coli*) (16.2%), *Pseudomonas aeruginosa* (*P. aeruginosa*) (11.7%), *Escherichia coli* (*E. coli*) (10.3%), and *Enterococcus faecalis* (*E. faecalis*) (10.3%) (table 4).

Table 1 Demographic data for the study population

Variables	Mean (SD)/Median (IQR)/Count (%) (N=103)
Mean Age (year), SD	59.1 (13.9)
Gender	
Male	35 (34%)
Female	68 (66%)
Comorbidity	
Diabetic mellitus	11 (10.7%)
Chronic kidney disease	46 (44.6%)
Immunocompromised ^a	20 (19.4%)
Cancer	92 (89.3%)
Genitourinary tract cancers	23 (22.3%)
Gastrointestinal cancers	19 (18.4%)
Gynecologic cancers	45 (43.7%)
Others cancer	5 (4.9%)
Stone	10 (9.7%)
Indication	
Acute kidney injury	88 (85.4%)
Infection	9 (8.7%)
Pain	3 (2.9%)
Others ^b	3 (2.9%)
Cause	
Malignant disease	83 (80.5%)
Stone	11 (10.7%)
Ureteric stricture	8 (7.8%)
Ureteric Injury	1 (1%)
Side	
Unilateral	71 (68.9%)
Bilateral	32 (31.1%)
Changed time (times), Median (IQR)	4 (2-7)
Indwelling time (days), Median (IQR)	143 (82.5-257.5)

Abbreviations: IQR, interquartile range; N, number; SD, standard deviation

^a= Patients who received chemotherapies or immunosuppressive drug within 1 year of PCN insertion

^b= Others indication included ureteric injury, ureteric stricture

Table 2 Prevalence of inflammatory and incidence of PCNI

Variables	Count (%), N=103
Pyuria	63 (61.1%)
Bacteriuria	50 (48.5%)
Asymptomatic bacteriuria	24 (23.3%)
Symptomatic: PCNI	26 (25.2%)
Sepsis	15 (14.5%)

Abbreviations: N, number; PCNI, percutaneous nephrostomy tube-associated urinary tract infections

Table 3 Mean time to develop pyuria and infectious conditions

Variables	Median time (day), (IQR)
Time from insertion to pyuria	25 (6-64)
Time from insertion to bacteriuria	46 (19-126.8)
Time from insertion to PCNI	76 (38.75-144.25)
Time from pyuria to PCNI	16 (2.25-48.6)
Time from bacteriuria to PCNI	4 (0-23)
Time from insertion to sepsis event	67 (44-91.5)
Length of stay for infection treatment	17 (7.3-30.5)

Abbreviation: IQR, interquartile range; PCNI, percutaneous nephrostomy tube-associated urinary tract infections

Table 4 Microbiological characteristics in PCN indwellers

Variables	Total Count (%) N=68 (%)	Symptomatic Count (%) N=39/68	Asymptomatic Count (%) N=29/68	P-value
Gram negative	23 (33.8%)	14 (35.9%)	9 (31%)	0.29
<i>Klebsiella pneumoniae</i>	4 (5.9%)	3 (7.7%)	1 (3.5%)	0.32
<i>Escherichia coli</i>	7 (10.3%)	5 (12.9%)	2 (6.8%)	0.26
<i>Pseudomonas aeruginosa</i>	8 (11.7%)	4 (10.3%)	4 (13.7%)	1.00
<i>Acinetobacter baumannii</i>	1 (1.5%)	0 (0%)	1 (3.5%)	-
<i>Stenotrophomonas maltophilia</i>	2 (2.9%)	1 (2.5%)	1 (3.5%)	1.00
<i>Proteus mirabilis</i>	1 (1.5%)	1 (2.5%)	0 (0%)	-
Gram positive	7 (10.3%)	4 (10.3%)	3 (10.3%)	0.71
<i>Enterococcus faecalis</i>	7 (10.3%)	4 (10.3%)	3 (10.3%)	0.71
Drug-resistant gram negative	36 (52.9%)	20 (51.3%)	16 (55.2%)	0.51
MDR <i>Klebsiella pneumoniae</i>	4 (5.9%)	3 (7.7%)	1 (3.5%)	0.32
MDR <i>Escherichia coli</i>	11 (16.2%)	5 (12.9%)	6 (20.7%)	0.76
MDR <i>Pseudomonas aeruginosa</i>	5 (7.3%)	3 (7.7%)	2 (6.8%)	0.66
MDR <i>Acinetobacter baumannii</i>	6 (8.8%)	5 (12.9%)	1 (3.5%)	0.10
MDR <i>Chryseobacterium indolgenes</i>	1 (1.5%)	0 (0%)	1 (3.5%)	-
MDR <i>Citrobacter freundii</i>	2 (2.9%)	1 (2.5%)	1 (3.5%)	1.00
MDR <i>Enterobacter Cloacae</i>	6 (8.8%)	2 (5.1%)	4 (13.7%)	0.41
MDR <i>Proteus mirabilis</i>	1 (1.5%)	1 (2.5%)	0 (0%)	-
Drug-resistant gram positive	1 (1.5%)	1 (2.5%)	0 (0%)	-
MRSA	1 (1.5%)	1 (2.5%)	0 (0%)	-
Fungal	1 (1.5%)	0 (0%)	1 (3.5%)	-
<i>Candida albican</i>	1 (1.5%)	0 (0%)	1 (3.5%)	-

Abbreviations: MDR, multi-drug-resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; N, number

Non-drug-resistant gram-negative bacteria, including *E. coli*, *P.aeruginosa*, and *Klebsiella pneumonia* (*K. pneumonia*), are susceptible to amikacin (100%, 100%, and 75%, respectively), carbapenem (100%), and piperacillin/tazobactam (100%, 87.5%, and 100%, respectively). Additionally, *E. coli* and *K. pneumonia* were susceptible to

cotrimoxazole at 71.4% and 75%, respectively, but fluoroquinolone and cephalosporin were relatively low (0%–25% and 25%–28.6%, respectively), whereas *P. aeruginosa*, regarding fluoroquinolone, was susceptible to levofloxacin at 12.5% and ciprofloxacin at 62.5%, and only 75% for ceftazidime in cephalosporin group. The majority

of the multi-drug-resistant gram-negative bacteria showed the highest susceptibility to amikacin and cotrimoxazole (50%–81.8% and 27.8%–83.3%, respectively) while being minimally susceptible to cephalosporin and fluoroquinolone (0%–18.2% and 0%–9.1%, respectively), as well as piperacillin/tazobactam (0%–63.6%). Multi-drug-resistant *Pseudomonas aeruginosa* (MDR *P. aeruginosa*) was resistant to most antibiotics but showed some susceptibility to colistin (20%).

Only two types of microorganisms were found for gram-positive bacteria, including *E. faecalis* (10.3%), which was more common than

methicillin-resistant *Staphylococcus aureus* (MRSA) (1.5%). Almost all types of the studied bacteria were resistant to amoxicillin/clavulanic acid and ampicillin, except *E. faecalis*, which was susceptible to ampicillin (85.7%). Among gram-positive bacteria, *E. faecalis* and MRSA were susceptible to vancomycin at 100% (table 5).

The type of microorganism and the presence of UTI demonstrated no correlation (table 4). A significant correlation was found between patients with PCNI and chronic kidney disease (CKD), number of tube changes, indwelling period, pyuria, and bacteriuria ($p < 0.05$) (table 6).

Table 5 Antibiotic susceptibility of isolated microorganisms from PCN cultures

Antibiotics / Organisms	<i>Escherichia coli</i>	MDR <i>Escherichia coli</i>	<i>Pseudomonas aeruginosa</i>	MDR <i>Pseudomonas aeruginosa</i>	<i>Klebsiella pneumoniae</i>	MDR <i>Klebsiella pneumoniae</i>	MDR <i>Enterobacter cloacae</i>	MDR <i>Acinetobacter baumannii</i>	<i>Enterococcus faecalis</i>	MRSA
	Counts (%) N=7/68	Counts (%) N=11/68	Counts (%) N=8/68	Counts (%) N=5/68	Counts (%) N=4/68	Counts (%) N=4/68	Counts (%) N=6/68	Counts (%) N=6/68	Counts (%) N=7/68	Counts (%) N=1/68
Amikacin	7 (100%)	9 (81.8%)	8 (100%)	R	3 (75%)	4 (100%)	3 (50%)	3 (50%)	N/A	N/A
Gentamicin	5 (71.4%)	1 (9.1%)	4 (50%)	R	4 (100%)	3 (75%)	3 (50%)	1 (16.7%)	3 (42.9%)	1 (100%)
Amoxi/clav	1 (14.3%)	N/A	N/A	N/A	1 (25%)	R	N/A	N/A	N/A	N/A
Ampicillin	R	R	N/A	N/A	R	R	R	N/A	6 (85.7%)	N/A
Ceftriaxone	2 (28.6%)	2 (18.2%)	N/A	N/A	1 (25%)	R	R	NA	N/A	N/A
Ceftazidime	2 (28.6%)	2 (18.2%)	6 (75%)	R	1 (25%)	R	R	1(16.7%)	N/A	N/A
Ciprofloxacin	R	R	5 (62.5%)	R	1 (25%)	R	R	R	N/A	N/A
Levofloxacin	R	1 (9.1%)	1 (12.5%)	R	R	R	N/A	R	N/A	N/A
Imipenem	7 (100%)	9 (81.8%)	8 (100%)	R	4 (100%)	3 (75%)	1 (16.7%)	R	N/A	N/A
Ertapenem	7 (100%)	8 (72.7%)	N/A	R	4 (100%)	2 (50%)	1 (16.7%)	N/A	N/A	N/A
Meropenem	7 (100%)	9 (81.8%)	8 (100%)	R	4 (100%)	3 (75%)	3 (50%)	R	N/A	N/A
Pip/tazobactam	7 (100%)	7 (63.6%)	7 (87.5%)	R	4 (100%)	2 (50%)	R	R	N/A	N/A
Cotrimoxazole	5 (71.4%)	3 (27.8%)	N/A	N/A	3 (75%)	2 (50%)	5 (83.3%)	N/A	N/A	1 (100%)
Vancomycin	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	7 (100%)	1 (100%)
Colistin	N/A	N/A	2 (25%)	1 (20%)	N/A	N/A	2 (33.3%)	2 (33.3%)	N/A	N/A
Tigecycline	N/A	N/A	N/A	N/A	N/A	N/A	N/A	6 (100%)	N/A	N/A

Abbreviations: MDR, multi-drug-resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; R, resisted; N, number; N/A, susceptibility testing is not performed

Table 6 Correlation of percutaneous nephrostomy tube-associated urinary tract infections

Variables	Mean (SD)/Median (IQR)/Count (%) (N=26/103, 52%)	r	P-value
Age (year), Mean (SD)	59.7 (12.1)	0.04	0.70
Comorbidity			
Diabetic mellitus	2 (7.7%)	-0.06	0.57
Chronic kidney disease	16 (61.4%)	0.20	0.05*
Immunocompromised ^a	8 (30.7%)	0.17	0.09
Genitourinary tract cancer	9 (34.6%)	0.17	0.08
Gastrointestinal cancer	2 (7.7%)	-0.16	0.10
Gynecologic cancer	12 (46.1%)	0.03	0.77
Stone	3 (11.5%)	0.04	0.72
Changed time (times), Median (IQR)	6 (4-13.75)	0.26	0.01*
Indwelling time (days), Median (IQR)	256 (127.3-403.5)	0.28	0.00*
Pyuria	26 (100%)	0.45	0.00*
Bacteriuria	26 (100%)	0.56	0.00*

Abbreviations: IQR, interquartile range; r, correlation coefficient; SD, standard deviation

* $p < 0.05$ significant

^a, Patients who received chemotherapies or immunosuppressive drug within 1 year of PCN insertion

DISCUSSION

This study revealed a higher incidence of PCNI than in previous studies in the United States of America, with 14%, 19%, and 20%⁸⁻¹¹, but lower than 38% in Sweden⁴. The incidence of sepsis was higher than that of other studies, which were 3%⁴ and 9%⁸ but similar to the 12% reported in a Brazilian study¹². The mean duration from PCN insertion to PCNI was both shorter and longer than that reported in previous studies (14 days⁴, 42 days¹⁰, and 100 days⁸) and longer than the duration from insertion to sepsis (67 days), demonstrating that patients with sepsis might have some factors that made them sensitive to more severe infection. Ramez et al.⁹ reported a correlation between acute pyelonephritis and PCN in patients with cancer. This study revealed that 89.3% of patients had cancer, which was probably the cause of the high infection incidence. However, the study did not observe any correlation.

The present study revealed a correlation between pyuria and bacteriuria with PCNI because it is a diagnostic criterion for the infection. Moreover, pyuria can result from the body's response to PCN, with or without concurrent infection. However, the comparable prevalence of asymptomatic and symptomatic bacteriuria (23.3% vs. 25.2%) suggests that the observed correlation may not have significant clinical relevance. Furthermore, no previous study explained the relationship between pyuria and bacteriuria as infection risk factors, related to Cronan et al.'s study revealed that bacteriuria after tube insertion did not usually cause disease unless there was obstruction¹³.

Pappas et al.¹⁴ reported that 6% of patients still have no renal function improvement, although urinary drainage was already used in patients with acute renal failure. In addition, CKD might damage body immunity through decreased response to kidney-affecting medications, a factor in complicated UTIs¹⁵⁻¹⁶. In contrast, Maramara et al.¹¹, indicating no association between CKD in the population with PCN and UTI or bacteriuria. Even though it could not be

interpreted as a risk factor for UTI, the correlation between PCNI and CKD was demonstrated in this study which may be explained by a higher proportion of the study population than other diseases. Besides the relatively high mean age of populations, other factors, such as delayed drainage time in some cases due to difficult medical treatment access or delayed diagnosis, may lead to permanent renal damage and restoration of function that was not as good as it should be.

The tube-indwelling period is another factor despite a lower urinary tract catheter¹⁷. A correlation was found between changing frequency, indwelling period, and PCNI, which was higher than that reported in previous studies⁹⁻¹⁰. This could be attribute to the necessity for frequent tube changes due to tube dislocation, tube obstruction, and the waiting time for specific treatment. Additionally, factors of personal hygiene, tube care, or delayed tube change might reinforce infection. However, timely replacement of PCN when indicated is crucial as delaying replacement beyond four days after symptom onset may increase the risk of recurrent infection⁸.

The proportion of drug-resistant microorganisms in terms of microbiological characteristics was higher (61%) than in previous studies, which was 37.7%¹¹ and 47%¹⁸. However, no microorganism was significantly associated with the presence of the signs. The remarkable proportion of both types of *E. coli* might be due to environmental factors, common microorganism prevalence, inadequate treatment time, antibiotic administration in asymptomatic patients, or a long PCN indwelling period¹⁹, which might lead to change in the biological properties of drug-susceptible strains *E. coli* in the urine of patients with PCN. Therefore, proper management should be considered to prevent changes to drug-resistant ones in the future due to the main proportion of organisms usually found in the symptomatic group. However, sepsis could be detected with the same or different microorganisms in the urine, and recurrent infection did not always require the same

microorganism as the previous culture²⁰. The following most common microorganisms for gram-negative and overall organisms were similar to those in the previous study, which were *P. aeruginosa* and *E. faecalis*¹⁸.

Non-drug-resistant *E. coli* and *K. pneumonia* were more susceptible to cotrimoxazole than fluoroquinolones regarding antibiotic susceptibility for the gram-negative group. The resistance rate of fluoroquinolones and cephalosporins was relatively high in almost every microorganism, but ciprofloxacin and ceftazidime could still be considered for treating *P. aeruginosa*. A previous study revealed that meropenem and amikacin are the most effective antibiotics against gram-negative bacteria²¹. Carbapenem and piperacillin/tazobactam remained susceptible to non-drug-resistant gram-negative microorganisms (87.5%–100%) in the study population, but susceptibility substantially decreased (0%–81.8%) in the drug-resistant group. Amikacin remains susceptible to more than half (50%–100%) of almost every group of gram-negative microorganisms, except MDR *P. aeruginosa*, which was resistant to nearly every antibiotic. Therefore, empirical treatment for nosocomial microorganisms, especially MDR *P. aeruginosa*, MDR *Enterobacter Cloacae* (MDR *E. cloacae*), and MDR *Acinetobacter baumannii* (MDR *A. baumannii*) must be primarily used with these drug groups that might partly affect specific results of culture so that the type of antibiotics could be appropriately adjusted. Vancomycin remains a good treatment choice for gram-positive bacteria because most bacteria in this group remain susceptible. However, ampicillin may be considered for the treatment of *E. faecalis*.

The statistical significance of the study may be lower than other studies due to the limited population size, and risk factors could not be analyzed despite finding a correlation between PCNI and certain factors. Additionally, the study did not compare the incidence rates of PCNI between patients who received unilateral or bilateral PCN insertion or between symptomatic

and asymptomatic patient populations. Furthermore, this was a retrospective study, which means that certain data may not have been recorded, such as the type of PCN tube, simultaneous urethral catheter insertion, and urine collection from an old or new tube, which might be contaminated by colonization and treatment for symptomatic patients. Moreover, this study was conducted in a single institution, so the data may only be applicable to similar institutions in the same area and may not generalize to institutions with different patient characteristics.

CONCLUSION

Quarter of patients with a PCN catheter develops PCNI. More than half of patients with PCN indwellers had pyuria or bacteriuria. *E. coli* has the most significant ratio. Carbapenem, piperacillin/tazobactam, and amikacin all had benefits but should be adjusted regarding culture results, especially in the MDR group. Early diagnosis and drainage and the shortest period before specific treatment may decrease the incidence of PCNI in the future.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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None

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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