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Characteristics of Sepsis or Acute Pyelonephritis Combined with Ureteral Stone in the United States: A Retrospective Analysis of Large National Cohort

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Abstract: Abstract: ObjectiveTo identify the characteristics of patients with sepsis or acute pyelonephritis (APN) combined with ureteral calculi and to analyze the risk factors in its causation. **Methods:** We included patients with sepsis or APN caused by ureteral calculi who received treatment in the United States from January 2003 to December 2017 using the Optum® deidentified Clinformatics® Datamart. Demographic factors and risk factors for the receipt of sepsis or APN were subsequently analyzed for statistical significance. **Results:** Of 467,502 urinary stone patients, age-matched multivariate analysis revealed that a history of urinary tract infection (OR 11.31, 95% CI 10.68–11.99, $p < 0.0001$) and female gender (OR 2.73, 95% CI 2.62–2.84, $p < 0.0001$) were significantly related to an increased risk of sepsis or APN. Conversely, a previous past medical history of urolithiasis (OR 0.91, 95% CI 0.87–0.95, $p < 0.0001$) and cancer (OR 0.91, 95% CI 0.87–0.95, $p < 0.0001$) were associated with a decreased risk of sepsis or APN. With regards to comorbidities, when more than one comorbidity was present, there was an additive effect with higher OR point estimates, rising to 11.31 (10.68–11.99) when three or more comorbidities present. History of urinary tract infection and female gender are risk factors for sepsis or APN in patients with ureteral calculi. **Conclusions:** This large national cohort reveals the characteristics of sepsis or APN combined with ureteral stone and provides an important baseline for the treatment of urolithiasis in the future.

Keywords: sepsis; pyelonephritis; ureteral calculi; chronic disease

1. Introduction

Urolithiasis is a common malady in the United States today, with an overall prevalence of urinary stone disease reported at 8.8%, with the prevalence in males at 10.6% and in females at 7.1%. The prevalence increases with age and in patients with obesity and diabetes mellitus [1].

In many cases, the prevalence of urinary stone disease is 7.8% based on a study screening asymptomatic patient with noncontrast computed tomography (CT) scans. This study reported an average of 2.1 stones per patient, an average stone size of 3 mm, and found a higher prevalence of stone disease among men, those with diabetes mellitus and obesity, and those over 60 years of age [2]. In general, asymptomatic urinary stones are often observed without treatment, and stones sized less than 4 mm have a natural expulsion rate of 76–87% without treatment [3].

However, in some cases, patients with ureteral calculi that do not spontaneously pass may develop ureteral obstruction, and consequently serious infections such as sepsis or complicated acute pyelonephritis (APN). Approximately 78% of urinary sepsis cases are caused by obstructive uropathy: 43% by urinary stones, 25% by an enlarged prostate, and 18% by urinary tract cancer [4]. If sepsis or APN is caused by ureteral obstruction, intensive treatment with surgical decompression, such as percutaneous nephrostomy or retrograde double J stenting, is necessary. In a retrospective study of patients with sepsis due to urinary stones, early surgical decompression yielded a significantly lower mortality rate compared with delayed surgical intervention [5].

Ureteric stones can be treated with medical expulsive therapy, shockwave lithotripsy, and endoscopic surgery, but if sepsis or APN is accompanied, the treatments are different. We aimed to analyze the risk factors and to recognize the characteristics of patients with sepsis or APN caused by ureteral calculi using a large private insurance claims-based dataset.

2. Patients and Methods

2.1. Data Source

This retrospective observational cohort study was performed using the Optum® deidentified Clinformatics® Datamart database from 2003 to 2017. This database contains retrospective claims information, including inpatient, outpatient, and member enrollment, and social economics in the United States. All costs were standardized based on Medicare Relative value Units and other pricing methods and inflation-adjusted. All data were deidentified to maintain compliance with the Health Insurance Portability and Accountability Act regulations. This method has been used in other studies [6–12], and given deidentified information, this study was deemed exempt from informed consent requirements by the Stanford University Medical Center Institutional Review Board. (Human Subjects Research Stanford University IRB eProtocol Number-49655).

2.2. Study Population

We included adult patients with sepsis or APN combined with ureteral calculi who were at least 18 years old from 2003 to 2017. We used the 9th and 10th revisions of the International Classification of Diseases, 9th and 10th revision, Clinical Modification (ICD-9-CM and ICD-10-CM) and CPT codes to identify the study cohort and comorbidities.

Ureteral calculi were classified into calculus of the ureter (ICD-9: 592.1, ICD-10: N20.1) and calculus of the kidney with calculus of the ureter (ICD-9: 592.1, ICD-10: N20.2). Severe infections were classified as APN (ICD-9: 590.10, 590.80, ICD-10: N10) and sepsis (ICD-9: 038.40, 038.42, 038.9, 790.7, 995.91, 995.92, ICD-10: A41.9).

Demographic factors and comorbidities: ischemic heart diseases (ICD-9: 410–414, ICD-10: I20–I25), hypertension (ICD-9: 401, ICD-10: I10–I13), diabetes mellitus (ICD-9: 249, 250, ICD-10: E08–E13), stroke (ICD-9: 430–438, ICD-10: I60, I61, I62, I63, I65, I66, I67, I68, and I69), Alzheimer's disease (ICD-9: 331.0, ICD-10: G30), chronic kidney disease (ICD-9: 585.3, 585.4, 585.5, 585.6, 585.9, ICD-10: N18, N19), chronic respiratory diseases (ICD-9: 490–496, 510, ICD-10: J40–J47), overweightness and obesity (ICD-9: 278, ICD-10: E66), history of UTI (ICD-9: 590, 595, ICD-10: N10 and N30), history of urinary stone (ICD-9: 592, 594, ICD-10: N20–N22), insurance type (EPO, HMO, POS, PPO, Indemnity, other), surgical treatment type, and cost data (total treatment cost for urinary stone without sepsis or APN vs. urinary stone with sepsis or APN), were analyzed. Surgical decompressions, such as retrograde double J stent insertion (CPT: 52332, 52005) and percutaneous nephrostomy (CPT: 50430, 50431, 50432, 50433, 50434, 50435, 50693, 50694, 50695), were analyzed.

We excluded patients with the following medical comorbidities or past surgical history from this study: kidney transplant status (ICD-9: V42.0, ICD-10: Z94.0), congenital malformations of the urinary system (ICD-9: 753.0, 753.3, 753.4, 753.9, ICD-10: Q60, Q62, Q63, and Q64), neuromuscular dysfunction of the bladder (ICD-9: 596.54, ICD-10: N31.2, N31.9), pregnancy (ICD9: V22, V23, V28, 630–679, 760–779, ICD-10: O00–O9A, P00–P96, Z32, Z33, Z34, Z36, Z3A), and major urologic surgery—nephroureterectomy (CPT: 50548), radical nephrectomy (CPT: 50545), partial nephrectomy (CPT: 50543), radical prostatectomy (CPT: 55866), and radical cystectomy (CPT: 51570, 51575, 51580, 51585, 51590, 51595, 51596, and 51999).

2.3. Statistical Analysis

To assess the differences between sepsis and nonsepsis patients, a Student's *t*-test was used to compare age and the Chi-square test was used for categorical variables. The treatment costs were compared by *t*-test. Linear logistic regression was applied to evaluate the risk factors of sepsis. To eliminate the possible confounding effect by age, the propensity score matching method was used to match one sepsis patient with two nonsepsis patients. Conditional logistic regression was applied for the age-matched data. All analyses were two-sided and $p < 0.05$ was considered statistically significant. The statistical software SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) was used in this study.

3. Results

Figure 1 shows the incidence of ureteric stones and sepsis or APN by region in the United States. The incidence of sepsis or APN due to ureteric stones was 5–6% in most regions, with the highest in the pacific region at 7.21% and the lowest in the east–south region at 4.52%.

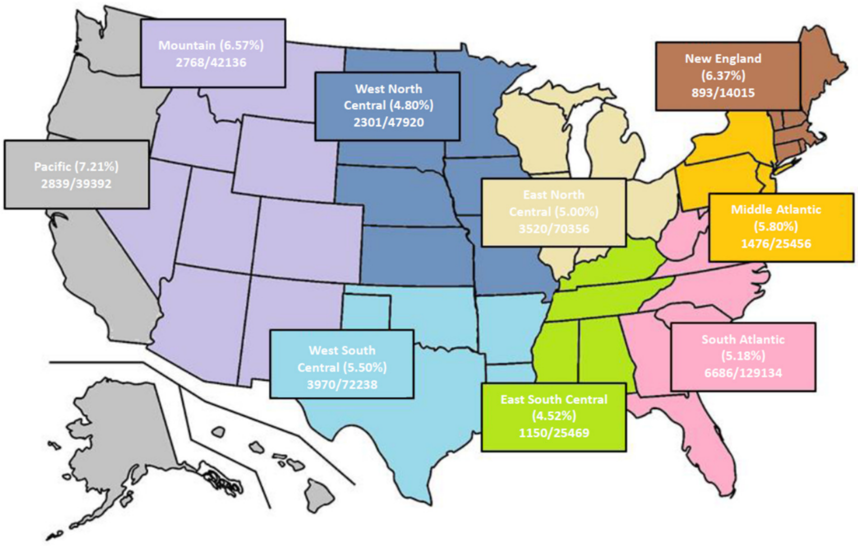

Figure 1. Current status of ureteral calculi and sepsis or APN by region in the United States for 15 years.

Table 1 lists demographic patient characteristics. A total of 467,502 patients diagnosed with ureteral calculi, from a total of 1,713,248 patients with urinary stones, were treated from January 2003 to December 2017. Of these, 25,747 were diagnosed with sepsis or APN for an overall incidence of 5.51%. Ureteral calculi without sepsis or APN were common in men (64.38%), but ureteral calculi with sepsis or APN were more common in women (67.13%). There was a significant difference in the age between the nonsepsis or APN group and sepsis or APN group (50.5 vs. 56.8 years).

Table 1. Demographics of the United States cohort with ureteric calculi (N = 467,502; 2003–2017).

	Nonsepsis/APN	Sepsis/APN	*p*
No. pts (%)	441,755 (94.5)	25,747 (5.5)	
Mean ± SD age	50.5 ± 15.5	56.8 ± 17.7	<0.0001
No. gender (%)			<0.0001
Female	157,336 (35.62)	17,285 (67.13)	
Male	284,419 (64.38)	8462 (32.87)	
No. race (%)			<0.0001
White	297,591 (67.37)	16,531 (64.21)	
Hispanic	35,489 (8.03)	2480 (9.63)	
Black	28,265 (6.4)	2155 (8.37)	
Asian	9777 (2.21)	491 (1.91)	
Unknown	70,633 (15.99)	4090 (15.89)	
No. insurance type (%)			<0.0001
POS	239,579 (54.23)	10,305 (40.02)	
HMO	82,190 (18.61)	6857 (26.63)	
EPO	43,632 (9.88)	1968 (7.64)	
PPO	26,337 (5.96)	1686 (6.55)	
Indemnity	5126 (1.16)	509 (1.98)	
Other	44,891 (10.16)	4422 (17.17)	
No. underlying disease (%)			
Hypertension	173,274 (39.22)	15,112 (58.69)	<0.0001
Diabetes mellitus	76,322 (17.28)	8675 (33.69)	<0.0001
Stroke	27,753 (6.28)	4602 (17.87)	<0.0001
Chronic kidney disease	14,004 (3.17)	3290 (12.78)	<0.0001
Chronic respiratory disease	73,179 (16.57)	8007 (31.1)	<0.0001
Ischemic heart disease	52,240 (11.83)	6088 (23.65)	<0.0001
Alzheimer's disease	1658 (0.38)	502 (1.95)	<0.0001
Overweight and obesity	55,863 (12.65)	5777 (22.44)	<0.0001
Cancer	145,897 (33.03)	11,513 (44.72)	<0.0001
No. medical history (%)			
History of UTI	18,807 (4.26)	11,554 (44.88)	<0.0001
History of urinary stone	124,916 (28.28)	10,328 (40.11)	<0.0001
No. surgical decompression (%)			<0.0001
DJ stent insertion	97,324 (22.03)	10,974 (42.62)	
Nephrostomy	1055 (0.23)	189 (0.73)	
Total cost ($)			
DJ stent insertion, median (IQR)	410 (125–2369)	274 (237–1446)	<0.0001
Nephrostomy, median (IQR)	1178 (669–2836)	952 (669–1748)	0.0053

APN = acute pyelonephritis; EPO = exclusive provider organization; HMO = health maintenance organization; POS = point of service; PPO = preferred provider organization; SD = standard deviation; UTI = urinary tract infection.

A total of 108,993 patients underwent surgical decompression, accounting for 23.31% of all ureteral calculi cases. A total of 97,890 patients (22.15%) with ureteral calculi without sepsis or APN and 11,103 patients (43.12%) with ureteral calculi with sepsis or APN underwent surgical decompression. Surgical decompression via retrograde double J stent insertion (22.03%, 42.62%) was more commonly performed than percutaneous nephrostomy (0.23%, 0.73%) in both groups.

Patients with ureteral calculi were divided into the non-sepsis or APN group and sepsis or APN group. Risk factors (e.g., ischemic heart diseases, hypertension, diabetes mellitus, stroke, Alzheimer's disease, chronic kidney disease, chronic lower respiratory diseases, obesity, cancer, history of urinary tract infection (UTI), and history of urolithiasis) were analyzed. All risk factors were found to be significant predictors of sepsis in this initial analysis.

Table 2 shows a univariate analysis of patients after matching the cohorts by age by a 2:1 propensity score matching analysis. After correcting for age, all assessed risk factors were significant. History of UTI was present in 44.88% of patients with sepsis or APN but present in only 5.05% of patients without sepsis or APN.

Table 3 demonstrates the multivariate analysis of risk factors significantly associated with sepsis or APN. The multivariate analysis using conditional logistic regression for the age-matched data revealed that history of UTI (OR 11.21, 95% CI 10.58–11.88, $p < 0.0001$) and female sex (OR 2.74, 95% CI 2.63–2.85, $p < 0.0001$) were associated with a higher risk of sepsis and APN. However, history of prior urinary stone disease (OR 0.89, 95% CI 0.86–0.93, $p < 0.0001$) and history of cancer (OR 0.93, 95% CI 0.89–0.97, $p = 0.0008$) were associated with decreased risk of sepsis and APN. Comorbidities, including a history of UTI, female sex, chronic kidney disease, Alzheimer's disease, stroke, diabetes mellitus, chronic lower respiratory diseases, hypertension, overweightness and obesity, and age (in decreasing order of the size of the point estimate) were all associated with a higher risk of sepsis and APN. When more than one comorbidity was present, there was an additive effect with higher OR point estimates, rising to 11.31 (10.68–11.99) when three or more comorbidities were present.

Table 2. Age-matched univariate analysis of the patients with ureteral calculi.

Predictors	Non-sepsis/APN	Sepsis/APN	*p*
No. pts	51,494	25,747	
Mean ± SD age	56.8 ± 17.7	56.8 ± 17.7	1
No. gender (%)			<0.0001
Male	33,249 (64.57)	8462 (32.87)	
Female	18,245 (35.43)	17,285 (67.13)	
No. race (%)			<0.0001
White	35,519 (68.98)	16,531 (64.21)	
Hispanic	3836 (7.45)	2480 (9.63)	
Black	3313 (6.43)	2155 (8.37)	
Asian	1106 (2.15)	491 (1.91)	
Unknown	7720 (14.99)	4090 (15.89)	
No. underlying disease (%)			
Ischemic heart diseases	9012 (17.5)	6088 (23.65)	<0.0001
Hypertension	24,843 (48.24)	15,112 (58.69)	<0.0001
Diabetes mellitus	11,298 (21.94)	8675 (33.69)	<0.0001
Stroke	5330 (10.35)	4602 (17.87)	<0.0001
Alzheimer's disease	476 (0.92)	502 (1.95)	<0.0001
Chronic kidney disease	3091 (6)	3290 (12.78)	<0.0001
Chronic respiratory disease	10,185 (19.78)	8007 (31.1)	<0.0001
Obesity	6699 (13.01)	5777 (22.44)	<0.0001
Cancer	20,541 (39.89)	11,513 (44.72)	<0.0001
No. medical history (%)			
History of UTI	2601 (5.05)	11,554 (44.88)	<0.0001
History of urinary stones	15,630 (30.35)	10,328 (40.11)	<0.0001
Total cost ($)			
Stent insertion, median (IQR)	376 (126–2111)	274 (237–1446)	0.1388
Nephrostomy, median (IQR)	1027 (669–2423)	952 (669–1748)	0.1910

APN = acute pyelonephritis; IQR = interquartile range; SD = standard deviation; UTI = urinary tract infection.

Table 3. Multivariate analysis of the patients with ureteral calculi.

Predictors	OR (95% CI)	*p*
History of UTI	11.31 (10.68–11.99)	<0.0001
Female gender	2.73 (2.62–2.84)	<0.0001
Race	Reference	-
White	1.28 (1.19–1.37)	<0.0001
Hispanic	1.19 (1.10–1.28)	<0.0001
Black	1.11 (0.97–1.27)	0.1496
Asian	0.94 (0.90–0.98)	0.0042
Cancer	0.91 (0.87–0.95)	<0.0001
Urinary Stone history	0.91 (0.87–0.95)	<0.0001
Sum of comorbidity *	Reference	
0	1.23 (1.16–1.30)	<0.0001
1	1.65 (1.55–1.76)	<0.0001
2	3.00 (2.82–3.18)	<0.0001
≥3	11.31 (10.68–11.99)	<0.0001
Alzheimer's disease	1.75 (1.49–2.06)	<0.0001
Chronic kidney disease	1.73 (1.61–1.86)	<0.0001
Stroke	1.50 (1.41–1.6)	<0.0001
Diabetes mellitus	1.46 (1.39–1.53)	<0.0001
Chronic respiratory diseases	1.32 (1.26–1.38)	<0.0001
Ischemic heart diseases	1.24 (1.17–1.31)	<0.0001
Obesity	1.23 (1.16–1.29)	<0.0001
Hypertension	1.22 (1.16–1.28)	<0.0001

* sum of Alzheimer, chronic kidney disease, stroke, diabetes, chronic respiratory diseases, ischemic heart diseases, overweight, and hypertension. APN = acute pyelonephritis; IQR = interquartile range; SD = standard deviation; UTI = urinary tract infection.

4. Discussion

Of the 31.5 million sepsis cases and 5.3 million deaths due to sepsis reported globally each year [13], approximately 15.9% of sepsis cases have a urinary source [14]. A total of 78% of urosepsis cases are associated with obstructive uropathy and 43% of obstructive uropathy cases are caused by urinary stones [4]. Surgical decompression is the most important factor in patients with obstructive urosepsis and which necessitates urgent decompression due to the attendant high mortality rate. Borofsky et al. compared the mortality rates of patients for those who did (78%) and for those who did not undergo surgical decompression (22%) among 1712 patients with sepsis due to ureteral calculi [15]. They reported mortality rates of 8.82% and 19.2% in the surgical decompression and nonsurgical decompression groups, respectively.

In most cases, surgical decompression is performed via retrograde double J stenting or percutaneous nephrostomy. While retrograde double J stenting is performed more frequently than percutaneous nephrostomy, there is no apparent difference between the two procedures regarding patient mortality [16]. However, the timing of surgical decompression is very important to reduce morbidity and mortality associated with obstructive uropathy and urosepsis and prioritizing expeditious surgical decompression significantly reduces patient mortality [17]. Known risk factors of urosepsis include older age, diabetes mellitus, immunosuppressed state, and urological treatment [18–20]. In our current study, we achieve further granularity, and we find that females and those with a prior history of UTI are at highest increased risk of developing sepsis or APN. Other comorbidity conditions such as diabetes, hypertension, and obesity also confer an increased risk, but not to the extent of female gender and a previous UTI history. Prior studies have clearly demonstrated that in females, a history of UTI is a major predisposing factor to subsequent UTI [21,22]. Thus, prioritizing active surgical treatment in this patient population may significantly reduce the prevalence of sepsis and potentially reduce patient mortality.

Our study also shows racial differences in non-sepsis and sepsis groups. Whites and Hispanics are at higher risk of sepsis than blacks and Asians. This result is similar to the study of critically ill patients who visited United States Academic medical center-affiliated hospitals from 2012 to 2014. This study concludes that blacks have lower adjusted sepsis hospital mortality than whites [23]. In cost of surgical decompression, however, there is no significant difference between the non-septic and sepsis groups.

Our study also demonstrates that a history of cancer and history of urinary stones decreased the risk of sepsis. There are logical explanations to why this is the case. Those with a history of urinary stones are likely to be under pre-existing urologic care and surveillance for repeat stone episodes. Moreover, patients with a history of urinary stones will recognize symptoms of ureteral obstruction and the necessity to seek care earlier than patients without a previous history. Similarly, in patients with history of cancer who may undergo more frequent laboratory testing and imaging studies compared to general population. Accordingly, these patients may also be more likely to be incidentally discovered to have urolithiasis and, as such, undergo earlier preemptive treatment to avoid APN or sepsis.

In general, small-sized urinary stones are naturally expelled, but some large-sized urinary stones are difficult to be expelled naturally [24,25]. In a recent study using noncontrast computed tomography, 392 consecutive patients with ureteric stone for 20 weeks were analyzed and reported the spontaneous passage rate by size. The natural rate of expulsion of 98%, 3 mm to 98%, 4 mm to 81%, 5 mm to 65%, 6 mm to 33%, and greater than 6.5 mm in 9% were revealed [26]. A recent study revealed that significant increases in white blood cell count, neutrophil count, NLR, and C-reactive protein were significant relation with failure in spontaneous expulsion of ureteral stones and associated chronic inflammatory urogenital conditions [27,28].

Of note, our work provides some significant evidence for future directions in the socioeconomic and cost-effectiveness of kidney stones management across USA. A significant economic burden is indeed associated with urolithiasis, with per-year assumptions of costs which do cross USD 5 billion [29]. This economic burden affects both direct in hospital and perioperative care cost, as well as the unpaid cares which include informal costs and productivity loss. Unfortunately, there has been limited cost-effectiveness research in the area of kidney stone management. In the present insurance-based retrospective analysis, the identification of independently associated risk factors for which a tailored and preventive management could be addressed to avoid the most dangerous and potential lethal harms such as sepsis and acute pyelonephritis could therefore influence future research and address a paradigmatic shift in the redefinition of risk group categories. Additionally, the cost per procedure and the specific odd clustered for the single stone lithotripsy procedure shall be evaluated in updated analysis to identify any possible cost-effectiveness scenarios for future risk-adapted strategies, as has been done for other Genito-Urinary oncological and non-oncological diseases [30–35]. This may lead to the definition of new predictors for which the risk of sepsis and acute pyelonephritis will be defined on the basis of clinical characteristics of the patient and the stone disease, as well as the adoption of one specific surgical approach over the other.

Our study has limitations, including the intrinsic limitations of a retrospectively designed study using the Optum®deidentified Clinformatics®Datamart database. First, the nature of the administrative dataset and use of diagnosis codes to identify patients with urinary stone disease, sepsis, and APN could include patients who are miscoded. Moreover, as the cohort of patients included in this study was collected using an employer-based health insurance database, and therefore introduces bias towards employed insured patients with potentially higher socioeconomic status and may limit the generalizability of our findings. Nevertheless, to our knowledge, our study is the largest study to date evaluating for risk factors of sepsis or complicated APN in patients with urinary stone disease. Second, it is difficult to conclude that all sepsis or APN was caused by ureteric stones. Sepsis or APN may have occurred due to other causes, and ureteric stones may have been discovered incidentally. Third, it is difficult to explain minute differences in the geographic incidence of sepsis.

5. Conclusions

This large national cohort reveals the characteristics of sepsis or APN combined with ureteral stone and provides an important baseline for the treatment of urolithiasis in the future. A history of urinary tract infection and female gender are the highest individual risk factors for development of sepsis or APN in patients with ureteral calculi. The presence of concomitant comorbidities also is significant, especially when there are multiple, and understanding all these factors should be the basis of risk stratification in the treatment of these high-risk patients. Future research will need to address the cost-effectiveness of such presurgical and patient-oriented implication in the identification of predictors for disease severe complications. Finally, additional studies on the influence of intraoperative and surgical technique-based factors influencing the postoperative clinical course are mandatory prior to redefine the risk profile of patients undergoing interventional management of kidney and ureteric stone disease.

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Abbreviations

APN	acute pyelonephritis
CI	confidence interval
CPT	Current Procedural Terminology
CT	computed tomography
EPO	exclusive provider organization
HMO	health maintenance organization
ICD	International Classification of Diseases
IQR	interquartile range
IRB	Institutional Review Board
POS	point of service
PPO	preferred provider organization
SD	standard deviation
UTI	urinary tract infection

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