

Original Article

Sepsis prevalence and associated hospital admission and mortality after ureteroscopy in employed adults

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Objective

To determine 30-day inpatient mortality, intensive care unit (ICU) admissions, inpatient admissions/readmissions, and yearly trends in sepsis prevalence and inpatient mortality after ureteroscopy (URS) in employed adults.

Materials and Methods

We performed a retrospective analysis of the IBM MarketScan Commercial Database to identify employed adults aged 18–64 years who underwent URS between 2015 and 2019. Patients were categorized as having no sepsis (controls), non-severe sepsis, or severe sepsis within 30 days of URS. The main outcomes included inpatient mortality, ICU admissions, inpatient admissions, readmissions, and annual rates of sepsis and associated inpatient mortality.

Results

Among 109 496 patients undergoing URS, 5.6% developed sepsis (4.1% non-severe, 1.5% severe). The 30-day inpatient mortality rates were 0.03%, 0.3% and 2.5% for controls, non-severe sepsis and severe sepsis, respectively ($P < 0.001$). In a multivariable analysis, diagnosis of sepsis regardless of severity (hazard ratio [HR] 17.2, 95% confidence interval [CI] 10.5–28.1; $P < 0.001$) or severe sepsis (HR 49.5, 95% CI 28.9–84.7; $P < 0.001$) increased the risk of 30-day inpatient mortality compared to no sepsis (controls). ICU admissions on the day of procedure (1.5%, 19.8% and 52.4%), inpatient admission rates (18.3%, 74.9% and 76.9%) and readmission rates (7.1%, 12.0% and 15.9%) were higher with severe sepsis and non-severe sepsis vs controls (all $P < 0.001$). During the study period, the prevalence of sepsis after URS increased from 4.7% to 6.6% ($P < 0.001$), while the associated mortality rate decreased from 0.7% to 0.2% ($P < 0.001$).

Conclusion

Among working adults aged 18–64 years, sepsis after URS increases the risk of 30-day inpatient mortality, ICU and hospital admission, and hospital readmission. Although the prevalence of sepsis after URS is increasing over time, associated mortality rates are declining. Urologists should be aware of the potentially deadly consequences of sepsis after URS in younger patients.

Keywords

ureteroscopy, sepsis, claims analyses, mortality, intensive care unit, hospital admissions

Introduction

One of the most common surgical treatments for stone disease is ureteroscopy (URS) [1]. Over the last decade, URS procedure volumes have increased by approximately 27% in adults with employer-sponsored health insurance and by 57% in the Medicare population [2,3]. Although URS has a high success rate and is considered a very safe procedure, there are a number of potentially serious yet rare complications that

may occur, such as sepsis and multi-organ failure [1]. The Third International Sepsis Consensus Definition Task Force defines sepsis as a life-threatening organ dysfunction caused by a dysregulated host response to infection [4]. Patients with sepsis may experience rapid deterioration in organ function, septic shock, prolonged intensive care unit (ICU) stay, and death, especially if sepsis is not recognized or treated promptly [4,5]. Sepsis is a serious medical complication that has become a major public health concern, accounting for

more than \$20 billion in hospital costs to the United States in 2011 (equivalent to \$28 billion in 2022) [4].

Sepsis after URS, although rare, poses a substantial clinical and economic burden [5]. Our recent meta-analysis quantifying the risk of postoperative sepsis after URS from 13 studies with 5597 patients found that 5.0% of patients developed postoperative sepsis [6]. An analysis of US healthcare claims data found that patients with sepsis after URS have substantially higher healthcare resource use (i.e., longer hospital stay, higher ICU utilization) and costs than patients without sepsis [7]. These results have been corroborated in other studies, in which sepsis after URS increased the risk of mortality and resulted in prolonged ICU stays and increased hospital readmissions [6,8]. To the authors' knowledge, no study has examined the impact of sepsis after URS on real-world outcomes in patients with employer-sponsored health insurance. The objectives of this study were to investigate: (i) 30-day all-cause inpatient mortality; (ii) rates of ICU admissions, inpatient admissions, and readmissions; and (iii) annual trends in sepsis prevalence and inpatient mortality after URS among employed patients enrolled in US commercial insurance plans.

Materials and Methods

Study Population

We performed retrospective analyses of a US commercial population using the IBM[®] MarketScan[®] Commercial Database to identify patients aged 18–64 years who underwent URS for stone disease between January 2015 and October 2019. The IBM MarketScan Commercial Database contains a nationally representative data sample of the US population with employer-sponsored health insurance consisting of medical and drug data for employees, their spouses, and their dependents. De-identified patient data are available from 120 contributing employers, 40 health plans, and 350 carriers, representing 39.7 million covered individuals [9]. This research was exempt from institutional review board review owing to the use of de-identified patient data.

Patients eligible for the study were adults undergoing URS during the study period, with continuous health plan enrolment in the previous 6 months. We excluded patients diagnosed with sepsis following a second URS procedure within 30 days of the first procedure. The index URS procedure was defined using International Classification of Diseases – 9th and 10th Revision (ICD-9 and ICD-10) procedure codes and Current Procedural Terminology codes (Table S1). Sepsis was defined as the first septic event within 30 days following the index URS and was categorized as severe or non-severe using ICD-9 and ICD-10 diagnosis codes (Table S2). Patients undergoing URS were then

categorized into three groups: no sepsis diagnosis (controls); non-severe sepsis; or severe sepsis.

Outcomes and Resource Utilization

Thirty-Day All-Cause Inpatient Mortality

In patients with sepsis, all-cause inpatient mortality and time to death were measured within 30 days of sepsis diagnosis. In controls, mortality and time to death were measured within 30 days of the index URS. We examined the association of patient characteristics with 30-day inpatient mortality, including sepsis after URS, patient demographics (age, sex, geographic region), comorbidities, Elixhauser Comorbidity Index, and relevant clinical characteristics, sepsis in previous 6 months, and surgery for stone disease (i.e., lithotripsy, percutaneous nephrolithotomy, or URS) in previous 6 months. Comorbidities examined included diabetes mellitus, hyperlipidaemia, severe obesity, non-severe obesity, and ischaemic heart disease, as defined by Quan et al. [10]. Comorbidities were defined based on ICD-9 and ICD-10 diagnostic codes identified within 6 months of the index URS.

Intensive Care Unit Admissions, Inpatient Admissions and Readmissions

In patients with sepsis, all-cause ICU admission and length of ICU stay were measured within 30 days of sepsis diagnosis. In controls, ICU admission and length of ICU stay were measured within 30 days of the index URS. Direct admission to the hospital and ICU were measured on the day of diagnosis among patients with sepsis and on the day of index URS among controls. The rate of all-cause readmission was measured within 30 days of inpatient discharge for each group.

Trends in Sepsis Prevalence and Sepsis-Related Mortality after Ureteroscopy

The annual prevalence of sepsis after URS was examined for the period from 2015 to 2019. The annual trend in 30-day sepsis-related inpatient mortality among patients diagnosed with sepsis after URS was also examined.

Statistical Analyses

Patient characteristics, comorbidities and healthcare resource utilization outcomes among the three study groups were compared using chi-squared tests for categorical variables and analysis of variance for continuous variables. Multivariate Cox regression analysis was performed to evaluate the association of sepsis with all-cause inpatient mortality, controlling for clinical and demographic variables. Results of this analysis

were reported using hazard ratios (HRs) and 95% CIs. Nationally weighted annual trends in sepsis prevalence after URS and associated 30-day inpatient mortality were calculated using the MarketScan National Weights file and compared using a chi-squared test.

Results

Patient Characteristics

A total of 109 496 patients who underwent URS during the study period were included in the analysis (Fig. 1). The prevalence of sepsis after URS was 5.6% of patients, including 4.1% who developed non-severe sepsis and 1.5% who developed severe sepsis. Patient characteristics and comorbidities are presented in Table 1. Sepsis was notably more prevalent with older age, diabetes mellitus, female sex, recent sepsis diagnosis, and higher Elixhauser Comorbidity Index.

Sepsis-Related Mortality after Ureteroscopy

The 30-day inpatient mortality after URS was 0.07% among all patients, and 0.03%, 0.3% and 2.5% in controls, patients with non-severe sepsis and patients with severe sepsis, respectively ($P < 0.001$; Table 2). Sepsis was responsible for 63% of all deaths after URS. The mean time to death in patients with severe sepsis was significantly shorter than in patients with non-severe sepsis and in controls (8.7 vs 11.1 vs 16.7 days; $P < 0.001$). In the multivariate Cox regression analysis, patients who developed sepsis after URS had higher inpatient mortality compared to controls (HR 17.2, 95% CI 10.5–28.1; $P < 0.001$ [Table 3]). Additional variables associated with higher inpatient mortality after URS included older age, diabetes mellitus, hyperlipidaemia, and higher Elixhauser Comorbidity Index score. Additionally, severe sepsis increased the risk of 30-day inpatient mortality compared to controls (HR 49.5; 95% CI 28.9–84.7; $P < 0.001$).

Fig. 1 Flow diagram depicting selection of the analytical cohort.

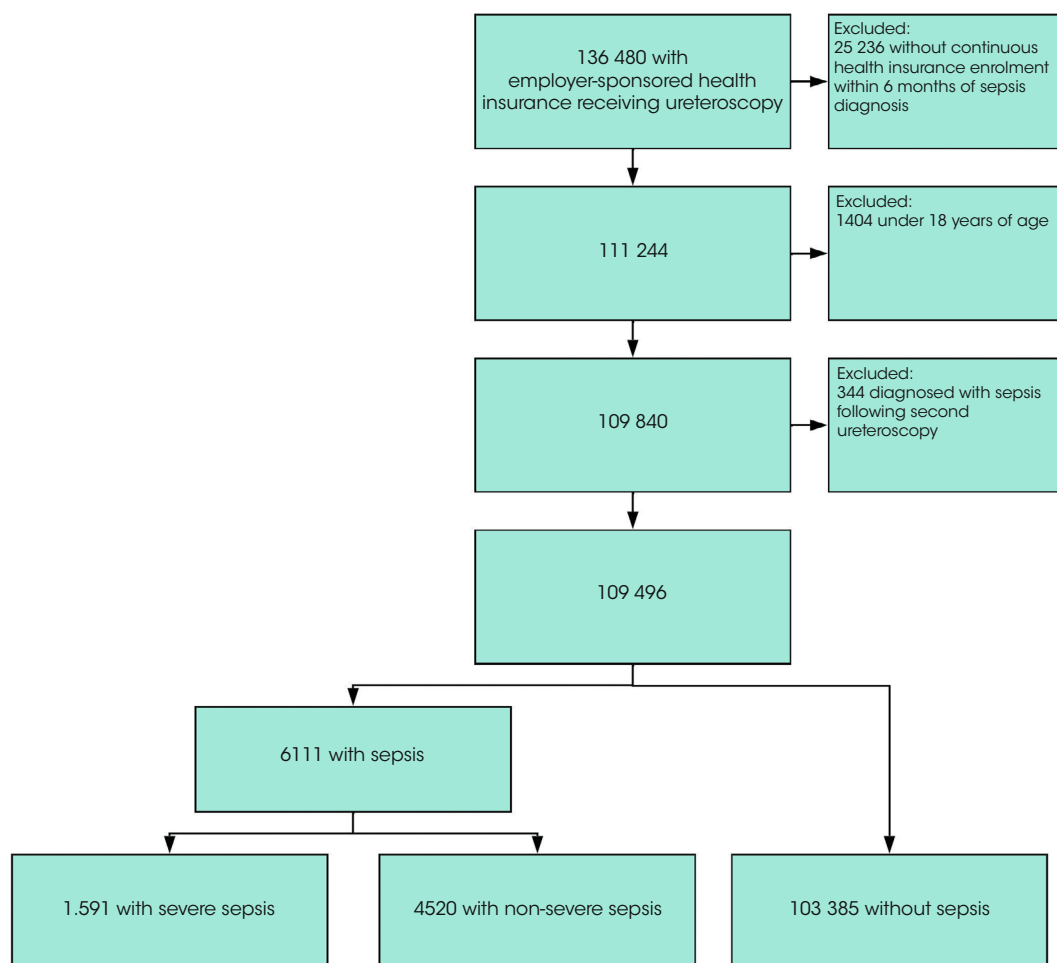


Table 1 Characteristics of employed adults undergoing ureteroscopy.

Variable	No sepsis (n = 103 385)	Non-severe sepsis (n = 4520)	Severe sepsis (n = 1591)	P value
Age, n (%)				
18–34 years	13 986 (13.6)	598 (13.3)	133 (8.4)	<0.001
35–44 years	19 251 (18.7)	695 (15.5)	189 (12.0)	
45–54 years	30 845 (30.0)	1252 (27.9)	457 (29.0)	
55–64 years	38 837 (37.7)	1940 (43.3)	797 (50.6)	
Sex, n (%)				
Female	48 625 (47.0)	3193 (70.6)	1158 (72.8)	<0.001
Male	54 760 (53.0)	1327 (29.4)	433 (27.2)	
Comorbidities, n (%)				
Recent sepsis	1820 (1.8)	392 (8.7)	141 (8.9)	<0.001
Recent stone surgery	8886 (8.6)	233 (5.2)	53 (3.3)	<0.001
Diabetes	16 029 (15.5)	1065 (23.6)	468 (29.4)	<0.001
Hyperlipidaemia	27 719 (26.8)	1146 (25.4)	478 (30.0)	0.004
Ischaemic heart disease	526 (0.5)	42 (0.9)	17 (1.1)	<0.001
Obesity (severe)	5259 (5.1)	358 (7.9)	127 (8.0)	<0.001
Obesity (non-severe)	10 821 (10.5)	527 (11.7)	176 (11.1)	0.005
Geographical region, n (%)				
Midwest	22 915 (23.2)	1030 (23.8)	362 (23.6)	0.008
Northeast	15 256 (15.4)	738 (17.1)	244 (15.9)	
South	48 750 (49.3)	2062 (47.7)	735 (48.0)	
West	11 957 (12.1)	493 (11.4)	192 (12.5)	
Elixhauser Comorbidity Index, mean (SD)	1.6 (1.8)	2.2 (2.4)	2.6 (2.8)	<0.001

Table 2 Mortality and hospital admissions after ureteroscopy in employed adults.

Variable	No sepsis (n = 103 385)	Non-severe sepsis (n = 4520)	Severe sepsis (n = 1591)	P value
Mortality				
30-day inpatient mortality, n (%)	30 (0.03)	12 (0.3)	39 (2.5)	<0.001
Days to inpatient mortality, mean (SD)	16.7 (7.8)	11.1 (7.8)	8.7 (7.5)	<0.001
30-day inpatient mortality in patients with ICU stay, n (%)	12 (0.6)	7 (0.6)	33 (3.2)	<0.001
ICU admission				
Index date, n (%)	1585 (1.5)	893 (19.8)	833 (52.4)	<0.001
Within 30 days, n (%)	2127 (2.1)	1113 (24.6)	1036 (65.1)	<0.001
ICU days, mean (SD)	3.0 (3.4)	3.8 (5.7)	4.1 (5.0)	<0.001
Hospital admission				
Index date, n (%)	18 913 (18.3)	3385 (74.9)	1223 (6.9)	<0.001
30-day readmission, n (%)	1338 (7.1)	405 (12.0)	194 (15.9)	<0.001

ICU, intensive care unit. *Reported as mean (standard deviation).

Intensive Care Unit, Inpatient Admission and Readmission Associated with Sepsis after Ureteroscopy

The rates of 30-day ICU admission were 2.1%, 24.6% and 65.1% in the control group, non-severe sepsis group and severe sepsis group, respectively ($P < 0.001$). The 30-day inpatient mortality among patients with an ICU stay was 0.6%, 0.6% and 3.2%, respectively ($P < 0.001$). The length of ICU stay in patients with severe sepsis was significantly longer than in patients with non-severe sepsis and in controls (4.1 vs 3.8 vs 3.0 days, respectively; $P < 0.001$). The incidence of patients directly admitted to the inpatient setting on the index date was higher among patients with severe sepsis (76.9%) and non-severe sepsis (74.9%) compared to controls

(18.3%; $P < 0.001$). ICU admission on the index date was higher in those with severe sepsis (52.4%) compared to those with non-severe sepsis (19.8%) and in controls (1.5%; $P < 0.001$). Similarly, readmissions were significantly higher in the severe sepsis group (15.9%) compared to controls (7.1%; $P < 0.001$).

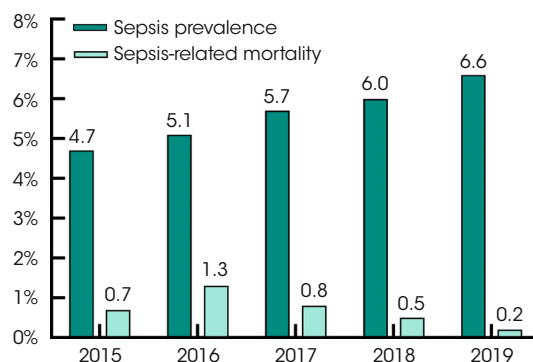
Trends in Sepsis Prevalence and Mortality after Ureteroscopy

The annual prevalence of sepsis after URS significantly increased from 4.7% in 2015 to 6.6% in 2019 ($P < 0.001$). The annual estimates for 30-day sepsis-related inpatient mortality after URS decreased from 0.7% in 2015 to 0.2% in 2019 ($P < 0.001$; Fig. 2).

Table 3 Factors associated with 30-day inpatient mortality after ureteroscopy in employed adults.

Variable	Unit of measure	Sepsis vs no sepsis		Severe sepsis vs no sepsis	
		HR (CI)	P value*	HR (CI)	P value*
Sepsis diagnosis	Yes vs no	17.2 (10.5–28.1)	<0.001	49.5 (28.9–84.7)	<0.001
Age	18–34 years	Reference		Reference	
	35–44 years	4.2 (0.5–34.7)	0.19	3.3 (0.4–28.4)	0.28
	45–54 years	7.7 (1.0–57.2)	0.047	6.9 (0.9–51.5)	0.06
	55–64 years	9.9 (1.3–72.8)	0.02	7.3 (1.0–54.2)	0.051
Sex	Male vs female	1.1 (0.7–1.7)	0.72	1.1 (0.6–1.8)	0.78
Comorbidities					
Recent sepsis	Yes vs no	0.5 (0.2–1.1)	0.07	0.5 (0.2–1.1)	0.10
Recent stone surgery	Yes vs no	0.5 (0.2–1.7)	0.28	0.4 (0.1–1.8)	0.24
Diabetes	Yes vs no	0.5 (0.3–0.9)	0.02	0.3 (0.2–0.7)	0.002
Hyperlipidemia	Yes vs no	0.4 (0.2–0.7)	0.002	0.5 (0.3–0.9)	0.02
Ischemic heart disease	Yes vs no	1.7 (0.5–5.7)	0.37	1.1 (0.2–4.7)	0.93
Obesity (severe)	Yes vs no	0.5 (0.3–1.1)	0.07	0.7 (0.3–1.4)	0.27
Obesity (non-severe)	Yes vs no	0.7 (0.3–1.5)	0.31	0.9 (0.4–2.0)	0.87
Geographic region	Midwest	Reference		Reference	
	Northeast	1.3 (0.6–2.8)	0.49	1.5 (0.6–3.4)	0.39
	South	1.8 (1.0–3.4)	0.06	1.9 (1.0–3.8)	0.07
	West	1.7 (0.7–3.9)	0.25	2.0 (0.8–5.0)	0.16
Elixhauser Comorbidity Index	Per 1-point increase	1.5 (1.4–1.6)	<0.001	1.5 (1.4–1.6)	<0.001

HR, hazard ratio. *Multivariate Cox regression analysis was used to evaluate the effect of (i) sepsis vs non-sepsis on all-cause inpatient mortality and (ii) severe sepsis vs non-sepsis on all-cause inpatient mortality controlling for clinical and demographic covariates.

Fig. 2 Annual trends in sepsis prevalence and 30-day inpatient sepsis-related mortality after ureteroscopy in employed adults.

Discussion

We conducted a population-based cohort study to examine the association of sepsis after URS with the risk of mortality, ICU stay, hospital admission, and readmission using a large-scale database of patients with employer-sponsored health insurance. Overall, we found that URS is a safe procedure with a low mortality risk. However, sepsis after URS significantly increases the risk of 30-day inpatient mortality and accounts for nearly two-thirds of all deaths after URS. We also found that sepsis after URS increases ICU admission, inpatient admission and readmission rates. Severe sepsis was associated with the highest rate of ICU admissions and hospital readmissions. Lastly, sepsis prevalence after URS increased over the 5-year study period, while mortality decreased over the same period.

The present study showed that the risk of mortality from sepsis after URS, although rare, is consistent with that of previously published studies [11,12]. A recent systematic review of 15 studies by Bhanot *et al.* found that sepsis was responsible for over 50% of deaths after URS [11]. Cole *et al.* [12] investigated infection-related hospitalizations following 1817 URS procedures and reported a mortality rate of 0.2%. The present study also showed that sepsis-related inpatient mortality after URS decreased over the 5-year study period. Potential reasons for this decrease in sepsis-associated mortality rate are unclear, but may include better preoperative care of patients at risk of sepsis after URS and increasing awareness among urologists to recognize and treat the initial phases of sepsis in the postoperative setting. We were unable to identify the comorbidity index of all patients in the database over time, so we were unable to determine if the changes in sepsis and mortality rates were attributable to changes in prevalence of overall comorbidities in the patient population.

Few studies have examined the association of sepsis after URS with hospital admissions, ICU admissions, or readmissions. In our previous claims analysis examining all-cause hospital resource utilization in 100 000 patients undergoing URS, we reported that 35% of septic patients were admitted to the ICU and the mean hospital stay for septic patients was 6.8 days [7]. The study by Cole *et al.* cited above found that 2.4% of patients required an inpatient admission due to an infection-related complication and that hospital stay for an infection-related hospitalization following URS was 3 days [12].

A unique aspect of this study was its inclusion of employed adults aged 18–64 years. Determination of sepsis prevalence and clinical sequelae in this age group is warranted since approximately 75% of URS procedures in the United States are performed in patients under 65 years of age (IBM MarketScan data on file). Compared to patients aged 18–34 years, we observed a significant increase in inpatient mortality risk with increasing age in the present study. Although not evaluated in the present study, mortality risk with sepsis after URS may be even higher in patients aged 65 years and older because of a higher prevalence of comorbidities.

The increasing prevalence of sepsis after URS observed in this study may be the result of the proliferation of URS procedures and the treatment of more complex patients and disease. Previously, we undertook a meta-analysis to examine the risk of sepsis after URS from 13 studies with 5597 patients and found that 5.0% of patients developed postoperative sepsis [6]. Primary risk factors for sepsis after URS included increasing age, ischaemic heart disease, and diabetes mellitus. Similarly, Lu et al. examined the rate of sepsis in 759 patients after flexible URS and reported that sepsis occurred in 5.7% of patients, with 0.8% developing septic shock [13]. While the exact reasons for increasing sepsis prevalence remain unclear, additional contributing factors may include improved recognition, awareness, identification, and coding of this condition, as well as newer clinical identification tools such as the quick Sequential Organ Failure Assessment (SOFA) score.

This study has a number of strengths. We examined 30-day inpatient mortality and hospital admission data for sepsis after URS from the perspective of commercial insurers in the United States using a large-scale database. The study employed a longitudinal comparative approach that followed two sepsis cohorts and a non-sepsis cohort over a 30-day period to comprehensively capture the inpatient mortality and hospital admissions data of more than 100 000 working-age adults undergoing URS. This large dataset comprises a representative sample of working adults in multiple settings of care and in all regions of the United States, which improves the validity and generalizability of the findings.

This study also had several limitations that warrant additional discussion. While recent stone surgery was a risk factor for sepsis following URS, we excluded anyone who underwent URS 6 months prior to the URS under study in an attempt to rule out stents placed following a previous URS. This 6-month 'wash-out' period would presumably allow enough time to conclude anything from a previous URS (e.g., stent removal), but it cannot ensure that a stent from a previous procedure was not in place for the index procedure. Our analysis was limited to examining the 30-day all-cause inpatient mortality and hospital admissions and readmissions

for septic and non-septic patients after URS in working-aged adults enrolled in commercial insurance plans. The analysis did not include an examination of clinical and resource utilization outcomes in Medicare patients. Mortality and resource utilization in the elderly population may be even higher than in working-age adults due to the presence of multiple comorbidities. The study included all-cause inpatient mortality and not mortality solely associated with sepsis. However, we showed a difference between all-cause inpatient mortality in the sepsis cohorts compared to the non-sepsis cohort. Additionally, we were not able to confirm whether patients diagnosed with sepsis presented with signs and symptoms consistent with the SOFA criteria or the systemic inflammatory response syndrome criteria. Because laboratory data such as preoperative urine culture were not available in the database, we were unable to determine if clinical guideline recommendations for the management of sepsis were followed. Finally, while the risk of miscoding is inherent to all analyses of claims data, the estimated misclassification risk with IBM MarketScan data is low (~1%) [14].

In conclusion, among working adults aged 18–64 years, sepsis after URS increases the risk of 30-day inpatient mortality, ICU and hospital admission, and hospital readmission. Although the prevalence of sepsis after URS is increasing over time, associated mortality rates are declining. Urologists should be aware of the potentially deadly consequences of sepsis after URS in younger patients.

Acknowledgements

Medical writing assistance was provided by Michael Mafilios at Health Economics Associates (San Diego, CA, USA).

Disclosure of Interests

Support for this research was provided by Boston Scientific, Marlborough, MA, USA. Ben Chew is a urologist and Associate Professor of Urology at the University of British Columbia and was engaged by Boston Scientific as a clinical expert and scientific advisor for this research. Brian Eisner is a urologist and Medical Director of Urology at Massachusetts General Hospital and was engaged by Boston Scientific as a clinical expert and scientific advisor for this research. Manoj Monga is Chair and Professor of Urology at the University of California San Diego School of Medicine and was engaged by Boston Scientific as a clinical expert and scientific advisor for this research. Naeem Bhojani is a urologist and Associate Professor of Urology at the University of Montreal and was engaged by Boston Scientific as a clinical expert and scientific advisor for this research. Drs Chew, Eisner, Monga and Bhojani were not compensated for their participation in this study. Rutugandha Paranjpe and Benjamin Cutone are employees of Boston Scientific. Portions of this research were presented in abstract form at the annual meeting of the AUA

in New Orleans, LA, USA from 13 to 16 May 2022 and at the annual meeting of the World Congress of Endourology and Uro-Technology (WCET) in San Diego, CA, USA from 1 to 4 October 2022.

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Abbreviations: HR, hazard ratio; ICD-9, International Classification of Diseases, 9th revision; ICD-10, International Classification of Diseases, 10th revision; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment; URS, ureteroscopy.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Coding scheme for ureteroscopy classification in employed adults.

Table S2. Coding scheme for sepsis classification after ureteroscopy in employed adults.