Diabetes mellitus is associated with increased risk of positive qSOFA score but not with increased ICU admission in patients undergoing ureteral stent placement for ureteral stone and suspected infection

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ABSTRACT

Introduction: Patients presenting with an obstructing ureteral stone and urinary tract infection (UTI) are at risk for severe infectious complications. Historically, diabetes mellitus (DM) was considered a risk factor for the development of septic shock in these patients. This study aims to evaluate DM's impact on risk of septic shock in ureteral stent placement for ureteral stone and presumed UTI.
Methods: An institutional review board-approved retrospective review was performed at two institutions. All patients who met the following criteria from July 2016 to April 2020 were included in the study: emergency department visit with obstructing ureteral stone, concern for UTI, and ureteral stent placement. The primary outcome of interest was the development of postoperative septic shock defined by sepsis with hypotension requiring vasopressor support for at least one hour.
Results: The study cohort was made up of 187 patients. Median age was 61 (range 16–91). Males represented 40.1% (n=75) of the population, while DM was present in 26.2% (n=49). Thirty-five of 143 patients (18.7%) met the criteria for postoperative septic shock. qSOFA criteria were met by 11 (22.4%) patients with DM compared to 13 (9.5%) of patients without DM (p=0.026). This difference did not translate into significant differences in use of vasopressors, with DM cohorts requiring pressors in 11 (22.4%) and 241 (17.5%) in non-DM

(p=0.523). Purulent urine was more frequently described in patients with DM (22 [44.9%] vs. 342 [4.8%], p=0.011). ICU admissions were similar between DM and non-DM, 13(27.1%) vs 29 (21.2%) respectively (p=0.543). ICU stay and length of stay were similar between cohorts.
Conclusions: In this multicenter study of patients who underwent ureteral stenting for ureteral stone and presumed UTI, DM was not associated with an increased risk of development of septic shock but was associated with an increased risk of positive qSOFA score.

INTRODUCTION

It is estimated that 1% of the United States population ages 18-65 will experience a kidney stone event each year – that is, renal colic or other symptoms which prompt the diagnosis of renal or ureteral stone.[1] Of all patients who experience a ureteral stone, roughly 25% will require intervention for that stone – intervention may include a temporizing ureteral stent placement followed by definitive therapy with shockwave lithotripsy, ureteroscopy, or percutaneous nephrolithotomy.[1] Patients who present with an acute obstructing ureteral stone and concomitant pyelonephritis or urinary tract infection, are at significant risk for infectious complications including urosepsis, and even a mortality rate of 9-19%.[2]

For patients with the latter clinical presentation (i.e. ureteral stone, ureteral obstruction, presumed urinary tract infection), standard of care is urgent decompression and drainage of the infection either with ureteral stent or with percutaneous nephrostomy and deferral of definitive stone treatment until infectious issues are resolved.[3] Prompt decompression in addition to intravenous antibiotics has been demonstrated to reduce mortality by nearly 50% when compared to antibiotics alone.[2] However, amongst the group of patients who undergo ureteral stent placement for decompression of ureteral stone and concomitant infection, specific risk factors for development of urosepsis and other significant complications are not well understood.

It has been hypothesized that patients with diabetes mellitus may be at increased risk for urinary tract infection, due to impairment of immune function associated with poor glycemic control.[4,5] The current study examines a cohort of patients who presented to the emergency department with ureteral stone and urinary tract infection and underwent emergent ureteral stent placement – the study compares the infectious outcomes in patients with and without diabetes mellitus.

METHODS

A IRB approved retrospective review was performed at 2 institutions. Records of patients admitted during July 2016 through April 2020 were screened for inclusion. Patients presenting to the emergency room with at least one unilateral obstructing stone and documented concern for concomitant infection, who were taken directly from the emergency room to the operating room for stent placement were included. Patients with bilateral obstructing stones, obstructed solitary

or transplanted kidneys, obstructions from other etiologies, diagnose as inpatients, documented pyelonephritis within prior 30 days or those were stented for other reasons such as acute kidney injury were excluded. Patients already on vasopressor support while in the ER were also excluded. The primary outcome of interest was the development of post-operative septic shock, as defined by the quick Sequential Organ Failure Assessment (qSOFA) with at least 2 of the following criteria: respiratory rate >22, altered mental status and or systolic blood pressure <100mmHg and vasopressor need to maintain mean arterial pressure >65mmHg.[5]

Patient definitions were as follows: Prior endourological procedure was considered for all patients who had shockwave lithotripsy, ureteroscopy and/or percutaneous nephrolithotomy within 30 days prior to admission. Diabetes mellitus was considered in patients who reported having DM, those with evidence in the electronic medical record, or those with prescription for oral or injected anti-diabetic medications. Diabetes control was assessed using most recent Hb1Ac, for which values <7% were considered adequately controlled. Patients with reports or evidence of prior urosepsis at any timepoint prior to admission were considered as positive for history of urosepsis. Recurrent urinary infection was defined as patients with history or evidence at any time of 2 episodes in 6 months or 3 in 12 months prior to admission. Advanced age was defined as 65 or older.

Data was analyzed using SPSS v25. The Kolmogorov-smirnov test was used to assess for normality. Parametric testing was performed using T-Student's or ANOVA with post-hoc Tukey, with results expressed as means and standard deviations. Nonparametric testing was performed using Mann-Whitney-U or Kruskall Wallis and results are expressed as medians and ranges. Qualitative variables are expressed as frequency and percentage, with testing performed through Chi-Square or Fisher's Exact test where applicable.

Single and multiple logistic regressions were performed for further analysis. Omnibus test was used to assess the model and Hosmer and Lemeshow test was used to assess data fitness to the model. Testing was done through Enter and Forward Wald's approach. Results are expressed in Odds Ratios and Adjusted Odds Ratios. Models with variables whose Odds Ratios approached infinity were excluded from modelling. P values under 0.05 were considered statistically significant.

RESULTS

Baseline characteristics

The study cohort was made up of 187 patients from 2 institutions. Median age was 61 (Range 16-91). Males represented 40.1%(75) of the population while females 59.9%(112). Patients over 65 years old made up 42.8%(80) of included cases. Median BMI was 27 (Range 17.33-59), with 34.6%(64) of patients having obesity. Diabetes Mellitus(DM) was reported in 26.3%(49) of which 41%(16) were inadequately controlled according to Hb1Ac levels. Hypertension was previously diagnosed in 45.4%(84) patients. History of prior urinary tract infection (UTI) was present in 21%(39) of patients while 13%(24) patients had prior history of pyelonephritis or

urosepsis. Prior endourological procedures were recorded in 3.3%(6) patients. Multiple stones were present in 7.7%(14) patients, while the majority of stones were either middle/proximal 52.7%(98) or distal 43%(80).

Twenty-two percent (42) of patients from the cohort were admitted to the ICU while qSOFA criteria was met in 12.8%(24) of patients. Vasopressors were utilized in 18.7%(35) patients. Median vasopressor pressor time was 12.5 hours(1-408) and median ICU stay was 2 days (1-24). Median Length of Stay for the entire cohort was 2 days(0-27). Baseline characteristics are fully summarized in Table 1.

Diabetes mellitus

Patient demographic information as well as baseline characteristics are displayed in table 2. Of note, median age for DM patients was 65 years (42-92) while non-DM was 60(16-93), these were statistically different p=0.019. The DM cohort had significantly higher median BMI (29.43[18.70-59.05] vs 24.15[19.22-36.28], p=0.001)

qSOFA criteria was met by 11(22.4%) patients with DM compared to 13(9.5%) of patients without DM (p=0.026). This difference did not translate into significant differences in use of vasopressors, with DM cohorts requiring pressors in 11(22.4%) as opposed to 241(17.5%) in non-DM (p=0.523). ICU admissions were also similar between DM and non-DM cohorts, 13(27.1%) vs 29 (21.2%) respectively (p=0.543). ICU stay and length of stay were similar between cohorts. Table 2 summarizes findings from analysis of these cohorts. In diabetic patients, HbA1c means were not different between qSOFA+(5.12% +- 1.22) and qSOFA(6.05 +- 0.65) p = 0.848. When comparing diabetic patients with septic shock, HbA1c levels were similar in those with shock (6.12% +- 1.2) vs those without(6.07 +- 0.89) p = 0.888.

Regression analysis

Single and multiple logistic regression analysis analyzing the effect of DM diagnosis on qSOFA criteria fulfillment, ICU Admission and septic shock adjusted for age, gender, weight and prior history of endourological procedures, recurrent UTI and urosepsis was performed. These revealed significant odds of positive qSOFA score in patients with DM (OR 3.07[1.01,9.36] p=0.038) but not for ICU Admission(OR 1.47[0.62,3.50] p =0.378) or septic shock (OR 1.49[0.56,3.90] p=0.417). Models are summarized in Table 3 and Figure 1.

DISCUSSION

Urosepsis refers to a clinical syndrome characterized by excessive, dysregulated host inflammatory response to an infection arising from the genitourinary tract.[6] The third International Consensus Definitions for Sepsis and Septic shock define septic shock as a lactate level >2mmol/L and necessity for vasopressor support to maintain a mean arterial pressure of 65mmHg in the absence of hypovolemia.[6] Worldwide, the overall prevalence trends to an increase, and while improvements in management stemming from better understanding has led to a decrease in mortality, it remains high in urosepsis at an estimated 40%.[7,8]This high morbidity

and mortality has led multidisciplinary teams to seek better understanding of the underlying risk factors and their impact on risk. Various studies have attempted to determine and stratify factors associated with sepsis in urologic pathologies and procedures.[9-11] Diabetes Mellitus' role in susceptibility to infection and sepsis has been previously described in both urologic and non-urologic procedures.[4,5]

Prior studies in cohorts with urinary tract infections, urolithiasis, even when non-obstructing, diabetes mellitus, acute kidney injury and heart failure were identified as an important risk factor for progression to septic shock in patients with urinary tract infections.[10-15] While patients with diabetes mellitus in this study were not at increased risk for septic shock, multivariate regression demonstrated a nearly 3-fold risk for diabetes mellitus patients to have a positive qSOFA score when compared with non-diabetic patients. qSOFA is an assessment score that was designed to evaluate patients for risk of sepsis and a recent consensus conference put forth qSOFA criteria as superior to SIRS criteria for the prediction of infectious complications in medicine in general. Few studies have evaluated this in the urologic literature.[6] This finding underscores the concept that these predictive scoring systems (e.g. qSOFA criteria, SIRS criteria) may demonstrate false positives in terms of their ability to predict septic shock as a clinical endpoint for patients with stone disease and concomitant urinary tract infection.

In the current study, it did not appear that diabetes mellitus was associated with increased risk of septic shock in patients who presented with obstructing ureteral stones and concomitant urinary tract infection who underwent ureteral stent placement. For this entire cohort, the rate of admission to the intensive care unit, the rate of prolonged vasopressor use, and the duration of ICU stay were the same for patients with and without diabetes mellitus. In our study, the ICU admission rate was above 20% for patients presenting with the aforementioned clinical scenario. It is important to note that in our study, patients without diabetes mellitus appear to experience the infectious complications that we defined as our endpoints as often as those with diabetes mellitus.

Our study faces various limitations. This is a retrospective study and is subject to the inherent biases of a non-prospective study. Also, sample size was small (<200 patients) which may also affect accurate statistical analysis of our findings. However, ICU admission rates were not negligible, which perhaps address strength to the findings. In addition, DM was analyzed as a binary factor and our analysis did not include possible modifying and confounding factors related to the management and control. For example, length of DM diagnosis, current management regimes, type of DM are unaccounted and unadjusted for. In addition, our pool of identified diabetes patients had a relatively well managed DM and further studies need to analyze the impact of management on studied outcomes. Other factors to consider as potential limitations are related to the management each patient received in the ED prior to stenting was non-protocolized per se and may have been dependent on the perceived condition and possibility to deteriorate for each patient, introducing heterogeneity. Further prospective studies are important

to examine these findings and to better understand the pathophysiology and risk factors for sepsis in these kidney stone patients.

CONCLUSIONS

In this multicenter study of patients who underwent ureteral stenting for ureteral stone and presumed urinary tract infection, diabetes mellitus was not associated with an increased risk of septic shock. This information may be useful when evaluating patients with ureteral stones and presumed infection.

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FIGURES AND TABLES

Figure 1. Displays forest plot of regression analysis of the impact of diabetes mellitus on measured outcomes.

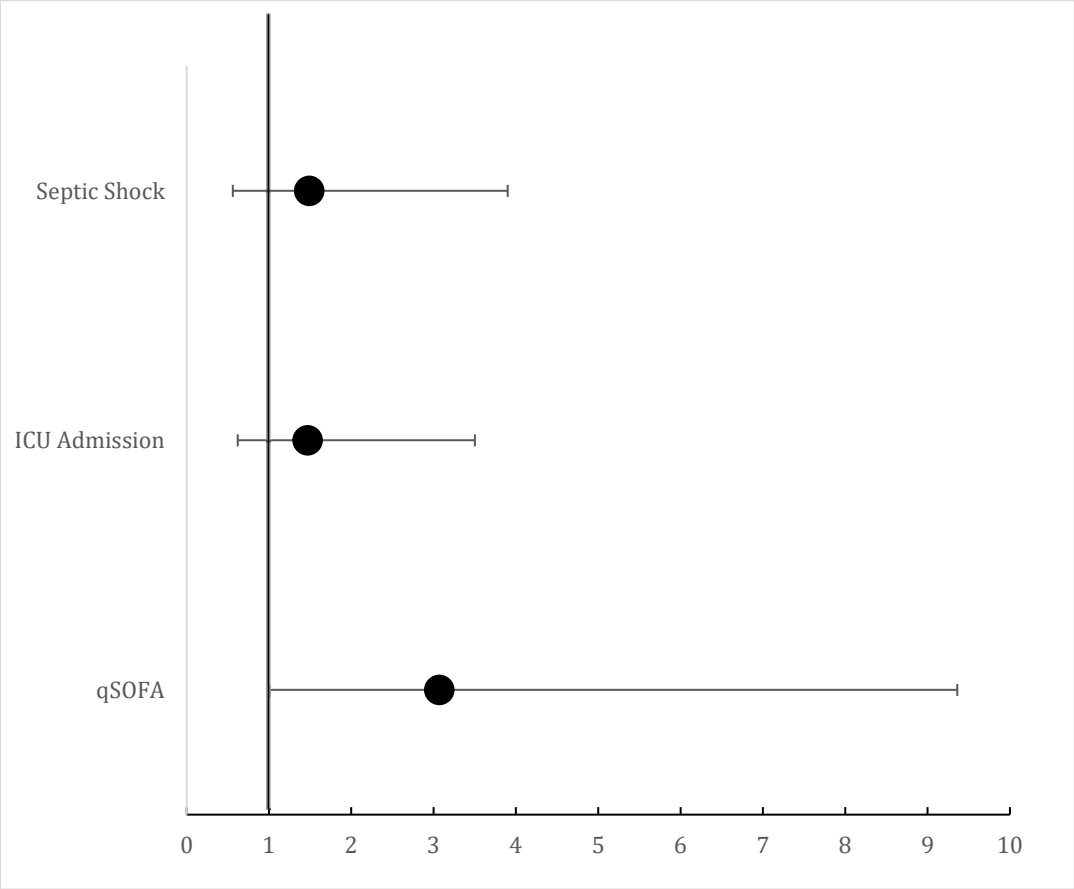

Table 1. Summarizes frequencies (percentages) and mean (standard deviation) or median(range) from the baseline characteristics and general outcomes of the included cohort	
Gender (male)	70 (40.1%)
Age	61 (16-93)*
Geriatrics	80 (42.5%)
BMI	27 (17-53)*
Obesity	64 (34.6%)

DM	49 (26.3%)
HTN	84 (45.4%)
Positive culture within 90 days of admission	8 (6.1%)
History of recurrent UTI	39 (21%)
History of prior pyelonephritis or urosepsis	24 (13%)
Prior endourological procedure	6 (3.3%)
Neuromuscular disorder Multiple sclerosis Other	10 (5.4%) 8 (4.3%) 2 (1.1%)
Charlson comorbidity index 0 1 2 3 4 5 6 7 8 9 10	 35 (24.5%) 20 (14%) 31 (21.7%) 22 (15.4%) 14 (9.8%) 13 (9.1%) 7 (4.9%) 0 0 0 1 (0.7%)
Multiple stones	14 (7.5%)*
Stone location Proximal Medial Distal	 8 (4.3%) 98 (52.7%) 80 (43%)
Struvite stones	33 (17.7%)
Hydronephrosis None Mild Moderate Severe	 10 (5.3%) 74 (39.6%) 61 (32.6%) 12 (6.4%)
Operative time	23 (4–58)*
Sepsis	24 (12.8%)

ICU admission	42 (22.6%)
Vasopressors	35 (18.7%)
ICU stay	2 (1–24)*
Length of stay	2 (0–27)*

*Range. BMI: body mass index; DM: diabetes mellitus; HTN: hypertension; UTI: urinary tract infection; ICU: intensive care unit.

Table 2. Summarizes findings of comparing baseline and outcomes of patients with DM vs, those without

	DM	**No DM**	**p**
Gender (males)	44.9% (22)	38% (52)	0.401
Age	65 (41–92)*	60 (16–93)*	0.019
Geriatric (>65)	53.1% (26)	38.7% (53)	0.093
BMI	29.43 (18.70–59.05)*	24.15 (19.22–36.28)*	0.001
Obesity	55.1% (27)	27.4% (37)	0.001
Hb1Ac	6.95 (1.27)†		
History of recurrent UTI	14.6% (7)	22.6% (31)	0.301
History of pyelonephritis or urosepsis	14.6% (7)	12.4% (17)	0.803
Prior endourological procedure	0% (0)	4.4% (6)	0.341
Stone location Proximal Medial Distal	 6.1% (3) 57.1% (28) 36.7% (18)	 3.7% (5) 51.5% (70) 44.9% (61)	0.496
Multiple stones	8.2% (4)	9 (6.6%)	0.747
Stone size	7 (3–17)*	5 (3–15)*	0.687

Purulent urine	44.9% (22)	24.8% (34)	0.011
Hydronephrosis None Mild Moderate Severe	 10.2% (5) 38.85% (19) 22.4% (11) 8.2% (4)	 3.6% (5) 40.1% (55) 36.5% (50) 5.8% (8)	0.154
Operative time	22 (10–46)*	32 (6–56)*	0.50
qSOFA	22.4% (11)	9.5% (13)	0.026
ICU admissions	27.1% (13)	21.2% (29)	0.426
Vasopressors used	22.4% (11)	17.5% (24)	0.523
Vasopressor time	39.25 (2–96)*	14 (1–408)*	0.581
ICU stay	2.5 (1–17)*	2 (1–24)*	0.330
Length of stay	10.5 (3–26)*	5 (2–27)*	0.193

*Range. †Standard deviation. BMI: body mass index; DM: diabetes mellitus; HTN: hypertension; UTI: urinary tract infection; ICU: intensive care unit.

Table 3. Summarizes single and multiple logistic regressions for target outcomes in relation to DM

	OR	**P value**	**AOR**	**p**
qSOFA	3.07 (1.01, 9.36)	0.048	2.90 (1.06, 7.93)	0.038
ICU admission	1.47 (0.62, 3.50)	0.378	-	-
Septic shock	1.49 (0.56, 3.90)	0.417	-	-

DM: diabetes mellitus; OR: odds ratio; AOR: adjusted odds ratio; ICU: intensive care unit.