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Median survival times are longer in azotemic cats that have a 25% or 50% reduction in creatinine at 24 or 48 hours, respectively, after subcutaneous ureteral bypass device placement

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Objective
To determine median survival time using predefined creatinine percentage changes after SC ureteral bypass (SUB) placement.

Methods
This was a retrospective cohort study. Data from cats admitted for SUB placement were collected between 2015 and 2022 from a single referral hospital. Serum creatinine values at presentation and at 24 and 48 hours after SUB placement and outcome data (dead or alive) were extracted, and percentage change was calculated. Cats with incomplete datasets or nonbenign obstruction were excluded. A priori decreases of 25% and 50% were regarded as acceptable changes at 24 or 48 hours, respectively. Median survival times were approximated using Kaplan-Meier curves.

Results
Records from 21 of 30 cats (14 female, 7 male) that were a median of 8 (7 to 10) years old had complete datasets for analysis. Median survival times were 241 (8, 719) and 989 (989, 1,510) days for cats that did not and did achieve the predefined decrease at 24 hours, respectively. Median survival times were 225 (8, 387) and 989 (2, 1,510) days for cats that did not and did achieve the predefined decrease at 48 hours, respectively. The overall median survival time was 387 (119, 989) days regardless of achieving the predefined percentage decreases.

Conclusions
The median survival time was significantly longer in cats that achieved or exceeded the predefined percentage reduction in creatinine at 24 or 48 hours after SUB placement.

Clinical Relevance
Evaluating percentage changes in serial serum creatinine after SUB placement can be useful to indicate survival and longevity.

Keywords: ureteral obstruction, feline SUB, ureterolithiasis, serum creatinine, azotemia

Feline ureteral obstruction can be partial or complete and can lead to azotemia and acute kidney injury. The most common etiology is intraluminal benign obstruction secondary to ureteral calculi.[1] Other causes of benign obstruction include ureteral strictures, noncancerous masses, and trauma, and nonbenign obstruction includes cancerous neoplasia.[2,3] When medical management is unsuccessful, then often emergent surgical intervention is required to resolve or bypass the obstruction.[4] One such surgical intervention is to bypass the obstruction by inserting an SC ureteral bypass (SUB) device, which is a tubular construct connecting the pelvis of the kidney to the urinary bladder.[2,4]

Serum creatinine is a widely used biomarker to estimate GFR, which is readily available and has low intraindividual variability.[5–7] Serial measurements of creatinine have shown to be useful in monitoring and detecting changes in kidney function.[7,8] Generally, elevated creatinine, before and after surgery, has been associated with a shorter survival time in cats with ureteral obstruction,[2,9–11] yet the early changes

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in creatinine after ureteral bypass surgery have not been widely investigated for prognostication in cats.

A method of quantifying change for comparison is to determine the percentage change that occurs over a fixed time interval. The percentage change is calculated by subtracting the latest value by the initial value, dividing this difference by the initial value, and then multiplying by 100 to obtain a percentage value. A percentage change in creatinine was calculated from published data in cats undergoing ureteral bypass surgery, and it ranged from a 39% to 77.3% reduction.[2,3,9,11,12] However, the postoperative blood sampling times differed greatly (12 hours to many days after SUB placement) among the studies. Furthermore, greater reductions were reported where blood samples were obtained on the day of discharge. In the absence of clear evidence, we propose that a reduction of creatinine by 25% in 24 hours or 50% in 48 hours after SUB placement is clinically reasonable to expect. These values were used to define the a priori percentage change thresholds the cats were expected to achieve following a successful SUB placement.

The aim of the study was to determine the median survival time in cats where a SUB was placed and to determine if there is a difference in survival times if creatinine is decreased by a predetermined percentage over a fixed period of time. A secondary aim was to evaluate the percentage change in creatinine at fixed periods of time to outcome data (dead or alive) to determine if evidence-based percentage reduction thresholds can be defined. We hypothesized that cats that achieved or exceeded the predefined percentage reduction in creatinine at 24 or 48 hours, respectively, had a longer median survival time than cats that did not.

Methods

Cohort case selection

A retrospective cohort study was conducted, and the Strengthening the Reporting of Observational Studies in Epidemiology checklist for cohort studies was used as a reporting guideline. Ethical approval was attained through the University of Pretoria animal use ethics and research ethics committees prior to data collection (REC147-22). Permission was granted by Bryanston Animal Hospital, the single-site referral practice where the cats presented. Practice management software used by the referral practice was queried using "cat," "feline," "subcutaneous ureteral bypass device," "SUB," "azotemia," and "urethral obstruction" as search terms from January 1, 2015, through December 31, 2022. Cat data were extracted by the practice manager, who was not involved in the study, and placed into a spreadsheet for further sorting and refinement by the principal investigator. None of the owner details or cats' names were extracted; only patient numbers were used to identify the different cats. Inclusion criteria were cats of any age and sex that (1) underwent a SUB placement; (2) had creatinine measured on the day before surgery, then at 24 and 48 hours after the procedure (a leeway of ± 5 hours was allowed); (3) had follow-up examinations for at least 1 year after placement (if alive); and (4) had a verified outcome of dead (natural or euthanized) or alive. Exclusion criteria were datasets of cats that were incomplete or if the ureteral obstruction was not benign. The dataset for each cat comprised the date of SUB placement, sex, age, serial creatinine values, date of death or last follow-up examination, and outcome.

A diagnosis of ureteral obstruction was made with ultrasonography performed by a board-certified internal medicine specialist or internal medicine resident under supervision. Diagnosis was based on evidence of > 5 mm renal pelvic dilation on transverse plane, concurrent hydroureter, and abdominal radiography demonstrating kidney, ureteral, or bladder calculi. The presence of structural chronic kidney changes and unilateral or bilateral obstruction was determined and recorded.

All serum creatinine concentrations were measured on a single in-house serum biochemistry analyzer (VetTest Catalyst Dx Chemistry Analyzer; IDEXX) to provide point-of-care reference.

For cats that did not survive to discharge, the cause of death or euthanasia and date of last contact were recorded. In cases where the date of death was unknown, telephonic follow-up was performed to confirm whether the cat was still alive or obtain the date and cause of death. Follow-up consisted of records or telephonic conversations at least a period of 1 year after discharge.

Statistical analysis

The percentage change in creatinine was calculated for 24 and 48 hours. An a priori percentage reduction in creatinine was set at 25% or 50% for 24 and 48 hours, respectively. The time (in days) was calculated using a spreadsheet formula (DAYS; Excel, version 16.89; Microsoft Corp) by determining the difference between the end date (day of last follow-up examination or death) and start date (day of surgery). These calculated values were used for various analyses.

Quantitative data were assessed for normality by inspecting descriptive statistics and histogram plots and applying the Anderson-Darling test for normality. Data were considered nonparametric and reported as median (95% CI of the median). For the primary aim, median survival times were estimated using Kaplan-Meier curves, where time to outcome was in days, outcomes were either "dead" or "alive," and cats were grouped based on if they "did not" or "did" achieve the predefined percentage decrease in creatinine at 24 or 48 hours, respectively. Comparison of survival curves was done by using the log-rank test. Hazard ratios were determined based on whether the cat achieved the predefined decrease in creatinine or not. For the secondary aim, Youden index *J* values and their associated criteria and optimal criteria were determined using receiver operating characteristic (ROC) curves.[13] The variable of interest was the percentage change in creatinine at 24 and 48 hours, and the outcome (dead or alive) was used. The prevalence was set as the ratio of cases in the positive (alive) and negative (dead)

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groups. For the ROC curve analyses, bootstrapping was applied, where 1,000 replications were run (random number seed was 978).[14,15] Data were analyzed using commercially available software (MiniTab Statistical Software, version 13.32 [Minitab Inc], and MedCalc, version 19.5 [MadCalm Software Ltd]). Significance was interpreted as $P < .05$.

Results

Records for a total of 30 cats were found; however, only 21 had complete datasets that could be used for analysis. For the excluded cat datasets, 3 cats were lost to follow-up because we were unable to contact owners. Six cats had incomplete creatinine datasets. The group comprised 14 female and 7 male cats that were a median of 8 (95% CI, 7 to 10) years old. A total of 14 cats died (8 female and 6 male), of which 6 were by elective euthanasia (4 female and 2 male) because of poor health and ill thrift.

The median survival times were 241 (95% CI, 8 to 719) and 989 (95% CI, 989 to 1,510) days for cats that did not and did achieve the predefined decrease at 24 hours, respectively ($P = .0365$; **Figure 1**). Cats that did achieve the predefined decrease in creatinine were 4.3 (95% CI, 1.5 to 12.5) times more likely to live longer compared to cats that did not. The median survival times were 225 (95% CI, 8 to 387) and 989 (95% CI, 2 to 1,510) days for cats that did not and did achieve the predefined decrease at 48 hours, respectively ($P = .0320$). Cats that achieved the predefined decrease in creatinine at 48 hours were 3.3 (95% CI, 1.1 to 9.5) times more likely to live longer than cats that did not. The overall median survival time was 387 (95% CI, 119 to 989) days regardless of achieving the predefined percentage decreases for creatinine.

At 24 hours, the Youden index J was 0.6429 (95% CI, 0.2857 to 0.8571) with an associated criterion of a decrease of 11% (95% CI, ≤ −23% to ≤ 1%) or more, which had a sensitivity of 86% (95% CI, 42% to 100%) and a specificity of 79% (95% CI, 49% to 95%) of the cat dying. The optimal criterion at 24 hours was a decrease of 23% (95% CI, ≤ −48% to ≤ −11%) or more, which had a sensitivity of 71% (95% CI, 29% to 96%) and a specificity of 86% (95% CI, 57% to 98%) of the cat dying **(Figure 2)**. A 100% (95% CI, 77% to 100%) specificity (indicating 100% absence of death) was achieved at a decrease of creatinine by 60% or more within 24 hours. None of the cats had an exact reduction of 25%; the closest value was that of the optimal criterion of ≤ −23%. At 48 hours, the Youden index J was 0.5714 (95% CI, 0.2857 to 0.7857) with an associated criterion of a decrease of 4% (95% CI, ≤ −25% to ≤ −4%), with a sensitivity of 100% (95% CI, 59% to 100%) and a specificity of 57% (95% CI, 29% to 82%) that the cat will die. The optimal criterion for 48 hours was a decrease of 75% (95% CI, ≤ −79% to ≤ −58%) or more, with a sensitivity of 29% (95% CI, 4% to 71%) and a specificity of 100% (95% CI, 77% to

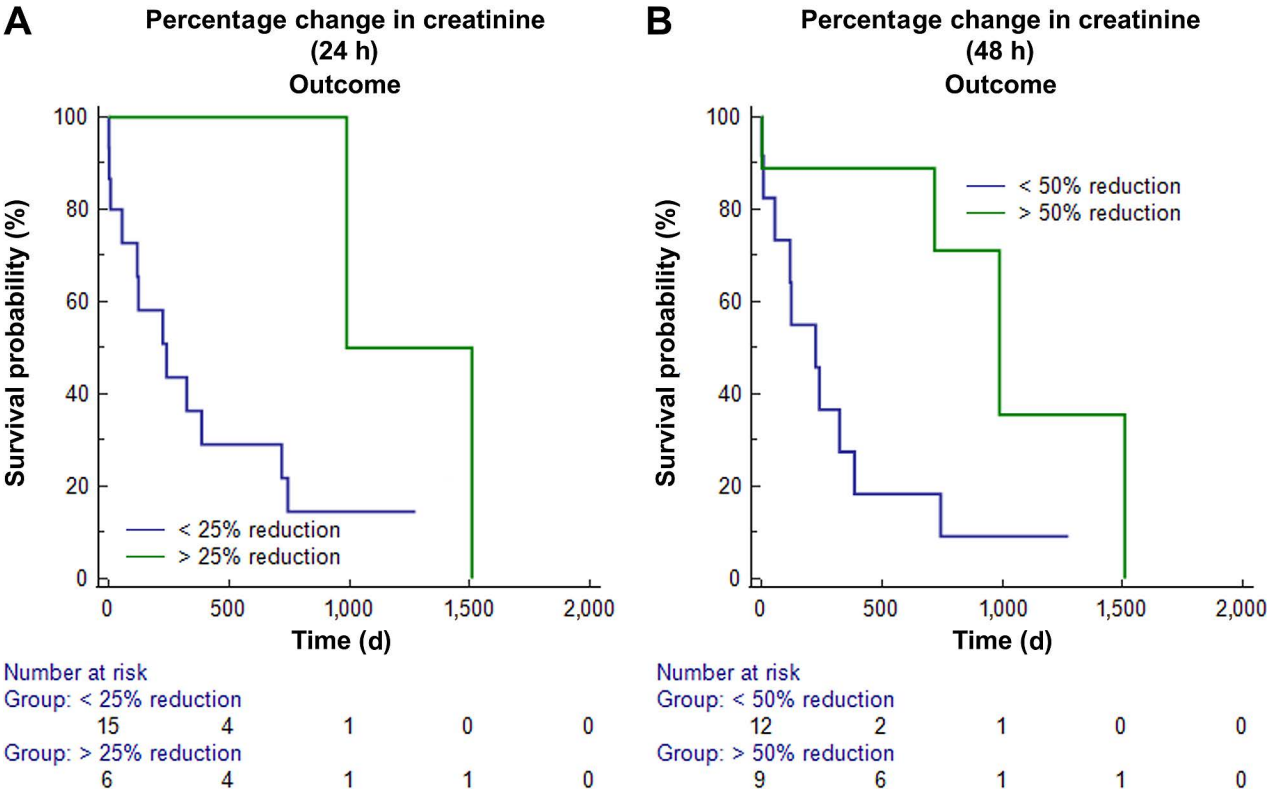

Figure 1—Kaplan-Meier survival curves for 21 azotemic cats that had an SC ureteral bypass device placed. Cats were grouped using a predefined expected percentage reduction in creatinine at 24 hours (A) and 48 hours (B) after surgery. Cats that achieved or exceeded the predefined reduction of time (green lines) lived longer than cats that did not (blue lines).

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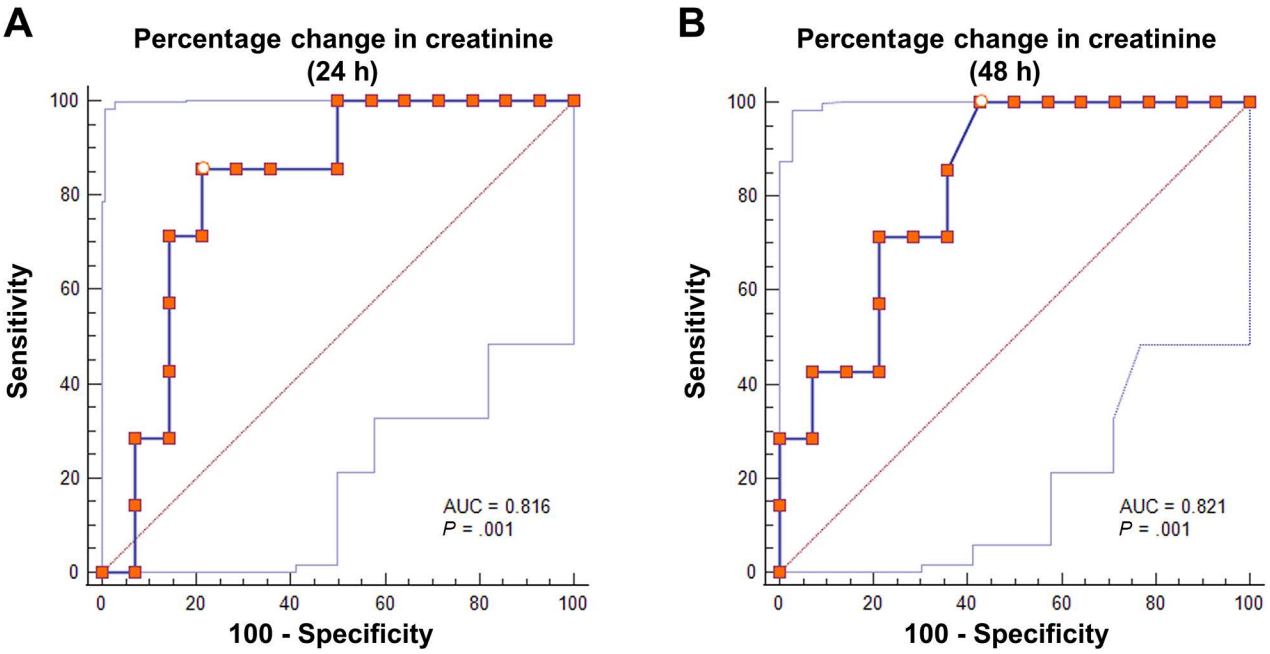

Figure 2—Receiver operating characteristic curves for a group of 21 azotemic cats that had an SC urethral bypass device placed. The variable of interest was the percentage change in creatinine at 24 hours (A) and 48 hours (B). The outcomes were either dead or alive. The prevalence was set as the ratio of cases in the positive (alive) and negative (dead) groups. Bootstrapping was applied, where 1,000 replications were run. The Yourdon index *J* is represented as a white circle within the red square on each plot. AUC = Area under the curve.

100%) of the cat dying. The predefined 50% reduction of creatinine at 48 hours had a sensitivity of 71% (95% CI, 29% to 96%) and a specificity of 71% (95% CI, 42% to 92%).

Discussion

Median survival times were longer in azotemic cats that demonstrated a hypothesized clinically relevant percentage reduction in creatinine up to 48 hours after SUB device placement. Optimal percentage reductions in creatinine at 24 and 48 hours after SUB device placement were determined, but they should be interpreted with a few caveats, which are discussed.

Overall median survival times in cats with SUB device placement have been reported as > 294,[3] 419,[10] 530,[9] and 827 days,[11] which is a wide range. Our overall median survival time is within this range but toward the lower end. However, after grouping, cats that did achieve the proposed percentage reduction in creatinine in 24 or 48 hours had median survival times toward the higher end of this range. The smaller the sample size used in each study tended to report shorter median survival times (10[3] and 26 cats,[10] respectively) compared to those that used more than 90 cats (95[9] and 134 cats,[11] respectively). Furthermore, the smaller sample size studies were reported in 2011[3] and 2014,[10] whereas the larger sample size studies were reported in 2018[11] and 2021.[9] We speculate that this observation could imply that as surgery to place a SUB device is becoming more common practice, fewer postoperative complications are noted, and improvements of the device have been made that have improved overall survival times. Various factors have been used in survival analysis to group cats to determine if there is an effect on survival time. The International Renal Interest Society chronic kidney disease scoring system has been used as a factor code to group cats. Cats in stages 1 and 2 have a longer survival time compared to cats in stages 3 and 4,[2] whereas more recently, cats with a creatinine value of > 440 µmol/L at presentation have a median survival time of 530 days compared to 949 days in cats with a creatinine < 440 µmol/L at presentation.[9] We are the first to use a percentage change in creatinine over fixed time periods as a grouping factor, and they are similar to reported day ranges by Kulendra et al.[9] This observation suggests that our a priori percentage change in creatinine thresholds for 24 and 48 hours can provide clinically relevant information on long-term survival and longevity in cats with SUB device placement. However, the major caveat of using these predefined percentage decreases in creatinine is that this information can only be obtained after placing the SUB device and after considerable cost to the client.

Associated and optimal criteria for identifying the best percentage change in creatinine were described for 24 and 48 hours after SUB device placement. However, these need to be interpreted with caution.[13] When interpreting an ROC curve, the area under the curve must be > 0.80 to be considered "clinically useful," which our curves are. However, the CI of the area under the curve is very wide. Another caveat is that the Youden index *J* values were both less than < 0.7 but above 0.5. These Youden index *J* values are too close to 0.5, which implies that the

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outcome of the associated criterion is no better than chance at distinguishing if the cat will die or not. Despite these caveats, the optimal criteria at 24 and 48 hours had very high specificities (interpreted as the cat not dying), and a recommendation of a 23% or 75% reduction in creatinine at 24 and 48 hours should be used in future studies to group cats to determine estimated median survival times.

The major limitations of this study included the retrospective nature of the study and the small population size. Complete datasets could not be obtained for all 30 cats, and we cannot state with confidence whether or not this could have influenced the overall results. However, our estimated median survival times are within ranges of those that have been reported, which suggests that enough datasets were collected.

A percentage change in creatinine within a fixed period of time could be used to predict survival and longevity in azotemic cats with SUB device placement. We recommend the use of a predefined reduction of 23% at 24 hours and 75% at 48 hours to group cats with SUB placement in future studies on survival analysis. Future studies with larger case numbers and longer follow-up periods are needed.

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