Drain fluid creatinine-to-serum creatinine ratio as an initial test to detect urine leakage following cystectomy: A retrospective study

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ABSTRACT

Introduction: Urine leak following radical cystectomy is a known complication. Among the various methods to diagnose this, assessment of drain fluid creatinine is a relatively easy procedure. We aimed to ascertain the validity of the drain fluid creatinine-to-serum creatinine ratio (DCSCR) as an initial indicator of urinary leak in patients undergoing radical cystectomy.

Methods: We retrospectively identified consecutive patients with documentation of drain fluid creatinine in the postoperative period following cystectomy and urinary diversion at our institution between January 2009 and December 2018. All continent diversions and any patient with a DCSCR >1.5:1 underwent contrast study postoperatively. A diagnosis of urine leak was made following confirmatory imaging. Receiver operative characteristic curves were created, and Youden's index was used to determine the strength and clinical utility of DCSCR as a diagnostic test.

Results: Two hundred forty-four of the 340 patients included in the study underwent cystectomy with conduit and 81 underwent neobladder creation. Sixteen out of 340 (4.7%) patients had radiologically confirmed urinary leak. DCSCR was elevated in all ureteric anastomotic leaks and in 1 out of the 7 neobladder-urethral anastomotic (NUA) leaks. The sensitivity and specificity of DCSCR to predict all urinary leaks were 68.8% and 80.9% at 1.12 (area under the curve [AUC] = 0.838), whereas at a value of 1.18 (AUC = 0.876) and with the exclusion of NUA leaks, the sensitivity was 77.8% and specificity was 87.6%.

Conclusions: DCSCR is a good preliminary test for identifying patients who need prompt confirmatory testing for localizing urinary leaks. A drain creatinine level just 18% higher than the serum creatinine level can signify a urine leak. This is different from general assumptions of a higher DCSCR.

INTRODUCTION

The incidence of urinary leak after cystectomy for bladder cancer has been reported between 0% and 7.7%[1] in the early postoperative period, and it depends not only on the etiology for which the surgery[2] is being performed but also on the method used to define urine leaks. Most earlier studies have relied on the diagnosis of urine leaks based on overt clinical symptoms which are often followed by extensive radiological testing to confirm the diagnosis.[3]

Assessment of creatinine in the drain fluid has been utilized by various researchers as a guide for the initial diagnosis of urinary leaks, and several arbitrary values have been labeled as being diagnostic for urinary leak.[4,5] However,
during cystectomy, spillage of urine into the peritoneal cavity is universal and the correct value for peritoneal fluid creatinine as measured in the drain fluid and the timing for this measurement are not well established. Peritoneum has the ability to absorb leaked urinary creatinine into plasma\footnote{6} raising serum creatinine.

Therefore, it is important to establish a threshold value of creatinine in the drain fluid that is likely to indicate the presence of a urinary leak, which can trigger appropriate diagnostic testing to confirm the leak. The importance of early identification of urinary leaks is highlighted by their association with health resource consumption as well as reduced survival.\footnote{2}

We retrospectively evaluated patients who had undergone cystectomy and attempted to establish the validity of the drain fluid creatinine-to-serum creatinine ratio (DCSCR) as an indicator of urinary leak.

**METHODS**

After approval for the study from the Institutional Review Board, we retrospectively collected data on all patients undergoing cystectomy at our institution between January 2009 and December 2018. Patients who had an intraperitoneal drain placed following surgery and had simultaneous drain fluid creatinine and serum creatinine assessments in the postoperative period were identified for analysis. Data were obtained from medical record review regarding demographics, indications for cystectomy, operative details and postoperative course, and diagnosis of urinary leak within the following surgery. Intraoperatively, the absence of urinary anastomotic leaks was confirmed in each case by direct visual inspection following irrigation of the ureteric anastomosis and urethral anastomosis (in cases of neobladder diversion). All patients underwent placement of single J urinary diversion and had a single 19F JP (Jackson-Pratt) drain left in place intra-abdominally postprocedure. Drains were normally left in place until both stents were removed (usually attempted at the end of the first week of surgery in most patients) and were removed earlier if the stents were contemplated to be left in place for a prolonged period of time (3–4 weeks) which was done in patients who had received prior radiation. Patients with neobladders had a urethral catheter in place for 3 weeks, and the catheter was only removed once the absence of urinary leak was confirmed on fluoroscopic or computed tomography (CT) cystogram. Drain creatinine was measured sequentially before and after any urinary diversion stent removal to identify and localize the laterality of the leak. Therefore, as a standard, all patients would have at least three assessments of both serum creatinine and drain fluid creatinine – postoperatively with all urinary diversion stent (s) in place, after removal of each stent separately, along with concomitant serum creatinine measurements. Patients who had long (>1 week) indwelling drains or a persistently high drain output would have a fourth assessment before drain removal. For analysis, in patients with DCSCR values >1.5, the first abnormal value was considered for evaluation.

All patients with neobladder creation and partial cystectomy or other forms of continent diversion underwent a cystogram (primarily with fluoroscopically and occasionally CT) before removal of the Foley catheter. Any patient who had a clinical suspicion of a significant urinary leak manifested by persistently high drain output (>500 ml of serous/sero-sanguineous drainage from an intraperitoneal drain at the end of the first week) and elevated DCSCR of >1.5:1 also underwent a confirmatory imaging study in the postoperative period. A diagnosis of urine leak was recorded if it was confirmed by CT or conventional imaging in the form of a cystogram, urogram, loopogram, and/or nephrostogram. Follow-up data on the patients with confirmed leaks were also evaluated to record further management and sequelae of these leaks.

**Statistical analysis**

All categorical variables were reported as frequencies and proportions. Continuous variables were reported with descriptive statistics using median and range. The DCSCR was also treated as a continuous variable. Mann–Whitney U test was used to compare the medians. Receiver operative characteristic (ROC) curves were created by charting sensitivity on y-axis against 1-specificity on x-axis and area under the curve (AUC) calculated to determine its clinical utility. Youden’s index, defined as the summation of sensitivity and specificity minus one, was used to indicate the strength of DCSCR as a diagnostic test. The highest value of this index closest to 1 was considered, with equal weight given to false-positive and false-negative values. An additional ROC curve and AUC analysis was also performed without the inclusion of neobladder-urethral anastomotic leaks. Data analysis was performed using SPSS v26.0 (IBM SPSS Statistics for Windows. Armonk, NY, USA: IBM Corp).

**RESULTS**

Based on the current procedural terminology codes for cystectomy, 410 patients were identified and charts of 386 patients were available for review. Results of serum and drain creatinine were available for 340 patients and thus were included in the study. All surgeries were transperitoneal, 244 of 340 patients underwent radical cystectomy with creation of a conduit, whereas 81 patients underwent urinary diversion with neobladder. All 81 neobladders and 201 out of 244 conduits were created for urothelial malignancy. Twelve had locally advanced colorectal carcinoma including one each with prostate cancer and advanced penile carcinoma. Table 1 highlights...
the indications and the surgical procedures performed. The median age of the cohort was 67 (range, 22–89) years; 82% of the patients were male, and the median time to drain removal was 6 days (interquartile range, 5–9 days).

The ratio of intraperitoneal (IP) drain to serum creatinine was calculated on the 1st day of planned IP drain removal. In total, 252 (74.1%) patients had normal renal function following surgery defined as a serum creatinine of 1.2 mg/dl on the day of the first attempted drain removal. The median serum creatinine drain fluid creatinine and DCSCR is presented in Table 2.

Ninety-two patients had persistent high drain output possibly due to postcystectomy lymphorrhea without suspicion of urinary leak, and 19 (5.6%) patients had a clinical suspicion of urinary leakage with DCSCR >1.5 and a higher-than-expected drain output. Sixteen patients underwent confirmatory radiological testing to detect the leak. Of the three patients who did not undergo any confirmatory radiological testing, one had wound dehiscence and visible urinary leak from the suprapubic catheter site and the other two had a subsequent dramatic decrease in levels of the drain creatinine/serum creatinine ratio confirming the possibility of a minor transient leak and hence were deemed not to require further evaluation. Of the 16 patients who underwent confirmatory testing, 8 (50%) had radiologic confirmation of a urine leak. Eight additional patients with urine leak were identified on routine postoperative cystograms. Therefore, 16/340 (4.7%) patients had radiologically confirmed urinary leaks. Five (1.5%) of these were ureteric anastomotic leaks, and all five (four ileal conduits and one neobladder) demonstrated an elevated DCSCR. All eight patients diagnosed solely on postoperative radiologic studies had DCSCR between 1 and 1.42 and were following neobladder diversion. A total of seven patients were leaking from the neobladder-urethral anastomosis (NUA). The detailed clinical course of all 16 patients is presented in Table 3.

As the cost incurred per DCSCR test is generally low ($14),[7] we also estimated that it would amount to between $84 (three separate assessments) and $112 (four assessments) per patient to detect a urine leak though overall costs may be different in other settings. Figure 1 represents the receiver operating characteristic curve generated for all patients included in the study using DCSCR based on a confirmed urine leak seen on radiologic imaging. The value for the AUC was 0.838, with a 95% confidence interval (CI) between 0.744 and 0.934. This indicated that DCSCR is a good initial test to detect urinary leak. Youden’s index reached its maximum value of 0.497 at a DFSCR of 1.12 corresponding to a sensitivity of 68.8% and specificity of 80.9%. The positive predictive value (PPV) and negative predictive value (NPV) were 15% and 98.1%.

Table 1: Surgical indication and spectrum of surgeries performed

| Indication for surgery | Type of surgery performed | Total |
|-----------------------|---------------------------|-------|
|                       | Cystectomy with conduit   |       |
| Malignancy            | 215                       | 215   |
| NGB                   | 15                        | 15    |
| Radiation cystitis    | 11                        | 11    |
| Miscellaneous         | 3                         | 3     |
| Total                 | 244                       | 244   |
|                       | Cystectomy with neobladder|       |
| Malignancy            | 81                        | 81    |
| NGB                   | 0                         | 0     |
| Radiation cystitis    | 0                         | 0     |
| Miscellaneous         | 0                         | 0     |
| Total                 | 81                        | 81    |
|                       | Cystectomy with continent pouch |       |
| Malignancy            | 2                        | 2     |
| NGB                   | 0                        | 0     |
| Radiation cystitis    | 0                        | 0     |
| Miscellaneous         | 0                        | 0     |
| Total                 | 2                        | 2     |
|                       | Cystectomy only           |       |
| Malignancy            | 1                        | 1     |
| NGB                   | 0                        | 0     |
| Radiation cystitis    | 0                        | 0     |
| Miscellaneous         | 0                        | 0     |
| Total                 | 1                        | 1     |
|                       | Partial cystectomy        |       |
| Malignancy            | 7                        | 7     |
| NGB                   | 0                        | 0     |
| Radiation cystitis    | 0                        | 0     |
| Miscellaneous         | 3                        | 3     |
| Total                 | 10                       | 10    |
|                       | Total                     | 306   |

This table summarizes the various indications and the types of surgeries performed for the patients included in the cohort. NGB: Neurogenic bladder

Table 2: Drain fluid creatinine, serum creatinine, and drain creatinine-to-serum creatinine ratio

| Patient Groups | Median, IQR | Drain creatinine in mg/dl | Serum creatinine in mg/dl | DCSCR |
|----------------|-------------|----------------------------|---------------------------|-------|
| All patients (n=340) | 1 (0.8-1.3) | 0.96 (0.8-1.23) | 1.02 (0.96-1.1) |
| Without leak (n=324) | 1 (0.8-1.3) | 0.96 (0.8-1.25) | 1.02 (0.96-1.09) |
| With leak (n=16) | 3.1 (1-11.17) | 0.92 (0.80-1.15) | 2.63 (1.06-16.08) |

This table compares the values of drain fluid creatinine, serum creatinine and DCSCR in patients with diagnosed urinary leaks to those without leaks. IQR: Interquartile range, DCSCR: Drain fluid creatinine-to-serum creatinine ratio

Figure 1: Receiver operating characteristic curve with urine leak detected by imaging based on drain fluid creatinine-to-serum creatinine ratio. Receiver operating characteristic curve obtained by plotting the sensitivity to 1-specificity of drain fluid creatinine-to-serum creatinine ratio for detection of all urinary leaks. AUC was 0.838
respectively. A subsequent ROC analysis was performed where only ureteric anastomotic and bladder/neobladder closure leaks (not NUA leaks) were considered. Here, AUC was 0.876 with CI between 0.752 and 1.000 [Figure 2] and Youden’s index was 0.654 at a DCSCR of 1.18 with 77.8% sensitivity and 87.6% specificity. The PPV and NPV for this analysis were 17% and 99.3%.

**DISCUSSION**

The timely detection of urinary leak following cystectomy should follow a standardized approach which rationalizes the performance of a simple, minimally invasive yet sensitive screening test which, if positive, can direct confirmatory radiological tests. The performance of routine contrast radiological tests following ileal conduit urinary diversion has been deemed unnecessary by several studies over the years.\(^8,9\) Neobladders, however, are mandated to the scrutiny of contrast pouchograms or cystograms.\(^10,11\) Therefore, a preliminary test, which can reliably signal the likelihood of a urine leak and thereby direct further management of anastomotic urinary leaks, would be valuable.

At an AUC of 0.839, our results suggest that DCSCR has a good diagnostic capability and therefore is a good initial
test for detecting urinary leaks. All NUA leaks in our series resolved with conservative management, whereas 89% of all other leaks needed intervention. Therefore, when not accounting for NUA leaks, AUC increased to 0.876, indicating that it may be a better indicator for leaks other than NUA.

This study also serves to fill a void in existing urological literature, which, despite being extensive, is severely limited in the initial approach for diagnosis of urine leaks.\(^{[12-14]}\) In fact, the most comprehensive data in this area come from the colorectal literature. Brown et al.\(^{[2]}\) highlighted the importance of analyzing DCSCR in the algorithmic approach to diagnosing urinary leaks following pelvic exenteration. Wang et al.\(^{[4]}\) found that in case of a higher peritoneal drainage, the assessment of peritoneal urea nitrogen and creatinine levels was useful in the diagnosis of intraperitoneal urinary injuries. However, neither of these authors ascertained a diagnostic cutoff to the index. Our findings, identify the cutoff value of DCSCR most likely to indicate a urinary leak.

Our cohort is also different from those of Wang et al.\(^{[4]}\) and Brown et al.\(^{[5]}\) where the entire population was comprised of patients of colorectal surgery and pelvic exenteration, respectively. The incidence of urinary leaks is higher in patients undergoing pelvic exenteration due to the high incidence of re-operation and previous pelvic irradiation in this population.\(^{[15]}\) Therefore, conclusions from these studies may not be applicable to the typical population of patients undergoing cystectomy.

There have been prior instances where an arbitrary value has been assigned as a cutoff for the upper limit of normal for DCSCR. Mattei et al.\(^{[16]}\) had assigned an arbitrary value of >130% to this while looking at stented versus nonstented ureteroileal anastomosis but found that this was not sensitive enough to indicate a higher incidence of urinary leaks in the unstented group. Williams et al.,\(^{[5]}\) while retrospectively looking at their partial nephrectomy series, had defined a value of >1.2 for DCSCR as indicative of urinary leak. It is important to note that this was not confirmed by radiological testing and can be assumed to be purely inferential. Similarly, Flores-Gama et al.\(^{[17]}\) found that in patients undergoing renal transplantation, DCSCR >6 after the 1st week represented a six times higher possibility of urinary leak. However, this study had a small sample size, and the methodology used for determining this value was different. Graft function in renal transplantation can have a significant impact on the biochemical profile of urinary leaks\(^{[18]}\) and this population differs from our cohort.

Therefore, the value of DCSCR >1.18, derived from our results, is scientifically sound with a sensitivity of 77.8% and specificity of 87.6% and appropriately identifies patients who are likely candidates for additional diagnostic radiographic testing and additional intervention. The estimation of DCSCR also does not increase the economic burden on the health system as the tests are relatively inexpensive. We used 1.5 as a cutoff for pursuing additional testing for a urine leak in our clinical practice. However, our analysis indicated that cutoff DCSCR values of 1.12 and 1.18 have good NPVs of 98.1% and 99.3%, respectively, and can serve as good references for ruling out leaks. This is also supported by existing literature\(^{[16]}\) where an arbitrary value of >130% assigned to the DCSCR was not statistically significant to identify the difference in urinary leaks between stented and nonstented ureteroileal anastomosis. We found that the true value of DCSCR comes at ≥1.18 where most leaks (ureteroileal and bladder/neobladder closure) needing intervention are reliably diagnosed, thereby influencing timely intervention.

Finally, the incidence of radiographically confirmed urinary leaks in our sample was 5% which is comparable to others reported in the literature.\(^{[1]}\) The incidence of ureteric anastomotic leaks in our series of 5/340 (1.5%) compares quite favorably with literature reports which is reported to be between 3% and 9%.\(^{[19]}\)

A single DCSCR value is not sufficient, and as highlighted, a step-by-step assessment is important. We begin assessment on the 4th or 5th postoperative day, as early on days 1–3, DCSCR can be high.\(^{[16]}\) Similarly, upon removal of a stent, an innocuous leak can manifest, as was seen with one of our patients who developed a retroperitoneal collection following a leak upon stent removal. Sometimes, DCSCR elevation in the drain placed at the time of surgery may not be evident if the urinoma is walled off or localized to the retroperitoneum. Therefore, localizing clinical signs and judicious use of cross-sectional imaging are indicated based on clinical judgment rather than only focusing on the DCSCR.

There are, however, some limitations to our study. The most important being the retrospective nature of the analysis with its inherent bias on the interpretation of results. Another bias is that almost all diversions apart from conduits had mandatory radiological testing independent of the DCSCR. This selection bias may have missed some leaks in the conduits, but as indicated by previous large series,\(^{[8,9]}\) routine radiological testing in conduits may not be clinically necessary or fruitful. On the other hand, small and clinically insignificant leaks were identified following routine radiological testing of continent diversions despite having normal DCSCR. Finally, in patients with a high clinical suspicion of leak, confirmatory radiological testing should be done. Despite these limitations, our study will help in setting a benchmark for further prospective research in this field.
CONCLUSIONS

The assessment of DCSCR in patients undergoing cystectomy with urinary diversion is a good preliminary test for identifying patients who will need further confirmatory testing for localizing urinary leaks. Although DCSCR may not identify some leaks in patients undergoing complex reconstruction following cystectomy, it should be a part of a standard management algorithm and a level >1.18 can identify clinically significant leaks with good sensitivity and specificity.

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