Renal deterioration index: Preoperative prognostic model for renal functional outcome after treatment of bilateral obstructive urolithiasis in chronic kidney disease patients.

ABSTRACT

Background: Patients presenting with varying severity of obstructive urolithiasis behave differently after the treatment. Some patients recover with improved renal function while others progress to renal failure.

Objective: To objectively quantify which patient would progress to renal failure following treatment for obstructive urolithiasis.

Material and methods: A prospective analysis of 167 patients with renal failure due to bilateral obstructive urolithiasis who were treated and subsequently followed for at least 1 year was done. Failure was defined as GFR values less than 15 ml/min at 1 year follow up. All patient had pre-operative placement of percutaneous nephrostomy tube for at least 5 day before treatment with either ureteroscopy or percutaneous nephrolithotomy. Multiple logistic regression analysis of affecting parameters was done. A Renal deterioration index (RDI) was constructed based on scores assigned to varying severity of multivariate significant factors and ROC analyzed.

Results: 48(28.7%) patients progressed to CKD stage V at 1-year follow-up. Combined cortical width (≤0.001), proteinuria (0.01), positive urine culture (0.004) and nadir preoperative GFR post bilateral PCN (0.016) were statistically significant factors affecting renal deterioration on multi-variate analysis. RDI has high ROC curve (AUR=0.90) for predicting renal functional outcome. Combining these parameters in a prediction table yielded RDI score ≥12 being associated with high odds risk (OR=11.2) of treatment failure.

Conclusion: RDI≥12 is associated with renal deterioration after appropriate treatment of bilateral obstructive urolithiasis.

Introduction

Kidney stones and chronic kidney disease (CKD) are common, affecting 5 and 13% of the adult population, respectively [1,2]. Management of urinary stone disease in patients with CKD is often difficult [3].

There are no tools at present that could explain the behavior of renal function after optimum treatment of obstructive nephrolithiasis in CKD patients. A crude method is of coarse prediction of long term renal function based on the presenting duration. Obstructive urolithiasis presentation as acute renal failure is likely to behave favorably than chronic renal failure. In both the scenarios, treatment of nephrolithiasis is likely to improve renal function. In patients with previously compromised renal function, this may be of temporary benefit in prolonging the ultimate requirement of renal replacement therapy (RRT) [4,5]. Some patients do not improve after the treatment of nephrolithiasis. They alternatively progress to CKD stage V rapidly [4,5,6,7]. Before embarking on an extensive stone removal, it is pertinent to preoperatively prognosticate the category of patients who are not going to improve after treatment.

In this context, a routine, economical but comprehensive method to predict renal functional outcome would be helpful to promote early awareness, patient counseling and better management of CKD among the obstructive urolithiasis population. Evidence from earlier published studies indicates that clinical factors are already present at time of initial clinical presentation [3,5-12]. Given the relative ease of measuring these risk factors, we attempted to develop a logistic regression model to establish their significance and then quantify in a scoring system to identify individuals at greatest risk for adverse renal functional outcome.

Design and Methods

Subjects The subjects were recruited from the hospital database in a prospective manner from Jan 2009 to July 2010. After the treatment, the patients were followed till July 2011 for disease progression assessment. The Ethics committee of the hospital approved this study. Inclusion criteria for the study was a patient presenting with altered renal function with bilateral obstructive renal or ureteric calculi prospectively followed up for at least 1 year after the treatment of the stone disease. Patients with acute renal failure, pediatric patients and solitary kidney with renal insufficiency were excluded.

Details on patient's age, sex, weight, co morbidity, presenting clinical features, and significant medical and surgical history were recorded. Since hypertension and diabetes are major risk criteria for development of CKD in general population, a note of these co morbidities and preexisting CKD was done. Laboratory evaluation included urine analysis and culture, basic hematology, and serum biochemistry. Proteinuria is a surrogate outcome in CKD and there appears to be sufficient evidence to recommend changes in proteinuria as a surrogate for kidney disease progression. We estimated proteinuria in this study by dipstick method. All patients were evaluated with plain X-ray and ultrasound (US) and or CT of the kidney, ureter, and bladder region. CT or US measured the maximum measurable cortical width in each kidney. The sum of cortical width of both kidneys constituted the combined cortical width. The general principle of care is as in our previous papers [13]. Specifically, all patients underwent stabilizing hemodialysis if required and percutaneous nephrostomy (PCN) placement in appropriate calyx. Our treatment strategy involves draining all hydronephrotic kidneys with PCN. The idea behind placing PCN in all patients was it being increasingly safe, being performed with increasing frequency in out patient basis, anticipated dwell time was shorter and that it may serve as a conduit for definitive ante grade treatment. The PCN tubes were placed strategically with careful planning, so that the matured tracts could be used for future PCNL or antegrade URS. Multiple nephrostomy tubes were placed if required for adequate drainage of all calyces. Urine obtained at the time of nephrostomy was sent for culture and sensitivity and treated with appropriate antibiotics. Nephrologist's help was obtained for correction of fluid overload, electrolyte imbalances, acidosis, and anemia. Appropriate temporary RRT was also be initiated if required.

There is no guideline determining the exact duration to wait till the nadir creatinine is achieved. To eliminate the element of acute renal obstruction as a cause of elevated creatinine, the patients with evidence of obstruction were drained with PCN for an adequate period till nadir serum creatinine (a minimum of two equal lowest values) was reached. Minimum 5 days of observation for the creatinine improvement was done. All patients achieving nadir creatinine below 1.5 mg% within 5 days were excluded from the prospective database to eliminate ARF as a cause of obstructive uropathy. GFR estimates at presentation and nadir before intervention (minimum 5 days of adequate deobstruction) was done by using the four-variable modification of diet in renal disease (MDRD) equation.

Subsequently, patients were treated with either percutaneous nephrolithotomy (PCNL) or ureteroscopy in stages until rendered stone free. Bilateral double J stent was placed prior to the discharge and removed at 1-month follow up. Complete clearance was defined as non-visualization of residual fragments in X-ray and ultrasonography at 1 month after the procedure. Patients were followed at 3 monthly interval till 1 year and then six monthly intervals. Selected patients with CKD received appropriate medical management. Treatment failure for the study was defined as the progression of the renal function to CKD stage V or requirement of RRT within 1 year of treatment.

Statistic analysis:

In the present study, all preoperative parameters were studied for the analysis. The relationship of pre-operative parameters and treatment failure was analyzed by univariate and multivariate logistic regression, with odds ratios (OR) and confidence intervals (CI) calculated for each variable. A forward stepwise multivariate logistic regression analysis was used to build a prediction table (renal deterioration index) for predicting the risk of renal deterioration. In order to evaluate the performance of the prediction table, the ROC curves of significant multivariate factors and RDI were generated, respectively, and their areas under ROC curve were compared with each other. Odds ratio for renal deterioration with different RDI scores were calculated. Analysis was performed using SPSS software version 15.0 (SPSS Inc. Chicago, IL). All P-values were 2-sided and a *p*-value of <0.05 was considered statistically significant.

Results Table 1 highlights the baseline clinical correlates and follow-up results. 48(28.7%) patients progressed to CKD stage V at 1-

year follow-up. Thirteen patients and three patients had clavien 3 and 4 complications, respectively. The complications were febrile UTI (6), bleeding requiring multiple bladder washes(1), bleeding requiring nephrostomy clamping(1), ureteric clot obstruction requiring double J stenting(1), prolonged urine leak(1), angio-embolization(2), septic shock syndrome(1) and frank sepsis(2).

Univariate analysis of risk factors and adverse outcome is as tabulated in table 2. Anemia, acidosis, cortical atrophy, positive urine culture, GFR at 5 days of deobstruction and proteinuria were associated with treatment failure at 1 year. Table 3 shows the results of the multiple logistic stepwise regression analysis for the subjects. Combined cortical width, proteinuria, positive urine culture and nadir GFR post bilateral PCN were the combined significant factors.

All the significant factors were then graded in increasing severity to provide a score to each variable (table 4). The sum of each variable provided RDI. For each patient, RDI ranged from 4 to 18. The sensitivity, specificity, positive and negative predictive value of RDI was compared with other individual significant factors by constructing ROC curves and calculating area under ROC curve. We performed ROC curves analysis for the regression model (figure 1). Areas under the ROC curves (AUC) of cortical width, nadir GFR, proteinuria, and urine culture and RDI were 0.85±0.04, 0.83±0.03, 0.74±0.04, 0.59±0.04 and 0.90, respectively. AUC for RDI was 0.9 indicating very high accuracy for the prediction table. Odds ratio table for various cut offs of RDI is as in table 5. The optimal threshold of RDI more than 12 was found in the regression model for high odds of treatment failure (Table 5).

Discussion

Most agree that stones in patients with CKD should be cleared. In patients with mild to moderate renal insufficiency, an aggressive approach is needed to render them stone free with an improved renal function [3,12]. In a cohort of 171 patients with severe idiopathic calcium stone disease, Marangella and associates reported on those patients with mild insufficiency and a mean GFR of 67 mL/min/ 1.73 m2 at referral, a significant decline occurred during a mean follow-up of nearly 3.5 years [15]. On the other hand, Worcester et al, reported that renal function determined by creatinine clearance decreases with age in stone formers at a higher rate than in non-stone-formers, and that patients with kidney stones do not have normal kidney function compared with healthy individuals [16]. Therefore, in clinical management, all efforts must be made to minimize renal injury while balancing the risks of obstruction from stones against those of urologic procedures.

PCNL and ureteroscopy are the primary endourological modality for treating CKD patients with urolithiasis; however, they are not without complications [17,18]. Hypothermia, bleeding, metabolic acidosis, disturbances in serum electrolytes, urosepsis, and even deaths are the main complications [9-13]. Despite technical advances, bleeding and urosepsis remain a major concern, even in patients with CKD who have sterile preoperative urine cultures [18]. Because of the inhibition of cell-mediated immunity and humoral defense mechanisms: septicemia can easily develop in patients with CKD. Agrawal et al, reported a mortality rate caused by sepsis of 3.8% among 78 patients with advanced uremia who were treated for urolithiasis [10]. Other authors have also reported higher overall complication rates in patients with CKD. Complex stones are associated with poorer results; necessitate longer operative time, multiple percutaneous tracts, and more ancillary procedures; and have a higher complication rate. The overall benefit of PCNL is evident, although the complication rate and mortality risk are high in these patients. Therefore, one may expect that aggressive treatment of such patients could prevent the need for RRT, or at least significantly delay it in most patients with renal stone. Complications are therefore acceptable in patients where the treatment defers RRT significantly. On the other hand, there are some patients with severe renal insufficiency, where inspite of the aggressive stone removal, due to complications or even otherwise, RRT cannot be significantly delayed. There are also other important decision making factors that need to be considered along with decision-making algorithm such as desire to eradicate urine infection by relieving obstruction/removing stone, and preservation of 'residual renal function' for easing water balance. However, RDI may be an important preoperative tool to prognosticate the ultimate outcome.

There have been some attempts to identify predictors of prognosis and treatment outcome in patients with CKD patients with urolithiasis. Kukreja et al reported proteinuria (>300 mg=day), atrophic cortex (<5 mm), recurrent urinary tract infection, stone bulk (>1500 mm2), and paediatric age group as predictors of adverse renal outcome [9]. Agarwal et al found parenchymal thickness of 7 mm, clear urine in the collecting system, no renal sepsis, and recent onset azotaemia as favorable predictors [10]. Associated hypertension and diabetes are aggravators of CKD [19]. In Kurien's study, majority of the patients were in CKD stages 3 and 4. Improved renal function after PCNL was seen in one third of the patients. Atrophic cortex and postoperative complications mainly infection and bleeding predicted renal deterioration [13]. Canes et al found the improvement in postoperative eGFR to be predictive of improvement of renal function[20].

Our goal was to develop a relatively simple preoperative approach allowing prediction of treatment outcome in patients with altered renal function in bilateral urolithiasis. The manuscript proposes to calculate RDI score in every patient presenting with chronic obstructive uropathy secondary to urolithiasis. We concentrate on four factors to determine the RDI score. CT or US measures the maximum measurable cortical width of each kidney. The sum of cortical width (in millimeters) of both kidneys constitutes the combined cortical width. Urine analysis determines proteinuria by dipstick method. Urine culture is estimated as either positive or negative. GFR estimates at nadir before intervention (minimum 5 days of adequate deobstruction) is done by using the four-variable modification of diet in renal disease (MDRD) equation. All these parameters are then fed into table 4 to calculate RDI score. The RDI score ranges from a minimum 4 to a maximum 18. RDI≥12 is associated with high odds of renal deterioration after appropriate treatment of bilateral obstructive urolithiasis. It can also be used to inform patients about their level of absolute risk to help them make an informed choice regarding the need for further intervention or not. Early identification of treatment failure may lead to more conservative intervention and early initiation of RRT. We studied all the factors that were predicted by other authors to affect the renal functional outcome. We found in our multivariate logistic regression analysis, that four factors were combinedly associated with functional outcome. Our study data showed that the treatment failure was relatively high in patients with reduced combined cortical width, proteinuria, low deobstruction GFR value and positive culture. This is consistent with the results from previous studies. We constructed an easily measurable score (RDI) of the four relevant factors in a prediction table. Compared to the individual multi variate risk factors, RDI represented a good predicting test (AUC= 0.90), and a useful aid for predicting adverse outcome. The prediction table represented the optimal combination of sensitivity and specificity at the optimal threshold.

The present regression model has some attractive features when compared with traditional anticipating tool. Our regression model is based on routinely available preoperative data; therefore, the model can be easily applied in clinical practices. We feel that the most important factor predicting renal recovery is the duration of obstruction. This variable was not included in the study since the actual duration of the obstruction cannot be predicted in most of the patients. However, it is more common for the short duration of obstruction being evident as acute renal failure. Those patients whose creatinine dropped down to nadir less than 1.5 mg% were excluded from the analysis. This ensured that patients had longer duration of obstruction.

Conclusion

There are no tools at present that could explain the behavior of renal function after optimum treatment of obstructive nephrolithiasis. Before embarking on an extensive stone removal, it is pertinent to preoperatively prognosticate the category of patients who are not going to improve after treatment. Our study data showed that the treatment failure was statistically high in patients with reduced combined cortical width, proteinuria, and low deobstruction GFR value at 5th day and positive culture. We constructed an easily measurable score (RDI) of the four relevant factors in a prediction table. Compared to the individual multi variate risk factors, RDI represented a good predicting test (AUC= 0.90), and a useful aid for predicting adverse outcome. RDI≥12 is associated with renal deterioration after appropriate treatment of bilateral obstructive urolithiasis.

Conflict of interest

The authors declare no conflict of interest.

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Abbreviations

CKD - chronic kidney disease

eGFR - estimated glomerular filtration rate

MDRD - modification of diet in renal disease

PCN - percutaneous nephrostomy

PCNL- percutaneous nephrolithotomy

URS - ureteroscopy

RRT- renal replacement therapy

RDI – renal deterioration index

ROC – receiver operative curve

AUC – area under curve

OR - odds ratios

CI - confidence intervals

USG – ultrasound

DJ- double j stent

Table 1: Patient characteristics, demography, clinical presentation, Intra and post operative parameters and outcome.

Patients (n)	169
Age; years (mean ± S.D)	48.06±14.09
Sex (Male/Female)	133/36
Serum creatinine at presentation;mg%(mean ± S.D)	7.26±4.42
Preoperative GFR (mL/min/1.73 m2)	13.9 ± 11.5
Number of calculi units	338
Renal units	
Partial staghorn	44
Compete staghorn	50
Other renal calculi	76
Ureteric units	168
Hemoglobin at presentation;gm%(mean ± S.D)	10.47±4.21
Serum bicarbonate at presentation;meq/L(mean ± S.D)	17.95±5.96
Combined cortical width;mm(mean ± S.D)	23.04±8.52
Proteinuria (urine dipstick method)	
0	64
1	69
>1	36
Positive pre-operative urine culture (n%)	20.4%
Comorbidity(hypertension, diabetes, CKD)	
0	103
1	49
2	15

3	2
Stablizing temporary pre PCN Dialysis (n%)	23.3%
CKD stage at presentation	
Stage 3	22
Stage 4	33
Stage 5	114
Serum creatinine at 5 days of deobstruction;mg%(mean ± S.D)	3.35±2.16
Endourological management in units	338
PCNL- Single tract	142
PCNL- Multiple tract	32
URS	124
Mean Operative time (Minutes)	
PCNL	62±34
URS	41±22
Peri-operative complication	
Clavien 1	30
Clavien 2	18
Clavien 3	13
Clavien 4	3
Clavien 5	0
Blood transfusion (n)	
PCNL (Preoperative)	20
PCNL (Preoperative)	8
URS (Preoperative)	6

URS (Preoperative)	1
Serum creatinine at 1 year ;mg%(mean ± S.D)	3.43±3.18
Treatment failure	49
GFR <15ml/min	11
MHD	38

Table 2: Univariate analysis of the preoperative parameters determining the outcome.

Variable	**Odd ratio**	**95% Confidence Interval**	**P value**
Age	0.9983	0.9749 - 1.0222	0.8877
Serum bicarbonate at presentation	0.9350	0.8803 – 0.9930	0.0242
Hemoglobin at presentation	0.7138	0.6094 – 0.8362	<0.0001
Combined cortical width	0.8143	0.7591 – 0.8734	<0.0001
Comorbidity	1.2417	0.7820 – 1.9716	0.3626
Proteinuria	2.8165	1.7943 -4.4209	<0.0001
GFR at 5 days of deobstruction	1.8348	1.4844 – 2.2680	<0.0001
Urine culture	2.7205	1.2475 – 5.9331	0.0127
GFR at presentation	1.0681	1.2475 – 5.9331	0.0811
Renal or ureteric stone	1.7157	1.1074-2.6581	0.0139

Uni-variate analysis of the preoperative parameters determining the outcome.

Table 3: Multivariate preoperative significant parameters affecting the outcome.

Variable	**Coefficient**	**Std Error**	**Odd ratio**	**95% Confidence Interval**	**P value**
Combined cortical width	-0.1764	0.0403	0.84	0.77 -0.90	<0.0001
Nadir GFR after adequate deobstruction	0.3167	0.1320	1.37	1.06 -1.78	0.016
Proteinuria	0.7261	0.2807	2.07	1.19 -3.58	0.010
Urine culture	1.6019	0.5518	4.96	1.68 -14.63	0.004
Constant	0.5182	-	0.00		<0.0001

Multivariate preoperative significant parameters affecting the outcome.

Table 4: Renal deterioration index scoring system.

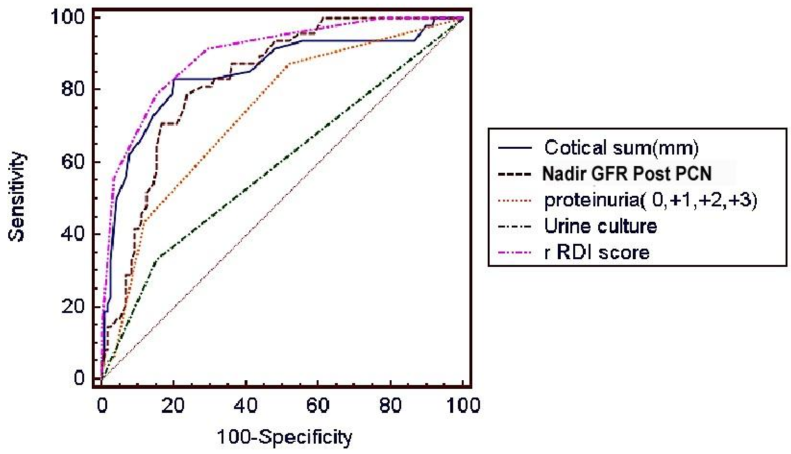
Score	**1**	**3**	**5**
Combined cortical width (mm)	>20	10-20	<10
GFR at 5th day(ml/min)	>60	30-60	<30
Proteinuria (dipstick method)	0	+1	>+1
Urine Culture	negative	positive	

Renal deterioration index scoring system.

Table 5: Odds ratio table for various cut offs of RDI.

RDI	Success	Failure	Odds ratio
<6	57	2	0.079
7-8	28	2	0.16
9-10	17	6	0.79
11-12	14	11	1.76
13-14	4	20	11.22
>14	0	8	37.95
Total	120	49	

Odds ratio table for various cut offs of RDI.



ROC curve analysis for regression model