Original Article

Cystatin C for early detection of acute kidney injury after laparoscopic partial nephrectomy

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Abstract

Introduction and Objectives: Mortality due to AKI has not changed significantly over the past 50 years. This is due in part to failure to detect early AKI and to initiate appropriate therapeutic measures. There is therefore a need to identify biomarkers that would improve the early detection of AKI. The objective of this study was to assess whether cystatin C levels obtained at specific timepoints during laparoscopic partial nephrectomy (PN) could be early predictors of AKI.

Materials and Methods: Twenty-five patients underwent laparoscopic PN for organ-confined tumors. All procedures were performed by two surgeons in a single institution. Plasma samples were collected preoperatively, and post-unclamping at 5, 20, 120 min and on the day following surgery. Plasma cystatin C was measured by enzyme-linked immunosorbent assay. Correlation between levels of cystatin C and other parameters of interest were assessed in order to define cystatin C ability to predict AKI and loss of renal function following laparoscopic PN.

Results: The mean baseline eGFR was 93 ml/min/1.73 m^2. Warm ischemia time varied between 16 and 44 min. Post-operative day 1 (POD1) cystatin C levels compared to baseline were increased in 13 (52%) of the patients. There was a high correlation between the difference of POD 1 and baseline value, and eGFR in the immediate postoperative period ($r = -0.681$; $P = 0.0002$) and at 12-month follow-up ($r = -0.460$, $P = 0.048$). However, the variation in cystatin C levels at earlier timepoints were not associated to AKI nor renal function.

Conclusions: High increase in POD 1 cystatin C levels from baseline may help identify patients with AKI and those at higher risk of chronic kidney disease, following laparoscopic PN.

Key Words: Cystatin c, laparoscopy, partial nephrectomy, renal function, warm ischemia

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INTRODUCTION

Incidental small renal masses (SRM) are frequently described on imaging studies. Consequently, they represent 48-66% of all renal tumors diagnosed and 38% of all renal tumors excised.[1] Partial nephrectomy (PN) is now established as the standard of care for the management of SRM because of its equivalent oncological outcomes[2] and superior renal function preservation[3] relative to radical nephrectomy. The evolution of minimally invasive surgery has led laparoscopic PN to be accepted as a surgical option. Although this technique is still considered challenging, this approach has become the first choice for the treatment of selected renal tumors in centers with high laparoscopic expertise.[4-6] To perform an optimal surgery, it is essential to operate in a bloodless field. This can be obtained by temporary occlusion of the renal artery

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or of the entire renal pedicle. However, the subsequent renal ischemia-reperfusion insult can cause acute impairment of renal function (acute kidney injury, AKI) and predispose to chronic kidney disease (CKD).[7]

It is usually accepted that limiting renal warm ischemia time within a range of 20-25 min is safe.[7-10] For instance, Godoy and colleagues reported that ischemia time <40 min is safe in patients with normal contralateral kidney.[11] A recent retrospective study of 362 patients with solitary kidneys who underwent partial nephrectomy with utilization of warm ischemia suggested that each minute of warm ischemia time was associated with a 6% (hazard ratio 1.06; $P < 0.001$) greater risk of acute renal failure and 4% (hazard ratio 1.04; $P = 0.03$) greater risk of stage IV CKD during follow-up. Furthermore, the authors evaluated cut-points of warm ischemia and reported that 25 min of warm ischemia was the best cut-point to distinguish between patients who did and did not develop short and long-term renal functional consequences.[8,9] In a different cohort of patients with bilateral functioning kidneys, Pouliot and colleagues.[10] demonstrated similar short-term results, with accelerated loss of function occurring when warm ischemia was beyond 30 min. However, it is important to acknowledge that our current understanding of renal ischemia is derived from animal studies and retrospective clinical studies in PN and renal transplantation populations, showing conflicting data regarding the tolerance of human kidney to an ischemic insult.[8,12-16] Thus, uncertainty remains with regard to our capacity to predict the consequences of a given ischemic insult following PN on kidney function.

New biomarkers of renal injury are receiving increasing attention in an effort to achieve earlier diagnosis of AKI than provided by serum creatinine. These biomarkers can potentially better assess the extent and severity of parenchymal insults from different causes and serve as markers of interest during clinical trials.[17-23] To the best of our knowledge, their usefulness in PN as not been widely studied. Consequently, this study was designed to assess whether plasma cystatin C levels obtained at specific timepoints in the first 24 h following renal hilum unclamping could be early predictor of AKI and if so, to see whether we can predict longer term functional outcomes following laparoscopic PN.

MATERIALS AND METHODS

Population description and study design

The Institutional Review Board at the *Centre Hospitalier Universitaire de Québec* has approved this research protocol and a written informed consent was obtained from each patient enrolled. Twenty-five consecutive patients with a renal tumor amenable to PN were recruited to participate to this study. We reviewed medical charts, including patient characteristics, tumor factors, intraoperative features and postoperative functional outcomes. Clinical data were collected in a protected database.

Preoperative planning and surgical procedure

Preoperative work-up included a chest X-ray, abdominal and pelvis computed tomography scan, nuclear renogram (split function) and biochemistry tests that included renal function assessment [serum creatinine (sCr) and estimated glomerular filtration rate (eGFR)]. The R.E.N.A.L. nephrometry score[24] was calculated for each patient using findings from the CT-scan. Patients underwent laparoscopic PN for organ-confined tumors. All procedures were performed by two surgeons, in a single institution. Transperitoneal or retroperitoneal approaches were selected according to tumor location and surgeon preferences. Hilar arterial clamping was achieved either *en bloc* by using a laparoscopic Satinsky clamp or by clamping the artery alone with a laparoscopic bulldog clamp.

Follow-up

During the follow-up, renal function biochemistry (sCr and eGFR) was evaluated postoperatively and reported on for day 2 (POD2, postoperative day 2) and 12-month periods. The renal split function on nuclear renogram was unfortunately not obtained systematically for all patients during follow-up because of radioisotopes shortage in our hospital. Being available only for a small number of patients, this information has not been included in the present analysis.

Biochemical measurements

Blood samples were collected preoperatively, 5 min before clamping, and post-unclamping at 5, 20, 120 min and on the day following surgery (POD1, postoperative day 1). These timepoints were chosen based on the marker kinetic reported in another publication[25] showing a rise in plasma cystatin C at 2 h and 24 h following an ischemic event. Earlier timepoints were also included in order to explore the kinetic of cystatin C rise in plasma following the ischemic insult related to PN. Collected samples were kept on ice until centrifugation (within 2 h). Plasma was separated by centrifugation (2500 × *g* for 10 min at 4°C), and samples aliquoted. All collected samples were stored at −80°C until analysis. Plasma creatinine was measured by enzymatic assay (Crea Plus, Roche Inc.) in the hospital core lab. Plasma Cystatin C was measured in *duplicata* by enzyme-linked immunosorbent assay (BioVendor Inc., North Carolina, USA) by our team according to the manufacturer's instructions.

Definitions

There are no accepted criteria to define the occurrence of an ischemic acute kidney injury (AKI) following PN. Thus, general definitions of AKI based on the Acute Kidney Injury Network classification (AKIN)[26] and Risk,

Injury, Failure, Loss and End-stage kidney disease (RIFLE) criteria[27] were used to identify patients who experienced significant AKI following their PN surgery. The criteria of these two classifications are summarized in Table 1. The global renal function was reported as eGFR, calculated with the abbreviated Modification of Diet in Renal Disease (aMDRD) formula, where eGFR = 32788 × serum creatinine$^{-1.154}$ × age$^{-0.203}$× (1.203 if black) × (0.742 if female).[28] CKD was reported as per KDOQI stages of kidney disease.[28] Plasma cystatin C concentration was measured in *duplicata* and reported as mean and standard deviation (SD). The surgical complexity of renal masses was scored according to the R.E.N.A.L nephrometry score,[24] defining low (score of 4-6), intermediate (score of 7-9) and high risk (score of 10-12) tumor category. The American Society of Anaesthesiologists physical status classification (ASA) was used as an indicator of patient's health status[29] where ASA Physical Status 1 represents a normal healthy patient, ASA Physical Status 2 a patient with mild systemic disease, ASA Physical Status 3 a patient with severe systemic disease, ASA Physical Status 4a patient with severe systemic disease that is a constant threat to life andASA Physical Status 5, a moribund patient.

Statistical analysis

Continuous variables are presented as a mean with SD, while discrete variables are expressed in percent. Biomarker concentration variations from preoperative baseline at different time intervals post-unclamping (5 min, 20 min, 2 h, POD1) were calculated. Linear correlation between variations of cystatin C level from baseline (at 5 min, 20 min, 2 h and POD1) and other important parameters [age, body mass index (BMI), tumor size, R.E.N.A.L. score, warm ischemia time (WIT) and eGFR at POD2 and at 12 months] were performed using a Pearson's correlation analysis. All time intervals (5 min, 20 min, 2 h, POD1) were analyzed but only statistically significant results were considered and presented herein. Factors potentially influencing variations of cystatin C levels were also assessed in univariate analysis. Multivariate analysis was not considered in the context of our small cohort of patients. Continuous variables were compared using the Mann–Withney U test. Qualitative variables were compared by Fisher's or Chi-square test, as appropriate. Statistical analyses were performed using Prism software (GraphPad, San Diego, USA).

RESULTS

Demographics are listed in Table 2. A total of 25 patients were enrolled (13 males, 12 females), with a mean age of 61 years. The mean BMI was 29.6 kg/m^2. Among our cohort of patients, 48% were treated for hypertension and 24% for diabetes. The ASA score was above 2 in 16% of patients. The mean baseline sCr and eGFR before surgery were 76 μmol/l and 93 ml/min/1.73 m^2, respectively. The preoperative mild (stage II) and moderate (stage III) CKD rates were 40% and 4%, respectively.

Table 2: Study population preoperative characteristics

No. patients	25
Gender	
Male	13 (52)
Female	12 (48)
Age (years)	61±13
BMI (kg/m^2)	29.6±5.4
Hypertension	12 (48)
Diabetes	6 (24)
Baseline sCr (μmol/L)	76±28
ASA	
1	4 (16)
2	17 (68)
3	4 (16)
Baseline eGFR (ml/min/1.73 m^2)	93±25
eGFR>90	14 (56)
eGFR 60-90	10 (40)
eGFR 30-60	1 (4)

Continuous variables are expressed as mean±standard deviation, discrete variable are expressed as number (%), BMI: Body mass index, ASA: American Society of Anesthesiologists score, sCr: Serum creatinine, eGFR: Estimated glomerular filtration rate

Table 1: RIFLE and AKIN criteria for the diagnosis of AKI

Risk, Injury, Failure, Loss, and End-Stage Kidney Disease (RIFLE) Criteria Class	GFR Criteria	Urine Output Criteria
Risk	Serum creatinine × 1.5	<0.5 ml/kg/h × 6 h
Injury	Serum creatinine × 2	<0.5 ml/kg/h × 12 h
Failure	Serum creatinine × 3, or serum creatinine ≥4 mg/dL with an acute rise >0.5 mg/dL	<0.3 ml/kg/h × 24 h, or anuria × 12 h
Loss	Persistent acute renal failure = complete loss of kidney function >4 wks	
ESKD	End-stage kidney disease >3 mo	

Acute Kidney Injury Network (AKIN) Classification Stage	Serum Creatinine Criteria	Urine Output Criteria
1	Increase in serum creatinine ≥ 0.3 mg/dL or increase to ≥150%-200% (≥1.5- to 2-fold) from baseline	<0.5 ml/kg/h × 6 h
2	Increase in serum creatinine to >200%-300% (>2- to 3-fold) from baseline	<0.5 ml/kg/h × 12 h
3	Increase in serum creatinine to >300% (>3-fold) from baseline (or serum creatinine of ≥4.0 mg/dL with an acute increase of at least 0.5 mg/dL)	<0.3 ml/kg/h × 24 h or anuria × 12 h

The tumors characteristics on preoperative imaging are shown in Table 3. The mean tumor size was 31 mm. The mean R.E.N.A.L. nephrometry score was 7. Overall, 48 and 12% of tumors were classified as moderately or highly complex masses, respectively. The mean operative time was 188 minutes. Mean estimated blood loss was 195 ml. Hilar control was achieved *en bloc* in 72% of the cases. Clamping time (or WIT) varied between 16 to 44 min for a mean of 27 min. 76% of patients had a malignant tumor with a predominant clear cell subtype histology.

Table 3: Tumor characteristics and peroperative outcomes

Tumor size (mm)	31±17
□4 cm	17 (68)
>4 cm	8 (32)
R.E.N.A.L. score	7.0±1.9
Low (4-6)	10 (40)
Intermediate (7-9)	12 (48)
High (10-12)	3 (12)
Radius parameter	1.3±0.5
1	17 (68)
2	8 (32)
3	0 (0)
Exophytic parameter	1.9±0.7
1	7 (28)
2	13 (52)
3	5 (20)
Nearness parameter	1.8±0.8
1	10 (40)
2	9 (36)
3	6 (24)
Anterior parameter	
a	8 (32)
p	7 (28)
x	10 (40)
Location parameter	1.9±0.8
1	9 (36)
2	9 (36)
3	7 (28)
Clamping technique	
Artery alone	7 (28)
Hilum en bloc	18 (72)
Operative time (min)	188±45
Estimated blood loss (ml)	195±186
Clamping time (min)	27±7
Histology	
Clear cell	15 (60)
Papillary	4 (16)
Benign	6 (24)

Continuous variables are expressed as mean±standard deviation, discrete variable are expressed as number (%)

Table 4: Postoperative renal function after laparoscopic partial nephrectomy

AKI	
AKIN classification[26]	4 (16)
RIFLE classification[27]	4 (16)
POD_2 renal function	
sCr (μmol/L)	87±44
eGFR (ml/min)	85±28
Absolute change in eGFR from baseline (ml/min)	−8±13
Relative change in eGFR from baseline (%)	−10±15
12-month renal function	
sCr (μmol/L)	89±48
eGFR (ml/min)	86±26
Absolute change in eGFR from baseline (ml/min)	−10±23
Relative change in eGFR from baseline (%)	−12±26

Continuous variables are expressed as mean±standard deviation, discrete variable are expressed as number (%), AKI: Acute kidney injury, AKIN: Acute kidney injury network, RIFLE: Risk, injury, failure, loss and end-stage kidney disease criteria, POD: Postoperative day; sCr: Serum creatinine, eGFR: Etimated glomerular filtration rate

The functional results are presented in Table 4. Post-operatively, 4 of the 25 patients had a 1.5 to 1.9-fold increase in serum creatinine from baseline and were identified with AKI (stage I according to the AKIN classification and risk category of injury according to RIFLE criteria). On POD2, the mean sCr and eGFR were 87 μmol/l and 85 ml/min/1.73 m^2, respectively. With regard to eGFR, the mean relative change from baseline was a reduction of 10%. At 12-month, the kidney function was similar to postoperative values with a mean sCr and eGFR of 89 μmol/l and 86 ml/min/1.73 m^2, respectively, representing a reduction of 12% in eGFR compared to baseline. In Figure 1, we can visually appreciate the difference in cystatin C elevation following the ischemic insult in patients that suffered AKI as compared to the rest of the cohort. Moreover, the kinetic of cystatin C concentration revealed a biphasic course with a first peak of elevation at 5 min and another at 24 h. For this reason, we have performed correlation and univariate analysis between the cystatin C variation at 5 min, 2 h and POD1 and other variables of interest. Despite cystatin C levels were increased from baseline in 12 (48%) patients early after unclamping (5 min and 2 h), none of the variables presented in Table 5 were correlated to cystatin C variation for these timepoints (data not shown). However, cystatin C variation at 24 h (POD1) showed interesting results. For these reasons the following observations will only applied to this timepoint.

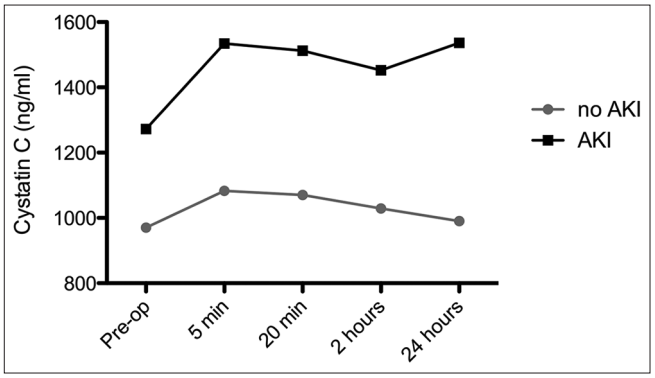

Figure 1: Post-unclamping kinetic of plasmatic cystatin C according to the presence or absence of Acute Kidney Injury (AKI). In patients suffering from AKI post-unclamping following laparoscopic partial nephrectomy, plasmatic cystatin C has reached higher values compared to patients without AKI (Mann–Whitney test, $P = 0.008$). The biomarker kinetic has shown a biphasic elevation pattern at 5 min and 24 h post-unclamping

Table 5: Factors associated with cystatin C variation at POD1 versus baseline: Linear regression and univariate analyses

Linear regression analysis	Δ cystatin C (continuous variable, ng/ml)		Δ cystatin C>100 ng/ml (qualitative variable)		
	Pearson's coefficient (r)	*P* value			
Age	0.162	0.450			
Tumor size	0.387	0.061			
R.E.N.A.L. score	0.038	0.860			
BMI	−0.068	0.754			
WIT	0.055	0.800			
Change in POD2 eGFR	−0.681	0.0002			
Change in 12-month eGFR	−0.460	0.048			
Univariable analysis	**Mann-whitney U test**		**Fisher's exact test**		
	Δ Cystatin C mean	***P* value**	**OR**	**95% CI**	***P* value**
Age (years)					
<60	46.5	0.751	Ref 1		
□60	97.0		1.68	0.32-8.76	0.684
Tumor size (cm)					
□4	−10.2	0.006	Ref 1		
>4	235.7		5.83	0.98-34.6	0.095
R.E.N.A.L. score					
Low	67.3	0.663	Ref 1		
Intermediate	95.6		1.50	0.56-8.19	0.691
High	78.2		1.27	0.43-7.39	1.000
BMI (kg/m²)					
<30	90.0	0.371	Ref 1		
□30	53.6		0.52	0.10-2.66	0.682
WIT (min)					
<25	63.6	0.908	Ref 1		
□25	78.7		0.75	0.15-3.83	1.000
AKI					
No	19.8	0.007	Ref 1		
Yes	435.9		14.3	0.68-300.1	0.039
Change in POD2 eGFR (from baseline) (%)					
<10	−47.0	0.005	Ref 1		
□10	190.5		15.0	2.02-111.2	0.012
Change in 12-month eGFR (from baseline) (%)					
<10	−20.5	0.01	Ref 1		
□10	180.4		14.0	1.54-127.3	0.023

POD: Postoperative day, Δ: Variation, BMI: Body mass index, WIT: Warm ischemia time, eGFR: Estimated glomerular filtration rate, AKI: Acute kidney injury as defined by AKNI/RIFLE classification, OR: Odds ratio, R.E.N.A.L.: Nephrometry scoring system for renal masses

The linear correlation and univariate analyses involving the variation of cystatin C at POD1 are summarized in Table 5. POD1 cystatin C levels compared to baseline were increased in 52% of the patients. There was a high correlation between POD1 cystatin C variation and eGFR in early postoperative period (POD2) ($r = -0.681$; $P = 0.0002$). Interestingly, the variation of POD1 cystatin C was also significantly correlated with longer term 12-month eGFR ($r = -0.460$, $P = 0.048$). None of the other variables considered in our analyses has demonstrated a significant correlation with POD1 cystatin C. In univariate analysis, similar findings were observed. When POD1 cystatin C variation was considered as a continuous parameter, a significant relationship was observed with either the occurrence of AKI and the loss of eGFR >10% (at both POD2 and 12-month intervals). Also, tumor size above 4 cm was significantly associated with higher level of cystatin C at POD1, potentially reflecting the impact of a more complex surgery on kidney damage, but not captured by other parameters such as R.E.N.A.L. score or WIT. Finally, if cystatin C was dichotomized for an increase of ≥100 or <100 ng/ml at POD1, results were similar. Taking together, these results confirmed the interest for cystatin C in predicting functional outcomes (the occurrence of AKI, loss of renal function early after the surgery and at 12-month) following a laparoscopic PN.

DISCUSSION

Several articles documented that prolonged renal ischemia lead to AKI, which may cause high morbidity and mortality.[30-32] In a population-based study of more than one million adults, Go *et al*.[33] demonstrated that longitudinal eGFR was inversely associated with higher rates of hospitalization, cardiovascular events (*i.e.*, acute myocardial infarction, heart failure, or stroke), and death from any cause. More specifically, patients with CKD stage III, IV, and V carried higher adjusted hazard ratios for death from any cause compared to those patients with stages I or II CKD. As a result, the initial conceptual framework behind the evolving surgical approach was that PN would lead to better renal function, which would then confer a better overall survival. Therefore, in this clinical context, identifying biomarkers that improve the early detection of AKI is important in order to identify patients at higher risk of bad outcomes such as CKD, after a PN.

Cystatin C is an interesting biomarker candidate. It is a protease inhibitor that is expressed by all nucleated cells and excreted solely by the kidney, independent of muscle catabolism. Cystatin C plasmatic concentrations may be more accurate than creatinine for estimating glomerular filtration rate in patients with diabetes or significant muscle wasting.[34,35] Furthermore, unlike creatinine, Cystatin C has some favorable characteristics. First of all, its production is a stable process that is not influencedby the constitution of the body or dietetic

factors. Creatinine levels are known to be strongly influenced by many non-renal factors such as protein intake, dehydration, gastrointestinal bleeding, infection or steroid use and muscle breakdown. Moreover, cystatin C biochemical characteristics allow free filtration in the renal glomerulus, and subsequent reabsorption and total catabolism by proximal tubules without re-entering the blood stream.[36,37] It has shown its advantages in detecting acute renal injury earlier and in a more sensitive manner than creatinine in several randomized studies.[38-40]

Cystatin C has also shown great clinical potential as a biomarker of AKI. For instance, in a study of 85 critically ill patients at risk of developing AKI, increases in serum cystatin C were shown to predict AKI 1-2 days before serum creatinine increased.[41] Similarly, in a prospective study of 72 adult cardiac surgery patients, elevations in urinary cystatin C levels 6 h after ICU admission were also significant predictors of AKI.[39]In addition, the urine cystatin C/urine creatinine ratio after surgery or in the ICU setting was significantly higher for patients with AKI who required renal replacement therapy (RRT) compared with those with AKI and no short-term need for RRT. Another study also confirmed that measurements of urinary cystatin C were able to predict the need for RRT in patients with established AKI at least one day earlier than conventional measurements.[38]A variety of other studies have also established cystatin C as a promising early marker of AKI.[39,40] Indeed, cystatin C has shown great clinical potential as a biomarker of AKI. However, to the best of our knowledge, there is no data available in the specific renal surgery setting of PN, where the ischemic insult is directly applied to the kidney.

The objective of this study was to assess whether plasma cystatin C levels obtained at specific timepoints during laparoscopic PN could be early predictors of AKI. We have demonstrated that cystatin C is rising early after unclamping. However, according to our study, the early variations of the biomarker at 5, 20 min and 2 h did not show correlation with any renal function parameters. Only the variation at POD1 was predictive of renal outcomes. Indeed, our results have demonstrated a high correlation between the cystatin C variation at POD1 and the occurrence of AKI (by using either AKIN or RIFFLE classification) and early loss of eGFR, following PN. To a wider extent, the correlation observed between the variation of cystatin C at POD1 and the loss of eGFR at 12-month was also strong, showing the ability of this biomarker to predict the future of renal function following PN. Interestingly, WIT and R.E.N.A.L. score were not associated with cystatin C biomarker variation at any timepoints. Thus, our data show that cystatin C can predict AKI earlier than creatinine but maybe more interesting, the evolution at 1 year follow-up. To the best of our knowledge this has not been reported or studied elsewhere.

This study has shown limitations that need to be discussed. Despite the interesting results obtained, the small number of patients enrolled in this study has unfortunately limited the strength of our observations. Moreover, it would have been very interesting to correlate the biomarker variation with the split function changes of the affected kidney over time, as a direct functional measure of the operated renal unit. These preliminary results are encouraging regarding the future of cystatin C as a biomarker of AKI and renal function in PN. However, larger studies will be necessary to confirm our findings in order to spread its utilization in urology.

CONCLUSIONS

High variation in cystatin C levels at POD1 may help identify patients with AKI and those at higher risk of CKD following laparoscopic PN. However, earlier intraoperative cystatin C levels do not seem to be indicators of AKI. A larger cohort of laparoscopic PN-treated patients will be needed to better assess the predictive potential of cystatin C.

CONSENT

Written informed consent was obtained from the patients for the publication of this study and accompanying results. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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