Association of rise in C-reactive protein with decline in renal function following partial nephrectomy

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Introduction: *To investigate association of C-reactive protein (CRP), a marker of systemic inflammation, with renal functional decline patients undergoing partial nephrectomy (PN) for renal mass.*

Materials and methods: *Retrospective study of patients who underwent PN between February2006-March 2011, with ≥ 6 months follow up. Data was analyzed between two groups: CRP increase ≥ 0.5 mg/L from 6 months postoperative ("CRP rise," CRPR), versus no CRP increase ≥ 0.5 ("CRP stable," CRPS). Primary outcome was change in estimated glomerular filtration rate (ΔeGFR, mL/min/1.73 m²), with de novo postoperative stage III chronic kidney disease (stage III-CKD, eGFR < 60 mL/min/1.73 m²) being secondary. Multivariable analysis (MVA) was conducted to identify risk factors for development of de novo stage III-CKD.*

Results: *A total of 243 patients (206 CRPS/37 CRPR) were analyzed. Demographics and R.E.N.A.L. nephrometry scores were similar. CRPR had significantly higher median ΔeGFR (-13.7 versus -32.0 mL/min/1.73 m², p < 0.001) and de novo stage III-CKD at last follow up (43.2% vs. 3.7%, p < 0.001). Median time to CRP rise was 10 (IQR 6.5-12) months. Median time from CRP rise to de novo stage III-CKD was 9 (IQR 7.5-11) months. MVA found RENAL score (OR 1.89, p = 0.001), hypertension (OR 4.75, p = 0.016), and CRP rise (OR 55.76, p < 0.001) were associated with de novo stage III-CKD. Sensitivity of CRP increase ≥ 0.5 for predicting CKD was 69.6%, specificity 93.3%, positive predictive value 55.2%, and negative predictive value 96.3%.*

Conclusion: *Rise in CRP postoperatively is independently associated with renal functional decline after PN and may be useful in identifying patients to evaluate for renoprotective strategies. Further studies are requisite to clarify etiology of this association.*

Key Words: carcinoma, renal cell, chronic kidney disease, C-reactive protein, glomerular filtration rate, nephron sparing surgery, partial nephrectomy

Introduction

Incidence of localized renal cell carcinoma is increasing.[1] Despite this, in the United States, an estimated 61,560 new diagnoses of renal malignancy and a continued rise in deaths at 14,080 deaths are expected to occur 2015.[2] Recognition of equivalent oncological outcomes between partial and radical nephrectomy,[3] in addition to the detrimental impact of chronic kidney disease (CKD) on overall health,[4-9] has increased scrutiny of surgical removal of significant amounts of functional nephron mass in the context of treatment for small renal cortical neoplasms.[10] These findings have prompted a paradigm shift, with partial nephrectomy (PN) becoming the reference standard for surgical treatment of clinical t1a renal masses.[11,12]

While association of CKD and metabolic and cardiovascular sequelae from renal surgery has been

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well documented.[5-9,13] A significant proportion of patients undergoing nephron sparing surgery may nonetheless still progress to CKD.[5,13] Recognizing that renal functional decline following PN is a multifactorial process nonetheless begs the question–can we identify risk factors or markers which may be associated renal functional decline even if renal function appears normal, so that strategies to delay progression of renal disease and the development of associated comorbidities are utilized or investigated? C reactive protein (CRP) is a marker of systemic inflammation, associated with declining renal function and cardiovascular disease in patients without pre-existing CKD, as well as a marker for mortality/prognosis after nephrectomy for RCC.[14-16] We sought to investigate the association of CRP and renal functional decline in patients who have undergone open PN for renal cortical neoplasms.

Materials and methods

Study population

Two-center (University of California San Diego Medical Center and the University of Tennessee Health Science Center, Memphis), Institutional Review Board approved, retrospective cohort analysis of patients who underwent open PN for renal masses and had CRP (mg/L) data available, between February 2006 and March 2011. Adult (age ≥ 18 years) patients diagnosed and treated for renal cortical masses were reviewed. Patients were offered open PN for elective and imperative indications (chronic renal insufficiency, bilateral tumors). Tumor resectability was determined by surgeon discretion based on preoperative imaging and intraoperative examination. Patients with urothelial tumors (n = 4), solitary kidney (n = 43), or who developed metastatic or recurrent disease (n = 26), as well as those with incomplete records, or follow up < 6 months (n = 24) were excluded. One surgeon performed surgeries at both institutions during the time interval of the study.

Surgical approach

Our technique has been described previously.[17] Initial surgical approach consisted of an extraperitoneal flank or subcostal transperitoneal incision, kidney mobilization, renal hilar dissection, and control, followed by tumor isolation. Tumors for which anticipated ischemia time was > 30 minutes underwent cold ischemia with ice slush, otherwise clamped OPN was then performed by sharp excision of the tumor and a surrounding margin of normal renal tissue after occlusion of the renal artery and vein with bulldog clamps or a Satinsky clamp. Absorbable sutured renorrhaphy with pinpoint collecting system and blood vessel closure was followed by parenchymal closure. Clampless OPN recapitulated the steps of clamped OPN, with clampless conditions facilitated by manual compression, radiofrequency biopolar device (Habib 4x, Angiodynamics, Queensbury, NY, USA), or hydrojet dissection (ERBEJET, ERBE, Marietta, GA, USA), followed by cold excision and renorrhaphy.

Data collection

Demographic, clinical, pathological, and cross sectional imaging characteristics were reviewed for all identified patients. The American Joint Committee on Cancer 2010 TNM classification was used to assign the renal cell carcinoma (RCC) stage for our cohort.[18] CRP (mg/L), serum creatinine (Cr) and estimated glomerular filtration rate (eGFR, mL/min/1.73 m^2), by the MDRD equation were measured preoperatively and postoperatively.[19] Complications were graded using the modified Clavien-Dindo classification and separated into low (1/2) and high grade (≥ 3).[20] CRP data included in the analysis was from at least 6 months after surgery, through time of last follow up.

A single reviewer at each institution was responsible for calculating the RENAL nephrometry score. RENAL score for each lesion was determined by preoperative CT or MRI scan. All components (R.E.N.A.L.) except the (A)nterior (a)/posterior (p) were scored on a 1-,2-, or 3-point scale.[21,22]

Statistical analysis

The patients were divided into two cohorts, using CRP as a binary variable: those with increase in CRP ≥ 0.5 mg/L between 6 month postoperative value and last follow up (termed "CRP rise," or CRPR); and those who did not have increase ≥ 0.5 mg/L (termed "CRP stable," or CRPS); a priori we chose a CRP value threshold of 0.5 mg/L as CRP increase, given that CRP increase has been described as being at least 0.5 mg/L whether on a measured assay,[23] or that corresponding with a change in risk of cardiovascular events.[24] Primary outcome was median change in eGFR (ΔeGFR, mL/min/1.73 m^2) from 6 months postoperative to last follow up. Secondary outcomes included median percentage change in eGFR between 6 months postoperative and last follow up (%ΔeGFR), presence of stage III-CKD (eGFR < 60 mL/min/1.73 m^2) at last follow up, and development of postoperative de novo stage III-CKD. Univariable analysis was conducted using Chi-square, Fisher's exact test, Students t-test, and Mann-Whitney U test for categorical and continuous variables, respectively. Multivariable analysis for factors associated with development of de novo stage III-CKD was conducted; factors were entered into the multivariate model if they were significant at the univariate level,

or clinically relevant. Sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) of postoperative increase in CRP ≥ 0.5 mg/L to predict de novo CKD was calculated. P value < 0.05 (two-tailed) was considered statistically significant. Statistical analysis was performed using SPSS software, version 17.0 (SPSS Inc, Chicago, IL, USA).

Results

A total of 243 patients were identified for inclusion in the study and analysis. Median follow up was 43.4 (IQR, 21.2-66) months. Thirty-seven patients were found to have CRP values which increased by ≥ 0.5 mg/L and were designated the CRPR cohort.

TABLE 1. **Demographics, clinico-pathologic characteristics, and operative outcomes/complications**

	CRPS (n = 206)	**CRPR (n = 37)**	**p value**
Mean age ± SD	56 ± 14.8	57 ± 15.2	0.558
Sex (male)	129 (62.6%)	21 (56.8%)	0.582
Race			0.857
Caucasian	117 (56.8%)	20 (54.1%)	
Other	89 (43.2%)	17 (45.9%)	
Mean BMI ± SD, kg/m^2	27.9 ± 5.8	29.3 ± 5.5	0.186
Hypertension	58 (28.2%)	17 (45.9%)	0.035
Smoking	120 (60.9%)	25 (69.4%)	0.357
Diabetes	121 (58.7%)	26 (70.3%)	0.206
Laterality (L/R/B)	47.6%/50.5%/1.9%	48.6%/ 48.6%/2.7%	0.943
Mean RENAL score ± SD	6.7 ± 1.5	7.1 ± 1.5,	0.131
RENAL score			0.150
Simple (4-6)	102 (51.3)	51 (41.7%)	
Intermediate (7-9)	87 (43.7%)	31 (58.3%)	
Complex (10)	10 (5%)		
Median EBL (IQR), mL	250 (150-400)	300 (225-500)	0.082
Ischemia type			0.430
None	59 (28.8%)	8 (21.6%)	
Warm/cold	146 (71.2%)	29 (78.4%)	
Median ischemia time (IQR), min	25 (22-27)	25 (22-29)	0.566
Patient(s) transfused	12 (5.9%)	4 (10.8%)	0.279
Positive margins	1 (0.5%)	1 (2.7%)	0.282
Central/mid tumor location	56 (27.2%)	10 (27%)	1.000
Pathologic t-stage			0.089
T1	167 (87%)	35 (97.2%)	
T2+	25 (13%)	1 (2.8%)	
Mean tumor size ± SD, cm	4.2 ± 2.2	3.1 ± 1.0	0.005
Pathology			0.814
Malignant	171 (83%)	30 (81.1%)	
Benign	35 (17%)	7 (18.9%)	
Complications (incl urine leak, Clavien)	36 (17.5%)	8 (21.6%)	0.642
Low grade	22 (10.7%)	4 (10.8%)	1.000
High grade	18 (8.8%)	5 (13.5%)	0.364
Urine leak	12 (5.8%)	4 (10.8%)	0.277

CRPS = C-reactive protein stable; CRPR = C-reactive protein rise

Two hundred and six patients did not have rise ≥ 0.5 mg/L in CRP and were designated as the CRPS cohort. Table 1 demonstrates demographics, tumor characteristics, and operative outcomes. There were no differences in age, sex, body mass index (BMI), diabetes, or complication rates. Hypertension was more prevalent in the CRPR cohort (45.9% versus 28.2%, p = 0.035). Mean tumor size was greater in the CRPS cohort (4.2 cm versus 3.1 cm, p = 0.005), though no significant difference was observed in mean RENAL nephrometry score (CPRS 6.7 ± 1.5 versus CPRR 7.1 ± 1.5, p = 0.131), and proportions with simple (4-6), intermediate (7-9), and complex (≥ 10) RENAL score (p = 0.150). Operative parameters such as estimated blood loss, and median ischemia time (25 minutes for both groups, p = 0.566) were similar between the groups, as were complication (total/Clavien high grade/Clavien low grade) rates.

Table 2a demonstrates comparative renal function between the cohorts. While there was no significant difference in baseline eGFR between the groups (p=0.721), mean eGFR at last follow up was significantly lower in the CRPR group (61.7 ± 25.2 mL/min/1.73 m^2 versus 79.8 ± 19.5 mL/min/1.73 m^2 for CPRS, p < 0.001). Median Δ eGFR (CRPS -13.7 versus CRPR -32 mL/min/1.73 m^2, p < 0.001) and median %ΔeGFR (-15.4% versus -34.6%, p < 0.001) were also significantly higher in the CPRR group. Patients with CRPR had increased frequency of stage III-CKD at last follow up (64.9% versus 11.7%, p < 0.001) and de novo stage III-CKD at last follow up (43.2% versus 3.7%, p < 0.001). Median time to development of de novo stage III-CKD was 19 (IQR 17-23) months in CRPR and 26 (22.5-28) months in CRPS groups, respectively (p = 0.182).

Table 2b demonstrates comparative CRP values between the two groups. There was no significant difference in mean baseline (0.372) or 6 month postoperative CRP (0.076). Median time to CRP rise was 10 (IQR 6.5-12) months. Median time from CRP increase ≥ 0.5 to development of de novo stage III-CKD was 9 (IQR 7.5-11) months.

Figure 1 demonstrates box plot showing CRP delta distribution for patients who did and did not develop de novo stage III-CKD. Patients who developed de novo stage III-CKD had a significantly higher CRP delta than patients who did not (0.9 versus -0.5 mg/L, p < 0.001).

TABLE 2. **a) Renal functional outcomes; b) CRP values**

	CRPS (n = 206)	**CRPR (n = 37)**	**p value**
a) Renal functional outcomes			
Mean preoperative eGFR ± SD (mL/min/1.73 m^2)	94.7 ± 22.9	97.1 ± 39.7	0.721
Mean eGFR at last follow up ± SD (mL/min/1.73 m^2)	79.8 ± 19.5	61.7 ± 25.2	< 0.001
Median ΔeGFR (IQR) (mL/min/1.73 m^2)	-13.7 (-20.7 to -6.9)	-32 (-50.2 to -16.8)	< 0.001
Median eGFR % change (IQR)	-15.4% (-21.1 to -.9.9)	-34.6% (-43.6 to -20.3)	< 0.001
Preoperative eGFR < 60	19 (9.2%)	8 (21.6%)	0.054
eGFR < 60 at last follow up (%)	24 (11.7%)	24 (64.9%)	< 0.001
de Novo eGFR < 60 at last follow up (%)	7 (3.7%)	16 (43.2%)	< 0.001
Median time to development of de novo eGFR < 60 (IQR), months	26 (22.5-28)	19 (17-23)	0.182
b) CRP values			
Mean preoperative CRP ± SD (mg/L)	3.2 ± 1.4	3.0 ± 1.2	0.372
Mean 6 month postoperative CRP ± SD (mg/L)	2.2 ± 1.0	1.9 ± 1.0	0.076
Mean CRP at time of CRP rise ± SD (mg/L)		3.1 ± 1.0	
Median time to CRP rise (IQR), months		10 (6.5-12)	
Median time from CRP increase ≥ 0.5 to development of de novo eGFR< 60 (IQR), months		9 (7.5-11)	

CRP = C-reactive protein; CRPS = C-reactive protein stable; CRPR = C-reactive protein rise; eGFR = estimated glomerular filtration rate

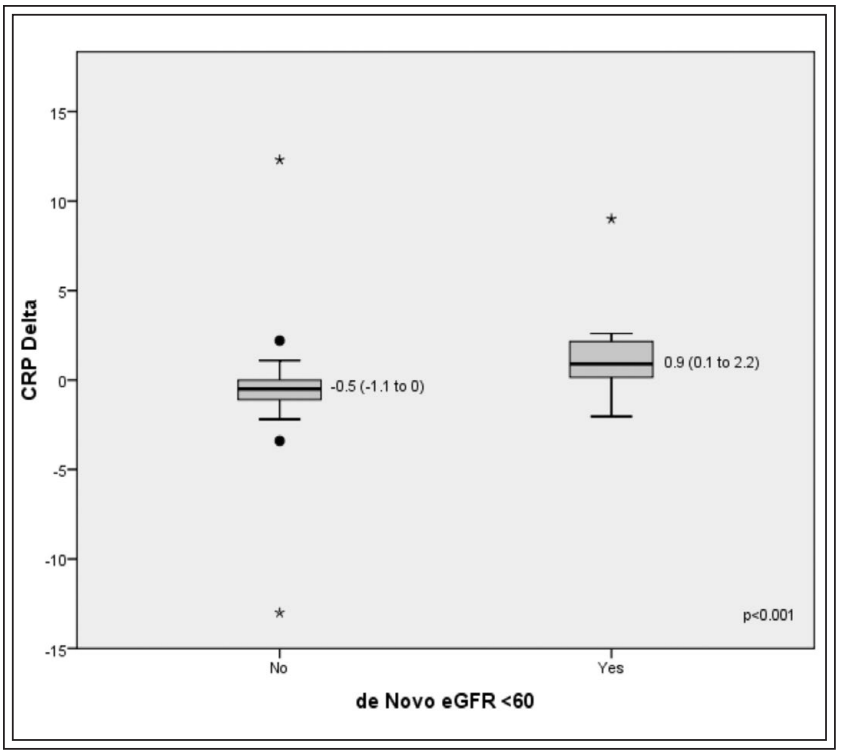

Figure 1. Box plot showing CRP delta distribution for patients who did and did not develop de novo eGFR < 60. Thick black line is median, top and bottom line of box is 75th and 25th percentiles (IQR) respectively. T's above and below box are 95% confidence interval and circles and asterisks are outliers.

Table 3a demonstrates a multivariable analysis for factors associated with development of de novo stage III-CKD at last follow up. Variables included in the multivariate model were those variables that were significant on univariate tests, or of clinical interest. These included: BMI, HTN, DM, ischemia time (0 versus < 30 versus ≥ 30 minutes), type of ischemia (none versus warm versus cold), complications, transfusion, and pathology (benign versus malignant). Analysis revealed increasing total RENAL nephrometry score (OR 1.89, p = 0.001), hypertension (OR 4.75, p = 0.016), and CRP increase ≥ 0.5 mg/L (OR 55.76, p < 0.001) to be factors independently associated with development of stage III-CKD postoperatively. Table 3b exhibits statistical measures of performance. CRP increase ≥ 0.5 mg/L had sensitivity of 69.6% for de novo stage III-CKD after partial nephrectomy. CRP increase ≥ 0.5 mg/dL had specificity of 93.3%, PPV of 55.2% and NPV of 96.3%.

TABLE 3. **(a) Multivariable analysis of factors associated with worsening renal function after partial nephrectomy; (b) Statistical measures of Performance: Sensitivity, Specificity, PPV, NPV of CRP increase ≥ 0.5 mg/L for de novo eGFR < 60 mL/min/1.73²**

a)	**De novo eGFR < 60 at last follow up**			
Variables		**95% C.I. for odds**		
	Odds ratio	**Ratio**		**p value**
		Low	**High**	
CRP increase ≥ 0.5 (6 months to last follow up)	55.76	14.27	217.84	< 0.001
Total RENAL score, cont.	1.89	1.28	2.78	0.001
HTN (yes vs. no)	4.75	1.33	16.88	0.016

b)		**de Novo eGFR < 60**		**Total**	
		Yes	**No**		
CRP increase ≥ 0.5	Yes	16	13	29	PPV 55.2%
	No	7	180	187	NPV 96.3%
Total		23	193	216	
		Sensitivity 69.6%	Specificity 93.3%		

eGFR = estimated glomerular filtration rate; CRP = C-reactive protein filtration rate

Discussion

A growing body of literature also suggests that CKD, which may be present in up to 40% of patients undergoing surgery for renal masses, is responsible in part for metabolically driving the malignancy through poorly understood mechanisms potentially involving chronic uremia state and immune inhibition, and suggesting a bidirectional relationship between CKD and renal tumors.[25] With increasing recognition of this interplay, and of the potential metabolic and cardiovascular sequelae of renal surgery for cortical neoplasms,[5-9,13] nephron sparing surgery has gained increasing credence as a management option, whether for imperative or select elective indications. Recognizing that renal functional decline following renal surgery is a multifactorial process nonetheless begs the question—can we identify risk factors or markers which may be associated with this phenomenon? We sought to characterize factors associated with renal functional decline after nephron sparing surgery, to aide in finding a potential serum marker which may help identify those patients at greatest risk for post surgical renal functional decline. CRP represents a provocative possibility, secondary to its overall utilization as a marker of systemic inflammation and renal functional decline in the medical setting.[14] It has also been utilized as a potential marker for mortality/prognosis after nephrectomy for RCC and with documented recurrence of RCC.[15,16] Our data demonstrated increased median change in eGFR between preoperative and last follow up, and an increased rate of de novo stage III-CKD postoperatively in the cohort with CPR elevation, Table 2. Furthermore, we noted that patients who developed de novo stage III-CKD had significantly higher CRP delta than patients who did not develop stage III-CKD, Figure 1, and that CRP increase preceded renal functional decline to eGFR < 60, Table 2, and was a factor independently associated with development of stage III-CKD after partial nephrectomy, Table 3a.

Recent reports have demonstrated accumulating evidence for a role of CRP as a marker for risk of renal insufficiency. In the Cardiovascular Health Study, population-based cohort study of 5888 subjects aged ≥ 65 years renal insufficiency (creatinine level ≥ 1.3 mg/dL in women and ≥ 1.5 mg/dL in men) was independently associated with elevation of CRP.[26] CRP administration in a rat model results in endothelial dysfunction, impaired vasoreactivity, and hypertension.[27] CRP has also been noted to promote proinflammatory cytokine production in human vascular endothelial cells in vitro,[28] leading to mesangial cell sclerosis, extracapillary proliferation, and glomerulosclerosis.[29] Indeed our finding that median time from CRP increase to development of de novo stage III CKD of 9 months suggests that a pro-inflammatory state is associated with a subsequent decline in renal function and efforts to further delineate underlying mechanisms and to develop pharmacoprotective strategies to decrease progression of renal disease, such as institution of statin therapy and renin-angiotensin-aldosterone system blockade, deserve further investigation.[30,31]

In our analysis the high specificity of CRP increase ≥ 0.5 (93.3%, Table 3b) suggests CRP increase ≥ 0.5 mg/L is a reliable indicator for renal functional decline after PN when noted. Therefore, presence of CRP increase ≥ 0.5 should alert the clinician to the high risk for renal functional degeneration. The high NPV (96.3%, Table 3b) of CRP increase ≥ 0.5 for de novo stage III-CKD means that if a patient has not had CRP increase of ≥ 0.5, then the likelihood of a patient developing significant renal functional decline may be low.

Non-modifiable factors (age, baseline eGFR, BMI, and comorbid conditions) may play the major role in contributing to renal functional decline after PN, a multifactorial effect on global renal function (decrease in the 'quality' of preserved nephrons, and increased susceptibility to lack of renal functional recovery, or to decline). Our finding that hypertension, Table 3a, is an independently associated with postoperative renal functional decline is consistent with the findings of other groups that non-modifiable and pre-existing comorbid drivers for chronic kidney disease play a major role in postoperative renal functional outcomes.[17,32,33]

Lane et al conducted a comparison of cold and warm ischemia during partial nephrectomy in solitary kidneys and demonstrated that percentage of parenchymal preservation at the time of PN is the most important predictor of ultimate renal function and that, for the most part, nonmodifiable factors predominately impact the ultimate renal function.[32] Our multivariate regression model identified RENAL nephrometry score as an independent factor associated with renal function decline post partial nephrectomy. Increasing RENAL score may reflect one of two potentially interlocking phenomena—a) increasing amount of parenchyma lost—whether due to loss of normal parenchyma to obtain clear margins and parenchymal atrophy due to tissue handling at the time of dissection and repair—(decline in the 'quantity' of preserved nephrons) and b) complexity of the resection, leading to increased ischemia times (and potential decline in the 'quality' of spared nephrons).[34-37]

Even in this context, the relationship between pre-existing non-modifiable medical and surgical drivers towards renal functional degeneration and ultimate

development of CKD is not linear and not guaranteed, and this is where the need for development of biomarkers of clinical outcomes is acute. Towards that end, we feel that utilization of CRP points the way towards further refinement of follow up strategies for both oncological and renal functional outcomes, and in the future the development of even more sensitive and specific markers for acute kidney injury and disease progression and their incorporation into follow up guidelines may improve the treatment and outcomes for renal cell carcinoma, a disease whose deaths continue to increase in the United States.[2,38,39]

Limitations of this study include its retrospective nature and inherent biases, use of serum creatinine to estimate GFR, and a lack of estimate of renal volume preserved at the time of operation. While RENAL score may be a surrogate of percent parenchyma spared, RENAL score may also impact other, modifiable factors, such as ischemia time which may influence renal functional recovery. Though we found increase in CRP ≥ 0.5 was associated with de novo eGFR < 60 in a temporal and independent manner, we do not have an underlying explanation of causation. Our data suggest that, in addition to being a maker of inflammation, there appears to be an association between increase in CRP and renal functional decline after PN. Also, the 95% CI for the OR for developing de novo eGFR with an increase in CRP is wide (14.27-217.83, Table 3a); we believe this is attributable to the size of the cohort, not to validity of this significance. The strengths of this investigation revolve around the correlation of CRP with renal function in two well-characterized, comparable cohorts of patients, comprised solely of survivors after PN, and with intermediate follow up (median 43.4 months). To our knowledge, this is the first report which demonstrates that changes in CRP are associated with renal functional decline following PN. Prospective investigation with a larger cohort size, and longer follow up, with utilization of ^{125}I-iothaamate clearance to directly calculate GFR and serum and tissue markers and CRP are requisite.

Conclusion

This is the first report to suggest utility of CRP in identifying patients at risk for functional decline after surgical therapy. Further prospective studies are requisite to determine etiology of this association. □

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