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Research Article

What is Abnormal? The Utility of C-Reactive Protein as a Marker of Sepsis Post Major Urological Surgery

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Abstract

Background: C-reactive protein (CRP) is an acute phase reactant released in response to cell injury of any cause. A rise in CRP in the immediate postoperative period may be misattributed to surgical tissue damage and not to infection, posing a diagnostic challenge for the clinician. We have evaluated its performance as a marker of infective complications following major urological surgery.

Materials and Methods: We reviewed all patients undergoing major urological surgery between March-December 2014. Data including operation, route, Charlson index, post-operative infection, and CRP measurements were recorded. We plotted receiver operating characteristic curves to evaluate the utility of CRP as a marker of infection and explored procedure specific and patient specific risks for CRP elevation.

Results: 117 patients were included. Differences in post-operative CRP measurement between procedures are statistically significant on days 1 to 3 ($p < 0.05$). Using receiver operator characteristics, CRP performs well as a marker of infection from post-operative days (POD) 2 to 8. Discriminatory power is best for patients with septic shock, peaking at POD 5 (<0.0001). In binary logistic regression, adjusting for operation, route, and Charlson Index, CRP remained a statistically significant independent marker of infection from POD 2 to 6.

Conclusion: CRP has high discriminatory power on PODs 2 to 6, particularly for septic shock. The individual major procedures and the route of access have a large influence on postoperative CRP.A larger cohort is required to accurately define normal ranges for CRP adjusted to both procedure specific and patient specific factors.

Keywords: C-reactive protein;Urology; Postoperative;Infection;Complication

Introduction

Post-operative infection following major urological surgery is associated with significantly increased morbidity and mortality. C-reactive protein (CRP) is an acute phase reactant synthesised in the liver with a half-life of 19 hours [1].

The normal value of CRP in a healthy adult is <3.0mg/L. Measurement of this biomarker is recommended by the National Institute for Health and Care Excellence (NICE) to help guide management of suspected sepsis [2]. However, a rise in CRP in the immediate postoperative period can be misattributed to surgical tissue damage and not to infection. This poses a diagnostic challenge for the clinician.

In the field of Colorectal surgery, several studies have reported the benefits of CRP both as a diagnostic marker of postoperative sepsis and as a predictor of anastomotic leakage [3-5]. Within Urology, CRP has been extensively examined as a prognostic indicator in urological cancers [6-8]. However, there is a paucity of evidence evaluating post-operative response of CRP to infection.

In many institutions, CRP is routinely measured from post-operative day 1 whether an infective complication is suspected or not. With a better understanding of the behaviour of CRP following major urological surgery, there is potential to both improve the patient recovery pathway through early detection of infective complications (enabling prompt treatment) and reduce the number of blood tests patients are exposed to, providing a cost saving. This study aims to evaluate the performance of CRP as a marker of infective complications following major urological surgery.

Patients and Methods

We retrospectively reviewed all patients undergoing partial or radical nephrectomy, nephroureterectomy, cystectomy, radical prostatectomy and retroperitoneal lymph node dissection at a single institution over a 10-month period. Patient characteristics, operation and route, Charlson index to grade morbidity [9], post-operative infection and CRP measurements for post-operative days 1-10 were recorded. All patient data were unidentifiable. Patients must have had at least 2 CRP measurements on different post-operative days to be included.

Definitions

We used the 3rd international consensus definitions for sepsis and septic shock, with sepsis defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, and septic shock defined as sepsis with persisting hypotension requiring vasopressors to maintain mean arterial pressure ≥65 mm Hg, and raised a serum lactate level >2 mmol/L despite adequate volume resuscitation [10]. Using those definitions, infectious complications were classified into the three categories of simple infection, sepsis and septic shock.

Statisticalanalysis

We report descriptive statistics including median, mean and standard deviation. We plotted receiver operating characteristic (ROC) curves evaluating the utility of CRP as a marker of infection and used binary logistic regression to adjust for potential confounders. We tested for differences between groups using the Kruskal-Wallace test. Finally, we compared outcomes for operative route using Fisher's exact test. All statistical analyses were conducted using Stata 12.

Results

Patient demographics and characteristics are outlined in Table 1. 117 patients were included in the study, with an average age of 65.5 years, and range 30-86. There were 84 males and 33 females. 60 patients underwent laparoscopic surgery and 57 had surgery via an open approach. The average Charlson index was 3.2, meaning the average grade of comorbidity was moderate. 96 patients (82.1%) had malignant disease, and 21 (17.9%) had benign disease. Of the 21 patients with benign disease histologically, 7 were suspected of having malignancy pre-operatively.

Table 1: Patient demographics and baseline characteristics.

Mean age (range)	65.5 (30-86)
Sex	
Male	84
Female	33
Operation	
Nephrectomy	52
Partial Nephrectomy	9
Nephroureterectomy	6
Cystectomy	8
Cystoprostatectomy	28
Radical Prostatectomy	13
Retroperitoneal lymph node dissection	1
Pathology	
Malignancy	96
Benign disease	21
Approach	
Open	57
Laparoscopic	60
Charlson index (average)	3.2
Infective Complication	
Simple infection	9
Sepsis	24
Septic Shock	6

39 patients (33.3%) developed an infectious complication post operatively. 9 patients (7.69%) developed a simple infection, 24 patients (20.5%) developed sepsis, and 6 patients (5.13%) developed septic shock. Sources of infection included wound infection, pneumonia, urosepsis and infected abdominal collections, with diagnoses made on the basis of clinical signs, blood, urine or sputum culture results and radiological findings.

In all patients, CRP rose from day 1 after major surgery and peaked on post-operative day 3 before falling (Table 2) (Figure 1). We noted a CRP elevation on day 9, which was attributable to the few cases who developed late abdominal sepsis. With only a small number of cases with available CRP data from post-operative day (POD) 8 onwards, the data on these days did not reach significance.

Table 2: Median, mean and standard deviation for C-reactive protein (CRP) on days 1 to 10 after major urological procedures.

Day	Median	Mean	Standard Deviation
1 (n=104)	65.7	76	53.2
2 (n=108)	142.5	151.9	86.2
3 (n=95)	159.8	172.9	103.8
4 (n=88)	130.6	149.2	109
5 (n=75)	93	128.4	108
6 (n=56)	83.9	120.3	101.2
7 (n=37)	86	121.4	103.5

8 (n=24)	93.5	121.4	103.5
9 (n=11)	160.2	142.6	80.7
10 (n=8)	163.3	163.1	87.8

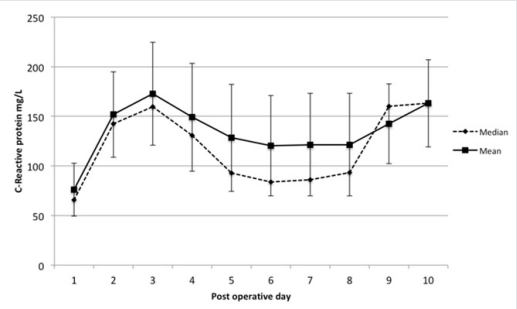

Figure 1: Median, mean and standard deviation for CRP on days 1 to 10 after major urological procedures.

Overall ROC analysis shows that CRP performs well as a marker of infection from day 2 to day 6. Discriminatory power is best for more serious infections, with best performance of CRP testing on day 5 as a marker of septic shock (p = <0.001) (Table 3). In binary logistic regression, adjusting for operation, route, and Charlson Index, CRP remained a statistically significant independent association of simple infection from day 2 to 6, of sepsis from day 2 to 6, and of septic shock from day 3 to 6.

Differences between procedures were statistically significant (Kruskal-Wallace test) on days 1 to 3 (p all < 0.05) (Table 4). Among seven major procedures, prostatectomy results in the least perturbation of CRP (Figure 2). Cystectomy resulted in the highest rates of septic shock (12.5%) and sepsis (37.5%). Simple infections occurred most commonly after nephroureterectomy (16.7%). The 1 RPLND case included in this study had no infective complications.

Table 3: Receiver operator characteristics for C-reactive protein (CRP) levels on days 1 to 10 post-operative. AUC = area under curve.

	Simple Infection		Sepsis		Septic Shock	
Day of CRP	AUC	p	AUC	p	AUC	p
1 (n=104)	0.612	0.073	0.62	0.075	0.539	0.793
2 (n=108)	0.674	0.003	0.699	0.002	0.631	0.283
3 (n=95)	0.661	0.009	0.698	0.002	0.758	0.035
4 (n=88)	0.692	0.003	0.74	<0.001	0.874	0.002
5 (n=75)	0.669	0.012	0.731	0.001	0.942	<0.0001
6 (n=56)	0.721	0.004	0.804	<0.001	0.857	0.005
7 (n=37)	0.641	0.144	0.74	0.014	0.834	0.017
8 (n=24)	0.63	0.297	0.741	0.046	0.812	0.053
9 (n=11)	0.444	0.814	0.625	0.54	0.643	0.45
10 (n=8)	0.286	0.513	0.667	0.505	0.533	0.881

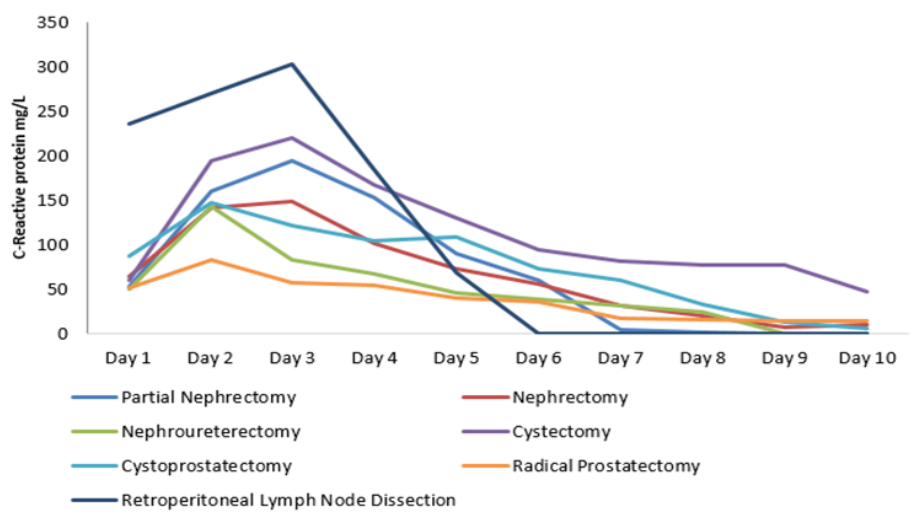

Figure 2: Mean Post-Operative CRP by Procedure.

Table 4: Outcome of Kruskal-Wallace Analysis on differences in CRP between procedures.

Day	χ2 Statistic	Degrees of Freedom	p-value
1	14.327923	6	0.026
2	11.830318	5	0.037
3	14.207779	6	0.027
4	10.602631	6	> 0.05
5	10.818802	6	> 0.05
6	4.543454	5	> 0.05
7	2.22183	5	> 0.05
8	4.412752	5	> 0.05
9	0.681818	3	> 0.05
10	6.083333	3	> 0.05

Laparoscopic as opposed to open surgery measurably conferred advantages, with lower CRP levels on all days (statistically significant differences were observed on post-operative days 1, 2, 3, 5, 6, 7 and 8) (Figure 3). ROC analysis shows that, following a laparoscopic procedure, CRP has the highest AUC on post-operative days 2 and 3 in the diagnosis of simple infections and sepsis. No patients whose procedure was conducted laparoscopically developed septic shock (hence valid AUC could not be calculated) (Table 5). Following open procedures, CRP had greater value as a marker of infection, with high AUC noted for simple infection on days 4-6 and from day 4 onwards for sepsis and septic shock (Table 6).

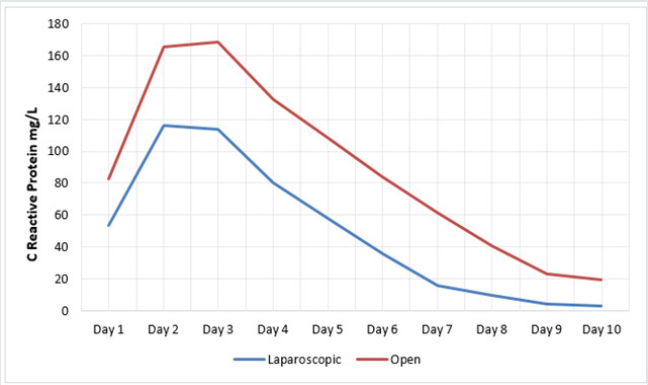

Figure 3: Average CRP levels in laparoscopic vs open procedures.

Table 5: Receiver operator characteristics for C-reactive protein (CRP) levels on post-operative days 1 to 10 in laparoscopic procedures. AUC = area under curve.

	Simple Infection		Sepsis		Septic Shock	
Day	AUC	p	AUC	p	AUC	p
1	0.659	0.105	0.606	0.352	n/a	n/a
2	0.729	0.002	0.691	0.032	n/a	n/a
3	0.715	0.006	0.758	0	n/a	n/a
4	0.6	0.296	0.686	0.042	n/a	n/a
5	0.521	0.84	0.604	0.33	n/a	n/a
6	0.579	0.532	0.727	0.032	n/a	n/a
7	0.458	0.805	0.533	0.843	n/a	n/a
8	0.467	0.89	0.467	0.89	n/a	n/a
9	n/a	n/a	n/a	n/a	n/a	n/a
10	n/a	n/a	n/a	n/a	n/a	n/a

Table 6: Receiver operator characteristics for C-reactive protein (CRP) levels on post-operative days 1 to 10 in open procedures. AUC = area under curve.

	Simple infection		Sepsis		Septic Shock	
Day	AUC	p	AUC	p	AUC	p
1	0.523	0.796	0.569	0.449	0.427	0.656
2	0.606	0.231	0.67	0.054	0.548	0.771
3	0.613	0.191	0.645	0.092	0.71	0.172
4	0.772	0	0.782	<0.001	0.859	<0.001
5	0.766	0.001	0.814	<0.001	0.91	<0.001
6	0.798	0	0.847	<0.001	0.801	0.001
7	0.698	0.095	0.822	<0.001	0.761	0.032
8	0.667	0.262	0.817	0.005	0.75	0.089
9	0.714	1	0.917	4.07	0.563	0.798
10	n/a	n/a	n/a	n/a	0.583	0.756

Discussion

CRP was first discovered by Tillet and Francis in 1930 when looking at serological reactions in pneumococcus infection [11]and named for its reaction with the C polysaccharide of pneumococcus. In the presence of calcium, CRP binds to the phosphocholine (PCh) residues in polysaccharides, as well as PCh expressed on damaged and apoptotic cells [12]. This initiates activation of the classical complement pathway via assembly of C3 convertase with opsonisation of the pathogen or damaged host cells [13].

Increased levels of inflammatory cytokines, particularly interleukin 6 (IL-6), stimulate expression of the CRP gene in hepatocytes [14]. IL-6 is mainly a pro inflammatory cytokine involved with the early host response to infection.It is secreted by many different cell lines, including adipocytes, myocytes, osteoblasts and immune cells such as macrophages. Changes in the immune response after tissue damage from surgery is a normal physiological reactionand correlates with the degree of injury [13]. Other pro-inflammatory cytokines include tumour necrosis factor alpha (TNF-a) and interleukin-8 (IL-8), and both have been shown to increase circulating levels of CRP [14,17]. Following a stimulus, serum concentrations of CRP will rise and peak at approximately 48 hours, before falling rapidly once the stimulus ceases [18].

It is clear from the evidence that both tissue damage and infection will stimulate the immune system, increase levels of circulating pro-inflammatory cytokines and CRP. The immune pathways leading to the rise in CRP in both infection and tissue injury are almost identical; an elevation in CRP following surgery may be entirely normal, even if the rise is significant.

The results from this study show that CRP performs well as a marker of infection in post-operative days 2 to 6, with best performance on post-operative day 5 (AUC 0.942, p=<0.0001). Measuring CRP on post-operative day 1 does not differentiate between surgical tissue injury or an infective process. Trabelssi et al recently looked at CRP as a marker of complications after radical cystectomy, and to date the only other urological study looking at post-operative CRP.They concluded that CRP >150mg/L on post-operative day 4 was strongly associated with risk of complication after cystectomy (p<0.001). Measurement of CRP on this day was also reliable in excluding infective complications, with high negative predictive value observed [19]. Our data on post-operative day 4 is concordant with these findings; however, we also found that CRP has high discriminatory power as a marker of infection on post-operative days 2-6. CRP has a half-life of 19 hours and peaks after approximately 48 hours [19], therefore a sustained rise over a few days with an infective process is expected.

Our data demonstrates lower CRP levels following laparoscopic surgery as opposed to open surgery, reaching statistical significance on the majority of post-operative days. The laparoscopic approach allows less tissue damage and stimulation of the immune response, so a greater rise in CRP following open surgery is expected. This has been looked at extensively in colorectal surgery, but not in urology. Straatman et al evaluated post-operative CRP following colonic surgery as a substudy of the LAFA randomised controlled trial (laparoscopy in combination with fast track multimodal management is the best perioperative strategy in patients undergoing colonic surgery) [20, 21].They found that in uncomplicated cases, the rise in CRP levels was significantly lower at 24 and 72 hours following laparoscopic resections in comparison to open, in keeping with our results. In patients with major complications, they found no difference in CRP levels when comparing laparoscopic to open surgery. Similar results following colonic surgery were found by Ramanathan et al, who noted a greater rise in CRP following open surgery; however, in those with an infective complication, there was no significant difference in CRP levels on post-operative days 1-4 between open and laparoscopic resections [22]. In contrast to these studies, we found statistically significant differences CRP levels between open and laparoscopic surgery in the septic shock group (p=0.012).

Limitations of this study include the retrospective design and heterogeneity of the study population. Although interesting to compare the behaviour of CRP following different urological procedures and approaches, a larger cohort would be required to accurately define procedure specific normal ranges for CRP.

Conclusion

CRP has little predictive value as a marker of infection or sepsis on the first post-operative day, or after 6 days, but has surprisingly high discriminatory power on days 2 to 6, particularly for more severe definitions of sepsis. Procedure and route of access have a large influence on CRP from day 1 and should be taken into account when considering what represents an abnormal CRP. Further prospective research examining the behaviour of CRP after major urological surgery is required and could enhance post-operative recovery whilst allowing a cost saving to be made.

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