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Preoperative C-reactive protein is related with renal cell tumor dimension? Preliminary results

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Abstract

Introduction: Renal tumors do not benefit from an unanimously accepted tumor marker. We tried to evaluate the advantages of preoperative C-reactive protein (CRP) values and monitor the dynamic of CRP values from the perspective of the evolution of patients diagnosed with Grawitz tumors. *Patients, Materials and Methods*: We researched the medical records of patients with renal parenchymal tumors admitted to the Urological Clinic in Iaşi, Romania, between 01.01.2018 and 01.08.2022. Data were collected regarding age, environment, comorbidities, paraclinical data, tumor characteristics, and treatment performed. Ninety-six patients were included. The data on the inflammatory syndrome pre- and postoperatively were evaluated comparatively. All patients were diagnosed with clear cell renal cell carcinoma (RCC). *Results*: We found that the renal tumor dimension correlates with an increased preoperative CRP level. For other variables, the correlations regarding age, sex, tumor, node, metastasis (TNM) stage, and size in relation to the increase or decrease of CRP had no statistical significance. *Conclusions*: The analysis of preoperative CRP and CRP dynamics could predict the tumor's aggressiveness and the treatment's effectiveness. A clear association between CRP levels and RCC pathogenesis is not yet defined, thus, further studies are necessary.

Keywords: renal cancer, Grawitz tumor, CRP, marker, neoplasm, kidney.

Introduction

The improvement in diagnosis and treatment of renal cell carcinoma (RCC) in the last two decades is very high, but it remains one of the most lethal urological illnesses. The incidence of RCC and mortality differ by region and country. Risk factors for this malignancy are smoking, obesity, hypertension, chronic kidney disease (CKD), environmental factors, comorbidities, and consumption of analgesics [1]. The incidence of RCC for both sexes is 4.4 per 100 000, with differences between countries [1]. Worldwide, this type of cancer represents the sixth most frequently diagnosed malignancy in men and the 10th in women [2].

Acute inflammation (like a bacterial infection, trauma, organ infarction, autoimmune or malignant diseases) determines the release of C-reactive protein (CRP) – an acute phase protein [3, 4]. CRP is a sensitive but nonspecific biomarker of both acute and chronic systemic inflammation [5]. CRP has been found to be a significant predictor of future cardiovascular events because of its role in atherosclerosis and as a prognostic marker for diabetes [3, 4, 6, 7]. The predictive potential of CRP in the preoperative period for patients with RCC of all pathological types and stages was investigated in recent studies [6].

The liver was previously thought to be the only organ that produced CRP [8]. Recent research, however, determined that other sites like the kidney, the respiratory tract, the thymus, adipose tissue, smooth muscle cells of normal or injured blood vessels, and neurons may also be a source for CRP synthesis [9–11].

The origin of "tumor CRP" is unexplained, and there are not many studies to research the expression of CRP by cancer cells, making it easier to understand tumor CRP increases [11]. However, other researchers have reported contradictory results; it is still unclear if inflammation is induced by cancer cells or if cancer aggressiveness is increased by inflammation.

Aim

We aimed to investigate the importance and correlation between the data on the inflammatory syndrome pre- and postoperatively comparatively.

Patients, Materials and Methods

Patients

Patients with RCC who underwent surgical treatment at the Urological Clinic of the Dr. C. I. Parhon Clinical Hospital, Iaşi, Romania, from January 2018 to August 2022 were included in this study. The data were collected from the medical records in the Hospital, with complete patient and tumor-specific characteristics. We evaluated all the patients who were diagnosed with renal cancer, and the data included: sex, age, weight, height, laboratory findings (total blood count, renal function, preoperative CRP), pathology result, and the evolution of CRP immediately

postoperative and after at least two months. 1997 *Union for International Cancer Control* (UICC) Classification was used to identify the tumor subtype from a histological point of view, and the 2020 Tumor, Node, Metastasis (TNM) Classification was used for disease staging.

Inclusion criteria: all patients hospitalized and had surgical intervention for renal cancer.

Exclusion criteria: patients lacking CRP prior to surgery, lack of pathology result.

We categorized preoperative CRP values according to Johnson *et al*. [12] into three groups: Group A – low (CRP <4 mg/L), Group B – intermediate (4–10 mg/L), and Group C – high (CRP >10 mg/L).

We measured the dimension of kidney tumors on computed tomography.

Statistical analysis

Statistical Package for the Social Sciences (SPSS) was used to conduct the statistical analysis; we reported continuous variables as mean value and standard deviation (SD) – analysis of variance (ANOVA) and χ^2 (*chi*-squared) tests were used to determine the statistical significance of CRP groups and Spearman's *rho* test was used to measure the correlation between preoperative CRP value and age, body mass index (BMI), initial creatinine level and maximum dimension of renal tumor. We also used the Pearson's correlation for neutrophiles, thrombocytes, lymphocytes, and preoperative CRP. Cox regression was performed for survival analysis with block for neutrophiles, lymphocytes, BMI, dimension of tumor, and preoperative CRP.

Results

The mean age of our patient sample, which consisted of 39 (40.62%) men and 57 (59.37%) women, was 61.65 years (SD ±11.53 years). Overall, the patients' mean BMI was 29.61 kg/m^2 (SD ±4.52 kg/m^2).

The mean white blood count was 7622.4/mm^3, and the mean hemoglobin was 13.46 g/dL (SD ±1.95 g/dL). The mean preoperative creatinine value was 1.08 mg/dL (SD ±1.11 mg/dL), and postoperative value was 1.35 mg/dL (SD ±0.75 mg/dL), respectively.

The mean preoperative CRP value for all patients was 34.77 mg/L (SD ±63.06 mg/L). The mean CRP value for every three subgroups (<4 mg/dL, 4–10 mg/dL and >10 mg/dL) was 0.93 mg/dL (SD ±0.3 mg/dL), 6.07 mg/dL (SD ±1.78 mg/dL) and 83.92 mg/dL (SD ±78.07 mg/dL), respectively; 74% (*n*=71) of patients had arterial hypertension, and 26% (*n*=26) had diabetes mellitus as comorbidities. Pathology for all patients revealed clear cell RCC.

The most interesting fact we found is that renal tumor dimension is correlated with the preoperative CRP value (p=0.03). We do not find any other statistical correlation between CRP value and sex, BMI, or RCC staging. All the details of the correlation and test are described in Table 1. CRP value was determined immediately postoperatively, and for nine (9.38%) patients, the value increased; for 16 (16.67%) patients, the value decreased, and for two (2.08%) patients, it remained constant. CRP values increased for five (5.2%) patients, fell for 11 (11.46%) patients, and remained stable for two (2.08%) patients – after a mean period of follow-up of two years. However, the dynamic of the CRP value did not have any statistical correlation (p=0.87).

Table 1 – ***Characteristics of patients with RCC and preoperative CRP values***

Variable	Group A (CRP <4 mg/L)	Group B (CRP 4–10 mg/L)	Group C (CRP >10 mg/L)	*p*-value
Age, mean [years] (95% CI)	61.52 (SD ±12.5)	64.25 (SD ±7.88)	60.97 (SD ±11.39)	0.69
Sex				0.42
Women	21 (45.65%)	3 (25%)	15 (39.47%)	
Men	25 (54.34%)	9 (75%)	23 (60.52%)	
BMI [kg/m^2]				0.47
<25	7 (15.22%)	1 (8.33%)	3 (7.89%)	
25–30	18 (39.13%)	6 (50%)	18 (47.37%)	
30–35	15 (32.61%)	4 (33.33%)	7 (18.42%)	
35–40	2 (4.35%)	0	3 (7.89%)	
>40	0	0	2 (5.26%)	
RCC staging				0.116
pT1a	18 (39.13%)	6 (50%)	7 (18.42%)	
pT1b	14 (30.43%)	4 (33.33%)	8 (21.05%)	
pT2a	2 (4.35%)	2 (16.67%)	5 (13.16%)	
pT2b	0	0	1 (2.63%)	
pT3a	10 (12.74%)	0	16 (42.11%)	
pT4	1 (2.17%)	0	0	
N	2 (4.35%)	1 (8.33%)	1 (2.63%)	0.72
M	0	0	2 (5.26%)	
Maximum diameter of tumor [mm]				0.0335
20–40	18 (39.13%)	3 (25%)	9 (23.68%)	
40–60	14 (30.43%)	5 (41.67%)	8 (21.05%)	
60–80	13 (28.26%)	3 (25%)	8 (21.05%)	
>80	1 (2.17%)	1 (8.33%)	10 (26.32%)	
Comorbidities				
HBP	32 (69.56%)	10 (83.33%)	29 (76.31%)	0.571
DM	9 (19.56%)	6 (50%)	11 (28.94%)	0.101

BMI: Body mass index; CI: Confidence interval; CRP: C-reactive protein; DM: Diabetes mellitus; HBP: High blood pressure; RCC: Renal cell carcinoma; SD: Standard deviation.

We calculate the correlation between preoperative CRP value and the dimension of the renal tumor, and we found a direct proportion with a p-value of 0.01. In other words, the greater the value of CRP, the higher the dimension of the tumor (Table 2).

Table 2 – ***Correlation between presurgical CRP values and different variables***

Variable	*p*-value	R_s value
Preoperative CRP Age	0.7	0.03
Preoperative CRP BMI	0.36	0.09
Preoperative CRP Dimension of tumor	0.01	0.26
Preoperative CRP Preoperative creatinine	0.48	0.07

BMI: Body mass index; CRP: C-reactive protein.

We also performed Pearson's test for correlation between neutrophiles, thrombocytes, and lymphocytes with preoperative CRP, and we didn't find any statistical significance.

Cox regression did not demonstrate any statistical correlation in the survival of patients reported for neutrophils, lymphocytes, preoperative CRP, BMI, or dimension of tumor (Table 3). Survival curve states that death is correlated with evolution in time (Figure 1).

Table 3 – *Cox regression equations*

						95% CI for Exp(B)	
	B	*SE*	*Wald*	*df*	*Sig.*	*Exp(B)*	*Lower*	*Upper*
Preoperative CRP	0.010	0.010	0.926	1	0.336	1.010	0.990	1.030
Neutrophiles	0.147	0.127	1.323	1	0.250	1.158	0.902	1.487
Lymphocytes	-1.013	1.019	0.988	1	0.320	0.363	0.049	2.676
Dimension of tumor	0.007	0.024	0.095	1	0.758	1.007	0.961	1.056
BMI	-0.114	0.158	0.516	1	0.472	0.893	0.655	1.217

BMI: Body mass index; CI: Confidence interval; CRP: C-reactive protein.

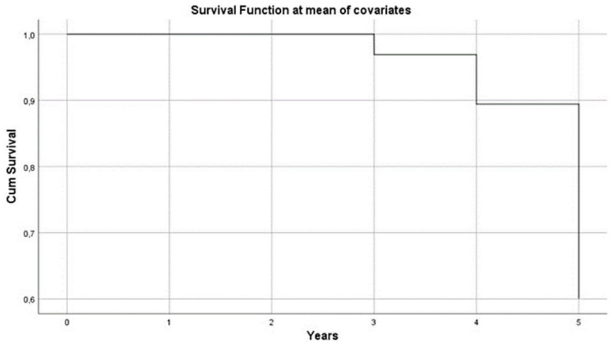

Figure 1 – *Survival curve.*

Discussions

In the present study, the preoperative CRP value was related just to the dimension of renal tumor. For other variables, such as sex, age, BMI, and RCC staging, the CRP value did not correlate.

Despite the numerous diagnostic imaging methods and intensive efforts for prevention, up to a third of renal cancers are still diagnosed in the metastatic stage. Then the research to find a tumor marker that draws attention to neoplasia and can also estimate the evolution or the prognosis must be intensified [13]. Recent research shows a strong relationship between cancer-associated inflammation and cancer progression [14].

The evolution of renal cancer is variable, the growth being slow. Some tumors invade and perforate the renal capsule, the sinus, or the pyelocalix system. In 10% of cases, cancer can invade the venous system, most frequently intrarenal veins, the renal vein, the inferior cava vein, and sometimes the right atrium. Tumor thrombus is very well vascularized, and some of them invade the wall of the renal vein or inferior cava vein wall directly, with a very reserved prognostic [15]. Lymphatic dissemination is variable; the lymph node dimension greater than 2 cm exacerbates the prognostic [16].

Clear cell RCC represents the most frequent entity of renal tumors (70–80%). They are circumscribed tumors, with pseudocapsule and golden yellow color on the section, very well vascularized. Microscopically, it can be observed in clear cells, glandular or mixed aspects. Sarcomatoid differentiation appears in 3–5% of cases, and the prognostic is more unfavorable than other types of renal cancer [17, 18].

A large population of patients with RCC preoperative CRP was shown to be a marker of poor survival [19]. In the past three decades, evidence has emerged that inflammation plays a significant role in the appearance of cancers. Patients with cancer and systemic inflammation had a more reserved prognosis [20, 21].

In the last few years, CRP has been shown to be helpful in predicting the evolution of diverse inflammatory diseases (like liver diseases) and in malignant diseases like urological cancers. Some authors demonstrated that higher CRP levels are linked to survival rates and can be used to monitor treatment efficiency and disease course in RCC, but also in upper urinary tract cancers, bladder cancers [urothelial carcinoma (UC)], and prostate cancer (PC) [12, 14, 22].

According to Allin *et al*. (2009), patients with high CRP levels are at a higher risk of cancer (lung or colorectal). Even in individuals without metastases, an increased CRP level was linked to a higher mortality rate [23]. According to various research, a high CRP level may increase the chance of getting bladder cancer [24].

Elevated CRP levels are associated with poor clinical outcomes in patients undergoing chemotherapy for bladder cancer [25]. Also, high CRP levels indicate a poor prognosis for individuals with upper-tract UC [26]. Moreover, recent studies showed that CRP level could be compared with prostate-specific antigen (PSA) as an additional independent prognostic marker in metastatic castration-resistant PC [27]. It is important to note that various publications show that RCC is more frequent in individuals with PC [28].

Numerous studies proved that CRP is adequate for evaluating, treating, and following up on RCCs. Hepatocytes secrete CRP in response to interleukin (IL)-6 secreted by renal cancer [29]. In a study of 143 patients, proinflammatory cytokines [IL-6, tumor necrosis factor (TNF), IL-1B – already used as predictive factors for different diseases] were correlated with CRP values [30, 31]. CRP can be used as an independent predictor of cancer-specific survival in patients with RCC, according to a previous study that included 313 patients [32]. In the case of patients with localized RCC who underwent surgical treatment, Lamb *et al*. showed that high preoperative CRP levels might be an unfavorable predictor for relapse-free survival, with a cut-off point level of >10 mg/L [33].

Another study conducted by Masuda *et al*. included patients with advanced RCC and observed that CRP level is a factor in tumor staging and grade [34]. In a cohort of 178 patients, Ito *et al*. performed research in which they found that an elevated CRP level >10 mg/L could be a standalone predictor for recurrence and prognosis in localized and metastatic RCC [35]. Also, researchers tried to correlate other acute phase reactants, such as platelets. They concluded that 85% of patients with thrombocytosis had CRP levels over 1.0 mg/dL, with an average CRP level of 7.4 mg/dL in these individuals. He noticed that patients with CRP levels ≥1.0 mg/dL and elevated thrombocytosis had more advanced disease with: “larger tumors, higher pathological T stages, higher percentages of lymph node metastasis and distant metastasis, higher histological grades

and higher percentages of microvascular invasion than did patients without thrombocytosis and patients with CRP levels <1.0 mg/dL, respectively" [36].

Karakiewicz *et al*. conducted an extensive study of 314 consecutive patients treated for RCC between 1984 and 2005, in which they practiced either partial or radical nephrectomy [32]. They demonstrated that the cohort had a median survival of 19.9 years and identified CRP as an independent predictor for disease-related mortality in the case of RCC. Additionally, after two and five years following nephrectomy, the model incorporating CRP outperformed the *University of California Los Angeles* (UCLA) *Integrated Staging System* (UISS) by 2.4% and 4.6% [31, 37] even though studies point to a possible role for CRP as a prognostic marker for RCC, its true potential to quantify.

In a study more similar to ours, Steffens *et al*. analyzed 1165 patients with RCC and had three cohorts differentiated through CRP levels according to Johnson *et al*. [11]: <4 mg/L, 4–10 mg/L, >10 mg/L [19].

Their results showed that CRP level was correlated with tumor staging and grading. Additionally, they used Kaplan–Meier analysis to determine cancer-specific survival. They discovered that the 5-year cancer-specific survival rates were 89.4%, 77.9%, and 49.5% for CRP levels of 4 mg/dL, 4–10 mg/dL, and >10 mg/dL, respectively [19]. Our study did not find any correlation between CRP level and tumor staging, but we demonstrated that a large tumor dimension is related to elevated CRP values.

Increased preoperative CRP level (>8 mg/dL) was an independent prognostic factor of overall survival (OS), as well as nuclear grade, metastasectomy, and lactate dehydrogenase (LDH) concentration for 99 patients with metastatic RCC treated with cytokines [36, 37]. Another Japanese study, which included a multicenter cohort of 1463 metastatic RCC patients, demonstrated that CRP is an independent predictor of OS [35, 37].

A retrospective study by Hu *et al*. analyzed 484 patients from the perspective of four preoperative markers, including CRP [38]. The cohort that evaluated CRP levels was split into two groups (CRP level <5.1 mg/L and >5.1 mg/L). They found out that elevated CRP values were associated with lower OS. Another study was performed in a cohort of 985 patients, which analyzed CRP values after nephrectomy for clear cell RCC. The authors stratified CRP into four quartiles, <2.2 mg/dL, 2.2–4.7 mg/dL, 4.7–7 mg/dL, and >7 mg/dL. They demonstrated that OS was poorer in cohorts with increased CRP values and metastatic-free survival [39]. A meta-analysis that they performed a couple of years earlier, in 2014, showed from the 24 included studies (a total of 4100 patients) that elevated CRP level was associated with higher stage and higher grade, and it was also associated with poorer OS and cancer-specific survival, in the analysis of all pathological types of RCCs [40].

Casamassima *et al*. concluded, in 110 patients study, that CRP was the most important independent prognostic factor predicting survival with a high degree of significance [high risk (HR) 4.12, p=0.002] on multivariate analysis and also they we confirmed its impact on survival [HR 1.1, 95% confidence interval (CI) 1.04 to 1.15, p=0.0003] when they evaluated CRP as a continuous variable showing that "CRP has prognostic role" [41].

O'Brian *et al*. raised the idea that CRP may have a role in genitourinary cancer (bladder, prostate, and kidney). In RCC, "postoperative CRP levels and CRP kinetics hold the most predictive value" [5].

Komai *et al*. studied the survival rates [disease-specific and recurrence-free survival (RFS)] of 101 patients who received surgical treatment for localized RCC (pT1–3N0M0). Very important in this study is that they exclude patients with other causes of increased CRP before surgery (hemodialysis, blood transfusions, radiotherapy, antimicrobial chemotherapy, antitumor chemotherapy, or immunotherapy). They conclude that "high preoperative serum CRP level is associated with a poor prognosis in patients with localized RCC and about half of the patients who presented with a high CRP level died from disease" [42].

Another study by Ramsey *et al*. tried to estimate the relationship between inflammatory markers and RFS in a group of 83 patients with renal cancer. According to their research, T stage, necrosis, and CRP were all independently significant predictors of RFS. They also found that elevated circulating CRP levels appeared to be superior to other measures of the systemic inflammatory response [43].

The impact of preoperative CRP on the oncological outcomes for patients having surgical treatment for RCC is examined in a recent retrospective analysis on the most significant cohort reported of 2445 individuals, which state that patients with elevated CRP had a higher incidence of grade III/IV disease and pathological stage 3 and stage 4 disease, a greater incidence of positive surgical margins, and a higher incidence of recurrence [44].

The dynamic of CRP value in a mean follow-up did not change the prognostic, but the limitations of this study were the small number of patients and lack of addressability; many patients were from other regions, and the follow-up was made by a current urologist/oncologist from territorial service.

The nephrology literature has identified CRP measurement as a predictor of future renal disease and a prognostic in patients with CKD [45, 46]. Cotta *et al*. conducted a retrospective multicenter analysis of 1987 who had radical nephrectomy or partial nephrectomy performed for RCC stage 1–2 [47]. They found that elevated preoperative CRP values correlated with progressive renal function decline and that patients with 1–2 stage RCC may be considered as having indications for nephron-sparing strategies. Our study did not find any renal decline function correlated with CRP values.

Buzulică *et al*. mention that neoplasia and terminal renal failure are two serious diseases that made the prognostic more difficult and determined some other complication to appear [48].

Conclusions

We found that the renal tumor's dimension (all patients had clear cell RCC) correlates with an increased preoperative CRP level, which is directly proportional to this. In our patients, we do not find any other correlation between CRP value and neutrophile, thrombocyte, lymphocyte values, sex, BMI, or RCC staging. After a mean follow-up of more than two years, the CRP value increased for five (5.2%) patients, for 11 (11.46%) patients, the value decreased and for 80 (83.33%) patients remained constant, respectively. However, the dynamic of the CRP value did not have any

statistical correlation. Preoperative CRP did not influence survival and evolution toward metastatic disease.

Conflict of interests

The authors declare that they have no conflict of interests.

Research Ethics Statement

The research was conducted in concordance with the Approval of Bioethics Commissions from Dr. C. I. Parhon Clinical Hospital, Iaşi, Romania, with respect to the precepts of the 1964 Helsinki Declaration and later amendments.

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