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ARTICLE

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Inflammatory response markers and survival prediction in patients with renal cell carcinoma

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ABSTRACT

Introduction: Many factors influence the clinical course of patients with renal cell carcinoma (RCC). The most commonly used prognostic indicators are TNM stage, tumor size and RCC type. In this study we evaluated the prognostic relevance of albumin and C-reactive protein (CRP), and Glasgow Prognostic scores (GPS), in patients with primary RCC.

Methods: We retrospectively reviewed all patients surgically treated for primary RCC between 1982 and 2018 at Umeå University Hospital. There were 872 patients, 527 males and 345 females. Data on albumin, CRP and GPS points before surgery were extracted, as well as TNM stage, RCC type, tumor grade, tumor size, and primary treatment. The patients were followed for recurrence and death for up to 37.2 years. We used Kaplan-Meier estimators, Cox-proportional hazards models, to assess the relation between potentially prognostic indicators and RCC-specific death, and all-cause mortality.

Results: Of 872 patients, 708 had clear-cell RCC, 114 papillary RCC, 36 chromophobe RCC and 9 undefined RCC type while 5 patients had missing RCC type data. Except that, women had a significantly ($p = 0.002$) lower proportion of pRCC, no difference in RCC types and levels of albumin and CRP was observed between genders. Albumin, CRP, and GPSs were all univariately associated to RCC survival ($p < 0.001$). CRP demonstrated the strongest prognostic association (HR 1.67 95% Ci (1.53–1.83, overriding both albumin and GPS in multivariable models. The AUC for CRP was 0.77 (95% CI: 0.74-0.80).

Conclusion: Elevated CRP, low albumin levels, and elevated GPSs were all associated to poor survival in patients with RCC, Only CRP remained independent in multivariate analysis.

Abbreviations: CRP: C-reactive protein; RCC: Renal Cell Carcinoma; TNM: Tumour Node Metastasis; GPS: Glasgow Prognostic Score; GPSm: Modified Glasgow Prognostic Score; pRCC: Papillary renal cell carcinoma; chRCC: Chromophobe renal cell carcinoma

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Introduction

Renal cell carcinoma (RCC) represents about 3% of all malignancies, with 100,000 new RCC diagnoses and 39,000 kidney cancer-related deaths within the European Union in 2018 [1]. The overall mortality rates for RCC is approximately 40% (39–43%), but varies widely [1,2]. The major prognostic variables for adverse survival are local and tumor spread and histological characteristics [3]. There are three major RCC types: Clear cell RCC (ccRCC), papillary RCC (pRCC) and chromophobe RCC (chRCC) with different clinical behaviour. Accurate prognostic models are crucial to guide future adjuvant or neoadjuvant treatments.

The immunological status and inflammatory response in individual patients are thought to influence tumour growth and disease progression, and related biomarkers such as albumin and c-reactive protein (CRP) may provide additional prognostic information to the standard clinical indicators [4]. Previous studies have shown that high levels of albumin and CRP are associated with adverse patient survival [5,6]. Albumin that constitutes the majority of the total protein in human serum and body fluids is an indication of the patient's nutritional status but also an important component of the inflammatory response [7]. CRP, an acute-phase protein, is part of the activation of the complement inflammatory response and plays a role in phagocytosis and T-lymphocyte function [8]. CRP is also known to be an indicator of cell destruction and level of inflammation after surgery [8]. CRP has been found associated with poor survival in RCC patients [9]. Prognostic scores that utilize CRP and albumin levels have been developed to improve the prognostic value of these acute-phase proteins. Both the original Glasgow Prognostic Score (GPS) and the modified GPS (GPSm) has

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been suggested to enhance the prediction of survival in patients with RCC [10,11].

The aim of this study was to investigate the prognostic value of albumin and CRP, as well as the GPS scores in patients with RCC.

Materials and methods

Material

Patients surgically treated for RCC between 1982 and 2018, at the Department of Urology at Norrland University Hospital, Umeå were retrospectively retrieved from the medical records. All patients with benign histology or other malignancies than RCC were excluded. There were 872 patients with histologically confirmed RCC, 527 males and 345 females. Data on prognostic indicators and other patient characteristics were extracted from their medical records. All patients were subject to yearly follow-up, screened in the medical records and screened for being alive in the Swedish National Population Register. The last follow-up was done in December 2020. Survival time was defined as the time from diagnosis to the date of death of any cause or alive at the end of December 2020.

Histopathologic classification of RCC type and tumour grade was performed according to the Heidelberg classification and Fuhrman nuclear grading, respectively [12,13]. The updated TNM classification 2017 was used for tumour stage grouping [14]. In the stage grouping, patients with Nx were joined with N0, and Mx joined with M0. Tumour size, defined as the largest tumour diameter, was measured primarily on the computed tomography (CT) or magnetic resonance imaging (MRI) scans.

The original GPS rated from 0 to 2. Albumin level below 37 mmol/L gave 1 point and CRP level above 10 mg/L gave 1 point [11]. The GPSm scoring was similarly rated as the original, except that in GPSm no point was given for albumin level below 37 mmol/L if at the same time CRP level was below 10 mg/L. ECOG performance status was estimated at the time of the primary diagnosis [15].

Ethics

The patients had informed consent, orally before year 2000, and informed and written consent from year 2000. The study was reviewed and approved by the Ethical Review Board (Dnr: 2015-146-31 M and Dnr: 2018-296-32 M) and the Ethical board of Sweden (Dnr: 2019-02579). The data used were anonymized and throughout the project all data was treated under the regulations of the General Data Protection Regulation Act.

Statistical methods

Initial statistical analysis was performed using non-parametric tests for continuous variables and χ^2-test to evaluate survival differences. Cancer-specific survival (CSS) and patient overall survival (OS) and was estimated by the Kaplan-Meyer method and survival differences were analysed by the log-rank tests. We estimated Kaplan-Meyer curves by four categories of CRP ($\leq$3 mg/L, 3–$\leq$10, 10–$\leq$40 and $>$40 mg/L), and albumin ($\leq$37.0, 37.0–40.0, 40.0–43.0 and $>$43.0 mmol/L). All subsequent biomarker analyses were carried out using log-standardized concentration measures, meaning that all association were estimated per standard deviation increment by log-transformed concentrations of CRP or albumin. Cox multivariate regression analysis was used to evaluate if independent statistical information remained after testing variables with univariate significance. The ROC analysis was made according to a standardized evaluation of the four markers/scores. For albumin, *the log-standardized measures* were multiplied by -1 for the ROC-analysis/curves, as albumin is a negative acute-phase reactant. Potential differences were considered statistically significant when $p < 0.05$ using a double-sided test.

Results

Among the 872 surgically treated patients, 363 (41.5%) were diagnosed with stage I RCC, 130 (14.9%) with stage II, 182 (20.8%) with stage III and 197 (22.3%) with stage IV RCC. The majority (708, 81.2%) of the patients were diagnosed with clear cell RCC (ccRCC), followed by papillary RCC (pRCC, no 114, 13.1%), and 36 patients had chromophobe (chRCC, 4.1%) (Table 1). Primary surgery was radical nephrectomy (RN) in 653 (74.9%) patients, partial nephrectomy (PN) in 212

Table 1. Distribution of patient's characteristics in relation to gender in 872 patients with surgically treated renal cell carcinoma at Umeå University Hospital between 1982 and 2018.

Patients	Women	Men	Total
No	345	527	872
Age (years)			
Median	69 (range 25–88)	67 (range 18–87)	67
Mean	66.8	65.3	65.9
TNM-stage groups 2017			
I	141	222	363
II	70	60	130
III	64	118	182
IV	70	127	197
RCC -type			
ccRCC	297	411	708
pRCC	30[a]	84	114
chRCC	15	21	36
other	2	7	9
Treatments			
RN	269	384	653
PN	71[b]	141	212
Other surgery	5	2	7
ECOG PS**			
0	175	318	493
1	97	130	227
2	56	54	110
3	16	23	39
4	0	2	2
Tumor size mm			
Mean (range)	75.2 (10 – 180)	73.3 (6 – 250)	872
Total no.	345	527	872

RN: radical nephrectomy; PN: partial nephrectomy; ccRCC: clear cell renal cell carcinoma; pRCC: papillary renal cell carcinoma; chRCC: chromophobe renal cell carcinoma; ECOG PS: Eastern Cooperative Oncology Group Performance Status.

*Data on RCC-type was missing in five patients, and **ECOG PS classification was missing in one patient. (a) $p = 0.002$ in pRCC between genders, (b) $p = 0.038$ in proportion of partial nephrectomy between genders.

(24.3%), and in 7 (0.8%) patients other or combined surgeries. Mean age at diagnosis was 65.3 years for men (range: 18–87 years) and 66.8 years (ranging 25–88 years) for women. Women had lower proportion of pRCC than men ($p = 0.002$), but there were no other important differences by sex in RCC type.

There was no important difference in levels of albumin and CRP between men and women, nor were there any noticeable differences in the distribution of GPS and GPSm points between genders. The majority of patients ($n = 446$) had a 0 GPS score, 235 scored 1 and 190 patients scored 2.

At the last follow-up, 262 (30.0%) patients were alive with no evidence of the disease, 26 (3.0%) patients were alive with evidence of the disease, 350 (40.1%) patients had died with RCC indicated as underlying cause of death, and 234 (26.8%) patients had died of unrelated causes. The mean overall survival for alive patients were 9.5 years (range 2.1–37.2 years), and mean OS was 6.5 years (range 0.0 – 37.2 years) for the entire cohort.

RCC-specific survival

Hazard ratio estimates for the standard clinical variables and tumour characteristics are presented in Table 2. In the initial Kaplan-Meier analysis, albumin and CRP levels, GPS and GPSm scores all showed univariate prognostic information for RCC-specific death (p-value for log-rank test [p_{rank}] < 0.0001) (Figure 1(A–D)). In Cox-regression analyses, the hazard ratio per standard deviation increment in log-concentrations [HR_{std}] were 0.69 (95% CI: 0.64–0.75) for albumin, and 1.67 (95% CI: 1.53–1.83) for CRP. The HR for one GPS point was 1.67 (95% CI: 1.36–2.04) and 3.02 (95% CI: 2.45–3.71) for two GPS points. In mutually adjusted multivariate Cox-regression, the HR estimates were attenuated for each marker, but they maintained a clear association with RCC specific death (Table 3). However, when additionally adjusting for TNM-stage, RCC-type, and ECOG performance status, we observed little evidence for independent associations of albumin ($p = 0.957$) and GPS ($p = 0.502$ and 0.917) with RCC-specific death, and only CRP remained clearly associated with RCC death (HR_{std}: 1.34, 95% CI: 1.12–1.61). Of the two GPS scores, when tested without CRP and albumin, GPSm had the highest independent HR values: GPSm 1 point (HR 1.57 (95% CI 1.14–2.01, $p = 0.002$), GPSm 2 points HR 2.39 (95% CI 1.82–3.13, $p < 0.001$). In ROC analyses, CRP had the highest area under the curve (AUC: 0.77, 95% CI: 0.74–0.80, Figure 2).

Table 2. Cox progression hazards regression analysis of cancer specific survival in 872 patients with RCC in association to age, gender, TNM stage, Tumor Size, ECOG performance status, RCC type, type of treatment, CRP, albumin and modified Glasgow prognostic scores (GPSm).

			95,0% CI for HR		
	No	HR	Lower	Upper	p-Value
Age (years, continuous)	872	1.01	1.00	1.02	0.165
Gender	872	1.01	0.80	1.27	0.969
Stage I	363		Reference		
Stage II	130	1.70	0.97	2.97	0.062
Stage III	182	4.87	3.00	7.89	<0.001
Stage IV	197	20.78	12.81	33.71	<0.001
Tumor size (mm, continuous)	872	1,00	1.00	1.01	0.232
ECOG PS0	493		Reference		
ECOG PS1	227	1.42	1.08	1.87	0.012
ECOG PS2	110	1.98	1.45	2.69	<0.001
ECOG PS3	39	2.72	1.65	4.47	<0.001
ECOG PS4	2	0.00	0.00	>75.96	0.944
ccRCC	708		Reference		
pRCC	1114	1.60	1.15	2.22	0.005
chRCC	36	0.52	0.19	1.42	0.200
Other RCC types	9	0.73	0.22	2.37	0.599
Radical Nephrectomy	653		Reference		
Partial Nephrectomy	212	0.64	0.33	1.21	0.168
Other Surgeries	7	2.09	0.65	6.74	0.216
CRP (log, continuous)	860	1.78	1.38	2.29	<0.001
Albumin (log, continuous)	862	0.91	0.76	1.09	0.303
GPSm 0 point	442		Reference		
GPSm 1 point	230	0.71	0.46	1.10	0.126
GPSm 2 points	190	1.03	0.62	1.72	0.914

ccRCC: clear cell RCC; pRCC: papillary RCC; chRCC: chromophobe RCC; CRP: C-reactive protein; GPSm: modified Glasgow prognostic score; Data on RCC-type was missing in 5 patients, ECOG classification in one, CRP in 12 and albumin was missing in 10 patients.

All-cause mortality

When considering all-cause mortality, all biomarkers, including albumin, CRP, GPS and GPSm, were associated with survival in Kaplan Meier analysis (Figure 3). In a multivariate Cox regression analysis (Table 4), when adjusting for clinical variables and tumour characteristics, neither CRP, GPS or GPSm displayed independent associations with overall survival, whereas CRP displayed a similar association with survival as in the RCC-specific analysis (HR: 1.32, 95% CI: 1.13–1.54) (Table 4).

Discussion

Multiple factors are considered in RCC prognostics, including TNM stage, RCC-type, tumour size, tumour grade and performance status. However, several biomarkers are routinely measured in the clinic, including albumin and CRP. In this study we evaluated if these biomarkers may improve RCC prognostics and found that only CRP carried independent prognostic information.

In the present study, we evaluated the prognostic significance of albumin and CRP levels for both OS and CSS, confirming results as previously reported [16,17]. We showed that CRP and albumin levels, analysed independently, gave significant survival information. However, in multivariate Cox-regression, only CRP remained independently associated with survival when accounting for the clinical variables. Previous studies have suggested that the Glasgow Prognostic Score (GPS), which weights pre-defined cut-offs of albumin and CRP, as a better prognostic indicator [10,18]. Our results also confirmed the prognostic information of GPS on its own, as well as of GPSm [10,18] But when also taking clinical information into account, we found little evidence of an independent prognostic role of GPS or GPSm in RCC, regardless of considering RCC specific death, or all-cause mortality. Taken together, these data support the use of CRP for RCC prognostics in addition to standard clinical variables and tumour characteristics.

CRP, an acute-phase protein, is involved in the inflammatory response and has a role in T-lymphocyte function [8]. CRP is

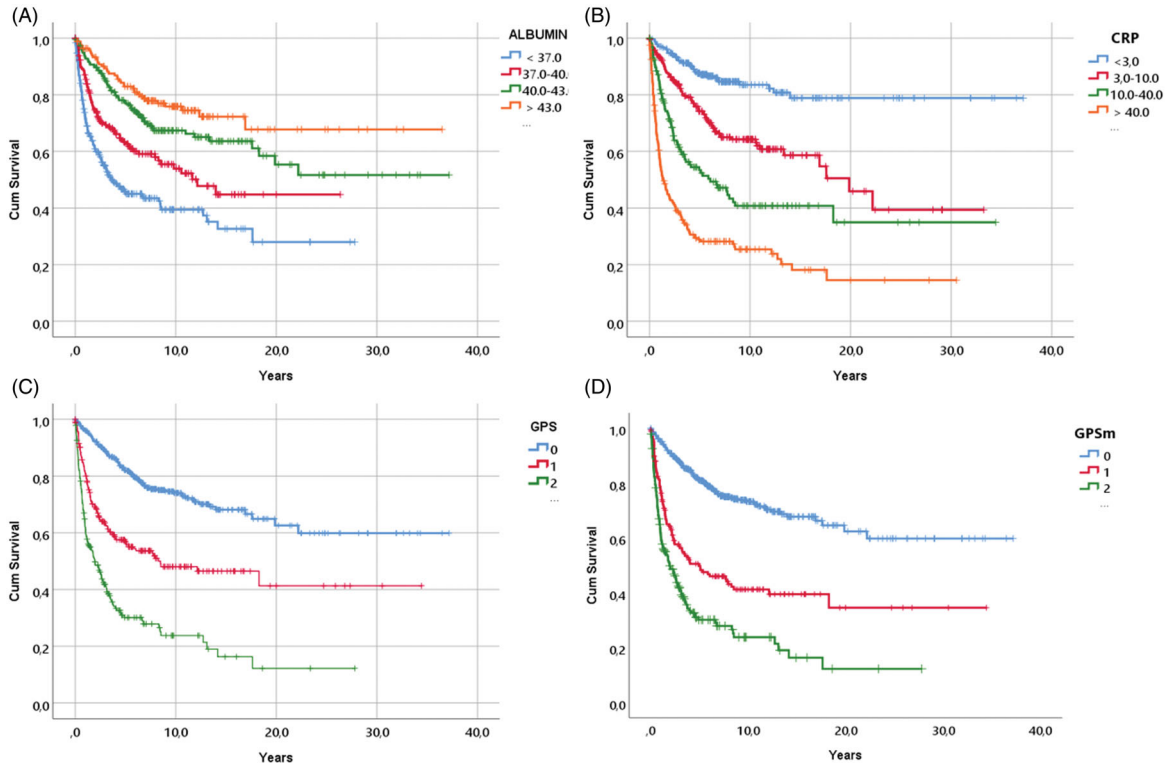


Figure 1. Kaplan-Meyer survival curves illustrating cancer specific survival in 872 patients with RCC, (A) in relation to albumin levels, (B) in relation to CRP levels, (C) in relation to Glasgow Prognostic Score points and (D) in relation to the modified Glasgow Prognostic Score points.

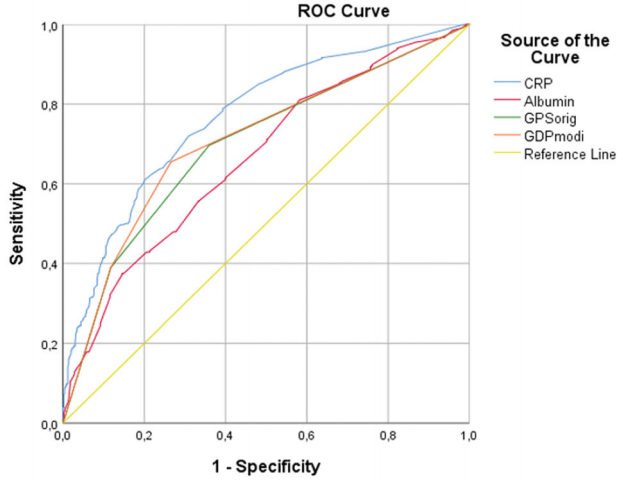
Table 3. Hazard ratios for cancer specific death for CRP, albumin and Glasgow prognostic score.

Clinical variables		Univariable analysis		Mutually adjusted		Additionally adjusted	
Variable	no	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
CRP (log)	860	1.67 (1.53–1.83)	<0.001	1.43 (1.30–1.58)	<0.001	1.34 (1.12–1.61)	<0.001
Albumin (log)	862	0.69 (0.64–0.75)	<0.001	0.85 (0.78–0.93)	<0.001	0.99 (0.87–1.14)	0.957
GPS 0 point	511	reference		reference		reference	
GPS 1 point	167	1.67 (1.36–2.04)	<0.001	1.32 (1.07–1.63)	0.009	0.98 (0.71–1.37)	0.917
GPS 2 points	188	3.02 (2.45–3.71)	<0.001	1.92 (1.54–2.40)	<0.001	1.15 (0.77–1.72)	0.502

CRP: C-reactive protein; GPS: Glasgow prognostic score.

also known to be an indicator of cell destruction and level of inflammation after surgery [8]. Using Cox multivariate analysis, we showed that CRP levels significantly correlated to both CSS and OS in this patient cohort, confirming the results of previous studies [9,16]. The importance of CRP is also shown in advanced RCC patients treated with targeted therapies [19]. In these patients, CRP can monitor treatment response and also predict treatment response. Similar experience with CRP as a prognostic biomarker has been observed in treatment with immune checkpoint inhibitors (ICI) [20]. Patients CRP might be a useful variable to monitor T-cells activation during systemic therapy in patients with advanced RCC [21]. In that study, the best result of ICI nivolumab treatment was found in the patients with CRP flare within one months of treatment and thereafter having a more than 30% decreased CRP levels. These results indicate that CRP provides powerful prognostic information that might be useful as monitor effects of ICI treatment.

With a future possibility of adjuvant treatment of patients with RCC, a number of important predictive variables will be needed for the selection of the treatment of an individual patient [3], in particular when considering ICI treatment [7].



	Area under the curve	95% Confidence Interval		p-value
		Lower	Upper	
CRP (log)	,768	,735	,800	< 0.001
Albumin (log)	,663	,626	,701	< 0.001
GPS original	,698	,661	,735	< 0.001
GDP modified	,708	,671	,745	<0.001

Figure 2. ROC curves showing areas under the curve for CRP, albumin, original and modified Glasgow Prognostic Scores in relation to cancer specific survival.

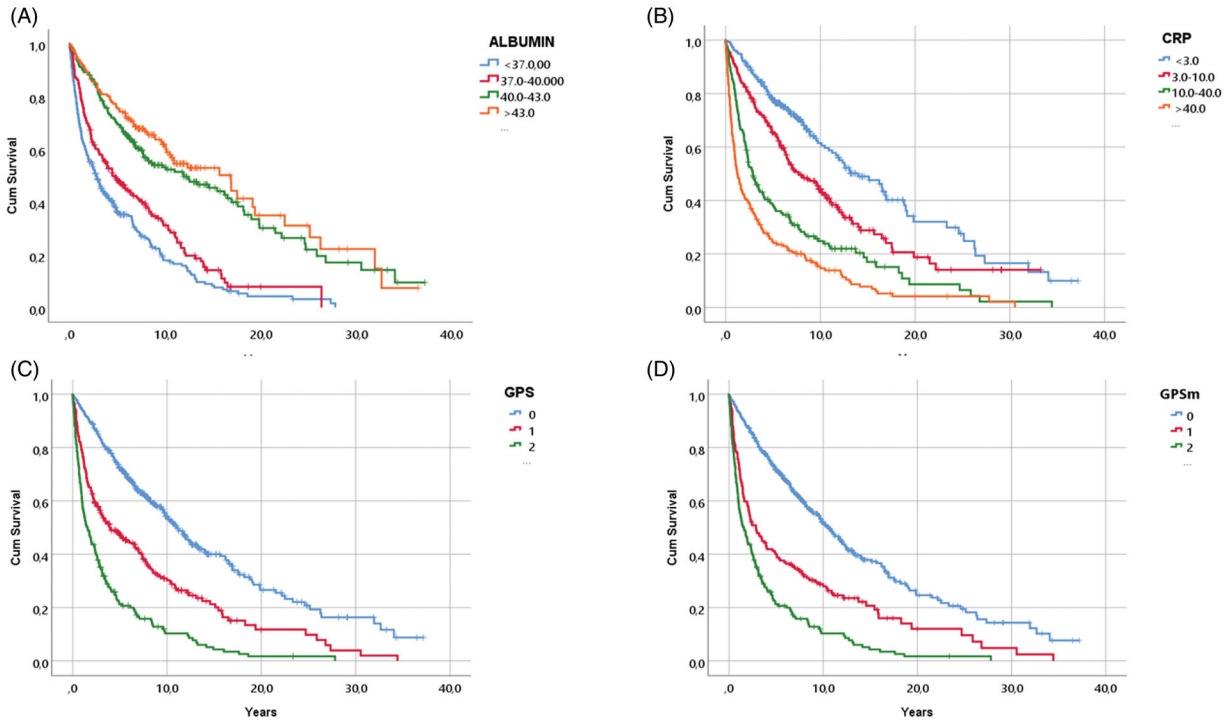


Figure 3. Kaplan-Meyer survival curves illustrating overall survival in relation to primary treatment in 872 patients with RCC, (A) in relation to albumin levels, (B) in relation to CRP levels, (C) in relation to Glasgow Prognostic Score points and (D) in relation to the modified Glasgow Prognostic Score points.

Table 4. Cox progression hazards regression analysis of Overall survival in 872 patients with RCC in association to (age, gender), TNM stage, Tumor Size, ECOG performance status, RCC type, type of treatment and Glasgow prognostic scores (GPS).

			95.0% CI for HR		
Variables	No	HR	Lower	Upper	*p*-Value
Age (years, continuous)	872	1.04	1.03	1.04	<0.001
Gender	872	0.86	0.72	1.04	0.111
TNM stage I	351		Reference		
TNM stage II	122	1.00	0.72	1.40	0.993
TNM stage III	173	1.79	1.34	2.40	<0.001
TNM stage IV	186	6.80	5.00	9.26	<0.000
Tumor size (mm)	872	1.00	1.00	1,01	0.136
ECOG PS 0	476		Reference		
ECOG PS 1	214	1.47	1.19	1.81	<0.001
ECOG PS 2	106	2.28	1.76	2.94	<0.001
ECOG PS 3	34	3.72	2.47	5.60	<0.001
ECOG PS 4	2	1.91	0.47	7.85	0.370
ccRCC	679		Reference		
pRCC	111	1.35	1.05	1.75	0.020
chRCC	33	1.04	0.63	1.71	0.879
Other RCC-types	9	0.95	0.41	2.18	0.895
Radical nephrectomy	616		Reference		
Partial nephrectomy	209	0.89	0.65	1.23	0.478
Other surgeries	7	1.23	0.49	3.04	0.661
CRP (log)	860	1.32	1.13	1.54	0.001
Albumin (log)	862	0.99	0.87	1.14	0.931
GPS 0 point	442		Reference		
GPS 1 point	230	1.00	0.76	1.32	0.997
GPS 2 points	190	1.17	0.76	1.81	0.466

ccRCC: clear cell RCC; pRCC: papillary RCC; chRCC: chromophobe RCC; CRP: C-reactive protein; GPS: Glasgow prognostic score.

Study limitations and advantages

One limitation of this study is that it is based-on patients from a single centre, which may theoretically limit the extent to which are findings translate to other settings. Another potential limitation is that the biomarker measurements were performed continuously in a clinical setting over a long period. This contrasts to studies with standardized biomarker measurements carried out in a coordinated fashion for academic purposes. Indeed, our setting is likely to encounter higher level of technical noise and drifts in biomarker measurements and may for this reason display poorer performance. However, we would argue that our data are likely to realistically reflect the performance of assessed biomarkers in this clinical setting. It is further important to highlight that during the study period, there have been continuous improvements in imaging techniques (which have greatly increased incidental detection), development of new surgical techniques, and developments of systemic therapies. All these enhancements have improved the overall survival in patients with RCC in general [22].

Conclusion

The prognosis for patients with RCC is dependent on multiple factors. Inflammatory response, as indicated by circulating CRP, appears to be an important prognostic indicator for patients with RCC. It also highlight the importance of considering the immune system response in predicting the clinical course, in the era of immunotherapy.

Disclaimer

Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily

represent the decisions, policy or views of the International Agency for Research on Cancer/World Health Organization.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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