Preoperative Leucocytosis, Thrombocytosis and Anemia as Potential Prognostic Factors in Non-metastatic Renal Cell Carcinoma

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Abstract. *Background: To validate the potential prognostic significance of preoperatively assessed inflammatory parameters leucocytosis, thrombocytosis and anemia in patients with non-metastatic renal cell carcinoma (RCC). Materials and Methods: We retrospectively evaluated a cohort comprising 736 consecutive patients with non-metastatic RCC, operated on between 2004 and 2012 with curative radical or partial nephrectomy at a single tertiary academic centre. Laboratory parameters were assessed within one week before surgical intervention. Patients were categorized using laboratory parameter cut-off values according to receiver operating characteristics (ROC) analyses. Cancer-specific survival (CSS) was assessed using the Kaplan–Meier method. To evaluate the potential prognostic significance of the preoperative laboratory parameters, multivariate Cox regression models were applied. Results: Multivariable analysis identified preoperative thrombocytosis (≥285,000/μl) as an independent prognostic factor for CSS (Hazard ratio=2.28, 95% confidence interval=1.24-4.20, p=0.008). Conclusion: Regarding CSS, an elevated preoperative platelet count represented an independent prognostic factor of poor survival. Our findings strengthen the potential prognostic significance of preoperative thrombocytosis in patients with non-metastatic RCC.*

The worldwide incidence rates of renal cell carcinoma (RCC) have slightly increased over the past three decades (1), whereby due to the more widespread use of radiological imaging techniques, a tendency towards diagnosis of small and organ-confined tumours has been observed (2, 3). The use of prognostic factors that can accurately predict clinical outcomes of patients with RCC are of specific importance for individualized risk assessment (4).

Several prognostic models comprising different histological RCC subtypes regarding different end-points have been established to better predict patients' RCC clinical outcomes (4-8). For instance, the Leibovich prognosis score integrates five clinicopathological features translated into a score and categorizes patients into eight score categories, which are then assigned to one of three different risk groups (7). According to this score, patients with non-metastatic RCC assigned into the low-, intermediate-, or high-risk groups the risk for the occurrence of metastatic disease after radical nephrectomy can accurately be assessed.

The predictive accuracy (PA) of such risk-assessment tools might be further improved by the incorporation of potential prognostic biomarkers (8). Surrogate peripheral blood-based parameters, such as C-reactive protein, the preoperative neutrophil-lymphocyte ratio, the lymphocyte-monocyte ratio, as well as the platelet count, have been shown to be able independently to predict the clinical outcomes of various cancer types (9-15).

In particular, the potential prognostic role of an elevated preoperative platelet count and thrombocytosis in patients with localized RCC, as well as in the metastatic setting, were recently investigated by several research groups, whereby the results are still controversial. In the largest pooled patient series to date, Brookman-May *et al.* recently demonstrated preoperative thrombocytosis to represent an independent predictor regarding patients' cancer-specific survival (CSS) in RCC, albeit they did not report on the potential prognostic role of the preoperative leucocyte count, nor the haemoglobin concentration (15). Thus, the aim of our study was to validate the potential prognostic

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significance of the preoperatively assessed inflammatory parameters leucocytosis, thrombocytosis and anaemia in a single-centre series of patients with non-metastatic RCC.

Materials and Methods

This retrospective analysis included data from 736 patients with non-metastatic RCC who underwent curative radical or partial nephrectomy at the Department of Urology at the Medical University of Graz between January 2004 and December 2012. All clinicopathological data were retrieved from the medical records from the Department of Urology, as well as from pathology reports from the Institute of Pathology at the same Institution. Pathological T-stages were uniformly adjusted according to the seventh edition of the TNM classification system (16). Other documented parameters included tumour size, histological RCC subtype, tumour grade, as well as patients' age and gender. All laboratory data were obtained within one week before surgical intervention. Patients' postoperative surveillance included routine clinical and laboratory examination; regarding imaging methods, X-rays of the chest and abdominal ultrasound were predominantly used, especially in patients with a low relapse risk (pT-1, G1-2), whereas computed tomography or magnetic resonance imaging was performed in all other patients as previously reported (17). Follow-up evaluations were performed every six months for the first five years and annually thereafter for locally advanced tumours. In organ-confined cancer, imaging was performed twice in the first year after surgery and annually thereafter. Dates of death were obtained from the central registry of the Austrian Bureau of Statistics. This study was approved by the Ethical Committee of the Medical University of Graz (26-135 ex 13/14).

Statistical analysis. The primary study end-point was CSS, which was calculated (in months) from the date of surgery to the date of the patients' cancer-related death. The ideal cut-off values for the continuously coded laboratory parameters (leucocytes, thrombocytes and haemoglobin) were calculated by testing all possible cut-offs that would discriminate between survival and cancer-related death by Cox proportional analyses as previously reported (18).

The relationship between the preoperatively assessed laboratory parameters and clinicopathological parameters was studied by non-parametric tests (χ^2- and Mann-Whitney's *U*-test). CSS was calculated using the Kaplan–Meier method and compared by the log-rank test. Backward stepwise multivariate Cox proportion analysis was performed. Hazard ratios (HRs) estimated from the Cox analysis are reported as relative risks with corresponding 95% confidence intervals (CIs). All statistical analyses were performed using the Statistical Package for Social Sciences version 18.0 (SPSS Inc., Chicago, IL, USA). A two-sided value of $p<0.05$ was considered statistically significant.

Results

Overall, a total of 736 patients with non-metastatic RCC were included in this study. Descriptive clinicopathological parameters of the study cohort are shown in Table I. Median follow-up was 16 months, during which 52 (7.1%) patients died as a consequence of their RCC. Applying receiver operating characteristics (ROC) analyses as mentioned above, the cut-off values regarding the preoperative leucocyte count, platelet count and haemoglobin concentration were 6,600 cells/μl, 285,000 cells/μl and 13.2 g/dl, respectively (Figure 1). The associations of the preoperative leucocyte and platelet counts with clinicopathological parameters are shown in Table II. The associations between the preoperative haemoglobin concentration with clinicopathological parameters, as well as the multivariate analysis of clinicopathological parameters for the prediction of CSS are provided in Table III. It reveals that pathological T-stage (pT-1+p-T-2 *vs*. pT-3+pT-4: HR=3.624, 95% CI=2.42-5.43; $p<0.001$) , tumour grade (G-1+G-2 *vs*. G-3+G-4: HR=1.786, 95% CI=1.16-2.75; $p=0.009$), as well as the preoperative platelet count (<285,000 *vs*. ≥285,000/μl: HR=2.282, 95% CI=1.24-4.20; $p=0.008$) achieved independent predictor status regarding patient CSS. Figure 2 shows the Kaplan–Meier curves for the preoperative leucocyte, platelet, as well as haemoglobin concentration predicting CSS and reveals statistical significance regarding the preoperative platelet count, as well as the haemoglobin concentration (both log-rank $p<0.001$), whereas the preoperative leucocyte count was of borderline significance (log-rank $p=0.051$).

Discussion

Despite enormous progress in the identification of genetic, epigenetic and common molecular alterations in RCC being made (19), the routine prognostic assessment of RCC currently still relies on traditional clinicopathological variables (20, 21). The complexity of newly discovered potential molecular markers, as well as high costs of analyses and the lack of evidence demonstrating how these biomarkers might influence diagnostic or therapeutic decisions, have led to none of these markers being currently available for routine testing. Regularly used blood-based parameters are easy to assess without additional laborious efforts, making them attractive potential parameters for improved individualised risk assessment in patients with RCC (8).

In the largest study published to date, Brookman-May and colleagues recently demonstrated that preoperative thrombocytosis represented an independent predictor regarding CSS in >2,800 patients with localized RCC, whereas in the metastatic setting it did not (15). Nevertheless, the authors reported an only marginal improvement regarding the PA when integrating preoperative thrombocytosis in multivariate models combined with standard clinicopathological variables. Their observation is largely corroborated in the literature. For instance, Karakiewicz *et al*. reported data exploring >1,800 patients with RCC, and despite equally finding preoperative thrombocytosis to be an independent predictor of CSS, its inclusion in a multivariate model did not improve PA in a statistically significant fashion (22). Others were also able to show preoperative thrombocytosis to represent an independent predictor regarding patient CSS in RCC (23-25).

Table I. *Descriptive clinico-pathological parameters of the study cohort comprising patients with non-metastatic renal cell carcinoma (n=736).*

Parameter	Value
Age at operation (years)	
Mean±SD	63.7±12.0
Median	65.4
IQR	56.2-73.2
<65 Years	354 (48.1)
≥65 Years	382 (51.9)
Gender, n (%)	
Male	451 (61.3)
Female	285 (38.7)
Histological subtype, n (%)	
Clear cell	596 (81.0)
Papillary	97 (13.2)
Chromophobe	36 (4.9)
Collecting duct	4 (0.5)
Unclassified	3 (0.4)
Tumour size (cm)	
Mean±SD	4.6±2.7
Median	4.0
IQR	2.5-6.0
Pathological T-stage (TNM 2009, Ref. 16), n (%)	
pT-1a	364 (49.5)
pT-1b	129 (17.5)
pT-2a	48 (6.6)
pT-2b	1 (0.1)
pT-3a	107 (14.5)
pT-3b	81 (11.0)
pT-3c	3 (0.4)
pT-4	3 (0.4)
Tumor grade, n (%)	
G-1	187 (25.4)
G-2	400 (54.3)
G-3	141 (19.2)
G-4	8 (1.1)
Preoperative leucocytes (cells/µl)	
Mean±SD	7550±2759
Median	7000
Range	2000-32000
Preoperative thrombocytes (cells/µl)	
Mean±SD	246450±81671
Median	234500
Range	72000-841000
Preoperative haemoglobin (g/dl)	
Mean±SD	13.6±1.8
Median	13.8
Range	7.6-19.1

In our recent single-centre study comprising >700 patients with non-metastatic RCC, exploring three different preoperatively assessed laboratory parameters, an elevated platelet count (≥285,000/µl) was an independent prognostic factor regarding CSS (p=0.008), whereas the preoperative leucocyte count and haemoglobin concentration were not (p=0.842 and 0.277, respectively). The distribution of patients with a low (<285,000 µl)

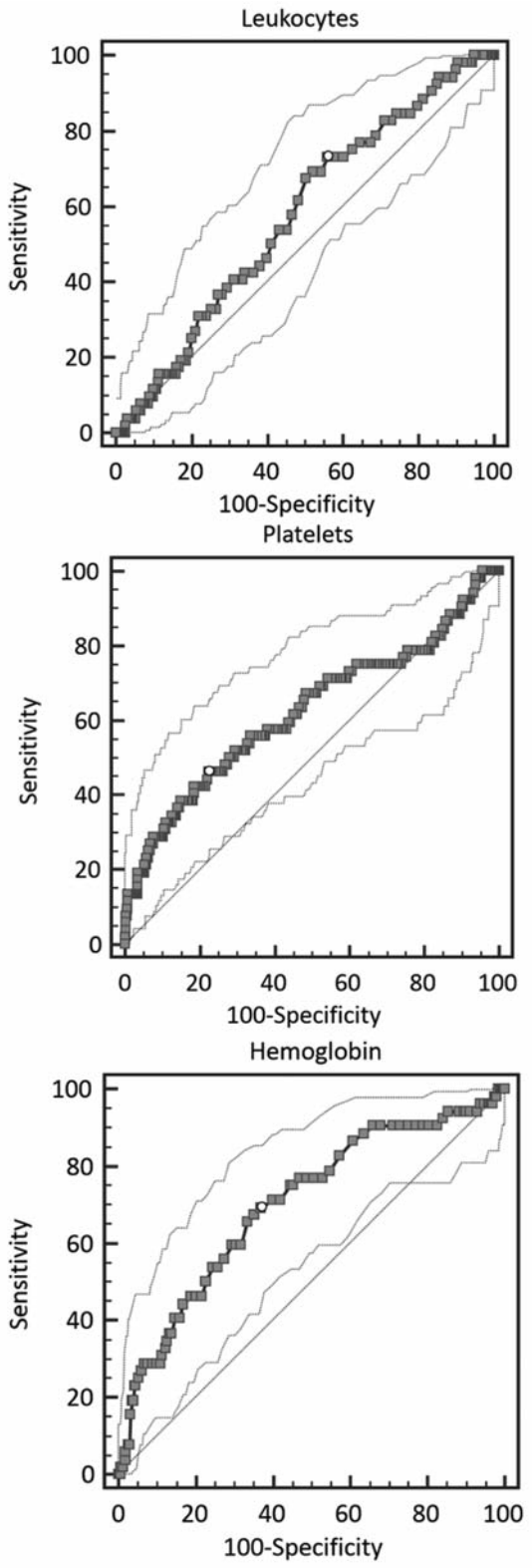

Figure 1. *The area under the curve (AUC) for the preoperative leucocyte count was 0.573 (95%CI=0.54-0.61). The AUC for the preoperative platelet count was 0.622 (95%CI=0.59-0.66). The AUC for the preoperative haemoglobin concentration was 0.699 (95%CI=0.66-0.73).*

Table II. *Crosstable demonstrating the association of the preoperative leucocyte, as well as platelet counts with various clinico-pathological parameters in the study cohort (n=736).*

Parameter	Leucocytes, n (%)		Total, n (%)	*p*-Value
	<6.6 cells/μl	≥6.6 cells/μl		
Age at operation (years)				0.166
<65 Years	154 (51.2%)	200 (46.0%)	354 (48.1%)	
≥65 Years	147 (48.8%)	235 (54.0%)	382 (51.9%)	
Gender, n (%)				0.402
Male	179 (59.5%)	272 (62.5%)	451 (61.3%)	
Female	122 (40.5%)	163 (37.5%)	285 (38.7%)	
Histological subtype, n (%)				0.624
Clear cell	238 (79.1%)	358 (82.3%)	596 (81.0%)	
Papillary	41 (13.6%)	56 (12.9%)	97 (13.2%)	
Chromophobe	19 (6.3%)	17 (3.9%)	36 (4.9%)	
Collecting duct	2 (0.7%)	2 (0.5%)	4 (0.5%)	
Unclassified	1 (0.3%)	2 (0.5%)	3 (0.4%)	
Pathological T-stage, n (%)				0.001
pT-1a + pT-1b	225 (74.8%)	268 (61.6%)	493 (67.0%)	
pT-2a + pT-2b	21 (7.0%)	28 (6.4%)	49 (6.7%)	
pT-3a-c	54 (17.9%)	137 (31.5%)	191 (26.0%)	
pT-4	1 (0.3%)	2 (0.5%)	3 (0.4%)	
Tumour grade, n (%)				0.491
G-1	85 (28.2%)	102 (23.4%)	187 (25.4%)	
G-2	160 (53.2%)	240 (55.2%)	400 (54.3%)	
G-3	53 (17.6%)	88 (20.2%)	141 (19.2%)	
G-4	3 (1.0%)	5 (1.1%)	8 (1.1%)	
Total	301 (40.9%)	435 (59.1%)	736 (100.0%)	
Parameter	Thrombocytes			
	<285,000 cells/μl	≥285,000 cells/μl		
Age at operation (years)				0.026
<65 Years	255 (45.8%)	99 (55.3%)	354 (48.1%)	
≥65 Years	302 (54.2%)	80 (44.7%)	382 (51.9%)	
Gender, n (%)				0.010
Male	356 (63.9%)	95 (53.1%)	451 (61.3%)	
Female	201 (36.1%)	84 (46.9%)	285 (38.7%)	
Histological subtype, n (%)				0.025
Clear cell	455 (81.7%)	141 (78.8%)	596 (81.0%)	
Papillary	72 (12.9%)	25 (14.0%)	97 (13.2%)	
Chromophobe	28 (5.0%)	8 (4.5%)	36 (4.9%)	
Collecting duct	2 (0.4%)	2 (1.1%)	4 (0.5%)	
Unclassified	0 (0.0%)	3 (1.7%)	3 (0.4%)	
Pathological T-stage, n (%)				0.007
pT-1a + pT-1b	392 (70.4%)	101 (56.4%)	493 (67.0%)	
pT-2a + pT-2b	32 (5.7%)	17 (9.5%)	49 (6.7%)	
pT-3a-c	131 (23.5%)	60 (33.5%)	191 (26.0%)	
pT-4	2 (0.4%)	1 (0.6%)	3 (0.4%)	
Tumour grade, n (%)				0.001
G-1	151 (27.1%)	36 (20.1%)	187 (25.4%)	
G-2	309 (55.5%)	91 (50.8%)	400 (54.3%)	
G-3	94 (16.9%)	47 (26.3%)	141 (19.2%)	
G-4	3 (0.5%)	5 (2.8%)	8 (1.1%)	
Total	557 (75.7%)	179 (24.3%)	736 (100.0%)	

preoperative and those with an elevated (≥285,000/μl) preoperative platelet count was unequal (557/75.7% *vs.* 179/24.3%).

Definitive explanations for our findings remain elusive. In the metastatic RCC setting, Heng *et al.* demonstrated that activated platelets facilitate the adhesion of tumour

Table III. *Crosstable demonstrating the association of the preoperative haemoglobin concentration with various clinico-pathological parameters and multivariate analysis of clinico-pathological parameters for the prediction of cancer-specific survival (CSS) in patients with non-metastatic renal cell carcinoma (n=736).*

Parameter	Haemoglobin, n (%)		Total	*p*-Value
	<13.2 g/dl	≥13.2 g/dl		
Age at operation (years)				0.006
<65 Years	115 (41.5%)	239 (52.1%)	354 (48.1%)	
≥65 Years	162 (58.5%)	220 (47.9%)	382 (51.9%)	
Gender, n (%)				<0.001
Male	124 (44.8%)	327 (71.2%)	451 (61.3%)	
Female	153 (55.2%)	132 (28.8%)	285 (38.7%)	
Histological subtype, n (%)				0.050
Clear cell	228 (82.3%)	368 (80.2%)	596 (81.0%)	
Papillary	32 (11.6%)	65 (14.2%)	97 (13.2%)	
Chromophobe	11 (4.0%)	25 (5.4%)	36 (4.9%)	
Collecting duct	4 (1.4%)	0 (0.0%)	4 (0.5%)	
Unclassified	2 (0.7%)	1 (0.2%)	3 (0.4%)	
Pathological T-stage, n (%)				<0.001
pT-1a + pT-1b	160 (57.8%)	333 (72.5%)	493 (67.0%)	
pT-2a + pT-2b	18 (6.5%)	31 (6.8%)	49 (6.7%)	
pT-3a-c	96 (34.7%)	95 (20.7%)	191 (26.0%)	
pT-4	3 (1.1%)	0 (0.0%)	3 (0.4%)	
Tumor grade, n (%)				<0.001
G-1	57 (20.6%)	130 (28.3%)	187 (25.4%)	
G-2	129 (46.6%)	271 (59.0%)	400 (54.3%)	
G-3	84 (30.3%)	57 (12.4%)	141 (19.2%)	
G-4	7 (2.5%)	1 (0.2%)	8 (1.1%)	
Total	277 (37.6%)	459 (62.4%)	736 (100.0%)	

Parameter	Multivariate analysis	
	Hazard ratio (95% confidence interval)	*p*-Value
Age at operation (years)		
<65 Years	1 (reference)	0.665
≥65 Years	0.880 (0.494-1.568)	
Gender		
Female	1 (reference)	0.189
Male	0.680 (0.383-1.208)	
Histological subtype		
clear cell	1 (reference)	0.640
others	1.095 (0.749-1.598)	
Pathological T-stage		
pT-1 + pT-2	1 (reference)	<0.001
pT-3 + pT-4	3.624 (2.420-5.428)	
Tumour grade		
G-1 + G-2	1 (reference)	0.009
G-3 + G-4	1.786 (1.159-2.752)	
Preoperative leucocyte count (cells/μl)		
<6.6	1 (reference)	0.842
≥6.6	0.936 (0.489-1.792)	
Preoperative platelet count (cells/μl)		
<285,000	1 (reference)	0.008
≥285,000	2.282 (1.240-4.199)	
Preoperative haemoglobin concentration (g/dl)		
<13.2	1 (reference)	0.277
≥13.2	0.690 (0.354-1.347)	

cells to the endothelium by interactions with platelet ligands and additionally might inhibit or delay immunological detection of circulating tumour cells (26). In addition, it was reported over a decade ago that activated platelets are able to produce angiogenic tumour growth factors, *e.g.* vascular endothelial growth factor and others, which might thus enhance tumour growth and metastatic spread (27).

As with all retrospective studies, limitations of our study are inherent to its design, including the retrospective data collection. No consistent data were available regarding the patients' Eastern Cooperative Oncology Group performance status, nor about postoperatively assessed laboratory parameters. In addition, patients from this study underwent surgical treatment by multiple surgeons. Finally, the ideal cut-off values for the preoperatively assessed laboratory parameters were calculated by testing all possible thresholds that would discriminate between patients' survival and cancer-related death by Cox proportional analyses. Nonetheless, even considering these limitations, our data clearly indicate that an elevated preoperative platelet count might represent an independent prognostic factor for poorer CSS in patients with non-metastatic RCC.

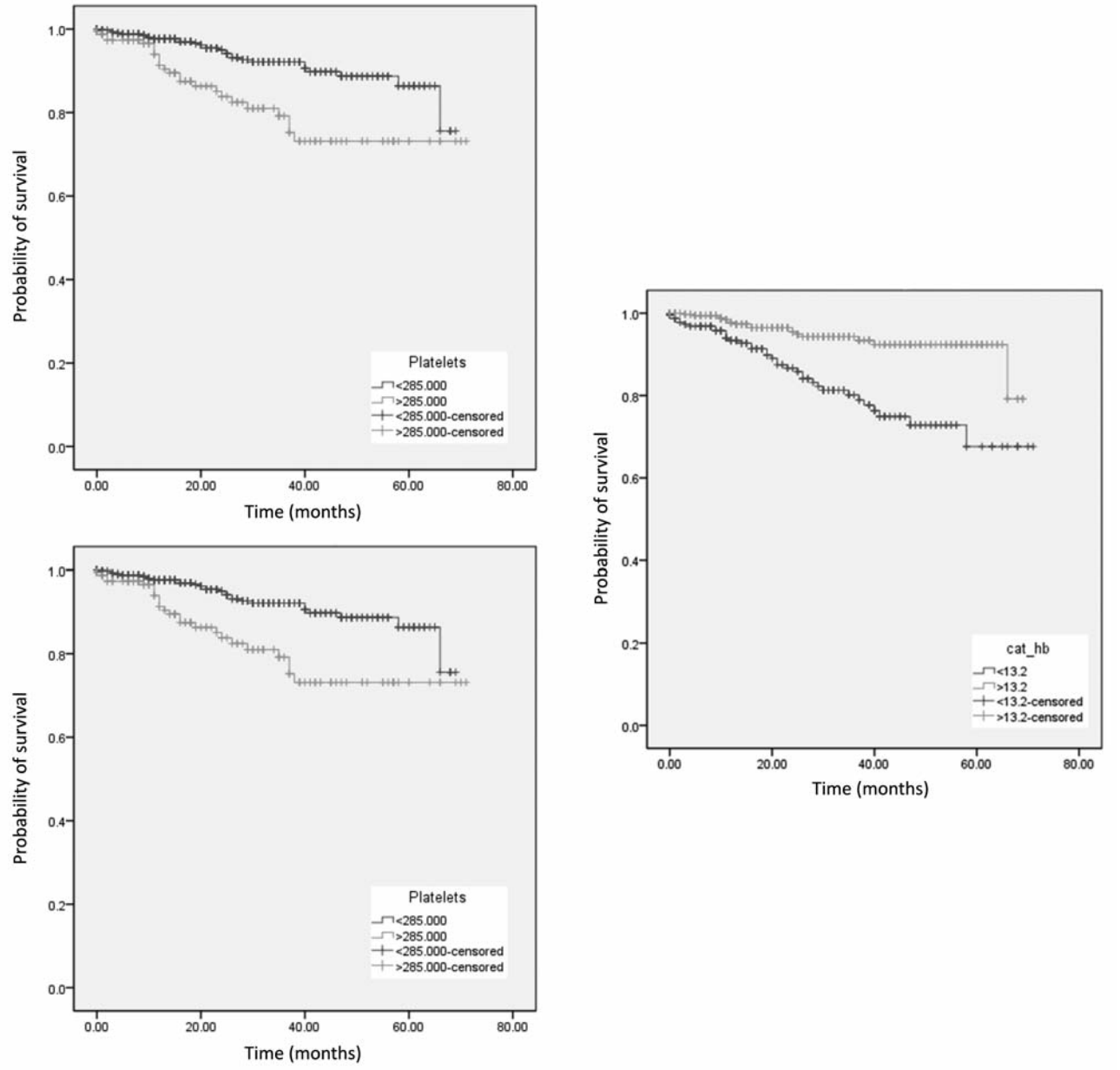

Figure 2. *Kaplan-Meier curves predicting renal cell carcinoma patients' cancer-specific survival (CSS), groups categorized according to the preoperative leucocyte-, thrombocyte-, as well as haemoglobin concentration.*

Conflicts of Interest

None of the contributing Authors have any conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the article.

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