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.
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 (pT1, 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 the Cox proportional analyses as previously reported (18).

The relationship between the preoperatively assessed laboratory parameters and clinicopathological parameters was studied by non-parametric tests (χ²- 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 (pT1-pT-2 vs. pT3+pT-4: HR=3.624, 95% CI=2.42-5.43; p<0.001), tumour grade (G1+G-2 vs. G3+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).
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) platelet count was not significantly different between different tumour stages or grades, whereas the preoperative leucocyte count and haemoglobin concentration were higher in patients with higher tumour stages and grades.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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<tr>
<td>Age at operation (years)</td>
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<td>Mean±SD</td>
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<tr>
<td>IQR</td>
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<tr>
<td>&lt;65 Years</td>
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<tr>
<td>≥65 Years</td>
<td>382 (51.9)</td>
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<td>Gender, n (%)</td>
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<tr>
<td>Male</td>
<td>451 (61.3)</td>
</tr>
<tr>
<td>Female</td>
<td>285 (38.7)</td>
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<tr>
<td>Histological subtype, n (%)</td>
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<tr>
<td>Clear cell</td>
<td>596 (81.0)</td>
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<tr>
<td>Papillary</td>
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<tr>
<td>Chromophobe</td>
<td>36 (4.9)</td>
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<tr>
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<td>Unclassified</td>
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<td>IQR</td>
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<tr>
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<tr>
<td>pT-1a</td>
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<tr>
<td>pT-1b</td>
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<tr>
<td>pT-2a</td>
<td>48 (6.6)</td>
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<tr>
<td>pT-2b</td>
<td>1 (0.1)</td>
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<tr>
<td>pT-3a</td>
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<td>pT-3b</td>
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<tr>
<td>pT-3c</td>
<td>3 (0.4)</td>
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<td>pT-4</td>
<td>3 (0.4)</td>
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<tr>
<td>Tumor grade, n (%)</td>
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<tr>
<td>G-1</td>
<td>187 (25.4)</td>
</tr>
<tr>
<td>G-2</td>
<td>400 (54.3)</td>
</tr>
<tr>
<td>G-3</td>
<td>141 (19.2)</td>
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<tr>
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<td>8 (1.1)</td>
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<td>Preoperative leucocytes (cells/μl)</td>
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<td>Range</td>
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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).
Definitive explanations for our findings remain elusive. In the metastatic RCC setting, Heng et al. demonstrated that activated platelets facilitate the adhesion of tumour cells.
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.

<table>
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<td>≥65 Years</td>
<td>162 (58.5%)</td>
<td>382 (51.9%)</td>
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<td>Gender, n (%)</td>
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<td>124 (44.8%)</td>
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<tr>
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<td>153 (55.2%)</td>
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<td>228 (82.3%)</td>
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<td>32 (11.6%)</td>
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<td>Chromophobe</td>
<td>11 (4.0%)</td>
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<tr>
<td>Collecting duct</td>
<td>4 (1.4%)</td>
<td>4 (0.5%)</td>
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<tr>
<td>Unclassified</td>
<td>2 (0.7%)</td>
<td>3 (0.4%)</td>
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<td>Pathological T-stage, n (%)</td>
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<tr>
<td>pT-1a + pT-1b</td>
<td>160 (57.8%)</td>
<td>493 (67.0%)</td>
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<tr>
<td>pT-2a + pT-2b</td>
<td>18 (6.5%)</td>
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<td>pT-3a-c</td>
<td>96 (34.7%)</td>
<td>191 (26.0%)</td>
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<td>pT-4</td>
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<td>3 (0.4%)</td>
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<td>Tumor grade, n (%)</td>
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<tr>
<td>G-1</td>
<td>57 (20.6%)</td>
<td>187 (25.4%)</td>
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<tr>
<td>G-2</td>
<td>129 (46.6%)</td>
<td>400 (54.3%)</td>
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<tr>
<td>G-3</td>
<td>84 (30.3%)</td>
<td>141 (19.2%)</td>
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<tr>
<td>G-4</td>
<td>7 (2.5%)</td>
<td>8 (1.1%)</td>
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<tr>
<td>Total</td>
<td>277 (37.6%)</td>
<td>736 (100.0%)</td>
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<table>
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</tr>
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<td>≥65 Years</td>
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<td>1 (reference) 0.640 (0.383-1.208)</td>
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<tr>
<td>others</td>
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<td>pT-1 + pT-2</td>
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<td>G-3 + G-4</td>
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<td>Preoperative leucocyte count (cells/μl)</td>
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<td>≥6.6</td>
<td>0.936 (0.480-1.792)</td>
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<td>Preoperative platelet count (cells/μl)</td>
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<td>≥285,000</td>
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<td>Preoperative haemoglobin concentration (g/dl)</td>
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<tr>
<td>&lt;13.2</td>
<td>1 (reference) 0.277 (0.354-1.347)</td>
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<tr>
<td>≥13.2</td>
<td>0.690 (0.354-1.347)</td>
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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.

References


