Resumen.- OBJETIVO: Analizar la relación existente entre trombocitosis y hematocrito prequirúrgicos y supervivencia en nuestra serie de pacientes tratados quirúrgicamente por adenocarcinoma renal.

MÉTODO: Estudio retrospectivo con análisis descriptivo estadístico de 139 pacientes intervenidos quirúrgicamente en nuestro servicio en los últimos 4 años por presentado como enfermedad avanzada o metastásica. Recopilamos datos sobre supervivencia y tiempo en vigilancia, imágenes y características histológicas del tumor y parámetros analíticos. Los datos se analizaron con el software estadístico SPSS.

RESULTADOS: La media de la cuenta de plaquetas y hematocrito antes de la intervención fueron 260,930 células/mm3 y 41.10%, respectivamente. Hallamos una correlación estadística entre el conteo de plaquetas al momento del diagnóstico y la supervivencia. Los pacientes con conteos de plaquetas superiores a 350,000 células/mm3 tuvieron una mala supervivencia (OR: 2.94; CI 95% 1.04-8.27). También encontramos que los pacientes con hematocritos altos al diagnóstico presentaron un menor riesgo de muerte (OR: 0.92; CI 95% 0.85-0.99). La supervivencia global al final del estudio fue de 88.4%. La análisis multivariado no mostró ningún resultado significativo debido al bajo número de defunciones.

CONCLUSIÓN: La presencia de altos conteos de plaquetas o bajos hematocritos correlaciona con mala supervivencia en un grupo de pacientes con cáncer de células renales tratados quirúrgicamente. Sin embargo, se requieren más estudios con mayor vigilancia y un número mayor de pacientes.

CORRESPONDENCIA
Carlos Javier Ortega Seda
Ramón y Cajal, 81 A
41510 Mairena del Alcor
Sevilla (Spain).
carlosjavierhuerta@hotmail.com

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Keywords: Célula plaquetaria. Hematocrito. Factores pronósticos. Cáncer de células renales.
Renal cell carcinoma (RCC) accounts for 3% of all malignancies and ranks third in frequency of urological malignancies (1), with a higher prevalence in developed countries. In the last two decades it has been found a progressive increase in its incidence, with an annual growth of 2% worldwide (2).

The standard treatment of localized disease remains the surgery, whereas in disseminated disease, the emergence of new therapies against specific molecular targets has achieved discrete but significant increases in survival (3). Several prognostic factors have been involved in the natural history of RCC, and the most important are the stage and tumour grade and the patient’s general condition (performance status). The appearance of possible biochemical prognostic factors has attracted increasing interest (4). These include platelet count, associated with the process of tumour neoangiogenesis, or hematocrit, reflecting an underlying anaemic state.

The study of the prognostic value of platelet counts in localized and metastatic RCC in more or less extensive series of patients with this diagnosis revealed an adverse effect of thrombocytosis on survival (5-9). These and other findings have encouraged us to analyze our series of RCC in order to find data on this subject.

The aim of this study is to analyze descriptively our RCC patients between 2006 and 2009, and to explore a possible relationship between the preoperative platelet count and hematocrit and overall survival.

MATERIAL AND METHODS

To this end we conducted a retrospective study with descriptive and statistical analysis of 139 patients treated by surgery in our centre after diagnosis of RCC since January 2006 to December 2009.

From each patient we took demographic data, those relating to follow up time and overall survival, imaging features, Fuhrman grade and histological subtype tumour, presence of metastases or lymph node invasion and laboratory parameters such as pre-and postoperative platelet count and hematocrit. “Thrombocytosis” was defined as the presence of a platelet count \( \geq \) than 350000 cells/ml.

The data were taken from Advanced Clinical Documentation Centre on Virgen del Rocío University Hospitals, they were stored in Access database ® and analyzed by SPSS statistical software®, using logistic regression tests and Kaplan-Meier curves for univariate analyzes. We carried out a multivariate analysis to try to identify independent prognostic factors, for this purpose we used a Cox proportional regression model.

Among the 139 patients, 52 were women (37.4%) and 87 men (62.6%), with an average age of 59 years (37- 84). Average tumour size prior to surgery (as measured by CAT or MRI) was 6.61 cm (0.2 to 20). The mean follow was of 11.7 months (1-34). In the Table I you can observe the clinical and demographic characteristics of the patients.

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For blood test data we checked laboratory studies of pre-anaesthesia consultation and urological review three months after surgery. In all cases, both

The diagnostic process as therapeutic and follow-up procedures were adjusted the recommendations of major clinical guidelines (EUA, NCCN...).

RESULTS

116 (83.4%) cases were diagnosed at clinically localized stage (T<= 2N0M0) and 23 (16.6%) as a locally advanced or metastatic disease (T>= 3, any N, any M). 10 patients presented with nodal metastases objectified by CT and in other 7 cases metastases in solid organs were found (7.19% and 5.03% respectively). 49 patients (35.2%) were symptomatic at diagnosis. In the remaining cases it was an incidental diagnose. Overall survival in the group at the end of the study (4 years) was 88.4%.

The average tumour size after histopathology sections was 6.78 cm with a range of between 20 and 1.5 cm. 36 samples (25.89%) presented areas of necrosis.

<table>
<thead>
<tr>
<th>Feature</th>
<th>Media</th>
<th>Ranges and absolute values</th>
</tr>
</thead>
<tbody>
<tr>
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<td>27- 84</td>
</tr>
<tr>
<td>Sex</td>
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</tr>
<tr>
<td>Men</td>
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<td>87</td>
</tr>
<tr>
<td>Women</td>
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<td>52</td>
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<td>49</td>
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<tr>
<td>Metastases</td>
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<td>7</td>
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<tr>
<td>Lymph node invasion</td>
<td>7,2</td>
<td>10</td>
</tr>
<tr>
<td>Clinical Stage&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
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<tr>
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<td>83,5</td>
<td>116</td>
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<tr>
<td>Unlocated</td>
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<td>23</td>
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<tr>
<td>Platelet count&lt;sup&gt;b, c&lt;/sup&gt;</td>
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<td>757000- 34000</td>
</tr>
<tr>
<td>Hematocrit&lt;sup&gt;b, d&lt;/sup&gt;</td>
<td>41</td>
<td>96- 23</td>
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<td>Size&lt;sup&gt;e&lt;/sup&gt;</td>
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<td>Histological subtype&lt;sup&gt;f&lt;/sup&gt;</td>
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<td></td>
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<tr>
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<td>94</td>
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<td>Papillary</td>
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<td>30</td>
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<td>Chromophobe</td>
<td>7,9</td>
<td>11</td>
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<tr>
<td>Sarcomatoid</td>
<td>2,8</td>
<td>4</td>
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<tr>
<td>Fuhrman</td>
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<td></td>
</tr>
<tr>
<td>1</td>
<td>31,6</td>
<td>44</td>
</tr>
<tr>
<td>2</td>
<td>33,8</td>
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<td>26,6</td>
<td>37</td>
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<tr>
<td>4</td>
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<td>9</td>
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<tr>
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<td>2</td>
</tr>
<tr>
<td>Necrosis</td>
<td>26</td>
<td>36</td>
</tr>
</tbody>
</table>

<sup>a</sup> Located: T<= 2N0M0; not located: T>= 3, any N, any M.
<sup>b</sup> Preoperative values.
<sup>c</sup> Cells/mm³.
<sup>d</sup> In%.
<sup>e</sup> In cm.
94 cases were histologically diagnosed as clear cell carcinoma (67.6%), 30 of them were papillary histopathological subtype (21.5%), 11 were chromophobe subtype (7.9%) and 4 were sarcomatoid (2.8%) (Figure 1). 44 cases (31.65%) had a nuclear grade (Fuhrman classification) of 1, 47 cases (33.81%) presented as grade 2, 37 of the samples (26.61%) presented as grade 3, and 9 (6.47%) as grade 4. In 2 cases the Fuhrman nuclear grade classification was undetermined (1.43%).

The mean platelet count prior to surgery was 260930 cells/mm\(^3\) (range 757000-34000 cells/mm\(^3\)), with a preoperative mean hematocrit of 41.10% (range 96 to 23%).

We found a statistically significant ratio (p=0.049) between the hematocrit at diagnosis and overall survival (OR: 0.92, 95% CI 0.85 to 0.99), so that patients who presented higher hematocrit levels prior to the intervention were associated with better survival. Inversely, patients who presented thrombocytosis at diagnosis had worse overall survival (OR: 2.94, 95% CI 1.04 to 8.27), and this relation, like the previous, was also statistically significant (p=0.04) (Table II) (Figure 2).

In addition, we made multivariate analysis to try to identify independent prognostic factors. However, we cannot reach statistical significance for any of the parameters examined in the study. In fact, due to small sample size, with a low number of exitus -16-, we only obtained a statistical significance for Fuhrman grade, identifying it like an independent prognostic factor (Table III).

**DISCUSSION**

The increased incidence of RCC seen in the last two decades is mainly attributable to two factors. On the one hand, it may be due to the increase in the detection of incidental solid renal masses caused by such increasingly widespread use of imaging techniques such as ultrasound or computed tomography (10). On the other side there are the environmental exposures and changes in lifestyle, with increased smoking, essentially, and obesity (2, 11).

Many prognostic factors have been established for renal cell carcinoma. They can be divided into anatomical ones, histological ones, clinical and molecular (12). The European Association of Urology (EAU) advises in its clinical guideline for the management of RCC the routine use of the 2009 TNM classification, Fuhrman nuclear grade and histological subtype of RCC, because they are the factors with more value in assessing prognosis and deciding treatment (3), being the pathological stage according to TNM classification the most important prognosis factor in RCC, followed by Fuhrman grade (6, 13).

Platelet count and anaemia have been recently included as clinical nature prognosis predictors in RCC, as well as weight loss, presence of symptoms and general condition as measured by performance status (14). Anaemia, reflect of the general state of the patient, and measured either by haemoglobin (Hb) or hematocrit (Hct) has been considered with more or less importance by different authors (12, 15). It seems very clear its prognostic value, in fact, it is a parameter included in some of the nomograms for metastatic RCC patients (16-18). However, it does not appear to improve prognostic accuracy afforded by the more established cancer specific- mortality factors as TNM stage, Fuhrman grade, histological subtype and performance status (19, 20).

The presence of thrombocytosis, defined as a pathologically high platelet count, has been demonstrated as an independent prognostic factor both in metastatic patients and in those with located
disease. Heng et al have evaluated the prognostic factors on overall survival of patients with metastatic RCC treated with vascular endothelial growth factor (VEGF) - targeted therapy. In this paper they show, in a significant statistical form, that elevated neutrophil or platelet counts and several items of the predictive model of the Memorial Sloan-Kettering Cancer Centre are able to classify patients into risk groups with impact on survival (21). In located tumours, Brookman-Amissah et al, prove an independent significant decrease of disease-free survival in patients with high platelet counts (22).

The platelet level used as a cut-off to define thrombocytosis varies depending on the study. Symbas et al on the one hand, with a group of 259 patients with metastatic RCC and Suppiah et al, with a 700 sample, on the other, found and independent but significant poor survival in those patients whose platelet count is greater than 400000 cells/mm$^3$ (23,24). O’Keefe et al, set the same cut-off point than previous ones and also show in their retrospective study the same independent prognostic value of thrombocytosis in patients with localized RCC (25).

Benzalah et al conducted a retrospective study with a series of 804 patients undergoing surgery for RCC, either localized or metastatic. In their work, platelet counts over 450.000cells/mm$^3$ were significantly associated with tumour size, stadium, presence of metastases and lymph nodes. Multivariate analysis revealed that patients with a platelet count greater than this count had independently and significantly worse overall survival, either localized or metastatic tumours (26).

Ito et al studied the influence of thrombocytosis and high level of C-reactive protein (CRP) in a series of 178 patients undergoing surgery for RCC. Establishing the level of thrombocytosis in 350000 cells/mm$^3$ they demonstrated a directly and significantly relationship between thrombocytosis and the other established prognostic factors and even with CRP. However, although multivariate analysis showed that elevated CRP levels are related with a worse survival, it could not do the same with the platelet count (27).

More recently, Johnson et al establish that elevated CRP levels prior to surgery and SIGN risk (stage, size, grade and necrosis), were independently correlated with decreased disease-free survival one year after surgery. In the same work, and also statistically significant in multivariate analysis, platelet count and CRP levels before surgery were correlated with overall mortality during the first year after surgery. These findings suggest that CRP and platelet counts are good predictors of metastasis and overall and cancer-specific mortality after surgery for RCC, and that in the pathophysiology of this, there are involved biochemical markers underlying an inflammatory process associated with tumoral burden (28).

The role of thrombocytosis in the greater aggressiveness of RCC is not well understood. The involvement of platelets in neoangiogenetic processes

![Image](image-url)

**FIGURE 2.** Kaplan-Meier curve of survival in relation to platelet count.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative platelet count</td>
<td>2.94</td>
<td>1.04- 8.27</td>
<td>0.049</td>
</tr>
<tr>
<td>Preoperative hematocrit</td>
<td>0.92</td>
<td>0.85- 0.99</td>
<td>0.046</td>
</tr>
</tbody>
</table>
through the release of different markers, being perhaps the most important endothelium-derived vascular growing factor (VEGF) is well-documented (29). High levels of VEGF have been demonstrated inside cancer patient platelets (30). However, platelets also release large amounts of procoagulant products with ability to inhibit angiogenesis (15). According Benzalah, thrombocytosis in RCC is a reflection of a biological cascade where VEGF and thrombopoietin would act synergistically, generating in bone marrow a increased production of VEGF-laden megakaryocytes, and a accelerated maturation from these to circulating platelets, resulting in a releasing of greater amounts of VEGF and thrombopoietin (26). Definitely, it is known very little about the pathophysiology of this paraneoplastic syndrome (32).

It has been demonstrated the presence of an arterio-venous gradient of IL-6 during a nephrectomy for RCC in a patient presenting with symptoms and preoperative leukocytosis and thrombocytosis (32). Therefore, and in relation to this respect, thrombocytosis and low levels of hematocrit appeared to be a reflection of the patient’s systemic inflammatory response to the tumour, as well as other studied factors (CRP, leukocytosis…) (33,28,34). Thus, a recent meta-analysis of 47 studies have revealed that the patient’s systemic inflammatory response correlates with poorer survival, being PCR, platelet count and ESR good predictors for both overall and cancer specific mortality (35).

Our work explores the demonstrated theory that thrombocytosis and anaemia are important prognostic factors in RCC, as we have found statistically significant relationships between platelet count and hematocrit and overall survival. These results agree with those of previous publications. In our series, in statistically significant form, the presence of low hematocrit levels is associated with lower overall survival. As for thrombocytosis, we found that platelet counts higher than 350000 cells/mm³ were associated with a worse prognosis. In the literature there are different cut-offs to define thrombocytosis. In our case we choose this cut-off because it is a level far enough of our population average level and ensures a high enough platelet count.

We are aware, however, about limitations in our series, too short when compared to the others in world literature and with a low rate of dead patients, minimizing the power to the study. In fact, multivariate analysis of the series could not identify neither thrombocytosis neither hematocrit as independent prognostic factors and we believe that it can be due to this reason. However we believe that the findings of our study are consistent and continue the way of previous researches, so it could be the basis for future analysis of larger series.

### CONCLUSIONS

In our series of patients with RCC and in a statistically significant form, a high platelet count prior to surgery, appears to be associated with decreased survival, although we could not demonstrate that this association is independent of others.

Similarly, high levels of preoperative hematocrit may be related to a mayor overall survival, at least in this series. However, and as well

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard Ratio</th>
<th>95% Confidence Interval</th>
<th>p Value</th>
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<tbody>
<tr>
<td>Clinical Stage</td>
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<td>0,74- 4,37</td>
<td>0,062</td>
</tr>
<tr>
<td>ECOG score performance status</td>
<td>2,63</td>
<td>0,94- 7,42</td>
<td>0,172</td>
</tr>
<tr>
<td>Preoperative platelet count</td>
<td>2,34</td>
<td>0,47- 2,85</td>
<td>0,264</td>
</tr>
<tr>
<td>Preoperative hematocrit</td>
<td>0,97</td>
<td>0,32- 1,79</td>
<td>0,086</td>
</tr>
<tr>
<td>Fuhrman grade</td>
<td>1,96</td>
<td>1,16- 3,48</td>
<td>0,038</td>
</tr>
<tr>
<td>Histological type</td>
<td>1,18</td>
<td>0,59- 2,43</td>
<td>0,48</td>
</tr>
</tbody>
</table>
as happens with thrombocytosis, multivariate analysis has not been able to show the independence of this relationship respect other factors.

There are needed more studies with larger series of patients, with a higher rate of events and more follow-up to corroborate these findings, so an multivariate analysis could show the independent prognostic value of our variables.

REFERENCES AND RECOMMENDED READINGS

(*of special interest, **of outstanding interest)


