

Thrombocytosis is a marker of reduced survival in patients with renal cell carcinoma. A multicenter study.

Luis Eduardo Cadena Castro*¹, Jorge Eduardo Cadena Vizúete¹

1. Postgraduate Department, Postgraduate Urology, Higher Research and Postgraduate Institute, Faculty of Medical Sciences, Central University of Ecuador, Quito.

Abstract

Introduction: Thrombocytosis occurs as an inflammatory bone marrow response in the presence of chronic diseases, generally infectious. The association of thrombocytosis and its prognostic impact on survival in patients with renal cell carcinoma (RCC) has not been definitively established. The objective of this study was to determine survival in two reference centers in Quito-Ecuador, for the treatment of patients with renal cell carcinoma.

Methods: The present longitudinal study was carried out at the "Carlos Andrade Marín" Specialty Hospital and the General Specialty Hospital Number 1, in Quito-Ecuador, from January 2005 to December 2016. Patients with RCC at one year of age were included. Survival since nephrectomy. Mortality, age, staging, and survival were determined. Two groups with the presence or absence of thrombocytosis were analyzed. The sample was probabilistic. Survival analysis is performed using the Kaplan Meier method, and a COX regression is performed on the associated variables.

Results: 183 patients, 62.2 ± 12.8 years old, were included. There were 132 cases (72.1%) of localized RCC, 35 cases (19.1%) of advanced stage, and 16 cases (8.7%) of the metastatic stage. The mean number of platelets was 300020 ± 102300 u/ul. Fifty patients (27.3%) presented thrombocytosis. Overall survival of the group with thrombocytosis was 50.4 (38.2-62.6) months versus 68.1 (60.8-75.3) months in the group without thrombocytosis, $P < 0.005$.

Conclusions: The presence of thrombocytopenia in patients with RCC decreases overall survival by an average of 7.7 months compared to the control group without thrombocytopenia.


Keywords:

DeCS: Trombocitosis, Neoplasias Renales, Análisis de Supervivencia, Carcinoma de Células Renales, Nefrectomía.

Received: December 03, 2021
Accepted: January 26, 2022
Published: February 28, 2022
Editor: Dr. Franklin Mora Bravo.

Cite:

Cadena L, Cadena J. Thrombocytosis is a marker of reduced survival in patients with renal cell carcinoma. A multicenter study. REV SEN 2022;10(1):43-48.

 Copyright Cadena L, et al. This article is distributed under the [Creative Commons CC BY-NC-SA 4.0 Attribution License](https://creativecommons.org/licenses/by-nc-sa/4.0/) which allows the use and redistribution citing the source and the original author for non-commercial purposes.

* Corresponding author



Recent studies have addressed the prevalence and prognostic impact of thrombocytosis in various malignant tumors, such as gastric, renal, lung, and gynecological tumors. Thrombocytosis also appears to have prognostic value in patients with malignant renal tumors; renal cell carcinoma (RCC) accounts for approximately 3% of all adult neoplasms and is the most common primary malignant tumor (85%) of the renal parenchyma [1]. The prognostic role of platelet counts, which are easy to obtain in peripheral blood, and the association between thrombocytosis and decreased survival have recently been studied in patients with CRC, with contradictory and inconclusive results. Reactive thrombocytosis in RCC is caused by the production of inflammatory cytokines such as IL-6 and endothelial growth factor (VEGF) [1].

The prognostic value of thrombocytosis in RCC is unknown in the Hispanic population, although it is assumed that the behavior is the same as in the Anglo-Saxon population. Thrombocytopenia has been described to facilitate tumor cell adherence and penetration through the endothelial wall by several pathways [2, 3]. For example, platelet granules contain a variety of angiogenic factors, such as vascular endothelial growth factor, platelet-derived growth factor, and transforming growth factor beta, all of which are involved in tumor progression [2, 3].

The objective of the present study was to carry out an observational survival study on a group of patients with CRC, analyzing the presence of thrombocytosis in the Hispanic population.

Materials and methods

Study design

The present study is observational and analytical with a longitudinal cut.

Scenery

The study was carried out in two reference centers for the treatment of CRC: The "Carlos Andrade Marín" Specialty Hospital of the Ecuadorian Institute of Social Security of Quito and the General Hospital of Specialties Number 1 of the Social Security Institute of the Ecuadorian Institute of Social Security. Armed Forces, Quito-Ecuador. The study period was from January 01, 2005, to December 31, 2016. The study ended the data collection phase on March 23, 2017.

Participants

Patients older than or equal to 18 years were included, with a diagnosis of CRC with at least one year of survival from its surgical resolution by nephrectomy. Patients without a confirmatory histopathological study and with incomplete data in the clinical history that did not allow analysis were excluded.

Variables

The dependent variable was the presence of mortality. Two groups of patients were analyzed, taking into account the presence or absence of thrombocytosis. Variables such as age, sex, staging, and survival time were described.

Data sources/measurements

The variables were taken from the institutional clinical file. The presence of thrombocytosis was defined as an increase in platelets >350 thousand u/ μ l.

Biases

To avoid possible interviewer, information, and memory biases, the data were guarded at all times by the principal investigator with a guide and records approved in the research protocol. Observation and selection bias was avoided by applying the participant selection criteria. All the clinical and paraclinical variables of the period as mentioned above were recorded. Two researchers independently analyzed each record in duplicate, and the variables were recorded in the database once their agreement was verified.

Studio size

The sample was probabilistic. The prevalence of thrombocytosis events was 12%, the confidence level was 95%, and the statistical power was 80%. With a total population of approximately 183 cases and reports of previous studies of OR 2.9, the sample calculation was 153 cases, 135 in the group without thrombocytosis and 18 in the group with thrombocytosis.

Quantitative variables

Inferential descriptive statistics were used. Scaled results are expressed as the means and standard deviations. Categorical data such as gender and staging in proportions.

Statistical analysis

Survival analysis was performed using the Kaplan–Meier method, and Cox regression was performed on the associated variables. The statistical package used was SPSS 22.0 for PC (IBM Corp. Released 2013. Armonk, NY.)

Results

Participants

A total of 183 patients entered the study. The diagram of the participants is presented in Figure 1.

Characteristics of the study population

The mean age was 62.2 ± 12.8 years. There were 132 cases (72.1%) of localized CRC, 35 cases (19.1%) of advanced stage, and 16 cases (8.7%) of metastatic stage. Radical nephrectomy was performed in 170 patients (92.9%), and partial nephrectomy was performed in 13 cases (13%). There were 164 cases (89.6%) from Hospital Carlos Andrade Marín (IESS) and 19 cases (10.4%) from Hospital General 1-(ISSFA).

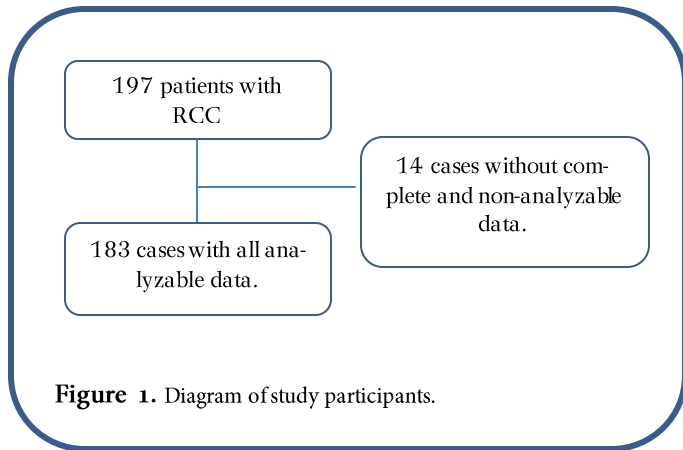


Figure 1. Diagram of study participants.

Main analysis

Platelet mean 300020 ± 102300 u/uL. Fifty patients (27.3%) had thrombocytosis, and 133 patients (72.2%) had a normal platelet count. The average survival time of the group was 30.4 ± 28.8 months. Survival in patients with CRC in the localized stage was 84 months; in the advanced stage, it was 27 months, and in the

advanced stage. Metastasis was 7.7 months. Table 1 shows survival in the stage groups, and survival was higher in the group without thrombocytosis.

Table 1. Survival in patients with CRC.

Variable	Group without thrombocytosis n=133	Group with thrombocytosis N=50	P
Localized CRC (months)	77.5 (70.6-84.5)	70.1 (61.7-78.6)	<0.005
Advanced CCR (months)	36.7 (23.1-50.2)	29.4 (16.1-42.8)	<0.005
Metastatic RCC (months)	13.2 (2.2-24.1)	7.8 (4-11.6)	<0.005
Overall survival in CRC	68.1 (60.8-75.3)	50.4 (38.2-62.6)	<0.005

RCC: renal cell carcinoma.

Cox regression

The statistically significant variables that predict survival time are presented with a factorial design. The primary variable was the stage, and the modifying covariate was platelet count (Table 2).

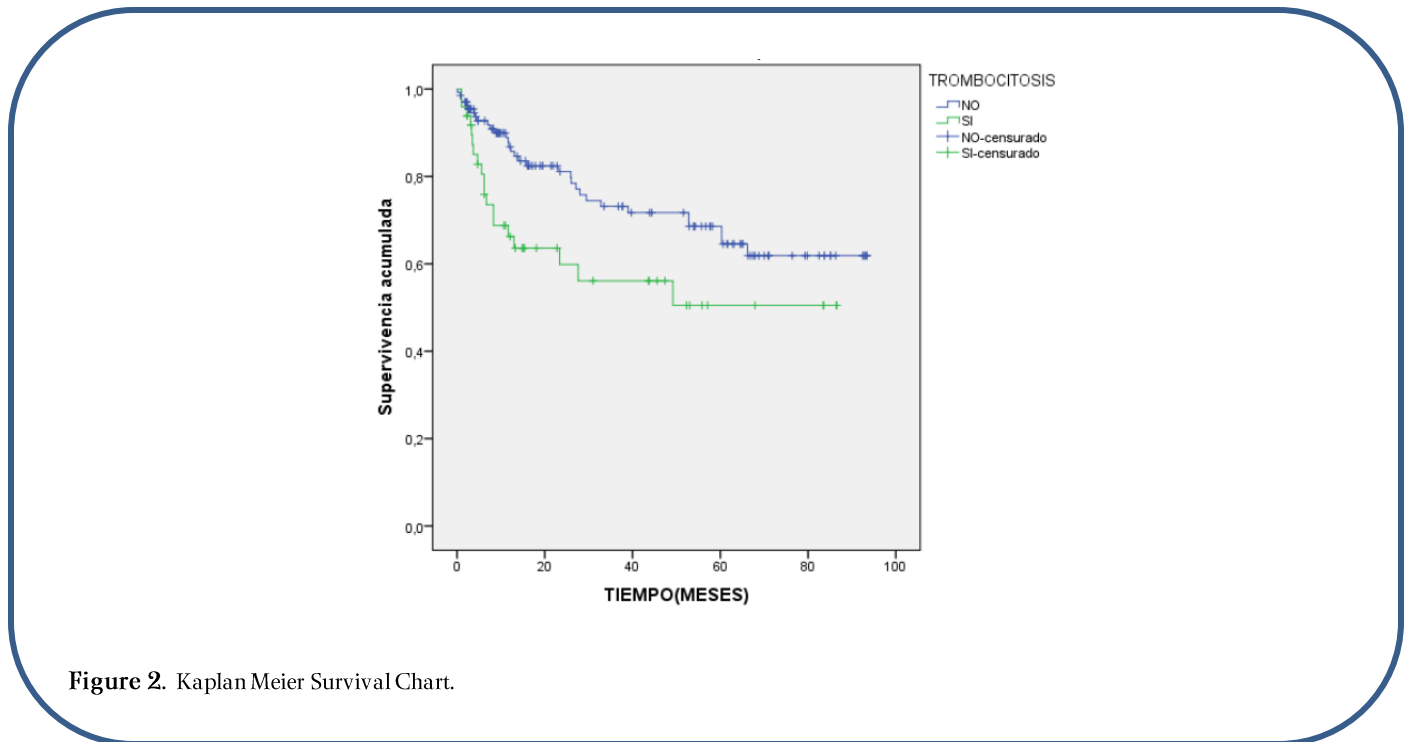


Figure 2. Kaplan Meier Survival Chart.

**Table 2.** COX regression.

Variable	B.	SE	Wald	GL	P	Exp (b)
platelets	0.004	0.001	9.246	1	0.002	1.004
T_VOC	0.060	0.010	35.403	1	<0.0001	1.062

log-likelihood 437.078; Overall X²: 68.39; GL: 2; P=<0.0001; X² previous step: 39.02, GL: 2, P<0.0001

Discussion

One of the factors for the increased incidence of CRC is the detection of incidental renal solid masses caused by the increasingly widespread use of imaging techniques. Numerous prognostic factors have been established for renal cell carcinoma, and they can be divided into anatomical, histological, clinical, and molecular factors. We must apply those that we have in our environment for support and evaluation. The European Association of Urology (USA) recommends in its clinical practice guidelines for the management of CRC the routine use of the 2002 TNM classification, the Fuhrman nuclear grade, and the histological subtype of CRC since they are the factors that have value to assess prognosis and decide on treatment, with the pathological stage according to the TNM classification being the most important prognostic factor in CRC [1]. The platelet count has been included as a prognostic factor of a clinical nature together with weight loss, the presence of symptoms, and the patient's general condition measured through the ECOG classification, which is accessible at all levels of health [4]. The presence of thrombocytosis, understood as a pathologically high platelet count, is an independent prognostic factor in metastatic patients and those with localized tumors. In the study population, survival in months was more significant if the stage was lower and thrombocytosis was absent (mean was: localized 77.5 months; advanced 36.7 months, metastatic 13.2, and global 68.1, with $P < 0.005$; in comparison with the thrombocytosis group, the mean was: localized CRC 70.1 months, advanced CRC: mean 29.4 months, metastatic CRC 7.8 months, and global CRC 50.4 months, with a P value < 0.005). In a previous study, the importance of thrombocytosis in localized RCC, patients with thrombocytosis were shown to have a median survival of 45.2 months compared with 76.6 months in patients without thrombocytosis ($P = 0.0002$) [5]. A total of 12.1% had thrombocytosis, and their estimated risk of death at five years was 1.61-fold higher than that of the regular platelet pool [RR=1.61, 95% CI=(1.31–1.98), $P < 0.001$] [6]. The level of thrombocytosis at 350,000 cells/mm³ demonstrates a direct and significant relationship between thrombocytosis and established prognostic factors and even with CRP, so we applied this parameter to the group studied. Recently, it has been established that in a statistically significant way in multivariate analysis, platelet count and CRP

levels in the preoperative period correlate with overall mortality during the first year after surgery [7]. The role of thrombocytosis in the increased aggressiveness of CRC is not fully known. On the one hand, the involvement of platelets in neoangiogenesis processes through the release of different markers is well documented, perhaps the most important being vascular endothelial-derived growth factor (VEGF), of which elevated levels have also been shown inside the platelets of cancer patients.

One of the possible explanations for the association is that thrombocytosis in CRC is the reflection of a biological cascade in which VEGF and thrombopoietin would act synergistically, generating a better production of VEGF-laden megakaryocytes in the bone marrow. Moreover, accelerated maturation toward circulating platelets occurs, with the consequent release of more significant amounts of VEGF and thrombopoietin [4]. The study focuses on the already proven theory that thrombocytosis is a critical poor prognostic factor in CRC, with statistically significant variables between platelet count and survival, the results that agree with those of previous publications [1]. The study showed in a statistically significant way that thrombocytosis shows that figures greater than 350,000 cells/mm³ were related to a worse prognosis. Different cutoff points are found in the literature to define thrombocytosis. In our case, we chose 350,000 cells/mm³ as it is a familiar figure for our population.

Conclusions

The presence of thrombocytopenia in patients with CRC decreases overall survival by an average of 7.7 months compared to the control group without thrombocytopenia.

Abbreviations

RCC: renal cell carcinoma.
UF: ultrafiltration.

Supplementary information

Supplementary materials have not been declared.

Acknowledgments

Does not apply.

Author contributions

Luis Eduardo Cadena Castro: Conceptualization, Data Curation, Formal Analysis, Fundraising, Research, Methodology, Project Management, Resources, Software, Writing – original draft.

Jorge Eduardo Cadena Vizuete: conceptualization, supervision, validation, visualization, and writing: revision and editing.

All authors read and approved the final version of the manuscript.

Financing

The authors provided research expenses. The laboratory studies were part of the regular institutional activity and were not expenses added to the institution or the patients.



Availability of data or materials

The data sets generated and analyzed during the current study are not publicly available due to participant confidentiality but are available from the corresponding author upon reasonable academic request.

Statements

Ethics committee approval and consent to participate

It was not needed.

Consent to publication

It does not apply when images or photographs of the physical examination or X-rays/tomographies/MRIs of patients are not published.

Conflicts of interest

The authors report having no conflicts of interest.

Author Information

Luis Eduardo Cadena Castro, Physician from the Central University of Ecuador (Quito, 2011). Specialist in Urology from the Central University of Ecuador (Quito, 2017). Treating physician in Uroendolap -Quito, Ecuador.

Jorge Eduardo Cadena Vizuete, Physician from the Central University of Ecuador (Quito, 2003), Specialist in Urology from the International University of Ecuador (Quito, 2007).

References

1. Men H, Liang C, Yu M. Thrombocytosis as a prognostic factor in patients with renal cell carcinoma: a meta-analysis of literature. *J Cancer Res Ther.* 2015 Jan-Mar;11 (1):67-72. DOI: 10.4103/0973-1482.150345. PMID: [25879339](#).
2. Vano YA, Tartour E, Fournier LS, Beuselinc B, Mejean A, Oudard S. Prognostic factors in patients with advanced renal cell carcinoma treated with VEGF-targeted agents. *Expert Rev Anticancer Ther.* 2014 May;14 (5):523-42. DOI: 10.1586/14737140.2014.882773. Epub 2014 March 18. PMID: [24640949](#).
3. Cho DS, Kim SJ, Lee SH, Ahn HS, Kim YS, Kim SI. Prognostic significance of preoperative C-reactive protein elevation and thrombocytosis in patients with nonmetastatic renal cell carcinoma. *Korean J Urol.* 2011 Feb;52 (2):104-9. DOI: 10.4111/kju.2011.52.2.104. Epub 2011 February 21. PMID: [21379426](#); PMID: PMC3045714.
4. Seda CJ, Salas AS, Sánchez CG, Blasco JM, García IO, Sánchez JM, Ruíz CB, Navarro SM, López RA. Thrombocytosis and hematocrit as prognostic factors in renal carcinoma. *Arch Esp Urol.* 2011 Nov;64 (9):883-90. English Spanish. PMID: [22155876](#).
5. Golriz M, Ghamarnejad O, Khajeh E, Sabagh M, Mieth M, Hoffmann K, Ulrich A, Hackert T, Weiss KH, Schirmacher P, Büchler MW, Mehrabi A. Preoperative Thrombocytopenia May Predict Poor Surgical Outcome after Extended Hepatectomy. *Can J Gastroenterol Hepatol.* 2018 Nov 1;2018:1275720. DOI: 10.1155/2018/1275720. PMID: [30515369](#); PMID: PMC6236772.
6. Men H, Liang C, Yu M. Thrombocytosis as a prognostic factor in patients with renal cell carcinoma: a meta-analysis of literature. *J Cancer Res Ther.* 2015 Jan-Mar;11 (1):67-72. DOI: 10.4103/0973-1482.150345. PMID: [25879339](#).
7. Alsaif SH, Rogers AC, Pua P, Casey PT, Aherne GG, Brannigan AE, et al. Preoperative C-reactive protein and other inflammatory markers as predictors of postoperative complications in patients with colorectal neoplasia. *World J Surg Oncol.* 2021 Mar 13;19 (1):74. DOI: 10.1186/s12957-021-02142-4. PMID: 33714275; PMID: [PMC7956109](#).

DOI: Digital Object Identifier. PMID: PubMed Identifier.

Editor's note

The REV SEN remains neutral concerning jurisdictional claims on published maps and institutional affiliations.