


Prognostic value of lymphocyte-to-monocyte ratio previously determined to surgery in patients with non-metastatic renal cell carcinoma

A systematic review and a prisma-compliant meta-analysis

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Abstract

Background: The prognostic value of pretreatment lymphocyte to monocyte ratio in patients with renal cell carcinoma and, especially, in non-metastatic patients remains controversial.

Methods: We conducted a PRISMA-compliant meta-analysis to systematically assess the prognostic value of LMR in patients with non-metastatic RCC. Overall survival, cancer-specific survival, and disease-free survival were analyzed. Pooled hazard ratios and 95% confidence intervals were calculated.

Results: Seven studies comprising 4666 patients were included in the analysis. Unlike those observed in a previous meta-analysis, a lower lymphocyte to monocyte ratio was associated with poorer cancer-specific survival (fix-effect model, hazard ratio 3.04, 95% confidence intervals 2.05–4.51, $P < .05$). Heterogeneity Chi-squared value $Q_{exp} = 0$. ($P = .82$) ($I^2 = 0\%$). However, the association between a low lymphocyte to monocyte ratio and overall survival or disease-free survival did not obtain significance.

Conclusion: A lower lymphocyte to monocyte ratio implied poor cancer-specific survival in patients with non-metastatic renal cell carcinoma. Prospective studies are required to confirm our findings.

Registration number: ClinicalTrials.gov (identifier: NCT04213664)

Abbreviations: CI = confidence interval, CSS = Cancer-specific survival, DFS = Disease-free survival, HR = hazard ratio, IL = interleukin, LMR = Lymphocyte to monocyte ratio, OS = Overall survival, PFS = Progression-free survival, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analysis, RCC = Renal cell carcinoma, TAMs = tumor-associated macrophages.

Keywords: lymphocyte to monocyte ratio, meta-analysis, prognosis, renal cell carcinoma

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The datasets generated during and/or analyzed during the current study are publicly available.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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1. Introduction

Renal cell carcinoma (RCC) represents 2% to 3% of adult malignant diseases. Although in the last 3 decades kidney cancer is detected incidentally in most cases, a third of cases are still diagnosed in locally advanced or metastatic stages, and up to 20% to 30% of initially localized tumors will show progression to metastasis in their evolution.^[1–3]

Although the comprehensive therapeutic strategy using surgery, immunotherapy, and therapies aimed at molecular targets has greatly improved the survival of these patients in recent years, a subset of them still has an unfavorable prognosis due to local recurrence or metastasis and the poor response to systemic medication. There are established clinicopathological prognostic factors such as the existence of clinical symptoms, tumor size, stage, tumor grade, histological type, or the presence of necrosis. It would be interesting to find biological markers that would allow us to provide additional prognostic information. Numerous studies have shown that systemic inflammation plays a key role in the initiation and progression of different tumors.^[1–23]

In the tumor microenvironment, both lymphocytes and monocytes are representatives of both host immunity and tumor aggressiveness for many types of cancer. Furthermore, RCC is known to be immunogenic cancer that responds to immune therapy.^[12]

Various systemic inflammatory biomarkers such as the neutrophil-lymphocyte ratio, the albumin or the -C-reactive protein have been considered to be potential prognostic markers

in a wide variety of tumors. Thus, in the 2020 European Urology Association clinical guide, it is admitted that a high neutrophil-lymphocyte ratio can be used as a prognostic factor in metastatic renal cell carcinomas, with a level of evidence type 3. Recently, many studies have shown that a lower proportion of the ratio of lymphocytes to monocytes (LMR) determined in peripheral blood was closely associated with a worse prognosis in different types of cancers, and maybe an easily available and reliable prognostic biomarker. Furthermore, due to the limitations of individual studies, in most cases with a small sample of patients, and the communication of contradictory conclusions, they have led to several meta-analysis to validate the prognostic value of LMR in different tumors.^[1–12]

We have found 3 meta-analysis that has evaluated LMR in kidney tumors, but we analyzed studies in patients with both localized and metastatic tumors. Currently, the vast majority of renal malignancies are detected incidentally, with clinically localized tumors, but, as previously mentioned, a high percentage of patients will progress to metastatic disease. For all these reasons, we believe it is important to perform a meta-analysis to evaluate the prognostic value of LMR in localized renal tumors undergoing partial or radical nephrectomy.^[4,11,12]

Thus, we performed a meta-analysis to systematically evaluate the preoperative prognostic value of LMR, exclusively, in patients with localized renal cell carcinoma.

2. Methods

We performed a systematic review of the literature and a meta-analysis according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) evaluation criteria. We used the PICO method (patient, intervention, comparison, and outcome), intending to answer the following clinical question: “Is a low value of the LMR determined before surgery a prognostic factor in non-metastatic renal cell carcinoma?”

All the articles analyzed were previously published studies. That is why patient consent and ethical approval are not requested.

A comprehensive search of PubMed, ScienceDirect, and Cochrane Database of Systematic Reviews was conducted for eligible studies exploring the prognostic role of LMR in patients with localized kidney tumors undergoing partial or radical nephrectomy from January 1965 to December 2019. The terms Search included: “lymphocyte-monocyte ratio,” “kidney cancer,” “prognosis.”

Inclusion Criteria: Any observational study (cross-sectional, case-control, longitudinal with cross-sectional data) was included. Articles about patients older than 18 years, with localized renal tumors that underwent partial or radical nephrectomy, with histopathologically confirmed neoplasms, who had access to the full text and without language limitation, were being discussed.

Studies reflected the hazard ratios (HR) and corresponding 95% confidence intervals (CI), in which overall survival (OS), cancer-specific survival (CSS) and disease-free survival (DFS). If data forms from both univariate and multivariate analyzes were available in the articles, data from the multivariate analysis was extracted for the cluster analysis. OS was defined as the interval from the date of surgery in the primary tumor until death. CSS was defined as the interval from the date of surgery in the primary tumor to death for RCC. DFS was defined as the interval from the date of surgery in the primary tumor to local, regional, or distant recurrence.

In each publication, information was extracted from the first author, year of publication, geographic location, study design and information: sample size, mean age, distribution by sex, LMR, the method of determining the cut-off value of LMR, treatment performed, duration of follow-up, multivariate or univariate analysis, the Hazard ratio (HR) and corresponding 95% confidence intervals (CI), as well as exact p values.

Case reports, reviews, editorials, letters, abstracts, animal-only and with not having access to the LMR were not considered eligible.

Two independent reviewers identified the relevant articles in duplicate by first selecting the titles and abstracts, followed by the full text according to the inclusion and exclusion criteria. Any disagreement was resolved by consensus with a third reviewer experienced in the treatment of kidney cancer.

The Newcastle-Ottawa quality assessment scale is one of the recommended tools to assess the quality of observational studies. The studies where a maximum score of 9 points can be given for each study in the categories of patient selection, comparability of study groups and evaluation of results. High-quality studies were defined as those with scores higher than 7.

Statistical study: The raw data from each study were combined to obtain the combined hazard ratio and corresponding 95% confidence intervals. The generic inverse-variance method with a random-effects model was used for pooled estimates. Statistical heterogeneity among studies was assessed with I^2 statistics. I^2 is interpreted as the percentage of total variation across several studies that is attributable to heterogeneity. Larger values of I^2 indicate greater heterogeneity (50%–100%) and I^2 percentages below 50% are generally considered an acceptable level of variability. If a P of less than .05 was observed, the studies were considered to present substantial heterogeneity. The fixed-effect model was used to calculate pooled results in the absence of heterogeneity ($I^2 < 50\%$ or $P > .1$). A funnel plot was performed to assess publication bias and small-study effects in the meta-analyses for OS, CSS and DFS, and the Duval and Tweedie trim-and-fill test was used to correct for possible publication bias.

All statistical tests were 2-sided and statistical significance was defined as P less than .05.

Statistical analysis was performed with the R 3.5.0 software (R Core Team, 2018) and the meta library (v4.1–5; Schwarzer, Guido, 2019).

The study was approved by the ethical research committee of our center (Consorcio Corporacion Sanitaria Parc Taulí), (identifier: 2019/679) and is registered at ClinicalTrials.gov (identifier: NCT04213664).

3. Results

A total of 29 studies were identified by searching PubMed, ScienceDirect, and Cochrane Database of Systematic Reviews. They were selected to be read in full 18. The selection process yielded only 7 studies that met the selection criteria for performing the meta-analysis. These 7 studies provided information on 4666 patients with non-metastatic renal cell carcinoma. The flowchart identifying the eligible studies is depicted in Figure 1. The studies were published between 2014 and 2019, 4 of them reported by groups from China, 2 Austrians, and 1 Korean.

The cutoff values for a low LMR were inconsistent, ranging from 2.5 to 5. The cut-off value was determined using different methods: ROC análisis curve in 4 studies, 25th percentile in 2

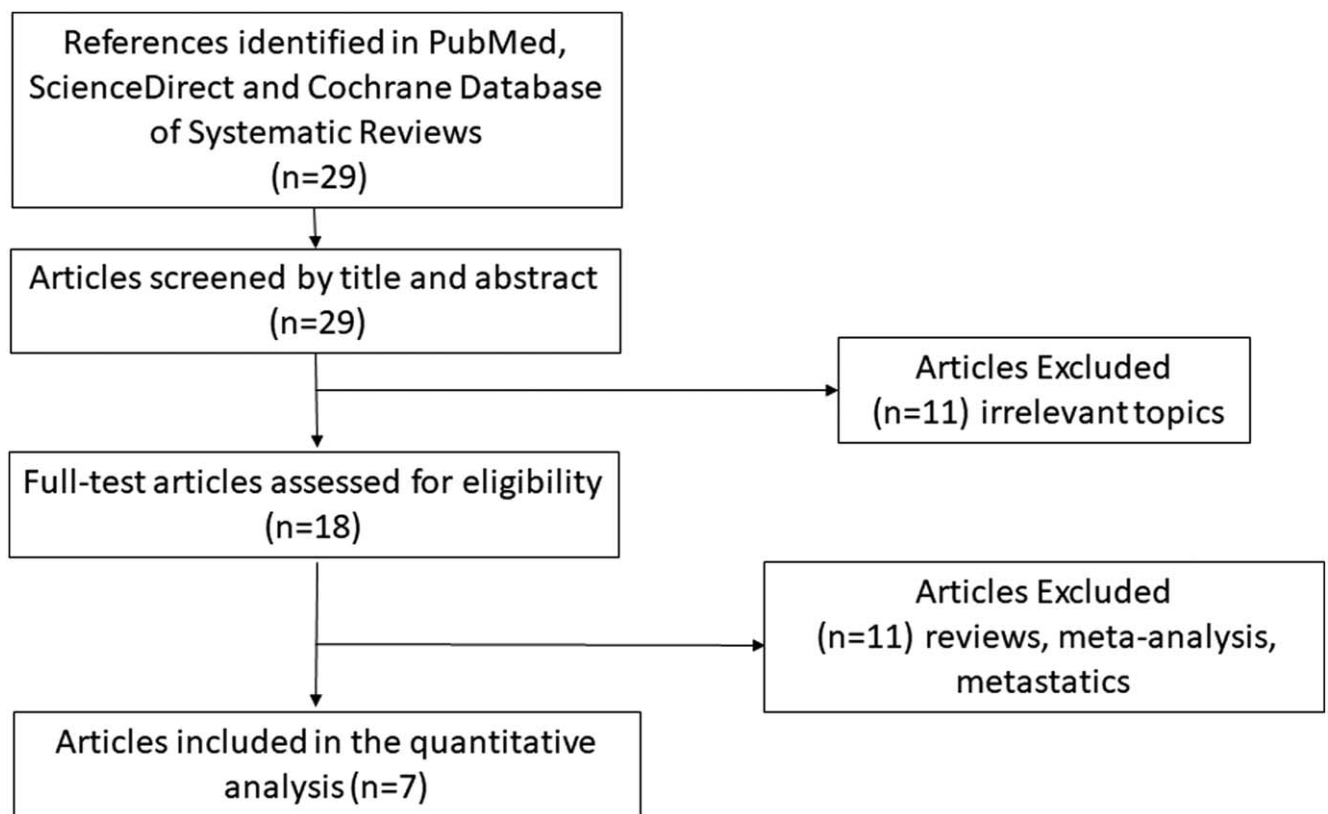


Figure 1. PRISMA flow diagram of the systematic literature search. (PRISMA, preferred reporting items for systematic reviews and meta-analysis).

studies or maximum survival difference in 1 study. More information on the main characteristics are summarized in Tables 1 and 2.

Quality scores according to the New Castle-Ottawa scale for all included studies were 8 out of 9, suggesting that all included studies were eligible for meta-analysis. (Table 3)

Analyzing these 7 studies evaluating the prognostic value of LMR in patients with non-metastatic RCC, in 5 they reported the results of OS (3099 patients), in 4 results of CSS (2821 patients), and in 5 results of DFS (3660 patients).

In summary, non-metastatic CRC patients with a low LMR were associated with a lower CSS (fixed effects model, HR 3.04, 95% CI 2.05–4.51, $P < .05$). In the analysis of heterogeneity, we obtained a value of $I^2 = 0\%$ (homogeneity) (Fig. 2). The funnel plot of the assessment of publication bias was symmetric (Fig. 3), which suggested that our meta-analysis is robust and reliable.

Because of the results, it was not deemed necessary to supplement the study with any statistical test.

However, the association between low LMR and OS (fixed effects model, HR 0.86, CI 95% 0.68–1.08, $P > .05$) and DFS (fixed effects model, HR 0.77 95%, CI 0.62–0.97, $P > .05$) did not obtain statistical significance. (Fig. 2)

4. Discussion

Tumor stage using TNM classification, degree of cell differentiation, tumor size, histological type, and the presence of tumor necrosis are known as prognostic factors established in RCC. Despite trying the most individualized treatment and follow-up possible, it is important to identify possible biomarkers that help clinicopathological parameters to make this decision.^[1–23]

Table 1

Characteristics of the studies subjected to meta-analysis.

Study [year]	Country	No. Patients	Mean Age [yrs]	Female [%]	Cut-off value of low LMR	Determine the cut-off value	Median followup [months]
Hutterer et al [2014]	Austria	678	65.0	40.3	< 3	ROC análisis curve	44 [0–130]
Lucca et al [2015]	Austria	430	65.5	40.2	< 2.5	Máximum survival difference	40 [17–73]
Chang et al [2016]	China	430	56	27.7	< 3.25	25th percentile	66 [63–70]
Xia et al [2016]	China	985	55	42.6	< 3	25th percentile	58 [3–60]
Chen et al [2017]	China	592	56.3	37.3	< 3.3	ROC análisis curve	69.2 [1–151]
Elghiaty et al [2018]	Korea	1137	56	28	< 5	ROC análisis curve	65 [43–91]
Chen et al [2019]	China	414	56.3	37.9	< 3.3	ROC análisis curve	69.2 [1–151]

Table 2
HRs [95% CI] showing the association between LMR and prognosis with localized renal cell carcinoma.

Study [yr]	OS	CSS	DFS
Hutterer et al [2014]	1.373 [0.929–2.031]	2.332 [1.100–4.942]	1.586 [0.936–2.690]
Lucca et al [2015]	NR	NR	2.44 [1.27–4.67]
Chang et al [2016]	0.336 [0.194–0.584]	NR	0.464 [0.282–0.765]
Xia et al [2016]	0.26 [0.16–0.41]	NR	0.24 [0.16–0.36]
Chen et al [2017]	3.406 [1.670–6.946]	2.961 [1.416–6.190]	NR
Elghaty et al [2018]	NR	4.06 [1.55–10.59]	2.17 [1.19–3.97]
Chen et al [2019]	3.417 [1.670–6.972]	3.416 [1.596–7.314]	NR

[LMR = lymphocyte-to-monocyte ratio, HR = hazard ratio, IC = confidence interval, NR = not reported, OS = overall survival, CSS = cancer specific survival, DFS = disease-free survival].

Different biomarkers have recently been determined as a potentials prognostic factors in patients treated for RCC. Urinary Raf Kinase Inhibitor Protein, a key regulator of cell signaling, already described in several cancer types as a metastasis suppressor, enabled a highly accurate prediction of Cancer-specific survival and Progression-free survival.^[17] Pentraxin-3 belongs to the pentraxine family, innate immune regulators involved in angiogenesis, proliferation and immune escape in cancer. Higher Pentraxin-3 serum levels were observed in patients with higher Fuhrman grade, lymph node, and visceral metastases. Patients with higher Pentraxin-3 levels also showed significantly lower cancer specific survival rates.^[18] Glucose-6-phosphate isomerase, also known as phosphoglucose isomerase, was initially identified as the second glycolytic enzyme that catalyzes the interconversion of glucose-6-phosphate to fructose-6-phosphate. Later studies demonstrated that Glucose-6-phosphate isomerase was the same as the autocrine motility factor, and that it mediates its biological effects through the interaction with its surface receptor. Lucarelli et al (2015) demonstrated that Glucose-6-phosphate isomerase was an independent adverse prognostic factor for CSS and progression free survival (PFS).^[19] The renoprotective antiaging gene, α Klotho, has recently been found to work as a tumor suppressor. Gigante et al (2015) observed statistically significant differences resulted between serum α Klotho levels and tumor size, Fuhrman grade, and clinical stage. CSS and PFS were significantly shorter in patients with lower levels of α Klotho.^[20] Lucarelli et al (2014), in a prospective study, observed statistically significant differences resulted

between CA 15–3, CA 125 and β -2 microglobulin serum values and tumor size, Fuhrman grade, presence of lymph node, and visceral metastases. CSS was significantly decreased for patients with high levels of CA 15–3, CA 125, and β -2 microglobulin. At multivariate analysis only age, the presence of visceral metastases, and high levels of CA 15–3 were independent adverse prognostic factors for CSS.^[21]

Various studies have demonstrated the prognostic significance of a low LMR in both localized and metastatic RCC.^[2–12] Thus, a low LMR is correlated with tumoral patients with a high histological grade, larger size, higher tumor stage, lower OS, lower CSS, lower recurrence-free survival, and lower PFS.^[2–12]

There are 2 meta-analysis where the prognostic value of LMR has been investigated in urological tumors and another in renal carcinoma. Patients with both localized and metastatic disease have been included in all 3 studies. And the patients were treated with either surgery, systemic therapy, or both. All 3 studies showed lower overall survival and specific cancer in patients with low LMR.^[4,11,12]

But to date, we have found no meta-analysis that specifically focuses on investigating the prognostic value of LMR in patients with localized kidney tumors.

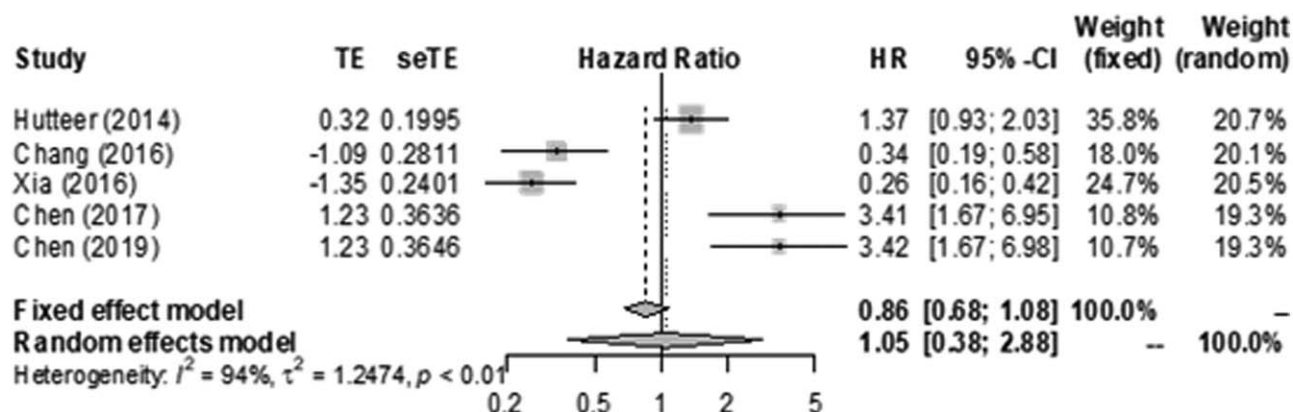
In the present study, we identified 7 studies that involved 4666 patients, and we investigated the prognostic value of LMR exclusively in patients with localized renal cell carcinoma who had undergone total or partial nephrectomy. Unlike those observed in the previous meta-analysis, our study showed that a low LMR, determined in peripheral blood prior to surgery, was

Table 3
The Newcastle-Ottawa Scale quality assessment of the included studies.

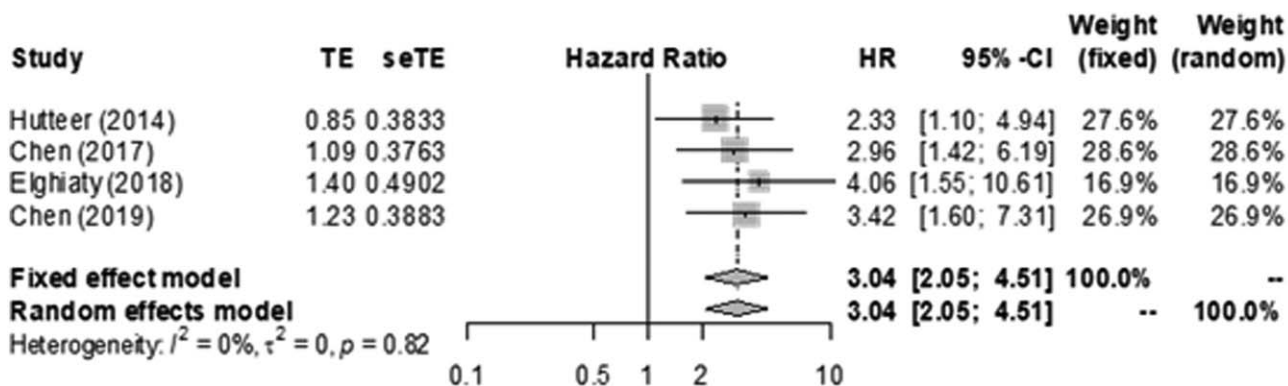
Study [Year]	Selection			Comparison			Outcome		Total
	Representativeness of the exposed cohort	Selection of the nonexposed cohort	Ascertainment of exposure	Demonstration of interest was not present at start of study	Demonstration that outcome of interest was not present at start of study	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	
Hutterer et al [2014]	*	*	*	*	*	*	*	*	8
Lucca et al [2015]	*	*	*	*	*	*	*	*	8
Chang et al [2016]	*	*	*	*	*	*	*	*	8
Xia et al [2016]	*	*	*	*	*	*	*	*	8
Chen et al [2017]	*	*	*	*	*	*	*	*	8
Elghaty et al [2018]	*	*	*	*	*	*	*	*	8
Chen et al [2019]	*	*	*	*	*	*	*	*	8

* Represents a score for the corresponding item. 0 Does not represent a score for the corresponding item.

OS



CSS



DFS

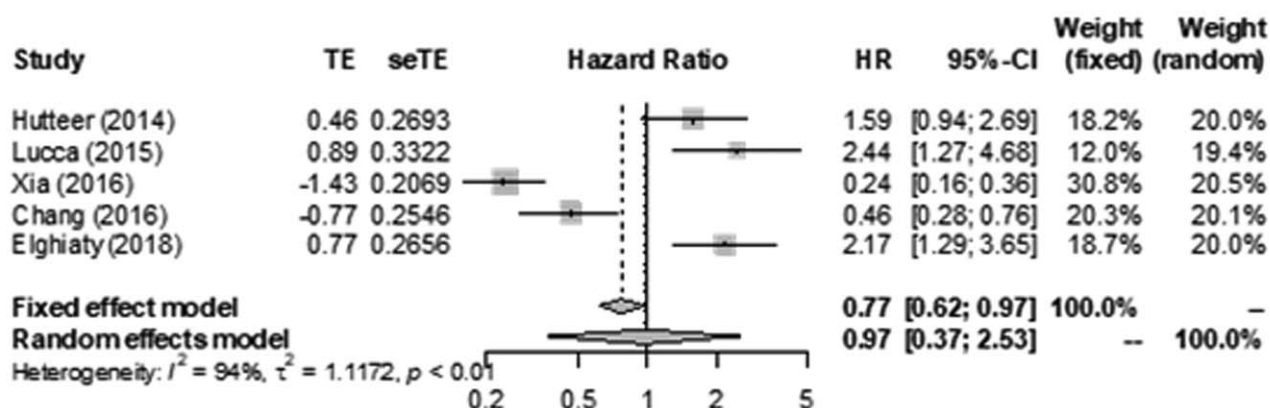


Figure 2. The forest plot of the relationship between the LMR and OS, CSS, and DFS in non-metastatic renal cell carcinoma. [CSS=cancer-specific survival, DFS=disease-free survival, LMR=lymphocyte-to-monocyte ratio, OS=overall survival].

associated with poorer CSS, but not with lower OS or DFS in patients with non-metastatic renal cell carcinoma.^[4,11,12]

Tumor-infiltrating immune cells are crucial for the clinical outcome of RCC, as they regulate cancer progression. Zu et al

(2019) demonstrated in tumor tissue that a higher proportion of regulatory T cells lymphocytes were associated with poor outcome in patients with RCC. Conversely, resting mast cells and monocytes were associated with a favorable prognosis in

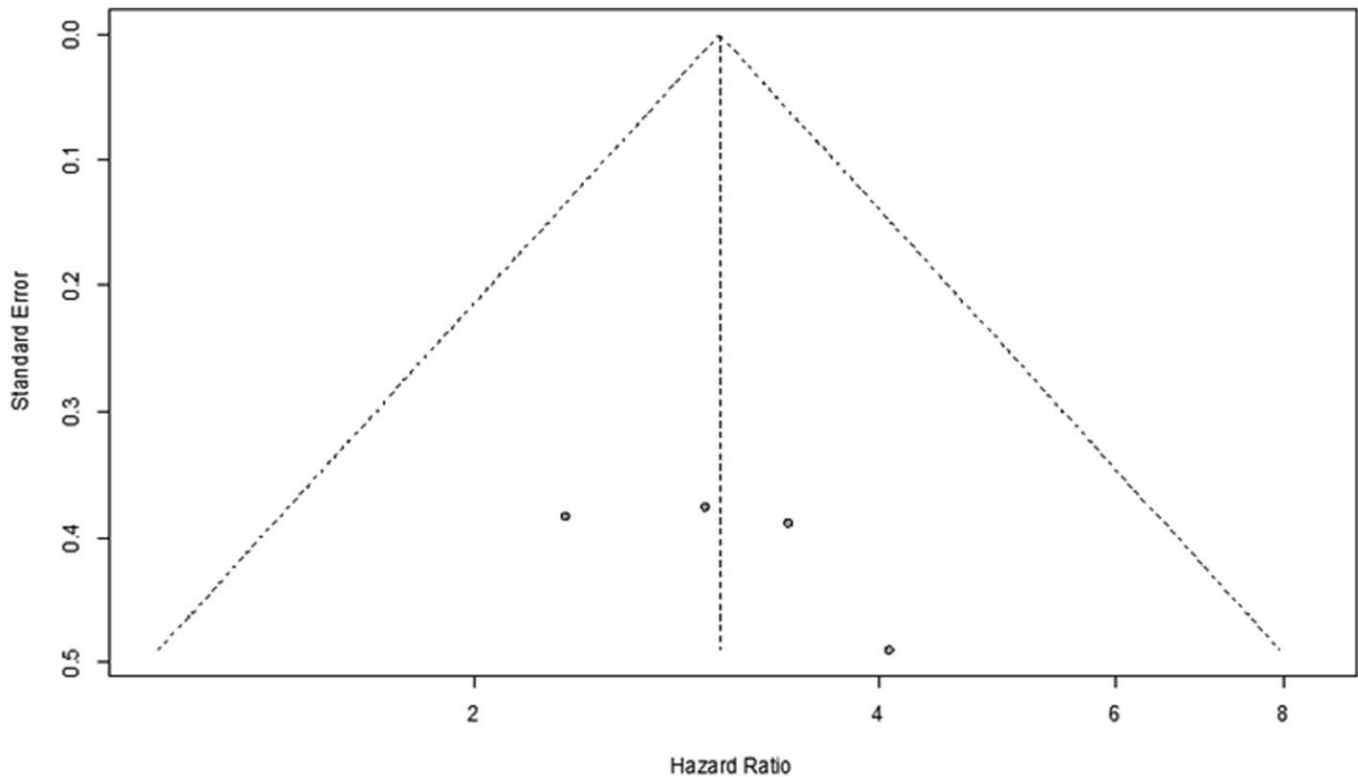


Figure 3. The funnel plot of the Begg test for the publication bias assessment of the synthesized HR assessing the prognostic value of pretreatment LMR for CSS in non-metastatic renal cell cancer. [CSS=Cancer-specific survival, HR=Hazard ratio, LMR=lymphocyte-to-monocyte ratio].

patients with RCC.^[22] On the other hand, Tumor-infiltrating lymphocytes, particularly CD8(+) T cells, could be a manifestation of antitumor immunity. Nakano et al (2001) clinicopathologically analyzed the biological significance of tumor-infiltrating lymphocytes in 221 patients with RCC without preoperative treatments. More abundant infiltration of tumor tissue not only by CD8(+) but also CD4(+) T cells was associated with shorter survival of the patients, because of the positive correlation between the number of lymphocytes and representative tumor grade factors. This suggests that immune cell reactions are more pronounced as the tumor grade/biological malignancy progresses, probably because of increased antigenicity of tumor cells. The same group analyzed the proliferative activity of CD8 (+) T cells that infiltrated in tumor cell nests, which could also reflect antitumor immunity. Higher labeling index of Ki-67, a proliferation-associated antigen, among CD8(+) T cells in contact to tumor cells was associated with a longer survival. This data in human renal cell carcinoma suggest that infiltration of tumor tissue by T cells itself does not denote the efficacy of antitumor immunity because of its dependence on the biological malignancy of tumor cells, but infiltration of tumor tissue by CD8(+) T cells bearing more pronounced proliferative activity could reflect effective antitumor immunity. This concept is important for immunotherapy of RCC treatment.^[23]

Recent studies suggest that an altered metabolism is involved in the development of RCC, and in this tumor many altered genes play a fundamental role in controlling cell metabolic activities. Thus, RCC is characterized by a reprogramming of energetic metabolism. In particular the metabolic flux through glycolysis is partitioned,^[13,14] and mitochondrial bioenergetics and OxPhox

are impaired.^[15] These metabolic changes induce the increased production of several oncometabolites such as kynurenine that modify the inflammatory infiltrate.^[16]

The exact mechanisms responsible for the correlation between low LMR and poor outcome in RCC are unclear. Various hypotheses help explain these observations. The inflammatory cell response secondary to tumor proliferation could cause the production and release of various inflammatory cytokines and mediators, ultimately promoting tumor invasion, migration, metastasis, and progression. Lymphocytes, especially tumor-infiltrating lymphocytes, play a critical role in cell-mediated antitumor. Low lymphocyte counts may, therefore, result in an insufficient immunological reaction, which would lead to poorer survival in a number of cancer immune response. Monocytes, especially those differentiated into tumor-associated macrophages (TAMs), are also involved in tumorigenesis. Several studies reported that the absolute monocyte count was associated with survival in patients with different types of cancer. However, the exact mechanisms underlying the role of monocytes in tumor progression have not been well elucidated yet. The link between monocytes and TAMs may explain how monocytes are involved in the inflammatory tumor response. The circulating level of monocytes may reflect a substrate for the formation or presence of TAMs. TAMs are sensitive to the chemotactic effect of the tumor microenvironment where there are cytokines and chemokines secreted by monocytes. Furthermore, the interaction between TAMs and cancer cells is capable of promoting tumor angiogenesis, migration, invasion, and depressing antitumor immunity, which ultimately leads to tumor progression and worse prognosis in neoplastic patients.^[2-12]

Additionally, there is another hypothesis that may also explain the role of monocytes in tumor progression. Thus, monocytes infiltrating the tumor could release many soluble factors, such as interleukin (IL) -1, IL-6, IL-10, and tumor growth factor- α , and it has been well studied that these factors play an important role in promoting neo-angiogenesis, tumor invasion, and migration, and correlates with an unfavorable prognosis in several malignant tumors. Furthermore, monocytes may contain mitogens that can impair lymphocyte-dependent anti-tumor defense in suppressing anti-tumor immunity. LMR represents the balance between the immune status of the host and the degree of tumor progression. However, the reason why LMR is altered in cancers has not been fully identified so far. One possibility is that there may be an inflammatory-immune imbalance in the genesis of cancer, in which the induction of inflammatory immune cells, such as lymphocytes or monocytes, are influenced by factors associated with the tumor. Moreover, as previously mentioned, monocytes can restrict the mitogen and the lymphocyte proliferative response antigen, which can also contribute to the alteration of LMR. Therefore, we can speculate that the LMR could reflect the state of antitumor immunity and predict the prognosis of patients with kidney cancer. And in this way, the LMR could serve a novel prognostic predictor of survival in patients with non-metastatic RCC and may be incorporated in any predictive prognostic model. Furthermore, LMR is an easy and inexpensive parameter to determine.^[2–12]

However, to date, LMR has not been recommended as a prognostic factor by the European Association of Urology in the clinical guidelines for renal carcinoma, since most of the evidence supporting the prognostic value of LMR in these tumors come from retrospective studies, with small sample size.^[1]

Several limitations we can observe in our meta-analysis. First, the included studies were designed retrospectively and in 3 of the 7, they represented the experience of a single-center, which can lead to bias. Second, most of the studies analyzed had a small sample size. Third, in some of the studies analyzed, the HR and 95% CI were obtained from survival curves, which may cause some statistical error. Fourth, the LMR cut-off value was not uniform across studies. Fifth, the HR and 95% CIs in some studies corresponded to a univariate analysis. Other inconsistent values in aspects such as the proportion of sex, age, geographic areas, and patient follow-up, may also result in bias and heterogeneity.

5. Conclusion

Studies that have been analyzed only corresponded to patients with renal cell carcinomas in localized stages and in whom the treatment had been partial or radical nephrectomy, contrary to the 3 previously published meta-analysis. This meta-analysis showed that a low LMR, determined in peripheral blood before surgery, was associated with poorer CSS, but not with lower OS or DFS in patients with non-metastatic renal cell carcinoma, unlike the results observed in the 3 previous meta-analysis. However, more prospective, heterogeneous, and larger sample studies are required to further confirm our findings before it can be applied for daily clinical decision making, such as identifying patients who may benefit from more postoperative surveillance intensive.

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References

- [1] European Association of Urology. Guidelines. Renal cell carcinoma.2019 update (Accessed July 31, 2020). Available at: <http://uroweb.org/guideline/renal-cell-carcinoma/>.
- [2] Grimes N, Tyson M, Hannan C, et al. A systematic review of the prognostic role of hematologic scoring systems in patients with renal cell carcinoma undergoing nephrectomy with curative intent. *Clin Genitourin Cancer* 2016;14:271–6.
- [3] Wang X, Su S, Guo Y. The clinical use of the platelet to lymphocyte ratio and lymphocyte to monocyte ratio as prognostic factors in renal cell carcinoma: a systematic review and meta-analysis. *Oncotarget* 2017; 8:84506–14.
- [4] Li J, Cheng Y, Ji Z. Prognostic value of pretreatment lymphocyte-to-monocyte ratio in patients with urologic tumors: A PRISMA-compliant meta-analysis. *Medicine (Baltimore)* 2019;98:e14091.
- [5] Hutterer GC, Stoeckigt C, Stojakovic T, et al. Low preoperative lymphocyte-monocyte ratio (LMR) represents a potentially poor prognostic factor in nonmetastatic clear cell renal cell carcinoma. *Urologic oncology: seminars and original investigations* 2014;32: 1041–8.
- [6] Lucca I, de Martino M, Hofbauer SL, et al. Comparison of the prognostic value of pretreatment measurements of systemic inflammatory response in patients undergoing curative resection of clear cell renal cell carcinoma. *World J Urol* 2015;33:2045–52.
- [7] Chang Y, Fu Q, Xu L, et al. Prognostic value of preoperative lymphocyte to monocyte ratio in patients with nonmetastatic clear cell renal cell carcinoma. *Tumour Biol* 2016;37:4613–20.
- [8] Xia WK, Wu X, Yu TH, et al. Prognostic significance of lymphocyte-to-monocyte ratio and CRP in patients with nonmetastatic clear cell renal cell carcinoma: a retrospective multicenter analysis. *Onco Targets Ther* 2016;9:2759–67.
- [9] Chen Z, Shao Y, Yao H, et al. Preoperative albumin to globulin ratio predicts survival in clear cell renal cell carcinoma patients. *Oncotarget* 2017;8:48291–302.
- [10] Elghiaty A, Kim J, Jang WS, et al. Predictive value of preoperative monocyte-lymphocyte ratio among patients with localized clear renal cell carcinoma of ≤ 7 cm on preoperative imaging. *Medicine (Baltimore)* 2018;97:e13433.
- [11] Chen Z, Wang K, Lu H, et al. Systemic inflammation response index predicts prognosis in patients with clear cell renal cell carcinoma: a propensity score-matched analysis. *Cancer Manag Res* 2019;11:909–19.
- [12] Li M, Deng Q, Zhang L, et al. The pretreatment lymphocyte to monocyte ratio predicts clinical outcome for patients with urological cancers: a meta-analysis. *Pathol Res Pract* 2019;215:5–11.
- [13] Lucarelli G, Loizzo D, Franzin R, et al. Metabolomic insights into pathophysiological mechanisms and biomarker discovery in clear cell renal cell carcinoma. *Expert Rev Mol Diagn* 2019;19:397–407.

- [14] Bianchi C, Meregalli C, Bombelli S, et al. The glucose and lipid metabolism reprogramming is grade-dependent in clear cell renal cell carcinoma primary cultures and is targetable to modulate cell viability and proliferation. *Oncotarget* 2017;8:113502–15.
- [15] Lucarelli G, Rutigliano M, Sallustio F, et al. Integrated multi-omics characterization reveals a distinctive metabolic signature and the role of NDUFA4L2 in promoting angiogenesis, chemoresistance, and mitochondrial dysfunction in clear cell renal cell carcinoma. *Aging (Albany NY)* 2018;10:3957–85.
- [16] Lucarelli G, Monica Rutigliano M, Ferro M, et al. Activation of the kynurenine pathway predicts poor outcome in patients with clear cell renal cell carcinoma. *Urol Oncol* 2017;35:461e15–27.
- [17] Papale M, Vocino G, Lucarelli G, et al. Urinary RKIP/p-RKIP is a potential diagnostic and prognostic marker of clear cell renal cell carcinoma. *Oncotarget* 2017;8:40412–24.
- [18] Netti GS, Lucarelli G, Spadaccino F, et al. PTX3 modulates the immunoflogosis in tumor microenvironment and is a prognostic factor for patients with clear cell renal cell carcinoma. *Aging (Albany NY)* 2020;12:7585–602.
- [19] Lucarelli G, Rutigliano M, Sanguedolce F, et al. Increased expression of the autocrine motility factor is associated with poor prognosis in patients with clear cell-renal cell carcinoma. *Medicine (Baltimore)* 2015;94:e2117.
- [20] Gigante M, Lucarelli G, Chiara Divella Ch, et al. Soluble serum α Klotho is a potential predictive marker of disease progression in clear cell renal cell carcinoma. *Medicine (Baltimore)* 2015;94:e1917.
- [21] Lucarelli G, Ditunno P, Bettocchi C, et al. Diagnostic and prognostic role of preoperative circulating CA 15-3, CA 125, and beta-2 microglobulin in renal cell carcinoma. *Dis Markers* 2014; 2014:689795.
- [22] Zhu G, Pei L, Yin H, et al. Profiles of tumor-infiltrating immune cells in renal cell carcinoma and their clinical implications. *Oncol Lett* 2019;18:5235–42.
- [23] Nakano O, Sato M, Naito Y, et al. Proliferative activity of intratumoral CD8(+) T-lymphocytes as a prognostic factor in human renal cell carcinoma: clinicopathologic demonstration of antitumor immunity. *Cancer Res* 2001;61:5132–6.