Cancer Management and Research

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ORIGINAL RESEARCH

Prognostic value of pretreatment neutrophil count in metastatic renal cell carcinoma: a systematic review and meta-analysis

This article was published in the following Dove Press journal:
Cancer Management and Research

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Background: In recent years, inflammation has become widely recognized as a crucial component in tumor development and progression. Neutrophils are one of the most common inflammatory markers during hematological examinations. The prognostic value of neutrophils in metastatic renal cell carcinoma (mRCC) remains inconsistent. The aim of this meta-analysis is to evaluate the prognostic value of pretreatment neutrophil count in patients with mRCC.

Methods: PubMed, Web of Science and Embase were searched for data on the association between pretreatment neutrophil count and mRCC prognosis up to October 7, 2017. We sorted out relevant studies and extracted the hazard ratio (HR) and its 95% confidence interval (CI) for overall survival (OS) and progression-free survival (PFS).

Results: A total of 13 studies containing 3,021 patients with mRCC were summarized in the present meta-analysis. An elevated pretreatment neutrophil count yielded a worse OS (HR=2.17, 95% CI=1.68–2.79, $P<0.001$) and PFS (HR=1.78, 95% CI=0.91–3.49, $P<0.001$). Furthermore, we performed a subgroup analysis based on cut-off value, ethnicity, treatment method and analysis type. As a result, the association between pretreatment neutrophil count and survival was statistically significant in the subgroups of cut-off value, ethnicity, treatment method and analysis type.

Conclusion: Our results show that the pretreatment neutrophil count is associated with mRCC outcomes and can be used as a valuable inflammatory marker for prognosis monitoring.

Keywords: neutrophils, clear-cell metastatic renal cell carcinoma, prognosis, meta-analysis

Introduction

Renal cell carcinoma (RCC) is a common cancer worldwide. Due to gender differences, it accounts for 5% of the adult tumors in men and 3% of the adult tumors in women.[1] Although the widespread use of non-invasive radiological techniques and new therapeutic strategies allows the diagnosis and treatment of RCC at an early stage,[2] nearly half of RCC patients still develop metastatic renal cell carcinoma (mRCC).[3,4] Once metastasis occurs, the 5-year survival rate is not satisfactory.[1] A 5-parameter prognostic score developed at the Memorial Sloan-Kettering Cancer Center (MSKCC)[5] is commonly used to estimate the prognosis in patients with mRCC. However, after taking into account the different circumstances of each patient, the 5-parameter panel developed at MSKCC may not be suitable for all mRCC patients. Hence, it is important to find a new biomarker that can assess the prognosis of mRCC quickly and specifically.

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http://doi.org/10.2147/CMAR.S199849

Nowadays, more and more studies have shown that inflammation plays a significant role in tumor development and progression.[6–8] The increase in the level of pro-inflammatory cytokines in cancer patients may indicate the innate immune response of the host to the tumor and disease activity.[9,10] During the inflammatory reaction, neutrophils are stimulated and activated by inflammatory cytokines such as IL-8 and TNF-α to promote their phagocytotic and bactericidal effects.[11] Several researches have clarified that neutrophil is a prognostic factor of mRCC.[12–14] Neutrophils could represent a useful and cheap biomarker to assess the prognostic value of mRCC patients. However, the precision and magnitude of the prognostic impact of pretreatment neutrophil count in mRCC patients remain inconsistent due to different study-specific factors. Thus, we pooled all related studies in this systematic literature review and meta-analysis to unveil prognostic value of pretreatment neutrophil count in mRCC patients.

Materials and methods

Search strategy

Databases including PubMed, Web of Science and Embase were searched completely up to October 7, 2017. The keywords used on the literature retrieval were "neutrophil", "kidney cancer or renal cancer or renal carcinoma or renal cell carcinoma" and "prognosis or prognostic or survival or outcome". Two authors (Jie Shen and Zhen Chen) researched the databases independently and unified disagreement through discussion to ensure the validity of the retrieved reference lists.

Selection criteria

All studies included were in accordance with the following criteria: (1) all patients only suffered from mRCC and were confirmed by pathology or imageology; (2) the amount of pretreatment neutrophil and the correlation between pretreatment neutrophils, mRCC patients' clinical features and prognosis was described; (3) hazard ratio (HR) and its 95% confidence interval (CI) of overall survival (OS) or disease-free survival (DFS) could be found directly or extrapolated from articles. Studies were excluded if they: (1) had localized RCC patients without metastasis; (2) were letters, reviews, case reports, comments and conference abstracts; (3) had studies with duplicate data and (4) had the missing data that precluded further analysis.

Data extraction

In order to ensure the validity, two authors extracted data from the articles independently. The primary information included was author, country, ethnicity, age of patients, patient numbers, follow-up time, cut-off value, HR and relative 95% CI and treatment method. In case of survival data only presented in Kaplan–Meier curves, software designed by Jayne F Tierney and Matthew R Syde[15] was chosen to digitize and calculate the HR values and 95% CIs. What's more, disputed data were resolved by discussion.

Statistical analysis

We divided pretreatment neutrophil counts into two levels (high and low) depending on the cut-off values mentioned in studies. We integrated the pooled HRs and 95% CIs to estimate the effect of pretreatment neutrophil count on the survival of mRCC. We used the Chi-square test and the I^2 statistic to test the heterogeneity of combined HRs. If the *P*-value was less than 0.05 or the I^2 was greater than 50%, meaning the existence of heterogeneity, a random-effects model was then used. Otherwise, a fixed-effects model was select. We conducted further analysis to explore the potential cause for the existence of heterogeneity. Begg's and Egger's tests were used to find out publication bias. Statistical analyses were performed with STATA 12.0 (Stata Corporation, College Station, TX, USA). A two-tailed *P*-value less than 0.05 was defined as statistically significant difference.

Results

Search results

Figure 1 displays the articles searching process. Initially, we identified 311 articles were potentially eligible. After examining the titles, abstracts and full text of each article carefully, 287 articles were excluded, and the remaining 24 articles were shortlisted. Among the adopted articles, 11 articles were excluded (3 lacked important data, 1 used continuous or two cut-offs, 4 only reported localized RCC patients, 2 reported both localized and metastatic RCC patients and 1 reported only the relative risk or odds ratios). Finally, a total of 13 articles comprised 3021 mRCC patients were included in our meta-analysis.[16–28]

Study characteristics and quality assessment

Characteristics of the included studies are presented in Table 1. Thirteen studies, which contained 3,021 patients totally, were published from 2002 to 2016. These patients came from eight different countries: Czech Republic,

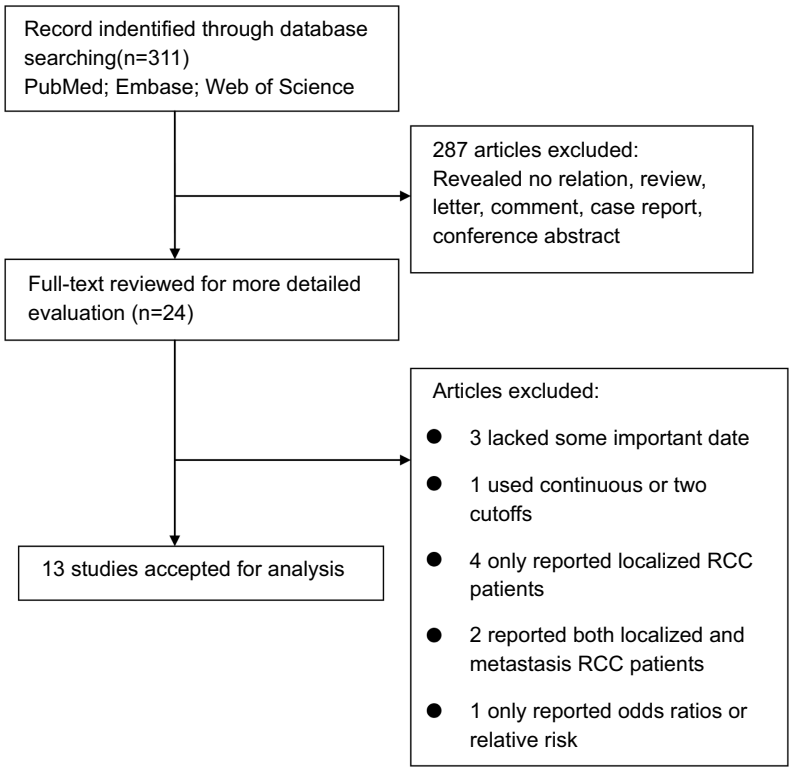

Figure 1 Flow diagram of the study selection process.

Canada, Germany, Turkey, Denmark, Italy, Korea and Japan. Asian nationals accounted for 11.4% (343 patients), whereas Caucasian patients accounted for the remaining 88.6% (2678 patients). A total of 2,271 patients in 9 articles received multiple therapies, while another 750 patients in the rest 3 articles received targeted therapy or kidney transplantation. Prognostic role of neutrophils in OS was found in 12 articles. Besides, PFS was evaluated in 5 articles. Newcastle–Ottawa Scale (NOS)[29] was taken to assess the quality of the included studies. The quality of the studies varied from scores of 5 to 9, with a mean of 6. A higher score was considered to be of better quality.

Relationship between pretreatment neutrophil and OS in mRCC patients

Thirteen studies including 3,021 mRCC patients researched the role of elevated pretreatment neutrophil count as a predictor of OS (Figure 2A). A random model was used due to statistical heterogeneity (I^2=78.9%, P<0.001) and the pooled data demonstrated that a high pretreatment neutrophil count predicted a worse OS (HR=2.17, 95% CI=1.68–2.79, P<0.001).

Relationship between pretreatment neutrophil and PFS in mRCC patients

Figure 3 showed the pooled data for PFS analysis in five studies (755 mRCC patients). The result demonstrated that a high pretreatment neutrophil count predicts a worse PFS (HR=1.78, 95% CI=0.91–3.49, P<0.001) and a random model was adopted in this analysis of PFS because of the statistical heterogeneity (I^2=85.8%, P<0.001).

Subgroup analysis

We performed a subgroup analysis for further exploring the heterogeneity. The results in Table 2 and Figure 2B showed that high pretreatment neutrophil count was linked to a worse OS for Asian mRCC patients (HR=4.04, 95% CI=2.48–6.57, P<0.001) and Caucasian mRCC patients (HR=1.9, 95% CI=1.49–2.43, P<0.001). Neutrophil pretreatment also showed a significant relation to a poor OS in the remaining subgroups: multivariate analysis (HR=2.13, 95% CI=1.62–2.8, P<0.001), univariate analysis (HR=2.4, 95% CI=1.41–4.1, P<0.001), multiple therapy (HR=2.3, 95% CI=1.84–2.87, P<0.001), target therapy or transplantation (HR=1.67, 95% CI=1.04–2.7, P<0.001), upper limits of

Table 1 Main characteristics of all studies included in the meta-analysis

Author	Year	Country	Number	Age	Follow-up	Ethnicity	Cut-off value	Survival analysis	Source of HR	Multivariate analysis	Tumor type	Treatment method	Metastatic sites
Artaç[16]	2016	Turkey	104	57 (29–88)	1.8–58.1	Caucasian	ULN	PFS	Report	Yes	All	TT	Bone, lung, liver, lymph nodes, brain
Santoni[17]	2014	Italy	151	64 (29–88)	51.6	Caucasian	ULN	OS/PFS	Report	No	All	MT	Lymph nodes, lung, bone, liver
You[18]	2014	Korea	171	58.1±11.6	1.5–70.3	Asian	ULN	OS	Report	Yes	All	MT	Bone, liver, brain
Poprach[19]	2013	Czech	319	62 (45–77)	15	Caucasian	$7x10^9$/L	OS/PFS	Report	Yes	All	MT	NR
Santoni[20]	2013	Italy	97	64 (44–82)	46.9	Caucasian	ULN	OS/PFS	Report	No	ccRCC	MT	Bone, lung, liver, lymph nodes
Kroeger[21]	2013	Canada	252	NR	22.3 (10.8–38.4)	Caucasian	ULN	OS	Report	Yes	All	MT	NR
Azuma[22]	2012	Japan	84	66.7 (40–82)	18.3 (1–168)	Asian	3300/ mm^3	OS/PFS	Report	Yes	All	MT	Bone, lung, liver, lymph nodes, brain
Lee[23]	2012	Korea	88	56 (17–83)	29.6	Asian	ULN	OS	Report	Yes	All	MT	Bone, lung, liver, lymph nodes, brain, adrenal gland
Heng[24]	2009	Canada	645	60 (13–88)	24.5	Caucasian	ULN	OS	Report	Yes	All	MT	Brain
Atzpodien[25]	2008	Germany	495	58 (22–79)	NR	Caucasian	$6.5x10^9$/ L	OS	Sc	Yes	All	MT	Bone, lung, liver, lymph nodes, brain, other
Donskov[26]	2006	Denmark	120	57 (19–74)	57 (32–73)	Caucasian	$6x10^9$/L	OS	Report	Yes	All	MT	Bone, lung, liver, lymph nodes, adrenal gland, soft tissue
Peccatori[27]	2005	Italy	70	NR	10	Caucasian	ULN	OS	Report	Yes	All	Transplantation	Liver, mediastinum
Atzpodien[28]	2002	Germany	425	NR	20 (0–157)	Caucasian	$6.5x10^9$/ L	OS	Report	Yes	All	TT	Bone, lung, liver, lymph nodes, brain, other

Abbreviations: ccRCC, clear cell renal cell carcinoma; OS, overall survival; PFS, progression-free survival; HR, hazard ratio; NR, not reported; MT, multiple therapy (including two or more of nephrectomy, target therapy, cytokine therapy); TT, target therapy; SC, survival curve; ULN, upper limits of normal.

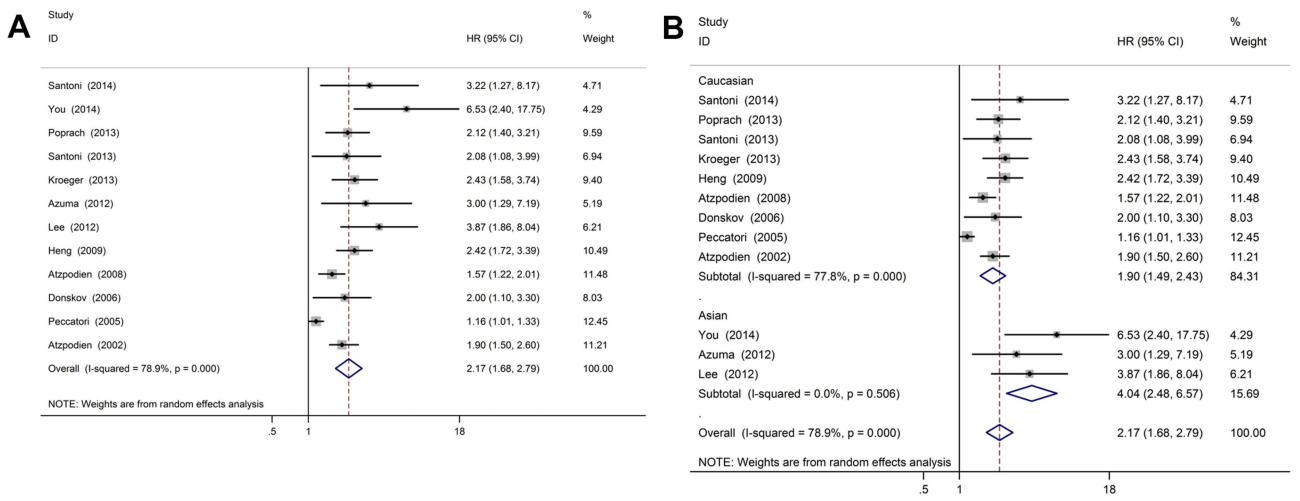

Figure 2 (**A**) Forest plots of studies evaluating hazard ratios of pretreatment neutrophil count in metastatic renal cell carcinoma (mRCC) for overall survival. (**B**) Forest plot of the relationship between pretreatment neutrophil count and overall survival in patients with different ethnicity.

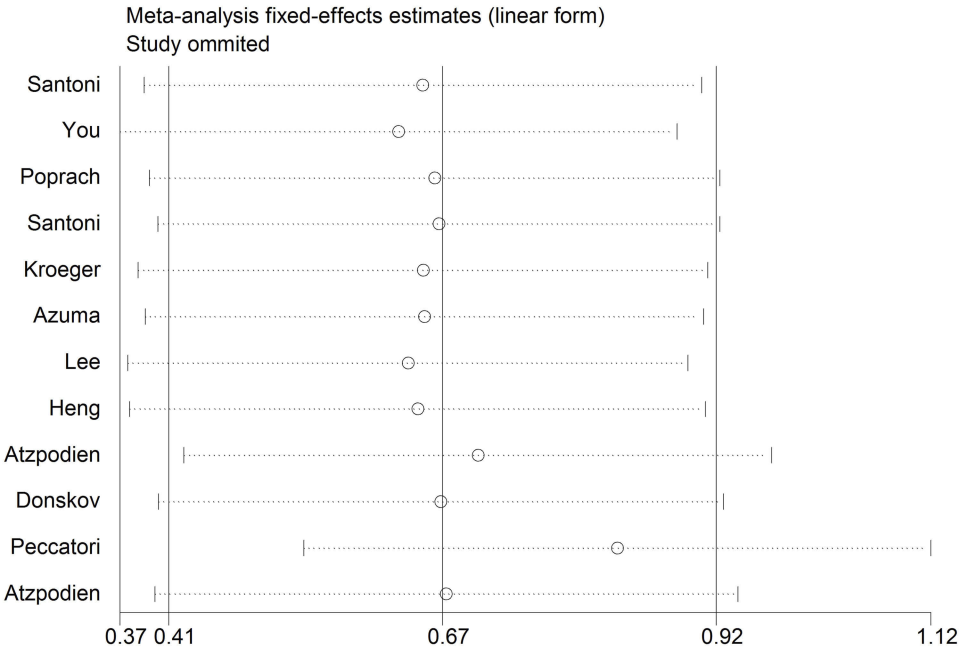

Figure 3 Forest plots of studies evaluating hazard ratios of pretreatment neutrophil count in metastatic renal cell carcinoma (mRCC) for progression-free survival.

normal (ULN) (HR=2.5, 95% CI=1.57–3.98, $P<0.001$) and others (HR=1.82, 95%CI=1.56–2.14, $P<0.001$).

Sensitivity analysis

Each selected study was sequentially removed to evaluate whether it could influence the pooled HRs. As shown in Figure 4, the results of the sensitivity analysis showed high robustness in our findings.

Publication bias

We evaluated the publication bias of OS and PFS using funnel plots, Egger's and Begg's tests. Funnel plots of OS and PFS are shown in Figure 5A and B. No publication bias was observed for OS ($P<0.001$ using Egger's test). For PFS, asymmetrically distributed plots indicated there was possible publication bias. However, considering that the number of included studies was only five, the funnel plots may not be noteworthy.

Table 2 Pooled hazard ratios for OS according to subgroup analyses

Outcome subgroup	No. of patients	No. of studies	HR (95% CI)	*P*-value	Model	Heterogeneity	
						I^2 (%)	*P*
Overall survival	2917	12	2.17 (1.68–2.79)	<0.001	Random	78.9%	<0.001
Ethnicity							
Asian	343	3	4.04 (2.48–6.57)	<0.001	Fixed	0	0.506
Caucasian	2574	9	1.9 (1.49–2.43)	<0.001	Random	77.8%	<0.001
Cut-off value							
ULN	1474	7	2.5 (1.57–3.98)	<0.001	Random	86.4%	<0.001
Others	1443	5	1.82 (1.56–2.14)	<0.001	Fixed	0	0.498
Analysis type							
Multivariate	2669	10	2.13 (1.62–2.8)	<0.001	Random	81.7%	<0.001
Univariate	248	2	2.4 (1.41–4.1)	<0.001	Fixed	0	0.451
Treatment							
Multiple therapy	2271	9	2.3 (1.84–2.87)	<0.001	Fixed	45.4%	0.066
Others	646	3	1.67 (1.04–2.7)	0.035	Random	85.3%	0.001

Abbreviations: OS, overall survival; HR, hazard ratio; CI, confidence interval; ULN, upper limits of normal.

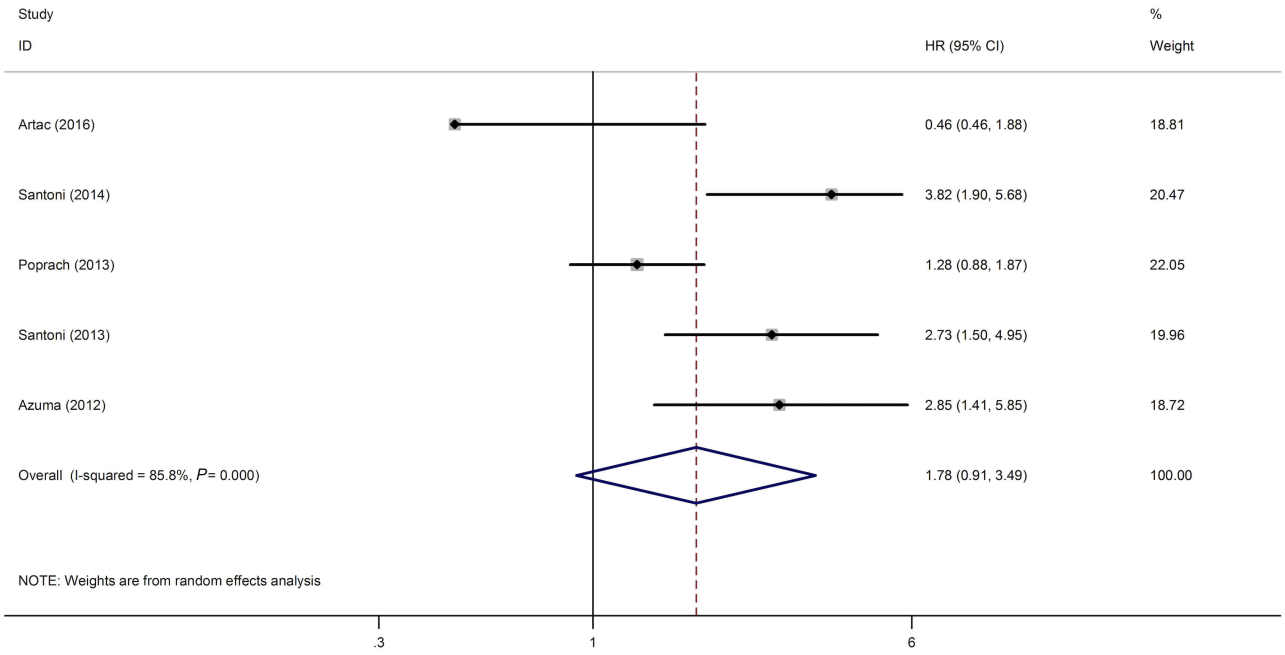

Figure 4 Sensitivity analysis on the relationships between pretreatment neutrophil count and overall survival in metastatic renal cell carcinoma (mRCC) patients.

Discussion

To our best knowledge, this is the first meta-analysis to synthetically analyze the prognostic value of pretreatment neutrophil count in mRCC patients. We proved that an elevated pretreatment neutrophil count could be a target biomarker for worse OS and PFS in mRCC patients. Results of subgroup analysis also demonstrated that an elevated pretreatment neutrophil count is a reliable biomarker regardless of analysis type, ethnic background and treatment method. Our meta-analysis also provides a theoretical basis for researches based on neutrophil count.

Recently, researches have proved indicators such as neutrophil-to-lymphocyte ratio (NLR) and lymphocyte-to-monocyte ratio (LMR) were a poor prognostic factor in

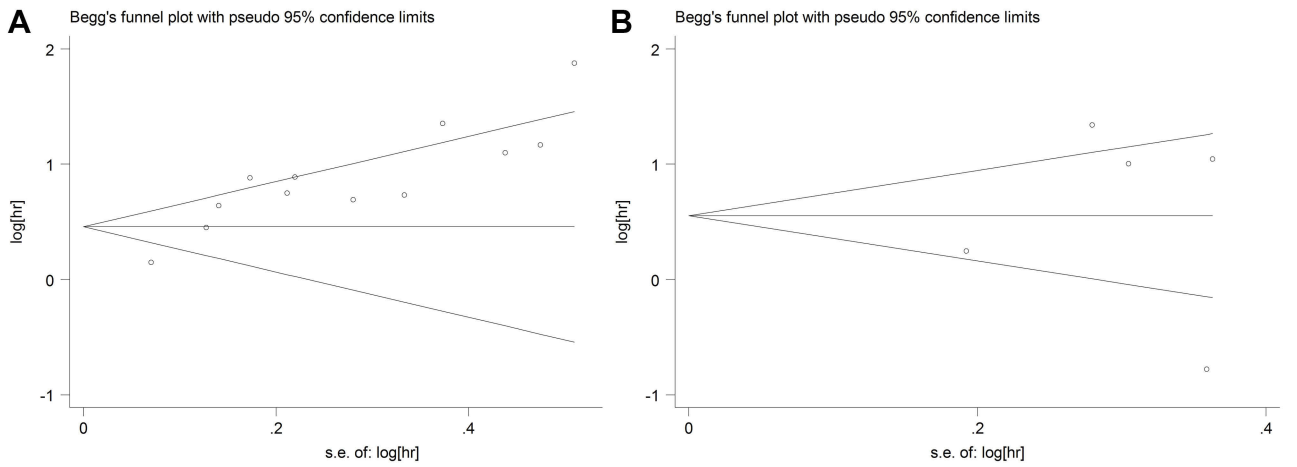

Figure 5 Funnel plots for the evaluation of potential publication bias. (**A**) Overall survival for metastatic renal cell carcinoma; (**B**) Progression-free survival for metastatic renal cell carcinoma.

renal cell carcinoma.[30–32] The ratio of two inflammation biomarkers works since cancer progression is influenced not only by the tumors' biologic characteristics but also by the host's inflammation response. However, depending on these researches, whether neutrophil, lymphocyte or monocyte alone is an independent prognostic factor in renal cell carcinoma is still unknown. Studies have reported lymphocyte could play an anti-tumor effect through inducing cell apoptosis and mediating cytotoxicity.[7] Although most articles have demonstrated the poor prognosis of neutrophil in renal cell carcinoma,[14,22] there still some articles hold the opposite conclusion.[33] Hence, we do this study to elucidate the definite role of neutrophil in renal cell carcinoma.

Neutrophils mainly occur in the blood. They are also called polymorphonuclear leukocytes (PMNs) and account for 50–70% of the total number of peripheral white blood cells.[34,35] Generally, neutrophils are well known for their potent phagocytic function. They can swallow bacteria, activate the immune system and induce tissue damage in infections.[36] However, in untreated tumors, several studies have reported that neutrophils could produce matrix-degrading enzymes and angiogenic factors to suppress the anti-tumor immune response and promote tumor metastasis.[37,38] In the tumor microenvironment, chemokines are generated by tumor tissues, and neutrophils in the blood move through the vascular wall into the tumor tissues following stimulation by chemokines. Those neutrophils that traffic into tumors are referred to as tumor-associated neutrophils (TANs).[39,40] TANs can be divided into two different phenotypes: an anti-tumorigenic (N1) phenotype and a pro-tumorigenic (N2) phenotype.[41] This plasticity of TANs is regulated by various cytokines in the tumor microenvironment. Fridlender[42] has demonstrated that transforming growth factor-β (TGF-β) could induce neutrophil polarization to an N2 neutrophil phenotype. Corresponding to his study, interferon-β (INF-β) was demonstrated by Jablonska[41] to induce neutrophil polarization to an N1 phenotype.

TAN promoted tumor progression primarily through the secretion of matrix metalloproteinase-9 (MMP-9), neutrophil elastase (NE) and chemokines.[43] MMP-9 is a kind of collagenase. It can promote tumor cell infiltration and metastasis by changing extracellular matrix structure.[43] MMP-9 can activate angiogenesis factors, such as vascular endothelial growth factor (VEGF) and fibroblast growth factor-2 (FGF-2), to stimulate tumor angiogenesis and increase tumor blood supply to encourage tumor growth.[44]

NE is an essential member of the chymotrypsin superfamily of serine proteases, which contains 218 amino acid residues and 4 glycoprotein disulfide bonds. NE primarily promotes the occurrence and development of tumors by stimulating the production of related cell growth factors and inhibiting tumor cell apoptosis.[45,46] Recently, Houghton found that NE could enter tumor cells and degrade insulin receptor substrate-1 (IRS1).[47] This process strengthened the interaction between phosphatidylinositol 3-kinase (PI3K) and the potent mitogen platelet-derived growth factor receptor (PDGFR), thereby skewing the PI3K axis towards tumor cell proliferation.

IL-8 is a member of the CXC chemokines secreted by TAN. It can bind to CXCR2 expressed on the surface of endothelial cells as well as TANs, which not only promotes tumor angiogenesis but also further recruits

neutrophils into the tumor microenvironment, suggesting that TANs secrete interleukin (IL)-8 and may create a positive feedback loop to maintain the number of TANs.[48,49]

On the other hand, N1 phenotype TANs inhibit tumor growth and metastasis. The major mechanisms are as follows: (1) activating the Fas ligand-related apoptosis pathway and directly promoting tumor cell apoptosis;[50] (2) activating dendritic cells and $CD4^+$ T cells to induce IL-12 dependent tumor rejection;[51] (3) improving the expression of IgGFc receptors to promote an antibody-dependent cellular cytotoxicity (ADCC) effect[52] and (4) releasing reactive oxygen species via the degranulation function, leading to tumor cell reactive oxygen species injury and subsequent tumor cell lysis.[53]

According to the many mechanisms mentioned earlier, neutrophils have been suggested as a novel therapeutic target for mRCC patients. Narrowing the neutrophil level in the blood and promoting neutrophil polarization to an N1 phenotype could inhibit tumor progression and extend survival time.

This meta-analysis has some limitations. First, all of the included studies in our meta-analysis were retrospective. It is very difficult to avoid selection bias in observational studies. Second, we only paid our attention to articles mentioning the HR and the 95% CI; others were removed because they reported only odds ratios and relative risk for survival. Moreover, the pretreatment neutrophil count could interact with some other cell populations and influenced by diverse conditions, such as hypoxia, acute hemolysis, chronic infection, chronic disease and autoimmune disorders, such as rheumatic disease. Most articles presented in this meta-analysis did not investigate those factors.

In conclusion, this meta-analysis proved that an elevated neutrophil level was linked to a poor prognosis in mRCC patients. The pretreatment neutrophil count was a convenient and cost-effective prognostic indicator that could be used for risk stratification and become an additional component of the MSKCC prognostic score. Furthermore, it can be utilized to formulate individualized treatments for mRCC patients. Finally, we propose that pretreatment neutrophil count may be considered as a completely novel therapeutic target for cancer patients. Our meta-analysis highlighted the probable theoretical foundation for the application of pretreatment neutrophil count in mRCC patients. Considering the limitations of the present analysis, further multicenter studies are required to research the underlying mechanisms and confirm our findings.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (Grant no. 81273267), the National Science Foundation of Jiangsu Province (Grant no. BK20150251), the National Science Foundation of Jiangsu Province (Grant no. BK20151180) and Major Scientific and Technological Projects of Changzhou Health Bureau (Grant no. ZD201405). We thank Professor Jingting Jiang for his excellent technical support.

Disclosure

The authors report no conflicts of interest in this work.

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