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The association of pre-treatment neutrophil to lymphocyte ratio with response rate, progression free survival, and overall survival of patients treated with sunitinib for metastatic renal cell carcinoma

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ABSTRACT

Background: Sunitinib is a standard treatment for metastatic renal cell carcinoma (mRCC). The neutrophil to lymphocyte ratio (NLR), an index of systemic inflammation, is associated with outcome in several cancer types.

Aims: To study the association of pre-treatment neutrophil to lymphocyte ratio with response rate, progression free survival (PFS) and overall survival (OS) of patients treated with sunitinib for mRCC.

Methods: We retrospectively studied an unselected cohort of patients with mRCC, who were treated with sunitinib. Logistic regression model was used to analyse response rate. Cox regression models were fitted to identify risk factors associated with PFS and OS. We investigated how pre-treatment NLR is associated with these clinical outcomes after adjusting for confounding covariates. Regression tree for censored data method was used to find the best NLR cut-off value.

Results: Between 2004 and 2011, 133 patients with mRCC were treated with sunitinib. One hundred and nine were included in the NLR analysis, from which were excluded patients without available data on pre-treatment NLR or with comorbidities/recent treatments known to be associated with a change of blood counts. Factors associated with PFS were low NLR $\leqslant 3$ (HR = 0.285, $p < 0.001$), past nephrectomy (HR = 0.38, $p = 0.035$), sunitinib dose reduction/treatment interruption (HR = 0.6, $p = 0.014$), and the use of antiotensin system inhibitors (HR = 0.537, $p = 0.008$). Low NLR $\leqslant 3$ was associated with OS (HR = 0.3, $p = 0.043$).

Conclusions: In patients with mRCC treated with sunitinib, pre-treatment NLR may be associated with PFS and OS. This should be investigated prospectively, and if validated applied in clinical practice and clinical trials.

1. Introduction

Renal cell carcinoma is the most common cancer of the kidney.[1] Thirty percent of patients present with metastatic disease,[2,3] and recurrence develops in 40% of patients treated for a localised tumour.[2,4] An understanding of the pathogenesis of renal cell carcinoma at the molecular level, and randomized clinical trials, have established the standard role of the

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orally administered vascular endothelial growth factor receptor and platelet derived growth factor receptor inhibitor sunitinib for the treatment of advanced renal cell carcinoma.[5]

Data suggests that inflammation plays a role in the tumourigenesis process and progression of many cancers, by promoting cancer cell proliferation and survival, angiogenesis, tumour metastasis, and impacting tumour response to systemic therapies.[6] This is mediated by the interaction between proinflammatory cytokines, oncogenes (RAS, MYC, RET), and pathways including NF-κB and STAT3.[6,7] The neutrophil-to-lymphocyte ratio (NLR) is an easily measured, reproducible, and inexpensive marker of systemic inflammation,[8–12] which is associated with outcome in different cancer types. The pre-treatment NLR was found to be an independent predictor of recurrence in patients with non-metastatic renal cell carcinoma,[8] and to predict survival in patients treated with systemic chemotherapy for malignant mesothelioma,[9] colorectal liver metastases,[10] advanced pancreatic cancer,[11] ovarian cancer,[12] and gastric cancer.[13]

Retrospective studies identified several clinical factors that are associated with outcome of patients with metastatic renal cell carcinoma (mRCC) that are treated with sunitinib.[14–19] In one study of sunitinib treatment in mRCC, the neutrophil count was found to be associated with overall survival (OS).[18] In another study of IL-2 treatment in mRCC, low lymphocyte count was associated with survival.[20] Data suggests that exploring the combined impact of neutrophil and lymphocyte counts may provide more prognostic information than either component alone.[11] To the best of our knowledge, the association between the NLR and outcome in mRCC patients has not been previously reported.

In the present study we sought to determine the association of pre-treatment neutrophil to lymphocyte ratio with response rate, progression free survival (PFS) and overall survival of patients treated with sunitinib for metastatic renal cell carcinoma.

2. Patients and methods

2.1. Study group

Between 1st January 2002 and 28th February 2011, 400 patients with histologically confirmed metastatic renal cell carcinoma were registered and seen in the division of medical oncology, Johns Hopkins Kimmel Cancer Center. Of these, 133 patients that were treated with sunitinib, between 1st February 2004 and 28th February 2011, comprised the study group. The other 267 patients were treated with therapies other than sunitinib. Data were retrospectively collected from patients electronic medical records, paper charts, pharmacy records, and by contacting patients and other treating physicians as needed. Collected data included the following clinicopathologic information: age, gender, tumour histology, the time interval from initial diagnosis to sunitinib treatment initiation, Eastern Cooperative Oncology Group (ECOG) performance status, prior treatments for renal cell carcinoma, sites of metastasis, laboratory findings, pre-treatment and on treatment blood pressure levels, concomitant use of medications, including angiotensin system inhibitors (angiotensin converting enzyme inhibitors and angiotensin II receptor blockers), sunitinib dose reduction and/or treatment interruption, and treatment outcomes including objective response rate, progression free survival, and overall survival. Outcome data was last updated on 28th February 2011.

2.2. Sunitinib treatment

All patients had objective disease progression on scans before starting sunitinib treatment. Sunitinib was prescribed as a part of standard treatment or clinical trial. It was administered orally, usually at a starting dose of 50 mg once daily, in 6-week cycles consisting of 4 weeks of treatment followed by 2 weeks without treatment. In patients with significant comorbidities, treatment was initiated at a reduced dose, with subsequent dose escalation if well tolerated. On treatment dose reduction or treatment interruption were done for the management of adverse events, depending on their type and severity, according to standard guidelines. Treatment was continued until evidence of disease progression on scans, unacceptable adverse events, or death. Patient followup generally consisted of regular physical examination and laboratory assessment (haematologic and serum chemical measurements), every 4–6 weeks, and imaging studies performed every 12–18 weeks.

2.3. Treatment outcomes

Follow-up time was defined as the time from sunitinib treatment initiation to 28th February 2011. For the evaluation of response, the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 was applied.[21] The response was assessed by independent radiologists and treating physicians, and personally reviewed by the investigator D.K. Progression free survival was defined as the time from the initiation of sunitinib treatment until evidence of disease progression on scans or death of any cause. Overall survival was defined as the time from the initiation of sunitinib treatment to death of any cause.

2.4. Statistical analysis

We analysed the pre-treatment NLR (calculated by dividing the neutrophil count value by the number of lymphocytes) and potential factors associated with outcome,[14–19] including past nephrectomy, clear cell versus non-clear cell histology, time from initial kidney cancer diagnosis to sunitinib treatment initiation, the presence of more than two metastatic sites, lung/liver/bone metastasis, Eastern Cooperative Oncology Group performance status, the presence of anaemia and corrected (for albumin) serum calcium level above 10 mg/dL, platelet count, sunitinib induced hypertension, past cytokines and/or targeted treatments, sunitinib dose reduction and/or treatment interruption, mean sunitinib dose/cycle, the use of angiotensin system inhibitors (angiotensin converting enzyme inhibitors and angiotensin II receptor blockers) before or within one month after initiation of sunitinib treatment,[19] and the risk according to the Heng prognostic model.[18] Patients without available data on pre-treatment NLR and those with baseline comorbidity such as Chronic lymphocytic leukemia (CLL), and recent (⩽1 month) treatment (surgery, steroids, tyrosine

kinase inhibitors, cytokines) known to be associated with a change of blood counts, were excluded from the NLR analysis.[22] Regression tree analysis for censored data was used to find the best NLR cut-off value. Patients who did not progress or die by 28th February 2011 were censored in progression free survival analysis or overall survival analysis, respectively. Univariate analysis (unadjusted) of association between each clinicopathologic factor and clinical outcome was performed using logistic regression for response rate and Cox regression model for survival outcomes (PFS and OS). Factors with significant association in the univariate analysis were included in multivariate Cox proportional hazards regression model to determine their independent effects. Survival probabilities and median survival times were estimated from Kaplan–Meier curves. Multivariate analysis using the large number of all baseline potential prognostic factors may be subject to problems, secondary to multiple variables effect. Therefore, a common approach in mRCC is to use one prognostic model. Thus, the analysis was further stratified by subgroups according to the Heng prognostic model,[18] patients with mRCC of the clear cell variety that were naïve to systemic targeted treatment, and those not using angiotensin system inhibitors. For each subgroup, we did a multivariate analysis of factors not included in the subgroup definition, i.e. the use of angiotensin system inhibitors, dose reduction/treatment interruption and mean dose in Heng subgroups. Finally, we also compared baseline clinical characteristics and known prognostic factors between patients with high and low NLR. Chi-square test was used to compare categorical end-points, and two-sample t-test was used to compare continuous end-points after necessary data transformation. Data were analysed using S-Plus 8.0 for Windows Enterprise Developer.

2.5. *Regulatory considerations*

The research was carried out in accordance with the approval by the IRB committee of our institution.

3. Results

3.1. *Patient characteristics*

One hundred thirty three patients (median age 61, range 24–85, mean ± SD 60.7 ± 11.3 years; male 71%, $n = 95$) with metastatic renal cell carcinoma were treated with sunitinib between 1st February 2004 and 28th February 2011. One hundred and nine patients (82%) were included in the pre-treatment neutrophil to lymphocyte ratio analysis, from which were excluded 24 patients without available data on pre-treatment NLR ($n = 15$) and those with baseline comorbidity (CLL, $n = 1$) and recent ($\leqslant$1 month) treatment (steroids, $n = 1$; interferon, $n = 1$; sorafenib, $n = 4$; surgery, $n = 2$) known to be associated with a change of blood counts.[22] The distribution of clinicopathologic and prognostic factors is shown in Table 1. The best NLR cut-off value was found to be $\leqslant$3 versus >3. Fifty four of 109 (50%) had an elevated NLR (>3) at baseline. The distribution of clinicopathologic factors between patients with pre sunitinib treatment NLR $\leqslant$3 versus >3 is shown in Table 2. Patients with pre-treatment NLR > 3 had a shorter time from diagnosis to sunitinib treatment initiation, and a higher prevalence of non-clear cell histology, Eastern Cooperative Oncology Group performance status >1, anaemia, and poor Heng risk. They also had a lower prevalence of sunitinib induced hypertension, and use of angiotensin system inhibitors.

3.2. *Sunitinib treatment outcomes*

Median followup time was 37 months (range 5–85, 38.3 ± 18.6 mean ± SD). Objective response at first imaging evaluation within the first three months of sunitinib treatment initiation was complete response 2% ($n = 2$), partial response 38% ($n = 51$), stable disease 37% ($n = 49$), and progressive disease 23% ($n = 31$). Median progression free survival was 8 months (10.9 ± 10.9 mean ± SD, range 1–69). Median overall survival was 17 months (22.5 ± 16.6 mean ± SD, range 1–74). One hundred and twenty patients (90%) have progressed, and 70 patients (53%) died.

3.3. *Univariate analysis of factors associated with response rate, progression free survival, and overall survival (Table 1)*

Past nephrectomy (OR 2.42, $p = 0.01$), anaemia (OR 5.15 without anaemia, $p = 0.02$), sunitinib induced hypertension (OR 9.44, $p = 0.02$), use of angiotensin system inhibitors (OR 4, $p = 0.044$), and low pre-sunitinib treatment neutrophil to lymphocyte ratio $\leqslant$3 (OR 5.2, $p = 0.02$) were associated with response to sunitinib (complete response, partial response, or stable disease, versus disease progression) at first imaging evaluation within the first three months of treatment initiation. Non-clear cell histology (HR = 1.47, $p = 0.0023$), past nephrectomy (HR = 0.499, $p = 0.0054$), time from diagnosis to sunitinib treatment (HR = 0.9, $p = 0.0028$), anaemia (HR = 1.48, $p = 0.051$), sunitinib induced hypertension (HR = 0.66, $p = 0.027$), sunitinib dose reduction/treatment interruption (HR = 0.6, $p = 0.0052$), use of angiotensin system inhibitors (HR = 0.547, $p = 0.002$), the HENG risk (HR = 1.6 and 2.5 with HENG 2 and 3 respectively, $p = 0.006$), and a low pre-sunitinib treatment neutrophil to lymphocyte ratio $\leqslant$3 (HR = 0.25, $p < 0.001$) were associated with progression free survival. Time from diagnosis to sunitinib treatment (HR = 0.9, $p = 0.008$), sunitinib induced hypertension (HR = 0.47, $p = 0.002$), sunitinib dose reduction/treatment interruption (HR = 0.48, $p = 0.003$), and a low pre-sunitinib treatment neutrophil to lymphocyte ratio $\leqslant$3 (HR = 0.24, $p < 0.001$) were associated with overall survival.

3.4. *Multivariate analysis of factors associated with response rate, progression free survival, and overall survival (Table 1)*

Past nephrectomy (OR = 2.64, $p = 0.025$), anaemia (OR = 1.76 without anaemia, $p = 0.03$), sunitinib induced hypertension (OR = 3, $p = 0.001$), use of angiotensin system inhibitors (OR 2.83, $p = 00.012$), and a low pre-sunitinib treatment neutrophil to lymphocyte ratio $\leqslant$3 (OR 1.8, $p = 0.043$) were associated with response to sunitinib (complete response, partial response, or stable disease, versus disease progression) at first imaging evaluation within the first three months. Factors associated

Table 1 – Distribution of clinicopathologic and prognostic factors, and univariate and multivariate analysis of their association with progression free survival and overall survival.

Factor (n = number of patients with data available)	Distribution	Univariate analysis (HR, p)		Multivariate analysis (HR, p)	
		PFS	OS	PFS	OS
Age (years) (n = 133)	60.7 ± 11.3 (24–85; 61) mean ± SD (range; median)	NS	NS		
Gender (n = 133)	Female: 29% (n = 38) Male: 71% (n = 95)	NS	NS		
Tumour histology (n = 133)	Non-clear cell: 20% (n = 26)	1.47, 0.0023	NS	NS	
ECOG PS (n = 133)	0–1: 92% (n = 122) >1: 8% (n = 11)	NS	NS		
Past nephrectomy (n = 133)	84% (n = 112)	0.499, 0.0054	NS	0.38, 0.035	
Time (mos) from dx to sunitinib tx (n = 132)	31 ± 42 (1–180; 12) mean ± SD (range; median)	0.9, 0.0028	0.9, 0.008	NS	NS
Prior systemic tx (n = 133)	29% (n = 39)	NS	NS		
Lung metastasis (n = 133)	68% (n = 91)	NS	NS		
Liver metastasis (n = 133)	26% (n = 34)	NS	NS		
Bone metastasis (n = 133)	35% (n = 47)	NS	NS		
$\geqslant$2 metastatic sites (n = 133)	79% (n = 105)	NS	NS		
Neutrophil count (n = 109)	4859 ± 2096 (1540–9880; 4530) mean ± SD (range; median)	NS	NS		
Lymphocyte count (n = 109)	1699 ± 824 (470–2910; 1620) mean ± SD (range; median)	NS	NS		
Anaemia (n = 120)	55% (n = 73)	1.48, 0.051	NS	NS	
Platelets count (n = 120)	278.8 ± 116.7 (114–625; 257) mean ± SD (range; median)	NS	NS		
Corrected Ca > 10 mg/dL (n = 120)	17% (n = 22)	NS	NS		
Sunitinib induced HTN (n = 133)	54% (n = 72)	0.66, 0.027	0.47, 0.002	NS	NS
Sunitinib DR/TI (n = 133)	50% (n = 67)	0.6, 0.0052	0.48, 0.003	0.6, 0.014	NS
Mean sunitinib dose (mg)/tx cycle (n = 133)	43 ± 9 (12–50; 48) mean ± SD (range; median)	NS	NS		
Users of ASIs (n = 133)	35% (n = 47)	0.547, 0.002	NS	0.537, 0.008	
Heng risk stratification (n = 128)	Favourable risk 23% (n = 30) Intermediate risk 56% (n = 74) Poor risk 18% (n = 24) Risk unknown 3% (n = 5)	1.6 and 2.5 with favourable and intermediate risk respectively, 0.006	NS	NS	
NLR $\leqslant$ 3 (n = 109)	50% (n = 55/109)	0.25, <0.001	0.24, <0.001	0.285, <0.001	0.3, 0.043

ASIs = angiotensin system inhibitors; Ca = calcium; DR = dose reduction; Dx = diagnosis; ECOG PS = Eastern Cooperative Oncology Group performance status; HTN = hypertension; Mos = months; NLR = Neutrophil to lymphocyte ratio; NS = non-significant; PFS = progression free survival; OS = overall survival; TI = treatment interruption; Tx = treatment.

with progression free survival were past nephrectomy (HR = 0.38, $p = 0.035$), sunitinib dose reduction/treatment interruption (HR = 0.6, $p = 0.014$), the use of angiotensin system inhibitors (HR = 0.537, $p = 0.008$), and a low pre-treatment neutrophil to lymphocyte ratio $\leqslant$3 (HR = 0.285, $p < 0.001$). Median progression free survival was 4 versus 15 months in patients with baseline NLR >3 versus $\leqslant$3 (fig. 1). A low NLR $\leqslant$ 3 was associated with overall survival (HR = 0.3, $p = 0.043$). The median overall survival was 14 months versus not reached with a median time of 29 months, in patients with NLR >3 versus $\leqslant$3 respectively (fig. 2).

3.5. *Subgroup analysis*

A multivariate analysis in patient subgroups according to the Heng prognostic model,[18] in those with clear cell variety that were naïve to systemic targeted treatment, and those not using angiotensin system inhibitors, is summarised in Table 3. It revealed a better progression free survival and overall survival of patients with pre-treatment neutrophil to lymphocyte ratio $\leqslant$3, although this was not statistically significant at 0.05 significance level in the relatively small cohort of patients with Heng poor risk.

3.6. *Post treatment neutrophil to lymphocyte ratio*

One hundred and nine patients had available data on post treatment NLR. The NLR measured after the completion of the first sunitinib treatment cycle was not found to be significantly associated with response rate, progression free survival, and overall survival.

4. Discussion

The present study suggests that pre-treatment neutrophil-to-lymphocyte ratio may be associated with response rate, progression free survival and overall survival of patients treated with sunitinib for metastatic renal cell carcinoma. In this retrospective study, patients with pre-treatment NLR $\leqslant$ 3 had a better response rate, and longer progression free survival

Table 2 – Distribution of clinicopathologic prognostic factors stratified by pre-treatment NLR.

Characteristic	NLR ⩽ 3 (*n* = 55)	NLR > 3 (*n* = 54)	*p*
Age (years): mean ± SD (range; median)	61.6 ± 10.6 (35–80; 64)	59.4 ± 11.6 (33–85; 60)	0.582
Tumour histology			
Clear cell	89% (*n* = 49)	72% (*n* = 39)	0.018
Non-clear cell	11% (*n* = 6)	28% (*n* = 15)	
ECOG PS: 0–1	96% (*n* = 53)	87% (*n* = 47)	0.032
>1	4% (*n* = 2)	13% (*n* = 7)	
Past nephrectomy	89% (*n* = 49)	76% (*n* = 41)	0.06
Time (months) from dx to sunitinib treatment: mean ± SD (range; median)	42 ± 45.2 (1–180; 23)	14.4 ± 24.3 (1–108; 5)	0.001
Prior systemic treatment	31% (*n* = 17)	22% (*n* = 12)	0.6
Prior targeted treatments	15% (*n* = 8)	13% (*n* = 7)	0.9
Lung metastasis	69% (*n* = 38)	70% (*n* = 38)	0.83
Liver metastatis	20% (*n* = 11)	28% (*n* = 15)	0.36
Bone metastasis	29% (*n* = 16)	44% (*n* = 24)	0.11
⩾2 metastatic sites	78% (*n* = 43)	80% (*n* = 43)	0.64
Anaemia	44% (*n* = 24)	76% (*n* = 41)	0.001
Platelets count: mean ± SD (range; median)	246 ± 74 (122–503; 239)	324 ± 143 (104–934; 290)	0.002
Corrected calcium > 10 mg/dL	24% (*n* = 13)	17% (*n* = 9)	0.628
Subgroups according to the Heng model			
Favourable	35% (n = 19)	7% (*n* = 4)	0.001
Intermediate	56% (*n* = 31)	63% (*n* = 34)	
Poor	9% (*n* = 5)	30% (*n* = 16)	
Sunitinib induced HTN	64% (*n* = 35)	39% (*n* = 21)	0.035
Use of ASIs	45% (*n* = 25)	20% (*n* = 11)	0.02
Sunitinib dose reduction/treatment interruption	58% (*n* = 32)	41% (*n* = 22)	0.18
Mean sunitinib dose (mg)/treatment cycle: mean ± SD (range; median)	42 ± 9.6 (12–50; 44.5)	45 ± 8.3 (16–50; 50)	0.3

ASIs = angiotensin system inhibitors; Dx = diagnosis; ECOG PS = Eastern Cooperative Oncology Group performance status; HTN = hypertension; NLR = neutrophil to lymphocyte ratio.

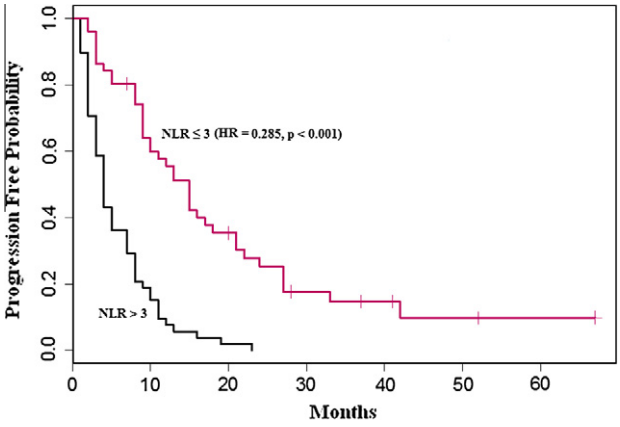

Fig. 1 – Kaplan–Meier curves showing progression-free survival, stratified by the pre-treatment neutrophil-to-lymphocyte ratio.

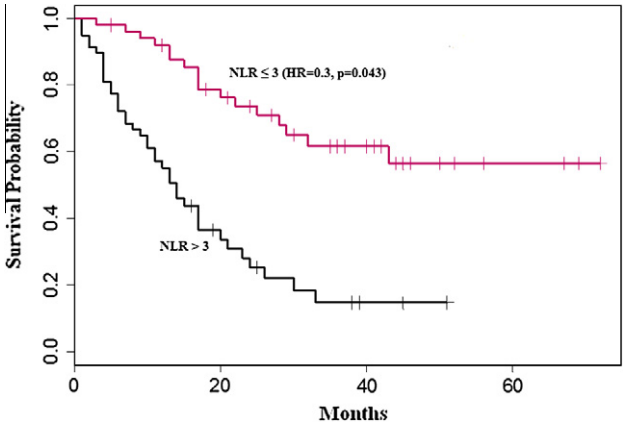

Fig. 2 – Kaplan–Meier curves showing overall survival, stratified by the pre-treatment neutrophil-to-lymphocyte ratio.

and overall survival, after adjustment for other known prognostic factors. Furthermore, a better progression free survival and overall survival of patients with pre-treatment neutrophil to lymphocyte ratio ⩽3 was noted in subgroups analysis according to the Heng prognostic model, and of patients with clear cell variety that were naïve to systemic targeted reatment, and in those not using angiotensin system inhibitors, although this was not statistically significant at 0.05 significance level in the relatively small cohort of patients with Heng poor risk. As we recently reported,[19] the present study also revealed a better progression free survival with the use of angiotensin system inhibitors.

Table 3 – The association between pre-treatment neutrophil to lymphocyte ratio and progression free survival and overall survival, by multivariate analysis in patient subgroups.

Subgroup	Number of patients	Pre-treatment neutrophil to lymphocyte ratio ⩽3 versus >3	
		Median PFS (months); HR, *p*	Median OS (months); HR, *p*
Heng favourable risk	30	14 versus 7; 0.71, 0.002	Not reached (28) versus 17; 0.54, 0.03
Heng intermediate risk	74	14 versus 4; 0.27, <0.001	Not reached (29) versus 11; 0.65, 0.025
Heng poor risk	24	6 versus 4; 0.85, 0.2	14 versus 13; NS
Patients with clear cell variety that are naïve to systemic targeted treatment	92	13 versus 4; 0.26, <0.001	Not reached (28) versus 13; 0.55, 0.04
Patients not using ASIs	86	11.5 versus 4; 0.287, 0.001	Not reached (29) versus 10 (0.5, 0.04)

ASIs = angiotensin system inhibitors; NS = non-significant; PFS = progression free survival; OS = overall survival.

Existing pre-clinical and clinical data suggest that inflammation plays a role in the tumourigensis process of many cancers.[6,7] Although previous studies suggested that inflammatory markers are associated with prognosis in mRCC, this was mainly reported in patients treated with immunotherapy (interferon alpha or IL-2).[23] In this setting, the lymphocyte count and the Glasgow prognostic Score, which is based on elevated C-reactive protein (CRP) and low albumin, have shown prognostic value.[20,23] In patient treated with tyrosine kinase inhibitors, studies did not unanimously find that the neutrophil and lymphocyte counts are associated with progression-free survival and overall survival. The neutrophil count was associated with prognosis in the Heng model,[18] but not in other studies.[14] In the present study, the neutrophil and lymphocyte count alone were not associated with outcome.

Our observation suggests that exploring the combined impact of neutrophil and lymphocyte counts may provide more prognosis information than either component alone.

This was previously suggested in other cancer types,[8–13] but to the best of our knowledge it was not previously reported in patients treated with tyrosine kinase inhibitors for metastatic renal cell carcinoma.

The association between NLR and outcome is complex and remains to be elucidated. A high NLR reflects both a heightened neutrophil-dependent inflammatory reaction, and a decreased lymphocyte mediated anti tumour immune response, that contribute to aggressive tumour biology, cancer progression and poor prognosis.[8,10,11] Circulating neutrophils have been shown to produce cytokines, such as tumour necrosis factor, IL-1, and IL-6, which contributes to cancer progression, and to secrete the angiogenic factor vascular endothelial growth factor.[11] A relative lymphocytopenia may reflect a lower count of CD4+ T-helper lymphocytes, resulting in a suboptimal lymphocyte mediated immune response to malignancy.[11] The neutrophil count alone may not reflect the prognostic information of a decreased lymphocyte mediated immune response, and a low lymphocyte count alone may not reflect the neutrophil driven tumourigenesis process. Thus, the NLR may reflect the combined prognostic information of these two processes, and be a stronger predictor of outcome than either alone.

Patients with pre-treatment NLR > 3 (versus ⩽3) had a higher prevalence of baseline negative prognostic characteristics (Table 2). We adjusted for these differences in the multivariate analysis, and the subgroups stratification (Table 3). Whether the NLR reflects the combined prognostic information of some of the clinicopathologic factors listed in Table 2 remains an open question.

A common toxicity of sunitinib is a decrease of blood cell counts. Thus a low post treatment NLR may reflect more sunitinib associated toxicity than a positive prognosis. This may explain the lack of association between the NLR measured after the completion of the first treatment cycle and response rate, progression free survival, and overall survival.

Our study has some limitations. First, this is a retrospective study of a widely varied patient population. We are unable to exclude the possibility that unequal distribution of unidentified clinicopathologic parameters in our patient cohort may have biased the observed results. Second, the total number of 109 patients analysed for NLR is relatively small. Other clinicopathologic factors[14–18] that were not found to be significantly associated outcome in the present study might have been important in a larger patient cohort. Previous literature suggests that inflammatory parameters may be superior to performance status in predicting outcome of patients with advanced renal cell carcinoma.[23] Thus, other clinicopathologic factors may not be significantly associated with outcome in the present study due to a stronger prognostic value of the NLR. Third, neutrophil and lymphocyte counts may be influenced by concurrent infection and drugs that cannot be accounted for in this analysis. However, we expect these to be small. Fourth, because other inflammatory markers as CRP are not routinely measured in our institution, we could not analyse their association with outcome. Finally, whether our findings are specific to sunitinib or generalizable to other tyrosine kinase inhibitors is not known.

Despite these limitations, our clinical observation that the pre-treatment neutrophil-to-lymphocyte ratio may be associated with response rate, progression free survival and overall survival of patients treated with sunitinib for metastatic renal cell carcinoma, may contribute to treatment decisions, patient selection, and clinical trials design. The neutrophil-to-lymphocyte ratio is an easily measured, reproducible, and inexpensive marker from a complete blood count, that can be easily incorporated into the routine clinical practice. External validation of our preliminary results by further studies is required, to test and confirm our hypothesis generating observation in larger patient cohorts, and to elucidate the underlying molecular mechanisms as the cytokines balance determining the NLR, and the influence of inflammatory

response on sunitinib treatment. These may include retrospective analysis of previously completed large randomized trials of sunitinib or other Vascular endothelial growth factor inhibitors therapy in metastatic renal cell carcinoma, as well as future prospective studies.

Conflict of interest statement

None declared.

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