Impact of diabetes mellitus on the prognostic value of the neutrophil-lymphocyte ratio in renal cell carcinoma

YANGQIN ZHENG[1*], LIAN MIN BAO[2*], JUNJIE YE[3*], YUE PAN[4], QINQUAN WANG[4] and XIAOMIN GAO[5]

[1]Department of Hematology, The Third Clinical Institute Affiliated to Wenzhou Medical University, People's Hospital of Wenzhou, Wenzhou, Zhejiang 325006; [2]Department of Respiratory Medicine, Ruian People's Hospital, The Third Affiliated Hospital of The Wenzhou Medical University, Wenzhou, Zhejiang 325200; [3]Department of Urology, Sixth Affiliated Hospital of Wenzhou Medical University, Lishui People's Hospital, Lishui, Zhejiang 323000; [4]Department of Urology, The First Affiliated Hospital of Wenzhou Medical University, Wenzhou, Zhejiang 325006; [5]Department of Urology, Changhai Hospital, Second Military Medical University, Shanghai 200433, P.R. China

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Abstract. The aim of the present study was to evaluate the effect of diabetes mellitus (DM) on the neutrophil-lymphocyte ratio (NLR)-based prediction of the prognosis of patients with renal cell carcinoma (RCC). The data of 662 patients who had undergone nephrectomy for RCC between January 2004 and July 2014 were retrospectively reviewed. X-tile analysis was used to determine the optimal cutoff value for the NLR. Kaplan-Meier curves were drawn and the log-rank test was applied to determine the impact of the NLR (high vs. low) on the overall survival (OS) and metastasis-free survival (MFS). Univariate and multivariate Cox regression analyses were used to identify prognostic factors for OS and MFS. The median follow-up period after surgery was 50.35 months (range, 30.30-85.08 months). The optimal cutoff value of the NLR was determined to be 3.2 using X-tile software. In the analysis of total subjects, patients with a high NLR (≥3.2) had significantly worse OS and MFS rates than those with a low NLR (<3.2) (21.60% vs. 78.40%, P=0.001 for OS and 21.60% vs. 78.40%, P<0.0001 for MFS). In the non-DM subgroup, the OS and MFS rates of patients with a high NLR were significantly worse compared with those of patients with a low NLR (21.69% vs. 78.31%, P=0.003 for OS and 21.69% vs. 78.31%, P<0.001 for MFS). In the DM subgroup, although a high NLR was still associated with the MFS (NLR≥3.2, 21.43% vs. NLR<3.2, 78.57%; P=0.015), it was no longer associated with the OS (NLR≥3.2, 21.43% vs. NLR<3.2, 78.57%; P=0.192). Furthermore, multivariate analysis identified the NLR as a risk factor for OS and MFS in all patients [hazard ratio (HR)=1.77, 95% confidence interval (CI): 1.04-3.01, P=0.037; and HR=2.31, 95% CI: 1.45-3.70, P<0.001, respectively) and in the non-DM subgroup (HR=2.03, 95% CI: 1.05-3.93, P=0.036; and HR=2.57, 95% CI: 1.47-4.49, P=0.001, respectively), but not in the DM subgroup (P>0.05). In conclusion, DM is a factor that impairs the evaluation of the prognosis of RCC using NLR.

Correspondence to: Dr Xiaomin Gao, Department of Urology, Changhai Hospital, Second Military Medical University, 168 Changhai Road, Yangpu, Shanghai 200433, P.R. China
E-mail: doctorgaoxiaomin@163.com

*Contributed equally

Abbreviations: RCC, renal cell carcinoma; NLR, neutrophil-lymphocyte ratio; DM, diabetes mellitus; OS, overall survival; MFS, metastasis-free survival; CSS, cancer-specific survival; SSIGN, Stage, Size, Grade and Necrosis Score

Key words: renal cell carcinoma, neutrophil-lymphocyte ratio, diabetes mellitus, prognosis

Introduction

The neutrophil-lymphocyte ratio (NLR) is a novel indicator of sub-clinical inflammation and has been identified as an independent risk factor for postoperative outcome in patients with various types of cancer (1). Previous studies have demonstrated that an elevated NLR is a significant adverse prognostic factor regarding overall survival (OS), disease-free survival and progression-free survival of metastatic or non-metastatic cancer patients (1). For liver cancer, Xue *et al* (2) performed a meta-analysis of 26 studies comprising 4,461 patients, which indicated that a high NLR was independently associated with poor OS and disease-free survival. For colorectal cancer, Walsh *et al* (3) reported that the pre-operative NLR is an independent risk factor and a predictor of worse OS and cancer-specific survival (CSS). The prognostic value of the NLR has also been confirmed in other cancer types, including small-cell lung (4), gastric (5) and ovarian cancer (6).

Previous studies have demonstrated that the preoperative NLR is a predictor of post-operative outcomes in patients with either non-metastatic (7,8) or metastatic renal cell carcinoma (RCC) (9,10). To date, several scoring systems and nomograms have been developed to improve the accuracy of survival prediction for localized RCC, including the Stage, Size, Grade, and Necrosis Score (SSIGN) (11), the Leibovich score as a modified version of the SSIGN score (12), the University of the California Los Angeles Integrated Staging System (13)

and Karakiewicz's nomogram (14). These predictive models include the pathological tumor-nodes-metastasis (pTNM) stage and clinical criteria (Eastern Cooperative Oncology Group or Karnofsky), histological grading criteria (Fuhrman), imaging parameters (e.g. tumor size) and biological criteria (e.g. hemoglobin, neutrophils). However, the NLR has not been included in any of the abovementioned prognostic scoring systems for RCC. As a sensitive indicator of the inflammatory status, the NLR may be influenced by various clinical factors. Several studies have confirmed the significant association between the NLR and diabetes mellitus (DM) (15,16). In addition, previous meta-analyses have indicated that DM increases the risk of the occurrence of RCC (17,18); furthermore, the increasing incidence of pre-existing DM may increase the incidence of RCC. The aim of the present study was to explore whether DM affects the NLR-based evaluation of the prognosis of patients with RCC after surgery.

Patients and methods

Patients. The present study retrospectively reviewed 662 consecutive patients with non-metastatic RCC treated with nephrectomy between January 2004 and July 2014 at the Department of Urology of the First Affiliated Hospital of Wenzhou Medical University, Wenzhou, China). Clinical data, including clinicopathologic and hematologic records, were collected and retrospectively analyzed.

Follow-up. Patients were generally followed up every 3-6 months for the first 2 years and annually thereafter by performing blood and urine tests, cystoscopy and image examination. Information on patient death was obtained from outpatient medical records, telephone interviews or the patient's social security death index. The OS was defined as the interval from the time-point of surgery to the date of death from all causes and metastasis-free survival (MFS) was defined as the interval from surgery to the date of recurrence of radiologically or histologically confirmed distant metastasis, according to the treating physician's assessment and radiologic criteria. The primary endpoint of the present study was MFS.

Statistical analysis. The NLR was calculated as the neutrophil count divided by the lymphocyte count. X-tile software (version 3.6.1; Yale University, New Haven CT, USA) was applied to calculate the discriminatory ability of NLR to identify the optimal cutoff value. The association of the clinicopathologic characteristics with low and high NLR was assessed using either Fisher's exact test or the Student's t-test and Pearson's Chi-square test. Kaplan-Meier survival curves were drawn to estimate OS and MFS and significant differences were determined using the log-rank test. Univariate analysis was performed with using Cox logistic regression. Variables with $P<0.05$ in the univariate analysis were included in the subsequent multivariate analysis. Multivariate analysis was performed using Cox regression analysis. All tests were two-sided and $P<0.05$ was considered to indicate a statistically significant difference. Statistical analyses were performed using the SPSS software package version 22.0 (IBM Corp., Armonk, NY, USA).

Results

Clinicopathological characteristics. A total of 662 consecutive patients were included in the current study, with 243 (36.71%) females and 419 (63.29%) males. The mean age of the cohort was 61.70 (12.65) years. To determine the most suitable cutoff value for NLR, X-tile software was applied with the MFS as the endpoint, and a cutoff value of NLR=3.2 was obtained (Fig. 1). The χ^2 log-rank value of NLR was 21.15. Therefore, patients were divided into two groups according to the cutoff value: NLR<3.2 and NLR≥3.2. The patient population comprised 519 patients (78.40%) with a low NLR and 143 (21.60%) with a high NLR. A total of 662 patients with non-metastatic RCC, with a mean follow-up duration of 59.21 months (median, 50.35 months; range, 30.30-85.08 months) were included in the present study. During the follow-up, 74 patients (11.18%) experienced distant metastasis and 60 (9.06%) died, of which 41 cases (6.19%) were cancer-specific deaths. The baseline clinicopathologic characteristics are summarized in Table I. Patients with a high NLR were more likely to be older, and had higher neutrophil and lower lymphocyte counts, as well as an advanced pathologic T stage and tumor grade (all $P<0.05$). The two groups were comparable with regard to sex, American Society of Anesthesiologists (ASA) grade, body mass index (BMI), type of surgery, mean tumor size, histologic subtype, platelet count and history of DM.

Factors affecting OS in total subjects. Univariate and multivariate analyses were used to determine the predictive value of the NLR value regarding the clinical prognosis of patients with RCC. According to the univariate analysis, an NLR of ≥3.2, a higher age (≥65 years), a higher ASA grade (≥III), a higher BMI (≥25 kg/m^2), a larger mean tumor size (≥7 cm), a higher pathological T stage (≥3) and a higher Fuhrman grade (≥3) were significantly associated with poorer OS (all $P<0.05$; Table II and Fig. 2A). Multivariate analysis revealed that an NLR of ≥3.2, a higher age (≥65 years), a higher BMI (≥25 kg/m^2), a larger mean tumor size (≥7 cm), a higher pathological T stage (≥3) and higher a Fuhrman grade (≥3) were independent negative prognostic factors regarding OS.

Factors affecting MFS in total subjects. According to the univariate analysis, an NLR of ≥3.2, a higher age (≥65 years), a higher ASA grade (≥III), a higher BMI (≥25 kg/m^2), a larger mean tumor size (≥7 cm), a higher pathological T stage (≥3) and a higher Fuhrman grade (≥3) were significantly associated with poor MFS (All $P<0.05$; Table III and Fig. 3A). Multivariate analysis revealed that an NLR of ≥3.2, a higher age (≥65 years), a higher BMI (≥25 kg/m^2), a larger mean tumor size (≥7 cm), a higher pathological T stage (≥3) and a higher Fuhrman grade (≥3) were independent prognostic factors associated with poor MFS.

Subgroup analysis. The patients were then divided into two subgroups according to the absence or presence of DM. There was no significant difference in NLR values between the two groups as indicated by the t-test ($P=0.654$; Fig. 4). Furthermore, according to univariate analysis, DM did not significantly affect OS or MFS ($P=0.712$ or 0.536, respectively), so that no subsequent multivariate analysis was performed for this factor.

Table I. Patient characteristics and influence of the NLR.

Factor	Total (n=662)	NLR<3.2 (n=519)	NLR≥3.2 (n=143)	P-value
Age (years)	61.70±12.65	61.10±12.42	63.90±13.27	0.019
Sex				0.203
Female	243 (36.71)	197 (37.96)	46 (32.17)	
Male	419 (63.29)	322 (62.04)	97 (67.83)	
ASA grade				0.110
I	85 (12.84)	72 (13.87)	13 (9.09)	
II	532 (80.36)	416 (80.16)	116 (81.12)	
III	45 (6.80)	31 (5.97)	14 (9.79)	
BMI (kg/m^2)	23.16±3.04	23.26±3.12	22.82±2.71	0.130
Type of surgery				0.262
Partial nephrectomy	143 (21.60)	117 (22.54)	26 (18.18)	
Radical nephrectomy	519 (78.40)	402 (77.46)	117 (81.82)	
Mean tumor size (SD; cm)	4.91 (3.42)	4.85 (3.46)	5.14 (3.30)	0.375
Pathological T stage				0.046
pT1	514 (77.64)	415 (79.96)	99 (69.23)	
pT2	77 (11.63)	56 (10.79)	21 (14.69)	
pT3	62 (9.37)	42 (8.09)	20 (13.98)	
pT4	9 (1.36)	6 (1.16)	3 (2.10)	
Fuhrman grade				0.005
1	210 (31.72)	173 (33.33)	37 (25.87)	
2	282 (42.60)	229 (44.12)	53 (37.06)	
3	148 (22.36)	101 (19.46)	47 (32.87)	
4	22 (3.32)	16 (3.09)	6 (4.20)	
Histologic subtype				0.682
Clear cell carcinoma	581 (87.76)	454 (87.48)	127 (88.81)	
Papillary carcinoma	41 (6.20)	31 (5.97)	10 (6.99)	
Chromophobe carcinoma	36 (5.44)	31 (5.97)	5 (3.50)	
Collecting duct carcinoma	1 (0.15)	1 (0.19)	0 (0.00)	
Unclassified carcinoma	3 (0.45)	2 (0.39)	1 (0.70)	
Mean nutrophil count $x10^9$ (mean; SD)	4.12±1.68	3.63±1.15	5.88±2.08	<0.001
Lymphocyte count $x10^9$ (mean; SD)	1.78±0.62	1.93±0.58	1.22±0.39	<0.001
Platelet count (mean; SD)	216.46±70.66	213.97±68.01	225.48±79.13	0.085
Diabetes mellitus				0.938
No	438 (66.16)	343 (66.09)	95 (66.43)	
Yes	224 (33.84)	176 (33.91)	48 (33.57)	

Values are expressed as n (%), the mean ± standard deviation or mean (SD). The normal range of neutrophil count, lymphocyte count and platelet count were 1.80-6.30x10^9/l, 1.10-3.20x10^9/l and 125-350x10^9/l, respectively. BMI, body mass index; NLR, neutrophil-lymphocyte ratio; ASA, American Society of Anesthesiologists; SD, standard deviation.

Kaplan-Meier analysis indicated that in the non-DM group, a high pre-operative NLR (≥3.2) was significantly associated with a worse OS and MFS (Fig. 2C and 3C). While a high NLR was still associated with MFS in the DM group, it was no longer associated with OS (Fig. 2C and 3C). Uni- and multivariate analysis of factors affecting survival was then performed for the DM and non-DM subgroups individually, as summarized in Tables II and III. In the non-DM group, the results demonstrated that a high NLR was still an independent predictive factor of poor OS and MFS in patients with RCC. However, in the DM group, an NLR of ≥3.2 was not a significant independent prognostic factor.

Discussion

According to previous studies, an elevated NLR is associated with poor prognosis for patients with RCC (7-10). In the present study, a retrospective review was performed to investigate the correlation between the pre-operative NLR and the post-surgical outcomes for patients with RCC. In line with the

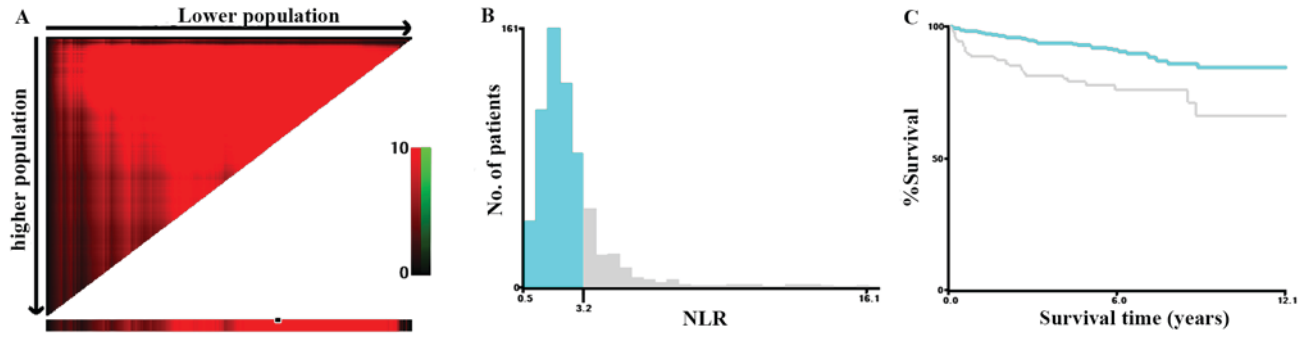

Figure 1. X-tile analyses of metastasis-free survival was performed to determine the optimal cutoff value for the NLR. NLR, neutrophil-lymphocyte ratio. (A) The red coloration of the cut-points indicates an inverse correlation with survival; while the green coloration represents direct associations. (B) Histograms of the entire cohort. (C) Kaplan-Meier plots. The optimal cut-off values highlighted by black circles in (A) are presented in of the entire cohort (B).

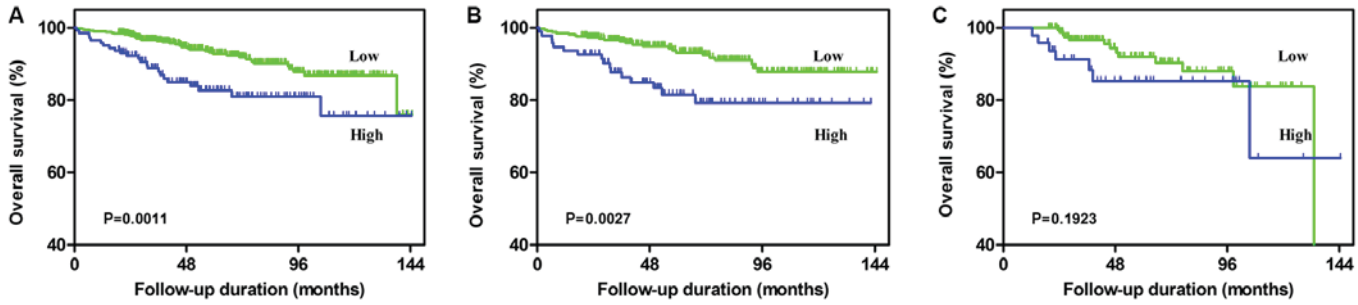

Figure 2. Kaplan-Meier curves for overall survival of patients stratifed by their neutrophil-lymphocyte ratio (high vs. low). (A) All patients, (B) patients without DM and (C) patients with DM. DM, diabetes mellitus.

results of previous studies (1,7-10), it was demonstrated that a high NLR has a prognostic value in patients with RCC. A high NLR was associated with old age, high neutrophil and lymphocyte counts, as well as an advanced pathologic T stage and tumor grade. In addition, multivariate analysis identified that an NLR of ≥3.2 is an independent adverse prognostic factor for RCC patients. The present study therefore confirmed that NLR is a significant prognostic factor for RCC and may be useful for tailoring therapies for patients with RCC. However, unlike other systemic inflammatory indicators, including C-reactive protein (CRP) and the platelet-to-lymphocyte ratio, NLR has still not been incorporated in any clinical evaluation system for RCC. Therefore, the primary aim of the present study was to identify the possible reasons.

Various studies have emphasized the importance of inflammation in carcinogenesis (19-21). According to them, one potential mechanism is that the response of systemic inflammation to various physiological challenges is characterized by increased neutrophil and decreased lymphocyte counts, largely favoring tumor development by preventing or suppressing the activation of anti-tumor cells in the immune system. Of note, cancer cells themselves are able to recruit and activate various types of leukocytes, particularly neutrophils and monocytes (22). Therefore, an increased NLR is thought to provide a favorable microenvironment for tumor development and metastasis. The NLR has also been associated with poor prognosis in conditions other than cancer, including cardiovascular diseases (23,24), respiratory diseases (25) and hypertension (26). Therefore, NLR is a non-specific parameter, which may be affected by concurrent conditions, including chronic obstructive pulmonary disease and coronary chronic total occlusion.

Previous meta-analyses indicated that DM may increase the risk of RCC (17,18). Of note, an increased NLR was also reported to be associated with DM, and a high NLR value may be a significant predictive marker of DM (15). In the present study, a high NLR was identified as an independent risk factor for RCC regarding OS and MFS. No significant difference in NLR values was identified between the patient groups with and without DM, and DM was not a significant influencing factor of OS and MFS according to the multivariate regression analysis. However, in the multivariate analysis for the subgroup of patients with DM, an elevated NLR was no longer identified as an independent predictive factor of OS and MFS, but it was still a significant independent predictor in the subgroup of patients without DM. The HR value of NLR for OS and MFS increased from 1.77 in the total subject group to 2.03 in the non-DM group. A further increase was identified from 2.31 in the total subject group to 2.57 in the non-DM group. Furthermore, the results of multivariate analysis demonstrate that an elevated NLR is no longer identified as the independent factor of OS and MFS in the DM group, but may still serve as an independent predictor in patients without DM. All of the above indicates that DM is a disturbance factor in the evaluation of prognosis of RCC using NLR. The link between DM and RCC-associated mortality has been evaluated in several previous studies. In 2013, Ha *et al* (27) published a multi-institutional analysis including a total of 2,597 patients, revealing that DM is an independent prognostic factor for recurrence-free survival

Table II. Univariate and multivariate analysis of the predictive value of clinicopathological parameters for the overall survival of patients with renal cell carcinoma.

	Total		With diabetes mellitus		Without diabetes mellitus	
Factor	Univariate analysis HR (95% CI), P-value	Multivariate analysis HR (95% CI), P-value	Univariate analysis HR (95% CI), P-value	Multivariate analysis HR (95% CI), P-value	Univariate analysis HR (95% CI), P-value	Multivariate analysis HR (95% CI), P-value
Sex (male vs. female)	1.50 (0.86-2.64), 0.155		2.95 (0.86-10.14), 0.085		1.16 (0.61-2.22), 0.652	
Age (≥65 vs. <65 years)	4.00 (2.19-7.28), <0.001	3.27 (1.77-6.04), <0.001	3.81 (1.26-11.54), 0.018	4.64 (1.47-14.70), 0.009	4.01 (1.96-8.20), <0.001	3.08 (1.46-6.50), 0.003
ASA grade (≥III vs. <III)	3.33 (1.55-5.80), 0.001	1.61 (0.82-3.18), 0.169	1.37 (0.38-4.95), 0.632		4.22 (1.94-9.16), <0.001	2.56 (1.08-6.07), 0.032
BMI (≥25 vs. < 25 kg/m^2)	0.28 (0.11-0.70), 0.006	0.27 (0.11-0.67), 0.005	0.48 (0.16-1.45), 0.192		0.10 (0.01-0.70), 0.020	0.10 (0.01-0.70), 0.021
Type of surgery (partial nephrectomy vs. radical nephrectomy)	0.51 (0.22-1.18), 0.115		0.62 (0.14-2.69), 0.521		0.47 (0.17-1.32), 0.152	
Mean tumor size (≥7 vs. <7 cm)	2.96 (1.75-5.01), <0.001	2.02 (1.17-3.48), 0.012	1.42 (0.51-3.99), 0.505		3.84 (2.05-7.19), <0.001	3.15 (1.59-6.25), 0.001
Pathological T stage (≥3 vs. <3)	4.40 (2.50-7.74), <0.001	3.24 (1.80-5.85), <0.001	5.98 (1.64-21.82), 0.007	9.77 (2.45-39.02), 0.001	4.82 (2.51-9.26), <0.001	2.83 (1.38-5.83), 0.005
Fuhrman grade (≥3 vs. <3)	2.84 (1.71-4.72), <0.001	2.00 (1.19-3.37), 0.009	3.02 (1.25-7.31), 0.014	2.91 (1.20-7.08), 0.019	2.77 (1.49-5.16), 0.001	1.66 (0.86-3.19), 0.132
Histologic subtype (clear cell carcinoma vs. non-clear cell carcinoma)	1.61 (0.82-3.18), 0.170		2.78 (0.97-7.95), 0.057		1.06 (0.41-2.71), 0.905	
NLR (≥3.2 vs. <3.2)	2.32 (1.38-3.90), 0.001	1.77 (1.04-3.01), 0.037	1.84 (0.73-4.66), 0.192		2.55 (1.35-4.81), 0.003	2.03 (1.05-3.93), 0.036
Diabetes mellitus (Positive vs. negative)	1.12 (0.65-1.90), 0.712					

HR, hazard ratio; CI, confidence interval; BMI, body mass index; NLR, neutrophil-lymphocyte ratio; ASA, American Society of Anesthesiologists.

Table III. Univariate and multivariate analysis of clinicopathological parameters for the prediction of metastatic-free survival in patients with renal cell carcinoma.

	Total		With diabetes mellitus		Without diabetes mellitus	
Factor	Univariate analysis HR (95% CI), P-value	Multivariate analysis HR (95% CI), P-value	Univariate analysis HR (95% CI), P-value	Multivariate analysis HR (95% CI), P-value	Univariate analysis HR (95% CI), P-value	Multivariate analysis HR (95% CI), P-value
Sex (male vs. female)	1.65 (0.99-2.76), 0.055		2.42 (0.81-7.21), 0.112		1.46 (0.81-2.63), 0.203	
Age (≥65 vs. <65 years)	2.67 (1.64-4.35), <0.001	2.24 (1.36-3.69), 0.002	3.55 (1.29-9.73), 0.014	3.35 (1.17-9.56), 0.024	2.45 (1.39-4.29), 0.002	1.94 (1.08-3.50), 0.028
ASA grade (≥III vs. <III)	2.14 (1.10-4.18), 0.025	1.37 (0.69-2.73), 0.363	0.89 (0.20-3.86), 0.873		3.05 (1.44-6.48), 0.004	2.74 (1.20-6.27), 0.017
BMI (≥25 vs. <25 kg/m^2)	0.32 (0.15-0.69), 0.004	0.32 (0.14-0.69), 0.004	0.46 (0.16-1.39), 0.169		0.22 (0.07-0.71), 0.011	0.22 (0.07-0.72), 0.012
Type of surgery (partial nephrectomy vs. radical nephrectomy)	0.50 (0.24-1.05), 0.068		0.77 (0.23-2.61), 0.670		0.41 (0.16-1.03), 0.058	
Mean tumor size (≥7 vs. <7 cm)	2.80 (1.74-4.52), <0.001	2.07 (1.27-3.38), 0.004	1.84 (0.71-4.77), 0.210		3.24 (1.86-5.66), <0.001	3.17 (1.73-5.78), <0.001
Pathological T stage (≥3 vs. <3)	3.26 (1.89-5.61), <0.001	2.49 (1.42-4.36), 0.001	3.28 (0.93-11.63), 0.005	3.24 (0.54-3.68), 0.009	3.21 (1.74-5.91), <0.001	2.06 (1.08-3.94), 0.028
Fuhrman grade (≥3 vs. <3)	2.60 (1.65-4.11), <0.001	1.90 (1.19-3.03), 0.007	2.28 (0.96-5.42), 0.013	2.02 (1.54-3.68), 0.011	2.71 (1.58-4.66), <0.001	1.88 (1.08-3.28), 0.026
Histologic subtype (clear cell carcinoma vs. non-clear cell carcinoma)	1.40 (0.74-2.67), 0.302		3.60 (1.28-10.12), 0.015	2.75 (0.87-8.67), 0.085	0.93 (0.40-2.17), 0.860	
NLR (≥3.2 vs. <3.2)	2.82 (1.78-4.48), <0.001	2.31 (1.45-3.70), <0.001	2.80 (1.18-6.66), 0.015	2.03 (0.82-5.04), 0.128	2.84 (1.64-4.90), <0.001	2.57 (1.47-4.49), 0.001
Diabetes mellitus (positive vs. negative)	0.85 (0.51-1.42), 0.536					

HR, hazard ratio; CI, confidence interval; BMI, body mass index; NLR, neutrophil-lymphocyte ratio; ASA, American Society of Anesthesiologists.

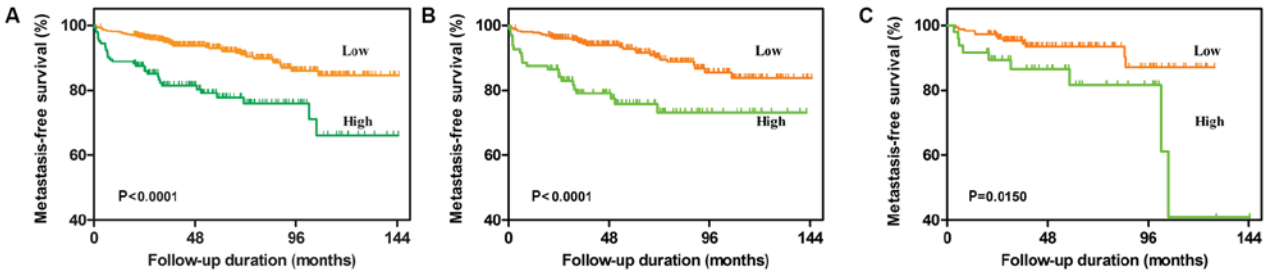

Figure 3. Kaplan-Meier curves for metastasis-free survival of patients stratified by their neutrophil-lymphocyte ratio (high vs. low). (A) All patients, (B) patients without DM and (C) patients with DM. DM, diabetes mellitus.

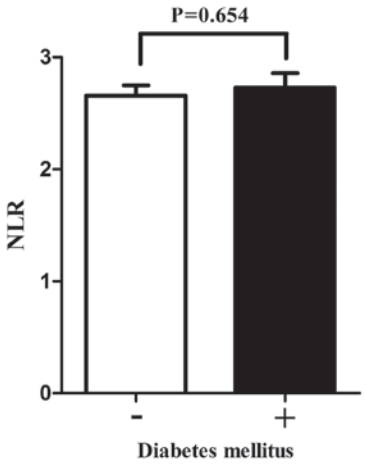

Figure 4. Comparison of NLR between renal cell carcinoma patients with or without diabetes mellitus. NLR, neutrophil-lymphocyte ratio.

(RFS), CSS and OS. Another meta-analysis published in 2015 including a total of 20,199 patients, also revealed a significant negative impact of DM on OS, CSS and RFS in patients with RCC (28). Therefore, more attention should be paid when evaluating the prognosis of patients with RCC based on the NLR and DM.

All of the factors included in the pTNM classification are able to provide reliable prognostic information. In addition, these factors, e.g. the pathological T stage, are confirmed from pathological specimens and are stable predictors that are not influenced by any physiological factors. However, the most widely used prognostic nomograms and risk scores for RCC, which are based on the pTNM stage, are established post-operatively. These conventional prognostic factors have limited accuracy. Furthermore, it is also important for clinical surgeons to identify prognostic factors prior to the surgery in order to conceive patient-specific therapeutic strategies. In recent years, the prognostic value of biomarkers of inflammation, including the NLR and CRP, has been evidenced in patients with cancer. Hu *et al* (7) reported that the NLR is superior to CRP as a predictor of RCC. However, the NLR is easily affected by numerous physiological factors, but its application still has potential value in patients with no underlying conditions (e.g. DM or cardiopulmonary diseases), as it is easily measured, inexpensive and repeatable.

Of note, the present study has several limitations. First, it was a retrospective single-center study. It may be argued that the size of the study population was insufficient; however, the results were representative and reliable, as our department is the largest urologic cancer center in the South of Zhejiang Province and provides access to a wide variety of patients with RCC Furthermore, the cutoff value of NLR was different in other studies (29). However, a threshold of NLR=3 is considered reasonable for RCC (29), which is close to the cutoff value of NLR=3.2 used in the present study. Finally, the measurement of NLR may be complicated by concurrent conditions, including infections and inflammation, as well as by certain medications. In the present study, all of the blood specimens were obtained prior to surgery. In addition, surgeons commonly delay procedures for patients with active infections. Therefore, it is unlikely that the NLR was influenced by any infections. However, the complicating effect of concurrent inflammatory conditions was not completely excluded.

In conclusion, the present study indicated that the prognostic value of NLR for patients with RCC was impaired by concurrent DM, as indicated by a subgroup analysis of patients with and without DM. It is therefore suggested that DM should be considered when evaluating the prognostic value of NLR in patients with RCC.

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Availability of data and materials

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

Authors' contributions

XG conceived and designed the study, YZ, BL, and YJ acquired the data, YP and QW analyzed and interpreted the data, and XG drafted the manuscript.

Ethics approval and consent to participate

The present study was approved by the ethics committee of the First Affiliated Hospital of Wenzhou Medical University (Wenzhou, China). The study protocol is in accordance with the Declaration of Helsinki.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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