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Serum C-NLR score, a new inflammatory marker, predicts tumor histopathology and oncological outcomes of localized clear cell renal carcinoma after nephrectomy: A single center retrospective analysis

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Ethics Committee Approval
The study was approved by the Institutional Board of Bagcilar Training and Research Hospital. 16.11.2022. Number: 2022/11/14/035.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Several blood and serum-based parameters have been described as prognostic markers of clear cell renal cell carcinoma (ccRCC). But most of these markers have inconsistent results and are not used in routine clinical practice. Therefore, novel potential predictor biomarkers are needed for the management of ccRCC patients in clinical practice. Here, we investigate the predictive value of a novel marker, serum C-NLR score, for pathological characteristics and oncological outcomes of ccRCC.
Methods: A total of 162 RCC patients who underwent radical or partial nephrectomy between January 2015 and January 2021 were evaluated in a retrospective cohort study setting. The serum C-NLR score was compared according to the tumor histopathology-associated parameters. The predictive role of those parameters and C-NLR score on the oncological outcomes of ccRCC was also investigated.
Results: The median serum C-NLR scores exhibited statistically significant increases in ccRCC patients with pathological necrosis, lymphovascular invasion, and variant differentiation. Among histopathological characteristics, only tumor necrosis and variant differentiation were associated with overall survival (OS) and tumor grade with metastasis-free survival (MFS) (no metastasis detected in grade 1–2 tumors) in Kaplan Meier analyses. Serum C-NLR score was also associated with OS but not MFS. In the univariate analyses, tumor necrosis, variant differentiation, and C-NLR score were associated with OS of localized RCC patients who underwent nephrectomy (HR: 0.29; 95% CI: 0.08–1.01; *P*=0.04, HR: 6.01; 95% CI: 1.66–21.82; *P*=0.006 and, HR: 1.21; 95% CI: 0.20–5.16; *P*=0.04). However, in the multivariate analysis, only variant differentiation and C-NLR score were associated with OS (HR: 1.43; 95% CI: 0.82–2.98; *P*=0.03 and HR: 1.21; 95% CI: 0.20–5.16; *P*=0.04). Tumor grade was directly associated with MFS because grade 1–2 tumors did not exhibit any metastasis.
Conclusion: Serum C-NLR score was higher in worse histopathological entities. Moreover, it predicts the OS for patients with ccRCC as an independent factor.

Keywords: clear cell renal cell carcinoma, c-reactive protein, neutrophils, lymphocytes, survival analysis

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Introduction

Renal cell carcinoma (RCC) raised from the renal tubular epithelium is a heterogeneous group of cancers. It represents 1% to 3% of adult malignancies in humans worldwide [1,2]. Among the urological cancers, RCC is the most lethal, and approximately 40% of patients with RCC die because of the disease progression [2]. Clear cell renal cell carcinoma (ccRCC) is the most common subtype and accounts for the majority of kidney cancer deaths [1,3]. Localized ccRCC can be treated with partial or radical nephrectomy, ablation treatment, or active surveillance. The removal of kidney cancer tissue with nephrectomy is a curative approach; however, up to 30% of patients with ccRCC with localized disease eventually develop metastases [1]. Because ccRCC has higher clinical and pathological heterogeneity, it is difficult to predict the survival outcomes of patients in clinical practice [3].

The well-known disease predictors for ccRCC are tumor grade and stage. Other important prognostic factors in ccRCC are lymphovascular invasion (LVI), variant differentiation (VD), and fat invasion. Their prognostic roles have been studied, with the authors reporting that they correlated with survival rates [4]. Alternative prognostic parameters (e.g., molecular prognostic factors) have also been proposed. However, their major limitations are higher costs and lower availability in routine clinical practice [5]. Therefore, several blood and serum-based parameters have been discussed as possible prognostic markers of ccRCC [5-8]. However, most such studies provide inconsistent results, and their prognostic value in ccRCC patients must be confirmed [8].

In our opinion, novel potential predictor biomarkers must be emphasized and used for clinical studies and, then, routine clinical settings. In the present study, we primarily aimed to investigate the predictive value of serum C-NLR score for pathological characteristics and oncological outcomes of ccRCC.

Materials and methods

After the approval of the study by the Review Board of Bagcilar Training and Research Hospital (Approval ID: 2022/11/14/035, Approval Date: 16/11/2022), we conducted a retrospective review of our institutional data, including radiology, laboratory, and pathology data. A total of 162 renal cell carcinoma (RCC) patients who underwent radical or partial nephrectomy between January 2015 and January 2021 were evaluated. Inclusion criteria were having a clear cell subtype of RCC with no history of previous or concomitant malignancy other than kidney cancer. Patients who had metastatic disease and N+ status at the diagnosis and cases with the final diagnosis of benign pathology and papillary and chromophobe subtypes after the surgery were not included. Additionally, patients with the N+ stage at final pathology and patients with incomplete follow-up and/or missing data were also excluded. The history of any anemia, active inflammatory diseases, and acute infection were other exclusion criteria.

Characteristics of the kidney masses, including size, side, polarity, localization, and egzofitic or endofitic nature, were assessed by cross-sectional imaging studies. Preoperative serum levels of the neutrophil count, lymphocyte count, neutrophil to lymphocyte ratio (NLR), and C-reactive protein (CRP) were extracted from our institutional data. CRP and NLR levels were classified as normal or elevated based on the cutoff points accepted as 10 mg/L and 2.26, respectively. The cutoff points for the parameters, CRP and NLR, were adapted from the associated previous studies [9,10]. The combined score of CRP and NLR levels was established as the C-NLR score, as reported by Zhu et al. [11]. It is classified as C-NLR score 2; with elevated serum CRP and NLR levels, C-NLR score 1; with elevated serum level in one of them, and C-NLR score 0; with normal serum CRP and NLR levels. Pathological findings were also extracted from our institutional data. All pathological investigations were performed by a single experienced neuropathologist. Tumor stage was determined based on the 2010 TNM classification of malignant tumors staging system, and tumor grade was defined according to the Fuhrman and WHO/ISUP grading systems.

The follow-up schedule was determined as physical examination, blood biochemistry, and radiologic imaging with a contrast-enhanced computerized abdominal tomography every 3–6 months for 2 years and 6–12 months in years 2–5 according to the individual patient and tumor characteristics. The last survival follow-up date was June 01, 2021. Overall survival (OS) and metastasis-free survival (MFS) were calculated as times from surgery to death or last follow-up and from surgery to metastasis or the last follow-up in localized ccRCC patients.

Statistical analysis

Statistical analysis was performed with SPSS Version 22.0 statistic software package (IBM SPSS Inc., Chicago, IL). Data distributions and tests of normality were evaluated with the Shapiro-Wilk test. Descriptive statistic methods, including mean (standard deviation), median (interquartile range) and percentages, were used to evaluate data. Two groups' comparisons were performed using the independent t-test, Mann-Whitney U test, or Chi-square test. Differences were considered significant at two-sided $P<0.05$ and 95% confidence interval. The serum C-NLR score was compared in patients with PT1 and PT2-T4 ccRCC, in patients with grade 1–2 and grade 3–4 tumors, in patients with and without tumor necrosis in pathology, in patients with and without LVI, and in patients with and without VD. Survival analysis and curves for serum C-NLR score and histopathological tumor characteristics were performed according to the Kaplan-Meier method and compared by the log-rank test.

Results

Out of 162 patients, 18 with incomplete follow-up and 26 with missing data were excluded. Additionally, seven patients with the pathological diagnosis of oncocytoma and seven and nine patients with the pathological diagnosis of chromophobe and papillary RCC, respectively, were also excluded. Fifteen pathological N+ patients were not included in the study. Ultimately, a total of 80 localized ccRCC patients were investigated.

The mean age and mean tumor volume were 56.76 (11.33) years and 54.35 (28.89) mm, respectively. The mean serum levels of NLR and CRP were 2.35 (1.15) and 21.82 (11.35) g/dL, respectively. The mean operative time was 180.187 (66.43) min. The mean age, tumor volume, ischemia time (in

partial cases), and operative time for partial and radical nephrectomy cases are shown in Table 1. The median ASA score and Clavien-Dindo complication score were 2 (2) and 1 (1), respectively. The median hospital stay was 4 (3) days. On the pathological reports, the median pT stage and Fuhrman/WHO-ISUP grade were 1 (2) and 2 (2), respectively. The median postoperative follow-up period was 48.00 (22.00) months with 4 to 50 months intervals. Out of 80 patients, 35 (43.75%) were female, and 55 (56.25%) were male. Forty-seven (58.3%) patients had comorbidities, and 17 (21.3%) of them had multiple comorbid disorders. Detailed information about frequencies of the comorbid diseases, anatomical tumor characteristics with solid-cystic discrimination, applied surgical methods for nephrectomy, characteristics of surgical complications, and pathological tumor characteristics are provided in Table 2.

Table 1: The mean age, tumor volume, ischemia time (in partial cases) and operative time for partial and radical nephrectomy cases.

	Partial nephrectomy cases	Radical nephrectomy cases	*P*-value
Age (Years), Mean(SD)	53.63 (10.94)	58.64 (11.26)	0.06*
Tumor diameter (mm), Mean(SD)	33.40 (11.21)	66.80 (4.10)	<0.001*
Ischemia time (min.), Mean(SD)	17.53 (9.02)	-	
Operative time (min.), Mean(SD)	187.50 (55.25)	165.80 (72.50)	0.44*

SD: Standard deviation, * Independent t test.

Table 2: Frequencies of the comorbid diseases, anatomical tumor characteristics with solid-cystic discrimination, applied surgical methods for nephrectomy, characteristics of surgical complications, and pathological tumor characteristics.

	n	%
Comorbidity		
DM	26	32.5
HT	35	43.8
CAD	26	32.5
CRF	8	10
HF	1	1.3
Tumor laterality		
Left	37	46.2
Right	43	53.8
Polar tumor localization		
Superior	25	31.2
Middle	34	42.5
Lower	17	21.2
Whole kidney	3	3.8
Anterior-posterior tumor localization		
Anterior	30	37.5
Posterior	30	37.5
Medial	20	25
Exophytic mass	64	80
Tumor nature		
Solid	53	66.3
Cystic	9	11.3
Mixed	18	22.4
Nephrectomy		
Partial	30	37.5
Radical	50	62.5
Nephrectomy		
Open	33	41.3
Laparoscopic	47	58.7
Complications	13	16.3
Clavien-Dindo		
1	0	0
2	8	61.5
3	4	30.8
4	0	0
5	1	7.7
Positive surgical margin	5	16.7
Tumor necrosis	21	26.3
Lymphovascular invasion	21	26.3
Variant differentiation	10	12.5
pT stage		
T1	48	60
T2	13	16.2
T3	17	21.3
T4	2	2.5
Tumor grade		
1	5	6.3
2	38	38
3	27	27
4	10	10

DM: Diabetes mellitus, HT: Hypertension, CAD: Coronary artery diseases, CRF: Chronic renal failure, HF: Heart failure.

One patient died on the third postoperative day due to a massive pulmonary embolus. During the 50 months follow-up, ten patients died. OS was estimated as 64.5%. The mean OS time was 44.78 (1.52) months (95% CI: 41.78–47.77). Seven patients exhibited metastatic progression during the follow-up. Two of them were in regional lymph nodes, and five were in the lungs. The mean time of metastasis was determined as 13.57 (3.74) months (95% CI: 6.22–20.96), and the mean MFS time was 46.08 (1.41) months (95% CI: 43.31–48.84).

The serum C-NLR score exhibited significant differences in the ccRCCs with pathological necrosis, lymphovascular invasion, and variant differentiation in comparison to the ccRCC's without them. On the other hand, it was also significantly different according to the pT stage and tumor grade (Table 3). Among histopathological characteristics, only tumor necrosis and variant differentiation were associated with OS and tumor grade with MFS (no metastasis detected in grade 1–2 tumors) in Kaplan Meier analyses (Table 4, Figures 1 and 2). OS was 46.49 (1.45) months (95% CI: 43.63-45.35) vs. 37.87 (3.89) months (95% CI: 30.24–45.50) for tumor necrosis - and + cases, respectively (P=0.03). They were 45.24 (1.70) months (95% CI: 42.68–47.80) vs. 29.87 (7.10) months (95% CI: 15.95–43.79) for variant differentiation - and + cases, respectively (P=0.002). On the other hand, serum C-NLR score was also associated with overall survival but not MFS (Table 5, Figure 2). In the univariate analyses, tumor necrosis, variant differentiation, and C-NLR score were associated with OS of localized RCC patients who underwent nephrectomy (HR: 0.29; 95% CI: 0.08–1.01; P=0.04, HR: 6.01; 95% CI: 1.66–21.82; P=0.006 and, HR: 1.21; 95% CI: 0.20–5.16; P=0.04, respectively). However, in the multivariate analysis, only variant differentiation and C-NLR score were associated with the OS of the patients (HR: 1.43; 95% CI: 0.82–2.98; P=0.03 and HR: 1.21; 95% CI: 0.20–5.16; P=0.04, respectively). Tumor grade was directly associated with MFS because grade 1–2 tumors did not exhibit any metastasis.

Figure 1: Overall survival Kaplan Meier graphs according to the parameters, tumor necrosis and variant differentiations, and metastasis free survival according to the tumor grade.

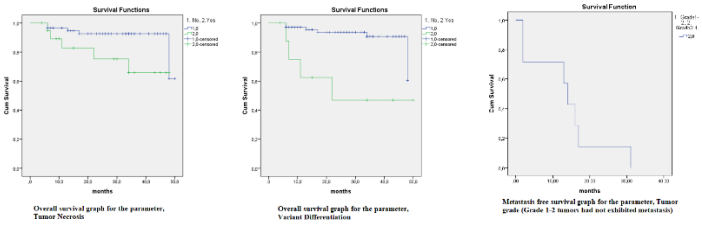

Figure 2: Overall survival Kaplan Meier graph according to the C-NLR scores.

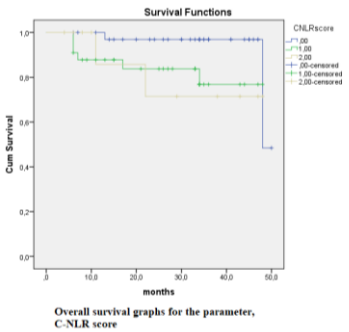

Table 3: Serum C-NLR scores according to the tumor histopathology and patient outcomes

	pT1	**pT2-T4**	***P*-value**
C-NLR Score, Median(IQR)	0.5 (1)	0.5 (1)	0.02*
	Grade 1-2	**Grade 3-4**	***P*-value**
C-NLR Score, Median(IQR)	0 (1)	1 (1.5)	0.03*
	Tumor Necrosis -	**Tumor Necrosis +**	***P*-value**
C-NLR Score, Median(IQR)	0 (1)	1 (1)	0.001*
	LVI -	**LVI+**	***P*-value**
C-NLR Score, Median(IQR)	0 (1)	1 (1.5)	0.005*
	VD -	**VD+**	***P*-value**
C-NLR Score, Median(IQR)	1 (1)	1 (1.5)	0.01*
	Survivors	**Dead**	***P*-value**
C-NLR Score, Median(IQR)	1 (1)	1 (0)	0.09*
	Metastasis -	**Metastasis +**	***P*-value**
C-NLR Score, Median(IQR)	1 (1)	1 (1.5)	0.02*

NLR: Neutrophil to lymphocyte ratio, IQR: Interquartile range, LVI: Lymphovascular infiltration, VDI: Variant differentiation, * Mann Whitney U test.

Table 4: OS and MFS according to tumor histopathology.

	pT1	**pT2-T4**	***P*-value**
OS, Mean(SD)	45.51 (1.86) months (95% CI: 40.86-48.16)	43.64 (1.52) months (95% CI: 38.45-48.83)	0.51
	Grade 1-2	**Grade 3-4**	***P*-value**
OS, Mean(SD)	44.05 (2.16) months (95% CI: 39.80-48.29)	44.02 (1.91) months (95% CI: 40.26-47.78)	0.62
	Tumor Necrosis -	**Tumor Necrosis +**	***P*-value**
OS, Mean(SD)	46.49 (1.45) months (95% CI: 43.63-45.35)	37.87 (3.89) months (95% CI: 30.24-45.50)	0.03
	LVI -	**LVI+**	***P*-value**
OS, Mean(SD)	45.77 (1.60) months (95% CI: 43.63-48.91)	39.47 (3.72) months (95% CI: 32.17-46.78)	0.18
	VD -	**VD+**	***P*-value**
OS, Mean(SD)	45.24 (1.70) months (95% CI: 42.68-47.80)	29.87 (7.10) months (95% CI: 15.95-43.79)	0.002
	pT1	**pT2-T4**	***P*-value**
MFS, Mean(SD)	13.00 (0.00) months (95% CI: 13.00-13.00)	13.66 (4.43) months (95% CI: 4.98-22.35)	0.39
	Grade 1-2	**Grade 3-4**	***P*-value**
MFS, Mean(SD)	- -	13.57 (3.74) months (95% CI: 6.22-22.91)	-
	Tumor Necrosis -	**Tumor Necrosis +**	***P*-value**
MFS, Mean(SD)	14.50 (1.50) months (95% CI: 11.56-17.44)	13.20 (5.39) months (95% CI: 2.62-23.78)	0.15
	LVI -	**LVI+**	***P*-value**
MFS, Mean(SD)	13.00 (0.00) months (95% CI: 13.00-13.00)	13.66 (4.43) months (95% CI: 4.98-22.35)	0.39
	VD -	**VD+**	***P*-value**
MFS, Mean(SD)	10.33 (4.25) months (95% CI: 1.99-18.67)	16.00 (5.95) months (95% CI: 4.32-27.67)	0.26

OS: Overall survival, MFS: Metastasis free survival, SD: Standard deviation, LVI: Lymphovascular infiltration, VDI: Variant differentiation.

Table 5: OS and MFS according to the serum C-NLR scores.

	CNL Score 0	**CNLR Score 1**	**CNLR Score 2**	***P*-value**
OS Mean(SD)	47.87 (1.30) months (95% CI: 45.32-50.42)	40.68 (2.69) months (95% CI: 35.39-45.97)	39.00 (5.49) months (95% CI: 28.23-49.76)	0.04
	CNL Score 0	**CNLR Score 1**	**CNLR Score 2**	***P*-value**
MFS Mean(SD)	16.00 (0.00) months (95% CI: 16.00-16.00)	10.66 (4.48) months (95% CI: 1.87-19.45)	15.66 (8.41) months (95% CI: 0.00-32.15)	0.76

OS: Overall survival, MFS: Metastasis free survival, SD: Standard deviation.

In brief, the C-NLR score is associated with worse tumor histopathology, and it can predict OS as an independent factor.

Discussion

The TNM stage, reflecting tumor invasion, lymph node metastasis and distant metastasis, and tumor grade, is the most widely used system for predicting RCC prognosis [12,13]. The current RCC staging system is an updated version of the American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) classification [14]. On the other hand, the Fuhrman and WHO/ISUP grading systems have been used to examine the pathological tumor grade [15]. Although TNM and grading systems are useful prognostic parameters, they are not perfect. The major component of the T staging is tumor diameter. However, tumor diameter could not be fully representative of tumor volume. Other well-known prognostic parameters about tumor histopathology, such as tumor necrosis, lymphovascular infiltration, and sarcomatoid and rhabdoid differentiations, are used in clinical practice. However, several studies reported that they were deficient [13]. Moreover, RCC is a heterogeneous group of tumors with some unusual clinical and pathological characteristics that make it difficult to predict outcomes [14].

In this regard, the conflicting knowledge about present prognostic factors has resulted in consideration of new factors in the literature [13].

Today, it is well known that inflammation is involved in the initiation and progression of various cancers, including RCC. Some hematologic parameters, including lymphocytes and neutrophil counts, neutrophil-to-lymphocyte ratio (NLR), and CRP, are simple and cheap laboratory data reflecting inflammation and have been extensively studied in cancers [12,16]. A large number of studies have reported their prognostic value for various cancers and RCC. However, all these parameters indicate only one aspect of inflammation, and the combination of those factors in an index could more accurately predict prognosis than a single index [12]. For RCC, it has been shown that most of these measurements are statistically significant prognostic factors for localized and metastatic RCC [16-18]. The immunological status and inflammatory response in individual patients are thought to influence tumor growth and disease progression, and several studies have suggested that systemic inflammation measured by NLR and CRP also plays a key role in RCC. Moreover, systemic inflammation-related biomarkers CRP and NLR may provide additional prognostic information [8,19].

In the late 2010s, the combination of CRP and NLR was discussed, and several types of research investigated its role in predicting the outcomes of some cancers and diseases [11,20-23]. To our knowledge, no study has addressed the combination of CRP and NLR for patients with RCC. In this regard, in the present study, we investigated the role of the recently developed C-NLR score, a novel inflammatory marker, in predicting the histopathological and survival outcomes of localized ccRCC cases. The serum C-NLR score exhibited significant differences with worse histopathological entities such as pathological necrosis, lymphovascular invasion, and variant differentiation. On the other hand, it was also significantly higher in the advanced pT stage and tumor grade. We determined the prognostic significance of the C-NLR score for OS and found that the C-NLR score provides significant OS information. In univariate Cox regression, the C-NLR score was associated with OS and remained independently associated with survival in multivariate analysis. Our findings are consistent with the literature. In 2012, Tomita et al. [23] showed that the combined use of preoperative NLR and CRP was an independent prognostic determinant for non-small cell lung cancer (NSCLC). Later on, similarly, Oh et al. [21] investigated its role in hepatocellular carcinoma (HCC). These authors found that CRP and NLR were utilized as prognostic indicators of HCC that appeared to be more evident when used in combination. They concluded that this is probably due to the significant synergistic effect of the two inflammatory markers. The predictive role of the combination of both parameters in soft tissue cancer was also reported by Nakamura et al. [20]. Recently, Zhu et al. [11] investigated the combination of both parameters in asthma. These authors concluded that since both NLR and CRP are

elevated in asthmatic patients, it is necessary to develop a novel marker – the combined score of CRP level and NLR (C-NLR score) – that can take full advantage of meanings of both NLR and CRP in asthmatic patients. The authors generated a C-NLR scoring system and found C-NLR, a novel inflammatory marker, is a promising marker to distinguish children with exacerbated asthma from healthy children. Similarly, Liu et al. [22] investigated the combined use of CRP and NLR in a newly generated nomogram for patients with COVID-19 and found that NLR and CRP are potential and reliable predictors of COVID-19 prognosis and can triage patients at the time of admission.

Limitations

Our study has some limitations. A major limitation is the retrospective nature of the study protocol, which limits the efforts to address potential sources of bias and establish the sample size. Another is the small sample size. Therefore, we aimed to plan optimal inclusion and exclusion criteria. Because of the small sample size, our numbers of metastatic patients and deaths were relatively small. Therefore, the analysis of survival outcomes might have been affected adversely. However, we specifically intended to investigate the role of C-NLR score in patients with localized ccRCC subtype. The major strength of the current study is that it is the first study investigating the C-NLR score in predicting RCC outcomes. This work can path the way for further large-scale studies.

Conclusion

Serum C-NLR score was higher in worse histopathological entities that are associated with mortality and morbidity, such as pathological necrosis, lymphovascular invasion, and variant differentiation. Moreover, it predicts the OS for patients with localized ccRCC as an independent factor. In our opinion, this is a promising finding for the management of ccRCC. With future confirmatory results, the C-NLR score may be used in routine clinical practice and become a practical guide for urologists in the management of the localized ccRCC.

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