Original Research

Complete blood count-derived inflammatory markers and survival in patients with localized renal cell cancer treated with partial or radical nephrectomy: a retrospective single-tertiary-center study

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Abstract

We aimed to compare the predictive value of different inflammatory markers in renal cell carcinoma (RCC). Four hundred ninety-five patients treated with nephrectomy for primary localized or locally advanced RCC between 2010 and 2018 were included in the retrospective analysis. The median follow-up for the entire cohort was 48 months. Based on the preoperative laboratory measurements, patients with higher neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), systemic inflammatory response index (SIRI), systemic immune-inflammation index (SII), neutrophil/erythrocyte ratio (NER), derived neutrophil/lymphocyte ratio (dNLR), and lower lymphocyte/monocyte ratio (LMR) and hemoglobin/platelet ratio (HPR) had worse cancer-specific survival (CSS). In the multivariate analysis tumour stage, grade, age and high SIRI constituted independent factors predicting CSS. The model including SIRI values achieved C-index 0.903 (alternative multivariate models with SII and NLR 0.902 and 0.890, respectively). Age, tumour grade and high NER (or high SIRI/ SII in alternative models) were prognostic for overall survival. Markers of systemic inflammation might provide additional prognostic information (especially SIRI, SII, NLR and NER) and further increase the predictive accuracy of available models in localized and locally advanced renal cell carcinoma. For the first time, we show the prognostic value of neutrophil-to-erythrocyte ratio, which constitutes an independent risk factor of overall survival.

Keywords: Renal cell carcinoma; Biomarkers; Survival analysis; Systemic inflammatory markers

1. Introduction

Localized or locally advanced renal cell carcinoma (RCC) remains the disease that is treated surgically with curative intent [1]. The main concern, though, is connected with a significant rate of late recurrence, reaching in some publications up to 12% [2]. Specific markers are under investigation to be used in prognostic models, as staging and grading appear to be insufficient, and one observes various outcomes in cases of the indistinguishable clinicopathological characters [3]. The preoperative, early assessment may enforce the optimization of personalized therapy and better risk stratification of patients treated surgically [4]. Then, the appropriate grouping of patients is important for the sake of future management techniques (e.g., surgery versus active surveillance), an adequate follow-up scheme implementation, and selection of optimal candidates for potential adjuvant treatment inside clinical trials [5].

As a great variety of studies focused on hematological markers, they are used more and more frequently for prognostic purposes [6,7]. The idea of their clinical implementation comes from the observations on specific interactions within the tumor microenvironment and immune system effector cells [8]. Peripheral blood neutrophils, lymphocytes, monocytes and platelets that are involved in systemic inflammatory reactions are available from routine preoperative blood tests [9]. Within the tumor microenvironment, certain differences in the subpopulations of leukocytes lie at the root of host immunity and reflect tumor aggressiveness [8]. As a consequence, respective peripheral blood count-derived parameters are under investigation for their use in oncology as potential markers, among them most recognizable are the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and monocyte-to-lymphocyte ratio (MLR) [6]. Other researchers estimated the role of combinations of the peripheral blood counts' values in a variety of scores, such as the systemic inflammatory response index (SIRI) [4], or the systemic immune-inflammation index (SII) [10]. The hope for their future incorporation into everyday practice is based on the fact that the combination of three parameters (e.g., neutrophils, lymphocytes, platelets) better reflects the prognosis and may result in greater accuracy of the respective predictive model [4]. However, the potential utility of the systemic inflammatory markers in the prediction of RCC treatment outcomes is still undetermined. Not to mention the fact that different markers were not simultaneously studied and sufficiently com-

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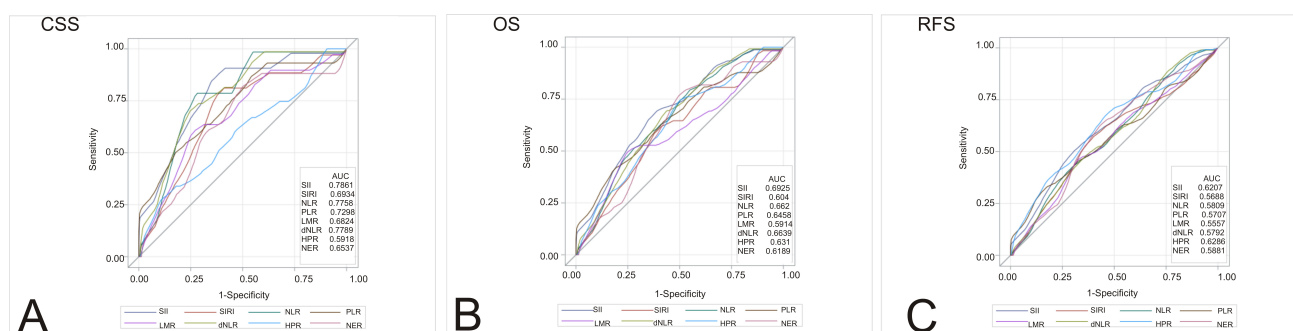
Fig. 1. Receiver operating curves (ROC) for prediction of cancer-specific survival (A), overall survival (B) and recurrence-free survival (C) for hematological markers (NLR, dNLR, SIRI, PLR, LMR, HPR, NER) in the whole cohort (with respective AUC) in long-term analysis (42 months). Abbreviations: NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; SIRI, systemic inflammatory response index; SII, systemic immune-inflammation index; NER, neutrophil/erythrocyte ratio; dNLR, derived neutrophil/lymphocyte ratio; LMR, lower lymphocyte/monocyte ratio; HPR, hemoglobin/platelet ratio.

pared in terms of their predictive accuracy. Additionally, the optimal cutoff values of several markers are still a matter of analyses [6]. Worth emphasizing is the fact that these markers are easily obtainable from routine laboratory tests performed in everyday practice, and hence provide an inexpensive and widely available tool for clinicians [9]. The additional use of hemoglobin-to-platelet-ratio (HPR) and neutrophil-to-erythrocyte ratio (NER) represent the novel idea of focusing on red blood cell lineage within anti-cancer response based on the experience coming, e.g., from the oncological outcomes of the bladder cancer management described in other papers [11], and in our previous studies [12].

The usefulness of the prognostic models to categorize the cancer progression risk is significantly increased, when the combination of pre-treatment data is engaged [9], while some of the inflammatory markers were found to act as independent prognostic factors also in non-metastatic RCC [7]. Lastly, if novel therapeutics that are targeted to inflammatory pathways are engaged, preoperative values of biomarkers may serve as critical inclusion criteria and become accessory prognostic factors for patients [13].

In the present paper, we aimed to re-evaluate the prognostic significance of clinicopathologic features and compare the predictive value of different inflammatory markers in patients with localized or locally advanced RCC, who received radical or partial nephrectomy.

2. Materials and methods

2.1 Study population

This is a retrospective single-tertiary-center study. Medical records of patients treated with partial or radical nephrectomy between 2010 and 2018 were reviewed. Among 778 nephrectomies, 654 were performed because of renal cell carcinoma. Fifty-four patients with distant metastases at the time of surgery and 5 patients with surgery for RCC recurrence (and no data on primary RCC) were ex-

cluded from further analysis. For further 6 patients the data were missing and for 90 patients there was no follow-up. Finally, 495 patients with primary localized and locally advanced RCC, who underwent nephrectomy in our center, were included in the analysis.

Information about demographic, clinical and pathological features were collected. None of the patients received additional treatment before radical surgery. Data on the modality of surgery, type of nephrectomy, perioperative complications and the length of hospitalization were gathered, as well. Data extracted from the pathology report included tumour stage, grade and histological subtypes. Tumours were graded according to the WHO/ ISUP or Fuhrman classification when adequate. Preoperative laboratory findings were also collected.

Ratio between the respective preoperative blood cell counts were calculated to produce several inflammatory markers (neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), lymphocyte/monocyte ratio (LMR), derived neutrophil/lymphocyte ratio (dNLR), hemoglobin/platelet ratio (HPR) and neutrophil/erythrocyte ratio (NER)). The systemic immune-inflammation index (SII) was calculated according to the following formula: SII = neutrophil $\times$ platelet/lymphocyte. The systemic inflammatory response index (SIRI) was calculated as in the formula: SIRI = neutrophil $\times$ monocyte/lymphocyte. Follow-up data included information about recurrence-free survival (RFS), overall survival (OS) and cancer-specific survival (CSS). The oncologic follow-up was based predominantly on the repetitive contrast-enhanced CT scans of the abdomen and pelvis in 6- or 12-month intervals. Recurrence was defined as the detection of a new enhancing lesion in the region of surgery (e.g., surgery bed, ipsilateral adrenal gland) or systemic distant sites during follow-up imaging. Patients were censored at the time of the last follow-up. All patients signed informed consent and the study was conducted under the Ethics committee vote AKBE/72/2021 of the Medical University of Warsaw.
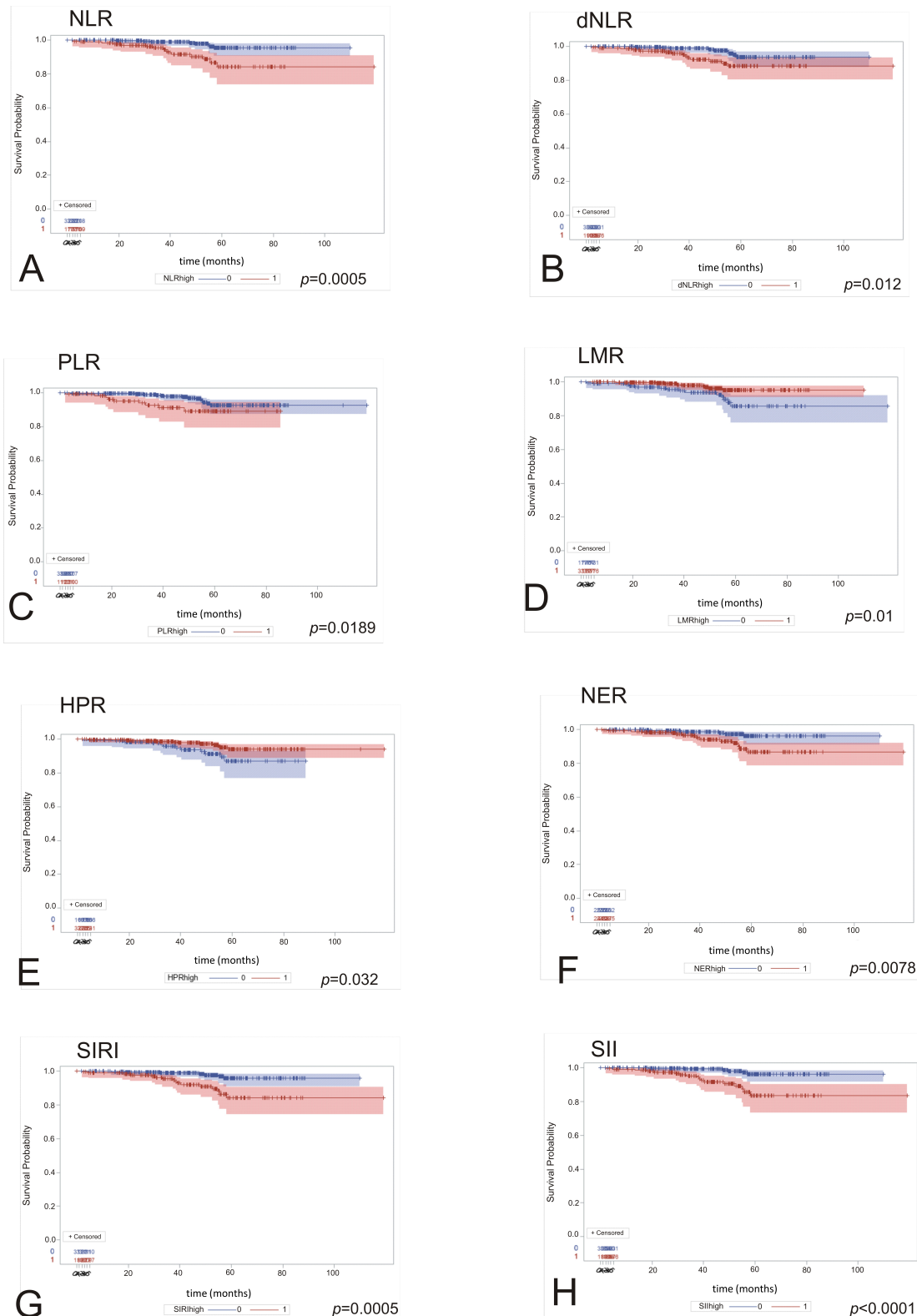
Fig. 2. The Kaplan–Meier curves for cancer-specific survival (CSS) in patients stratified by low (blue line) vs. high (red line) values of the following biomarkers: NLR (A), dNLR (B), PLR (C), LMR (D), HPR (E), NER (F), SIRI (G) and SII (H). Abbreviations: NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; SIRI, systemic inflammatory response index; SII, systemic immune-inflammation index; NER, neutrophil/erythrocyte ratio; dNLR, derived neutrophil/lymphocyte ratio; LMR, lower lymphocyte/monocyte ratio; HPR, hemoglobin/platelet ratio.
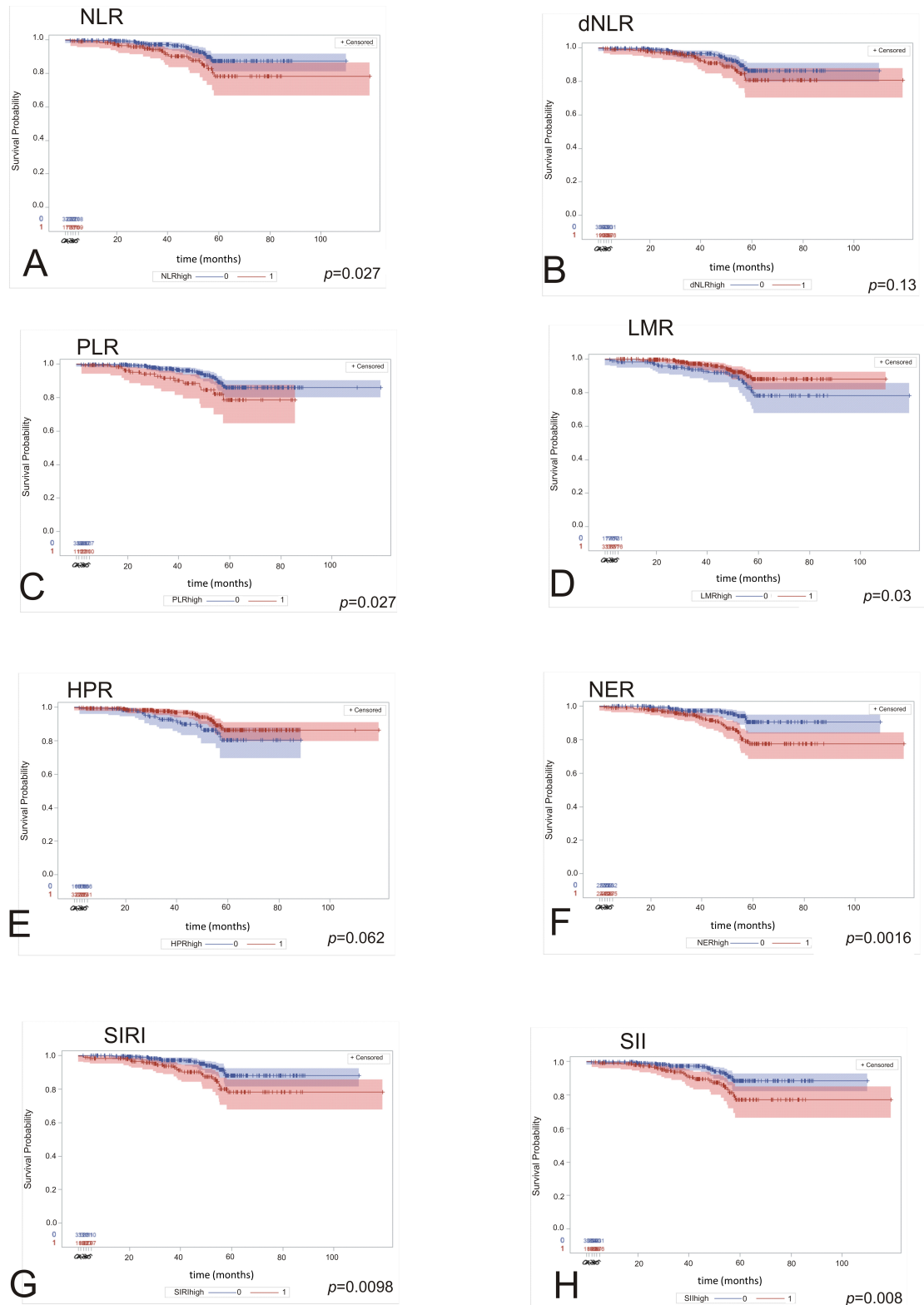
Fig. 3. The Kaplan–Meier curves for overall survival (OS) in patients stratified by low (blue line) vs. high (red line) values of the following biomarkers: NLR (A), dNLR (B), PLR (C), LMR (D), HPR (E), NER (F), SIRI (G) and SII (H). Abbreviations: NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; SIRI, systemic inflammatory response index; SII, systemic immune-inflammation index; NER, neutrophil/erythrocyte ratio; dNLR, derived neutrophil/lymphocyte ratio; LMR, lower lymphocyte/monocyte ratio; HPR, hemoglobin/platelet ratio.
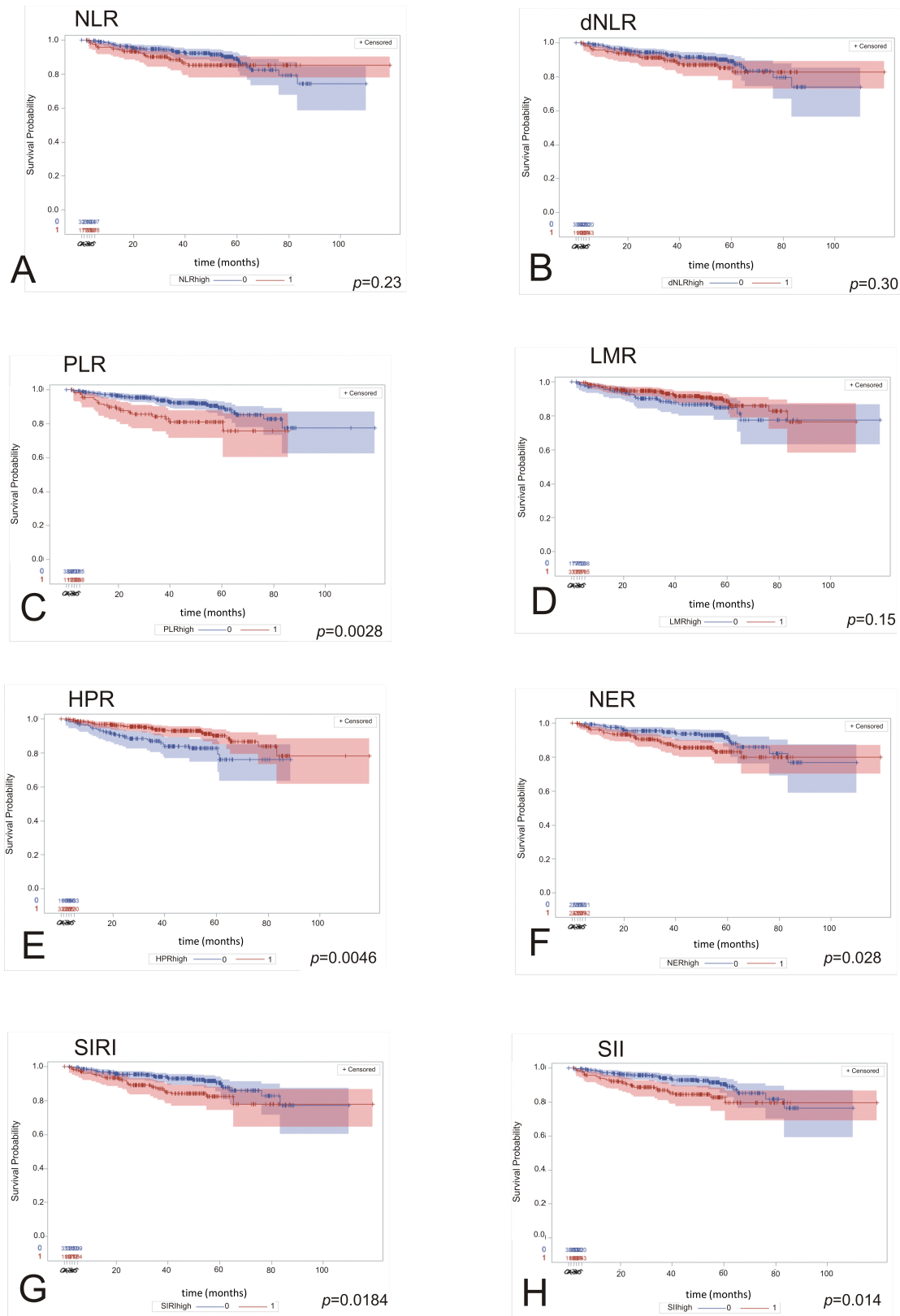
Fig. 4. The Kaplan–Meier curves for recurrence-free survival (RFS) in patients stratified by low (blue line) vs. high (red line) values of the following biomarkers: (a), dNLR (B), PLR (C), LMR (D), HPR (E), NER (F), SIRI (G) and SII (H). Abbreviations: NLR, neutrophil/lymphocyte ratio; PLR, platelet/lymphocyte ratio; SIRI, systemic inflammatory response index; SII, systemic immune-inflammation index; NER, neutrophil/erythrocyte ratio; dNLR, derived neutrophil/lymphocyte ratio; LMR, lower lymphocyte/monocyte ratio; HPR, hemoglobin/platelet ratio.

Table 1. Overall characteristics of the cohort.

Characteristics		No./Mean	%/IQR
Gender	female	195	39.4
	male	300	60.6
Age		63	54–70
BMI	kg/m^2	24.7	27.8–31.3
Stage	T1a	327	66.06
	T1b	100	20.20
	T2a	21	4.24
	T2b	9	1.82
	T3	36	7.27
	T4	2	0.40
Grade	1	136	27.47
	2	305	61.62
	3	41	8.28
	4	13	2.63
Tumour diamater	cm	3.7	2.5–5.0
Histology type	clear cell	395	79.80
	papillary type 1	58	11.72
	papillary type 2	18	3.64
	chromofobe	24	4.85
Surgical treatment	Radical nephrectomy	156	31.52
	NSS	339	68.48
Outcomes			
Recurrence	No	442	89.29
	Yes	53	10.71
Death	No	452	91.31
	Yes	43	8.69
Cancer Death	No	472	95.35
	Yes	23	4.65
Follow-up	months	48.2	30.1–58.1
Laboratory parameters			
Hemoglobin		139	127–148
Neutrophils		4.42	3.37–5.73
Lymphocytes		1.85	1.48–2.38
Platelets		225	191–280
Red blood cells		4.69	4.34–4.98
SIRI		1.87	1.26–2.84
SII		506	346–807

2.2 Statistical analysis

Statistical analysis was performed in SAS software version 9.4 (SAS Institute, Warsaw, Poland). Results are presented as the number and percentage for categorical variables and medians, accompanied by the interquartile range (IQR) for continuous variables. Differences between groups were tested with Fisher's test for categorized variables and Mann-Whitney U test for continuous variables. The differences in the time to the event were analyzed using the Kaplan–Meier method and log-rank test. In univariable analyses Cox proportional hazards were used to identify factors associated with RFS, OS and CSS. Continuous values of inflammatory markers were categorized based on the cutoff determined with receiver operating curve (ROC) and Youden's index analysis. Correlations between variables were checked using the Spearman test. Univariable analyses provided variables for multivariable analyses performed with Cox proportional hazard. Hazard ratio (HR) supplemented with 95% confidence interval (95% CI) were generated. Several multivariable models were constructed using alternative inflammatory markers, which demonstrated significance in univariable analyses. Inflammatory markers showing strong correlations between each other were not incorporated into a single model. To assess the predictive accuracy for each model the Harell's C-index was calculated. For all statistical analyses, a two-sided p-value < 0.05 was considered statistically significant.

3. Results

3.1 Basic characteristics

There were 495 consecutive patients enrolled in the study, predominantly male (60%) (Table 1). The majority of tumors were T1a stage (66%) and grade 2 (61%). Pathological examination revealed clear-cell carcinoma in nearly 80% of cases. Patients were treated surgically with radical intent and, in the majority of cases, nephron-sparing surgeries were performed (68%). During the median follow-up of 48 months (IQR 30–58) cancer-specific survival reached 95.35%, overall survival—91.31%, while recurrence-free survival—89.29%. Baseline patients' characteristics are presented in Table 1.

The associations between the values of selected markers and clinicopathologic features were analyzed. Elevated SIRI, SII and NLR were related to advanced staging, larger tumor size, and performance of radical nephrectomy, whereas high SIRI was additionally associated with male gender and tumour grade. The associations in the subgroups with low and high values of inflammatory markers (NLR, SII, SIRI) are summarized in Table 2.

Cut-off values for SIRI, SII, NLR, PLR, LMR, dNLR, HPR and NER were calculated to predict cancer-specific survival using ROC. For comparison different ROCs with respective areas under the curve (AUC) were demonstrated (Fig. 1).

3.2 Systemic inflammatory markers in the prediction of CSS in Kaplan–Meier analysis

When analyzing the preoperative systemic inflammatory markers, the CSS was worse in patients presenting with elevated NLR ($\geq$2.76 vs. $<$2.76, $p = 0.0005$), dNLR ($>$1.8 vs. $\leq$1.8, $p = 0.012$), PLR ($>$170 vs. $\leq$170, $p = 0.0189$), NER ($>$0.95 vs. $\leq$0.95, $p = 0.0078$), SIRI ($>$2.25 vs. $\leq$2.25, $p = 0.0005$), and SII ($>$628 vs. $\leq$628, $p < 0.0001$), and lower HPR ($\leq$0.53 vs. $>$0.53, $p = 0.03$) and LMR values ($<$2.0 vs. $\geq$2.0, $p = 0.01$) (Fig. 2).

Table 2. Association of clinicopathologic features and treatment outcomes with values of inflammatory markers (NLR, SII, SIRI).

		NLR <2.75	NLR ≥2.76	p	SIRI ≤2.25	SIRI >2.25	p	SII ≤628	SII >628	p
		No. (%)/Median (IQR)	No. (%)/Median (IQR)		No. (%)/Median (IQR)	No. (%)/Median (IQR)		No. (%)/Median (IQR)	No. (%)/Median (IQR)	
Gender	Male	189 (59)	111 (64)	0.25	173 (55)	127 (69)	0.002	194 (63)	106 (56)	0.11
	Female	133 (41)	62 (36)		139 (45)	56 (31)		112 (37)	83 (44)	
Age		63 (54–69)	63 (55–71)	0.23	63 (54–69)	62 (55–71)	0.38	63 (55–70)	62 (52–69)	0.37
BMI	kg/m^2	27.8 (24.8–31.2)	27.7 (24.6–31.8)	0.89	27.6 (24.7–31.2)	28 (25.2–31.8)	0.58	27.8 (25.2–31.2)	27.3 (24.2–31.8)	0.56
Stage	T1	287 (89)	139 (80)	0.016	283 (91)	143 (78)	0.001	280 (92)	146 (77)	<0.0001
	T2	15 (5)	16 (9)		13 (4)	18 (10)		11 (4)	20 (11)	
	T3	20 (6)	16 (9)		16 (5)	20 (11)		15 (5)	21 (11)	
	T4	0 (0)	2 (1)		0 (0)	2 (1)		0 (0)	2 (1)	
Grade	1	91 (28)	45 (26)	0.245	91 (29)	45 (25)	0.22	94 (31)	42 (22)	0.032
	2	200 (62)	105 (61)		18 (6)	116 (63)		184 (60)	121 (64)	
	3	26 (8)	15 (9)		27 (9)	14 (8)		24 (8)	17 (9)	
	4	5 (2)	8 (5)		5 (2)	8 (4)		4 (1)	9 (5)	
Tumour diamater	cm	3.4 (2.5–5.0)	4 (2.5–6.0)	0.071	3.45 (2.4–5.0)	4 (2.5–6.5)	0.026	3.4 (2.1–4.5)	4 (3–7)	<0.0001
Histology type	clear cell	257 (80)	138 (80)	0.127	248 (79)	147	0.9	245 (80)	150 (79)	0.9
	other	65 (20)	35 (20)		64 (21)	36 (20)		61 (20)	39 (21)	
Surgery	RN	91 (28)	65 (38)	0.042	85 (27)	71 (39)	0.009	77 (25)	79 (42)	0.0001
	NSS	231 (72)	108 (62)		227 (73)	112 (61)		229 (75)	110 (58)	
Outcomes										
Recurrence	No	290 (90)	152 (88)	0.45	285 (91)	157 (86)	0.07	280 (92)	162 (86)	0.052
	Yes	32 (10)	21 (12)		27 (9)	26 (14)		26 (8)	27 (14)	
Death	No	299 (93)	153 (88)	0.13	292 (94)	160 (87)	0.021	286 (93)	166 (88)	0.034
	Yes	23 (7)	20 (12)		20 (6)	23 (13)		20 (7)	23 (12)	
Cancer death	No	314 (98)	158 (91)	0.003	305 (98)	167 (91)	0.002	300 (98)	172 (91)	0.0006
	Yes	8 (2)	15 (9)		7 (2)	16 (9)		6 (2)	17 (9)	

Note: Number of patients (no.) with percentage (%) is shown for categorized variables and median with interquartile range (IQR) for continuous variables. Differences were tested with Fisher's test for categorized variables and Mann-Whitney U test for continuous variables.

3.3 Univariate and multivariate analysis of CSS

Univariate analysis of the associations between CSS and clinicopathologic factors revealed that age ($p = 0.009$), tumour grade ($p < 0.0001$), staging ($p < 0.0001$), diameter of tumor ($p < 0.0001$) but not the histological type of RCC ($p = 0.55$) were found to be significant predictors (Table 3). As for hematological markers, higher SIRI ($p = 0.001$), SII ($p = 0.0004$), NLR ($p = 0.001$), NER ($p = 0.01$), PLR (0.02), dNLR ($p = 0.02$) and lower LMR ($p = 0.015$) and HPR ($p = 0.04$) values were associated with worse CSS.

In multivariate analysis, staging ($p < 0.0001$), grade ($p = 0.001$), age ($p = 0.02$) and high SIRI ($p = 0.015$) (alternatively high SII ($p = 0.013$) and high NLR ($p = 0.043$)) were significant predictors of CSS with eminent accuracy (C-index 0.903) (Table 4). As inflammatory markers demonstrated a strong correlation between each other (SII vs. SIRI r = 0.76, $p < 0.0001$; SIRI vs. NLR r = 0.80, $p < 0.0001$; NLR vs. SII r = 0.89, $p < 0.0001$), we decided to create three alternative models using a single systemic inflammatory marker for each model. Model without the inclusion of any inflammatory marker was characterized by a slightly lower C-index (C-index 0.882).

3.4 Systemic inflammatory markers in the prediction of OS in Kaplan–Meier analysis

Overall survival was significantly shorter in individuals with high NLR (≥ 2.76 vs. < 2.76, $p = 0.027$), PLR (>170 vs. ≤ 170, $p = 0.027$), NER (>0.95 vs. ≤ 0.95, $p = 0.0016$), SIRI (>2.25 vs. ≤ 2.25, $p = 0.0098$), SII (>628 vs. ≤ 628, $p < 0.008$), and lower LMR (<2.0 vs. ≥ 2.0, $p = 0.03$) (Fig. 3). HPR and dNLR values were not significantly associated with OS.

3.5 Univariate and multivariate analysis of OS

Associations between OS and selected clinicopathological variables or laboratory parameters are shown in Tables 5,6. in the univariate analysis age ($p = 0.004$), tumour grade ($p < 0.0001$), staging ($p < 0.0001$), diameter of tumor ($p = 0.001$), but not type of RCC ($p = 0.15$) were proved to be significant prognostic factors (Table 5). Results of peripheral blood counts reveled that higher SIRI ($p = 0.01$), SII ($p = 0.009$), NLR ($p = 0.03$), NER ($p = 0.0025$), PLR ($p = 0.03$), and lower LMR ($p = 0.03$) values were associated with OS.

In multivariate analysis, tumour grade ($p < 0.0001$), age ($p = 0.002$) and high NER ($p = 0.01$) (high SII ($p = 0.04$) and high SIRI ($p = 0.04$) in alternative models) were significant predictors of OS with acceptable accuracy (C-indexes 0.75) (Table 6).

3.6 Systemic inflammatory markers in the prediction of RFS in Kaplan–Meier analysis

The RFS was shorter in individuals with elevated PLR (>170 vs. ≤ 170, $p = 0.0028$), NER (>0.95 vs. ≤ 0.95, $p = 0.0016$), SIRI (>2.25 vs. ≤ 2.25, $p = 0.018$), SII (>628 vs.

≤ 628, $p = 0.01$), and lower HPR values (≤ 0.53 vs. >0.53, $p = 0.0046$) (Fig. 4). NLR, dNLR, and LMR failed to prove to be significantly associated with RFS.

3.7 Univariate and multivariate analysis of RFS

In univariate analysis, the associations between RFS and pathologic factors, tumour grade ($p < 0.0001$), stage ($p < 0.0001$), diameter of tumour ($p < 0.0001$) were found to be significant (Table 7). Furthermore, higher SIRI ($p = 0.02$), SII ($p = 0.02$), PLR ($p = 0.004$), NER ($p = 0.03$) and lower HPR ($p = 0.01$) values were associated with RFS.

In multivariate analysis, only tumour grade ($p < 0.0001$) and tumor diameter ($p = 0.009$) were independent predictors of RFS (Table 8).

4. Discussion

In this study, we evaluated the prognostic value of several systemic inflammatory markers in patients with localized or locally advanced renal cell carcinoma. We focused on the role of the markers of the well-established usefulness (NLR, dNLR, PLR, LMR) in the survival analysis, together with the new tools that are easily calculated from peripheral blood count (SII and SIRI), and, finally, the implementation of red blood cells lineage derivatives (HPR and NER).

There is a growing number of studies focusing on the involvement of inflammatory markers in the clinical practice of individuals that developed RCC [4,6,7,9,14]. The available papers, however, emphasize the role of particular parameters (e.g., NLR, PLR, LMR) derived from peripheral blood counts, but direct comparisons between different markers are lacking. Recently, novel inflammatory indices such as systemic SIRI and SII were also reported as prognostic for RCC oncological outcomes [4,15]. Furthermore, hematological parameters have a well-documented prognostic role only in the setting of metastatic disease, in which IMDC and MSKCC models are mainly used [16,17].

In the present paper, we found that patients treated surgically for localized or locally advanced RCC, who presented preoperatively with higher NLR, PLR, SIRI, SII, NER, dNLR, and lower LMR and HPR, had a significantly worse CSS. Multivariate analysis showed that tumour stage, grade, age and inflammatory markers constituted independent factors predicting CSS. As the markers of systemic inflammatory response demonstrate a strong correlation between each other, we decided to create three alternative models using a single systemic inflammatory marker for each multivariate model. The model based on clinicopathologic features, which did not include any inflammatory markers was characterized by already high accuracy (C-index 0.877). Further addition of inflammatory indices provided more accurate prognostic information. The CSS predictive model with the highest accuracy included SIRI values and achieved a C-index of 0.903, while alternative multivariate models included SII and NLR and were characterized by C-index 0.902 and 0.890, respectively. There-

Table 3. Univariate analysis for CSS in patients with RCC treated with partial or radical nephrectomy with respective values of the hematological markers.

Univariate analysis - whole cohort - CSS					
Clinicopathological features		HR	Lower 95% CI	Upper 95% CI	*p*
Age	(years)	1.05	1.01	1.09	0.009
Gender	male vs. female	0.67	0.30	1.52	0.33
Grade	ref = Grade 1	1			<0.0001
	Grade 2	3.121	0.698	13.889	0.13
	Grade 3	6.389	1.065	38.462	0.042
	Grade 4	90.31	17.544	500	<0.0001
Staging	ref = stage T1a	1	-	-	<0.0001
	stage T1b	6.79	1.7	27.03	0.007
	stage T2a	16.83	3.4	83.33	0.001
	stage T2b	23.71	3.97	142.86	0.001
	stage T3	21.52	5.56	83.33	<0.0001
	stage T4	345.13	55.56	-	<0.0001
Tumour diameter		1.27	1.16	1.40	<0.0001
Type of RCC	clear cell vs. other	1.45	0.43	4.89	0.55
Hematological markers					
SIRI	high vs. low	4.24	1.75	10.32	0.001
SII	high vs. low	5.33	2.10	13.54	0.0004
NLR	high vs. low	4.11	1.74	9.70	0.001
NER	high vs. low	3.33	1.30	8.38	0.01
PLR	high vs. low	2.63	1.14	6.08	0.02
HPR	low vs. high	2.382	1.050	5.40	0.04
dNLR	high vs. low	2.79	1.21	6.46	0.02
LMR	low vs. high	2.84	1.23	6.56	0.015

Table 4. Multivariate analyses for CSS in patients with RCC treated with partial or radical nephrectomy with respective values of the hematological markers.

Multivariate analysis- whole cohort- CSS					
Predictive factor		HR	Lower 95% CI	Upper 95% CI	*p*
Staging	ref = stage T1a	1			<0.0001
	stage T1b	5.16	1.28	20.83	0.02
	stage T2a	13.18	2.43	71.43	0.003
	stage T2b	4.30	0.53	35.71	0.2
	stage T3	6.53	1.43	30.3	0.02
	stage T4	17.09	1.51	200	0.02
Grade	ref = Grade 1	1			0.001
	Grade 2	1.630	0.347	7.634	0.53
	Grade 3	1.542	0.218	10.87	0.66
	Grade 4	25.837	3.367	200	0.002
Age	(years)	3.512	1.272	9.701	0.02
SIRI*	high vs. low	3.154	1.174	8.472	0.013
SII**	high vs. low	3.30	1.21	8.99	0.02
NLR***	high vs. low	2.616	1.006	6.802	0.043

Note: hematologic markers were included in separate models, three models were developed with the following accuracy- C-index: *0.903, **0.902, ***0.890. Model without markers achieved C-index = 0.877.

Table 5. Univariate analysis for OS in patients with RCC treated with partial or radical nephrectomy with respective values of the hematological markers.

Univariate analysis - whole cohort - OS					
Clinicopathological features		HR	Lower 95% CI	Upper 95% CI	*p*
Age	(years)	1.040	1.013	1.067	0.004
Gender	male vs. female	1.404	0.732	2.693	0.30
Grade	ref = Grade 1	1			<0.0001
	Grade 2	2.818	1.085	7.299	0.03
	Grade 3	4.293	1.241	14.925	0.02
	Grade 4	36.813	10.989	125	<0.0001
Staging	ref = stage T1a	1			<0.0001
	stage T1b	1.61	0.73	3.55	0.24
	stage T2a	3.61	1.23	10.64	0.02
	stage T2b	3.73	0.87	16.13	0.076
	stage T3	3.42	1.44	8.13	0.005
	stage T4	62.5	13.89	250	<0.0001
Tumour diameter		1.149	1.055	1.250	0.001
Type of RCC	clear cell vs. other	2.099	0.750	5.876	0.15
Hematological markers					
SIRI	high vs. low	2.161	1.186	3.936	0.01
SII	high vs. low	2.206	1.210	4.022	0.009
NLR	high vs. low	1.946	1.067	3.548	0.03
NER	high vs. low	2.735	1.426	5.247	0.0025
PLR	high vs. low	2.027	1.070	3.839	0.03
HPR	low vs. high	1.761	0.964	3.217	0.06
dNLR	high vs. low	1.587	0.870	2.892	0.13
LMR	low vs. high	1.915	1.053	3.482	0.03

Table 6. Multivariate analysis for OS in patients with RCC treated with partial or radical nephrectomy with respective values of the hematological markers.

Multivariate analysis - whole cohort - OS					
Predictive factor		HR	Lower 95% CI	Upper 95% CI	*p*
Grade	ref = Grade 1	1			<0.0001
	Grade 2	2.733	1.05	7.09	0.04
	Grade 3	4.012	1.155	13.89	0.03
	Grade 4	34.011	10	111.11	<0.0001
Age	(years)	1.04	1.01	1.07	0.002
NER*	high vs. low	2.395	1.236	4.643	0.01
SIRI**	high vs. low	1.87	1.02	3.43	0.04
SII***	high vs. low	1.873	1.016	3.455	0.04

Note: hematologic markers were included in separate models, three models were developed with the following accuracy- C-index: *0.750, **0.747, ***0.745. Model without markers achieved C-index = 0.725.

fore, different inflammatory markers seem to provide the same prognostic information, as they show a strong correlation with each other (SIRI, SII and NLR) and their incorporation into the model results in similar accuracy increment.

Cut-off values for the categorization of particular markers into elevated or decreased largely differ between studies. In the paper by Elghiaty *et al*. [3] patients with non-metastatic RCC up to 7 cm in diameter, who presented with higher MLR (cut-off value of 0.21), were at greater

Table 7. Univariate analysis for RFS in patients with RCC treated with partial or radical nephrectomy with respective values of the hematological markers.

Univariate analysis- whole cohort-RFS					
Clinicopathological features		HR	Lower 95% CI	Upper 95% CI	p
Age	(years)	1.008	0.986	1.030	0.45
Gender	male vs. female	0.705	0.411	1.210	0.20
Grade	ref = Grade 1				<0.0001
	Grade 2	2.132	0.934	4.878	0.07
	Grade 3	5.593	2.079	15.152	0.001
	Grade 4	30.950	10.989	90.909	<0.0001
Staging	ref = stage T1a	1			<0.0001
	stage T1b	1.86	3.88	0.89	
	stage T2a	6.41	15.15	2.7	
	stage T2b	6.41	21.74	1.9	
	stage T3	5.62	11.76	2.69	
	stage T4	19.23	142.86	2.55	
Tumour diameter		1.215	1.133	1.304	<0.0001
Type of RCC	clear cell vs. other	1.517	0.684	3.361	0.30
Hematological markers					
SIRI	high vs. low	1.895	1.104	3.254	0.02
SII	high vs. low	1.946	1.133	3.343	0.02
NLR	high vs. low	1.392	0.801	2.419	0.24
NER	high vs. low	1.843	1.059	3.206	0.03
PLR	high vs. low	2.309	1.313	4.059	0.004
HPR	low vs. high	2.147	1.250	3.689	0.006
dNLR	high vs. low	1.328	0.771	2.288	0.30
LMR	low vs. high	1.484	0.862	2.556	0.15

Table 8. Multivariate analysis for RFS in patients with RCC treated with partial or radical nephrectomy with respective values of the hematological markers.

Multivariate analysis- whole cohort-RFS					
Predictive factor		HR	Lower 95% CI	Upper 95% CI	p
Grade	ref = Grade 1	1			<0.0001
	Grade 2	1.847	0.80	4.26	0.15
	Grade 3	4.701	1.12	9.80	0.03
	Grade 4	23.92	5.46	52.63	<0.0001
Tumour diameter	(cm)	1.129	1.03	1.23	0.007

risk of recurrence and had worse CSS. Then, Hu *et al*. [6] evaluated the prognostic significance of NLR (cut-off 2.78), dNLR (cut-off 2.05) and PLR (cut-off 185) in RCC cases treated with nephrectomy and found the association between poorer OS and increased values of NLR, dNLR and PLR. On the contrary, Lucca *et al*. [18] enrolled localized RCC cases and described MLR as potentially the best prognostic tool (when compared to NLR and PLR) that reflects the systemic inflammatory response. Conversely, another study proposed PLR as the most reliable marker for overall and cancer-specific survival prediction in patients with non-metastatic clear cell RCC, who underwent nephrectomy [19]. To sum up, conflicting reports on the superiority of different inflammatory markers exist and none have been clearly proven as of highest prognostic value yet. Here, based on the predefined threshold values, Kaplan–Meier curves revealed that higher NLR ($\geq$2.76), PLR (>170), NER (>0.95) and dNLR (>1.8), and lower LMR (<2.0) and HPR ($\leq$0.53) were associated with worse CSS, while only elevated NLR from the markers mentioned above was found to be an independent factor for CSS in multivariate analysis. Similarly, high NLR (but not dNLR) and PLR

and lower LMR were associated with OS, but none of the above-mentioned, well-known markers constituted an independent predictor of OS. We also observed associations between increased PLR and worse RFS, while no influence was observed in the case of NLR, dNLR and LMR.

There is still limited evidence on the prognostic value of the novel markers of systemic inflammation such as systemic inflammatory response index and systemic immune-inflammation index [4,15,20]. Interestingly, in our study the novel markers of systemic inflammation i.e., higher SIRI and SII, occurred to be associated with worse CSS and represented independent predictors of CSS, comparably to NLR. CSS prognostic models including SIRI and SII outperformed the model that based on staging, grading and age alone. Moreover, in the multivariate analysis these inflammatory markers were also significant predictors of OS but did not prove to be an independent tool for RFS estimations. This observation complies with the paper by Chen *et al.* [4], in which the authors reported worse CSS and OS in individuals with elevated SIRI. Worth emphasizing is the fact that AUC for SIRI was far greater, when compared to NLR, PLR and MLR [4]. In our study SII exhibited superior AUC compared to other markers (including SIRI) for all investigated outcomes, as well. Another retrospective study reported that elevated SII is associated with OS and CSS in non-metastatic RCC even after propensity score matching but on the contrary to our results the authors did not provide data on other inflammatory markers that could be obtained simultaneously [20].

In the current study, we also included hematological biomarkers derived from red blood cell lineage, i.e., HPR and NER. Among the potential mechanisms involved in the association between red blood cells and RCC, other authors listed e.g., anemia, systemic inflammation leading to iron deficiency or decrease in renal erythropoietin production [21]. Here, elevated NER was related to shorter recurrence-free, cancer-specific and overall survival in univariate analysis. Moreover, NER proved to be an independent risk factor for shorter overall survival, together with age and tumour grade in multivariate analysis. Decreased HPR was associated with poorer OS and CSS in univariate analysis, as well. Furthermore, the prognostic values of HPR and NER in RCC were hardly studied, and only few studies were performed that were focused on red blood cell derivatives [22,23]. Tang *et al.* [11] described that low HPR (<0.615) was associated with worse CSS, OS and PFS, but not RFS in bladder cancer patients. To the best of our knowledge, neutrophil to red blood cell ratio (called NER in our study) has not been investigated in renal cell cancer, but was shown to be associated with worse disease-free survival and OS in breast cancer patients [24]. In our previous paper, we found that NER >0.93 was a predictor of poorer oncological outcomes (BCG failure) in high-risk non-muscle invasive bladder cancer [12].

None of the studied inflammatory markers were independently associated with recurrence-free survival. Although higher SIRI, SII, NER, PLR and lower HPR were related to shorter time to reccurence, only tumour diameter and grade served as independent predictors for RFS in the multivariable model. This corresponds with the majority of prognostic scores, which rely solely on histopathologic (staging, grading, necrosis, tumour diameter) and clinical features (age, symptoms) [25]. On the other hand, one of the meta-analysis reported the predictive value of elevated NLR for RFS/PFS in RCC (HR = 2.18) [26]. Some authors pinpoint the phenomena of retrospective study bias as the clue for the incoherence of the published data [25]. Furthermore, worth mentioning is the fact that our cohort consisted of non-metastatic cases. Other authors found the correlation between predefined threshold of NLR and PFS in the metastatic setting [27,28]. Further studies investigating the role of inflammatory markers on the recurrence risk are warranted.

We are conscious of several limitations of our study that are listed below. It was a single-center retrospective analysis and selection bias could not be excluded. Some clinical data were not collected, and some other biomarkers easily obtained from peripheral blood count were not included e.g., lymphocyte to red blood cell ratio (LRR) [24]. Furthermore, no data on the postoperative values to be used in the follow-up were collected. Local and distant RCC recurrences were not analyzed separately. Due to the retrospective nature of the study, the follow-up was inconsistent between patients. Nevertheless, we managed to analyze in the relatively large contemporary cohort the impact of several markers of the inflammatory response, easy to adopt in the patients with RCC for clinical purposes.

5. Conclusions

In our study, we compared the prognostic value provided by different inflammatory markers in patients with localized or locally advanced RCC. We have found that markers of systemic inflammation might provide additional prognostic value (especially SIRI, SII, NLR and NER), and further increase the predictive accuracy of available models. Clinicopathological features (tumour stage, grade and patient's age), however, remain the most important independent prognostic factors for oncological outcomes in RCC patients treated with nephrectomy. For the first time, we show the prognostic value of neutrophil-to-erythrocyte ratio, which constitutes an independent risk factor for overall survival

Abbreviations

AUC, area under the curve; CI, confidence interval; CSS, cancer-specific survival; dNLR, derived neutrophil/lymphocyte ratio; HPR, hemoglobin/platelet ratio; HR, hazard ratio; IQR, interquartile range; LMR, lymphocyte/monocyte ratio; LRR, lymphocyte to red blood

cell ratio; MLR, monocyte/lymphocyte ratio; NER, neutrophil/erythrocyte ratio; NLR, neutrophil/lymphocyte ratio; OS, overall survival; PLR, platelet/lymphocyte ratio; RCC, renal cell carcinoma; RFS, recurrence-free survival; ROC, receiver operating curve; SII, systemic immune-inflammation index; SIRI, systemic inflammatory response index.

Author contributions

Conceptualization, ŁZ and AŚ; methodology, ŁZ, and AŚ; software, AŚ; validation, ŁZ, AŚ, and PZ; formal analysis, ŁZ, and AŚ; investigation, ŁZ, AŚ; resources, ŁZ, AŚ, KG, ŁM, CŚ, PZ; data curation, ŁZ, and AŚ; writing, ŁZ; writing and re-editing, ŁZ, AŚ; visualization, ŁZ, AŚ; supervision, AW, PR; project administration, ŁZ, and AŚ; funding acquisition, not applicable. All authors have read and agreed to the published version of the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was conducted under the Ethics committee vote AKBE/72/2021 of the Medical University of Warsaw. Informed consent was obtained from all subjects involved in the study.

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Conflict of interest

The authors declare no conflict of interest.

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