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Preoperative hemogram-related parameters to distinguish renal cell carcinoma from benign kidney masses: HERR score

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ABSTRACT

Objectives: Renal cell carcinoma (RCC) accounts for approximately 90% of all kidney malignancies, and it is difficult to preoperatively distinguish between tumors and benign masses without a kidney biopsy in small renal masses. We investigated whether any preoperatively defined hemogram-related parameters had a predictive value that would distinguish RCC from benign kidney masses using a novel scoring method.

Methods: Between January 2011 and November 2017, 330 patients diagnosed with kidney masses and who received an operation were included. Fifty-six masses were benign. The neutrophil-to-lymphocyte count (NLR), platelet-to-lymphocyte count, lymphocyte-to-monocyte count, mean platelet volume, platelet count ratio, and hemoglobin to red cell distribution width ratios were calculated. The hemogram-related parameters were combined with the tumor size to establish the hemogram-related risk (HERR) score. The area under the receiver operating characteristics curve, sensitivity, specificity, and likelihood ratios were evaluated to preoperatively diagnose RCC.

Results: Histological findings confirmed RCC in 274 patients. The NLR [median (interquartile range)] was higher in patients with RCC, 3.7 (4.7), compared to a benign kidney mass, 2.4 (2.2) ($p < 0.001$). A HERR score cut-off of ≥ 3 showed a good sensitivity at 78% with an LR+ of 10.8 [95% confidence interval (CI): 7.0-16.4] and an LR- of 1.2 (95% CI: 1.0-1.5).

Conclusion: Our study, despite being a preliminary validation, is the first to evaluate hemogram-related parameters for preoperatively discriminating between RCC and benign renal masses, and the HERR score serves as a potential diagnostic biomarker for this

Keywords: Renal cell carcinoma, kidney mass, hemogram-related risk score

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Renal cell carcinoma (RCC) is the most common solid kidney lesion, and it accounts for approximately 90% of all kidney malignancies [1]. Old age, hypertension, and lifestyle factors, such as smoking and obesity, are among the etiologic factors of RCC [1, 2].

Kidney masses are mostly asymptomatic until the late stages of the disease. However, with the development and widespread use of imaging modalities, such as ultrasound and computed tomography, the incidental diagnoses of RCC are increasing [3]. Because of the earlier diagnosis, these

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tumors are usually smaller in size and low-grade [4]. Studies indicate that it's difficult to distinguish between benign and malign kidney tumors radiologically without a kidney biopsy in small renal masses [5]. In fact, multiple studies demonstrated that the incidence of surgically treated benign renal tumors can be up to 20% [4, 6].

Host inflammatory response plays critical role in the initiation and progression of various malignancies, including RCC [7]. Cancer patients frequently present with systemic inflammatory responses as alterations in peripheral blood cell counts. Recently, a number of studies about circulating blood-cell-based biomarkers, such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), which reflect the systemic inflammation, were shown to be effective predictors of the prognosis across various cancers, including RCC [8, 9].

A low lymphocyte-to-monocyte count ratio (LMR) was shown to be indicative of the aggressiveness of RCC [9]. Meanwhile, the hemoglobin (Hb) to red cell distribution width (RDW) ratio has been shown to be a new prognostic parameter in cancer patients [10]. A low preoperative MPV and high platelet count were demonstrated to be independent predictors of tumor-specific mortality in RCC patients [11]. The identification of noninvasive markers that can be used to screen RCC patients in the early stages is one of the challenges of urologists [12]. Currently, there is no diagnostic biomarker available for an accurate diagnosis of RCC other than incidental radiological discovery.

In this study, we aimed to investigate whether any of the preoperatively defined hemogram-related parameters, namely NLR, PLR, Hb to RDW, MPV to platelet count, and lymphocyte-to-monocyte count, had a predictive value for distinguishing RCC from benign kidney masses and to design a scoring system for this purpose.

METHODS

This study was performed in accordance with Declaration of Helsinki in 1965 (as revised in 2013). Ethical clearance was granted by the Regional Ethics Committee. We performed a search of the database of our hospitals' Laboratory Information System, which integrates information from several databases and includes the patient demographics, clinical diagnosis, order entry database, and laboratory results database. Between January 2011 and November 2017, patients diagnosed with a kidney mass and who had a radical nephrectomy or partial nephrectomy treated by either open or laparoscopic methods in our institute were included in the study. The exclusion criteria included patients with other known malignancies, hematologic diseases, autoimmune diseases, active infections, preoperative blood transfusions, those under anticoagulant treatment or prior steroid or anticancer therapy, or patients where perioperative routine laboratory tests were unavailable.

A total of 354 patients with a complete blood panel performed within 30 days prior to the surgery and available medical records were discovered. Finally, 330 out of 354 patients were included in the study, and 56 of them had benign tumors. The longest diameter of the tumor size (TS), histological cancer type, T-stage, Fuhrman grade, status of lymph node metastasis, and necrosis, defined as the presence of microscopic coagulative necrosis, were taken from the pathology reports.

The NLR was calculated by dividing the absolute number of neutrophils by the lymphocyte count. The PLR was calculated by dividing the absolute platelet count by the lymphocyte count. MPV to platelet count ratio, Hb to RDW ratio, and lymphocyte-to-monocyte count ratios were also calculated.

Statistical Analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS, version 21; SPSS Inc., Chicago, IL, USA). The normality of the continuous variables was analyzed with the Kolmogorov Smirnov test. Results are expressed as mean ± standard deviation (SD) or median (interquartile range). Normally distributed continuous variables were compared using the independent-samples t-test, and the Mann–Whitney U test was used if the distribution was skewed. Categorical data were compared using the chi-square test. The Kruskal-Wallis test was used for computing differences across groups. A *p*-value of 0.05 was considered to be statistically significant.

The ROC curve, a parameter that reflects the sensitivity and specificity of continuous variables, was

used to determine the cut-off values of the parameters. Youden's index was applied to determine the optimal cut-off value.

Next, we stratified the hemogram-associated markers and analyzed them as categorical variables. We combined the hemogram-related parameters with tumor size to establish the hemogram-related risk (HERR) score as follows: patients with increased NLR (≥ 2.47 and < 4.0, 1 point; > 4.0, 2 points), and MPV to PLT (≥ 0.028, 1 point), tumor size (≥ 4 cm, 1 point), decreased LMR (≤ 4.20, 1 point), and Hb to RDW ratio (≤ 0.86, 1 point). The HERR score was calculated by totaling these individual scores. Using the postoperative pathological report as the gold standard, the sensitivity (SE), specificity (SP), positive and negative predictive values (PPV, NPV), positive likelihood ratio (LR+) and negative likelihood ratio (LR–) were calculated.

RESULTS

The histological findings confirmed RCC in 274 patients (Table 1). Of these, 168 (61%) were men, and 106 (39%)were women. The mean age of the patients with benign masses was 58.5 ± 12.7 (22 to 82 years) and 59.5 ± 11.9 (18 to 89 years) for malignant cases (Table 2). Out of these total RCC patients, 225 (82%) had renal clear-cell carcinoma, 26 (9.4%) had a papillary RCC, 11 (4%) had a chromophobe RCC, and 12 (4%) were unclassified.

In the benign group, 17 of the patients had a tumor

Table 1. The diagnosis of patients

Diagnosis	Number of patients
Benign masses	**56**
Renal cyst	26
Renal cortical adenoma	2
Oncocytoma	15
Anjomyolipom	13
Renal cell cancers	**274**
Clear renal cell carcinoma	225
Papillary renal cell carcinoma	26
Chromophobe renal cell carcinoma	11
Unclassified renal cell carcinoma	12

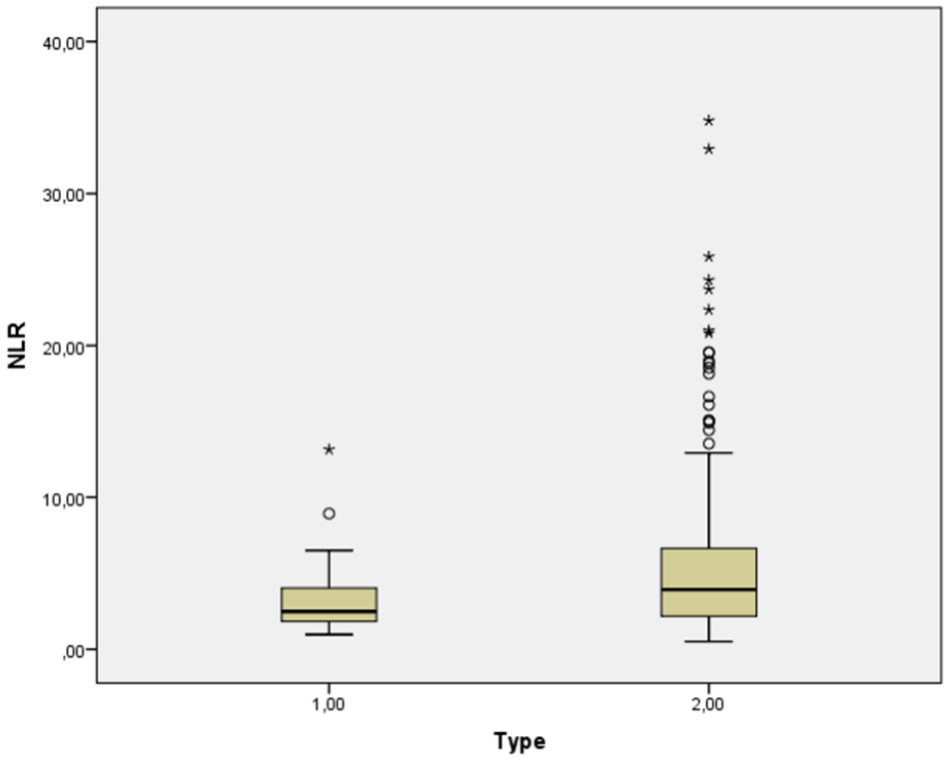

Figure 1. Neutrophil to lymphocyte ratio. The bar graphs show blood neutrophile to lymphocyte (NLR) levels in benign (type 1) and renal cell carcinoma (type 2) patients.

size ≤ 4 cm, 64 of the RCC patients had a tumor size ≤ 4 cm. Three of the benign patients had a tumor size > 10 cm, and 53 of the RCC patients had a tumor size > 10 cm. When the patients were stratified according to pathological stage, 51% were at stage pT1, 24% at stage pT2, 21% at stage pT3, and 2% at stage pT4 (Table 2). When renal clear-cell patients were stratified according to the Fuhrman grade, 47 patients were classified as grade I, 120 as grade II, 45 as grade III, and 14 as grade IV. Of the RCC patients, 154 underwent an open radical nephrectomy, 76 had a laparoscopic radical nephrectomy, 38 had an open partial nephrectomy, and 6 had a laparoscopic partial nephrectomy. In the benign patient group, 22 underwent an open radical nephrectomy, 16 had a laparoscopic radical nephrectomy, 14 had an open partial nephrectomy, and 4 had a laparoscopic partial nephrectomy.

The NLR levels [median (interquartile range)] were higher in the patients in the malignant kidney mass group with a value of 3.7 (4.7) compared to a value of 2.4 (3.2) for the benign kidney mass group ($p < 0.001$; Figure 1). The RDW, PLT, LMR, PLR, Hb to RDW, and MPV to PLT levels were similar between

Table 2. Characteristics of the entire study population (n = 330)

	Benign (n = 56)	**RCC (n = 274)**	***p* value**
Gender (M/F)	31/25	170/104	0.018
Age (years)	58.5 ± 12.7	59.5 ± 11.9	0.995
TNM Stage			
pT1a		60	
pT1b		81	
pT2a		34	
pT2b		34	
pT3a		49	
pT3b		7	
pT3c		3	
pT4		6	
WBC (10^9/L)	7.9 (3.7)	9.2 (5.0)	**0.001***
Neutrophile (10^9/L)	5.0 (2.5)	6.3(4.7)	**< 0.001***
Lymphocyte (10^9/L)	1.8(1.0)	1.7 (1.1)	0.113
RDW	14.2 (2.1)	14.5 (2.3)	0.843
PLT (10^9/L)	266 (112)	249 (102)	0.050
MPV, fl	8.5(1.5)	8.4	0.651
PCT	0.23 (0.07)	0.21 (0.09)	0.056
PDW	16.6 (0.4)	16.5 (1.6)	0.604
Hb (g/dl)	13.8 (2.7)	12.7 (2.8)	**0.008***
Hct (%)	41.1 (7.4)	37.9 (7.8)	**0.014***
Hb to RDW	0.92 ± 0.18	0.87 ± 0.19	0.092
LMR	3.1 (2.58)	3.1 (2.48)	0.680
PLR	142 (106)	147 (109)	0.533
MPV to PLT	0.031 (0.015)	0.033 (0.017)	0.127
NLR	2.4 (2.2)	3.7 (4.7)	**< 0.001***
HERR score	3.0 (1.0)	4.0 (2.0)	**< 0.001***

Data are shown as median (interquartile range). or number or mean ± standard deviation. F = female, Hb = hemoglobin, HbRDW = hemoglobin to red cell distribution width, Hct = hematocrit, HERR = hemogram-related risk, LMR = lymphocyte to monocyte ratio, M = male, MPV = mean platelet volume, NLR = neutrophile to lymphocte ratio, RCC = renal cell carcinoma, PLR = platelet to lymphocte ratio, PLT = platelet count, RDW = red blood cell distribution width, ROC = receiver operating characteristic, SE = standard error, WBC = white blood cell, *$p < 0.05$

Table 3. ROC curve analysis, and cut-off values for prediction of RCC from hemogram

Parameter	AUC	SE	*p* value	95% confidence interval	Cut-off value
MPV to PLT	0.564	0.042	0.129	0.481-0.647	0.029
Hb to RDW	0.582	0.041	0.053	0.501-0.663	0.86
PLR	0.526	0.041	0.533	0.447-0.606	120
LMR	0.508	0.041	0.842	0.429-0.588	4.2
NLR	0.657	0.035	0.000*	0.588-0.727	2.47

AUC = Area under curve, Hb = hemoglobin, LMR = lymphocyte to monocyte ratio, MPV = mean platelet volume, NLR = neutrophile to lymphocte ratio, RCC = renal cell carcinoma, PLR = platelet to lymphocte ratio, PLT = platelet count, RDW = red blood cell distribution width, ROC = receiver operating characteristic, SE = standard error

the RCC and benign-mass patients (Table 2). The ROC analysis (Table 3) showed the ideal cut-off value for the NLR was 2.47 (area under curve [AOC]: 0.657), and 4.2 was the ideal cut-off value for the LMR (AUC: 0.508). The ROC analysis also showed that the discriminatory power for NLR was greater than any other individual parameter.

As mentioned above, the continuously coded parameters were analyzed as categorical variables that were subsequently used to calculate the HERR score. Using the Hb to RDW ratio alone (≤ 0.86) for diagnosing RCC, we obtained a specificity of 67, meaning that it correctly identified 67% of those who did not have RCC. Patients with benign masses showed a median HERR score of 3 (IQR: 2.7) while the RCC median HERR score was 4 (2.0) ($p < 0.001$; Figure 2). We found the cut off value of the HERR Score as 3. The best value of the sensitivity and specificity of the parameters related to the hemogram is the cut off value. We calculated the cut off value as 3, in this sampling. Patients with a high HERR score (≥ 3) were more likely to have RCC. Using the ≥3

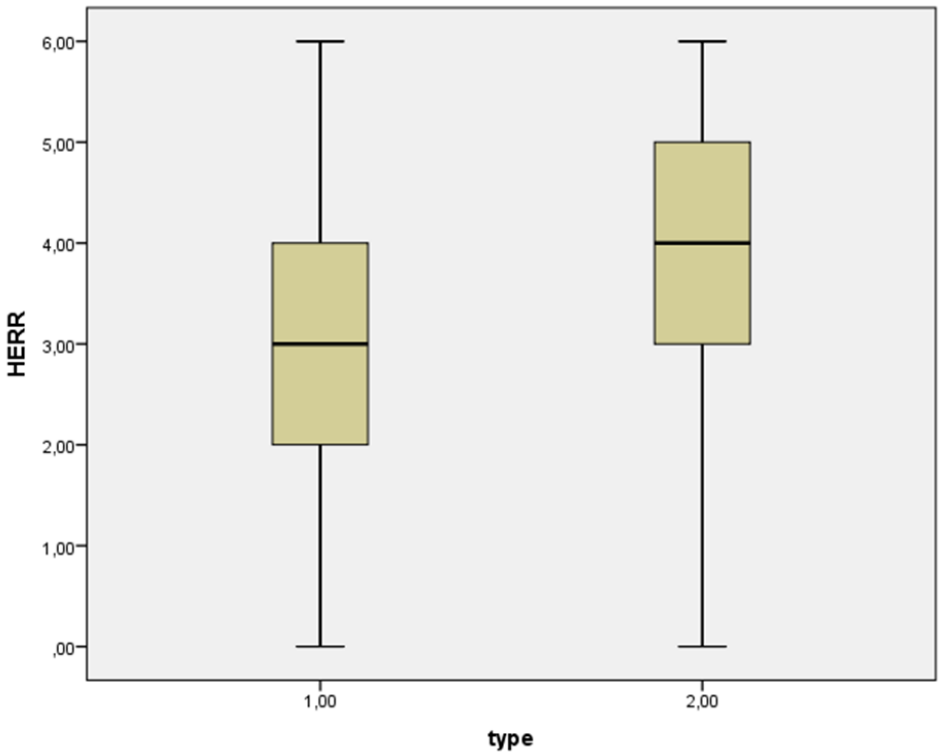

Figure 2. Hemogram related risk score. The bar graphs show blood HERR scores in benign (type 1) and RCC (type 2) patients.

Table 4. Diagnostic power of hemogram-related indices

Parameter	SE (%) (95% CI)	SP (%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)	LR+* (95% CI)	LR-* (95% CI)
Tumor size (≥ 4 cm)	37 (31-43)	75 (61-85)	88 (80-93)	20 (15-26)	7.3 (4.4-12.0)	4.0 (3.6-4.5)
MPV to PLT (≥ cut-off)	82 (77-87)	26 (16-40)	84 (79-88)	24 (14-37)	5.5 (4.1-7.3)	3.1 (2.4-3.9)
Hb to RDW (< cut-off)	47 (41-53)	67 (53-79)	88 (81-92)	12 (15-27)	7.2 (4.7-11.2)	3.7 (3.3-4.2)
PLR (≥ cut-off)	69 (63-74)	44 (31-58)	86 (80-90)	22 (15-31)	6.0 (4.3-8.4)	3.4 (2.9-4.0)
LMR (< cut-off)	70 (65-75)	29 (24-34)	83 (77-87)	17 (12-22)	4.8 (3.5-6.4)	5.1 (4.2-6.2)
NLR (≥ cut-off)	68 (62-73)	51 (38-65)	87 (82-91)	25 (17-34)	6.9 (4.8-9.8)	3.0 (2.5-3.5)
HERR score (≥ 3)	78 (73-83)	69 (56-80)	91 (87-94)	44 (34-54)	10.8 (7.0-16.4)	1.2 (1.0-1.5)

Hb = hemoglobin, HERR = hemogram-related risk, LMR = lymphocyte to monocyte ratio, LR+ = positive likelihood ratio, LR- = negative likelihood ratio, MPV = mean platelet volume, MPV to PLT = mean platelet volume to platelet ratio, PPV = positive predictive value, NLR = neutrophile to lymphocte ratio, NPV = negative predictive value, PLR = platelet to lymphocte ratio, PLT = platelet count, RDW = red blood cell distribution width, SE = sensitivity, SP = specificity, *weighted by prevelance

HERR score cut-off, we obtained a specificity of 69% (95% confidence interval [CI]: 56-80), meaning that it correctly identified of 69% of those who did not have a malign tumor. We obtained a high LR+ ratio (10.8) for the HERR scores that are in the best indicator range for ruling the diagnosis as RCC, and a PPV of 91 (87-94) within this category of HERR score (Table 4).

DISCUSSION

We hypothesized that there might be different degrees of circulating blood cell indices in RCC as compared to benign masses, and we explored the possibility that these indices could distinguish RCC from other benign renal masses. To provide comprehensive information for diagnosing RCC patients, we evaluated the NLR, PLR, LMR, and Hb to RDW ratios, and integrated them into a reliable scoring system that could be performed from a routine blood count to detect samples that could indicate RCC. While calculating the HERR score, platelet, monocyte, lymphocyte, neutrophil, and erythrocyte levels were evaluated simultaneously. Thus, a high HERR score might reflect alterations that favor cancer initiation and progression.

Our findings demonstrated that combining hemogram parameters into an integrated HERR score to discriminate among the kidney masses preoperatively offered a low rate of false positives and an adequate LR+ level as compared to using these values separately. In the current study, we found that none of the evaluated hematological indices mentioned in the literature were significantly correlated with a diagnosis of RCC and that the HERR score was significantly better than any of these parameters.

Additionally, the preoperative NLR score had powerful diagnostic abilities compared to the other hematologic indices, and it showed the highest diagnostic specificity and sensitivity. The NLR combined the measurements of the increased protumor activity of neutrophils with those of the reduced antitumor immune response by lymphocytes into a single value [7, 8]. We found that the NLR levels were higher in the RCC group, which can reflect the status of the tumor microenvironment. Similarly to our study, a number of researchers have demonstrated that the preoperative NLR value was significantly higher in malignant renal masses compared to benign ones [8,

13, 14].

Platelets have been shown to facilitate tumor progression by contributing to the metastatic cascade, regulating tumor cell invasion, and playing a role in angiogenesis [15]. A meta-analysis reported by Wang *et al*. [9] reported that an elevated PLR and reduced LMR were associated with poorer overall survival in RCC patients. Monocytes can be recruited in tumor tissues and exert pre-tumoral actions, meaning that a decreased LMR could be associated with the less favorable prognosis that was observed in RCC [9].

Previously, the MPV/PLT ratio as a predictor of cancer gave inconsistent results [16, 17]. In our study, this ratio for RCC patients and the benign group was comparable. We did not find any previous reports assessing the MPV/PLT ratio for patients with RCC.

The Hb to RDW levels were non-significantly reduced in RCC compared to benign cases. Recently, a low Hb/RDW ratio was reported to be significantly associated with poor clinical outcomes and a greater risk of death in esophageal squamous cell carcinoma patients [10]. Because both HB and RDW are influenced by various non-cancer-related conditions, the Hb/RDW could therefore theoretically reflect generalized health information, such as the nutrition status, inflammatory status, and immune function.

All of the blood parameters measured are available in routine blood tests, are easy to perform by the vast majority of automated analyzers, and do not increase the cost of diagnosis. The HERR score in combination with a summary of clinical symptoms might alert physicians to the early detection of RCC. The goal of a reliable screening test is to get as close as possible to zero false negative results with a minimal percentage of false positive results. Although hematologic indices are easy to measure, their utility might be affected by several factors that could lead to different cut-off points from those already mentioned in every hospital [18].

Limitations

The limitations of the present study include its retrospective nature and relatively small number of patients located at only one center. Due to biological differences between distinct patient cohorts, further studies in different cohorts with external validation are needed.

CONCLUSION

In conclusion, our study, despite being a preliminary validation, is the first to evaluate hemogram-related parameters for preoperatively discriminating between RCC and benign renal masses. The HERR score developed herein is a potential diagnostic biomarker that aids in this discrimination.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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