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ORIGINAL ARTICLE

Clinical Relevance of Haematologic Parameters in Predicting the Malignant Potential of Suspicious Renal Masses

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SUMMARY
Introduction. The expanded use of imaging technology has led to improvements in the early diagnosis of kidney cancer. However, providing correct diagnoses regarding the malignant potential of small renal lesions remains problematic for clinicians. In addition to imaging, pre-operative investigations usually include a complete blood count and biochemistry tests.
Aim of the study. To evaluate whether the pre-operative blood cell count, cell ratios, C-reactive protein (CRP) levels, and erythrocyte sedimentation rate (ESR) can be helpful in predicting the malignancy of visually suspicious renal masses prior to surgery.
Material and methods. Data on pre-operative blood tests were retrospectively collected from 84 cases of stage I renal cell carcinoma (RCC) and 55 benign lesions from patients hospitalized after a radiological finding of renal cancer and following nephrectomy. The predictive ability of various blood tests for malignant potential was analysed using the following statistical methods: the Mann-Whitney U test, receiver operating characteristic (ROC) curves and binary logistic regression.
Results. The mean CRP levels, monocyte (Mo) counts, platelet (PLT) counts and monocyte/lymphocyte ratios (MLRs) varied significantly between the patients with stage I RCC and patients that had benign renal lesions with a small effect size. Among these tests, the highest AUCs were displayed by CRP [0.704, 95% confidence interval: 0.567 – 0.807] and MLR [0.736, 0.612 – 0.861]. Based on the ROC curves, optimal cut-off values of 0.26 for MLR and 1.75 mg/L for CRO were selected. A binary logistic regression was used to determine if the combination of CRP and MLR could be used to predict whether patients with renal lesions had cancer resulting in increase of area under the curve (AUC) to 0.798 [0.690 –0.905].
Conclusions. In cases of diagnostic difficulties observing small renal lesions radiologically, the combination of elevated CRP levels and MLRs above 0.26 may help to confirm the presence of renal cancer.
Key words: renal cell carcinoma, benign renal lesions, haematologic parameters, monocytes, C-reactive protein

INTRODUCTION

Over the last two decades, the frequency at which renal neoplasms are found incidentally has increased because of the extensive use of widely available imaging tools, such as ultrasound (US) and computed tomography (CT) (6), and this trend is also observed in the Latvian population. According to the data provided by the Centre for Disease Prevention and Control of Latvia for the years 2000 to 2013, the incidence of renal carcinoma (C64) increased from 16.6 to 22.5 per 100 000 (18), particularly due to localized disease. Fifty seven percent of all newly diagnosed renal cancers in 2013 were of stage I and II. Combined with recent innovations introduced in the treatment of renal cancer this explain the observed stability in mortality rates over the last eight years, which was 9.2 in 2006 and 9.7 in 2013 (19). Although the expanded use of imaging technology has led to improvements in the early detection of kidney cancer, providing correct diagnoses of the malignant potential of small renal lesions remains an issue for clinicians. Twenty percent of renal masses sized 4 cm or less that are suspicious for malignancy according to CT and surgically excised are histologically benign (9). Percutaneous sampling of the ambiguous renal mass can be performed using core biopsy as recommended by the European Association of Urology guidelines, which consider data from studies provided by experienced centres, but at the same time indicate that 2.5 to 22% of core biopsies are non-diagnostic (10).

The 2004 World Health Organization (WHO) classification of renal tumours in adults distinguishes several entities that are usually benign, including oncocytomas and angiomyolipomas (11). However, CT findings are not sufficient to differentiate oncocytomas from other renal neoplasms (2), and active surveillance may not be helpful because the growth rate of benign tumours is close to that of malignant (7, 8). In addition, percutaneous biopsy may be misleading in certain cases because the eosinophilic variant of chromophobe renal cell carcinoma (RCC) may look similar to oncocytoma on haematoxylin and eosin stained histologic sections (1).

In typical cases, angiomyolipomas do not cause diagnostic difficulties, although fat-poor lesions require special imaging techniques that may not be readily available in daily practice (4). Because angiomyolipomas are also associated with a slow but consistent growth rate, surveillance may be uninformative. Symptomatic

presentation and sizes exceeding 3 cm alone do not define need for surgery (14), and the histological appearance of angiomyolipomas may also be quite different (3).

In addition to imaging, pre-operative investigations usually include a complete blood count and certain biochemistry tests.

AIM OF THE STUDY

To evaluate if the following blood markers and ratios can be used to predict malignancy of visually suspicious renal masses before surgery: white blood cell count (WBC), absolute neutrophil count (ANC), platelet (PLT) count, lymphocyte (Ly) count, monocyte (Mo) count, neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), monocyte/lymphocyte ratio (MLR), C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR).

MATERIAL AND METHODS

This study is a retrospective investigation of patients who were referred to the Oncology Department of the Urology Clinic at one of the largest hospitals in Riga between January 2013 and December 2014. The Ethics Committee of Riga Stradins University granted approval before the study. Patients with concomitant chronic infections, other malignancies and autoimmune diseases were not included in the study. All of the patients were hospitalized because of a primary diagnosis of RCC found on abdominal US or CT and were therapy naive. Patients were staged according to the tumour-node-metastasis (TNM) criteria of the American Joint Committee on Cancer (AJCC) 7th edition. Data collection included patient demographics, pre-treatment haematological parameters and histological data obtained from the postoperative pathology reports. Two groups of patients were selected for comparison: the first group had benign renal masses and second group had stage I RCC; pre-operative blood results were collected from both groups. To assess the haematological tests, the same methods as applied in routine practices of the hospital laboratory were used. The complete blood count was analysed on a Sapphire Cell-Dyn 5-diff Auto Analyser (Abbott Diagnostics) with MultiAngle Polarized Scatter Separation (MAPSS) technology. CRP was analysed on a Biochemical Analyser (Cobas 6000, Roche) using the immunoturbidimetric method employing original reagents. ESR was assessed with an Analyser Test 1 (Alifax) using the capillary photometry method.

For statistical analyses, SPSS version 21.0 was used. Initially, the normality of distribution was analysed for continuous variables by using the Shapiro Wilk test. Non-parametric tests were applied to data with non-normal distributions, whereas parametric tests were used for normally distributed data. The Mann-Whitney U test was used to compare the values of pre-treatment haematological tests between the two patient groups. The effect size measurements were calculated by dividing the Z score by the square root of the number of subjects (N). Cohen's rules were used to interpret the effect sizes, and an r of |.1| represented a 'small' effect size, |.3| represented a 'medium' effect size and |.5| represented a 'large' effect size. For continuous variables, data that were not normally distributed were shown as the medians (Mdn) with interquartile ranges (IQR) and data that were normally distributed as mean values (M) with standard deviations (SD). Categorical data were presented as numbers and percentages and analysed with the chi-square test. To compare the predictive ability of various blood tests for malignant potential, receiver operating characteristic (ROC) curves were analysed by estimating the area under the curve (AUC). AUCs were compared using Henley's nonparametric approach (5). A logistic regression was used to analyse the effect of the combined parameters on the likelihood that the subjects have a malignant tumour; p-values less than 0.005 were considered statistically significant.

RESULTS

In total, 434 patients underwent renal surgery in the years 2013 and 2014 at our clinic. Among them, 12 underwent surgery because of urothelial cancers, sarcoma, lymphoma and metastases in the kidney from other primary cancers or abscesses. In 364 cases, post-operative histology results confirmed RCC (clear cell, papillary, and chromophobe carcinomas); 251 (70.0%) were stage I, 49 (13.5%) were stage II, 35 (9.6%) were stage III and 29 (6.9%) stage IV disease; however, benign lesions were diagnosed in 58 (13.4%) patients, with 39 cases of oncocytomas, 14 cases of angiomyolipomas, 3 cases of cysts, 1 case of a leiomyoma and 1 case of a haemangiopericytoma. For further analysis, we selected 84 cases of stage I RCC and 55 cases of benign neoplasms. Patients with concomitant conditions, which is defined in the 'Material and methods' section, or a lack of pre-treatment blood tests were excluded. Baseline characteristics are summarized in Table 1. Statistically significant differences were not observed in age or sex between the groups ($p = 0.998$; $p = 0.488$). The largest renal carcinomas did not exceed 7 cm because only stage I tumours were selected. Among the benign lesions, one case of a 13 cm large oncocytoma was found. The average tumour size was not significantly different between groups ($p = 0.876$).

Table 1. Baseline characteristics

Variables	Benign neoplasms (N = 55)	RCC stage I (N = 84)	Min	Max	p
Female, N (%)	33 (60)	45 (54)			0.488
Male, N (%)	22 (40)	39 (46)			
Partial nephrectomy, N (%)	23 (42)	53 (63)			0.016*
Total nephrectomy, N (%)	32 (58)	31 (37)			
Age, years	63.40 ± 8.97	63.40 ± 10.32	38	84	0.998
Tumour, largest diameter (cm)	3.89 ± 2.85	3.80 ± 1.48	0.9	13.0	0.876

To compare both groups, categorical data were analysed using the chi-square test and continuous variables were analysed using independent-samples t-test. Data are presented as the mean (M) ± standard deviation (SD) or number (percentage), Min: minimal value, Max: maximal value.

The median values for the analysed pre-operative blood tests and comparison results are shown in Table 2. The results of the Mann-Whitney U test, which was used to compare the mean levels of blood tests, demonstrated significant differences in CRP levels, PLT, Mo counts and MLRs among the patients with RCC stage I and benign renal lesions with a small effect size.

Table 2. Comparison of preoperative haematological tests in patients with benign renal lesions and RCC stage I

Variables	Benign lesions	RCC stage I	N	r	p
WBC, 10^9/L	5.08 ± 2.01	6.37 ± 2.45	138	0.13	0.126
ANC, 10^9/L	2.87 ± 1.69	3.65 ± 1,71	138	0.11	0.204
PLT, 10^9/L	244 ± 49.50	209 ± 82.00	138	0.23	0.006*
Ly, 10^9/L	1.91 ± 0.88	1.78 ± 0.73	138	0.01	0.376
Mo, 10^9/L	0.43 ± 0.19	0.55 ± 0.28	138	0.24	0.004*
NLR	1.79 ± 0.72	2.12 ±1.35	138	0.14	0.098
PLR	132.39 ± 56.85	113.33 ± 61.31	138	0.05	0.521
MLR	0.22 ± 0.12	0.29 ± 0.11	138	0.28	0.001*
CRP, mg/L	0.90 ± 2.25	2.20 ± 3.35	104	0.25	0.003*
ESR, mm/h	8.00 ± 10.50	9.00 ± 9.00	134	0.12	0.158

Data are represented as the median (Mdn) ± interquartile range (IQR). Statistics were analysed by the Mann-Whitney U test.
N: Number of cases analysed, r: Effect size ($r = Z/\sqrt{N^2}$), p: Two tailed p-value.
WBC: White blood cell count, ANC: Absolute neutrophil count, PLT: Platelet count, Ly: Lymphocyte count, Mo: Monocyte count, NLR: Neutrophil/lymphocyte ratio, PLR: Platelet/lymphocyte ratio, MLR: Monocyte/lymphocyte ratio, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate.
Based on the results of the Mann-Whitney U test, ROC curves were plotted for the blood tests to determine their diagnostic efficiency. The measurements of various individual markers, including optimal cut-off values, corresponding sensitivity and specificity, predictive values and likelihood ratios for positive tests, are summarized in Table 3.

Table 3. Diagnostic efficiency of haematological parameters in differentiating RCC from benign lesions

Test	AUC	95% CI	Cut-off value	Se %	Sp %	PPV %	NPV %	LR+
PLT, 10^9/L	0.638	0.544-0.732	240	70	56	0.71	55	1.59
Mo, 10^9/L	0.687	0.567-0.807	0.51	58	62	0.70	50	1.52
CRP, mg/L	0.704	0.567-0.807	1.75	60	62	0.86	28	1.58
MLR	0.736	0.612-0.861	0.26	70	58	0.72	56	1.63

AUC: Area under the ROC curve, CI: Confidence interval, Se: Sensitivity, Sp: Specificity, PPV: Positive predictive value; NPV: Negative predictive value; LR+: Positive likelihood ratio.
MLR: Monocyte/lymphocyte ratio, CRP: C-reactive protein, Mo: Monocyte count, PLT: Platelet count.

Among the tests, the MLR displayed the highest AUC and provided the greatest ability to discriminate RCC from benign lesions (Figure 1).

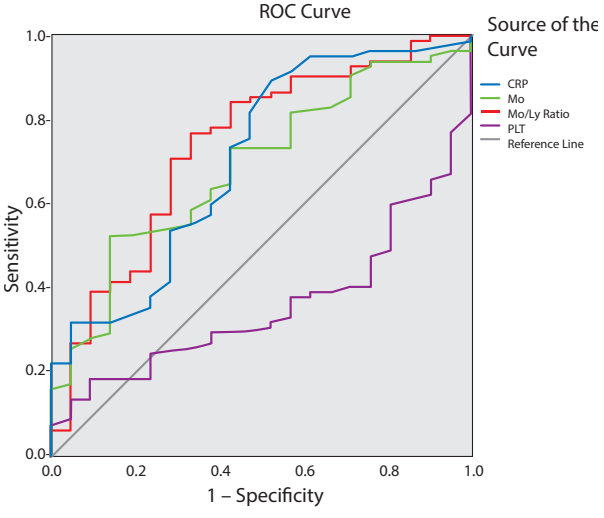

Fig. 1. Receiver operating characteristic (ROC) curves for C-reactive protein (CRP), platelet (PLT) count, monocyte (Mo) count and monocyte/lymphocyte ratio for differentiating renal cell carcinoma (RCC) from benign renal lesions

Based on the ROC curves, the optimal cut-off values were selected as follows: 0.26 for MLR, 1.75 mg/L for CRP, 0.51 10^9/L for Mo and 240 10^9/L for PLT. The diagnostic accuracy in distinguishing RCC from benign lesions was analysed for positive cases in one or a combination of several parameters. The data outlined in Table 4 indicate that combinations of one to four tests improved the specificity, positive predictive values and likelihood ratios because of decreased sensitivity. However, if the CRP levels were above 1.75 mg/L or MLR was higher than 0.26, the test provided adequate sensitivity and reduced specificity.

Table 4. Diagnostic efficiency of combined haematological tests in differentiating RCC from benign lesions

Test	Se %	Sp %	PPV %	NPV %	LR+
Either CRP > 1.75 mg/L or MLR > 0.26	88	43	86	47	1.54
CRP > 1.75 mg/L + MLR > 0.26	41	90	94	28	4.10
CRP > 1.75 mg/L + MLR > 0.26 + Mo > 0.51 10^9/L	32	95	96	26	6.40
CRP > 1.75 mg/L + MLR > 0.26 + Mo > 0.51 10^9/L + PLT < 240 10^9/L	21	95	94	24	4.20

Se: Sensitivity, Sp: Specificity, PPV: Positive predictive value; NPV: Negative predictive value; LR+: Positive likelihood ratio.
MLR: Monocyte/lymphocyte ratio, CRP: C-reactive protein, Mo: Monocyte count, PLT: Platelet count.

Binary logistic regressions were performed to determine whether the combined effects of CRP levels and MLRs above 0.26 had an increased ability to differentiate among patients with renal lesions that have RCC. The logistic regression model was significant at $\chi^2(2) = 18.41$ ($p < 0.001$). The model explained 25.7% (Nagelkerke R^2) of the variance in RCC and correctly classified 84.5% of the cases. Of the two analysed predictor variables, only the MLR appeared to be significant ($p = 0.004$). The coefficients of the binary logistic equation and odds ratios are summarized in Table 5.

Table 5. Logistic regression predicting the likelihood of RCC in cases of renal lesions based on CRP levels and MLR

	B	SE	p	Odds Ratio	95% CI for Odds Ratio
MLR > 0.26	1.58	0.55	0.004*	4.85	1.64-14.34
CRP	0.31	0.19	0.104	1.37	0.94-1.99
Constant	- 0.15	0.48	0.758		

B: B coefficient, SE: Standard error, CI: Confidence interval.
MLR: Monocyte/lymphocyte ratio, CRP: C-reactive protein.

The predictive probabilities calculated by binary logistic regressions confirmed the improved diagnostic accuracy with the combination of CRP and MNR because the AUC of the ROC curve was increased to 0.798 [95% confidence interval: 0.690 – 0.905] compared with separate measurements for CRP with AUC of 0.704 [0.567 – 0.807] and MLR with AUC of 0.736 [0.612 – 0.86]. However, Henley's test did not demonstrate statistically significant difference between the curves ($p = 0.389$, $p = 0.517$) (Figure 2).

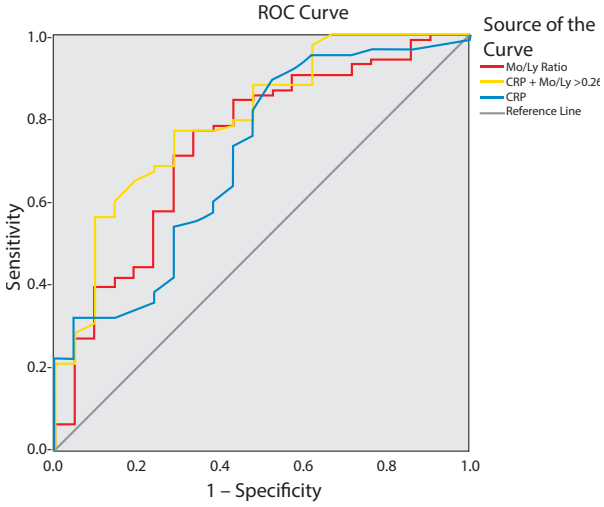

Fig. 2. Receiver operating characteristic (ROC) curves for C-reactive protein (CRP), monocyte/lymphocyte ratio and the combined parameters for differentiating renal cell carcinoma (RCC) from benign renal lesions

DISCUSSION

The results of our study suggest that routinely available peripheral blood parameters may help to differentiate between malignant and benign renal lesions. Stage I RCC patients expressed significantly higher pre-operative Mo, MLR and CRP levels and lower PLT levels compared with subjects that have benign renal lesions, including oncocytomas and angiomyolipomas.

The reduced PLT counts in patients with stage I RCC is difficult to explain because it is inconsistent with the data supported by a number of studies, which have shown worse RCC prognoses in cases of elevated PLT levels. As suggested by a review article compiling data on 15 studies, thrombocytosis is predictive for reduced RCC survival (20). As PLT counts are regarded to be an indicator of systemic inflammatory response associated with cancer progression, it is likely, that our findings is accidental because of the rather small sample size. However it cannot be excluded, that increased PLT counts occur during the later stages of the disease and are not representative of localized renal cancers.

Elevated Mo, MLR and CRP levels in cancer patients are readily apparent. Herein, several probable pathways explaining these findings are discussed. Inflammation

appears to play an important role in the development and progression of cancer by promoting cell proliferation and angiogenesis (12). After moving from the bone marrow to the peripheral blood, monocytes enter tissues and differentiate into macrophages. The presence of extensive infiltration of tumour-associated macrophages derived from peripheral blood monocytes is found in the RCC microenvironment and leads to cancer progression (17). Eventually this may reflect in peripheral blood as well. It is also known, that cells representing the myelomonocytic line, which includes macrophages as one of the most important units, secrete various inflammatory mediators with immunosuppressive ability and inhibit tumour-reactive T cells and natural killers, thereby leading to reduced peripheral Ly counts (13).

CRP was discovered almost a century ago and is the most studied acute-phase inflammation-associated protein. It is used in clinical settings as a non-specific early marker of inflammation. Growing evidence suggests that cancer patients often have elevated CRP levels (16). The previously mentioned meta-analysis of 18 studies conducted by Wu Ying et al. showed that CRP was the strongest survival predictor in RCC patients (20). CRP is produced in the liver and released in the blood stream as a non-specific response to various stimuli associated with inflammation, including tumour-induced local tissue hypoxia, damage and necrosis. Elevated CRP levels are also associated with compromised cell-mediated immunity, which presents as lymphocytopaenia (15).

The previously described effects mediated by tumour-induced inflammation may appear less pronounced in benign renal lesions than in cancer, even during early stages. Although extensive research has been conducted on the role of chronic inflammation in cancer, most of the related evidence has been acquired in advanced disease; thus, the timing at which such effects begin to manifest during cancer development is not clear. If systemic inflammatory responses to cancer emerge in initial stages, then elevated Mo counts and CRP levels and reduced Ly counts can be considered enough sensitive parameters for use as additional diagnostic tools in the differentiation of malignant and benign renal lesions.

If radiological findings are suspicious for renal cancer but a benign lesion cannot be excluded because of the growth of the tumour and core biopsies have not been performed, then preoperative CRP and MLR may provide additional information on the malignant potential of the suspicious mass. In cases where both parameters are positive, the use of cut-off values of 0.26 for MLR and 1.75 for CRP provides the specificity of the assessment of 90% and sensitivity of 41%. This effect suggests that out of 100 subjects with benign lesions, only 10 will be positive for both parameters with the aforementioned values, but out of 100 RCC patients, 59 will be negative for both tests. If both parameters exceed the recommended cut-off values, then the positive predictive value of the assessment reaches 94%, indicating a high probability of cancer. However, considering the low negative predictive value of 28%, the combination of both parameters does not provide enough information to rule out the presence of malignant disease. If only one parameter is above the cut-off value, sensitivity is increased (88%) but specificity is reduced (43%), which provides fewer false-negative results but causes more false-positive results.

Because of the limited number of subjects involved in the study, it is too early to draw any strict conclusions. Our study only provides a basis for future research.

CONCLUSIONS

- In the case of diagnostic difficulties in subjects with a radiological finding of a small renal mass, an assessment of the MLR and evaluation of CRP levels may provide additional information on the nature of the tumour.
- To differentiate malignant from benign renal lesions, it is recommended to consider the combination of both tests, with CRP levels above 1.75 and MLRs above 0.26, which may help to confirm the presence of renal cancer.
- For cases where cancer cannot be excluded and visual evaluations are more indicative of a benign mass in the kidney and the CRP and MLR markers do not exceed the cut-off levels, then every second subject will likely not have cancer. However, additional observations and investigations should be considered.

Conflict of interest: None

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