THE MEDICAL BULLETIN OF
SISLI ETFAL HOSPITAL

DOI: 10.14744/SEMB.2019.95770
Med Bull Sisli Etfal Hosp 2021;55(1):53–61

Original Research

Can we Avoid the Unnecessary Loss of nephrons in the Management of Small Solid Renal Masses? Additional Clinical Parameters to Predict Benign-malign Distinction

Ismail Selvi,[1] Halil Basar[2]

[1]Department of Urology, Karabuk University Training and Research Hospital, Karabuk, Turkey
[2]Department of Urology, University of Health Science Turkey, Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Ankara, Turkey

Abstract

Objectives: We aimed to investigate the predictive value of additional parameters for distinguishing benign-malign tumors and to prevent the loss of nephrons in small (≤4 cm) solid renal masses.

Methods: The data of 56 patients underwent partial or radical nephrectomy between September 2009 and December 2017 due to diagnosis of localized renal cell carcinoma were retrospectively analyzed. Demographic datas, histopathological tumor types, neutrophil/lymphocyte ratio (NLR), monocyte/lymphocyte ratio (MLR), platelet/lymphocyte ratio (PLR), red blood cell distribution width (RDW), mean platelet volume (MPV), the Framingham risk score and its components, postoperative follow-up results were recorded. Patients were divided into two groups as benign and malign.

Results: Among 56 patients with a median age of 60 (min: 35-max: 74) years, 13 patients had benign and 43 patients had malign pathologies. MLR (p=0.011), NLR (p=0.032), PLR (p=0.006), MPV (p=0.025), eGFR (p=0.019) and the Framingham score (p=0.008) were significantly higher in malign group. Among the components constituting the Framingham score, only presence of smoking (p=0.032), presence of hypertension (p=0.041) and total cholesterol values (p=0.021) were significantly higher. In multivariate analysis, NLR>2.02 (OR:7.184, p=0.037), PLR>109.65 (OR:12.692, p=0.002), MPV>3.44 (OR:10.543, p=0.046) and Framingham score >10.5 (OR:12.287, p=0.007) were found as predictive factors for distinguishing small solid renal masses concerning malignancy.

Conclusion: We think that NLR, PLR, MPV and the Framingham scores may be used in the clinical evaluation of small solid renal masses. In this way, we may prevent the unnecessary loss of nephrons in benign masses with suspicion of malignancy.

Keywords: Framingham risk score; nephron-sparing approach; predictive value; serum hemogram parameters; small solid renal masses.

Please cite this article as "Selvi I, Basar H. Can we Avoid the Unnecessary Loss of nephrons in the Management of Small Solid Renal Masses? Additional Clinical Parameters to Predict Benign-malign Distinction. Med Bull Sisli Etfal Hosp 2021;55(1):53–61".

As a result of the frequent use of abdominal imaging methods in recent years, the rate of incidentally detected solid renal masses has been increasing. The rates in the general population are around 2-3%.[1] These solid masses, which are encountered incidentally, are usually ≤4 cm in size and are called small renal masses (SRM).[2] In recent series, it has been reported that the incidence of benign pathology has gradually increased in masses of this size, and malignancy has not been detected in 15-30% of nephrectomies performed with suspected renal cell carcinoma (RCC).[3] While 46% of masses <1 cm in size are benign, this rate is 22% in masses <2 cm.[4] These high rates give rise to the thought that excessive treatment is applied as a result of not being able to differentiate SRMs clinically.[3] Depending on

Address for correspondence: Ismail Selvi, MD. Karabuk Universitesi Egitim ve Arastirma Hastanesi Uroloji Klinigi, Karabük, Turkey
Phone: +90 370 415 80 00 **E-mail:** ismselvi33@hotmail.com

Submitted Date: April 08, 2019 **Accepted Date:** May 17, 2019 **Available Online Date:** March 17, 2021

the performed unnecessary surgeries, a decrease in kidney functions and various surgical complications can be seen, and psychosocial stress may develop due to organ loss.[5]

Diagnostic accuracy cannot be achieved in 20% of percutaneous renal biopsies. Especially in masses smaller than 3 cm, the rate of obtaining false-negative results in biopsy is high.[6, 7] Preoperative biopsy of renal masses is performed only for limited indications because it is an invasive procedure, its diagnostic power is not at the desired levels, and the possibility of tumor seeding during the procedure. Therefore, contrast-enhanced computed tomography (CT) and Magnetic Resonance Imaging (MRI) are widely used to provide a differential diagnosis.[8] Among the SRMs with benign pathology, the most difficult to distinguish from malignant masses by radiological diagnostic methods are lipid-poor angiomyolipoma and oncocytoma.[1, 9] The clinical condition of the patient often determines the treatment approach in SRMs. Active surveillance or ablation treatments stand out in cases with low life expectancy and high comorbidity, while partial or radical nephrectomy is performed in patients with the good general condition, depending on the anatomical location and spread of the mass with suspected RCC.[5] The high rates of benign pathology reported in SRMs undergoing nephrectomy raise the need to investigate non-invasive parameters that distinguish between benignity and malignancy preoperatively with higher predictions.

Since the diagnosis and treatment approach to be applied in SRMs with a size of ≤4 cm still differ, in this study, we aimed to investigate the predictive value of additional parameters that can increase the diagnostic accuracy and reliability in preoperative evaluation by examining the clinical and pathological characteristics of benign and malignant cases diagnosed after nephrectomy in our clinic.

Methods

The data of 162 patients who underwent partial or radical nephrectomy with a prediagnosis of localized RCC between September 2009 and December 2017 in our clinic were retrospectively analyzed. Among these patients, 63 patients with solid renal masses of ≤4 cm in size were included in this study. Demographic data of the patients, histopathological tumor type, Fuhrman grade of the tumor, tumor side, location, size, presence of necrosis, operation type, follow-up time after nephrectomy, local recurrence, metastasis and survival rates were recorded. Estimated glomerular filtration rate (eGFR) was calculated using the short Modification of Diet in Renal Disease (MDRD) formula using creatinine, age, gender and race parameters measured in the preoperative period. In addition, preoperative serum hemogram parameters [(neutrophil/lymphocyte ratio (NLR), monocyte/lymphocyte ratio (MLR), platelet/lymphocyte ratio (PLR), mean platelet volume (MPV), erythrocyte distribution width (RDW)] were recorded.

Due to the retrospective design of our study, ethics committee approval was not obtained, and all procedures in our study were conducted in accordance with the ethical standards of the institutional and national research committee involving human participants and the principles of the Declaration of Helsinki. Each patient was informed before the surgery that the oncological follow-up information of the patients could be used in various oncological studies to be performed in the clinic without mentioning the patient names and identity information, and the information of patients who did not consent was not used.

Framingham Risk Score

The Framingham risk score, first edited in 1976 by the National Cholesterol Education Program-Adult Treatment Panel III (NCEP ATP III) and the National Heart, Lung and Blood Institute, evaluates the 10-year cardiovascular disease (e.g., myocardial infarction, coronary death and angina) development and associated mortality risk with mathematical equations in individuals between the ages of 30-74.[10] This risk score was updated in the following years.[11] The parameters used in risk calculation are age, gender, smoking, presence of diabetes, blood pressure, total cholesterol and high-density lipoprotein (HDL) levels, which are predisposing factors in the development of the cardiovascular disease. Scoring is made for each parameter and the total score is calculated. Percentages corresponding to the determined score range for males and females are expressed separately. According to this, <10% indicates low risk, 10-20% moderate risk, and ≥20% indicates high risk.[12]

The information regarding patient age, gender, total cholesterol, HDL level, systolic blood pressure, smoking status, presence of diabetes required for this risk classification were scanned from the hospital archive and electronic patient information system. Values checked in the week just before the date of nephrectomy were used in calculating the risk score. Among 63 patients with SRM who underwent nephrectomy, 56 individuals whose data regarding this scoring could be fully accessed, were included in this study without randomization. Thirteen patients with the benign histopathological diagnosis were named Group I and 43 patients with RCC diagnosis were named Group II, and patients were divided into two main groups without randomization.

Statistical Analysis

To compare the differences between the two main groups with benign and malignant pathology, the normality status

was evaluated with the Kolmogorov-Smirnov and Shapiro-Wilk tests. Pearson's chi-square analysis or Fisher's exact test for categorical variables; and for continuous variables, independent sample t-test in parametric conditions, and Mann-Whitney U test in non-parametric conditions were used. Receiver operating characteristic (ROC) curve analysis was performed to determine the predictive values of serum hemogram parameters and Framingham risk score. Univariate and multivariate logistic regression analyses were used to determine independent factors that might predict the distinction between benign and malignant masses. Analyzes were performed using IBM SPSS Statistics 21 (IBM, Armonk, NY USA) software. P<0.05 values were considered statistically significant.

Results

The median age of diagnosis of 56 patients with SRM that we included in our study was 60 (min: 35- max: 74), and 30 (53.6%) of the patients were male and 26 (46.4%) were female. While RCC was detected in 43 (76.8%) patients in total, 13 (23.2%) patients had benign histopathology. The masses with benign pathology were reported as oncocytoma (n=4, 30.7%), angiomyolipoma (n=5, 38.5%), metanephric adenoma (n=2, 15.4%) and xanthogranulomatous pyelonephritis (n=2, 15.4%) (Table 1).

During the median 50 (10-98) month follow-up period of 43 patients with RCC, four (9.3%) patients had local recurrence, three (6.9%) patients had distant metastasis, and four (9.3%) patients died due to cancer. Distant metastases occurred in the lung in two patients and the lung and bone in one patient. The demographic, pathological, clinical data and oncological results of the patients are shown in Tables 1 and 2.

When hemogram parameters were examined, MLR (p=0.011), NLR (p=0.032), PLR (p=0.006) and MPV (p=0.025) were found to be significantly higher in the malignant group; while there was no difference between the groups concerning RDW (p=0.396) (Table 2). We found that the preoperative eGFR level was significantly lower in the malignant group (p=0.019). While we calculated the Framingham score significantly higher in malignant cases (p=0.008); we observed that smoking (p=0.032), presence of hypertension (p=0.041), and total cholesterol (p=0.021) levels were significantly higher among the parameters forming this risk score. While 61.5% of benign cases were low-risk patients in terms of Framingham grading, it was observed that the malignant group was formed predominantly (41.9%) of high-risk patients (Table 2).

The predictive values of NLR, MLR, PLR, MPV, eGFR, Framingham score and total cholesterol parameters, which show statistically significant difference between the two groups, are shown in Table 3. The predictive values of these parameters were 2.02 (AUC: 0.698, p=0.032) for NLR, 0.26 (AUC: 0.750, p=0.007) for MLR, 109.65 for PLR (AUC: 0.755, p=0.006), 3.44 for MPV (AUC: 0.707, p=0.025), 86.25 for eGFR (AUC: 0.699, p=0.03), 10.5 for Framingham score (AUC: 0.743, p=0.008), and 164.5 for total cholesterol (AUC: 0.712, p=0.021).

Table 1. Pathological characteristics and oncological results of patients

Parameters	Group I (n=13) Benign	Group II (n=43) Malign
Histopathological tumor type, n (%)		
Clear cell RCC		32 (74.4)
Papillary type 1 RCC		3 (3.7)
Papillary type 2 RCC		4 (9.3)
Chromophobe RCC		2 (4.7)
Multilocular cystic RCC		2 (4.7)
Angiomyolipoma	5 (38.5)	
Oncocytoma	4 (30.7)	
Xanthogranulomatous pyelonephritis	2 (15.4)	
Metanephric adenoma	2 (15.4)	
Pathological stage, n (%)		
T1a		43 (100.0)
Fuhrman grading, n (%)		
1		6 (14.0)
2		22 (51.2)
3		14 (32.6)
4		1 (2.3)
Presence of necrosis, n (%)		
Present		6 (14.0)
Absent		37 (86.0)
Follow up time (months)		
Median (minimum–maximum)	60 (23-98)	50 (10-98)
Local recurrence rate, n (%)	-	4 (9.3)
Distant metastasis rate, n (%)	-	3 (6.9)
Cancer-specific survival rate, n (%)	-	4 (9.3)

RCC: Renal cell carcinoma.

In univariate analysis, smoking status, presence of hypertension, NLR, MLR, PLR, MPV, eGFR, total cholesterol levels and Framingham score were found as independent predictive factors in distinguishing benign from malignant masses in SRMs. In multivariate analysis, NLR (OR: 7.184, p=0.037), PLR (OR: 12.692, p=0.002), MPV (OR: 10.543, p=0.046) and Framingham score (OR: 12.287, p=0.007) were observed to be more significant in terms of predicting malignity (Table 4).

Discussion

Depending on the loss of nephrons, renal reserve decreases after both radical and partial nephrectomy. Although

Table 2. Demographic and clinical data of patients

Parameters	Group I (Benign) (n=13, %23.2)	Group II (Malign) (n=43, %76.8)	Total (n=56, %100)	p
Age				
(Median, 25.-75. percentile)	60.00 (50.00-67.50)	60.0 (51.00-65.00)	60.0 (50.25-65.00)	§0.741
Gender, n (%)				
Male	5 (38.5)	25 (58.1)	30 (53.6)	‡0.213
Female	8 (61.5)	18 (41.9)	26 (46.4)	
Body mass index (kg/m^2)				
Mean±standard deviation	24.20±2.28	24.90±3.28	24.74±3.07	†0.480
Smoking, n (%)				
Yes	6 (46.2)	27 (62.8)	33 (58.9)	‡0.032*
No	7 (53.8)	16 (37.2)	23 (41.1)	
Hypertension, n (%)				
Present	2 (15.4)	13 (86.7)	15 (26.8)	¶0.041*
Absent	11 (84.6)	30 (69.8)	41 (73.2)	
Diabetes, n (%)				
Present	3 (23.1)	14 (32.6)	17 (30.4)	¶0.733
Absent	10 (76.9)	29 (67.4)	39 (69.6)	
Tumor side, n (%)				
Right	6 (46.2)	19 (44.2)	25 (44.6)	‡0.900
Left	7 (53.8)	24 (55.8)	31 (55.4)	
Tumor localization, n (%)				
Upper pole	6 (46.2)	11 (25.6)	17 (30.4)	‡0.310
Mid pole	3 (23.1)	18 (41.9)	21 (37.5)	
Lower pole	4 (30.8)	14 (32.6)	18 (32.1)	
Pathological tumor size (cm) (Median, 25.-75. percentile)	3.00 (2.40-3.25)	3.00 (2.50-3.50)	3.00 (2.50-3.50)	§0.445
Surgical method, n (%)				
Radical nephrectomy	3 (23.1)	12 (27.9)	15 (26.8)	‡0.900
Partial nephrectomy	10 (76.9)	31 (72.1)	41 (73.2)	
MLR (Mean±standard deviation)	0.21±0.06	0.30±0.12	0.28±0.11	†0.011*
NLR (Median 25.-75. percentile)	1.68 (1.36-2.27)	2.31 (1.66-3.48)	2.19 (1.62-2.82)	§0.032*
PLR (Median (25.-75. percentile)	90.75 (81.25-103.89)	136.90 (96.75-191.41)	122.74 (88.35-176.34)	§0.006*
MPV (fL) Median (25.-75. percentile)	3.29 (2.60-4.09)	4.12 (3.18-5.01)	3.91 (3.08-4.44)	§0.025*
RDW (fL) (Mean±standard deviation)	13.50±0.84	13.79±1.11	13.72±1.05	†0.396
eGFR (ml/dk/1.73 m^2) (Mean±standard deviation)	95.66±15.44	84.43±14.40	87.04±15.28	†0.019*
Total cholesterol (Median (25.-75. percentile)	159.00 (156.00-167.00)	170.00 (160.00-205.00)	165.50 (158.25-190.00)	§0.021*
HDL (Median (25.-75. percentile)	41.00 (37.00-47.50)	40.00 (36.00-50.00)	40.00 (36.25-48.00)	§0.734
Framingham score				
Median (min-max) months	8.00 (7.00-12.00)	15.00 (8.00-20.00)	13.00 (7.25-20.00)	§0.008*
Framingham risk class, n (%)				
Low	8 (61.5)	11 (25.6)	19 (33.9)	‡0.009*
Moderate	5 (38.5)	14 (32.6)	19 (33.9)	
High	0 (0.0)	18 (41.9)	18 (32.1)	

MLR: Monocyte/lymphocyte ratio; NLR: Neutrophil/lymphocyte ratio; PLR: Platelet/lymphocyte ratio; MPV: Mean platelet volume; RDW: Red cell distribution width; eGFR: Estimated glomerular filtration rate; HDL: High-density lipoprotein; †: Independent sample t-test; §: Mann-Whitney U; ‡: Chi-square; ¶: Fisher's exact test. *p<0.05 (There is a significant difference between the groups).

with partial nephrectomy, the nephron quantity is tried to be protected at the highest level, the decrease observed in eGFR levels in the postoperative period is inevitable.[13] This situation negatively affects cardiovascular morbidity and overall survival in the following years.[14] This is particularly undesirable in patients with benign pathology detected with nephrectomy. Since 15-30% of benign pathologies are detected in SRMs according to the literature, if we can pre-

Table 3. Prediction values of parameters used to predict benign-malignant differentiation in small renal masses

	NLR	MLR	PLR	MPV (fL)	eGFR (ml/dk/1.73 m²)	Framingham score	Total cholesterol (mg/dl)
Prediction value	2.02	0.26	109.65	3.44	86.25	10.5	164.5
Sensitivity (%)	69.2	76.9	84.6	61.5	76.9	69.2	76.9
Specificity (%)	67.4	65.1	69.8	69.8	60.5	69.8	60.5
PPV (%)	67.9	68.7	73.6	67.1	66.1	69.6	66.1
NPV (%)	68.6	73.8	81.9	64.4	72.3	69.3	72.3
AUC	0.698	0.750	0.755	0.707	0.699	0.743	0.712
p	0.032	0.007	0.006	0.025	0.03	0.008	0.021

NLR: Neutrophil/lymphocyte ratio; MLR: Monocyte/lymphocyte ratio; PLR: Platelet/lymphocyte ratio; MPV: Mean platelet volume; eGFR: Estimated glomerular filtration rate; PPV: Positive predictive value; NPV: Negative predictive value; AUC: Area under the curve.*p<0.05 (There is a significant difference between the groups).

Table 4. Predictive factors predicting malignancy in small renal masses

	Univariate Model				Multivariate Model			
		%95 CI				%95 CI		
	OR	Lower	Upper	p	OR	Lower	Upper	p
Smoking	1.969	0.562	6.896	**0.029**				
Presence of hypertension	2.383	0.462	12.301	**0.003**				
Total cholesterol >164.5	5.098	1.223	21.254	**0.025**				
MLR >0.26	4.200	1.106	15.950	**0.035**				
NLR >2.02	4.661	1.221	17.789	**0.024**	7.184	1.125	45.871	**0.037**
PLR >109.65	12.692	2.459	65.509	**0.002**	12.692	2.459	65.509	**0.002**
MPV>3.44	3.692	1.013	13.455	**0.048**	10.543	1.045	106.364	**0.046**
eGFR>86.25	0.951	0.909	0.994	**0.026**				
Framingham score>10.5	5.192	1.352	19.942	**0.016**	12.287	1.971	76.598	**0.007**

MLR: Monocyte/lymphocyte ratio; NLR: Neutrophil/lymphocyte ratio; PLR: Platelet/lymphocyte ratio; MPV: Mean platelet volume; eGFR: Estimated glomerular filtration rate; OR: Odds ratio; CI: Confidence interval. *p<0.05 indicates statistically significant difference. Logistic regression analysis.

dict this group clinically, perhaps we can prevent unnecessary nephron losses.[3]

Imaging techniques failed at a rate of 13-28% to detect benign renal masses <4 cm in size.[2, 15] There are different opinions about the ability of kidney biopsy to distinguish benignity-malignancy in SRMs and its use in clinical practice.[5, 16] Although there are publications reporting the sensitivity, specificity and diagnostic accuracy of biopsies in the diagnosis of malignancy as 99.1%, 99.7% and 92-96%, respectively,[17, 18] it is observed in various meta-analyzes that biopsies are insufficient at a rate of 0-22.6% in diagnosis, and it is stated that false-negative results and insufficient sampling frequency increase especially in masses below 3 cm in size.[6, 19] Thus, kidney biopsy, which is an invasive procedure, is not recommended routinely in the current guidelines of the European Urology Association, published in 2019.[19]

According to the study of the American Urology Association, 37% of urologists did not prefer biopsy in the clinical evaluation of SRMs, 63% rarely used it, and 8% reported that they preferred biopsy more frequently (in >20% of the cases).[20] In a similar study conducted in the UK, it was observed that 43% of urologists did not use biopsy in the pre-diagnosis of SRM, and 23% rarely preferred it.[16] The most common reasons for not choosing biopsy are that the possibility not to obtain reliable sampling due to intra-tumor heterogeneity, the possibility of false-negative results, the risk of tumor seeding and to avoid possible complications. In addition, most urologists stated that the results of the biopsy would not change the treatment approaches in cases with suspected malignancy.[16] Similar to the current guideline recommendation, these findings show that biopsy in the differential diagnosis of SRM is not routinely used in clinical practice. On the contrary, there are also opinions arguing that the probability of false-negative results and

complication rates are low in biopsy.[21, 22]

Using the recent developments in imaging techniques, methods that will increase diagnostic accuracy in SRMs are being investigated. The annual growth rate of renal masses on CT and MRI, growth pattern,[1] perinephritic fat surface area,[23] and combination of volumetric apparent diffusion coefficient (ADC) histogram analysis calculated according to ADC on MRI with diffusion MRI findings,[24] and multiphasic contrast-enhanced MRI techniques[6] are current clinical parameters used in the differentiation of malignancy. Using the average ADC value measured in MRI alone was not found successful in distinguishing benign and malignant SRMs.[24, 25] Hoang et al.[6] found the sensitivity of multiphasic MRI to be 64.7%, specificity 85.9% and accuracy as 77.9% in distinguishing oncocytomas from papillary and clear cell RCCs smaller than 4 cm in size. However, in this study, only three tumor types were examined, and the success of multiphasic MRI was not investigated in distinguishing other benign and malignant histopathological types.[6] Studies that report that typical imaging characteristics cannot be clearly differentiated due to the increase in tumor homogeneity in SRMs, especially in the differential diagnosis of clear cell RCC and oncocytoma, and the sensitivity of the diagnosis of oncocytoma decreased by 19%, contradict this issue.[26] Rosenkrantz et al.[27] reported that since clear cell and chromophobe RCCs show similar features to oncocytoma, MRI cannot make a definite distinction between these subtypes. In the American Society of Clinical Oncology guidelines, it is stated that there is still no reliable imaging method that can distinguish between benign and malignant SRMs.[28]

In a recent study conducted in Korea, in parallel with the developments in imaging techniques in the last 15 years, an increase in the rate of using CT and MRI and biopsy was found. As a result of this clinical approach, the rate of benign pathology detection in SRMs undergoing nephrectomy has decreased from 9.7% to 6.3% within 15 years.[29] Due to the selection bias and Asian characteristics of the patients included in the study, high rates of benign pathology (15-30%) as found in western populations were not observed.[29] In this study, although it was stated that the use of imaging techniques and biopsy has increased, it is also mentioned that which imaging technique will be recommended in which cases, how often and whom to perform biopsy and imaging are not standardized in clinical practice.[29]

In the preoperative evaluation, 56 patients we included in our study had RCC suspicion according to CT. MRI was used in 18 cases for whom the differential diagnosis could not be made definitely, and biopsy was performed in eight (14.2%) cases whose benign-malignant distinction could not be made completely. Benign pathology was detected in two cases in nephrectomy performed in five patients with malignant biopsy results. In three cases with benign biopsy results, nephrectomy was performed because of clinical suspicion and malignant pathology was encountered in one of these three patients. Benign pathology was obtained as a result of nephrectomy in 10 of 48 patients who were thought to be malignant by imaging and who were thought to not require biopsy. According to our findings, while the false positivity rate of imaging methods was 20.8%, the false positivity rate in biopsy was 40%, the false negativity rate was 33.3%. With the combination of imaging methods and biopsy, we found the diagnostic accuracy to be 50%. Although this low rate can be attributed to the small number of cases, our findings coincide with the publications stating that the diagnostic power of biopsy in SRMs is low and it is difficult to obtain sufficient tissue samples.[6, 16, 19, 20]

In the literature, it is seen that other non-invasive parameters to be used in the differential diagnosis are investigated in addition to biopsy and imaging techniques.[5, 30] While the increase in aquaporin 1 and perilipin 2 levels measured in urine is effective in predicting clear cell and papillary RCC, their power in detecting other malignant and benign cases is insufficient.[5] These results show that parameters with higher predictive power are still needed in the differentiation of malignancy.

Recently, we see that the number of studies examining the effects of serum hemogram parameters and inflammatory markers on oncological outcomes in genitourinary malignancies has increased. Especially, high NLR (>4) and PLR (>195) levels have been reported to be a valuable parameter in predicting an increase in the likelihood of recurrence and progression in follow-up after nephrectomy in RCC and a decrease in overall survival.[31, 32] In animal experiments, it has been shown that platelets have a role in tumor development by affecting the immune system through the secretion of cytokines and bioactive molecules.[33] Unlike the studies in the literature, we investigated the reliability of non-invasive hemogram parameters, which are easy to measure, in predicting benign-malignant differentiation in solid renal masses ≤4 cm in size. According to our findings, we observed that increased NLR, PLR, MLR and MPV levels were significant in predicting the presence of malignancy in SRMs.

The condition named as metabolic syndrome constitutes the presence of impaired glucose tolerance/diabetes, high triglyceride levels, low HDL levels, obesity and hypertension. There are studies indicating that these individual components and also metabolic syndrome are a poor prognostic factor for RCC and affect oncological outcomes.

[34, 35] It has been stated that in the presence of three or more components, the incidence of RCC may increase 4-6 times, and tumor size and pathological grade may be higher.[34] Kriegmair et al.[36] reported that progression-free survival was shortened in the follow-ups after nephrectomy in localized stage RCC in the presence of metabolic syndrome; and Kocher et al.[37] showed that the main component associated with tumor aggressiveness was hypertension. According to the findings of Eskelinen et al.,[38] when locally advanced stage RCC is diagnosed, hypertension and dyslipidemia are seen at higher rates and the main factor that increases cancer-related mortality at this stage is hypertension. When we examine the literature, as can be seen, the effects of metabolic syndrome and its components on oncological results in RCC have been investigated in many studies. On the other hand, we could not find a comprehensive study in which the relationship between the prognosis of RCC and Framingham score, which determines the 10-year risk of cardiovascular disease development and mortality in individuals according to age, gender, smoking, presence of diabetes, blood pressure value, total cholesterol and HDL levels. In our study, we aimed to investigate the usability of this risk classification as a different parameter in predicting the distinction between benignity and malignancy in the preoperative evaluation of SRMs.

Smoking, obesity and hypertension, which are components of the Framingham score, are also the most important predisposing factors proven in RCC.[13] Consistent with this, while smoking and hypertension rates were significantly higher in malignant cases in our study, the body mass indexes of the two groups were similar. We also found that the total cholesterol level, which is another component forming the Framingham score, was high in RCC cases. When we calculate the predictive value for Framingham score as 10.5 (AUC: 0.743, p=0.008) in making the distinction between benignity and malignancy, according to multivariate analysis, we see that the Framingham score (OR: 12.287, p=0.007) is a reliable marker for distinguishing benignity-malignancy.

Due to the concern that the loss of nephrons after nephrectomy will increase the progression to chronic kidney disease (CKD) in patients who underwent nephrectomy due to malignancy suspicion, partial nephrectomy technique has been the recommended approach, especially in T1 stage SRMs.[13] eGFR is one of the most important parameters showing the kidney reserve. It has been reported that the eGFR value of 45-60 ml/min/1.73 m^2, which is an indicator of third-degree CKD, is observed to decrease at a rate of 65% after radical nephrectomy and 20% after partial nephrectomy. eGFR values of <45 ml/min/1.73 m^2, which is a further indicator of CKD, were observed in 36% after radical nephrectomy and 5% after partial nephrectomy.[39] These nephron losses observed after nephrectomy may also lead to an increase in cardiovascular disease and mortality rates and a decrease in overall survival besides the development of CKD.[14, 40] In one of the studies conducted on this subject, in the presence of preoperative lower eGFR levels, cancer-specific survival and recurrence-free survival after nephrectomy were further reduced.[13] Unlike these findings, when we used the predictive value of 86.25 (AUC: 0.699, p=0.03) for the eGFR in the differential diagnosis of SRMs, in the univariate analysis, we observed that eGFR (OR: 0.951, p=0.026) was a significant marker.

Limitations of the Study

The main limiting factors are the retrospective design of our study, the small number of patients, therefore no randomization, limited statistical analysis, short follow-up times, and single-center follow-up results.

Conclusion

The rate of benign pathology detection in incidentally detected small solid renal masses is up to 15-30%. Although attempts are made to increase the predictive power in differential diagnosis with advanced imaging techniques and diagnostic biopsies, in cases whose malignancy suspicion cannot be precisely excluded, the surgeries performed cause nephron losses. We think that we can detect benign masses with higher predictive power using NLR, PLR, MPV and Framingham score in these masses where malignancy cannot be distinguished clinically, thus preventing nephron losses caused by unnecessary nephrectomies.

Disclosures

Ethics Committee Approval: Due to the retrospective design of our study, ethics committee approval was not obtained, and all procedures in our study were conducted in accordance with the ethical standards of the institutional and national research committee involving human participants and the principles of the Declaration of Helsinki.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – I.S.; Design – H.B.; Supervision – H.B.; Materials – H.B.; Data collection &/or processing – I.S.; Analysis and/or interpretation – I.S. H.B.; Literature search – I.S.; Writing – I.S.; Critical review – H.B.

References

1. Lim RS, McInnes MDF, Siddaiah M, Flood TA, Lavallee LT, Schieda N. Are growth patterns on MRI in small (< 4 cm) solid renal masses useful for predicting benign histology? Eur Radiol 2018;28:3115–24. [CrossRef]

2. Schachter LR, Cookson MS, Chang SS, Smith JA Jr, Dietrich MS, Jayaram G, et al. Second prize: frequency of benign renal cortical tumors and histologic subtypes based on size in a contemporary series: what to tell our patients. J Endourol 2007;21:819–23.
3. Sohlberg EM, Metzner TJ, Leppert JT. The Harms of overdiagnosis and overtreatment in patients with small renal masses: a mini-review. Eur Urol Focus 2019;5:943–5. [CrossRef]
4. Frank I, Blute ML, Cheville JC, Lohse CM, Weaver AL, Zincke H. Solid renal tumors: an analysis of pathological features related to tumor size. J Urol 2003;170:2217–20. [CrossRef]
5. Song JB, Morrissey JJ, Mobley JM, Figenshau KG, Vetter JM, Bhayani SB, et al. Urinary aquaporin 1 and perilipin 2: Can these novel markers accurately characterize small renal masses and help guide patient management? Int J Urol 2019;26:260–5.
6. Hoang UN, Mojdeh Mirmomen S, Meirelles O, Yao J, Merino M, Metwalli A, et al. Assessment of multiphasic contrast-enhanced MR textures in differentiating small renal mass subtypes. Abdom Radiol (NY) 2018;43:3400–9. [CrossRef]
7. Menogue SR, O'Brien BA, Brown AL, Cohen RJ. Percutaneous core biopsy of small renal mass lesions: a diagnostic tool to better stratify patients for surgical intervention. BJU Int 2013;111:E146–51. [CrossRef]
8. Leveridge MJ, Finelli A, Kachura JR, Evans A, Chung H, Shiff DA, et al. Outcomes of small renal mass needle core biopsy, nondiagnostic percutaneous biopsy, and the role of repeat biopsy. Eur Urol 2011;60:578–84. [CrossRef]
9. Park SY, Jeon SS, Lee SY, Jeong BC, Seo SI, Lee HM, et al. Incidence and predictive factors of benign renal lesions in Korean patients with preoperative imaging diagnoses of renal cell carcinoma. J Korean Med Sci 2011;26:360–4. [CrossRef]
10. Levy D, Wilson PW, Anderson KM, Castelli WP. Stratifying the patient at risk from coronary disease: new insights from the Framingham Heart Study. Am Heart J 1990;119:712–7. [CrossRef]
11. Tekkesin N, Kılınc C, Ökmen AS. Investigation of Framingham Risk Factors in Turkish adults. J Clin Exp Invest 2011;2:42–9. [CrossRef]
12. Kannel WB, McGee D, Gordon T. A general cardiovascular risk profile: the Framingham Study. Am J Cardiol 1976;38:46–51. [CrossRef]
13. Kaushik D, Kim SP, Childs MA, Lohse CM, Costello BA, Cheville JC, et al. Overall survival and development of stage IV chronic kidney disease in patients undergoing partial and radical nephrectomy for benign renal tumors. Eur Urol 2013;64:600–6. [CrossRef]
14. Weight CJ, Lieser G, Larson BT, Gao T, Lane BR, Campbell SC, et al. Partial nephrectomy is associated with improved overall survival compared to radical nephrectomy in patients with unanticipated benign renal tumours. Eur Urol 2010;58:293–8. [CrossRef]
15. Kutikov A, Fossett LK, Ramchandani P, Tomaszewski JE, Siegelman ES, Banner MP, et al. Incidence of benign pathologic findings at partial nephrectomy for solitary renal mass presumed to be renal cell carcinoma on preoperative imaging. Urology 2006;68:737–40. [CrossRef]
16. Khan AA, Shergill IS, Quereshi S, Arya M, Vandal MT, Gujral SS. Percutaneous needle biopsy for indeterminate renal masses: a national survey of UK consultant urologists. BMC Urol 2007;7:10.
17. Yang CS, Choi E, Idrees MT, Chen S, Wu HH. Percutaneous biopsy of the renal mass: FNA or core needle biopsy? Cancer Cytopathol 2017;125:407–15. [CrossRef]
18. Marconi L, Dabestani S, Lam TB, Hofmann F, Stewart F, Norrie J, et al. Systematic review and meta-analysis of diagnostic accuracy of percutaneous renal tumour biopsy. Eur Urol 2016;69:660–73.
19. Ljungberg B, Albiges L, Bensalah K, Bex A, Giles RH, Hora M, et al. European Association of Urology guidelines on renal cell carcinoma: the 2019 Update. Arnhem, The Netherlands: EAU Guidelines Office. Available at: http://uroweb.org/guidelines/compilations-of-all-guidelines/. Accessed Apr 01, 2019.
20. Breau RH, Crispen PL, Jenkins SM, Blute ML, Leibovich BC. Treatment of patients with small renal masses: a survey of the American Urological Association. J Urol 2011;185:407–13. [CrossRef]
21. Lane BR, Samplaski MK, Herts BR, Zhou M, Novick AC, Campbell SC. Renal mass biopsy-a renaissance? J Urol 2008;179:20–7.
22. Richard PO, Jewett MA, Bhatt JR, Kachura JR, Evans AJ, Zlotta AR, et al. Renal Tumor Biopsy for Small Renal Masses: A Single-center 13-year Experience. Eur Urol 2015;68:1007–13. [CrossRef]
23. Bernstein AP, Fram EB, Sankin A, Kovac E, Srivastava A, DiVito J, et al. A comparison of perinephric fat surface area and Mayo Adhesive Probability score in predicting malignancy in T1 renal masses. Urol Oncol 2018;36:499.e17–499.e22. [CrossRef]
24. Li A, Xing W, Li H, Hu Y, Hu D, Li Z, et al. Subtype differentiation of small (≤ 4 cm) solid renal mass using volumetric histogram analysis of DWI at 3-T MRI. AJR Am J Roentgenol 2018;211:614–23.
25. Gaing B, Sigmund EE, Huang WC, Babb JS, Parikh NS, Stoffel D, et al. Subtype differentiation of renal tumors using voxel-based histogram analysis of intravoxel incoherent motion parameters. Invest Radiol 2015;50:144–52. [CrossRef]
26. Cornelis F, Tricaud E, Lasserre AS, Petitpierre F, Bernhard JC, Le Bras Y, et al. Routinely performed multiparametric magnetic resonance imaging helps to differentiate common subtypes of renal tumours. Eur Radiol 2014;24:1068–80. [CrossRef]
27. Rosenkrantz AB, Hindman N, Fitzgerald EF, Niver BE, Melamed J, Babb JS. MRI features of renal oncocytoma and chromophobe renal cell carcinoma. AJR Am J Roentgenol 2010;195:W421–7.
28. Finelli A, Ismaila N, Bro B, Durack J, Eggener S, Evans A, et al. Management of Small Renal Masses: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2017;35:668–80.
29. Yoo S, You D, Song C, Hong B, Hong JH, Kim CS, et al. Declining incidence of benign lesions among small renal masses treated with surgery: Effect of diagnostic tests for characterization. Urol Oncol 2018;36:362.e9–362.e15. [CrossRef]
30. Morrissey JJ, Mobley J, Song J, Vetter J, Luo J, Bhayani S, et al. Urinary concentrations of aquaporin-1 and perilipin-2 in patients with renal cell carcinoma correlate with tumor size and stage but not grade. Urology 2014;83:256.e9–14. [CrossRef]
31. Grimes N, Hannan C, Tyson M, Thwaini A. The role of neutro-

phil-lymphocyte ratio as a prognostic indicator in patients undergoing nephrectomy for renal cell carcinoma. Can Urol Assoc J 2018;12:E345–8. [CrossRef]
32. Boissier R, Campagna J, Branger N, Karsenty G, Lechevallier E. The prognostic value of the neutrophil-lymphocyte ratio in renal oncology: a review. Urol Oncol 2017;35:135–41. [CrossRef]
33. Atılgan CÜ, Şendül SY, Kösekahya P, Çağlayan M, Alkan A, Güven D, et al. Evaluation of neutrophil-to-lymphocyte ratio and mean platelet volume in patients with active and inactive thyroid orbitopathy. Sisli Etfal Hastan Tip Bul 2018;52:26–30.
34. Bulut S, Aktas BK, Erkmen AE, Ozden C, Gokkaya CS, Baykam MM, et al. Metabolic syndrome prevalence in renal cell cancer patients. Asian Pac J Cancer Prev 2014;15:7925–8. [CrossRef]
35. Lafci A. Determination of factors related to perioperative mortality in cardiovascular surgery. Sisli Etfal Hastan Tip Bul 2017;51:109–14. [CrossRef]
36. Kriegmair MC, Mandel P, Porubsky S, Dürr J, Huck N, Nuhn P, et al. Metabolic syndrome negatively impacts the outcome of localized renal cell carcinoma. Horm Cancer 2017;8:127–34. [CrossRef]
37. Kocher NJ, Rjepaj C, Robyak H, Lehman E, Raman JD. Hypertension is the primary component of metabolic syndrome associated with pathologic features of kidney cancer. World J Urol 2017;35:67–72. [CrossRef]
38. Eskelinen TJ, Kotsar A, Tammela TLJ, Murtola TJ. Components of metabolic syndrome and prognosis of renal cell cancer. Scand J Urol 2017;51:435–41. [CrossRef]
39. Russo P, Huang W. The medical and oncological rationale for partial nephrectomy for the treatment of T1 renal cortical tumors. Urol Clin North Am 2008;35:635–43. [CrossRef]
40. Kambara T, Tanimoto R, Araki M, Saika T, Hashimoto H, Oeda T, et al. Renal function after nephrectomy influences the risk of cardiovascular events. Acta Med Okayama 2018;72:241–7.