Evaluation of the Preoperative Haematological Parameters Predicting the High T-Stage and Fuhrman Grade in Renal Cell Carcinoma

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ABSTRACT

Objective: To investigate the role of cost-effective and widely used hemogram parameters in predicting stage and histological grade.

Study Design: An analytical study.

Place and Duration of Study: Konya Research and Training Hospital, Turkey from January to June 2020.

Methodology: Pre-nephrectomy hemogram parameters and post-nephrectomy pathology reports of 180 renal cell carcinoma patients, among 553 patients, who had undergone nephrectomy between 2009-2019 were evaluated. The patients were grouped as low risk and high risk in terms of TNM stage and Fuhrman grade; and clinicopathological variables were compared between the groups. Multivariate logistic regression analysis was used to determine the parameters predicting independently the high T stage (T3-T4) and the high Fuhrman grade (G3-G4).

Results: While 31 (17.2%) of 180 patients were in the high T stage; 69 (38.3%) were in the high Fuhrman grade. In the logistic regression analysis, NLR, LMR, and hematocrit predicted independently high T stage, while hematocrit and LMR predicted independently the high Fuhrman grade.

Conclusion: LMR, NLR, and hematocrit were found to be more significant than other parameters, which are among the hemogram parameters that can guide clinicians during staging, which is important for prognosis and treatment decisions.

Key Words: Renal cell carcinoma, Tumor staging, Tumor grading.

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INTRODUCTION

In 2018, among all cancers in the world, kidney cancers ranked 14th with 403,262 new cases; and ranked 16th in cancer-related mortality with 175,098 deaths. Survival rates have increased 2-fold in the last 50 years due to curative surgical approaches, early detection of tumours in smaller sizes, and highly effective systemic treatments. Although surgical resection can be curative in localised disease. Since the renal cell carcinoma (RCC) is silent due to its nature, it cannot be diagnosed until it is locally advanced and unresectable or metastatic in approximately one-third of the newly diagnosed cases; between 10 and 30 per cent of nephrectomy cases due to undetected micrometastases return with local recurrence or distant metastasis.[1]

The stage and prognosis in RCC vary depending on anatomical, clinical, histological and molecular factors.[2] The presence of many cytokines, released from the renal tumour with immuno-suppressive properties, affecting the immune system and bone marrow, is important in terms of providing more information about active cancer in the hemogram examinations performed before nephrectomy. There are many studies on this subject because of the cost-effectiveness and widespread use of hemogram parameters, which are affected by all factors related to particularly systemic treatment, stage and prognosis.

The use of laboratory parameters as supportive in addition to imaging methods in determining the prognosis of the disease is important for the follow-up and treatment of the patient. Thus, the aim of this study was to investigate the roles of pre-nephrectomy hemogram parameters in predicting both the high Fuhrman grade (FG) and high T-stage.

METHODOLOGY

After obtaining ethical approval, the clinicopathological data of 180 kidney cancer patients diagnosed with renal cell cancer carcinoma, who underwent partial or total nephrectomy between 2009-2019, were evaluated retrospectively. The

study was conducted in Konya Research and Training Hospital, Turkey between January 2020 and June 2020. Patients with history of other haematological or solid organ malignancies, autoimmune diseases, inflammatory diseases, infectious diseases and whose Fuhrmann grade was not specified in the pathology report, and those under 18 years of age, were excluded from the study.

Preoperative hemogram parameters include hemoglobin, hematocrit (HCT), red blood cell count (RBC), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), platelet, mean platelet volume (MPV), plateletcrit (PCT), platelet distribution width (PDW), white blood cell count (WBC), neutrophil, lymphocyte, monocyte, basophil and eosinophil counts were evaluated according to the postoperative pathology report results. Platelet to lymphocyte ratio (PLR), neutrophil to lymphocyte ratio (NLR), and lymphocyte to monocyte ratio (LMR) were calculated.

Pathological staging was done according to the American Joint Committee on Cancer (AJCC); 8th Edition. Histological subtypes were determined according to the 1997 WHO Heidelberg classification, and tumour nuclear grading was performed according to the Fuhrman nuclear grading system. The patients were classified as the low stage (T1-T2) and high stage (T3-T4), according to their pathological results. The patients were also classified according to the Fuhrman grade as low grade (G1-G2) and high grade (G3-G4).

Statistical analysis was performed with SPSS version 25.0 (SPSS Inc., Chicago, Illinois, USA). The clinicopathological variables of the patients were first evaluated in terms of normal distribution by the Kolmogorov-Smirnov test. Normally distributed variables were shown as mean ± standard deviation, while non-normally distributed variables were shown as median (minimum--maximum). Numeric variables were compared with Student's t-test or Mann-Whitney U-test, according to normal distribution status; and the categorical variables were compared with Chi-square or Fisher's Exact test, according to their suitability.

Receiver operating curve (ROC) analysis was performed to determine the area under curve (AUC), cut-off values, sensitivity, and specificities of the variables that were found to be significant between the groups. In addition, logistic regression analysis was performed to determine the parameters indicating stage and nuclear grade, independently among the variables that were found to be statistically significant between the groups in terms of stage and nuclear grade. Statistically, p <0.05 was considered significant.

RESULTS

Of the 180 patients analysed, 78 were females (43.3%) and 102 were males (56.7%). The mean age of the patients at the time of nephrectomy was 60.6 ± 15.4 years. According to tumor pathological staging, 82.8% of the patients were in the low stage, while 17.2% of them were in the high stage. According to the histopathological nuclear grading, 61.7% of the patients were in the low grade, while 38.3% of them were in the high grade. The groups were compared in terms of clinicopathological characteristics (Table I).

There was no statistically significant difference between the low T stage and high T stage groups in terms of age, gender and histological subtype. Among the hemogram parameters, hematocrit (p = 0.045), NLR (p <0.001), LMR (p = 0.005), neutrophil percentage (p = 0.044), and lymphocyte percentage (p=0.012) were statistically significantly different between the two groups (Table I).

There was no statistically significant difference between low Fuhrman grade and high Fuhrman grade groups in terms of age and gender. When the groups were compared in terms of histological subtypes, it was seen that the mixed type in the other category was more in the Fuhrman high-grade group. Among the hemogram parameters, haemoglobin (p = 0.001), hematocrit (p = 0.001), red blood cell count (RBC) (p = 0.008), red cell distribution wide (RDW) (p = 0.007), PLR (p = 0.046), NLR (p = 0.011), monocyte count (p = 0.036), and LMR (p = 0.006) were statistically significantly different between the groups (Table I).

NLR, LMR, and haemoglobin were statistically different between low and high groups in both T staging and Fuhrman grading. In logistic regression analysis, NLR (OR: 6.268) (2.088-18.816) (p = 0.001) and percentage of neutrophils (OR: 0.869) (0.777-0.971) (p = 0.013) were found as haematological parameters independently indicating the high T stage. Haemoglobin (OR: 0.804) (0.695-0.930) (p = 0.003) and LMR (OR: 0.761) (0.618-0.937) (p = 0.010) were also found as haematological parameters that independently showed the high Fuhrman nuclear grade (Table II).

In ROC analysis indicating the high T stage, while hematocrit (cut-off ≤43.7) (AUC: 0.615 (0.539-0.686) (p = 0.040), NLR (cut-off >3.5) (AUC: 0.634 (0.559-0.704) (p = 0.029), LMR (cut-off ≤3.1) (AUC:0.662) (0.588-0.731) (p = 0.006), and lymphocyte percentage (cut-off ≤20.5) (AUC: 0.644) (0.570-0.71 4) (p = 0.017) were statistically significant. The percentage of neutrophils (cut-off >62.5) (AUC: 0.607 (0.531-0.679) (p = 0.086) was statistically insignificant but at borderline. In indicating the high Fuhrman grade, while RDW (cut-off >13.3) (AUC: 0.620) (0.545-0.691) (p = 0.004), hematocrit (cut-off ≤40.3) (AUC: 0.642 (0.568-0.712) (p <0.001), haemoglobin (cut-off ≤14.8) (AUC: 0.643 (0.568-0.713) (p <0.001), RBC (cut-off ≤ 5.05) (AUC: 0.636 (0.561-0.706) (p = 0.001), and LMR (cut-off ≤2.9) (AUC: 0.622 (0.547-0.693) (p = 0.004) were statistically significant; monocyte count (cut-off >0.48) (AUC: 0.580 (0.504-0.653) (p = 0.066), and PLR (cut off >186.6) (AUC: 0.589 (0.513-0.661) (p = 0.051) were statistically insignificant but at borderline (Table III).

DISCUSSION

Despite advances in diagnostic methods, routine diagnosis and prognostic evaluation of RCC is still performed with pathological tissue examination and traditional clinicopathological prognostic variables.

Table I: Clinical characteristics according to T-stage and Fuhrman grade (low *vs.* high).

	Total (n=180)	Low stage (T 1-2) (n=149)	High stage (T 3-4) (n=31)	p-value	Low grade (Fuhrman 1-2) (n=111)	High grade (Fuhrman 3-4) (n=69)	p-value
Age	60.6±15.4	60.7±15.2	59.8±16.6	0.758	60.4±16.1	60.7±14.2	0.897
Gender				0.171			0.975
Female	78(43.3%)	68(45.6%)	10(32.3%)		48(43.2%)	30(43.5%)	
Male	102(56.7%)	81(54.4%)	21(67.7%)		63(56.8%)	39(56.5%)	
Histology				0.133			0.006
Clear cell	116(64.4%)	99(66.4%)	17(54.8%)		77(69.4%)	39(56.5%)	
Papillary	29(16.1%)	23(15.4%)	6(19.4%)		17(15.3%)	12(17.4%)	
Chromophobe	14(7.8%)	13(8.7%)	1(3.2%)		11(9.9%)	3(4.3%)	
Others	21(11.7%)	14(9.4%)	7(22.6%)		6(5.4%)	15(21.7%)	
Haemoglobin	14(6.4-18.3)	14.1(6.4-18.3)	13.6(8.1-17.6)	0.114	14.4(8.1-18.3)	13.5(6.4-16.7)	0.001
Low haemoglobin*	37(20.6%)	26(17.4%)	11(35.5%)	0.024	17(15.3%)	20(29%)	0.024
High haemoglobin	143(79.4%)	123(82.6%)	20(64.5%)		94(84.7%)	49(71%)	
Hematocrit	42.2(21.2-57.6)	42.3(21.2-57.6)	41.5(26.3-50.3)	0.045	43(24.7-57.6)	41.2(21.2-50.2)	0.001
Low hematocrit**	40(22.2%)	28(18.8%)	12(38.7%)	0.015	18(16.2%)	22(31.9%)	0.014
High hematocrit	140(77.8%)	121(81.2%)	19(61.3%)		93(83.8%)	47(68.1%)	
RBC	4.9±0.7	4.9±0.6	4.7±0.8	0.112	5±0.6	4.7±0.7	0.008
MCV	86.2(61.1-103.5)	86.3(61.6-103.5)	84.9(61.1-102.9)	0.293	86.4(61.6-103.5)	84.9(61.1-102.9)	0.245
MCH	28.7(18-33.2)	28.7(19.4-33.2)	28.6(18-33.1)	0.420	28.9(19.4-33.2)	27.9(18-33.1)	0.109
MCHC	33±1.5	33±1.4	33±1.6	0.853	33.2±1.4	32.7±1.5	0.064
RDW	14.1(11.7-33.4)	14.1(11.7-33.4)	14.1(12.3-19.4)	0.997	13.8(11.7-33.4)	14.5(12.7-32)	0.007
Platelet	293.3±91.8	293.2±88.7	294.1±107.3	0.960	283.7±81.9	308.8±104.6	0.074
PLR	126.5(10.8-471.1)	123.9(10.8-462.4)	137.3(68.6-471.1)	0.133	123.2(10.8-289.4)	137.2(68.6-471.1)	0.046
MPV	10.1(6.6-13)	10.1(6.6-13)	10.2(8.4-12)	0.295	10.1(6.6-13)	10.1(6.8-12.2)	0.934
WBC	7.8(3.8-17.1)	7.8(3.9-17.1)	7.2(3.8-15.5)	0.953	7.7(4.2-17.1)	7.8(3.8-15.5)	0.693
Neutrophil	4.9±1.6	4.8±1.4	5.4±2.4	0.085	4.8±1.4	5.1±1.9	0.224
Lymphocyte	2.2(0.8-12.9)	2.3(1-12.9)	2(0.8-4.1)	0.063	2.3(1.1-12.9)	2.1(0.8-4.6)	0.118
NLR	2.3±1.1	2.2±0.7	3.1±2.1	<0.001	2.2±0.7	2.6±1.6	0.011
Monocyte	0.6±0.2	0.6±0.2	0.7±0.2	0.112	0.6±0.2	0.7±0.2	0.036
LMR	3.7(0.9-18.9)	3.7(1.6-18.9)	2.9(0.9-7.1)	0.005	3.8(1.6-18.9)	3.3(0.9-7.9)	0.006
Basophil	0(0-0.2)	0(0-0.2)	0(0-0.1)	0.468	0(0-0.2)	0(0-0.1)	0.369
Neutrophil %	61±8.3	60.4±7.8	63.7±10	0.044	60.3±8.1	62.1±8.5	0.147
Lymphocyte %	28.9(7.2-75.1)	29.6(16.5-75.1)	25.4(7.2-44.8)	0.012	29.6(17.6-75.1)	27.4(7.2-44.8)	0.134
Monocyte %	7.7(1.7-16.6)	7.6(1.7-13.7)	8.3(4.8-16.6)	0.230	7.6(1.7-13.3)	8(4.8-16.6)	0.074
Basophil %	0.4(0-2.9)	0.4(0-2.9)	0.4(0-0.7)	0.331	0.4(0-2.9)	0.4(0-1.2)	0.370
PCT	0.3(0.1-0.6)	0.3(0.1-0.6)	0.3(0.2-0.6)	0.417	0.3(0.1-0.5)	0.3(0.1-0.6)	0.265
PDW	12.3(9.5-57.2)	12.4(9.5-57.2)	12(9.7-52.5)	0.291	12.2(9.5-57.2)	12.6(9.7-52.5)	0.861
Eosinophil	0.1(0-1.1)	0.1(0-1.1)	0.2(0-0.6)	0.594	0.1(0-1.1)	0.1(0-0.6)	0.261
Eosinophil %	1.7(0-8.8)	1.7(0-8.1)	2.1(0.1-8.8)	0.976	1.9(0-8.1)	1.6(0-8.8)	0.233

Data were shown as number (per cent) for categoric variables and median (minimum-maximum) for numeric skewed distributed variables and mean ± standard deviation for numeric normally distributed variables. Numeric variables were compared with Student's t-test or Mann-Whitney U-test according to normal distribution status, and categorical variables were compared with chi-square or exact test according to their suitability. *Defined low as haemoglobin <11 g/dL for female and haemoglobin <13 g/dL for male. **Defined low as hematocrit <35% for female and hematocrit <40% for male.

Table II: Determination of haematological parameters that independently predict the high stage and grade.

	OR	95% CI	p-value
T stage (low versus high)[1]			
Neutrophil %	0.869	0.777-0.971	0.013
NLR	6.268	2.088-18.816	0.001
Constant	13.951		0.257
Fuhrman grade (low versus high)[2]			
Haemoglobin	0.804	0.695-0.930	0.003
LMR	0.761	0.618-0.937	0.010
Constant	35.057		0.001

OR: Odds ratio, CI: Confidence interval, NLR: Neutrophil to lymphocyte ratio, LMR: Lymphocyte to monocyte ratio.

[1]*Logistic regression Backward Stepwise (Likelihood Ratio); χ2 (2) = 19.207, p <0.001, Nagelkerke R Square=0.168; Hct, Hct subgroup, Hgb subgroup, Neutrophil, Lymphocyte, NLR, LMR and Neutrophil % are included in multivariate analyses. The last step (step 7) is shown in the Table.*

[2]*Logistic Regression Backward Stepwise (Likelihood Ratio); χ2 (2) = 19.873, p <0.001, Nagelkerke R Square=0.142 Histology, haemoglobin, haemoglobin subgroup, hematocrit, hematocrit subgroup, RBC, MCHC, RDW, Plt, PLR, NLR, Monocyte, LMR, Monocyte % are included in multivariate analyses. The last step (step 13) is shown in the Table.*

New molecular diagnostic methods cannot be used routinely because of the high costs, the time-consuming preparation of the samples to be examined, and the lack of sufficient clinical data on how these new molecular markers might affect both diagnostic and therapeutic decisions.[3] For this reason, widespread use, cost-effectiveness, and easy evaluation make hemogram parameters to be more preferred in RCC risk assessment.[4]

Increasing scientific evidence shows that systemic inflammatory response plays an important role in all stages of malignancies from the onset to progression. Various inflammatory response markers such as NLR, LMR, PLR, platelet count, and C-reactive protein (CRP) are used as potential prognostic factors in RCC patients.

Table III: Receiver operating characteristic (ROC) analysis of haematological parameters to predict stage and grade.

	Cut off	AUC	95% CI	Sensitivity	Specificity	Maximum Youden index	p-value
T stage (low versus high)							
RDW	≤13.3	0.500	0.425-0.562	19.4%	71.1%	0.095	0.996
PCT	>0.4	0.554	0.465-0.641	30.4%	84.3%	0.147	0.443
PLT	≤185	0.519	0.444-0.594	22.6%	90.6%	0.132	0.763
Neutrophil	>7.0	0.536	0.460-0.610	25.8%	93.3%	0.191	0.580
MPV	>10.3	0.560	0.484-0.634	45.2%	67.8%	0.130	0.292
NLR	>3.5	0.634	0.559-0.704	29.0%	97.3%	0.263	0.029
LMR	≤3.1	0.662	0.588-0.731	58.1%	75.5%	0.325	0.006
Hematocrit	≤43.7	0.615	0.539-0.686	83.9%	39.6%	0.235	0.040
Neutrophil %	>62.5	0.607	0.531-0.679	64.5%	59.1%	0.236	0.086
Lymphocyte %	≤20.5	0.644	0.570-0.714	32.3%	93.3%	0.256	0.017
PLR	>186.8	0.586	0.510-0.659	32.3%	88.6%	0.209	0.158
Fuhrman grade (low versus high)							
RDW	>13.3	0.620	0.545-0.691	87.0%	36.1%	0.230	0.004
PCT	>0.3	0.559	0.469-0.645	38.3%	81.0%	0.193	0.288
PLT	>309	0.571	0.495-0.644	52.2%	67.6%	0.197	0.125
Neutrophil	>5.8	0.537	0.461-0.611	33.3%	83.8%	0.171	0.428
MPV	>7.9	0.504	0.428-0.579	97.1%	9.0%	0.061	0.934
NLR	>3.3	0.564	0.489-0.638	23.2%	92.8%	0.160	0.160
HCT	≤40.3	0.642	0.568-0.712	47.8%	75.7%	0.235	<0.001
HGB	≤14.8	0.643	0.568-0.713	82.6%	39.6%	0.223	<0.001
RBC	≤5.05	0.636	0.561-0.706	72.5%	54.1%	0.265	0.001
Monocyte	>0.48	0.580	0.504-0.653	82.6%	33.3%	0.160	0.066
LMR	≤2.9	0.622	0.547-0.693	37.7%	84.7%	0.223	0.004
PLR	>186.6	0.589	0.513-0.661	27.5%	91.9%	0.194	0.051

RDW: Red cell distribution width, PCT: Plateletcrit PLT: Platelet, MPV: Mean platelet volume, NLR: Neutrophil to lymphocyte ratio, LMR: Lymphocyte to monocyte ratio, PLR: Platelet to lymphocyte ratio.

Tumour-associated macrophages are produced from circulating monocytes *via* chemokines produced in the tumour microenvironment. These tumour-associated macrophages play a role in increased angiogenesis, tumour invasion, and poor prognosis in many types of cancer.[5] Potential biomarkers such as tumour-associated macrophages and the absolute lymphocyte/monocyte ratio in peripheral blood are well documented in predicting the clinical outcome of malignancies such as colorectal cancers, sarcomas, and lymphoid neoplasms. In some studies, it has been shown that LMR has a prognostic value in postoperative non-metastatic RCC patients.[3,6] LMR was also found to be an important prognostic determinant in many different studies. Liangyou *et al.* also demonstrated that both haemoglobin and LMR are independent prognostic factors in predicting overall survival (OS) in patients with mRCC.[7] The fact that LMR and haemoglobin, as independent predictors for high Fuhrman grade in this study, support the Fuhrman grade may be more important than T staging in determining the prognosis of RCC for clinicians.

The prognostic role of anaemia in operated RCC patients is still not clearly defined. Anaemia is quite common in malignancies, including RCC. Karakiewicz *et al.* emphasised that preoperative haemoglobin level predicted RCC-specific mortality in all-stage RCC patients.[8] In a meta-analysis, a significant increase was found in all-cause mortality, cancer-specific mortality, and disease recurrence in anaemic patients compared to non-anaemic patients, according to preoperative haemoglobin values.[9]

Seda *et. al.* showed that low hematocrit levels were associated with poor survival in surgically treated RCC patients.[10] Although there are studies on the importance of low hematocrit levels in cancers such as lung cancer, colon cancer, and oesophagal cancer, no other comprehensive study was found in the literature showing the importance of low hematocrit in RCC. In this study, the association of anemia with higher grade and stage indirectly indicates poor prognosis in RCC.

While high RDW values are a poor prognostic factor in some types of cancer, it has also been shown to be a negative predictor for cancer-specific survival and OS in some types of cancer. Some studies have shown the prognostic importance of RDW value in urological cancers.[11-13] In their study, Kisa *et al.* found that high RDW value was associated with high FG and kidney-limited T stage.[14] In this study, while there was a relationship between RDW and high FG, there was no relationship between RDW and high T stage; which suggests that high FG is more important in terms of prognosis.

High neutrophil levels cause the release of free oxygen radicals that provide a microenvironment for tumour invasion and metastasis, trigger cell DNA damage, and genetic instability.[15] The decrease in lymphocyte count plays a role in the inflammatory response in tumour biology. While lymphopenia shows the impaired cell-mediated immune system, neutrophilia shows the response to systemic inflammation. NLR, which is obtained by dividing the neutrophil number by the number of lymphocytes, is important for

cancers in this respect. Some studies emphasise the increased prognostic value of NLR, especially in malignancies such as colorectal cancers and HCC.[16,17] In the studies conducted, the high pretreatment NLR rate in RCC indicates that the clinical course will be worse.[18] In this study, the authors showed NLR was significant in predicting the higher FG and the higher T stage. In this regard, Kisa *et al.* also showed that NLR is significant in predicting both the T stage and the Fuhrman grade.[14]

According to the 2016 WHO classification, RCC is divided into histological types such as clear cell, papillary, chromophobe, collecting duct, *etc*. While the clear cell histological subtype is the most common, and has the best prognosis, other subtypes and especially those with sarcomatoid differentiations are more aggressive. Viers *et al.* divided kidney tumours into histological subtypes as benign and malignant tumours.[19] They could not find a significant difference in terms of NLR levels between subtypes of benign kidney tumours. However, they found a significant difference between malignant subtypes in terms of NLR levels. In their study, they found the lowest NLR rate in the clear cell cancer subtype and the highest NLR rate in the collecting duct cell subtype, and this difference was statistically significant. In this study, while the authors found a difference in high FG in terms of histological subgroups, they did not find a difference in terms of high T stage.

Numerous studies have shown that pretreatment PLR is a predictive factor in the metastatic RCC patients.[20] The prognostic significance of PLR has been investigated in few studies performed on non-metastatic RCC patients.[21,22] Studies are showing that PLR, a potential marker of the systemic inflammatory response, can predict clinical outcomes in metastatic RCC patients treated with tyrosine kinase inhibitör (tKI).[23-25] In the present study, the relationship between PLR and high FG, reminds the importance of high FG in terms of prognosis. Prospective studies with a larger number of patients are needed on this subject.

CONCLUSION

LMR, NLR, and haemoglobin were found to be more significant than other parameters, which are among the hemogram parameters that can guide clinicians in predicting stage and determining prognosis and treatment plan. Clinicians are advised to be conscious with regard to micrometastases that cannot be seen in the staging of nephrectomised patients with LMR ≤2.9, and to consider this value in planning and monitoring systemic treatment.

ETHICAL APPROVAL:
The study was approved by the local Ethics Committee of the Selcuk University (2019-335) prior to the initiation of the research work; and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

PATIENTS' CONSENT:
The informed and written consents of the patients were signed by the patients before the beginning of the study.

CONFLICT OF INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
IO: Conseptualisation, methodology, investigation, formal analysis, writing and original draft preparation.
FS: Conseptualisation, methodology, software, formal analysis, writing and original draft preparation, visualisation, writing review and editing, supervision.
DO: Investigation, visualisation.

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