THE MEDICAL BULLETIN OF
SISLI ETFAL HOSPITAL

DOI: 10.14744/SEMB.2023.14306
Med Bull Sisli Etfal Hosp 2023;57(2):250–256

Original Research

The Role of Serum Inflammation-Based Scores in Diagnosis and Assessing Remission in Cushing's Disease

Muhammed Masum Canat,[1] Ceren Yarkutay Turkkan,[2] Hazan Erhan,[2] Feyza Yener Ozturk,[1] Yuksel Altuntas[1]

[1]Department of Endocrinology and Metabolism, University of Health Sciences Türkiye, Sisli Hamidiye Etfal Training and Research Hospital, Istanbul, Türkiye
[2]Department of Internal Medicine, University of Health Sciences Türkiye, Sisli Hamidiye Etfal Training and Research Hospital, Istanbul, Türkiye

ABSTRACT

Objectives: Chronic hypercortisolism causes diverse alterations in the immune system and inflammatory disruptions. Serum inflammation-based scores (SIBS) are indicators of systemic inflammatory status. This study aims to determine the role of SIBS in the diagnosis and evaluation of remission in patients with Cushing's disease (CD).

Methods: This retrospective cross-sectional study was conducted on 195 participants; 52 patients diagnosed and followed up after treatment with CD, 65 patients with subclinical Cushing's syndrome (SCS), and 78 healthy individuals whose complete blood counts (CBC) were obtained for analysis. Participants with additional diseases or drug use that could affect CBC were excluded from the study. SIBS of the three groups were compared. Scores considered were neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII). The correlations between SIBS and initial diagnostic tests for hypercortisolism were analyzed. The SIBS of patients with CD at the diagnosis were compared with those after remission. In addition, receiver operator characteristic curve analyses were used to determine the diagnostic accuracy, specificity, and sensitivity of the scores significantly high in the CD group.

Results: MLR and SII values were significantly higher in CD patients than in the healthy group ($p<0.01$). NLR and SII were significantly higher in patients with CD than those with SCS ($p<0.05$). There were no significant differences between the SCS and the control groups in all SIBS. We determine significant, positive, and moderately correlated findings between SIBS and initial diagnostic tests for hypercortisolism in the CD group ($0.30<r<0.70$; $p<0.05$). All of the scores evaluated were significantly lower in the remission of the disease compared to the active period ($p<0.001$). An optimal cut-off MLR value of 0.20 showed the best diagnostic value ($p=0.003$; sensitivity, 78.4%; specificity, 51.4%), and an optimal cut-off SII value of 776.20 showed the best diagnostic value ($p=0.017$; sensitivity, 54.9%; specificity, 70.0%).

Conclusion: The SIBS, which can be easily calculated with the data obtained from CBC and do not have additional costs, can contribute to the diagnosis and assessment of remission in patients with CD.

Keywords: Cushing's disease, monocyte-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, serum inflammation-based scores, systemic immune-inflammation index

Please cite this article as "Canat MM, Yarkutay Turkkan C, Erhan H, Yener Ozturk F, Altuntas Y. The Role of Serum Inflammation-Based Scores in Diagnosis and Assessing Remission in Cushing's Disease. Med Bull Sisli Etfal Hosp 2023;57(2):250–256".

Address for correspondence: Muhammed Masum Canat, MD. Department of Endocrinology and Metabolism, University of Health Sciences Türkiye, Sisli Hamidiye Etfal Training and Research Hospital, Istanbul, Türkiye
Phone: +90 505 530 18 94 **E-mail:** mmasumcanat@gmail.com

Submitted Date: May 04, 2023 **Revised Date:** May 26, 2023 **Accepted Date:** May 26, 2023 **Available Online Date:** June 20, 2023

Cushing's syndrome (CS) is a serious endocrine disorder characterized by chronic excessive tissue exposure to circulating corticosteroids. External use of synthetic glucocorticoids (GCs) is the most common cause of this syndrome and is called iatrogenic (or exogenous) CS. Endogenous CS is a rare condition resulting from heterogeneous disorders leading to cortisol hypersecretion. The causes of endogenous CS may be divided into those that are corticotropin (ACTH) dependent and those that are ACTH independent. ACTH-dependent CS constitutes 80-85% of all endogenous CS; the most common reason for this rate is excessive ACTH production from a corticotroph adenoma in pituitary gland, called Cushing's disease (CD). The association of chronic hypercortisolemia with several morbidities has been well known, and if left untreated, it significantly negatively impacts survival.[1]

Specific symptoms and signs suggest the possible presence of CS. Unfortunately, none of these are pathognomonic, and many are non-specific (e.g., glucose intolerance, hypertension, menstrual irregularity, and obesity). Consequently, the diagnosis must be confirmed by biochemical tests. The initial diagnostic tests for hypercortisolism are low-dose dexamethasone suppression tests, 24-h urinary-free cortisol (UFC) excretion, late-night salivary cortisol, and late-night serum cortisol. Once the diagnosis is established, additional evaluation is done to identify the cause of the hypercortisolism.[2] However, none of the initial tests have ideal sensitivity or specificity.[3] Therefore, tests would be selected based on the individual's clinical history.

Autonomous glucocorticoid production from incidentally detected adrenal tumors without signs and symptoms of CS is entitled subclinical Cushing's syndrome (SCS). In these patients, glucocorticoid production is supposed to be insufficient to cause CS. Only a minority of patients with SCS progress to overt CS. Therefore, it is recommended to follow these cases without treatment.[4]

GCs play a substantial role in inflammation, and chronic exposure causes various alterations in the immune system. CS is associated with leukocytosis, lymphopenia, monocytopenia, and low eosinophils.[5] After remission, patients significantly recover their blood components.[6]

Serum inflammation-based scores (SIBS) are indicators of systemic inflammatory status and predict outcomes in inflammation-related diseases and cancer.[7] Several SIBS can easily be calculated from complete blood count (CBC) data: Neutrophil-to-lymphocyte ratio (NLR),[8] monocyte-to-lymphocyte ratio (MLR),[9] platelet-to-lymphocyte ratio (PLR),[10] and systemic immune-inflammation index (SII).[11]

Strict conditions concerning sample collection and methods induce difficulties in initial screening testing for the diagnosis of CS, particularly in primary care clinics. Therefore, more readily measurable biomarkers are needed for screening and post-treatment follow-up for CS.

This study aims to determine the role of SIBS in the diagnosis and evaluation of remission in patients with Cushing's disease (CD).

Methods

This retrospective cross-sectional study was conducted on 52 CD patients diagnosed and followed up after treatment in the Endocrinology and Metabolism Clinic between March 2020 and 2023. CS was diagnosed with typical systemic symptoms, physical examination, and laboratory results according to the last guidelines.[2] The diagnosis was confirmed by pathological evaluation after pituitary surgery. Biochemical remission was assessed according to the current guidelines: Post-operative cortisol <1.8 mcg/dL, cortisol <5 mcg/dL measured 3 months after surgery, normal UFC on two different samples, and 1 mg dexamethasone suppression to cortisol <1.8 mcg/dL, as clinically appropriate.[12,13] A total of 65 SCS patients and 78 healthy hospital staff were also included in the study. The diagnosis of SCS is based on the presence of the following three criteria: (I) The patient has an incidentally detected adrenal adenoma; (II) the patient does not have an evident cushingoid phenotype; and (III) endocrine workup shows autonomous (ACTH independent) cortisol secretion.[4,14] Patients diagnosed with SCS have been following up annually without medical or surgical treatment. Healthy individuals, the control group (CG), have had their CBC values checked for health screening in the past 6 months. The exclusion criteria for all individuals were as follows: (I) Patients with hematological or chronic inflammatory disease that may affect CBC; (II) patients with acute/chronic infections; (III) cases who had been taking corticosteroids and immunosuppressants; (IV) age <18 and >70 years old; and (V) pregnancy.

The demographic, laboratory, clinical, and follow-up data of cases were retrieved from the electronic patient records. SIBS were used to assess systemic inflammatory status. The scores, NLR, MLR, PLR, and SII, were calculated using the following formulas: NLR=neutrophils/lymphocytes, MLR=monocytes/lymphocytes, PLR=platelets/lymphocytes, and SII=(neutrophils × platelets)/lymphocytes.[7,11] SIBS of the CD group were compared with the other groups. Correlations between SIBS and initial diagnostic tests for hypercortisolism were analyzed. The scores of cases with CD

at diagnosis were compared with those after remission. In addition, receiver operator characteristic (ROC) curve analyses were used to establish a threshold value for diagnostic accuracy, specificity, and sensitivity of the scores significantly high in the CD group.

Ethical Standards

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The institutional clinical research ethic committee was approved this study protocol on December 13, 2022 (Approval number: 3738).

Statistical Analysis

Statistical analyses were conducted using IBM SPSS® Statistics for Windows, Version 17.0 (IBM Corp. Armonk, NY, USA). The Kolmogorov–Smirnov test was used to determine whether data were normally distributed, and if not, non-parametric assessments were used, including Spearman's correlation of the different variables. Categorical data were reported as percentages and compared using the Chi-square test. In cases where the data did not show normal distribution, Mann–Whitney *U*-test and Kruskal–Wallis *H*-test were used for comparisons. ROC curve analyses were used to obtain the optimal threshold value for a particular variable predicting a certain outcome. $p<0.05$ was considered as statistically significant.

Results

The demographic and laboratory data of all subjects, including 52 CD patients, 65 SCS patients, and 78 healthy subjects, are shown in Table 1. The mean age of the SCS group was significantly higher than the other groups. There was no significant difference in gender between the three groups.

White blood cells (WBC), neutrophils, monocytes, platelets, MLR, and SII were significantly higher in the CD group when compared with the CG. However, there were no significant differences in NLR and PLR between the CD and CGs. A comparison of the SIBS between the CD and SCS groups showed that the NLR and SII were significantly higher in patients with CD than in those with SCS; there were no significant differences in the other scores. There were no significant differences in all SIBS between the SCS group and the CG; only lymphocytes were significantly higher in the SCS group (Table 1).

Significant and positively correlated findings between SIBS and initial diagnostic tests for hypercortisolism were moderate in the CD group as follows: (I) Between NLR and UFC ($r=0.460$, $p=0.001$) and late-night serum cortisol ($r=0.426$, $p=0.003$) levels; (II) between PLR and UFC ($r=0.348$, $p=0.017$) levels; (III) between MLR and UFC ($r=0.392$, $p=0.006$) and standard 2-day 2 mg DST ($r=0.295$, $p=0.041$) levels; and (IV) between SII and UFC ($r=0.443$, $p=0.002$) levels. There were no correlations in the SCS group between SIBS and initial diagnostic tests for hypercortisolism (Table 2).

The values of the SIBS in patients with CD at diagnosis were compared with those after remission (Table 3). It was determined that all of the scores evaluated were lower in remission of the disease compared to the active period ($p<0.001$).

ROC curve analyses were applied for the significantly high MLR and SII scores in the CD group. An optimal cut-off MLR

Table 1. The demographic and laboratory data of the CD group, SCS group, and control group

	CD group (n=52) n/Mean±SD	SCS group (n=65) n/Mean±SD	Control group (n=78) n/Mean±SD	p
Gender (F/M)	42/10	56/9	59/19	0,459
Age (years)	49.88±11.99	60.23±8.92	45.1±12.48	**<0.001**
WBC (10^9/L)	9.29±3.61	7.93±2.19	7.05±2.00	**<0.001**
Neutrophils (10^9/L)	6.18±3.62	4.89±1.74	4.58±1.65	**<0.001**
Lymphocytes (10^9/L)	2.21±0.82	2.35±0.74	1.97±0.61	**0,006**
Monocytes (10^9/L)	0.59±0.21	0.46±0.13	0,43±0.15	**<0.001**
Platelets (10^9/L)	299.67±78.39	283.03±84.22	260.6±56.99	**0.006**
NLR	3.83±7.39	2.23±0.97	2.65±1.67	**0.011**
PLR	161.26±107.13	132.33±61.04	149.65±61.81	0,086
MLR	0.29±0.12	0.21±0.06	0.24±0.10	**<0.001**
SII	1239.46±2756.10	666.01±490.07	695.31±416.78	**0.004**

CD: Cushing's disease; SCS: Subclinical Cushing's syndrome; F: Female; M: Male; WBC: White blood cell; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; MLR: Monocyte-to-lymphocyte ratio; SII: Systemic immune-inflammatory index.

Table 2. Correlation between serum inflammation-based scores and initial diagnostic tests for hypercortisolism in the CD and SCS groups

	NLR		PLR		MLR		SII	
	CD	SCS	CD	SCS	CD	SCS	CD	SCS
8 am serum cortisol								
r	0.191	0.191	–0.044	0.042	0.086	0.123	0.175	0.117
p	0.178	0.127	0.761	0.742	0.547	0.328	0.220	0.355
Overnight 1 mg DST								
r	–0.042	0.018	0.059	0.089	0.304	0.116	0.201	0.035
p	0.712	0.884	0.682	0.482	**0.032**	0.357	0.162	0.780
Standard 2-day 2 mg DST								
r	–0.011	0.077	0.181	0.094	0.295	0.011	0.219	0.064
p	0.927	0.551	0.219	0.464	**0.041**	0.929	0.134	0.617
UFC								
r	0.460	0.040	0.348	0.016	0.392	–0.078	0.443	0.027
p	**0.001**	0.756	**0.017**	0.903	**0.006**	0.542	**0.002**	0.835
Late-night serum cortisol								
r	0.426	0.028	0.130	0.019	0.249	0.076	0.377	0.011
p	**0.003**	0.831	0.388	0.885	0.096	0.563	**0.010**	0.935
Late-night salivary cortisol								
r	0.416	0.057	0.130	0.018	0.237	0.032	0.239	–0.003
p	**0.007**	0.659	0.419	0.889	0.136	0.801	0.132	0.984

NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; MLR: Monocyte-to-lymphocyte ratio; SII: Systemic immune-inflammatory index; DST: Dexamethasone suppression test; UFC: 24-h urinary-free cortisol.

Table 3. Comparison of pre-operative and post-operative values of the serum inflammation-based scores in the CH group

	Pre-operative value (Mean±SD)	Post-operative-remission value (Mean±SD)	p
NLR	3.83±7.39	2.06±1.29	<0.001
PLR	161.26±107.13	124.81±59.23	0.002
MLR	0.29±0.12	0.21±0.08	<0.001
SII	1239.46±2756.10	621.96±479.05	<0.001

NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; MLR: Monocyte-to-lymphocyte ratio; SII: Systemic immune-inflammatory index.

value of 0.20 showed the best diagnostic value (area under the curve=0.659; 95% confidence interval: 0.560–0.758; p=0.003; sensitivity, 78.4%; and specificity, 51.4%) (Figure 1). An optimal cut-off SII value of 776.20 showed the best diagnostic value (area under the curve=0.627; 95% confidence interval: 0.525–0.729; p=0.017; sensitivity, 54.9%; specificity, 70.0%) (Figure 2).

Discussion

This study provides information on the effectiveness of SIBS in the diagnosis of patients with CD and the evaluation of remission after treatment. The MLR and SII levels were significantly high in the CD group. In addition, we determined cut-off values with diagnostic accuracy, sensitivity, and specificity for these scores that we concluded could be used to diagnose CD. Moreover, we showed that all the scores we evaluated (NLR, PLR, MLR, and SII) were significantly reduced after CD treatment.

Harvey Cushing considered that "the malady seems to leave the patients with a definite susceptibility to infections" when he discovered endogenous hypercortisolism.[15] Increased glucocorticoid exposure in chronic hypercortisolism influences all immune cells, leading to defective immune responses.[5] It was shown in a study that increased WBC counts in CS were associated with hypercortisolemia.[6] In addition, CS is associated with

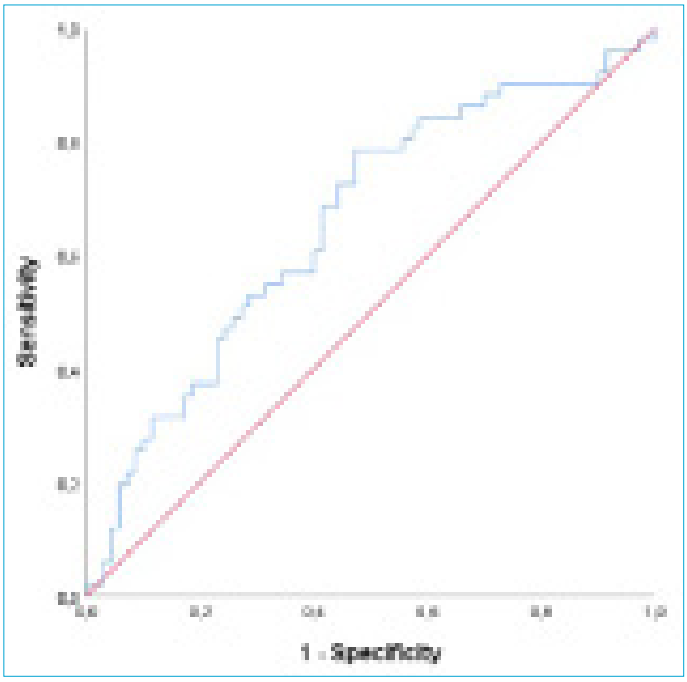

Figure 1. ROC curve of MLR with positive discrimination of CD diagnosis. *MLR: Monocyte-to-Lymphocyte Ratio.*

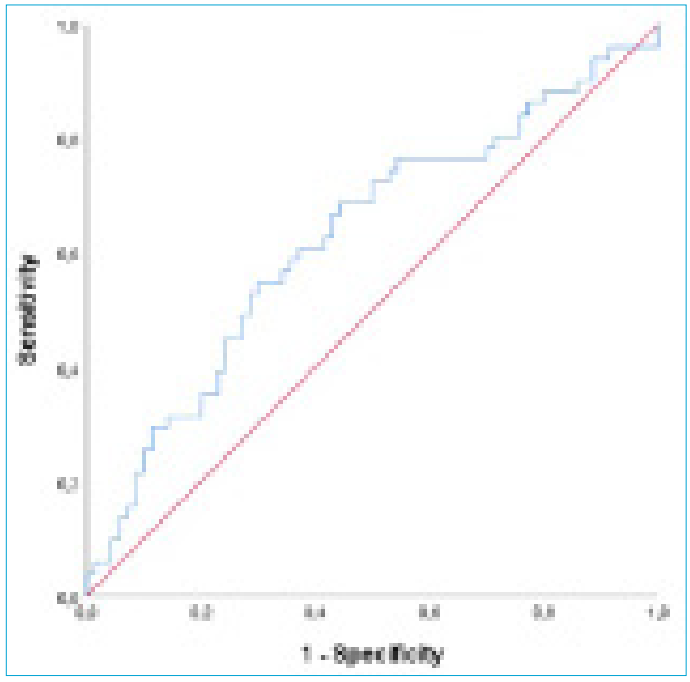

Figure 2. ROC curve of SII with positive discrimination of CD diagnosis. *SII: Systemic Immune-Inflammation Index.*

neutrophilia, lymphopenia, low eosinophils, and variability in monocyte counts.[16] In our study, WBC, neutrophil, monocytes, and platelet counts were significantly higher in the CD group than in the SCS and CGs. Curiously, the lymphocyte counts of the CD group were not lower than the CG. However, the lymphocyte count of the CD group was lower than in the SCS group, which was interpreted as a supportive finding.

NLR, MLR, PLR, and SII are the SIBS based on CBC. Levels of these scores may better reveal a disease's inflammatory status than counting a single cell.[17] Increased SIBS are generally associated with poor clinical outcomes in cancer.[7,8] In addition, they have been studied in the literature to establish the prognosis of various diseases.[18-20] In this study, we evaluated diagnostic role of these scores in CD.

Early diagnosis is essential to prevent the complications and excess mortality associated with CS. However, it takes years for most patients to be diagnosed.[21] This delay is due to both the non-specificity of hypercortisolism symptoms/signs and the complexity of screening tests (UFC, late-night salivary and serum cortisol, and low-dose DSTs). There is no initial screening test with ideal sensitivity or specificity. Moreover, the fact that special endocrine tests such as UFC and salivary cortisol can only be performed in large centers makes them unavailable. In addition, false-positive and negative results may occur if the test selection is not individualized to history and lifestyle.[3]

Due to the close association of cortisol hormone with inflammatory processes and the easy accessibility of CBC, SIBS can be a useful supportive method in Cushing's screening.

There are limited studies that employ SIBS to diagnose endogenous hypercortisolism in the literature. These few studies evaluated scores either in patients with cortisol-producing adrenal adenomas or in patients with pituitary adenomas (PA). To the best of our knowledge, our study is first to determine the value of SIBS in the diagnosis of CD patients.

Wang et al.[22] conducted a retrospective study that included a total of 270 patients with CS and non-functional adrenal adenoma. They compared only the NLR score between the two groups. NLR was significantly higher in the CS group than in the CG. In a study conducted with 73 patients with CS (40 of them; CD), WBC counts and NLR showed a significant difference between cases and controls.[23] Another study evaluated a panel of inflammatory scores in 288 pediatric patients diagnosed with CS. NLR, PLR, and MLR differed between patients with CS and controls. In addition, the inflammatory scores correlated with the tests of cortisol secretion, such as late-night serum cortisol, UFC, and morning cortisol.[24] However, in our study, significant differences were not found in NLR between the CD and CGs. Several studies have suggested that SII may more comprehensively represent the inflammatory state than NLR.[25] Consistent with these studies, we found that

SII was significantly higher in the CD group than in the SCS and CG (p=0.004). In addition, MLR was also significantly higher in the CD group (p<0.001). A study analyzed the SIBS of 424 patients (72 acromegalies, 70 CD, 68 prolactinomas, 6 thyrotropinomas, and 208 non-functional pituitary adenomas) who operated for PA. While SIBS (NLR, SII, and neutrophil–platelet ratio) were high in patients with CD, they did not vary among other PA patients.[26] The most significant difference between our study and similar publications is that we compared our study group not only with the healthy group but also with the SCS patients with less glucocorticoid production group. Comparing the CD and SCS group's scores showed that the NLR and SII were significantly higher in patients with CD than those with SCS. The fact that NLR was not significantly higher in the CD group compared to the CG but was significantly higher than in the SCS group suggested that it could be important in evaluating hypercortisolemia.

We determine significant, positive, and moderately correlated findings between SIBS and initial diagnostic tests for hypercortisolism in the CD group. In particular, the UFC correlated with all four scores. Similarly, in the study of Wurth et al.,[24] SIBS were found to correlate with tests of hypercortisolism (such as midnight serum cortisol and UFC).

Another distinctive characteristic of our study is comparing the values of the SIBS in patients with CD at diagnosis with those after remission. Similar studies conducted in patients with endogenous hypercortisolism did not evaluate the post-treatment change in scores. However, this evaluation was made in some of the studies conducted with patients with malignancy. It was shown that the scores significantly decreased after the treatment, similar to our study.[18]

In our study, ROC curve analyses were performed to evaluate the diagnostic sensitivity and specificity for MLR and SII, which were significantly high compared to the CG among the four systemic inflammatory scores. MLR, with an optimal cut off of 0.20, showed the best diagnostic value with a sensitivity of 78.4% and a specificity of 51.4%. Wurth et al.[24] also found a similar cut-off value for MLR in their study. With an optimal cut off of 776.20, SII showed the best diagnostic value with a sensitivity of 54.9% and a specificity of 70.0%. Although sensitivity and specificity seem low when evaluated separately, it is clear that these values will increase when both scores are used together.

Our study has several limitations. First, it is a single-center, retrospective study. Therefore, data such as pro-inflammatory cytokine levels and CRP could not be evaluated. In addition, the patients may have had underlying undiagnosed conditions influencing the CBC. Second, the relationship between hypercortisolemia and inflammation has been shown. However, the direct effect of ACTH-POMC on inflammation has not been investigated here; larger volume studies comparing ACTH-independent CS and ACTH-dependent CS are needed.

Conclusion

The SIBS, SII, MLR, NLR, and PLR are simpler to calculate during routine blood testing than current initial tests for CD. The SII and MLR in patients with CD were significantly higher than in patients with SCS and healthy controls. If these scores are combined, their diagnostic value for CD would be higher than applied individually. In addition, it was shown that all four scores significantly decreased after the successful treatment of CD. Therefore, we think that they may be an alternative parameter for CD to evaluate clinical activity, follow-up and response to treatment.

Disclosures

Ethics Committee Approval: The study was approved by the Ethics Committee of University of Health Sciences Türkiye, Sisli Hamidiye Etfal Training and Research Hospital (No: 3738, dated 13.12.2022).

Patient Informed Consent: Informed consent was obtained from all participants included in the study.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – M.M.C., Y.A. C.Y.T.; Design – M.M.C.; Supervision – Y.A., F.Y.O.; Materials – C.Y.T., H.E.; Data collection &/or processing – C.Y.T., H.E.; Analysis and/ or interpretation – M.M.C., H.E., C.Y.T.; Literature search – M.M.C., F.Y.O.; Writing – M.M.C.; Critical review – Y.A., F.Y.O.

References

1. Ntali G, Asimakopoulou A, Siamatras T, Komninos J, Vassiliadi D, Tzanela M, et al. Mortality in Cushing's syndrome: systematic analysis of a large series with prolonged follow-up. Eur J Endocrinol 2013;169:715-23. [CrossRef]
2. Nieman LK, Biller BM, Findling JW, Newell-Price J, Savage MO, Stewart PM, et al. The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2008;93:1526-40. [CrossRef]
3. Baid SK, Rubino D, Sinaii N, Ramsey S, Frank A, Nieman LK. Specificity of screening tests for Cushing's syndrome in an overweight and obese population. J Clin Endocrinol Metab 2009;94:3857-64. [CrossRef]
4. Reincke M. Subclinical Cushing's syndrome. Endocrinol Metab Clin North Am 2000;29:43-56. [CrossRef]
5. Hasenmajer V, Sbardella E, Sciarra F, Minnetti M, Isidori AM, Venneri MA. The immune system in Cushing's syndrome. Trends Endocrinol Metab 2020;31:655-69. [CrossRef]

6. Masri-Iraqi H, Robenshtok E, Tzvetov G, Manistersky Y, Shimon I. Elevated white blood cell counts in Cushing's disease: association with hypercortisolism. Pituitary 2014;17:436-40. [CrossRef]
7. Bugada D, Allegri M, Lavand'homme P, De Kock M, Fanelli G. Inflammation-based scores: a new method for patient-targeted strategies and improved perioperative outcome in cancer patients. Biomed Res Int 2014;2014:142425. [CrossRef]
8. Chang X, Zhang F, Liu T, Wang W, Guo H. Neutrophil-to-lymphocyte ratio as an independent predictor for survival in patients with localized clear cell renal cell carcinoma after radiofrequency ablation: a propensity score matching analysis. Int Urol Nephrol 2017;49:967-74. [CrossRef]
9. Bhatti I, Peacock O, Lloyd G, Larvin M, Hall RI. Preoperative hematologic markers as independent predictors of prognosis in resected pancreatic ductal adenocarcinoma: neutrophil-lymphocyte versus platelet-lymphocyte ratio. Am J Surg 2010;200:197-203. [CrossRef]
10. Chan JC, Chan DL, Diakos CI, Engel A, Pavlakis N, Gill A, et al. The lymphocyte-to-monocyte ratio is a superior predictor of overall survival in comparison to established biomarkers of resectable colorectal cancer. Ann Surg 2017;265:539-46. [CrossRef]
11. Liang R, Li J, Tang X, Liu Y. The prognostic role of preoperative systemic immune-inflammation index and albumin/globulin ratio in patients with newly diagnosed high-grade glioma. Clin Neurol Neurosurg 2019;184:105397. [CrossRef]
12. Nieman LK, Biller BM, Findling JW, Murad MH, Newell-Price J, Savage MO, et al. Treatment of Cushing's Syndrome: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 2015;100:2807-31. [CrossRef]
13. Pereira AM, van Aken MO, van Dulken H, Schutte PJ, Biermasz NR, Smit JW, et al. Long-term predictive value of postsurgical cortisol concentrations for cure and risk of recurrence in Cushing's disease. J Clin Endocrinol Metab 2003;88:5858-64. [CrossRef]
14. Terzolo M, Pia A, Reimondo G. Subclinical Cushing's syndrome: definition and management. Clin Endocrinol (Oxf) 2012;76:12-8. [CrossRef]
15. Cushing H. The basophil adenomas of the pituitary body and their clinical manifestations (pituitary basophilism). 1932. Obes Res 1994;2:486-508. [CrossRef]
16. Detomas M, Altieri B, Chifu I, Remde H, Zhou X, Landwehr LS, et al. Subtype-specific pattern of white blood cell differential in endogenous hypercortisolism. Eur J Endocrinol 2022;187:439-49. [CrossRef]
17. Zinellu A, Paliogiannis P, Sotgiu E, Mellino S, Mangoni AA, Zinellu E, et al. Blood cell count derived inflammation indexes in patients with idiopathic pulmonary fibrosis. Lung 2020;198:821-7. [CrossRef]
18. Hu B, Yang XR, Xu Y, Sun YF, Sun C, Guo W, et al. Systemic immune-inflammation index predicts prognosis of patients after curative resection for hepatocellular carcinoma. Clin Cancer Res 2014;20:6212-22. [CrossRef]
19. Kim Y, Choi H, Jung SM, Song JJ, Park YB, Lee SW. Systemic immune-inflammation index could estimate the cross-sectional high activity and the poor outcomes in immunosuppressive drug-naïve patients with antineutrophil cytoplasmic antibody-associated vasculitis. Nephrology (Carlton) 2019;24:711-7. [CrossRef]
20. Barutcu S, Yildirim AE, Sahin A, Gulsen MT. Lymphocyte to monocyte ratio and C-reactive protein combination as the best simple predictor of treatment response in cirrhotic patients with culture negative neutrocytic ascites. Sisli Etfal Hastan Tip Bul 2022;56:77-83. [CrossRef]
21. Rubinstein G, Osswald A, Hoster E, Losa M, Elenkova A, Zacharieva S, et al. Time to diagnosis in Cushing's syndrome: a meta-analysis based on 5367 patients. J Clin Endocrinol Metab 2020;105:dgz136. [CrossRef]
22. Wang W, Wang J, Shen C, Zhu S, Gao Y, Zhang J. Neutrophil-lymphocyte ratio as an initial screening biomarker for differential diagnosis of Cushing's syndrome from nonfunctional adenoma in patients with an adrenal mass. Biomed Res Int 2021;2021:6635594. [CrossRef]
23. Paja M, Merlo I, Rodríguez-Soto J, Cruz-Iglesias E, Moure MD, Elías C, et al. White blood cell count: a valuable tool for suspecting Cushing's syndrome. J Endocrinol Invest 2023;46:141-9. [CrossRef]
24. Wurth R, Rescigno M, Flippo C, Stratakis CA, Tatsi C. Inflammatory biomarkers in the evaluation of pediatric endogenous Cushing syndrome. Eur J Endocrinol 2022;186:503-10. [CrossRef]
25. Huang Y, Gao Y, Wu Y, Lin H. Prognostic value of systemic immune-inflammation index in patients with urologic cancers: a meta-analysis. Cancer Cell Int 2020;20:499. [CrossRef]
26. Marques P, de Vries F, Dekkers OM, van Furth WR, Korbonits M, Biermasz NR, et al. Pre-operative serum inflammation-based scores in patients with pituitary adenomas. Pituitary 2021;24:334-50. [CrossRef]