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Hematological changes in Cushing's disease from diagnosis to remission: comparison with non-functioning pituitary adenomas

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Abstract

Introduction: Cushing's disease (CD) results in chronic hypercortisolism with multisystem complications. Although glucocorticoids affect hematopoiesis, sex-specific hematological alterations and their reversibility following treatment remain incompletely characterized. Most previous studies have compared patients with CD with healthy controls, limiting the ability to isolate cortisol-specific effects from tumor- or surgery-related confounders. We investigated hematological parameters in patients with CD at diagnosis and after remission, using patients with non-functioning pituitary adenoma (NFA) as controls to specifically identify hypercortisolism-driven changes.

Material and methods: This retrospective study included 117 patients: 59 with CD and 58 with NFA who underwent transsphenoidal surgery. Complete blood count and hormonal parameters were evaluated at diagnosis and 3 months postoperatively. Changes in hematological parameters were compared between groups using repeated-measures analysis of variance, with subgroup analyses examining remission status and sex-specific differences.

Results: At baseline, patients with CD showed significantly elevated white blood cells (WBC) counts (9.50 ± 2.67 *vs.* $7.32 \pm 1.71 \times 10^3/\mu L$, $p < 0.001$), neutrophil counts (6.41 ± 2.35 *vs.* $4.30 \pm 1.44 \times 10^3/\mu L$, $p < 0.001$), neutrophil-to-lymphocyte ratio (NLR) (3.27 ± 2.03 *vs.* 2.04 ± 0.91, $p < 0.001$), and red blood cells (RBC) counts (4.70 ± 0.50 *vs.* $4.51 \pm 0.46 \times 10^6/\mu L$, $p = 0.03$), with significantly lower eosinophil counts (0.111 ± 0.093 *vs.* $0.166 \pm 0.140 \times 10^3/\mu L$, $p = 0.01$) compared with NFA patients. No sex-specific differences were observed in baseline hematological parameters within the CD group. At 3 months postoperatively, significant decreases in hemoglobin ($p = 0.02$), WBC ($p < 0.001$), neutrophil counts ($p < 0.001$), and NLR ($p = 0.006$) were observed in patients with CD compared with NFA controls. Importantly, the magnitude of postoperative reductions in WBC ($p = 0.01$) and neutrophil counts ($p = 0.009$), as well as increases in eosinophil counts ($p = 0.03$), was significantly associated with achieving biochemical remission. Neutrophil recovery was greater in women ($p = 0.03$). No correlations were found between baseline cortisol levels and hematological parameters.

Conclusions: Cushing's disease demonstrates specific hematological alterations — elevated WBC, neutrophils, NLR, and RBC, with decreased eosinophils — that are attributable to hypercortisolism rather than the presence of a pituitary tumor. These parameters normalize rapidly following surgical remission, with changes correlating with biochemical cure. Routine complete blood counts may serve as accessible biomarkers for monitoring disease activity and treatment response in CD. **(Endokrynol Pol 2026; 77 (4): 319–326)**

Keywords: *Cushing's disease; hypercortisolism; complete blood count; neutrophil-to-lymphocyte ratio; leukocytosis*

Introduction

Cushing's disease (CD), resulting from adrenocorticotropic hormone (ACTH)-producing pituitary adenomas, is the leading cause of endogenous Cushing's syndrome, accounting for approximately 70% of cases [1]. This disorder is characterized by sustained hypercortisolism, which results in significant morbidity, including metabolic dysfunction, cardiovascular complications, psychiatric disturbances, and an increased risk of mortality if left untreated [2].

Although the classic clinical features of CD are well characterized, recent evidence has revealed significant alterations in hematological parameters, particularly in red blood cells (RBC) [3]. Glucocorticoids exert complex and paradoxical effects on hematopoiesis that vary considerably by sex. Recent evidence indicates that women with Cushing's syndrome demonstrate elevated hematocrit, hemoglobin, and mean corpuscular volume (MCV) compared with healthy controls, suggesting a stimulatory effect of chronic hypercortisolism on erythropoiesis in females [4]. In contrast, men with Cushing's

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syndrome present with lower hematocrit, RBC counts, and hemoglobin levels than male controls, despite also showing increased MCV [4]. These sex-specific differences highlight the importance of sex-dependent mechanisms underlying the hematological manifestations of hypercortisolism.

Furthermore, hypercortisolism consistently induces leukocytosis in both sexes, primarily characterized by neutrophilia and lymphopenia, reflecting the immunomodulatory effects of excessive glucocorticoids. These white blood cells (WBC) alterations typically normalize rapidly after successful surgical treatment and restoration of normal cortisol levels. Interestingly, the recovery kinetics of erythroid parameters appear more complex, with hemoglobin and hematocrit levels decreasing in both sexes during the early postoperative period before eventual normalization [5].

Despite increasing evidence of hematological alterations in Cushing's syndrome, most studies have compared patients with healthy controls, limiting the ability to distinguish cortisol-specific effects from confounding factors such as pituitary tumor presence, hypopituitarism, or surgical intervention. Direct comparisons between patients with CD and non-functioning pituitary adenoma (NFA) — who share similar tumor burden and surgical exposure but lack hypercortisolism — are notably scarce. This retrospective study aimed to evaluate complete blood count parameters in patients with CD and NFA at diagnosis and 3 months postoperatively. By using patients with NFA as controls, this comparative design enabled us to isolate the specific effects of hypercortisolism on hematological parameters and evaluate their reversibility following successful surgical treatment, with particular attention to sex-specific differences.

Material and methods

Study design and setting

In this retrospective single-center study, patients with CD and NFA were identified at multidisciplinary neuroendocrine and outpatient clinics between October 2021 and October 2025. The study was approved by the Ethics Committee of Basaksehir Cam and Sakura City Hospital (approval number: E-96317027-514.10-300980184). We collected data on demographic characteristics, clinical features, tumor pathology, and biochemical laboratory parameters. Patients were evaluated for hematological parameters at two time points: at diagnosis, before surgery (baseline/preoperative period), and 3 months after surgery (postoperative follow-up).

Diagnostic criteria

Patients were included if they met the diagnostic criteria for CD based on laboratory tests used to investigate pathological hypercortisolism, including 24-hour urinary free cortisol (UFC), late-night salivary cortisol (LNSC), and serum cortisol response to 1-mg or low-dose dexamethasone suppression testing (DST). The criteria for Cushing's syndrome diagnosis included: 1) two UFC measurements greater than the normal range, 2) serum cortisol greater than 1.8 μg/dL (50 nmol/L) after overnight 1-mg dexamethasone, and 3) two LNSC measurements greater than the normal range. Cushing's syndrome was diagnosed if patients had positive results for at least two of these three tests [6]. The diagnosis of CD was established by first excluding ACTH-independent Cushing's syndrome through suppressed ACTH levels, followed by ruling out ectopic ACTH-dependent Cushing's syndrome using high-dose DST, pituitary adenoma identification via magnetic resonance imaging (MRI), and inferior petrosal sinus sampling in cases where the diagnosis remained uncertain [7]. Patients with NFA who were indicated for surgery and did not exhibit hormonal deficiency preoperatively were included.

Patients were excluded if they had conditions that could affect hematological parameters, including other causes of anemia (iron, vitamin B12, or folate deficiency; chronic kidney disease with estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2; documented blood loss, bleeding or hemolytic disorders; or known hematological diseases), secondary causes of polycythemia (chronic lung disease, sleep apnea, chronic hypoxia, or polycythemia vera), active infection at baseline, active or recent malignancy within the past 5 years, use of medications influencing hematological parameters within 3 months before surgery, recent blood transfusion, pregnancy, prior pituitary surgery or radiotherapy, adrenal or ectopic ACTH-dependent Cushing's syndrome, or liver cirrhosis.

Remission of CD was evaluated using UFC, LNSC measurement, and the 1-mg DST, all performed 24 h after the discontinuation of hydrocortisone [8, 9].

Data collection

Age at diagnosis, sex, and body mass index (BMI) at baseline were recorded for all patients. Baseline hormonal parameters were systematically evaluated in all patients. Serum cortisol and ACTH levels were measured at 8:00 AM at diagnosis. Histopathological findings, including confirmation of pituitary adenoma and immunohistochemical staining results for ACTH, prolactin, growth hormone, follicle-stimulating hormone (FSH), luteinizing hormone (LH), and thyroid-stimulating hormone (TSH), when available, were systematically recorded from pathology reports. Complete blood count analyses were performed using a Sysmex XN-1000 hematology autoanalyzer (Sysmex Corporation, Kobe, Japan).

Statistical analysis

Statistical analyses were performed using Jamovi statistical software (v. 2.6.25). Descriptive statistics were calculated for continuous variables, and categorical variables were summarized as frequencies and percentages. Data are presented as means ± standard deviation or numbers (%), as appropriate. The Kolmogorov–Smirnov test was used to assess the normality of the distribution. Continuous variables with normal distributions were compared using Student's t-test, whereas those with non-normal distributions were analyzed using the Mann–Whitney U test. Categorical variables were compared using the chi-square test. Associations between variables were evaluated using Pearson's correlation coefficient. Repeated-measures analysis of variance (ANOVA) was used to evaluate changes over time between groups. Statistical significance was set at $p < 0.05$.

Results

A total of 117 patients were included in the study, comprising 59 patients in the CD group and 58 in the NFA group. In the CD group, 49 (83.1%) and 10 (16.9%) patients were female and male, respectively. In the NFA group, 47 (81.0%) and 11 (19.0%) patients were female and male, respectively. There was no significant difference between the groups in terms of sex distribution ($p = 0.77$). There was no significant difference in age between the CD and NFA groups (48.9 ± 12.0 *vs.* 49.0 ± 10.8

Table 1. *Demographic and clinical characteristics of the Cushing's disease (CD) and non-functioning pituitary adenoma (NFA) groups*

Variable	CD (n = 59)	NFA (n = 58)	p
Female, n (%)	49 (83.1%)	47 (81.0%)	0.770
Age [years]	48.90 ± 12.00	49.00 ± 10.80	0.980
BMI [kg/m^2]	53.00 ± 127.00	29.10 ± 5.08	0.170
1-mg DST	11.30 ± 10.90	0.78 ± 0.36	< 0.001

Data are presented as mean ± standard deviation; BMI — body mass index; DST — 1-mg overnight dexamethasone suppression test

Table 2. *The biochemical characteristics of the Cushing's disease group*

Variable	Median (IQR)
Preoperative serum cortisol [μg/dL]	15.3 (13.2–19.3)
Preoperative ACTH [pg/mL]	40.5 (19.9–70.1)
Late-night serum cortisol [μg/dL]	13.5 (10.7–17.0)
24-hour urinary free cortisol [μg/24 h]	44.3 (21.1–92.3)
Late-night salivary cortisol [μg/dL]	0.430 (0.320–0.750)

Data are presented as median [interquartile range (IQR)]; ACTH — adrenocorticotropic hormone

Table 3. *Preoperative hemogram parameters for both groups*

Parameter	CD	NFA	p
Hb [g/dL]	13.10 ± 1.45	12.80 ± 1.53	0.300
Hct [%]	39.60 ± 5.84	38.30 ± 3.83	0.150
RBC [$\times 10^6/\mu$L]	4.70 ± 0.50	4.51 ± 0.46	0.030
WBC [$\times 10^3/\mu$L]	9.50± 2.67	7.32 ± 1.71	< 0.001
Neutrophils [$\times 10^3/\mu$L]	6.41 ± 2.35	4.30 ± 1.44	< 0.001
Lymphocytes [$\times 10^3/\mu$L]	2.29 ± 0.82	2.31 ± 0.75	0.880
NLR	3.27 ± 2.03	2.04 ± 0.91	< 0.001
Eosinophils [$\times 10^3/\mu$L]	0.111 ± 0.093	0.166 ± 0.140	0.010
Platelets [$\times 10^3/\mu$L]	286.0 ± 71.5	262.0 ± 61.5	0.060

Data are presented as mean ± standard deviation; comparisons were performed using Student's t-test; CD — Cushing's disease; Hb — hemoglobin; Hct — hematocrit; NFA — non-functioning pituitary adenoma; NRL — neutrophil-to-lymphocyte ratio; RBC — red blood cells; WBC — white blood cells

years; p = 0.98). The general characteristics of the groups are shown in Table 1. The biochemical characteristics of patients with CD are presented in Table 2.

In the preoperative period, WBC and neutrophil counts and neutrophil-to-lymphocyte ratio (NLR) were significantly higher in the CD group than in the NFA group (p < 0.001 for both). Red blood cells levels were significantly higher in the CD group than in the NFA group (p = 0.03). In addition, eosinophil counts were significantly lower in the CD group (p = 0.01). The preoperative complete blood count parameters are presented in Table 3.

The effect of age on preoperative complete blood count parameters was also evaluated in the CD group. Age was negatively correlated with NLR (r = −0.29, p = 0.02) and positively correlated with lymphocyte count (r = 0.27, p = 0.03). Body mass index was positively correlated only with lymphocyte count (r = 0.35, p = 0.01).

No significant correlation was found between preoperative complete blood count parameters and basal cortisol, ACTH, late-night serum cortisol, 24-hour UFC, salivary cortisol, or the 1-mg DST results in the CD group (all p > 0.05).

At the 3-month postoperative visit, remission was achieved in 39 patients (70.9%) with CD, whereas 16 patients (29.1%) had no remission. Postoperative adrenal insufficiency was observed in 41 patients (69.5%) in the CD group and in eight patients (13.8%) in the NFA group.

When changes in complete blood count parameters at postoperative month 3 were evaluated, marked

Table 4. *Postoperative hemogram parameters for both groups*

Parameter	CD		NFA		p
	Preoperative	Postoperative	Preoperative	Postoperative	
Hb [g/dL]	13.10 ± 1.45	12.7 ± 1.37	12.80 ± 1.53	12.70 ± 1.23	0.020
Hct [%]	39.60 ± 5.84	39.50 ± 3.83	38.30 ± 3.83	38.8 ± 3.16	0.080
RBC [$\times 10^6/\mu L$]	4.70 ± 0.50	4.72 ± 0.44	4.51 ± 0.46	4.67 ± 0.39	0.070
WBC [$\times 10^3/\mu L$]	9.50 ± 2.67	7.76 ± 1.90	7.32 ± 1.71	7.37 ± 1.82	< 0.001
Neutrophils [$\times 10^3/\mu L$]	6.41 ± 2.35	4.49 ± 1.56	4.30 ± 1.44	4.05 ± 1.49	< 0.001
Lymphocytes [$\times 10^3/\mu L$]	2.29 ± 0.82	2.47 ± 0.72	2.31 ± 0.75	2.55 ± 0.78	0.570
NLR	3.27 ± 2.03	1.96 ± 0.90	2.04 ± 0.91	1.81 ± 1.35	0.006
Eosinophils [$\times 10^3/\mu L$]	0.111 ± 0.093	0.170 ± 0.106	0.166 ± 0.140	0.178 ± 0.131	0.080
Platelets [$\times 10^3/\mu L$]	286.0 ± 71.5	292.0 ± 69.4	262.0 ± 61.5	296.0 ± 66.1	0.790

Data are presented as mean ± standard deviation; comparisons were performed using repeated-measures analysis of variance (ANOVA); CD — Cushing's disease; Hb — hemoglobin; Hct — hematocrit; NFA — non-functioning pituitary adenoma; NRL — neutrophil-to-lymphocyte ratio; RBC — red blood cells; WBC — white blood cells

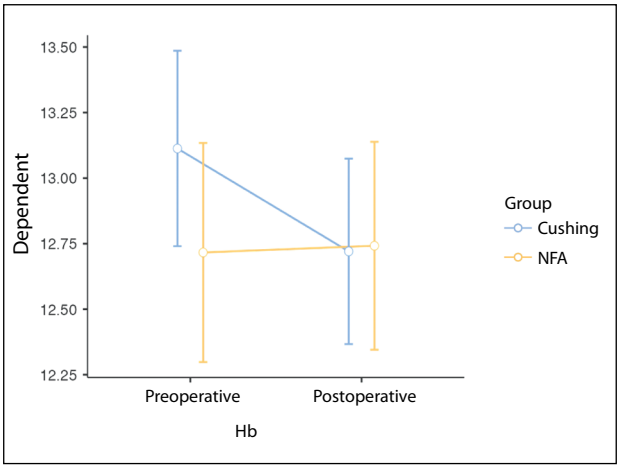


Figure 1. *Preoperative and postoperative changes in hemoglobin (Hb); NFA — non-functioning pituitary adenoma*

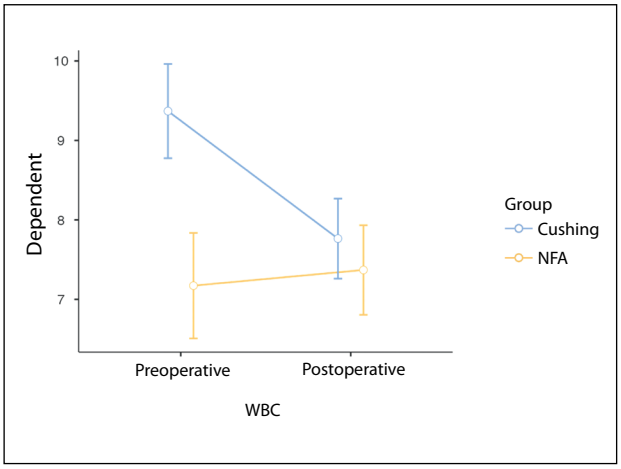


Figure 2. *Preoperative and postoperative changes in white blood cells (WBC); NFA — non-functioning pituitary adenoma*

decreases in hemoglobin, WBC count, neutrophil count, and NLR were observed in the CD group compared with the NFA group, based on repeated-measures ANOVA ($p = 0.02$, $p < 0.001$, $p < 0.001$, and $p < 0.001$, respectively). Eosinophil levels tended to increase ($p = 0.08$). The postoperative 3-month values are shown in Table 4. The intergroup preoperative and postoperative changes in hemoglobin (Hb), WBC count, neutrophils, and NLR are shown in Figures 1–4, respectively.

In the CD group, a significant sex-related difference in postoperative changes was observed only in neutrophil count ($p = 0.03$), with a more pronounced decrease in females than in males. A trend toward a sex-time interaction was found for NLR ($p = 0.05$), WBC count ($p = 0.09$), lymphocyte count ($p = 0.07$), and eosinophil count ($p = 0.07$), all indicating greater changes in females. In contrast, changes in hemoglobin, hematocrit, RBC, and platelet counts were similar between sexes ($p > 0.05$). Table 5 presents the changes according to sex.

When the results were evaluated according to remission status in the CD group, hematocrit level was significantly associated with remission ($p = 0.04$). In addition, postoperative decreases in WBC ($p = 0.01$) and neutrophil counts ($p = 0.009$), as well as an increase in eosinophil count ($p = 0.03$), were significantly associated with remission. Changes in WBC, neutrophil, hematocrit, and eosinophil counts according to remission status are shown in Figures 5–8.

In contrast, decreases in hemoglobin levels showed a borderline association with remission ($p = 0.06$), as did the reduction in NLR ($p = 0.09$). No significant relationship was found between changes in lymphocyte count and remission status ($p = 0.33$).

Discussion

The present study examined the effects of chronic cortisol excess on complete blood count parameters in patients with CD by using patients with NFA as a control group and evaluating the reversibility of these changes following surgical treatment. In the preoperative period, CD was associated with significantly elevated

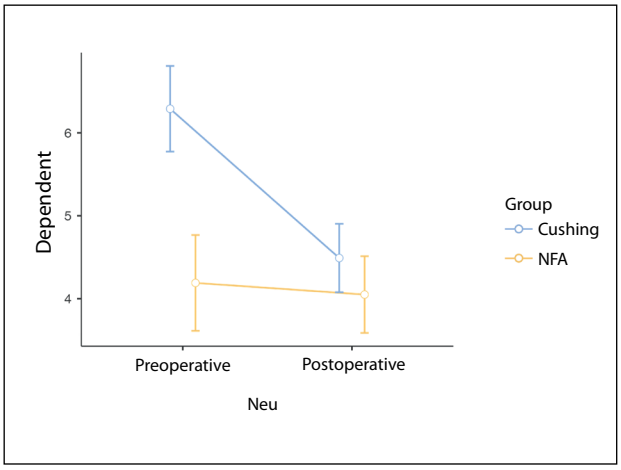


Figure 3. *Preoperative and postoperative changes in neutrophils (Neu); NFA — non-functioning pituitary adenoma*

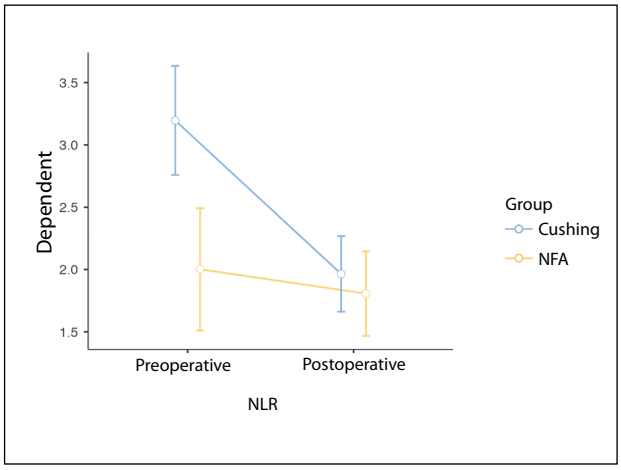


Figure 4. *Preoperative and postoperative changes in neutrophil-to-lymphocyte ratio (NLR); NFA — non-functioning pituitary adenoma*

Table 5. *Hematological parameters according to sex in the Cushing's disease group*

Parameter	Female		Male		p
	Preoperative	Postoperative	Preoperative	Postoperative	
Hb [g/dL]	13.00 ± 1.37	12.60 ± 1.39	13.80 ± 1.72	13.10 ± 1.24	0.52
Hct [%]	39.90 ± 4.91	39.50 ± 3.96	38.10 ± 9.38	39.20 ± 3.25	0.46
RBC [$\times 10^6/\mu L$]	4.68 ± 0.5	4.74 ± 0.46	4.81 ± 0.53	4.61 ± 0.33	0.10
WBC [$\times 10^3/\mu L$]	9.68 ± 2.74	7.77 ± 1.99	8.63 ± 2.19	7.75 ± 1.44	0.09
Neutrophil [$\times 10^3/\mu L$]	6.57 ± 2.39	4.43 ± 1.65	5.63 ± 2.07	4.80 ± 0.99	0.03
Lymphocyte [$\times 10^3/\mu L$]	2.31 ± 0.84	2.54 ± 0.73	2.16 ± 0.71	2.08 ± 0.59	0.07
Eosinophil [$\times 10^3/\mu L$]	0.10 ± 0.09	0.17 ± 0.10	0.14 ± 0.09	0.15 ± 0.10	0.07
Platelet [$\times 10^3/\mu L$]	296.0 ± 69.0	300.0 ± 61.8	238.0 ± 67.3	249.0 ± 92.1	0.66
NLR	3.33 ± 2.11	1.88 ± 0.93	2.94 ± 1.64	2.40 ± 0.59	0.05

Data are presented as mean ± standard deviation; Hb — hemoglobin; Hct — hematocrit; NRL — neutrophil-to-lymphocyte ratio; RBC — red blood cells; WBC — white blood cells

WBC, neutrophil, RBC, and NLR and significantly reduced eosinophil counts compared with the NFA group ($p < 0.001$, $p < 0.001$, $p = 0.03$, $p < 0.001$, and $p = 0.01$, respectively). Following surgery, WBC, neutrophil count, and NLR decreased markedly in the CD group, whereas eosinophil levels showed a trend toward recovery. These postoperative changes were largely dependent on remission status, as improvements in WBC count, neutrophil count, and eosinophil levels were significantly more pronounced in patients who achieved remission.

Glucocorticoids increase neutrophil release from the bone marrow while simultaneously inducing lymphocyte apoptosis and promoting lymphocyte sequestration in lymphoid tissues, resulting in neutrophilia, lymphopenia, and consequently elevated NLR [10–12]. The elevated NLR observed in our cohort of patients with CD is attributable to the simultaneous occurrence of neutrophilia and lymphopenia. Neutrophil-to-lymphocyte ratio is increasingly recognized as a straightforward and effective marker of systemic inflammation and immune dysregulation. Additionally, it is emerging as a valuable biomarker for evaluating disease activity in Cushing's syndrome [13, 14]. Cortisol suppresses eosinophil production in the bone marrow, accelerates eosinophil apoptosis, and promotes tissue sequestration of circulating eosinophils in organs such as the spleen and lungs, thereby reducing blood eosinophil counts [15–17]. Our findings indicate that the elevations in WBC counts, neutrophil counts, and NLR observed in patients with CD at baseline were independent of sex. Notably, these hematological aberrations were absent in the cohort with NFA. This discrepancy is a critical observation, as it suggests that such alterations are specifically driven by chronic hypercortisolism rather than the localized mass effect or the general presence of a pituitary neoplasm.

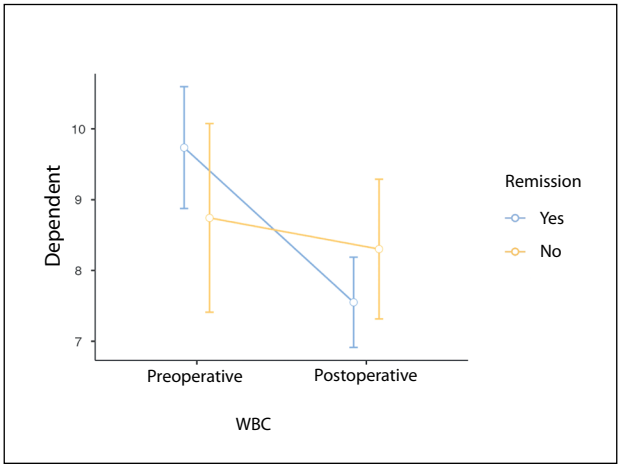


Figure 5. *Change in white blood cells (WBC) levels according to remission status in the Cushing's disease group*

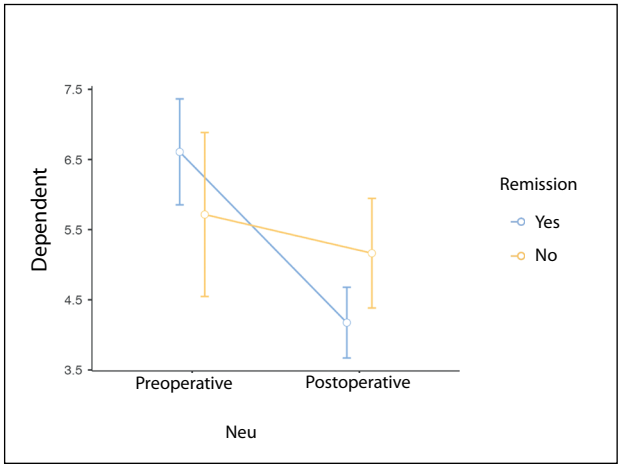


Figure 6. *Change in neutrophil levels according to remission status in the Cushing's disease group*

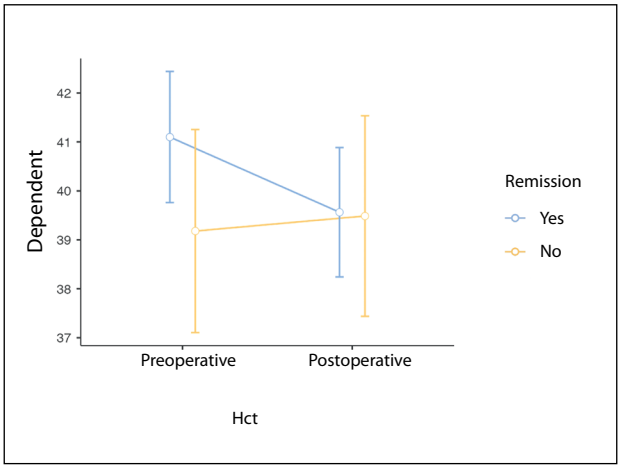


Figure 7. *Change in hematocrit (Hct) levels according to remission status in the Cushing's disease group*

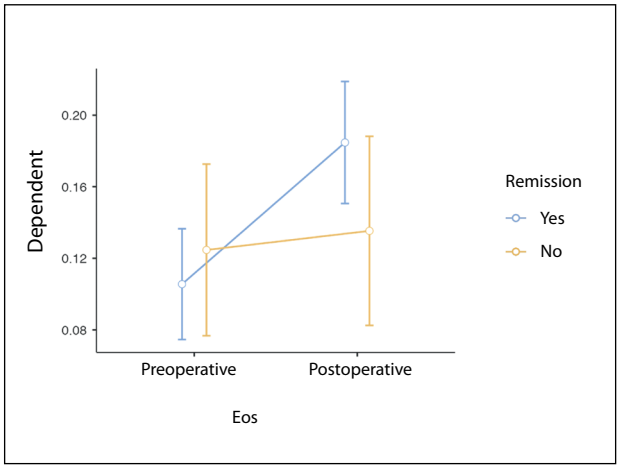


Figure 8. *Change in eosinophil (Eos) levels according to remission status in the Cushing's disease group*

In our study, we found that RBC counts were significantly higher in patients with active CD than in the NFA group at baseline. Although hemoglobin and hematocrit levels showed a trend toward elevation in the CD group, these differences were not statistically significant. Data on sex-related differences in the erythrocytic profile in patients with Cushing's syndrome remain controversial. While higher hemoglobin and hematocrit levels have been reported in male patients compared with controls [18], Detomas et al. [4] observed lower mean values in male patients with Cushing's syndrome than in the control group. In our cohort, both male and female patients with CD showed similar patterns, with males having higher baseline hemoglobin levels than females. Several mechanisms may contribute to the elevation of RBC parameters in CD, including the direct effects of glucocorticoids on erythropoiesis, stimulation by adrenal androgens, alterations in plasma volume, and hypoxia associated with obesity [4, 19]. Patients with CD exhibit erythrocytosis and a distinct subset of $CD34^+$ progenitors influenced by the glucocorticoid receptor (GR), which produce a substantial number of immature erythroid cells. This suggests that GR remains consistently active in these erythroid progenitors [20]. Since both patient groups harbored pituitary adenomas and underwent identical surgical procedures, yet only CD patients exhibited elevated RBC parameters, these findings confirm that hypercortisolism is the primary driver of erythroid changes rather than tumor-related mechanical effects or generalized pituitary dysfunction.

Interestingly, we found no significant correlation between preoperative hematological parameters and various cortisol measurements (basal serum cortisol, 24-hour UFC, late-night serum cortisol, or salivary cortisol) in patients with CD. Several factors may explain this observation. The duration of hypercortisolism exposure might be more relevant than absolute cortisol levels at a single time point [20]. Individual differences in glucocorticoid receptor sensitivity and tissue-specific cortisol metabolism could result in varying hematological responses despite similar circulating cortisol

concentrations [21]. Moreover, associated metabolic complications, obesity, and sleep disturbances may independently influence hematological parameters, potentially masking direct cortisol-related effects [3]. This finding suggests that the relationship between hypercortisolism and hematological changes is likely multifactorial and not solely dependent on circulating cortisol levels.

Following surgery, when the NFA and CD groups were compared, WBC, neutrophil count, and NLR decreased significantly over time in the CD group, whereas eosinophil levels showed a significant increase. These changes are consistent with the restoration of normal immune homeostasis after the removal of excess cortisol [5, 10]. The increase in eosinophils is particularly noteworthy, as eosinopenia is considered a classic hallmark of hypercortisolism, and its reversal may serve as a useful clinical indicator of successful cortisol withdrawal [5]. However, in our study, this change showed only a trend toward an increase and did not reach statistical significance.

Interestingly, in contrast to the rapid postoperative normalization observed in WBC counts and NLR, erythroid parameters remained largely unchanged during the early postoperative period in both groups. Hemoglobin levels showed a significant postoperative decrease, whereas RBC count and hematocrit demonstrated a downward trend without reaching statistical significance in the CD group when compared with the NFA group. This difference is most likely related to the markedly longer lifespan of erythrocytes (approximately 120 days) compared with the short turnover time of circulating leukocytes [3, 4]. Consequently, while glucocorticoid withdrawal leads to an early reversal of leukocyte demargination and redistribution, the resolution of cortisol-related erythrocytosis may require a longer follow-up period to become clinically and statistically evident. Therefore, this temporal dissociation should be considered when interpreting early postoperative hematological outcomes. Crucially, although both the CD and NFA cohorts underwent similar surgical procedures, significant postoperative hematological shifts were exclusive to the Cushing's group. This observation suggests that the observed changes are directly attributable to the resolution of hypercortisolism rather than the physiological stress or systemic inflammatory response associated with the surgical intervention itself.

Within the CD group, we observed that the postoperative decline in neutrophil counts was notably more pronounced in women ($p = 0.03$). Furthermore, NLR demonstrated a strong downward trend specifically in women ($p = 0.05$), while the reduction in total WBC and the increase in lymphocyte counts were also more apparent in the female cohort, although the differences did not reach formal statistical significance. This finding should be interpreted with caution, as most patients in the CD group were women, which may have provided greater statistical power for the female subgroups. This imbalance is consistent with the known female predominance in CD; however, larger multicenter studies with a more balanced sex distribution are needed to clarify whether these hematological changes are truly sex-related or mainly influenced by sample size differences.

Importantly, when remission status was examined, postoperative reductions in WBC ($p = 0.01$) and neutrophil counts ($p = 0.009$) and increases in eosinophil counts ($p = 0.03$) were significantly associated with achieving biochemical remission. The reduction in NLR showed a borderline association with remission ($p = 0.09$). This may reflect the complex interplay of factors during early recovery, including the high rate of postoperative adrenal insufficiency (69.5%) requiring glucocorticoid replacement therapy, which itself may delay lymphocyte recovery due to the lymphocytotoxic effects of exogenous glucocorticoids [22, 23].

In summary, our results demonstrate that hypercortisolism in CD is associated with characteristic and reversible complete blood count alterations, particularly in neutrophil count, NLR, and eosinophil levels. The normalization of these parameters following successful surgery and their differential recovery according to remission status support the direct causal role of cortisol excess in driving these hematological changes. These findings contribute to a better understanding of the systemic immunological and erythropoietic consequences of chronic hypercortisolism.

This study has several limitations that should be acknowledged. The retrospective, single-center design limited data standardization and generalizability. The small sample size, particularly the limited number of male patients ($n = 10$), reduced the statistical power to detect sex-specific differences. A 3-month follow-up may be insufficient to capture complete hematological recovery, especially for lymphocyte reconstitution. Additionally, the high rate of postoperative adrenal insufficiency (69.5%) requiring glucocorticoid replacement may have influenced the lymphocyte recovery assessment. Incomplete data on confounders such as sleep apnea, sex hormones, and adrenal androgens, as well as the lack of detailed immunophenotyping, represent further limitations.

Conclusions

To the best of our knowledge, this is one of the few studies that directly compares longitudinal hematological

changes in patients with CD and NFA who undergo the same surgical procedure, thereby allowing differentiation of hypercortisolism-specific effects from tumor- and surgery-related alterations. Furthermore, this study demonstrates distinct temporal recovery patterns of leukocyte and erythroid lineages following remission and highlights the potential role of eosinophil dynamics as an early marker of cortisol withdrawal, with additional insight into sex-specific postoperative responses. Future prospective studies with larger sample sizes, longer follow-up periods, and comprehensive immunological assessments are warranted to validate these findings.

Data availability statement
The data underlying this article are available from the corresponding author upon reasonable request.

Ethics statement
The study protocol was reviewed and approved by the Ethics Committee of Basaksehir Cam and Sakura City Hospital (approval number: E-96317027-514.10-300980184; date: December 12, 2025).

Author contributions
E.S.H.: conceptualization; S.B., E.S.H.: methodology; S.B., E.A., D.A.B., A.U.O.: data collection; S.B.: formal analysis; S.B., A.P.: writing — original draft; S.B., E.S.H.: writing — review and editing; E.S.H: supervision. All authors have read and approved the final manuscript.

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Conflict of interest
The authors have no relevant financial or non-financial interests to disclose.

Supplementary material
None.

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