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**CONTENTS****RESEARCH ARTICLES**

- 1 Vitamin D Levels and Inflammatory Markers in Patients with Active Graves Disease and a Possible Role of Vitamin D for Ophthalmopathy**  
M. Ersoy, A. Akalın
- 9 The Effect of MCV on Prognosis in Patients with Gastric Cancer and its Relationship with C-ERBB2 Positivity**  
İ. N. Ökten, R. U. Gürsu
- 17 Prognostic Importance of Neutrophil to Lymphocyte and Platelet to Lymphocyte Ratios in Multiple Myeloma Patients**  
A. Kızıklı, V. Okan
- 25 Mortality and Related Factors in Patients Admitted to Intensive Care Unit**  
B. Kılıçtaş, K. Konur, T. Ayaz
- 32 Clinical and Demographic Characteristics of Patients with Non-Functional Pituitary Adenomas: A Retrospective Single-Center Study**  
A. Türker, R. Gen
- 39 Prognostic Impact of FLT3, NPM1 and CEBPA Mutations in Cytogenetically Normal Acute Myeloid Leukemia**  
S. İleri, O. Ayyıldız

## Research Article

# Vitamin D Levels and Inflammatory Markers in Patients with Active Graves Disease and a Possible Role of Vitamin D for Ophthalmopathy

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### Abstract

**Objectives:** This study investigated the role of vitamin D in Graves' disease and autoimmune thyroid disease and examined the relationship between vitamin D levels and thyroid ophthalmopathy, inflammation, body mass, and thyroid autoantibodies.

**Methods:** The study included 80 participants: 40 active Graves' disease patients before treatment, 20 patients with euthyroid autoimmune thyroid disease, and 20 healthy individuals. All Graves' disease patients were evaluated for ophthalmopathy. Measurements included 25(OH)D, high-sensitivity CRP, erythrocyte sedimentation rate, fibrinogen, and anthropometric assessments. Thyroid function tests and autoantibodies were evaluated in the autoimmune thyroid disease group.

**Results:** Vitamin D levels were significantly lower in Graves' disease and autoimmune thyroid disorder patients compared to healthy controls. Lower vitamin D correlated with higher thyroid receptor and anti-thyroid peroxidase antibodies. Patients with thyroid ophthalmopathy had even lower vitamin D levels. Vitamin D deficiency was associated with inflammation and higher body mass index.

**Conclusion:** Lower vitamin D levels were linked to Graves' disease, autoimmune thyroid disorders, and thyroid ophthalmopathy. Vitamin D deficiency was also associated with increased inflammation in these conditions, suggesting a potential role for vitamin D in the pathogenesis of autoimmune thyroid disorders, particularly thyroid ophthalmopathy.

**Keywords:** Autoimmune thyroid disease, Graves disease, inflammation, ophthalmopathy, vitamin D

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Autoimmune thyroid disorders include Graves disease (GD), Hashimoto thyroiditis, and postpartum thyroiditis. The major pathogenesis in Graves disease is TSH receptor antibodies (TRAb) acting against the TSH receptor (TSHR), similar to TSH.<sup>[1–3]</sup> Diffuse goiter and thyrotoxicosis occur due to autoimmune stimulation of the thyroid gland. Besides, retroorbital and dermal infiltrations lead to other

characteristics of the disease, which are ophthalmopathy and dermatopathy.<sup>[4,5]</sup>

Graves disease is the most common cause of hyperthyroidism.<sup>[6]</sup> Graves ophthalmopathy is also observed in almost half of the patients.<sup>[7]</sup> Preferred treatment alternatives for Graves disease are antithyroid treatment, radioactive io-

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dine (RAI), and/or surgery. However, these treatments do not target the pathogenesis but only provide symptomatic cure. Mostly, permanent remission is not achieved after long-term therapies.<sup>[8]</sup>

The main function of vitamin D is the absorption of calcium and phosphate and maintenance of body calcium/phosphate balance along with PTH. It is well proven that, besides calcium and phosphate metabolism, vitamin D has many effects on growth and development, such as cell differentiation, brain development, and the immune system. Vitamin D deficiency is implicated in rickets and osteomalacia, as well as multiple sclerosis, type 1 diabetes, several cancers, immune system disorders, and a tendency toward infectious diseases.<sup>[9]</sup> The discovery of vitamin D receptors (VDR) in many tissues led to additional studies beyond calcium and phosphate metabolism. Identification of VDRs on almost all immune system cells, mainly on active T and B lymphocytes and antigen-presenting cells such as activated macrophages and dendritic cells, suggested its role in immune regulation.<sup>[10]</sup>

After the discovery of the relationship between vitamin D, immune function, and autoimmune disorders, its association with autoimmune thyroid disorders has also been taken into consideration.<sup>[11]</sup> In animal models, if cyclosporin was given with vitamin D supplements for the treatment of autoimmune thyroid disorder, disease remission was accelerated. Also, in a study on mice, subjects with vitamin D deficiency had a tendency toward thyrotoxicosis.<sup>[12]</sup> In studies on humans, vitamin D levels in Graves patients were significantly lower than in control groups.<sup>[13]</sup> In various studies, vitamin D levels have been found to be associated with obesity, inflammation, and thyroid function tests.<sup>[13]</sup>

In this study, we aimed to evaluate the role of vitamin D in the activation of Graves disease and the pathogenesis of autoimmune thyroid disorders. Besides, we planned to investigate whether a significant alteration existed in inflammatory markers with Graves disease activation or autoimmune thyroid disorder and also the possible relation of inflammatory markers and thyroid ophthalmopathy with vitamin D.

## Methods

### Study Design and Participants

The study consisted of three groups, the first of which included 40 active Graves patients; the second, 20 euthyroid patients with autoimmune thyroid disease (ATD); and the third, 20 healthy controls. In all groups, patients had similar age and gender characteristics. In the Graves group, newly diagnosed Graves patients who had thyrotoxicosis and TRAb positivity or remitted Graves patients who were

reactivated and had thyrotoxicosis were included before starting antithyroid treatment. The autoimmune thyroid disease group included patients who were under follow-up and euthyroid while using L-thyroxin treatment. The control group consisted of healthy volunteers who did not have a goiter on physical examination and were euthyroid.

### Clinical Assessments

Body weight, height, and waist measurements were taken, and body mass index (BMI) was calculated according to the body weight (kg)/height (m<sup>2</sup>) formula for all patients. All patients admitted with active Graves disease were evaluated for ophthalmopathy by ophthalmological examination and orbital MRI if required. According to the findings, patients with Graves disease were classified as with and without ophthalmopathy. None of the euthyroid patients with autoimmune thyroid disease or the control group had ophthalmopathy.

### Laboratory Measurements

Blood tests were performed after at least 8 hours of fasting. In all patients, 25(OH)D, serum calcium, phosphate, total alkaline phosphatase (ALP), parathormone, albumin, as well as inflammatory markers, including high-sensitivity C-reactive protein (hsCRP), erythrocyte sedimentation rate (ESR), and fibrinogen levels, were measured. Serum calcium, phosphorus, albumin, and parathormone (PTH) levels were also studied since the levels might be affected by vitamin D. Serum calcium levels were corrected according to serum albumin levels.

In the active Graves group, TSH receptor antibody (TRAb), anti-thyroid peroxidase antibody (anti-TPO), anti-thyroglobulin antibody (anti-Tg), free T3 (FT3), free T4 (FT4), and TSH levels were recorded. In the autoimmune thyroid disease group and the control group, anti-TPO, anti-Tg, FT3, FT4, and TSH levels were also measured. In all patients, 24-hour urine was collected, and urinary calcium excretion was calculated.

Patients were included in the study during fall and winter in order to exclude seasonal effects on vitamin D measurements. Patients using drugs that may affect vitamin D levels, those who have diseases related to calcium, phosphate, or bone metabolism, renal or hepatic failure, or chronic inflammatory conditions were not included in the study.

To measure 25(OH)D levels, blood was centrifuged for 10 minutes at 3000 rpm, and sera were separated, stored, and frozen at -20°C until analysis. 25(OH)D was measured by the ELISA method using immunodiagnostic kits with a Biotech Microplate (Biotech ELx 800, USA) analyzer.

## Ethical Approval

This study was undertaken at Eskisehir Osmangazi University Medical Faculty, Department of Endocrinology and Metabolism, and the study was evaluated and approved by the Eskisehir Osmangazi University Medical Faculty Ethical Committee (29.06.2015, No: 80558721/207). Written informed consent was obtained from each participant.

## Statistical Analysis

Statistical analysis of the variables was performed using SPSS 21.0. Categorical measures were presented as numbers and percentages; numerical outcomes as mean and standard deviation. The chi-square test was used for comparison of categorical variables between groups. Distribution of numerical variables was evaluated with the Kolmogorov–Smirnov test.

If assumptions were met, independent t-tests were used for between-group comparisons of numerical values (patient–control, vitamin D deficiency +/–, etc.); otherwise, the Mann–Whitney U test was used. For comparisons of numerical values between more than two groups, one-way analysis of variance was used if assumptions were met; otherwise, the Kruskal–Wallis test was applied.

For significant cases, dual subgroup comparisons were performed using relevant post hoc tests (Scheffé, Bonferroni, Tamhane, etc.) or Bonferroni-corrected Mann–Whitney U tests. Correlations between numerical variables were assessed using Spearman correlation coefficients. In all tests, statistical significance was accepted as  $p < 0.05$ ,  $p < 0.01$ , or  $p < 0.001$ .

## Results

### Biochemical and Anthropometric Parameters

Serum phosphate levels of the patients with active Graves disease were significantly lower than those of healthy subjects ( $p = 0.026$ ). Serum corrected calcium, total alkaline phosphatase, parathormone, 24-hour urinary calcium excretion level, and inflammatory parameters, including ESR, hsCRP, and fibrinogen levels, did not differ significantly between the groups. BMI and waist circumference of the patients with active Graves disease were significantly lower than those of patients with autoimmune thyroid disease and the healthy group ( $p = 0.024$ ,  $p < 0.001$ , respectively) (Table 1).

### Serum 25(OH)D Levels in Study Groups

The mean 25(OH)D levels were found to be 13.56 ng/ml in patients with active Graves disease, 13.26 ng/ml in patients with autoimmune thyroid disease, and 22.09 ng/ml in the healthy control group. Serum 25(OH)D levels of the patients with active Graves disease and those with autoimmune thyroid disorders were significantly lower than those of the healthy group ( $p = 0.03$ ) (Table 1–3, Fig. 1).

In our study, 30 of 40 active Graves disease patients (75%), 17 of 20 autoimmune thyroid disease patients (85%), and 10 of 20 individuals in the healthy control group (50%) had 25(OH)D levels below 20 ng/ml and had severe vitamin D deficiency. Moreover, when 30 ng/ml was selected as the lower limit for 25(OH)D level, 39 of 40 active Graves disease patients (97.5%), 19 of 20 autoimmune thyroid disease patients (75%), and 5 of 20 individuals in the healthy group

**Table 1.** Anthropometric measurements and biochemical parameters of the study groups

Parameter	Active graves (n=40)	ATD (n=20)	Healthy control (n=20)	p	Significant comparisons
25(OH)D (ng/mL)	13.50±7.77	13.26±7.98	22.09±16.54	0.030*	1 vs. 3, 2 vs. 3
Calcium (mg/dL)	9.35±0.43	9.49±0.43	9.43 ± 0.35	0.263	–
Phosphorus (mg/dL)	3.13±0.69	3.43±0.60	3.59±0.55	0.026*	1 vs. 3
ALP (U/L)	74.45±34.26	72.70±31.40	64.65±27.27	0.399	–
PTH (pg/mL)	49.42±17.85	51.85±17.50	49.40±14.62	0.635	–
ESR (mm/h)	6.75±3.84	4.80±4.34	7.55±6.30	0.135	–
hsCRP (mg/dL)	3.19±2.65	2.45±1.98	3.60±2.23	0.232	–
Fibrinogen (mg/dL)	301.70±33.58	286.75±43.10	294.25±36.02	0.414	–
Urinary Calcium (mg/day)	110.32±63.70	107.50±48.90	132.80±78.02	0.720	–
BMI (kg/m <sup>2</sup> )	25.67±4.05	28.45±3.48	27.70±4.05	0.024*	1 vs. 2, 1 vs. 3
Waist Circumference (cm)	92.15±13.32	103.75±11.80	105.20±8.09	0.001***	1 vs. 2, 1 vs. 3

Data are presented as mean ± standard deviation. ATD: Autoimmune thyroid disease; ALP: Alkaline phosphatase; PTH: Parathormone; ESR: Erythrocyte sedimentation rate; hsCRP: High-sensitivity C-reactive protein; BMI: Body mass index. \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$  indicate statistical significance. Group comparisons: 1 = Active graves, 2 = ATD, 3 = Healthy control.

**Table 2.** Comparison of parameters between graves patients with 25(OH)D Levels  $\leq 20$  ng/mL and  $> 20$  ng/mL

Parameter	25(OH)D $\leq$ 20 ng/mL	25(OH)D $>$ 20 ng/mL	P
Phosphorus (mg/dL)	3.14 $\pm$ 0.61	3.77 $\pm$ 0.54	<0.001***
ALP (U/L)	79.82 $\pm$ 32.87	51.08 $\pm$ 16.38	<0.001***
PTH (pg/mL)	53.17 $\pm$ 17.40	42.21 $\pm$ 12.55	0.008**
ESR (mm/h)	6.59 $\pm$ 4.66	6.13 $\pm$ 4.99	0.693
hsCRP (mg/dL)	3.20 $\pm$ 2.61	2.86 $\pm$ 1.81	0.574
Fibrinogen (mg/dL)	294.35 $\pm$ 37.66	300.43 $\pm$ 35.09	0.507
Urinary Calcium (mg/day)	92.35 $\pm$ 44.27	171.95 $\pm$ 72.02	<0.001***
TRAb (U/L)	11.92 $\pm$ 12.30	2.94 $\pm$ 1.21	0.028**

Data are presented as mean  $\pm$  standard deviation. ALP: Alkaline phosphatase; PTH: Parathormone; ESR: Erythrocyte sedimentation rate; U Calcium: Urinary calcium; TRAb: Thyroid-stimulating hormone receptor antibody; Phos: Serum phosphorus. \*p<0.05, \*\*p<0.01, \*\*\*p<0.001 indicate statistical significance.

**Table 3.** Correlations between 25(OH)D levels and biochemical parameters in active graves patients

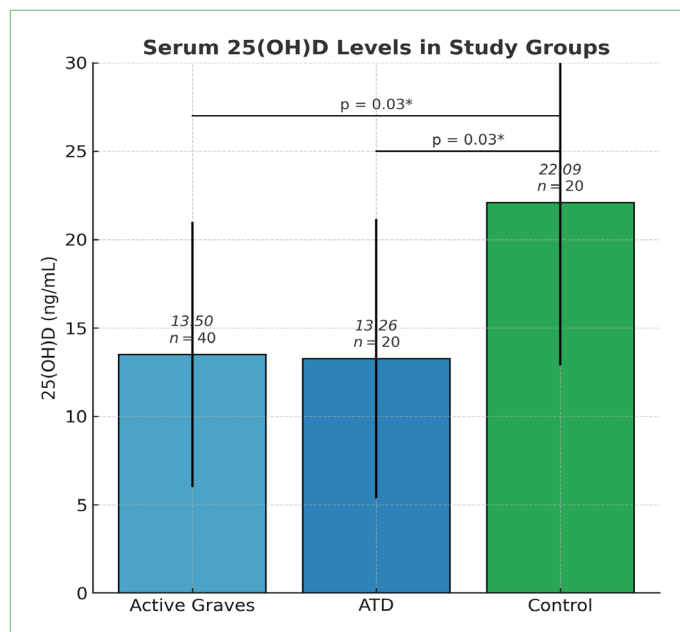
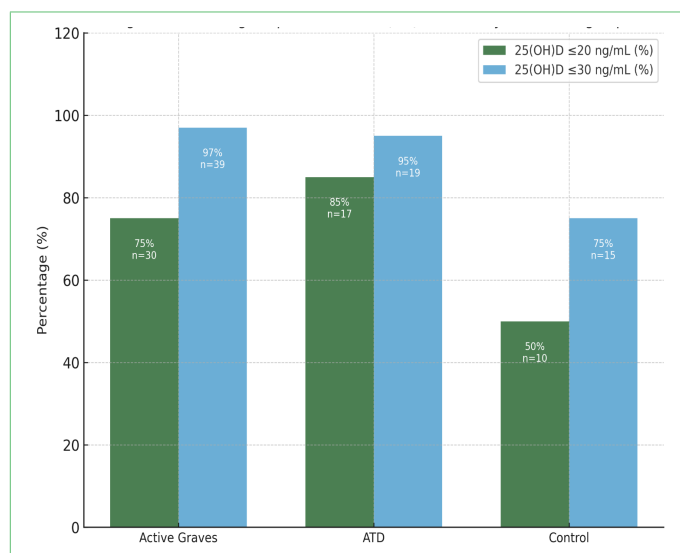
Parameter	r	p
Calcium (mg/dL)	0.565	<0.001***
Phosphorus (mg/dL)	0.551	<0.001***
ALP (U/L)	-0.669	<0.001***
PTH (pg/mL)	-0.648	<0.001***
ESR (mm/h)	-0.402	0.010*
hsCRP (mg/dL)	-0.502	<0.001***
Urinary Calcium (mg/day)	0.658	<0.001***
TRAb (U/L)	-0.363	0.021*

r: Pearson correlation coefficient. ALP: Alkaline phosphatase; PTH: Parathormone; ESR: Erythrocyte sedimentation rate; U Calcium: Urinary calcium; TRAb: Thyroid-stimulating hormone receptor antibody. \*p<0.05, \*\*p<0.01, \*\*\*p<0.001 indicate statistical significance.

(25%) had 25(OH)D levels below 30 ng/ml and had insufficient vitamin D levels. The ratio of the patients with vitamin D levels below 20 ng/ml and 30 ng/ml to the total number of patients in the groups is shown in Figure 2.

### Vitamin D Levels and Thyroid Ophthalmopathy

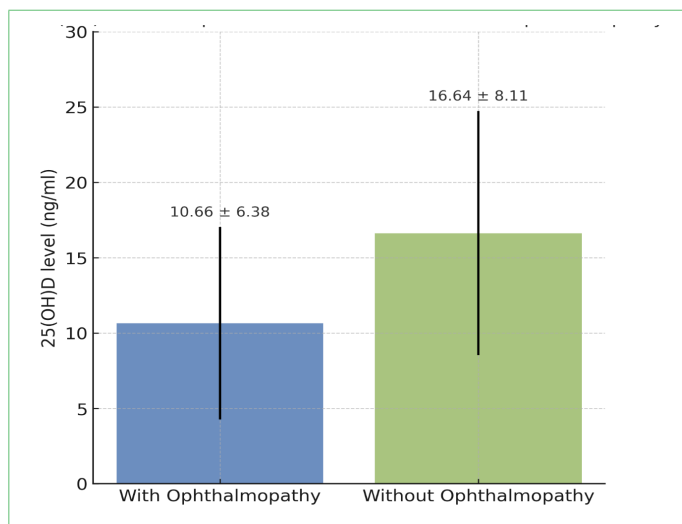
Among Graves disease patients, 21 patients had thyroid ophthalmopathy, and 19 did not have thyroid ophthalmopathy. The mean 25(OH)D level was 10.66 ng/ml in patients with thyroid ophthalmopathy and 16.64 ng/ml in patients without thyroid ophthalmopathy. 25(OH)D levels of the Graves disease patients with ophthalmopathy were significantly lower than those of the Graves disease patients without ophthalmopathy (p=0.016) (Fig. 3). Serum TRAb levels were also significantly higher in patients with

**Figure 1.** 25(OH)D levels in active Graves disease (n=40, 13.50 $\pm$ 7.7 ng/ml), autoimmune thyroid disease (n=20, 13.26 $\pm$ 7.9 ng/ml), and the control group (n=20, 22.09 $\pm$ 16.5 ng/ml, p=0.03).**Figure 2.** Percentage of 25(OH)D level less than or equal to 20 ng/ml and 30 mg/dl in active Graves disease [(n=40, n=30( $\leq 20$  ng/ml), n=39 ( $\leq 30$  ng/ml)], autoimmune thyroid disease (ATD) [(n=20, n=17( $\leq 20$  ng/ml), n=19 ( $\leq 30$  ng/ml)] and the control group [(n=20, n=10( $\leq 20$  ng/ml), n=15( $\leq 30$  ng/ml), p<0.05].

Graves disease who had 25(OH)D levels  $\leq 20$  ng/ml compared to Graves patients with 25(OH)D levels  $> 20$  ng/ml (11.92 $\pm$ 12.30 vs. 2.94 $\pm$ 1.21, p=0.028).

### Correlation Analyses in Graves' Disease

In patients with Graves disease, 25(OH)D levels correlated positively with serum calcium (r=0.565, p<0.001), uri-



**Figure 3.** 25(OH)D levels in patients with Graves ophthalmopathy (n=21, 10.66±6.38 ng/ml), and without ophthalmopathy (n=19, 16.64±8.11 ng/ml, p=0.016).

nary calcium ( $r=0.363$ ,  $p=0.021$ ), and serum phosphorus ( $r=0.551$ ,  $p<0.001$ ) levels. There was also a significant negative correlation between 25(OH)D levels and serum total ALP ( $r=-0.669$ ,  $p<0.001$ ), PTH ( $r=-0.648$ ,  $p<0.001$ ), ESR ( $r=0.402$ ,  $p=0.01$ ), hsCRP ( $r=-0.502$ ,  $p<0.001$ ), and TRAb ( $r=0.363$ ,  $p=0.021$ ) levels. In all patients, including those with autoimmune thyroid disease and Graves disease, 25(OH)D levels also correlated negatively with anti-TPO levels ( $r=-0.310$ ,  $p=0.016$ ).

## Discussion

The prevalence of vitamin D deficiency is globally rising, and it is becoming an important health problem. Many ecological factors, such as seasonal change, local climate, characteristics of the atmosphere and altitude, and lifestyle features including clothing, diet, and exposure to sunlight, all affect plasma vitamin D levels.<sup>[14,15]</sup>

In recent years, it has been shown that vitamin D has not only effects on calcium, bone, and mineral metabolism but also on many other organ systems. Vitamin D has been implicated in cardiovascular function and blood pressure, innate and adaptive immunity, insulin secretion, occurrence of metabolic syndrome and diabetes, muscle function and strength, production of cancer cells, and counteraction of infectious diseases. Vitamin D deficiency has been associated with many diseases that have an autoimmune pathogenesis.<sup>[16]</sup> This relationship between autoimmune disorders and vitamin D deficiency has led to studies in autoimmune thyroid disorders, and many researchers have found associations that might be valuable in shedding light on the pathogenesis.<sup>[17-21]</sup>

In our study, we found that vitamin D levels of patients with active Graves disease and those with autoimmune thyroid disease were lower than those of healthy controls. Also, more patients with Graves disease and autoimmune thyroid disorders had vitamin D levels below 20 ng/ml and below 30 ng/ml compared to the healthy group. However, there was no significant difference between active Graves disease patients and autoimmune thyroid disease patients regarding vitamin D levels. This shows that vitamin D may play a role in the emergence of thyroid autoimmunity.

However, low levels of vitamin D do not seem to be as operative in the activation of Graves disease, since the achievement of the euthyroid state does not alter its serum levels. Besides, it may be the consequence of not testing and replacing vitamin D after the onset of autoimmune thyroid disease as a routine practice. We, like previous studies, found that vitamin D deficiency might be a risk factor for autoimmune thyroid disorders. Meanwhile, since no difference was found between vitamin D levels of the active Graves group and the autoimmune thyroid group, it may suggest that vitamin D deficiency generally leads to autoimmune pathologies and that its unique role in Graves pathogenesis is less apparent.

Supporting the role of vitamin D deficiency in the development of autoimmune thyroid disease, the induction of experimental thyroiditis was shown to be prevented by the administration of active vitamin D.<sup>[1]</sup> In another study conducted on animals, vitamin D-deficient mice were found to be more susceptible to resistant hyperthyroidism after induction with TSH receptor antibody compared to mice replaced with adequate vitamin D.<sup>[2]</sup> In human studies, abnormal thyroid function tests and thyroid antibody titers were found to be more prevalent in patients with deficient vitamin D levels.<sup>[3]</sup> There are data showing polymorphism in the VDR gene to play a role in Graves pathogenesis.<sup>[18]</sup>

In a study, vitamin D levels of newly diagnosed Graves disease patients and patients with Hashimoto thyroiditis and postpartum thyroiditis, all of which are considered autoimmune thyroid disorders, were found to be lower than those of the control group.<sup>[19]</sup> There are also studies showing no difference in 25(OH)D levels between anti-TPO antibody-positive and negative subjects.<sup>[4]</sup> However, overall data about thyroid autoimmunity and vitamin D suggest a link between the two, and our findings support this evidence.

In our study, waist circumference and BMI were lower in patients with active Graves disease. These findings may be related to the weight loss experienced by Graves disease patients during the activation phase of the disease. Also, serum phosphorus levels were significantly lower in pa-

tients with Graves disease compared to both the autoimmune thyroid disease group and the healthy control group. Although the reason for this finding is not apparently clear, it may be related to the phosphaturic effect of PTH increase secondary to low vitamin D levels or the high rates of bone turnover seen in hyperthyroid patients.

When patients with vitamin D deficiency (25(OH)D <20 ng/ml) were compared to patients with 25(OH)D levels >20 ng/ml, serum phosphorus level and urinary calcium excretion rates were significantly lower, and total alkaline phosphatase and PTH levels were significantly higher in patients with deficient vitamin D levels. There was also a positive correlation between 25(OH)D levels and serum calcium, phosphate, and urinary calcium excretion, and a negative correlation between 25(OH)D levels and total alkaline phosphatase and PTH levels. These findings reflect the secondary effects of vitamin D deficiency.

Another important result obtained from this study was that the TRAb levels of patients with Graves disease and vitamin D deficiency were significantly higher compared to those of Graves disease patients with relatively higher vitamin D levels. In accordance with these findings, 25(OH)D levels correlated negatively with TRAb levels and also with inflammatory markers hsCRP and ESR. Also, anti-TPO levels correlated with 25(OH)D levels in all patients with autoimmune thyroid disease. This is an important finding that suggests a role of vitamin D in the emergence of thyroid antibodies. These findings also indicate that low vitamin D levels may induce low-grade inflammation seen in autoimmune thyroid disorders.

In a study, the adaptive immune response developed by dendritic cells stimulated by endogenous antigens such as TSH receptor peptide was shown to have a preventive role in the pathogenesis of Graves disease.<sup>[22,23]</sup> IL-4 rise due to an increase in T helper 2 activity is a mechanism effective in the pathogenesis of Graves disease. However, in Hashimoto thyroiditis, IFN- $\gamma$  rise due to T helper 1 activity is observed. Moreover, T helper 17 and IL-17 were shown to have a role in autoimmune thyroid disorder development. Vitamin D is closely related to T helper 1, T helper 2, and T helper 17 levels and IL-4, IFN- $\gamma$ , and IL-17 levels. Therefore, it is possible that vitamin D deficiency might have a role in the pathogenesis of autoimmune thyroid disorders, including Graves disease.<sup>[24]</sup>

In a previous study, it was shown that vitamin D levels of TRAb-positive Graves patients were significantly lower than those of TRAb-negative patients. In that study, no significant relation was found between vitamin D levels and thyroid antibodies anti-TPO and anti-thyroglobulin levels.<sup>[25]</sup> Ünal et al.<sup>[26]</sup> showed a negative correlation between vi-

tamin D levels and anti-TPO and anti-thyroglobulin levels in a study conducted on newly diagnosed autoimmune thyroid disease patients, including newly diagnosed Graves disease patients.

In our study, in patients with Graves disease activation, a significant negative correlation was found between vitamin D and TRAb levels. Identification of a negative correlation between vitamin D and TRAb levels may indicate that vitamin D deficiency has a role in immune activation.

Another interesting finding of our study was that 25(OH)D levels of Graves disease patients with ophthalmopathy were significantly lower compared to those without ophthalmopathy. To the best of our knowledge, this is the first study to show the relationship between Graves ophthalmopathy, TSH receptor antibodies, and vitamin D deficiency. Main risk factors for ophthalmopathy are suggested to be smoking, male gender, and exposure to radioiodine in Graves disease patients. TSH receptor antibody levels are also valuable in predicting the course of the disease. Our findings suggest that vitamin D deficiency might be listed among the risk factors for ophthalmopathy. Since our study includes a small number of Graves disease patients with ophthalmopathy, larger studies are required to test our hypothesis.

In a study, Mellenthin et al.<sup>[27]</sup> observed a relationship between vitamin D levels and inflammatory parameters. Correlation was investigated between vitamin D, hsCRP, fibrinogen, and total leukocyte count. A negative correlation was observed between vitamin D and hsCRP and fibrinogen. In our study, ESR and hsCRP levels were higher in patients with vitamin D levels  $\leq$ 20 ng/ml than in patients with vitamin D levels >20 ng/ml. Moreover, in the active Graves disease group, there was a negative correlation between vitamin D and ESR and hsCRP. Also, in our study, patients with vitamin D deficiency can be considered to have a tendency toward inflammation. However, there were additional factors that might have a relationship with inflammatory markers, such as Graves disease activation and thyroid ophthalmopathy. For more reliable results, advanced studies are required that specifically target the relationship between vitamin D and inflammation.

There are some limitations to our study that should be acknowledged. First, the relatively small number of patients may limit the generalizability of our findings, and the results should therefore be interpreted with caution. Nevertheless, the study carries clinical value, as it specifically included patients with Graves' disease during the activation period and prior to the initiation of any antithyroid medication, thereby minimizing the potential confounding effects of treatment on vitamin D status and inflammatory mark-

ers. In addition, the cross-sectional design of the study precludes causal inferences; longitudinal studies would be required to establish a definitive relationship between vitamin D deficiency and the pathogenesis of Graves' disease or ophthalmopathy. Despite these limitations, the results provide important preliminary insights and may serve as a basis for future larger-scale, prospective studies.

## Conclusion

In conclusion, our study suggests that vitamin D deficiency is associated with an increased tendency toward systemic inflammation and may play an important role in the pathogenesis of Graves' disease and other autoimmune thyroid disorders. Furthermore, vitamin D deficiency might also contribute to the development and severity of Graves' ophthalmopathy, as indicated by its correlation with both inflammatory markers and higher TRAb levels in affected patients. These findings highlight the possibility that vitamin D status could be an important, yet often overlooked, factor influencing both disease activity and clinical outcomes in patients with autoimmune thyroid disorders. From a clinical perspective, assessment and correction of vitamin D deficiency may represent a simple and cost-effective strategy that could potentially improve disease management and reduce the risk of ophthalmopathy progression. Future research should further clarify the mechanistic role of vitamin D in thyroid autoimmunity and investigate whether vitamin D supplementation, either alone or in combination with standard antithyroid therapy, can provide therapeutic benefits. Longitudinal and interventional studies are warranted to determine whether maintaining adequate vitamin D levels could help prevent disease recurrence, modulate inflammatory activity, and improve quality of life in patients with Graves' disease.

## Disclosures

**Ethics Committee Approval:** The study was approved by the Local Ethical Committee of Eskisehir Osmangazi University with an approval date and number of (29.06.2015, No:80558721/207).

**Informed Consent:** Written consent was obtained from all participants.

**Conflict of Interest:** The authors have no conflicts of interest to declare.

**Financial Disclosure:** The authors declared that this study has received no financial support.

**Use of AI for Writing Assistance:** Not declared.

**Authorship Contributions:** Concept – ME, AA; Design – ME, AA; Supervision – ME, AA; Materials – ME, AA; Data collection and/or processing – ME, AA; Analysis and/or interpretation – ME, AA; Literature search – ME, AA; Writing – ME, AA; Critical review – ME, AA.

**Peer-review:** Externally peer-reviewed.

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## Research Article

# The Effect of MCV on Prognosis in Patients with Gastric Cancer and its Relationship with C-ERBB2 Positivity

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### Abstract

**Objectives:** Many factors considered to influence prognosis in gastric cancers have been investigated. In this study, we aimed to present the demographic characteristics of gastric cancer patients followed in the medical oncology unit, to investigate the effects on prognosis of MCV values measured at diagnosis, after surgery, and after chemotherapy, and to evaluate the effect on prognosis among C-ERB B2–positive patients.

**Methods:** 248 patients who presented to and were followed by the İstanbul Eğitim ve Araştırma Hastanesi Medical Oncology Unit between 2010 and 2015 were examined retrospectively using the hospital automation system and the oncology unit file archive.

**Results:** A total of 248 patients diagnosed with gastric cancer (169 male, 79 female) were included. Among 50 stage 4 patients in whom C-ERB B2 was assessed, 8% (n=4) were 2+, 34% (n=17) were 3+, and 58% (n=29) were negative. Overall survival rates were 62.7% at 1 year, 44.6% at 2 years, 37.7% at 3 years, 30.7% at 4 years, and 28.8% at 5 years. On quantitative analysis of MCV values at diagnosis and after treatment, having MCV > 100 fL at any time point was not statistically significant in terms of prognosis. Likewise, a post-/pre-treatment MCV ratio >1.1 was not statistically significant. These parameters were also evaluated in the C-ERB B2–positive population and no significant difference was detected.

**Conclusion:** Although changes in MCV values did not show a significant effect on prognosis, it was considered that increasing the patient population might yield statistical significance.

**Keywords:** C-ERBB2, Gastric Cancer, MCV

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Cancer is the second most common cause of death in Türkiye after cardiovascular diseases.

Gastric cancer ranks fifth worldwide in cancer incidence and third among causes of cancer-related mortality. It is estimated that approximately 9,000 new gastric cancer cases occur annually in Türkiye. The incidence is about five times higher than in European countries and increases toward the eastern provinces, with the highest rates reported

in Diyarbakır and Van. According to hospital registries and the Ministry of Health Cancer Control Department, gastric carcinoma is the fifth most common cancer in men and the sixth in women.<sup>[1]</sup> The average age at diagnosis in Türkiye is 64 years, with the youngest reported at 19 and the oldest at 85.<sup>[2]</sup>

The male-to-female ratio in gastric cancer is 2:1. The disease is rare before the age of 40, and its incidence increas-

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es with age, peaking in the sixth decade. Since the 1930s, the incidence of gastric cancer has declined in the United States and now ranks around the 15<sup>th</sup> most common cancer.<sup>[3]</sup> Although the precise reason is unclear, this decline has been attributed to planned public health services, advances in cancer screening, improved diet, reduced smoking, increased vitamin C intake, and active control of *Helicobacter pylori* infection.<sup>[4]</sup> Despite this, gastric cancer remains difficult to treat due to late diagnosis; even patients eligible for curative surgery with favorable prognostic indicators are often lost due to recurrence. Nevertheless, the use of postoperative chemoradiotherapy and preoperative chemotherapy has improved survival.<sup>[5,6]</sup>

The anatomic distribution of gastric cancer has shifted over the years toward the proximal stomach. Over the past two decades, especially in patients under 40 years of age, there has been a sharp increase in proximal gastric cancers, from approximately 10% to 30%. This may reflect differences in risk factors between proximal and distal gastric cancers. Despite the decline in the United States, the 5-year survival rate remains around 10–20%.

While the effects of some factors on prognosis in gastric cancer have been consistently observed, results vary among studies. Factors studied include gender, age, tumor location, tumor diameter, macroscopic type, histologic grade, stage, metastatic lymph node status, tumor markers (CEA, CA 19-9), preoperative albumin, perioperative hemogram parameters, type of operation, lymph node dissection (D1, D2), chemotherapy (yes/no), and radiotherapy in resected gastric cancer.

In this study, we retrospectively evaluated proposed prognostic factors—particularly elevations and changes in MCV—and investigated their effects on survival.

## Methods

This retrospective study was approved by the Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (approval number: 2016/04-07, approval date: 25 April 2016). The study was conducted in accordance with the Declaration of Helsinki.

In our thesis, data for 248 patients who presented with a diagnosis of gastric cancer to the Department of Medical Oncology, Health Sciences, Istanbul Training and Research Hospital Outpatient Clinic between January 2010 and December 2013 were obtained retrospectively from the oncology unit file archive and the hospital automation system. Variables potentially associated with survival—age, gender, type of operation, disease stage (WHO 2010), histologic type, C-ERB B2 status, receipt of systemic adjuvant therapy, tumor markers such as CA 19-9 and CEA, MCV at

diagnosis, and the ratio of post-treatment MCV to diagnostic MCV—were examined. CEA and CA 19-9 were measured using the Dxl 800 Access (Beckman Coulter) analyzer, and hemogram parameters using the Mindray BC-6800 device. We also evaluated the effects on survival of these prognostic factors within the subgroup in whom C-ERB B2 was tested, comparing C-ERB B2–positive and –negative patients. At last follow-up, patients were categorized as disease-free, with disease, or deceased; deaths were verified through the national death notification system.

Overall survival (OS) was defined as the time from diagnosis to death, or to the date patient information was last updated for those alive. Disease-free survival (DFS) was defined as the time from diagnosis to local recurrence and/or development of metastasis.

For statistical analysis, SPSS 15.0 for Windows was used. Descriptive statistics were presented as number and percentage for categorical variables, and mean, standard deviation, minimum, and maximum for numerical variables. Comparisons between two independent groups were performed using the Student's t-test when normal distribution assumptions were met and the Mann–Whitney U test when they were not. Ratios of categorical variables between groups were tested with the chi-square test; when assumptions were not met, the Monte Carlo simulation method was applied. Survival analyses were performed using the Kaplan–Meier method. A statistical alpha significance level of  $p < 0.05$  was accepted.

## Results

### General Patient Characteristics

A total of 248 patients diagnosed with gastric cancer were included: 169 male and 79 female, with a mean age of  $57.7 \pm 10.8$  (range 28–80) years. According to TNM staging, 5.7% ( $n=14$ ) were stage 1a, 3.6% ( $n=9$ ) stage 1b, 8.5% ( $n=21$ ) stage 2a, 9.7% ( $n=24$ ) stage 2b, 10.1% ( $n=25$ ) stage 3a, 9.7% ( $n=24$ ) stage 3b, 15.8% ( $n=39$ ) stage 3c, and 36.8% ( $n=91$ ) stage 4. By histologic subtype, 71.9% ( $n=161$ ) were adenocarcinoma, 3.1% ( $n=7$ ) GIST, 4% ( $n=9$ ) neuroendocrine tumor, and 21% ( $n=47$ ) signet-ring cell carcinoma. Of 248 patients, 36.3% ( $n=90$ ) were inoperable, 48.4% ( $n=120$ ) underwent total gastrectomy, 14.5% ( $n=36$ ) subtotal gastrectomy, and 0.4% distal esophagectomy with proximal gastrectomy.

Chemotherapy was administered to 75.8% ( $n=188$ ). Regimens included MAYO (fluorouracil, folinic acid) in 78 patients (41.5%), DCF (docetaxel, cisplatin, fluorouracil) in 58 (30.9%), ECF (epirubicin, cisplatin, fluorouracil) in 35 (18.6%), cisplatin-capecitabine in 6 (3.2%), and other protocols (cisplatin-etoposide, DC) in 4 (3.3%). The duration of

chemotherapy varied between 1 and 6 months depending on tolerability and survival (Table 1).

### Tumor Location

Tumor localization could be evaluated in 55% (n=135) of patients: antrum 51.9% (n=70), pylorus 5.9% (n=8), lesser curvature 7.4% (n=10), greater curvature 3% (n=4), corpus 5.2% (n=7), fundus 5.9% (n=8), cardia 16.3% (n=22), gas-

troesophageal junction 2.2% (n=3), diffuse/entire stomach 4.4% (n=6), posterior wall 0.7% (n=1).

### C-ERBB2 / FISH

C-ERBB2 IHC staining was performed in 50 patients: 34% (n=17) were 3+, 8% (n=4) were 2+, and 58% (n=29) were negative. FISH was performed in 43 of these patients: 37.2% (n=16) were positive and 62.8% (n=27) negative. FISH was not performed in 4 C-ERB B2-negative patients, 1 patient with C-ERB B2 2(+), and 2 patients with C-ERB B2 3(+). All patients with C-ERB B2 3(+) who underwent FISH were FISH-positive; among the four C-ERB B2 2(+) patients, one was FISH(+), two FISH(-), and one not tested by FISH.

### Tumor Markers

CEA was measured in 174 patients. Mean CEA was 26.3±124.2 (0–1083); 23.6% (n=41) had CEA > 5 and 76.4% (n=133) ≤5. CA 19-9 was 890.1±7883.2 (0.6–102,255); 27.6% (n=48) had CA 19-9 > 37 and 72.4% (n=126) ≤37 (Table 2).

### MCV Values

At diagnosis, the mean MCV was 82.1±10.0 fL (20.9–105.3); 97.9% (n=233) had MCV<99 and 2.1% (n=5) had MCV>99. After treatment, the mean MCV was 89.8±9.4 fL (55.1–113.8); 87.5% (n=189) had MCV<99 and 12.5% (n=27) had MCV >99. A 10% increase in MCV after treatment (post/diagnosis ratio >1.1) was evaluated as a separate parameter for its potential prognostic value: 60.2% (n=127) had such an increase, while 39.8% (n=84) did not (Table 3).

### Patient Status and Survival Rates

Final status was available for all 248 patients: 39.5% (n=98) disease-free, 2.5% (n=6) with disease, and 58% (n=144) deceased.

Overall survival rates were 62.7% at 1 year, 44.6% at 2 years, 37.7% at 3 years, 30.7% at 4 years, and 28.8% at 5 years. Median estimated survival was 20.3 months (SE 3.0; 95% CI 14.5–26.2) (Table 4a, b).

Table 1. Demographic and clinical characteristics	
Variable	Mean ± SD (Min–Max) / n (%)
Age	57.7±10.8 (28–80)
Sex	
Male	169 (68.1)
Female	79 (31.9)
Stage (new staging system)	
IA	14 (5.7)
IB	9 (3.6)
IIA	21 (8.5)
IIB	24 (9.7)
IIIA	25 (10.1)
IIIB	24 (9.7)
IIIC	39 (15.8)
IV	91 (36.8)
Operability / Surgical type	
Inoperable	90 (36.3)
Total gastrectomy	120 (48.4)
Subtotal gastrectomy	36 (14.5)
Distal esophagectomy + proximal gastrectomy	1 (0.4)
Histologic subtype	
Adenocarcinoma	161 (71.9)
GIST	7 (3.1)
Neuroendocrine tumor	9 (4.0)
Signet-ring cell adenocarcinoma	47 (21.0)
Chemotherapy administered	188 (75.8)
Chemotherapy regimen	
Cisplatin–Etoposide	4 (2.1)
Cisplatin–Capecitabine	6 (3.2)
DCF (Docetaxel–Cisplatin–5FU)	58 (30.9)
Supportive	5 (2.7)
ECF (Epirubicin–Cisplatin–5FU)	35 (18.6)
FUF(A) (5FU–Leucovorin)	78 (41.5)
Herceptin–Cisplatin	1 (0.5)
Imatinib	1 (0.5)

Table 2. CEA and CA 19-9 levels	
Variable	Mean ± SD (Min–Max)/n (%)
CEA (Mean ± SD, Min–Max)	26.3±124.2 (0–1083)
CEA n (%)	
>5	41 (23.6)
≤5	133 (76.4)
CA 19-9 (Mean ± SD, Min–Max)	890.1±7883.2 (0.6–102255)
CA 19-9 n (%)	
>37	48 (27.6)
≤37	126 (72.4)

**Table 3.** MCV values at diagnosis and after treatment

Variable	Mean ± SD (Min–Max) / n (%)
MCV at diagnosis (Mean ± SD, Min–Max)	82.1±10.0 (20.9–105.3)
MCV at Diagnosis n (%)	
≤99	233 (97.9)
>99	5 (2.1)
MCV After treatment (Mean ± SD, Min–Max)	89.8±9.4 (55.1–113.8)
MCV after treatment n (%)	
≤99	189 (87.5)
>99	27 (12.5)
Post/Diagnosis MCV ratio (Mean ± SD, Min–Max)	
Post/Diagnosis MCV ratio n (%)	
≤1.1	127 (60.2)
>1.1	84 (39.8)

**Table 4a.** Survival outcomes

Variable	Median	SE	95% CI
Estimated survival time (months)	20.3	3.0	14.5–26.2

**Table 4b.** Cumulative survival rates

Time	Survival (%)
6 months	79.2
1 year	62.7
2 years	44.6
3 years	37.7
5 years	30.7
6 years	28.8

**Survival by Stage**

Among patients alive at last follow-up, stage distribution was: 1a 13.5% (n=14), 1b 6.7% (n=7), 2a 11.5% (n=12), 2b 11.5% (n=12), 3a 12.5% (n=13), 3b 8.7% (n=9), 3c 19.2% (n=20), and 4 16.3% (n=17). Among the deceased: 1a 0%, 1b 1.4% (n=2), 2a 6.3% (n=9), 2b 8.4% (n=12), 3a 8.4% (n=12), 3b 10.5% (n=15), 3c 13.3% (n=19), and 4 51.7% (n=74). Stage distributions differed significantly between groups (p<0.001).

**Other Survival Comparisons**

Survival differed significantly by histologic subtype (adenocarcinoma, GIST, signet-ring cell carcinoma, neuroendocrine tumor) (p<0.001). Survival differed significantly by tumor stage (Fig. 1).

By operability, subtotal gastrectomy was associated with significantly different survival (p<0.001 across groups). Receipt of chemotherapy was also associated with survival (p=0.019).

By C-ERB B2 status, among 21 positive patients 42.8% (n=9) were alive and 57.2% (n=12) deceased; among 29 negative patients 44.8% (n=13) were alive and 55.2% (n=16) deceased—no significant difference (p=0.890).

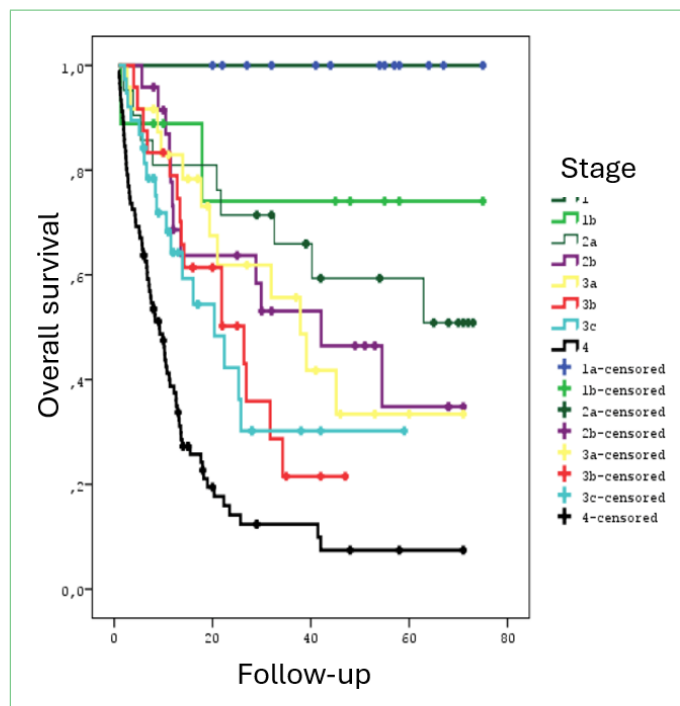
For CEA, among 174 tested patients, 76 were alive; of these, 13.2% (n=10) had high CEA and 86.8% (n=66) low CEA. Among 98 deceased patients, 31.6% (n=31) had high CEA and 68.4% (n=67) low CEA; elevated CEA indicated higher mortality (p<0.004).

For CA 19-9, among 174 tested patients, 76 were alive; of these, 14.5% (n=11) had high CA 19-9 and 85.5% (n=65) low. Among 98 deceased patients, 37.8% (n=37) had high CA 19-9 and 62.2% (n=61) low; elevated CA 19-9 indicated higher mortality (p<0.001) (Table 5a,b).

No significant associations with mortality were found for diagnostic MCV, post-treatment MCV, or a post/diagnosis MCV ratio >1.1 (Table 6).

In the subgroup with C-ERB B2 testing, overall survival did not differ by C-ERB B2 status (p=0.859) (Fig. 2).

Among patients with C-ERB B2 testing, no significant differences in survival were observed according to post/diagnosis MCV increase (10%) within C-ERB B2-positive or -negative groups.



**Figure 1.** Overall survival by stage.

**Table 5a.** Survival analysis by CEA and CA 19-9 levels

Variable	Alive (Mean $\pm$ SD or n (%))	Exitus (Mean $\pm$ SD or n (%))	P
CEA (Mean $\pm$ SD)	3.6 $\pm$ 8.1	43.9 $\pm$ 163.5	0.006
>5	10 (13.2)	31 (31.6)	0.004
$\leq$ 5	66 (86.8)	67 (68.4)	

**Table 5b.** CA 19-9 levels and survival

Variable	Alive (Mean $\pm$ SD or n (%))	Exitus (Mean $\pm$ SD or n (%))	P
CA 19-9 (Mean $\pm$ SD)	45.7 $\pm$ 133.7	1544.8 $\pm$ 10480.0	0.001
>37	11 (14.5)	37 (37.8)	0.001
$\leq$ 37	65 (85.5)	61 (62.2)	

**Table 6.** Survival analysis by MCV levels at diagnosis, after treatment, and post/diagnosis ratio

Variable	Alive (Mean $\pm$ SD or n (%))	Exitus (Mean $\pm$ SD or n (%))	P
MCV at Diagnosis (Mean $\pm$ SD)	82.6 $\pm$ 8.7	81.7 $\pm$ 10.9	0.770
$\leq$ 99	100 (98.0)	133 (97.8)	1.000
>99	2 (2.0)	3 (2.2)	
MCV After Chemotherapy (Mean $\pm$ SD)	90.8 $\pm$ 8.5	89.2 $\pm$ 10.0	0.208
$\leq$ 99	76 (86.4)	113 (88.3)	0.675
>99	12 (13.6)	15 (11.7)	
Post/Diagnosis MCV ratio (Mean $\pm$ SD)	1.11 $\pm$ 0.12	1.12 $\pm$ 0.26	0.359
$\leq$ 1.1	49 (56.3)	78 (62.9)	0.336
>1.1	38 (43.7)	46 (37.1)	

## Discussion

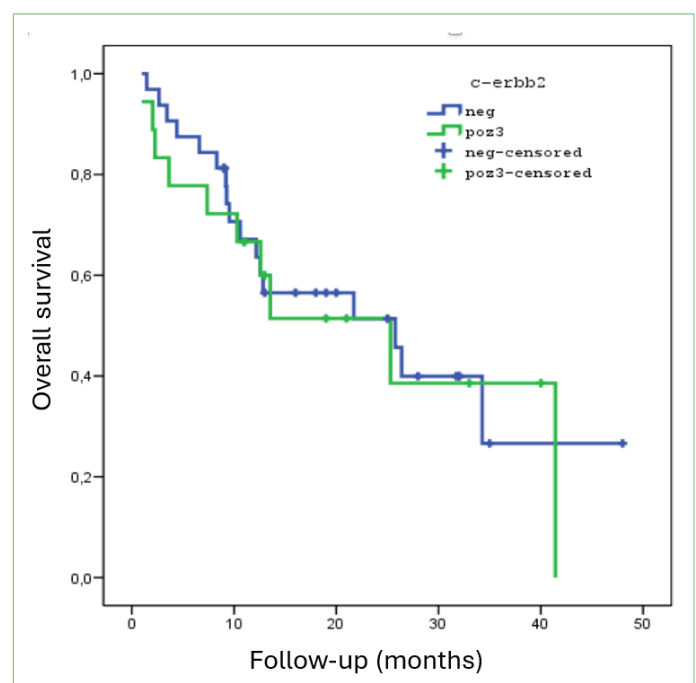
Although the incidence of gastric cancer continues to decline today, it remains the third leading cause of cancer-related death worldwide. The disease is often detected at advanced stages due to late symptoms and diagnosis, minimizing the chance for curative surgery. In countries with high incidence such as Japan, screening programs have increased early-stage detection and improved curative treatment success.

Gastric cancer occurs more frequently in men than in women worldwide—fifth most common in men and sixth in women—and ranks third among cancer-related deaths. In our cohort, 31.9% were women and 68.1% men, consistent with the literature. The average age for gastric cancer in Türkiye is 56; its frequency increases after age 60. Our patients' mean age was 57.7 $\pm$ 10.8.<sup>[7,8]</sup>

By tumor site, 51.9% were antral, 5.9% pyloric, 7.4% lesser curvature, 3% greater curvature, 5.2% corpus, 5.9% fundus, 16.3% cardia, 2.2% gastroesophageal junction, 4.4% diffuse, and 0.7% posterior wall. Histologically, 71.9% were adenocarcinoma, 3.1% GIST, 4% neuroendocrine tumor, and 21% signet-ring cell carcinoma. TNM distribution was: stage 1a 5.7%, 1b 3.6%, 2a 8.5%, 2b 9.7%, 3a 10.1%, 3b 9.7%, 3c 15.8%, and 4 36.8%. Compared with the literature (Table 4), proportions up to stage 3B were almost identical; our stage 3C was slightly higher and stage 4 slightly lower.

Despite short survival, many prognostic factors relate to outcomes after treatment in gastric cancer. The most important are stage and lymph node metastasis; others include gender, age, tumor location and size, histologic grade, perineural invasion, vascular invasion, intestinal metaplasia, preoperative tumor markers (CEA, CA 19-9), preoperative albumin, received treatments, and hemogram parameters. Knowing prognosis after treatment is important not only for postoperative survival assessment but also for determining whether closer follow-up and earlier treatment at recurrence are warranted.

Links between immune system–cancer progression and hematologic parameters—leukocyte and platelet counts, MPV, and MCV—have been studied, demonstrating prognostic importance.<sup>[9–11]</sup> The neutrophil-to-lymphocyte ratio (NLR) has been shown as a marker of systemic inflammatory response; similarly, the preoperative platelet-to-lymphocyte ratio is an important prognostic factor in pancreatic

**Figure 2.** Overall survival by C-ERBB2 status.

cancer.<sup>[12]</sup> NLR and thrombocytosis have also been reported as prognostic factors in cancer patients.<sup>[13,14]</sup>

High MCV levels occur in alcohol users and in folate or vitamin B12 deficiency. Elevated MCV is more common among alcohol consumers with inactive aldehyde dehydrogenase-2 deficiency; alcohol use predisposes to esophageal squamous cell carcinoma. In May 2013, Yu-Zhen Zhang et al. hypothesized a link between esophageal squamous cell carcinoma and high MCV, evaluated preoperative MCV in 298 patients via ROC analysis (cut-off 95.6 fL), and concluded that higher preoperative MCV correlated with worse overall survival. Another reason to suspect an association between MCV and prognosis is that macrocytosis may indicate malnutrition, a negative prognostic factor. In gastric cancer, dysphagia may reduce oral intake and lower electrolyte, glucose, and amino acid concentrations, reducing the crystalloid osmotic pressure—the major regulator of erythrocyte volume—and thus causing erythrocyte enlargement.<sup>[15]</sup>

Jung et al.<sup>[16]</sup> evaluated MCV in “Changes in the mean corpuscular volume after capecitabine treatment are associated with clinical response and survival in patients with advanced gastric cancer. Capecitabine is known to increase MCV. Eighty-nine patients receiving first-line capecitabine+cisplatin ( $\pm$ epirubicin) had MCV measured on day 1 and week 3; an increase  $>10$  fL was defined as macrocytosis. Day-1 macrocytosis was present in  $\sim 90\%$  and week-3 macrocytosis in 42%. The study assessed the relationship between macrocytosis and response; patients received chemotherapy every 3 weeks absent toxicity or progression, and were evaluated by abdominopelvic CT or baseline imaging after two cycles. Analyses considered age, sex, ECOG, treatment arm ( $\pm$ epirubicin), peritoneal dissemination, baseline hemoglobin, number of cycles, and cumulative capecitabine dose. Macrocytosis was associated with greater treatment efficacy and favorable overall and progression-free survival.

Based on these data, we investigated whether elevated MCV at diagnosis is a negative prognostic factor and whether post-chemotherapy MCV elevation might be a positive prognostic factor. We also evaluated general demographics such as age, sex, stage, tumor site, CA 19-9, CEA, and C-ERBB2 positivity.

Our survival rates were 62.7% at 1 year, 44.6% at 2 years, 37.7% at 3 years, 30.7% at 4 years, and 28.8% at 5 years. By stage, survival was significantly higher in stages 1a ( $p<0.001$ ) and 1b, and—as expected—declined with increasing stage thereafter. Another survival marker was elevated CA 19-9: among 174 tested patients, 14.5% of survivors had high CA 19-9 versus 37.8% of deceased patients ( $p<0.001$ ). No significant associations with mortality were

observed for diagnostic MCV, post-treatment MCV, or a post/diagnosis MCV ratio  $>1.1$ .

At diagnosis, only five patients had MCV above our laboratory cut-off of 99 fL; the remaining 243 were below 99 fL, suggesting that a ROC-based cut-off might be explored in a future analysis. Among 248 patients with diagnostic MCV, post-treatment MCV was available for 211; 84 (39.8%) had a  $\geq 10\%$  increase (post/diagnosis  $>1.1$ ) and 127 (60.2%) did not. A 10% increase in MCV was not associated with mortality (Table 6).

We also examined the frequency of C-ERB B2 positivity and its relationship with MCV. In Western countries, because many gastric cancer patients are diagnosed at unresectable stages, systemic chemotherapy is the mainstay to improve survival and quality of life. Objective response with combination regimens can reach 30–60%. Platinum agents, fluoropyrimidines, anthracyclines, taxanes, and irinotecan are used for this purpose. Although many regimens have been tested in randomized trials, a standard protocol has not been agreed upon. Given the poor survival despite chemotherapy, new treatments are being sought. Understanding molecular alterations has enabled targeted therapies aimed at improving survival. HER-2, a transmembrane tyrosine kinase receptor of the EGFR family encoded on chromosome 17q21, activates signaling that influences proliferation, apoptosis, adhesion, migration, and differentiation. Acting as an oncogene, high-level amplification leads to protein overexpression, conferring a survival advantage to malignant cells. HER-2 is positive in 10–34% of invasive breast cancers and is associated with poor prognosis and inferior response to chemotherapy and endocrine therapy. HER-2 overexpression has also been observed in colon, bladder, ovary, endometrium, lung, cervix, head-neck, esophagus, and gastric cancers. Trastuzumab, a monoclonal antibody binding the extracellular domain of HER-2, improves survival in HER-2–positive breast cancer.

TNM classification is the most important prognostic factor in gastric cancer; however, because prognosis varies among patients with the same stage, additional parameters are needed to delineate biological subgroups. HER-2 overexpression in gastric cancer was first described immunohistochemically in 1986; in 1990, series reported HER-2 positivity rates of 9–38%. More recent studies, using IHC (Herceptest) and FISH amplification, reported similar frequencies. In our study, C-ERB B2 IHC was performed in 50 patients: 34% 3+, 8% 2+, and 58% negative; FISH was performed in 43, with 37.2% positive. These data indicate a higher frequency of HER-2 expression in our population.

The prognostic significance of HER-2 in gastric and gastroesophageal junction cancers is controversial. Early studies

found no association with prognosis.<sup>[17,18]</sup> Some authors proposed HER-2 expression as a direct adverse prognostic factor; a retrospective study of 108 patients associated HER-2 with poor 10-year survival.<sup>[19]</sup> Nakajima et al.<sup>[20]</sup> reported HER-2 expression as the worst prognostic variable after nodal status. In ToGA, HER-2–positive patients were randomized to chemotherapy (capecitabine+cisplatin or fluorouracil+cisplatin) vs chemotherapy+trastuzumab: OS was 13.8 months with trastuzumab vs 11.1 months with chemotherapy alone.<sup>[21]</sup> The Lancet discussion noted the 11.1-month OS in the chemo-only arm was longer than expected; although other studies linked HER-2 with aggressive disease, ToGA suggested HER-2 expression might not indicate poor prognosis—warranting further investigation. Jørgensen and colleagues performed a 2012 systematic analysis of studies from 1986 to August 2011 assessing HER-2 expression and survival (overall, disease-free, or stage) in cohorts with  $\geq 100$  patients and IHC/FISH data.<sup>[22]</sup> Among 12,749 patients, most articles (71%) indicated that HER-2 positivity correlated with survival; while not as definitive as in breast cancer, HER-2 overexpression appeared to be a negative prognostic factor.

## Conclusion

In our study, among 50 patients tested for C-ERB B2, 18 were positive and 32 negative. C-ERB B2 positivity had neither a favorable nor unfavorable effect on overall survival (Table 5). We also examined whether post-treatment MCV increase influenced prognosis within the C-ERB B2–positive subgroup; no significant differences in survival rate or time were detected between C-ERB B2–positive and –negative groups according to MCV increase (Table 6).

Limitations of our study include its retrospective design; variability in surgical and chemotherapy standards because some patients presented from other centers; incomplete follow-up related to economic constraints; and lack of systematic assessment of BMI, nutritional status, and hypovitaminoses (B1, B6, B12). Expanding the patient population and conducting prospective follow-up may yield more robust conclusions.

## Disclosures

**Ethics Committee Approval:** This retrospective study was approved by the Bakırköy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (approval number: 2016/04-07, approval date: 25 April 2016).

**Conflict of Interest:** None declared.

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## Research Article

# Prognostic Importance of Neutrophil to Lymphocyte and Platelet to Lymphocyte Ratios in Multiple Myeloma Patients

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### Abstract

**Objectives:** To evaluate the prognostic significance of baseline neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) in newly diagnosed multiple myeloma (MM).

**Methods:** We retrospectively analyzed 327 MM patients (2012–2018) from a single tertiary center. Baseline clinical, hematologic, and biochemical data were collected. NLR and PLR were calculated. OS was estimated via Kaplan–Meier and Cox regression. ROC analysis determined an NLR cutoff.

**Results:** Median OS was 46.1 months; 1-, 2-, and 5-year OS rates were 77.4%, 64.5%, and 44.0%, respectively. Each one-unit increase in NLR raised the risk of death by 9.3% (HR 1.093;  $p=0.015$ ). NLR correlated with poorer OS in ISS stage II, hemoglobin  $<10$  g/dL,  $\geq 40\%$  bone marrow plasma cell infiltration, and calcium  $\geq 11$  mg/dL. PLR showed no association with OS ( $p=0.957$ ). ROC analysis identified an NLR cutoff of 1.7 (AUC 0.584).

**Conclusion:** Higher baseline NLR is associated with worse survival and adverse MM features but is insufficient as a standalone marker alongside ISS/R-ISS. PLR lacks prognostic value.

**Keywords:** Multiple myeloma, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, prognosis

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Multiple myeloma (MM) is a malignant plasma cell disorder that accounts for about 1–2% of all cancers and approximately 10–15% of hematologic malignancies.<sup>[1,2]</sup> The annual incidence in the United States is around 4–5 per 100,000 persons.<sup>[2]</sup> Almost all cases of MM are preceded by a premalignant clonal plasma cell disorder, monoclonal gammopathy of undetermined significance (MGUS).<sup>[3]</sup> Several clinical and biological factors have been identified as important prognostic markers in MM. These include patient performance status, cytogenetic risk, serum lactate dehydrogenase (LDH) level, bone marrow plasma cell pro-

liferation, and plasma cell leukemia. Advanced age, International Staging System (ISS) stage, C-reactive protein, serum creatinine, platelet count, and immunophenotypic plasma cell markers have also been associated with outcomes. Bone marrow biopsy, cytogenetic analysis, and fluorescence in situ hybridization (FISH) are integral to staging but are invasive and/or costly. Therefore, there is ongoing interest in simple, inexpensive, and non-invasive laboratory markers that could complement existing prognostic systems.<sup>[4]</sup>

The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR), derived from routine com-

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plete blood counts, have been proposed as markers of systemic inflammation and host immune status. Elevated NLR and PLR have been associated with poor outcomes in several solid tumors and some hematologic malignancies. In MM, data are more limited, and reported cutoff values vary. In this retrospective study, we aimed to evaluate whether NLR and PLR at diagnosis are associated with overall survival in MM, to explore their relationships with established clinical and laboratory parameters, and to determine whether a clinically useful cutoff value for NLR could be identified.

In routine clinical practice, inexpensive markers derived from complete blood counts are appealing because they are universally available, rapidly reported, and do not require additional sampling. However, their interpretation in multiple myeloma is challenging due to frequent baseline cytopenias, renal dysfunction, and heterogeneity in disease burden at presentation. Therefore, evaluating NLR and PLR in a real-world cohort treated across an evolving therapeutic era may help clarify whether these indices provide clinically actionable information beyond established staging systems and readily available laboratory parameters.

## Methods

### Study Population and Inclusion Criteria

This retrospective study included patients diagnosed with MM between January 2012 and September 2018, according to IMWG criteria. Patients were required to have been diagnosed, treated, and followed at our center, with available baseline clinical and laboratory data.

Exclusion criteria at the time of diagnosis were acute infection, human immunodeficiency virus infection, chronic liver disease, collagen vascular disease, any previous or concomitant malignant neoplasm, primary or secondary thrombocytopenia, and chronic use of anti-inflammatory drugs. Because inflammatory indices can be influenced by non-myeloma conditions, we applied prespecified exclusion criteria to reduce confounding from acute infection, chronic inflammatory disease, and concomitant malignancy. Nevertheless, residual confounding is possible in retrospective datasets, particularly related to unmeasured comorbidities, corticosteroid exposure around diagnosis, and differences in supportive care. These considerations were taken into account when interpreting effect sizes and the clinical utility of the identified cutoff. Both deceased and surviving patients who met these criteria were included, resulting in a final cohort of 327 patients.

Our center is a tertiary university hospital that provides diagnostic workup, first-line therapy, and longitudinal fol-

low-up for patients with plasma cell dyscrasias. Follow-up information was obtained from outpatient visit records, inpatient charts, and the hospital information system. Vital status and date of last contact were verified through the hospital registry, national death registry, and phone contact, when applicable, to minimize outcome misclassification.

### Clinical and Laboratory Data

Demographic and clinical variables collected from hospital records included age at diagnosis, sex, vital status at last follow-up, follow-up duration, performance status according to the Eastern Cooperative Oncology Group (ECOG) scale, ISS stage, percentage of bone marrow plasma cell infiltration, treatment type (conventional chemotherapy vs. regimens containing immunomodulatory drugs and/or proteasome inhibitors), and autologous stem cell transplantation (ASCT) status.

Baseline hematologic parameters were defined as values obtained at the time of diagnostic evaluation and prior to initiation of anti-myeloma therapy. When multiple measurements were available within the diagnostic window, the sample closest to the date of diagnosis was selected. This approach aimed to capture the patient's inflammatory and immune status at presentation and to reduce variability introduced by supportive treatments or early therapeutic intervention.

Baseline laboratory parameters at diagnosis included hemoglobin (Hb), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), white blood cell (WBC) count, absolute neutrophil count, absolute lymphocyte count, platelet count, blood urea nitrogen (BUN), serum creatinine, estimated glomerular filtration rate (eGFR; calculated using the Modification of Diet in Renal Disease formula), serum calcium, albumin, albumin/globulin ratio, total protein, LDH, and  $\beta_2$  microglobulin. NLR was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count, and PLR by dividing the platelet count by the absolute lymphocyte count.

Overall survival (OS) was defined as the time from the date of diagnosis to death from any cause or last follow-up for censored patients.

### Statistical Analysis

Receiver operating characteristic (ROC) analysis was performed on continuous variables to determine cutoff points. ROC curves were examined for the relationship between baseline NLR and PLR and survival outcomes. The optimal cutoff was defined as the value providing the best combination of sensitivity and specificity for OS.

The Shapiro–Wilk test was used to assess the normality of continuous variables. Non-normally distributed variables were compared between two groups using the Mann–Whitney U test. Spearman rank correlation analysis was used to assess relationships between continuous variables.

Survival probabilities were estimated using the Kaplan–Meier method, and hazard ratios (HRs) were calculated by univariable Cox proportional hazards regression. A p value <0.05 was considered statistically significant. Statistical analyses were performed using SPSS for Windows, version 22.0 (IBM Corp., Armonk, NY, USA).

Missing data were handled using a complete-case approach for each analysis; the number of patients included in each model is reported where relevant. Given the retrospective design and the long study period, some laboratory variables were not available for all patients. No imputation was performed, and results should be interpreted with the awareness that missingness may not be completely at random.

## Results

### Baseline Characteristics

A total of 327 MM patients fulfilling the inclusion criteria were analyzed. Baseline characteristics and main treatment details are presented in Table 1.

The mean age at diagnosis was 60.04±11.03 years (range 29–85), and 54.7% of the patients were male. The mean follow-up duration was 32.80±25.04 months. At the time of analysis, 49.2% of the patients were alive. The estimated median OS was 46.06±6.85 months. The 1-, 2-, and 5-year OS rates were 77.4%, 64.5%, and 44.0%, respectively.

The mean hemoglobin level was 10.41±1.99 g/dL. The mean absolute neutrophil and lymphocyte counts were 4,460.6±2,049.9/μL and 2,159.6±1,069.2/μL, respectively, and the mean platelet count was 236,960±101,749/μL. The mean NLR was 2.49±1.78 (range 0.30–13.61), and the mean PLR was 132.30±86.07 (range 10.09–735.00).

The mean eGFR was 68.24±35.64 mL/min/1.73 m<sup>2</sup>; mean serum creatinine was 1.65±1.81 mg/dL; albumin was 3.48±0.69 g/dL; total protein was 9.26±2.39 g/dL; albumin/

**Table 1.** Baseline characteristics and main treatment details of the patients (n=327)

Variable	Minimum	Maximum	Mean	Standard deviation
Age at diagnosis (years)	29	85	60.04	11.03
Followup period (months)	1	80	32.80	25.04
Hemoglobin (g/dL)	5.3	16.5	10.41	1.99
MCV (μm <sup>3</sup> )	61.8	109.3	90.11	7.23
MCH (pg/cell)	19.5	37.7	30.03	2.83
MCHC (g/L)	27.2	36.8	33.26	1.29
RDW (%)	11.5	30.8	16.49	2.87
Neutrophil count (μL)	1,000	13,130	4,460.60	2,049.88
Lymphocyte count (μL)	380	10,670	2,159.60	1,069.21
Platelet count (μL)	28,000	580,000	236,960.20	101,749.22
N/L ratio	0.30	13.61	2.49	1.78
P/L ratio	10.09	735.00	132.30	86.07
eGFR (mL/min/1.73 m <sup>2</sup> )	2.60	160.00	68.24	35.64
Creatinine (mg/dL)	0.37	19.48	1.65	1.81
Albumin (g/dL)	1.60	5.12	3.48	0.69
Total protein (g/dL)	3.89	20.20	9.26	2.39
Albumin/globulin ratio	0.09	5.85	0.83	0.62
Calcium (mg/dL)	3.22	17.70	9.78	1.61
β2microglobulin (mg/L)	1.71	49.97	8.73	8.52
LDH (U/L)	81.00	824.00	221.96	101.25

MCV: Mean corpuscular volume; MCH: Mean corpuscular hemoglobin; MCHC: Mean corpuscular hemoglobin concentration; RDW: Red cell distribution width; N/L: Neutrophil/lymphocyte; P/L: Platelet/lymphocyte; eGFR: Estimated glomerular filtration rate; LDH: Lactate dehydrogenase.

globulin ratio was  $0.83 \pm 0.62$ ; calcium was  $9.78 \pm 1.61$  mg/dL;  $\beta_2$  microglobulin was  $8.73 \pm 8.52$  mg/L; and LDH was  $221.96 \pm 101.25$  U/L.

The most common myeloma subtypes were IgG kappa (50.5%) and IgG lambda (30.0%), followed by IgA kappa (11.9%). ECOG performance status was 0–1 in 57.5% and 2–4 in 42.5% of patients. ISS stage I, II, and III were present in 19.6%, 28.1%, and 52.3% of cases, respectively. Overall, 82.6% of patients received regimens including immunomodulatory drugs and/or proteasome inhibitors, while 17.4% received conventional chemotherapy alone. ASCT was performed in 23.2% of patients (Table 2).

**Table 2.** ECOG performance status, ISS stage, plasma cell subtype, treatment and autologous stem cell transplantation status (n=327)

Variable	n	%
ECOG performance status		
0–1	188	57.5
2–4	139	42.5
ISS stage		
Stage I	64	19.6
Stage II	92	28.1
Stage III	171	52.3
Plasma cell subtype		
IgA kappa	39	11.9
IgA lambda	20	6.1
IgM kappa	1	0.3
IgM lambda	0	0.0
IgG kappa	165	50.5
IgG lambda	98	30.0
Nonsecretory	4	1.2
Treatment regimen		
Conventional chemotherapy	57	17.4
IMiD and/or proteasome inhibitorbased	270	82.6
Autologous stem cell transplantation		
Yes	76	23.2
No	251	76.8

ECOG: Eastern Cooperative Oncology Group; ISS: International Staging System; IMiD: Immunomodulatory drug.

### Association of NLR and PLR with survival

In univariable Cox regression analysis, each one-unit increase in NLR increased the risk of death by 9.3% (HR 1.093; 95% CI 1.018–1.173;  $p=0.015$ ) (Table 3). Changes in PLR had no significant effect on the relative risk of death (HR 1.000; 95% CI 0.998–1.002;  $p=0.957$ ). Since PLR showed no prognostic significance, further correlation and survival analyses focused on NLR.

### Subgroup analyses and correlations

In patients younger than 65 years, a significant correlation was observed between increasing NLR and mortality; each unit increase in NLR predicted a 12.9% increase in the risk of death (HR 1.129; 95% CI 1.016–1.255;  $p=0.024$ ). In patients with hemoglobin  $<10$  g/dL, each unit increase in NLR predicted a 24.3% increase in mortality (HR 1.243; 95% CI 1.074–1.440;  $p=0.004$ ).

Regression analysis examining the impact of bone marrow plasma cell infiltration on mortality identified 40% as the optimal cutoff. In patients with bone marrow infiltration  $\geq 40\%$ , each unit increase in NLR predicted a 16.6% increase in the risk of death (HR 1.166; 95% CI 1.071–1.270;  $p<0.001$ ), whereas no significant association was found in those with  $<40\%$  infiltration ( $p=0.728$ ).

NLR showed a very weak but significant positive correlation with serum creatinine ( $r=0.142$ ;  $p=0.010$ ) and LDH ( $r=0.139$ ;  $p=0.012$ ), whereas no significant correlations were found with eGFR ( $p=0.072$ ) or  $\beta_2$  microglobulin ( $p=0.283$ ).

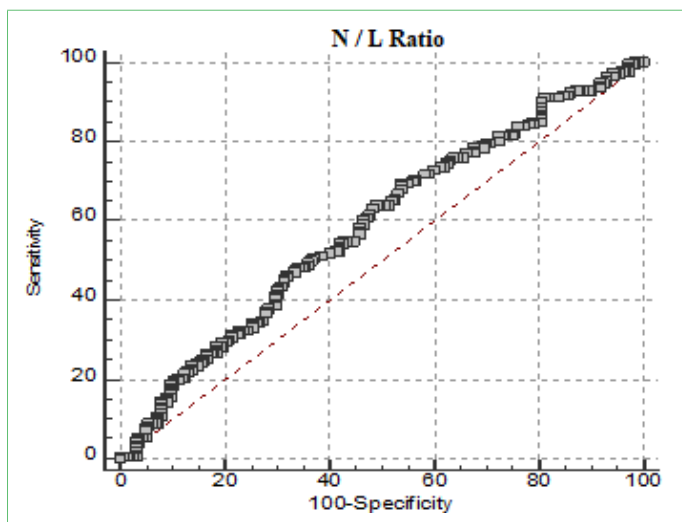
When ISS stage and NLR were evaluated together, a significant association was observed only in ISS stage II. In this group, each unit increase in NLR predicted a 43.1% increase in the risk of death (HR 1.431; 95% CI 1.145–1.788;  $p=0.002$ ); no significant association was detected in ISS I or III.

In patients treated with regimens containing immunomodulatory drugs and proteasome inhibitors, each unit increase in NLR predicted an 8.2% increase in mortality (HR 1.082; 95% CI 1.003–1.166;  $p=0.040$ ), whereas no significant association was observed in the group treated with conventional chemotherapy alone ( $p=0.147$ ). In patients with baseline calcium  $\geq 11$  mg/dL, each unit increase in NLR predicted a 30.4% increase in mortality (HR 1.304; 95% CI 1.042–1.632;  $p=0.040$ ).

**Table 3.** Effect of neutrophil to lymphocyte (N/L) and platelet to lymphocyte (P/L) ratios on risk of death (Cox regression analysis)

Variable	Coefficient (B)	Standard error	Wald $\chi^2$	df	p value	Hazard ratio (HR)	95% CI for HR (lower–upper)
N/L ratio	0.088	0.036	5.973	1	0.015	1.093	1.018–1.173
P/L ratio	0.000	0.001	0.003	1	0.957	1.000	0.998–1.002

N/L: Neutrophil to lymphocyte; P/L: Platelet to lymphocyte; CI: Confidence interval; df: Degrees of freedom.



**Figure 1.** ROC curve of baseline neutrophil-to-lymphocyte ratio for predicting overall survival. The optimal cutoff was N/L=1.7 (AUC 0.584; sensitivity 69.3%; specificity 46.0%).

### ROC analysis and NLR cutoff

ROC curve analysis was performed to determine an optimal cutoff for NLR in predicting OS (Fig. 1). Since PLR was not associated with survival, no cutoff for PLR was determined. The optimum cutoff for NLR, defined as the value providing the highest combined sensitivity and specificity, was 1.7. The AUC was 0.584 (95% CI 0.528–0.638;  $p=0.0078$ ). At this threshold, sensitivity was approximately 69.3% and specificity 46.0% (95% CI 38.1–54.0). Thus, an NLR of 1.7 at diagnosis provides only weak clinical prediction for survival.

### Discussion

In this retrospective study of 327 patients with multiple myeloma (MM), we investigated the prognostic significance of the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) measured at diagnosis. The mean age at diagnosis was  $60.04 \pm 11.03$  years, and the mean follow-up duration was  $32.80 \pm 25.04$  months. The median overall survival (OS) was  $46.06 \pm 6.85$  months, with 1-, 2-, and 5-year OS probabilities of 77.4%, 64.5%, and 44%, respectively. At baseline, the mean NLR was  $2.49 \pm 1.78$ , and the mean PLR was  $132.30 \pm 86.07$ , indicating a wide distribution of systemic inflammatory status across the cohort.

Our main finding is that NLR at diagnosis shows a statistically significant but clinically modest association with overall survival, whereas PLR does not. In the entire cohort, each one-unit increase in NLR increased the risk of death by 9.3% (HR 1.093; 95% CI 1.018–1.173;  $p=0.015$ ). By contrast, PLR had no significant effect on mortality (HR 1.00; 95% CI 0.998–1.002;  $p=0.957$ ). These results support the hypothesis that an elevated NLR, reflecting a relative pre-

dominance of neutrophil-mediated inflammation over lymphocyte-mediated immune surveillance, is associated with poorer outcomes in MM, while PLR appears to be less informative in this setting.

The lack of association between PLR and survival in our cohort may reflect the multifactorial determinants of platelet counts in multiple myeloma, including marrow infiltration, treatment-related effects, bleeding risk, and inflammatory or infectious complications. Platelets can also be affected by renal dysfunction and nutritional status, which may dilute any direct relationship between PLR and tumor biology. Consequently, PLR may be a less stable proxy of systemic inflammation than NLR in this disease context.

From a biological standpoint, this is plausible. Neutrophils can promote tumor progression through pro-angiogenic cytokines, proteolytic enzymes, and growth factors, whereas lymphocytes are central to anti-tumor immunity. An increased NLR therefore suggests a shift toward a pro-tumor inflammatory milieu and impaired immune control.<sup>[4]</sup> Our findings are consistent with previous studies reporting adverse outcomes in MM patients with higher NLR values<sup>[5–7]</sup>. Onec et al.<sup>[5]</sup> found that NLR was predictive of survival in MM, Wongrakpanich et al.<sup>[6]</sup> and Li et al.<sup>[7]</sup> also reported prognostic associations of baseline NLR, though results for PLR were inconsistent, and Shi et al.<sup>[8]</sup> showed that elevated NLR and monocyte-to-lymphocyte ratio, together with decreased PLR, were associated with poor prognosis. Taken together, these data suggest that NLR is a reproducible, albeit not highly discriminative, prognostic marker in MM.

The modest AUC observed in our ROC analysis suggests that baseline NLR behaves more like a contextual risk correlate than a high-performing discriminative test. In other words, while NLR may capture aspects of host–tumor interaction and systemic stress, its overlap between survivors and non-survivors limits its use for individual-level decision-making at diagnosis. This emphasizes that statistically significant associations do not necessarily translate into clinically useful classification performance.

However, when we examined the discriminative performance of NLR using ROC analysis, the clinical utility appeared limited. The optimum cutoff point for NLR in predicting survival in our study was 1.7, yielding the highest combined sensitivity and specificity. At this threshold, sensitivity was approximately 70%, while specificity was only 46%, with an area under the ROC curve in the range of 0.528–0.638 ( $p=0.0078$ ). Within the 95% confidence interval (38.1%–54.0% for specificity), NLR thus provides only a weak prediction for clinical use at diagnosis. This is in contrast to some previous studies that proposed various cutoff values—1.72, 2.78, or 4.0—for NLR with stronger dis-

criminative performance.[5,6,8] The differences may reflect variability in patient populations, treatment eras, and statistical methods, but they also underline that no universally accepted NLR cutoff has emerged for MM.

When we evaluated clinical and laboratory subgroups, NLR displayed differential associations with outcome:

- In patients with hemoglobin <10 g/dL, a one-unit increase in NLR predicted a 24.3% increase in the risk of death (HR 1.243; 95% CI 1.074–1.440;  $p=0.004$ ), suggesting that NLR may be particularly relevant in patients with more advanced anemia and possibly higher disease burden.
- When bone marrow plasma cell infiltration was stratified at a 40% cutoff, no significant correlation between NLR and mortality was seen in patients with <40% infiltration ( $p=0.728$ ), whereas in those with  $\geq 40\%$  infiltration, each one-unit increase in NLR predicted a 16.6% increase in mortality risk (HR 1.166; 95% CI 1.071–1.270;  $p<0.001$ ).
- A significant association was also detected in patients with ISS stage II, where a one-unit increase in NLR increased the risk of death by 43.1% (HR 1.431; 95% CI 1.145–1.788;  $p=0.002$ ). This suggests that NLR may capture additional risk particularly in intermediate-stage patients.
- Regarding renal and biochemical parameters, NLR showed a very weak but statistically significant positive correlation with creatinine ( $r=0.142$ ;  $p=0.010$ ) and LDH ( $r=0.139$ ;  $p=0.012$ ), while no significant correlation was observed with GFR ( $p=0.072$ ) or beta-2 microglobulin ( $p=0.283$ ).
- For hypercalcemia, we used a calcium level  $\geq 11$  mg/dL as a cutoff, consistent with established MM risk factors. In this subgroup, each one-unit increase in NLR was associated with a 30.4% increase in mortality risk (HR 1.304; 95% CI 1.042–1.632;  $p=0.040$ ).

These subgroup findings indicate that NLR tends to be more prognostically informative in patients with markers of higher tumor burden or organ dysfunction (anemia, high marrow infiltration, elevated calcium, higher LDH, and impaired renal function), which is in line with the pathophysiology of MM.

Treatment-related analyses also yielded informative results. In our cohort, the majority of patients received regimens containing immunomodulatory drugs (IMiDs) and/or proteasome inhibitors (82.6%), while 17.4% received conventional chemotherapy alone; 23.2% underwent autologous stem cell transplantation (ASCT). In the group treated with IMiDs and proteasome inhibitors, a one-unit increase in NLR predicted an 8.2% increase in the risk of death attributable to poor treatment response (HR 1.082; 95% CI 1.003–1.166;  $p=0.040$ ). No similar relationship was ob-

served in the conventional chemotherapy group ( $p=0.147$ ). These findings suggest that even in the era of novel agents, host-related inflammatory status, as reflected by NLR, may influence response outcomes and survival.

On the other hand, in patients who underwent ASCT, NLR did not show a significant difference in predicting OS compared with the non-transplant group ( $p=0.178$ ). According to our results, NLR has no clear role in identifying candidates for autologous transplantation or in predicting post-transplant survival, which partially contrasts with studies that reported better post-transplant outcomes in patients with lower NLR values. [9–11]

The prognostic landscape of MM is further complicated by its well-recognized precursor state, monoclonal gammopathy of undetermined significance (MGUS), which precedes virtually all cases of MM. [3,12] Current MGUS and smoldering MM risk models rely on parameters such as M protein level, bone marrow plasma cell percentage, and free light chain ratio. [12] While we did not include MGUS or smoldering MM patients in our cohort, our results raise the broader question of whether inflammatory indices like NLR may play any role in identifying high-risk precursor states. This remains speculative and should be addressed in specifically designed prospective studies.

It is important to interpret these findings in the context of established prognostic systems. The International Staging System (ISS), based on serum  $\beta 2$  microglobulin and albumin, [13] and the Revised ISS (R-ISS), which additionally incorporates LDH and cytogenetic abnormalities, remain the standard tools for risk stratification in MM. [14,15] In our study, although NLR showed statistically significant associations with survival and several adverse clinical features, it did not add meaningful predictive value to staging beyond systems such as ISS and R-ISS. In other words, NLR appears to be a weak independent prognostic factor and does not substantially improve risk stratification when established markers are already taken into account.

From a practical standpoint, NLR can be viewed as a readily accessible marker that may raise clinical suspicion for higher-risk features when interpreted alongside anemia, renal impairment, LDH elevation, and hypercalcemia. However, our findings do not support using NLR alone to guide treatment intensity, transplant decisions, or counseling at diagnosis. Instead, NLR may be most appropriate as an adjunct variable in future composite scores that integrate established staging systems with routinely available laboratory data.

Our study has several limitations. First, it is a single-center, retrospective analysis, which may introduce selection bias and unmeasured confounding. Second, while the sample size of

327 patients is reasonable for a single-center study, it is still modest compared with large multicenter trials. Third, NLR and PLR were assessed only at baseline; we did not evaluate dynamic changes over time or during treatment, although studies performed at day +100 after ASCT suggest that post-treatment values may also be prognostically relevant.<sup>[9]</sup> Fourth, the ROC-derived cutoff for NLR in our cohort (1.7) showed weak discriminative power ( $p=0.078$ ), suggesting that NLR alone is insufficient as a robust clinical decision-making tool at diagnosis. Finally, we did not incorporate R-ISS systematically due to the retrospective nature of the data and limitations in the availability of cytogenetic testing during the study period, which we acknowledge as a point of criticism.

Notable strengths of this study include the relatively large single-center cohort, consistent diagnostic criteria, and the inclusion of patients managed in a real-world setting where laboratory indices are routinely obtained. In addition, our analyses explored clinically relevant subgroups (e.g., anemia, marrow infiltration, calcium elevation), which may help clinicians understand in which scenarios NLR is more likely to reflect adverse disease biology.

Despite these limitations, our study contributes real-world data from a sizable, single-center cohort treated in the era of novel agents. It confirms that NLR is statistically associated with worse survival and with markers of higher tumor burden and organ dysfunction but, at the same time, demonstrates that its practical prognostic contribution is weak and does not replace or significantly enhance established staging systems. PLR, in contrast, did not show any independent prognostic value in our analysis.

## Conclusion

In this retrospective cohort of 327 multiple myeloma patients, we found that:

- The baseline neutrophil-to-lymphocyte ratio (NLR) is statistically associated with overall survival; each one-unit increase in NLR increases the risk of death by approximately 9.3% (HR 1.093; 95% CI 1.018–1.173;  $p=0.015$ ).
- The platelet-to-lymphocyte ratio (PLR) has no significant prognostic impact on survival (HR 1.00; 95% CI 0.998–1.002;  $p=0.957$ ).
- The ROC-derived cutoff value of 1.7 for NLR provides weak discriminative power, with sensitivity around 70% but specificity of only 46% (AUC within 0.528–0.638;  $p=0.078$ ), limiting its practical utility as a standalone prognostic marker at diagnosis.
- NLR shows stronger prognostic associations in subgroups with adverse clinical and laboratory features (hemoglobin  $<10$  g/dL, bone marrow plasma cell infiltration  $\geq 40\%$ , ISS stage II, calcium  $\geq 11$  mg/dL, higher creatinine

and LDH values), and among patients treated with IMiD- and proteasome inhibitor-containing regimens. However, NLR does not significantly influence survival after autologous stem cell transplantation and does not help in selecting transplant candidates.

Taken together, these findings indicate that while NLR reflects aspects of systemic inflammation and host–tumor interaction and is weakly prognostic, it does not meaningfully enhance staging or risk stratification when added to established systems such as ISS and R-ISS. PLR appears to be of no prognostic value in our cohort.

Given that bone marrow biopsy, cytogenetic and FISH analyses, and advanced imaging recommended by the International Myeloma Working Group are invasive and/or costly,<sup>[13,14]</sup> simple and inexpensive indices such as NLR and PLR are attractive in principle. However, based on our results, baseline NLR should currently be regarded as an auxiliary marker with limited clinical impact rather than a primary tool for risk-adapted treatment decisions in MM. PLR cannot be recommended as a prognostic marker in this context.

We recommend that future prospective, multicenter studies with larger patient numbers and standardized methodology:

- further investigate the prognostic value of NLR and other inflammatory indices,
- explore dynamic changes in these ratios during treatment (e.g., at day +100 post-ASCT),

and evaluate combined models that integrate inexpensive hematologic and biochemical ratios with established staging systems and modern biomarkers, from precursor states such as MGUS through to symptomatic MM.<sup>[14,15]</sup>

Such research may clarify whether more robust cutoff points or composite scores derived from routine laboratory tests can provide clinically meaningful prognostic information and contribute to truly individualized management strategies in multiple myeloma.

## Disclosures

**Ethics Committee Approval:** The study was approved by the Gaziantep University Clinical Research Ethics Committee and was conducted in accordance with the Declaration of Helsinki.

**Informed Consent:** Written consent was obtained from all participants.

**Conflict of Interest:** The authors have no conflicts of interest to declare.

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**Authorship Contributions:** Concept – AK; Design – AK; Supervision – AK; Data collection and/or processing – AK; Analysis and/or interpretation – AK; Literature search – AK; Writing – AK, VO; Critical review – VO.

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## Research Article

# Mortality and Related Factors in Patients Admitted to Intensive Care Unit

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### Abstract

**Objectives:** Intensive care units (ICUs) provide advanced monitoring and treatment for patients with life-threatening organ failure. This study aimed to evaluate the impact of vital signs and laboratory parameters on mortality in ICU patients.

**Methods:** A total of 498 patients were retrospectively analyzed. Patients aged  $\geq 18$  years who were hospitalized for at least 24 hours in the internal medicine ICU were included. Trauma patients, those admitted for surgical procedures, and postoperative patients were excluded. Demographic data, comorbidities, laboratory values, vital signs, nutritional status, respiratory support, and survival outcomes were obtained from electronic medical records.

**Results:** Of 498 patients, 266 (53.4%) died and 232 (46.6%) survived. Mortality was significantly associated with age, chronic renal disease, respiratory disease, impaired consciousness, APACHE score, and mechanical ventilation requirement. Deceased patients had higher levels of urea, creatinine, bilirubin, ALT, AST, CRP, MPV, lactate, and potassium, and lower levels of albumin, pH, HCO<sub>3</sub>, sodium, and calcium ( $p < 0.05$ ).

**Conclusion:** Age, APACHE score, urea, albumin, eosinophil count, MPV, and lactate were identified as independent predictors of mortality in ICU patients.

**Keywords:** Intensive care unit, Mortality, Prognostic factors, Albumin

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Intensive care units (ICUs) provide advanced supportive therapies for patients with life-threatening acute or chronic organ failure and are associated with higher mortality rates compared with other hospital departments<sup>[1,2]</sup> Despite significant medical and technological advances, ICU mortality remains a major clinical challenge, particularly among elderly patients and those presenting with multi-

ple comorbidities and severe physiological derangements.<sup>[3]</sup> Therefore, identifying reliable and easily applicable predictors of mortality at the time of ICU admission is of considerable clinical importance.<sup>[4]</sup>

Several scoring systems, including APACHE, SAPS, and MPM, have been developed to estimate mortality risk in ICU patients.<sup>[5]</sup> Although these models are useful for pop-

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ulation-level risk stratification and inter-institutional comparisons, their prognostic accuracy at the individual patient level is limited.<sup>[6]</sup> Moreover, many of these scoring systems were developed prior to current ICU patient profiles and treatment strategies and may not always be practical for routine clinical use.<sup>[7]</sup>

In recent years, increasing attention has been directed toward the potential prognostic value of simple clinical and laboratory parameters routinely obtained at ICU admission. Parameters such as serum albumin level, lactate, mean platelet volume (MPV), and eosinophil count reflect systemic inflammation, metabolic stress, and organ dysfunction and are readily available and cost-effective markers.<sup>[8]</sup> Although these parameters have been reported to be associated with ICU mortality, their independent prognostic value in heterogeneous populations admitted to internal medicine ICUs has not been clearly established.

The aim of this study was to evaluate the relationship between admission clinical characteristics, routine laboratory parameters, and mortality in patients admitted to an internal medicine intensive care unit and to identify independent predictors of mortality using multivariate analyses.

## Methods

### Study Design and Population

This retrospective observational study included a total of 498 patients who were admitted to the internal medicine intensive care unit (ICU) of our institution between January 1, 2016, and December 31, 2019. Ethical approval for the study was obtained from the local Ethics Committee on August 28, 2019 (protocol number: 2019/144). The study was conducted in accordance with the principles of the Declaration of Helsinki, and informed consent was obtained from all participants or their legal representatives in accordance with institutional policy.

Patients aged 18 years and older who were hospitalized in the internal medicine ICU for at least 24 hours were eligible for inclusion. Patients admitted for trauma, those hospitalized for perioperative monitoring, patients prepared for elective surgical procedures, and individuals followed postoperatively were excluded from the study.

### Data Collection

Demographic characteristics (age and sex), comorbid conditions, laboratory parameters, complete blood count results, arterial blood gas values, vital signs, nutritional status, respiratory support modalities, and survival outcomes were retrospectively retrieved from the hospital's electronic medical record system. All data were collected using a standardized data extraction approach to ensure consistency.

## Statistical Analysis

Statistical analyses were performed using SPSS software for Windows, version 22.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as median and interquartile range (IQR), while categorical variables were expressed as frequencies and percentages.

The normality of continuous variables was assessed using both visual methods (histograms and probability plots) and analytical methods (Kolmogorov-Smirnov test). Comparisons between two independent groups were conducted using the Mann-Whitney U test for variables that were not normally distributed. Categorical variables were compared using the Pearson chi-square test or Fisher's exact test, as appropriate.

Multivariate logistic regression analysis was performed to identify independent predictors of mortality. Variables that were clinically relevant or showed significance in univariate analyses were included in the regression model. Statistical significance was defined as a two-sided p-value <0.05.

Artificial intelligence-assisted technology (ChatGPT, OpenAI, GPT-5.3) was used only for language editing and formatting purposes. No AI tool contributed to study design, data analysis, or scientific conclusions.

## Results

A total of 498 patients admitted to the internal medicine intensive care unit were included in the analysis. The overall mortality rate was 53.4% (n=266), while 46.6% of patients survived (n=232).

The most common reasons for ICU admission were pneumonia (18.1%), sepsis (14.7%), respiratory failure (14.1%), cardiac arrest (10.8%), cerebral infarction (7.0%), pulmonary edema (7.0%), gastrointestinal bleeding (5.4%), acute renal failure (3.6%), acute coronary syndrome (2.8%), and pulmonary embolism (2.4%), while intracranial hemorrhage accounted for 2.0% and other causes accounted for 12.0% of admissions.

Significant differences were observed between deceased and surviving patients with respect to age, level of consciousness, APACHE score, need for mechanical ventilation, presence of chronic renal disease, and respiratory system disease (p<0.05). Patients who died were significantly older and had higher APACHE scores compared with survivors. Mortality was significantly higher in patients with chronic renal disease, whereas it was lower in patients with underlying respiratory diseases. In addition, mortality was significantly higher among patients presenting with impaired consciousness and those requiring mechanical ventilation (Table 1).

**Table 1.** Distribution of some descriptive and clinical features by mortality status

	(n=498)	Status		p
		Survived (n=232)	Deceased (n=266)	
Age (years)	75(64-84)	72(60-81)	77(67-85)	<0.001***
Gender				0.060 <sup>b</sup>
Female	222(44.6)	93 (40.1)	129(48.5)	
Male	276(55.4)	139(59.9)	137(51.5)	
Presence of comorbidity	459(92.2)	212(91.4)	247(92.9)	0.540 <sup>b</sup>
Comorbid disease				
Hypertension	193(38.8)	90 (38.8)	103(38.7)	0.987 <sup>b</sup>
Cardiovascular disease	137(27.5)	55 (23.7)	82 (30.8)	0.076 <sup>b</sup>
Neurological disease	118(23.7)	52 (22.4)	66 (24.8)	0.530 <sup>b</sup>
Diabetes mellitus	112(22.5)	57 (24.6)	55 (20.7)	0.299 <sup>b</sup>
Chronic renal disease	107(21.5)	39 (16.8)	68 (25.6)	0.018 <sup>b*</sup>
Malignity	104(20.9)	41 (17.7)	63 (23.7)	0.100 <sup>b</sup>
Respiratory disease	53 (10.6)	32 (13.8)	21 (7.9)	0.033 <sup>b*</sup>
Hemodialysis	23 (4.6)	11 (4.7)	12 (4.5)	0.903 <sup>b</sup>
Hepatobiliary tractus disease	13 (2.6)	9(3.9)	4(1.5)	0.157 <sup>c</sup>
Presence of infection	312(62.7)	137(59.1)	175(65.8)	0.121 <sup>b</sup>
Consciousness				
Coma	73 (14.7)	28 (12.1)	45 (16.9)	
Conscious	143(28.7)	94 (40.5)	49 (18.4)	
Confusion	193(38.8)	81 (34.9)	112(42.1)	<0.001 <sup>b***</sup>
Lethargia	50 (10.0)	19 (8.2)	31 (11.7)	
Stupor	39 (7.8)	10 (4.3)	29 (10.9)	
APACHE score				
Mechanical ventilation				
NIMV	43 (8.6)	27 (11.6)	16 (6.0)	

#Continuous variables are presented as "median (interquartile range (IQR))" and categorical variables as "number (percent of column)"; a Mann-Whitney U test; b Pearson chi-square test; c Fisher's exact test; \*p<0.05; \*\* p<0.01

No statistically significant association was found between mortality and sex, hypertension, cardiovascular disease, neurological disease, diabetes mellitus, hepatobiliary disease, hemodialysis, infection development, duration of ICU stay, or presence of malignancy ( $p>0.05$ ) (Table 1).

Laboratory analyses demonstrated significant differences between survivors and non-survivors in terms of blood urea, creatinine, albumin, total bilirubin, direct bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and C-reactive protein (CRP) levels ( $p<0.05$ ). Deceased patients had significantly higher urea, creatinine, bilirubin, ALT, AST, and CRP levels, while albumin levels were significantly lower. No significant differences were observed for blood glucose or magnesium levels (Table 2).

Hematological parameters also differed significantly between groups. White blood cell count, neutrophil count, and mean platelet volume (MPV) were significantly higher in deceased patients, whereas eosinophil count and platelet count were significantly higher among survivors ( $p<0.05$ ). No significant differences were found in lymphocyte, monocyte, basophil, red blood cell counts, hemoglobin, hematocrit, or mean corpuscular volume values ( $p>0.05$ ) (Table 3). Coagulation parameters, including activated partial thromboplastin time (APTT), prothrombin time (PT), and international normalized ratio (INR), were significantly higher in patients who died compared to survivors ( $p<0.05$ ).

Arterial blood gas and electrolyte analyses revealed significant associations between mortality and pH, partial pres-

**Table 2.** Distribution of biochemical parameters by mortality status

	(n=498)	Status		p <sup>a</sup>
		Survived (n=232)	Deceased (n=266)	
		Median (IQR)	Median (IQR)	
Glucose (g/dL)	142(112.0-204.2)	140(113.5-211.5)	146.5(109-202.2)	<b>0.269</b>
Urea (mg/dL)	85(47.0-136.5)	63(39-121)	98(63.8-156.5)	<b>&lt;0.001**</b>
Creatinine (mg/dL)	1.45(0.82-2.86)	1.12(0.75-2.20)	1.80(1.00-3.37)	<b>&lt;0.001**</b>
Albumin (g/dL)	2.9(2.5-3.5)	3.0(2.7-3.7)	2.8(2.4-3.3)	<b>&lt;0.001**</b>
Total bilirubin (mg/dL)	0.90(0.56-1.60)	0.80(0.50-1.34)	0.92(0.60-1.90)	<b>0.004**</b>
Direct bilirubin (mg/dL)	0.40(0.20-0.74)	0.36(0.20-0.60)	0.48(0.28-1.00)	<b>0.001**</b>
ALT (U/L)	22(13-45)	20.0(12.0-37.0)	24.0(14.0-54.2)	<b>0.008**</b>
AST (U/L)	29(20-64)	26.0(17.0-52.0)	36.0(22.0-89.0)	<b>&lt;0.001**</b>
Magnesium (mEq/L)	1.91(1.70-2.20)	1.90(1.60-2.14)	1.98(1.70-2.21)	0.051
CRP (mg/L)	7.4(3.0-14.0)	5.4(2.0-12.2)	9.8(4.0-16.0)	<b>&lt;0.001**</b>

n: Number of patients; IQR: Interquartile range; a Mann-Whitney U test; \*p<0.05; \*\*p<0.01

sure of oxygen (pO<sub>2</sub>), bicarbonate (HCO<sub>3</sub>), base excess (BE), lactate, sodium, potassium, and calcium levels (p<0.05). Deceased patients exhibited higher pO<sub>2</sub>, BE, lactate, and potassium levels, while pH, HCO<sub>3</sub>, sodium, and calcium levels were significantly lower. No significant differences were observed for partial pressure of carbon dioxide (pCO<sub>2</sub>), oxygen saturation (SO<sub>2</sub>), or chloride levels.

Vital signs also differed significantly between groups. Body temperature and heart rate were significantly higher in deceased patients, whereas systolic and diastolic blood pressure values and oxygen saturation were significantly lower (p<0.05).

Regarding nutritional support, most deceased patients were fed via nasogastric tube (86.1%), followed by closed oral intake (8.3%), oral feeding (2.6%), PEG feeding (2.6%), and total parenteral nutrition (0.4%). Among survivors, 69.0% received nasogastric feeding, 10.8% had closed oral intake, 15.5% were orally fed, and 4.7% received PEG feeding. Nasogastric feeding was significantly more common among survivors (p<0.05).

In multivariate logistic regression analysis, age, APACHE score, blood urea, albumin, eosinophil count, MPV, and lactate levels were identified as independent predictors of

**Table 3.** Distribution of complete blood count parameters by mortality status

	(n=498)	Survived (n=232)	Deceased (n=266)	p <sup>a</sup>
		Median (IQR)	Median (IQR)	
		Median (IQR)	Median (IQR)	
WBC (/mCL)	11.7(7.5-15.5)	10.9(7.0-15.4)	12.1(8.4-16.0)	<b>0.046*</b>
Lymphocyte (/mCL)	1.00(0.60-1.60)	1.08(0.60-1.60)	0.90(0.57-1.60)	0.272
Monocyte (/mCL)	0.53(0.31-0.85)	0.54(0.33-0.80)	0.52(0.30-0.90)	0.858
Neutrophil (/mCL)	9.6(5.8-13.0)	8.6(5.0-13.0)	10.0(6.4-13.6)	<b>0.035*</b>
Eosinophil (/mCL)	0.02(0-0.09)	0.03(0-0.11)	0.02(0-0.7)	<b>0.005**</b>
Basophil (/mCL)	0.02(0-0.03)	0.01(0.01-0.03)	0.02(0-0.04)	0.831
Red blood cell (/mCL)	3.5(3.0-4.2)	3.6(3.1-4.3)	3.5(3.0-4.2)	0.223
Hemoglobin (g/dL)	10.0(8.8-12.0)	10.0(8.8-12.2)	10.0(8.7-12.0)	0.225
Hematocrit (%)	31.4(27.0-37.0)	31.8(27.4-38.0)	89.0(85.0-94.0)	0.381
MCV (fL)	89(85-93)	88.1(85-92)	89(85-94)	0.150
PLT (/mCL)	201.0(135.8-280.2)	216.5(155.2-295.0)	186.0(120.5-264.8)	<b>0.009**</b>
MPV (fL)	9.4(8.6-10.4)	9.2(8.4-10.2)	9.6(8.7-10.7)	<b>&lt;0.001**</b>

n: Number of patients; IQR: Interquartile range; aMann-Whitney U test; \*p<0.05; \*\*p<0.01

**Table 4.** Independent effect of some possible predictors on mortality status (*Multivariate logistic regression analysis*)

	<b>B</b>	<b>SE</b>	<b>Waldχ<sup>2</sup></b>	<b>sd</b>	<b>OR (95 CI)</b>	<b>p</b>
Age	0.020	0.008	7.2	1	1.020(1.005-1.036)	<b>0.007</b>
APACHE score	0.042	0.014	9.6	1	1.043(1.016-1.071)	<b>0.002</b>
Urea	0.004	0.002	6.0	1	1.004(1.001-1.007)	<b>0.014</b>
Albumin	-0.392	0.165	5.6	1	0.676(0.489-0.935)	<b>0.018</b>
CRP	0.025	0.013	3.8	1	1.026(1.000-1.052)	0.051
Eosinophil	-1.420	0.716	3.9	1	0.242(0.059-0.983)	<b>0.047</b>
MPV	0.122	0.065	3.5	1	1.130(0.995-1.284)	<b>&lt;0.001</b>
Lactate	0.166	0.037	20.2	1	1.181(1.098-1.270)	<b>&lt;0.001</b>
Fever	0.278	0.167	2.8	1	1.320(0.952-1.830)	0.095
Heart rate	0.004	0.004	0.9	1	1.004(0.995-1.013)	0.350

B: Regression coefficient; SH: Standard error; sd: degrees of freedom; OR: odds ratio; CI: Confidence interval Cox & Snell R: 0.22; Nagelkerke R: 0.29; Hosmer-Lemeshow  $\chi^2$ : 10.2, p=0.254

mortality ( $p < 0.05$ ). CRP, body temperature, and heart rate did not retain independent significance in the multivariate model (Table 4).

## Discussion

Age has long been discussed as a prognostic factor in intensive care unit (ICU) patients, although its independent impact on mortality remains controversial. Kölgeliet al.<sup>[9]</sup> reported that advanced age was a significant factor affecting mortality, supporting our findings. Similarly, Nicolas et al.<sup>[10]</sup> demonstrated that mortality rates were more than twofold higher in patients over 65 years of age compared with those younger than 45 years, concluding that age is an important prognostic indicator, albeit less influential than disease severity.

In contrast, Chelluri et al.<sup>[11]</sup> suggested that age alone is not a reliable independent predictor of long-term survival or quality of life in critically ill patients. In our study, age emerged as a strong predictor of mortality. The discrepancies between these findings may be attributed to differences in disease severity at ICU admission, variations in patient populations, and heterogeneity in admission criteria across ICUs.

Mechanical ventilation is a well-established marker of disease severity and poor prognosis in ICU settings. Ünal et al. reported that 44.1% of patients required mechanical ventilation for an average of  $12.7 \pm 13.5$  days, with a mortality rate of 85.7%.<sup>[2]</sup> Our findings regarding mechanically ventilated patients were consistent with previously published data. Moreover, our ICU frequently provided care to patients with poor prognostic profiles due to severe comorbidities or those receiving palliative support, which may have contributed to the higher mortality observed among mechanically ventilated patients.

The relatively low rate of non-invasive mechanical ventilation (NIMV) in our cohort also warrants consideration. Patients who tolerated NIMV were predominantly managed in hospital wards and were transferred to the ICU only in cases of clinical deterioration. This practice pattern likely resulted in a lower proportion of NIMV use within the ICU population.

Severity scoring systems such as APACHE II are commonly used to predict outcomes in critically ill patients. Uysal et al.<sup>[12]</sup> reported higher-than-expected mortality rates across all APACHE II subgroups, emphasizing that while these scoring systems are valuable for comparing study populations, their predictive accuracy decreases in ICUs with heterogeneous patient profiles. They recommended recalibration of scoring systems according to unit-specific characteristics. Delayed initiation of organ-supportive therapies prior to ICU admission and the time elapsed before ICU transfer, factors not fully captured by scoring systems, may partially explain these discrepancies.

Comorbidities have also been variably associated with ICU mortality. Ceylan et al. reported that although most patients had underlying diseases, no significant association was observed between mortality and comorbidity burden or length of ICU stay.<sup>[13]</sup> Conversely, the EPIC study identified organ failure, malignancy, and diabetes as mortality risk factors in univariate analysis, with cancer remaining significant in multivariate models.<sup>[14]</sup> In our cohort, mortality was significantly higher in patients with chronic renal disease, whereas patients with respiratory diseases demonstrated lower mortality. Subgroup analyses according to multiple comorbidities were not performed, and our cohort consisted exclusively of patients admitted to an internal medicine ICU, which may explain these findings.

Biochemical parameters provided important prognostic information in our study. Higher levels of blood urea, creatinine, total and direct bilirubin, ALT, AST, and CRP, along with lower serum albumin levels, were significantly associated with mortality. Serum bilirubin has been described as a stable and reliable marker of hepatic dysfunction and is incorporated into several prognostic scoring systems.<sup>[15,16]</sup> Kramer et al.<sup>[17]</sup> demonstrated that even mild elevations in bilirubin were associated with significantly reduced survival, findings that strongly support our results.

Hypoalbuminemia is frequently observed in the early stages of critical illness and has been linked to prolonged ICU stay, mechanical ventilation, infection development, and increased mortality.<sup>[18–20]</sup> Similarly, elevated serum creatinine has consistently been associated with adverse outcomes. Akkoç et al.<sup>[7]</sup> reported increased mortality with higher creatinine levels at admission, and multiple studies have shown that even small increases in creatinine are linked to increased mortality risk.<sup>[21]</sup> Acute renal failure remains a major contributor to ICU mortality, with reported mortality rates ranging from 40% to 60%.<sup>[22,23]</sup> In our study, elevated urea and creatinine were associated with mortality; however, the absence of baseline creatinine values and urine output data represents a limitation.

Inflammatory markers also played a significant role. CRP, a widely used acute-phase reactant, was significantly associated with mortality in our cohort. Lobo et al. demonstrated that elevated CRP levels at ICU admission were associated with increased risk of organ failure and death.<sup>[24]</sup> Although procalcitonin has been reported to outperform CRP in predicting outcomes in septic shock,<sup>[25]</sup> it was not routinely available during the study period. Nonetheless, CRP showed strong prognostic value in our population.

Hematological parameters further contributed to mortality prediction. Higher white blood cell count, neutrophil count, and mean platelet volume (MPV), together with lower eosinophil and platelet counts, were observed in deceased patients. Previous studies, including those by Zhang et al., have shown that elevated MPV and thrombocytopenia are associated with increased mortality, consistent with our findings.<sup>[26]</sup>

Finally, disturbances in acid-base balance, electrolytes, and lactate levels were significantly associated with mortality. Elevated lactate, reflecting tissue hypoxia and impaired microcirculation, has been repeatedly shown to be a strong predictor of mortality, particularly when present at ICU admission.<sup>[27,28]</sup> Base deficit, an indirect marker of lactic acidosis, has similarly been associated with poor outcomes in critically ill patients.<sup>[29]</sup>

## Conclusion

Based on the findings of this study, age, APACHE score, blood urea, serum albumin, eosinophil count, mean platelet volume (MPV), and lactate levels were identified as independent predictors of mortality in patients admitted to the intensive care unit. These results highlight the prognostic value of routinely available clinical and laboratory parameters in critically ill patients. Incorporation of these variables into mortality risk assessment models may improve prognostic accuracy and assist clinicians in early risk stratification, clinical decision-making, and resource allocation in intensive care settings.

## Disclosures

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**Ethics Committee Approval:** The ethics committee approval has been granted by Recep Tayyip Erdogan University on 28/08/2019 and protocol number: 2019/144. The study complied with the Declaration of Helsinki.

**Informed Consent:** Written consent was obtained from all participants.

**Conflict of Interest:** The authors declare that they have no competing interests.

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## Research Article

# Clinical and Demographic Characteristics of Patients with Non-Functional Pituitary Adenomas: A Retrospective Single-Center Study

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### Abstract

**Objectives:** Non-functioning pituitary adenomas (NFPAs) are typically diagnosed due to tumor mass effects rather than hormone hypersecretion. However, variability in clinical presentation and outcomes remains incompletely defined.

**Methods:** This retrospective study included 200 patients diagnosed with NFPAs between 2013 and 2020. Clinical features, hormonal parameters, tumor size, and follow-up outcomes were analyzed.

**Results:** The mean age at diagnosis was 41.31 years. Macroadenomas were more frequent in males, whereas microadenomas predominated in females ( $p=0.002$ ). Headache, hypogonadal symptoms, and fatigue were the most common presenting complaints. Mass effect–related symptoms were more prominent in males and larger tumors ( $p<0.05$ ). The most frequent hormonal abnormalities were growth hormone deficiency (22%), central hypogonadism (17.5%), and central hypothyroidism (15.5%), with a higher prevalence in larger tumors ( $p<0.05$ ). Visual field defects were identified in 16% of patients and were strongly associated with larger tumors ( $p<0.001$ ). Tumor size remained stable at one year, although new hormonal deficiencies developed during follow-up.

**Conclusion:** NFPAs demonstrate distinct sex- and size-related clinical patterns. Men tend to present later with larger tumors and a higher burden of mass effect–related symptoms. Progressive endocrine dysfunction may occur despite radiological stability, underscoring the need for long-term follow-up.

**Keywords:** Hypopituitarism, macroadenoma, non-functioning pituitary adenoma, pituitary incidentaloma, transsphenoidal surgery

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Pituitary adenomas are among the most common intracranial tumors, accounting for approximately 10–15% of all primary brain neoplasms. These tumors arise from adenohypophyseal cells and are broadly classified as functional or non-functional based on their hormonal activity. Pituitary adenomas are also classified by tumor size: lesions  $<10$  mm are defined as microadenomas,  $\geq 10$  mm as macroadenomas, and  $\geq 40$  mm as giant adenomas.<sup>[1,2]</sup>

Most pituitary adenomas present with clinical findings related to hormone hypersecretion, such as hyperprolactinemia, acromegaly, and Cushing's disease. However, approximately 25–35% of pituitary adenomas are clinically silent and are classified as non-functioning pituitary adenomas (NFPAs).<sup>[3]</sup> NFPAs represent one of the most common subtypes of pituitary adenomas and are defined by the absence of clinically significant hormone hypersecretion.

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NFPAs are frequently detected incidentally on imaging performed for unrelated indications (pituitary incidentalomas) or become clinically evident due to local mass effects, most commonly hypopituitarism, headache, and visual field defects resulting from optic chiasm compression.<sup>[4-6]</sup> Consequently, the absence of clinically significant hormone hypersecretion often delays diagnosis until tumor enlargement produces compressive symptoms.

Although classified as non-functioning, NFPAs constitute a biologically heterogeneous group. Some tumors demonstrate no evidence of hormone production, whereas others show positive immunohistochemical staining for pituitary hormones without clinically evident hormone excess. These lesions are therefore referred to as clinically silent adenomas.<sup>[7,8]</sup>

Approximately 70–90% of clinically non-functioning pituitary adenomas are gonadotroph adenomas, arising from cells capable of producing follicle-stimulating hormone (FSH) and luteinizing hormone (LH).<sup>[9]</sup> Owing to their limited hormonal activity, patients typically present with symptoms related to local tumor expansion, including visual disturbances, headache, and varying degrees of pituitary dysfunction.<sup>[10]</sup> In addition, clinically silent variants of somatotroph, corticotroph, thyrotroph, and lactotroph adenomas have also been described, demonstrating immunohistochemical hormone expression without corresponding clinical syndromes.<sup>[11-15]</sup>

After the detection of a pituitary adenoma, evaluation should focus on the presence of hormone hypersecretion and symptoms related to tumor mass effects. In patients with NFPA, the primary goals of treatment are relief of compressive symptoms, preservation or improvement of pituitary function, and prevention of tumor progression or recurrence. Transsphenoidal surgical resection is considered the standard first-line treatment modality, and surgery is generally recommended in the presence of compressive symptoms or documented tumor growth. Radiotherapy is infrequently used as primary treatment and is mainly reserved for patients unsuitable for surgery or as adjuvant therapy for residual disease. No medical therapy has demonstrated clear efficacy in NFPAs. Patients managed with observation are typically monitored every 3–6 months with clinical and radiological follow-up.<sup>[16]</sup>

The aim of this retrospective study was to evaluate the clinical, radiological, and pathological characteristics of patients diagnosed with non-functioning pituitary adenoma and to identify factors associated with tumor progression, recurrence, and treatment outcomes. In addition, we sought to assess the impact of tumor size, invasiveness, and treatment modalities on disease course and follow-up outcomes.

## Methods

This retrospective cross-sectional study was conducted following approval from a Mersin University Ethics Committee (Decision no: 347, dated May 13, 2020). Patient records of individuals diagnosed with NFPA and managed between January 1, 2013, and March 31, 2020, at a tertiary referral center were systematically reviewed. The study was carried out in accordance with the principles of the Declaration of Helsinki.

Inclusion criteria were age between 18 and 65 years and confirmed diagnosis based on clinical, hormonal, and radiological findings. Patients with incomplete hormonal evaluation or insufficient imaging data were excluded. A total of 200 patients (137 female, 63 male) were included. Demographic data, presenting symptoms, baseline hormonal parameters (PRL, FSH, LH, ACTH, TSH, cortisol, GH, IGF-1), tumor size, and imaging findings were recorded. Adenomas were classified as microadenomas (<10 mm) or macroadenomas (≥10 mm).

Patients were categorized according to treatment approach (surgical vs. non-surgical) and follow-up status. Follow-up duration, hormonal deficiencies, visual field defects, residual tumor, recurrence, and additional treatment requirements were evaluated.

## Statistical Analysis

Statistical analyses were performed using STATISTICA version 13.5 (TIBCO Software Inc., Palo Alto, CA, USA). The normality of data distribution was assessed using the Kolmogorov–Smirnov and Shapiro–Wilk tests. Continuous variables were expressed as mean ± standard deviation or as minimum–maximum values, depending on the distribution characteristics, while categorical variables were presented as frequencies (n) and percentages (%). Comparisons of continuous variables, including age at diagnosis, hormone levels, and tumor size, according to sex and tumor classification (microadenoma vs. macroadenoma), were performed using the independent samples t-test. Comparisons of categorical variables, such as presenting symptoms and hormonal abnormalities, were conducted using the chi-square test or Fisher's exact test when appropriate. All statistical tests were two-sided, and a p-value <0.05 was considered statistically significant.

## Results

A total of 200 patients were included in the study, of whom 137 (68.5%) were female and 63 (31.5%) were male. Microadenomas were detected in 106 patients, and macroadenomas were detected in 94 patients. Microadenomas were more commonly observed in females (60.6% vs.

36.5%), whereas macroadenomas were significantly more frequent in males (63.5% vs. 39.4%), and both of these differences were statistically significant ( $p=0.002$ ). The mean age at diagnosis was  $41.31\pm 15.36$  years. Male patients were diagnosed at a significantly older age than female patients ( $47.54\pm 18.33$  vs.  $38.44\pm 12.87$  years). Similarly, patients with macroadenomas were older than those with microadenomas ( $49.09\pm 15.98$  vs.  $34.41\pm 10.88$  years,  $p<0.001$ ).

The most common presenting symptoms were headache, hypogonadal symptoms (menstrual irregularity, decreased libido, and impotence), and fatigue. In female patients, the most frequent symptoms were headache (59.9%), menstrual irregularity (44.5%), and fatigue (19%), whereas in male patients, headache (79.4%), fatigue (34.9%), and decreased libido (34.9%) were more prominent. Headache, visual disturbance, ophthalmoplegia, and fatigue were significantly more frequent in male patients ( $p<0.05$ ). Table 1 shows the distribution of presenting symptoms according to sex.

When stratified by tumor size, patients with macroadenomas more commonly presented with headache, visual disturbance, and ophthalmoplegia, whereas hypogonadal symptoms and galactorrhea were more frequently observed in patients with microadenomas ( $p<0.001$ ). Importantly, in all patients presenting with galactorrhea, the symptom was attributed to non-pituitary causes, and NFPA was identified incidentally during the diagnostic workup. Visual field defects were detected in 32 patients (16%), with a significantly higher prevalence in macroadenomas compared to microadenomas (32% vs. 0.9%,  $p<0.001$ ) (Table 2). The most common hormonal abnormalities were growth hormone deficiency (22%), central hypogonadism (17.5%), and central hypothyroidism (15.5%). In male patients, growth hormone deficiency (34.9%), central hypogonadism (25.4%), and central hypothyroidism were the most

**Table 1.** Distribution of presenting symptoms according to sex

Symptom	Female (n=137), n (%)	Male (n=63), n (%)	p
Headache	82 (59.9)	50 (79.4)	0.007
Blurred vision	26 (19.0)	21 (33.3)	0.032
Ophthalmoplegia	4 (2.9)	7 (11.1)	0.038
Fatigue	26 (19.0)	22 (34.9)	0.020
Decreased libido	26 (19.0)	22 (34.9)	—
Menstrual irregularity	61 (44.5)	—	—
Galactorrhea	25 (18.2)	1 (1.6)	0.016
Short stature	0 (0.0)	1 (1.6)	—
Impotence	—	17 (27.0)	—
Weight change	5 (3.6)	2 (3.2)	—

**Table 2.** Distribution of presenting symptoms according to tumor size

Symptoms	Microadenoma (n=106), n (%)	Macroadenoma (n=94), n (%)	p
Headache	48 (45.3)	84 (89.4)	<0.001
Blurred vision	12 (11.3)	35 (37.2)	<0.001
Ophthalmoplegia	0 (0.0)	11 (11.7)	<0.001
Fatigue	22 (20.8)	26 (27.7)	—
Hypogonadal symptoms (menstrual irregularity, decreased libido, impotence)	60 (56.6)	25 (26.6)	<0.001
Short stature	1 (0.9)	0 (0.0)	—
Weight change	4 (3.8)	3 (3.2)	—
Galactorrhea	24 (22.6)	2 (2.1)	<0.001

frequent abnormalities, whereas in female patients, hyperprolactinemia (18.2%), growth hormone deficiency (16%), and central hypogonadism (13.9%) were more common. Growth hormone deficiency ( $p=0.005$ ) and central hypothyroidism ( $p=0.035$ ) were significantly more frequent in male patients, while hyperprolactinemia was more common in female patients ( $p=0.016$ ). Hormonal abnormalities were more prevalent in macroadenomas, particularly central hypogonadism (24%), central hypothyroidism (23.4%), and growth hormone deficiency (28.7%) ( $p<0.05$ ). The distribution of hormonal abnormalities according to tumor size and sex is presented in Tables 3 and 4, respectively.

Regarding the initial point of contact, the majority of patients presented to the neurosurgery ( $n=79$ , 39.5%) and endocrinology ( $n=71$ , 35.5%) departments, while the remainder visited neurology ( $n=20$ , 10%), obstetrics and gynecology ( $n=11$ , 5.5%), and other clinics ( $n=19$ , 9.5%),

**Table 3.** Distribution of hormonal abnormalities according to tumor size

Hormonal abnormality	Macroadenoma (n=94), n (%)	Microadenoma (n=106), n (%)	p
Hyperprolactinemia	16 (17.0)	14 (13.2)	—
Hypoprolactinemia	8 (8.5)	3 (2.8)	—
Central hypogonadism	22 (23.4)	13 (12.3)	0.042
Central hypothyroidism	22 (23.4)	9 (8.5)	0.006
Cortisol deficiency	18 (19.1)	7 (6.6)	0.017
Growth hormone deficiency	27 (28.7)	17 (16.0)	0.040

**Table 4.** Distribution of hormonal abnormalities according to sex

Hormonal abnormality	Male (n=63), n (%)	Female (n=137), n (%)	P
Hyperprolactinemia	5 (7.9)	25 (18.2)	0.016
Hypoprolactinemia	7 (11.1)	4 (2.9)	—
Central hypogonadism	16 (25.4)	19 (13.9)	—
Central hypothyroidism	15 (23.8)	16 (11.7)	0.035
Cortisol deficiency	13 (20.6)	12 (8.8)	—
Growth hormone deficiency	22 (34.9)	22 (16.1)	0.005

including the emergency department, ophthalmology, general surgery, and urology.

Visual field examination was performed in all patients at initial presentation, revealing adenoma-related visual field defects in 32 patients (16%), including 1 patient (0.9%) with microadenoma and 31 patients (32%) with macroadenoma, with a significantly higher prevalence observed in macroadenomas ( $p < 0.001$ ). Notably, the microadenoma associated with visual field defect measured 9.5 mm and was located in close proximity to the optic chiasm.

Among the 112 patients who remained in follow-up, surgical intervention was performed in 41 cases, predominantly in those with macroadenomas ( $p < 0.001$ ). Surgical indications mainly included optic chiasm compression, hormonal deficiencies, and persistent headache. Residual tumor was detected in 20 patients (48%), and recurrence occurred in 7 patients (17.1%). Postoperative hormonal evaluation showed that 12 patients (29.3%) had normal hormone profiles, 20 patients (48.8%) had panhypopituitarism, and the remaining 9 patients had one or more hormonal deficiencies. Postoperative radiotherapy was required in 8 patients (19.5%). Patients managed conservatively were followed at 3–6 month intervals, and a minority developed new hormonal deficiencies, including hypoprolactinemia, central hypogonadism, and growth hormone deficiency during follow-up.

Follow-up MRI at one year demonstrated no meaningful change in tumor size among 54 non-operated patients, with comparable mean diameters at baseline and at one year ( $8.74 \pm 6.34$  mm vs.  $8.69 \pm 6.09$  mm).

## Discussion

Non-functioning pituitary adenomas (NFPAs) demonstrate variability in demographic characteristics across different study populations. Previous studies have reported that NFPAs are more common in females before the fourth decade of life, whereas male predominance becomes more apparent in the later decades.<sup>[17-20]</sup> In addition, several reports

have indicated that diagnosis typically occurs in the fifth decade in females and in the sixth decade in males, with an overall mean age ranging between 50 and 55 years.<sup>[18]</sup>

In line with previous studies, female patients constituted the majority in our cohort, and men were diagnosed at a significantly older age than women ( $47.54 \pm 18.33$  vs.  $38.44 \pm 12.87$  years). Overall, the mean age at diagnosis in our cohort was lower than that reported in the literature. This difference may be attributed to earlier imaging, greater accessibility to healthcare, or differences in referral patterns. The statistically significant age difference between sexes and between tumor size groups suggests that tumor growth and delayed clinical presentation are closely related.

Consistent with previous studies, macroadenomas were more frequently observed in males, whereas microadenomas predominated in females. In addition, patients with macroadenomas were diagnosed at older ages compared to those with microadenomas, which is likely related to the absence of early endocrine symptoms and the delayed development of mass effect-related clinical findings. These findings are in line with prior reports demonstrating that tumor size is associated with both age at diagnosis and clinical presentation.

The initial point of healthcare contact for patients with NFPA remains an underexplored area in the literature. While some studies have suggested that patients commonly present to ophthalmology clinics,<sup>[21]</sup> our findings indicate that the majority of patients initially presented to neurosurgery outpatient clinics, likely due to the high prevalence of headache as the presenting symptom. Only a minority of patients presented initially to endocrinology clinics, highlighting the importance of multidisciplinary evaluation in these patients.

In our cohort, the most common presenting symptoms were headache, hypogonadal symptoms, and fatigue, which are consistent with the known effects of tumor mass and pituitary dysfunction. Although symptom distribution varies across populations, our findings were largely in agreement with previous studies.<sup>[16,18,19,22-26]</sup> Evidence regarding sex-related differences in the presenting symptoms of non-functioning pituitary adenomas remains limited and, at times, inconsistent across studies. Di Somma et al.<sup>[25]</sup> reported a higher prevalence of headache and visual disturbances in male patients, whereas other analyses did not demonstrate a clear association between headache and sex.<sup>[27]</sup> Similarly, Ferrante et al.<sup>[19]</sup> observed comparable rates of hypogonadal symptoms between females and males (42.5% vs. 37.9%)<sup>[19]</sup>, while Cury et al.<sup>[28]</sup> reported a markedly higher prevalence in females (78% vs. 35%)<sup>[28]</sup>. In contrast to these heterogeneous findings, our results sug-

gest a more distinct sex-related pattern of clinical presentation. Specifically, male patients in our cohort more frequently exhibited symptoms related to tumor mass effect, including headache, visual disturbance, ophthalmoplegia, and fatigue. Our findings indicate a distinct sex-related pattern in clinical presentation, likely reflecting differences in tumor burden as well as variations in symptom perception and referral pathways.

Tumor size also played a significant role in symptom presentation. Patients with macroadenomas more frequently presented with symptoms related to local mass effect, including headache, visual disturbance, and ophthalmoplegia, whereas hypogonadal symptoms and galactorrhea were more commonly observed in microadenomas. These findings are consistent with prior reports showing that mass effect–related symptoms are more prominent in larger tumors.<sup>[29]</sup>

Previous studies have reported a wide range in the prevalence of hormonal abnormalities in non-functioning pituitary adenomas, varying between 30% and 85%, while panhypopituitarism has been reported in approximately 10% of cases. The most frequently described deficiencies include growth hormone deficiency (61–100%), gonadotropin deficiency (36–96%), and adrenal insufficiency (17–62%), although these rates differ substantially depending on the studied population and diagnostic criteria.<sup>[16,19,30,31]</sup> In comparison, our cohort demonstrated a lower overall frequency of hormonal abnormalities, with growth hormone deficiency (22%), central hypogonadism (17.5%), and central hypothyroidism (15.5%) being the most common findings. This discrepancy may be attributed to differences in patient selection, earlier-stage disease at diagnosis, or the retrospective nature of our study. Notably, new hormonal abnormalities developed during follow-up in a subset of patients, suggesting a dynamic and potentially progressive course of pituitary dysfunction.

Sex-based differences in hormonal abnormalities were also evident. Growth hormone deficiency and central hypothyroidism were significantly more frequent in males, whereas hyperprolactinemia was more commonly observed in females. Although partially consistent with previous studies, these findings also highlight variability across different cohorts, which may reflect differences in tumor characteristics, hormonal evaluation methods, and population-specific factors.

Hormonal dysfunction was more pronounced in patients with macroadenomas. Central hypogonadism, central hypothyroidism, cortisol deficiency, and growth hormone deficiency were all significantly more frequent in macroadenomas, supporting the concept that larger tumors exert a

greater mass effect on normal pituitary tissue. These findings are consistent with previous studies demonstrating a strong association between tumor size and hypopituitarism.

Visual impairment is a well-recognized complication of NF-PAs, primarily resulting from compression of the optic chiasm. Previous studies have reported visual field defects in approximately one-third of patients. In our cohort, visual field defects were identified in 16% of patients at initial endocrinology outpatient evaluation and were significantly more frequent in macroadenomas. Notably, the only microadenoma associated with a visual field defect measured 9.5 mm and was located in close proximity to the optic chiasm, emphasizing the importance of tumor location in addition to size.

Surgical management remains the mainstay of treatment in symptomatic patients. In our study, all operated patients underwent transsphenoidal surgery. Postoperatively, a substantial proportion of patients had persistent hormonal deficiencies, and nearly half had residual tumor tissue. Recurrence and the need for adjuvant radiotherapy were observed in 17.1% (n=7) and 19.5% (n=8) of patients, respectively. These findings are consistent with previous reports indicating that complete resection is often challenging due to tumor size and invasiveness.<sup>[5,19,32-34]</sup>

Long-term follow-up is essential in patients with NF-PAs. In our study, newly developed hormonal abnormalities were observed during follow-up, despite overall stability in tumor size. Among non-operated patients with available imaging at one year, no significant change in tumor size was detected, in line with previous studies suggesting that a considerable proportion of NF-PAs remain stable over time. However, the emergence of new hormonal abnormalities underscores the need for regular endocrine evaluation, even in patients managed conservatively.

Several limitations of this study should be acknowledged. The retrospective design and single-center setting may have influenced the interpretation of the findings; however, the comprehensive clinical characterization and real-world data provide meaningful insight into the clinical behavior of NF-PAs.

## Conclusion

In conclusion, this study provides a comprehensive characterization of patients with non-functioning pituitary adenomas, demonstrating that delayed diagnosis—particularly in male patients—is associated with a higher prevalence of macroadenomas and a predominance of mass effect–driven presentation. Additionally, the observed sex-specific differences in clinical features suggest that both biological

and diagnostic factors may influence disease recognition and should be considered in clinical evaluation.

Importantly, our findings highlight the dynamic nature of pituitary dysfunction in NFPA, as hormonal axes that are initially preserved may deteriorate over time, even in the absence of overt radiological tumor progression. Furthermore, the high frequency of residual disease and recurrence following surgical intervention underscores the need for long-term, multidisciplinary follow-up. Taken together, these findings support a more individualized and longitudinal approach to NFPA management. Future prospective, multicenter studies incorporating standardized follow-up strategies are warranted to further refine surveillance and improve patient outcomes.

### Disclosures

**Ethics Committee Approval:** This retrospective cross-sectional study was conducted following approval from a Mersin University Ethics Committee (decision no: 347, dated May 13, 2020).

**Informed Consent:** Informed consent was not obtained due to the retrospective design of the study.

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## Research Article

# Prognostic Impact of FLT3, NPM1 and CEBPA Mutations in Cytogenetically Normal Acute Myeloid Leukemia

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### Abstract

Cytogenetically normal acute myeloid leukemia (CN-AML) represents nearly half of adult AML cases and demonstrates significant clinical heterogeneity. Cytogenetics alone is insufficient for risk stratification, and molecular markers such as FLT3, NPM1, and CEBPA have emerged as key prognostic determinants. This study evaluated the frequency and prognostic impact of FLT3-ITD, FLT3-D835, NPM1, and CEBPA mutations in CN-AML patients. We retrospectively analyzed 55 CN-AML patients diagnosed at a tertiary center (September 2012–2013). Molecular profiling was performed using PCR-based methods. Overall survival (OS) was assessed using Kaplan–Meier analysis and log-rank testing. Mutation frequencies were: FLT3-ITD % 12.7, FLT3-D835 1.8%, NPM1 20%, and CEBPA 14.5%. Complete remission was achieved in % 63.6 of patients. FLT3-ITD mutations were associated with significantly shorter OS ( $p=0.004$ ), whereas FLT3-ITD(-)/NPM1(+) status correlated with improved OS ( $p=0.0032$ ). No significant differences in remission rates were observed among subgroups. These findings confirm the prognostic relevance of FLT3 and NPM1 mutations in CN-AML and support routine molecular profiling to guide risk-adapted therapeutic strategies.

**Keywords:** Acute myeloid leukemia, FLT3, Prognosis

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Acute myeloid leukemia (AML) is a genetically heterogeneous clonal disorder of hematopoietic progenitor cells, characterized by impaired differentiation, accumulation of immature blasts in the bone marrow and peripheral blood, and consequent marrow failure.<sup>[1]</sup> AML remains the most common form of acute leukemia in adults, with an estimated incidence of 3–5 cases per 100,000 individuals annually.<sup>[2]</sup> Despite advances in risk-adapted therapy and supportive care, clinical outcomes in AML remain highly variable, underscoring the need for refined prognostic models. Prognosis in AML is influenced by several variables, including age, performance status, white blood cell (WBC)

count at diagnosis, treatment intensity, and, most importantly, cytogenetic and molecular characteristics.<sup>[3]</sup>

Among AML patients, approximately 40–50% present with cytogenetically normal karyotypes, commonly referred to as cytogenetically normal AML (CN-AML).<sup>[4]</sup> Historically considered an intermediate-risk group, CN-AML encompasses a highly diverse set of clinical behaviors, ranging from long-term remission to early relapse and death.<sup>[5]</sup> This clinical heterogeneity reflects the underlying molecular complexity, which traditional cytogenetic analysis fails to capture.<sup>[6]</sup> Therefore, increasing emphasis has been placed on understanding the molecular landscape of CN-AML,

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with the goal of identifying prognostic and predictive biomarkers to refine risk stratification and guide therapy.<sup>[7]</sup>

With the advent of molecular diagnostics and next-generation sequencing (NGS), several recurrent mutations have been identified in CN-AML.<sup>[8]</sup> Among these, mutations in FLT3, NPM1, and CEBPA have been most extensively studied and are now firmly integrated into the European LeukemiaNet (ELN) and National Comprehensive Cancer Network (NCCN) risk classifications.<sup>[9]</sup> These molecular aberrations not only serve as prognostic markers but also as therapeutic targets, thereby forming the backbone of personalized medicine in AML. Accordingly, molecular risk stratification has become an essential component of routine clinical decision-making in CN-AML.

The FLT3 gene encodes a receptor tyrosine kinase expressed on early hematopoietic progenitor cells and is involved in cell proliferation, differentiation, and survival.<sup>[10]</sup> The most common pathogenic variant, FLT3 internal tandem duplication (FLT3-ITD), occurs within the juxtamembrane domain, leading to constitutive activation of the receptor.<sup>[11]</sup> This results in aberrant activation of downstream signaling cascades, including STAT5, PI3K-AKT, and MAPK pathways. FLT3-ITD is detected in approximately 25–30% of CN-AML cases and is consistently associated with adverse clinical outcomes, including high leukocyte counts, increased risk of relapse, and poor overall survival.<sup>[12]</sup> The prognostic impact of FLT3-ITD is further modulated by the allelic ratio (high vs. low) and co-existing mutations such as NPM1.<sup>[13]</sup> In recognition of its clinical significance, FLT3 inhibitors such as midostaurin, gilteritinib, and quizartinib have been developed and are now part of the therapeutic armamentarium in AML.<sup>[14]</sup>

NPM1 mutations, most commonly involving a 4-bp insertion in exon 12, result in aberrant cytoplasmic localization of nucleophosmin, a nucleolar phosphoprotein involved in ribosomal biogenesis, genomic stability, and centrosome duplication.<sup>[15]</sup> These mutations are highly specific to AML and are found in approximately 50–60% of CN-AML cases.<sup>[16]</sup> Importantly, NPM1 mutations are associated with a favorable prognosis when not accompanied by FLT3-ITD.<sup>[17]</sup> Patients with the NPM1(+)/FLT3-ITD(-) genotype often achieve complete remission with conventional chemotherapy and have excellent long-term outcomes without the need for allogeneic stem cell transplantation in first remission.<sup>[18]</sup>

CEBPA is a transcription factor crucial for granulocytic differentiation.<sup>[19]</sup> Mutations in CEBPA are present in 5–15% of AML cases, with biallelic mutations (double mutations) being particularly significant for prognostication. Biallelic CEBPA mutations are associated with normal karyotype, high complete remission rates, and prolonged survival.<sup>[20]</sup>

These patients are classified in the favorable-risk category under the ELN 2022 guidelines and often do not require stem cell transplantation in first remission.<sup>[21]</sup> However, monoallelic CEBPA mutations have a less favorable impact and must be distinguished from biallelic forms through sequencing-based methods.<sup>[22]</sup>

This study aimed to evaluate the frequency and clinical impact of FLT3, NPM1, and CEBPA mutations in a cohort of Turkish CN-AML patients. We sought to examine their relationship with treatment response and overall survival and to compare our findings with existing global data. However, real-world data regarding the prognostic impact of these mutations remain limited in certain populations, including Turkish patients.

## Methods

### Study Design and Patient Selection

This retrospective study was conducted at a hematology center in Turkey and included adult patients diagnosed with cytogenetically normal acute myeloid leukemia (CN-AML) between September 2012 and September 2013. Inclusion criteria were: age  $\geq 18$  years, de novo AML diagnosis based on WHO criteria, and confirmation of normal karyotype via conventional cytogenetic analysis. Patients with secondary AML, prior myelodysplastic syndromes, or complex karyotypes were excluded.

### Cytogenetic and Molecular Analysis

Conventional karyotyping was performed on bone marrow samples using G-banding techniques. Cases with 20 metaphases and no detectable structural or numerical abnormalities were considered cytogenetically normal.<sup>[23]</sup>

Molecular testing was conducted on diagnostic bone marrow aspirates using polymerase chain reaction (PCR) and fragment length analysis. The following mutations were screened:

- FLT3 internal tandem duplication (FLT3-ITD)
- FLT3 tyrosine kinase domain point mutation (FLT3-D835)
- NPM1 exon 12 mutations
- CEBPA mutations (monoallelic or biallelic, by Sanger sequencing)

Allelic burden for FLT3-ITD was not quantified due to technical constraints.

### Treatment Protocol

All patients received induction chemotherapy consisting of the standard “3+7” regimen (cytarabine for 7 days and an anthracycline for 3 days). Consolidation treatment included high-dose cytarabine or allogeneic hematopoietic stem

cell transplantation (allo-HSCT) in eligible patients, according to risk classification and donor availability.

### Response Assessment and Follow-Up

Treatment response was evaluated using standard ELN criteria. Complete remission (CR) was defined as <5% blasts in bone marrow with hematologic recovery. Patients were followed for a minimum of 12 months or until death.

### Statistical Analysis

Descriptive statistics were used to summarize patient demographics and mutation frequencies. The association between mutation status and clinical outcomes was assessed using the chi-square or Fisher's exact test. Kaplan–Meier survival curves were generated for overall survival (OS), and comparisons between groups were made using the log-rank test. A p-value of <0.05 was considered statistically significant. Statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA).

## Results

### Baseline Patient Characteristics

A total of 55 patients with cytogenetically normal acute myeloid leukemia (CN-AML) were included in this retrospective study. The median age at diagnosis was 47 years (range: 19–73), and 60% (n=33) of the patients were male. All patients had a normal karyotype confirmed by standard G-banding cytogenetics. The most common presenting symptoms were fatigue (78%), fever (65%), and bleeding tendency (43%). Baseline median white blood cell (WBC) count was 25,500/ $\mu\text{L}$  (range: 1,800–175,000), and median blast percentage in bone marrow was 68% (range: 23–98%).

### Mutation Frequencies

Among the cohort, molecular profiling revealed the following mutation distribution:

(Table 2 provides a visual overview of mutation distribution.)

### Treatment Response

All patients received standard induction chemotherapy with a “3+7” regimen. The overall complete remission (CR) rate post-induction was 63.6% (n=35). Stratification by mutation subgroup revealed the following CR rates:

Although higher CR rates were observed in NPM1(+) and CEBPA(+) patients, these differences did not reach statistical significance ( $p = 0.190$ ), likely due to the limited sample size.

**Table 1.** Baseline Demographic and Clinical Characteristics of Patients with CN-AML (n = 55)

Characteristic	Value
Age, years	
Median (range)	47 (19–73)
<40 years, n (%)	18 (32.7)
40–59 years, n (%)	24 (43.6)
$\geq 60$ years, n (%)	13 (23.7)
Sex, n (%)	
Male	33 (60.0)
Female	22 (40.0)
Performance status at diagnosis, n (%)	
ECOG 0–1	38 (69.1)
ECOG $\geq 2$	17 (30.9)
Cytogenetic status, n (%)	
Cytogenetically normal AML	55 (100)
Clinical presentation at diagnosis, n (%),	
Fatigue	43 (78.0)
Fever / infection	36 (65.0)
Bleeding tendency	24 (43.0)
Weight loss / night sweats	19 (34.5)
Baseline laboratories characteristics	
WBC count ( $\mu\text{L}$ ), median (range)	25,500 (1,800–175,000)
WBC $\geq 30,000/\mu\text{L}$ , n (%)	21 (38.2)
Hemoglobin (g/dL), median (range)	8.9 (5.6–12.4)
Platelet count ( $\times 10^9/\text{L}$ ), median (range)	42 (8–168)
Bone marrow blasts (%), median (range)	68 (23–98)
Treatment-related baseline variables	
De novo AML, n (%)	55 (100)
Induction therapy (3+7), n (%)	55 (100)
Allogeneic HSCT planned at diagnosis, n (%)	18 (32.7)

### Overall Survival Analysis

At a median follow-up of 26.5 months (range: 5–61 months), Kaplan–Meier survival analysis demonstrated distinct differences in overall survival (OS) between molecular subgroups.

- FLT3-ITD(+) patients exhibited significantly inferior OS, with a median OS of 8.4 months.
- FLT3-ITD(-)/NPM1(+) patients showed superior outcomes, with median OS not reached at the last follow-up.
- Patients with CEBPA mutations trended toward improved survival (median OS: 30.2 months), though this was not statistically significant.

**Table 2.** Provides a visual overview of mutation distribution

Mutation	Frequency (n)	Percentage (%)
FLT3-ITD	7	12.7%
FLT3-D835	1	1.8%
NPM1	11	20.0%
CEBPA	8	14.5%
FLT3-ITD(-)/NPM1(+)	9	16.4%

(Table 3 presents OS and 2-year OS values.)

The survival advantage of the FLT3-ITD(-)/NPM1(+) subgroup was statistically significant compared to other groups ( $p = 0.0032$ ). In contrast, FLT3-ITD(+) status conferred an independently adverse prognostic impact, consistent with previous reports.

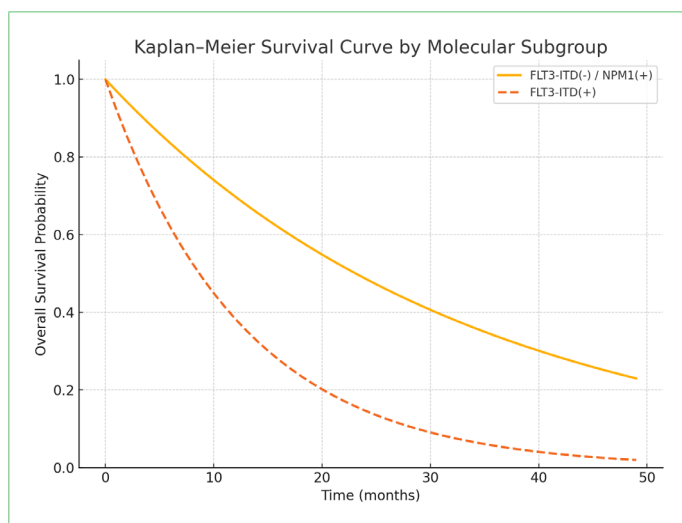
(Figure 1. Kaplan–Meier curves showing OS stratified by molecular subgroup: FLT3-ITD(+), FLT3-ITD(-)/NPM1(+), and others.)

### 3.5 Hematopoietic Stem Cell Transplantation

Allogeneic HSCT was performed in 14 patients (25.4%) during first complete remission. Among transplanted patients, 2-year OS was 71.4%, compared to 48.1% in non-transplanted patients. However, this survival advantage was most pronounced in FLT3-ITD(+) patients undergoing HSCT, suggesting a possible mitigation of adverse prognostic impact through transplantation.

## Discussion

In this study, we investigated the prognostic implications of FLT3, NPM1, and CEBPA mutations in a Turkish cohort of patients diagnosed with cytogenetically normal acute my-



**Figure 1.** Kaplan–Meier curves showing OS stratified by molecular subgroup: FLT3-ITD(+), FLT3-ITD(-)/NPM1(+), and others.

**Table 3.** Median OS and 2-year OS rates by subgroup

Subgroup	Median OS (months)	2-Year OS (%)	Log-rank p
FLT3-ITD(+)	8.4	14.3%	0.004
FLT3-ITD(-)/NPM1(+)	Not Reached	81.8%	0.0032
CEBPA(+)	30.2	75.0%	0.087
Other mutations	18.6	55.6%	–

eloid leukemia (CN-AML). Our findings confirm previously established associations from the global literature, while providing important real-world data from a single-center experience. Notably, FLT3-ITD mutations were associated with significantly inferior overall survival (OS), whereas the FLT3-ITD(-)/NPM1(+) genotype was linked to favorable outcomes. Although CEBPA mutations appeared to confer a trend toward improved survival, statistical significance was limited, likely due to the relatively small cohort.

### Prognostic Impact of FLT3-ITD

FLT3-ITD mutations are among the most common molecular lesions in CN-AML and have consistently been associated with poor prognosis, high relapse rates, and reduced OS across numerous studies. In a large cohort of over 900 AML patients, it was demonstrated that FLT3-ITD positivity significantly shortened remission duration and OS. Similarly, the Cancer and Leukemia Group B (CALGB) and UK NCRI trials confirmed the adverse impact of FLT3-ITD, especially in patients with a high allelic ratio.<sup>[24]</sup>

In our cohort, FLT3-ITD was detected in 12.7% of patients, which aligns with the frequency range (15–30%) reported in the literature. These patients exhibited a median OS of 8.4 months and 2-year OS of only 14.3%, both significantly worse than other subgroups. These findings reinforce the ELN 2022 recommendation that FLT3-ITD(+) patients, especially those with high allelic burden, should be classified into the intermediate- or adverse-risk categories and considered for early allogeneic stem cell transplantation (allo-HSCT) or FLT3 inhibitor-based therapy.

### Favorable Prognosis with NPM1 Mutations

The NPM1 gene mutation, particularly when unaccompanied by FLT3-ITD, is well established as a favorable prognostic marker. Döhner et al.<sup>[1]</sup> reported improved remission rates and longer OS in NPM1(+) patients, especially in those who are FLT3-ITD(-). In our study, 20% of patients had NPM1 mutations, and 16.4% had the favorable FLT3-ITD(-)/NPM1(+) genotype.<sup>[25]</sup>

These patients exhibited the most favorable outcomes in our cohort, with a 2-year OS rate of 81.8% and median OS not reached. Furthermore, the complete remission rate was

also highest (88.9%) in this group. These findings support the notion that this molecular profile can serve as a criterion to forgo allo-HSCT in first remission and to guide de-intensified therapy in future trials.

### Prognostic Relevance of CEBPA Mutations

CEBPA mutations, especially when biallelic, are associated with a distinct subset of CN-AML with favorable prognosis. In our cohort, 14.5% of patients carried CEBPA mutations, and they showed a high CR rate (75%) and 2-year OS of 75%. However, due to a lack of allelic status confirmation (biallelic vs. monoallelic), we could not stratify these patients into their respective ELN risk categories.

Previous studies have shown that biallelic CEBPA mutations are linked with improved survival and long-term remission, whereas monoallelic variants have limited prognostic value. Our data suggest a favorable trend, yet emphasize the importance of detailed molecular testing for allelic discrimination, which remains a limitation in many developing settings.<sup>[26]</sup>

### Real-World and Regional Data

One of the major strengths of our study lies in its contribution to real-world data from a Middle Eastern population, where AML molecular epidemiology remains underreported. While our mutation frequencies largely align with global data, subtle regional differences may exist due to ethnic, socioeconomic, or environmental factors.

For instance, our FLT3-ITD frequency (12.7%) was slightly lower than commonly reported, which may be due to underdetection in retrospective analysis or sample size limitations. Similarly, our NPM1 mutation rate (20%) was lower than the 30–50% range seen in Western CN-AML populations, possibly reflecting ethnic differences.<sup>[27]</sup>

### Implications for Clinical Practice

Our findings support the routine integration of FLT3, NPM1, and CEBPA mutation testing into the diagnostic workup of CN-AML. Identifying high-risk patients early allows for prompt referral to transplant centers or inclusion in clinical trials exploring FLT3 inhibitors. Conversely, recognition of favorable-risk subgroups such as FLT3-ITD(-)/NPM1(+) or biallelic CEBPA can prevent overtreatment and reduce transplant-related morbidity.

Moreover, the availability of novel targeted therapies such as midostaurin, gilteritinib, and quizartinib further highlights the importance of precise molecular characterization, especially as FLT3-targeted maintenance therapy gains regulatory approval.

### Study Limitations

The main limitations of this study include its retrospective design, single-center setting, and limited cohort size.

Allelic burden for FLT3-ITD and biallelic status for CEBPA could not be determined due to technical limitations. Also, treatment regimens were not standardized with respect to risk-adapted strategies or FLT3 inhibitor usage. Nevertheless, the study provides valuable baseline data for future prospective multicenter studies in Turkey and similar settings.

This study reinforces the critical prognostic role of molecular mutations in cytogenetically normal acute myeloid leukemia (CN-AML). Our findings align with the international literature and underscore the following key conclusions:

- FLT3-ITD mutations are strongly associated with inferior overall survival and lower complete remission rates. These patients should be considered for intensified therapy, including early allogeneic hematopoietic stem cell transplantation and FLT3 inhibitor-based treatment strategies.
- NPM1 mutations, particularly in the absence of FLT3-ITD, define a favorable-risk subgroup with excellent treatment response and survival outcomes. These patients may benefit from chemotherapy alone and may not require transplantation in first remission.
- CEBPA mutations, while limited by allelic status in our cohort, demonstrated trends toward improved prognosis, supporting their inclusion in favorable-risk classifications as per ELN guidelines
- The mutation frequencies observed in this Turkish cohort are broadly consistent with global data but also emphasize the need for local epidemiologic insights in precision hematology.

Routine molecular profiling of FLT3, NPM1, and CEBPA at the time of diagnosis is essential to refine risk stratification, guide treatment intensity, and ensure optimal use of targeted therapies in CN-AML. Integration of these molecular markers into everyday clinical decision-making represents a crucial step toward personalized AML therapy.

### Conclusion

This study highlights the important prognostic role of FLT3, NPM1, and CEBPA mutations in patients with cytogenetically normal acute myeloid leukemia (CN-AML). In this Turkish cohort, FLT3-ITD mutations were associated with inferior overall survival and lower complete remission rates, supporting their role as adverse prognostic markers. In contrast, NPM1 mutations, particularly in the absence of FLT3-ITD, were associated with favorable treatment response and improved survival outcomes. CEBPA mutations also showed a trend toward better prognosis, although further stratification according to allelic status is needed.

Routine molecular testing at diagnosis is essential for accurate risk stratification and individualized treatment planning in CN-AML. The integration of molecular markers into clinical decision-making may help identify patients who require intensified therapy, allogeneic hematopoietic stem cell transplantation, or targeted treatment approaches, while also preventing overtreatment in favorable-risk groups. Larger prospective multicenter studies are needed to confirm these findings and better define the molecular epidemiology of CN-AML in Turkish and regional populations.

### Disclosures

**Ethics Committee Approval:** The study was approved by the institutional review board of Dicle University in accordance with the ethical standards of the institutional and/or national research committee and the 1964 Helsinki (455772/23.11.2013).

**Informed Consent:** Patient consent was waived due to the retrospective and anonymized nature of the study.

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