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Immature Granulocyte Percentage and Hematocrit for Prediction of Severe Obstructive Sleep Apnea in a PSG-Referred Cohort

Polisomnografiye Yönlendirilen Bir Kohortta Şiddetli Obstrüktif Uyku Apnesinin Öngörülmesinde İmmatür Granülosit Yüzdesi ve Hematokrit

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Abstract

Objective: To determine whether hematocrit (HCT) and immature granulocyte percentage (IG%) are independently associated with severe obstructive sleep apnea (OSA) and to quantify whether IG% improves discrimination beyond age, body mass index (BMI), neck circumference, and HCT among symptomatic adults referred for polysomnography (PSG).

Materials and Methods: This retrospective cross-sectional study included 275 adults referred for attended PSG between January 2019 and July 2020. Severe OSA was defined as an apnea-hypopnea index ≥30 events/hour. The primary multivariable analysis used 238 complete cases and five prespecified predictors: HCT, IG%, BMI, age, and neck circumference. Predictor-level missingness was characterized; participants included in and excluded from the complete-case analysis were compared. A reduced model without IG% was compared with the full model using DeLong's test, and a multiple-imputation sensitivity analysis using 50 imputed datasets was performed. Discrimination, calibration, bootstrap internal validation, and exploratory decision curve analysis were assessed.

Results: Severe OSA cases had higher BMI, neck circumference, HCT, and IG% than participants without severe OSA (all p≤0.045). In the complete-case model, HCT [odds ratio (OR): 1.09, 95% confidence interval (CI): 1.03-1.16; p = 0.003], IG% (OR: 2.11, 95% CI: 1.05-4.24; p = 0.035), and neck circumference (OR: 1.09, 95% CI: 1.01-1.18; p = 0.030) were independently associated with severe OSA. The full-model area under the curve (AUC) was 0.731 (95% CI: 0.661-0.802), compared with 0.715 (95% CI: 0.644-0.787) for the model without IG%; the AUC difference was 0.016 (95% CI -0.013 to 0.045; DeLong p = 0.282). In multiple imputation, HCT remained associated with severe OSA

Öz

Amaç: Semptomatik olup polisomnografi (PSG) için yönlendirilen erişkinlerde hematokrit (HCT) ve immatür granülosit yüzdesinin (IG%) şiddetli obstrüktif uyku apnesi (OSA) ile bağımsız olarak ilişkili olup olmadığını belirlemek ve IG%'nin yaş, vücut kitle indeksi (VKİ), boyun çevresi ve HCT'ye ek olarak ayırt edici performansa katkı sağlayıp sağlamadığını nicel olarak değerlendirmektir.

Gereç ve Yöntem: Bu retrospektif kesitsel çalışmaya, Ocak 2019 ile Temmuz 2020 tarihleri arasında gözetimli PSG için yönlendirilen 275 erişkin dahil edildi. Şiddetli OSA, apne-hipopne indeksinin ≥30 olay/saat olması olarak tanımlandı. Birincil çok değişkenli analiz, tam verisi bulunan 238 olgu üzerinde ve önceden belirlenmiş beş prediktör kullanılarak gerçekleştirildi: HCT, IG%, VKİ, yaş ve boyun çevresi. Prediktör düzeyindeki eksik veriler değerlendirildi; tam olgu analizine dahil edilen ve edilmeyen katılımcılar karşılaştırıldı. IG% içermeyen indirgenmiş model ile tam model DeLong testi kullanılarak karşılaştırıldı ve 50 imputasyonlu veri seti kullanılarak çoklu imputasyon duyarlılık analizi gerçekleştirildi. Ayırt edici performans, kalibrasyon, bootstrap yöntemiyle iç doğrulama ve keşifsel karar eğrisi analizi değerlendirildi.

Bulgular: Şiddetli OSA bulunan olgularda VKİ, boyun çevresi, HCT ve IG% değerleri şiddetli OSA bulunmayan katılımcılara göre daha yüksekti (tümü için p≤0,045). Tam olgu modelinde HCT [olasılık oranı (OR): 1,09; %95 güven aralığı (GA): 1,03-1,16; p = 0,003], IG% (OR: 2,11; %95 GA: 1,05-4,24; p = 0,035) ve boyun çevresi (OR: 1,09; %95 GA: 1,01–1,18; p = 0,030) şiddetli OSA ile bağımsız olarak ilişkiliydi. Tam modelin eğri altında kalan alanı (AUC) 0,731 (%95 GA: 0,661-0,802) iken, IG% içermeyen modelde bu değer 0,715 (%95 GA: 0,644-0,787) idi. AUC farkı 0,016 (%95 GA: -0,013 ile 0,045; DeLong p = 0,282) olarak bulundu. Çoklu imputasyon analizinde HCT, şiddetli OSA ile ilişkisini

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(OR: 1.09, 95% CI: 1.03-1.15; p = 0.004), whereas the IG% estimate was attenuated (OR: 1.87, 95% CI: 0.98-3.54; p = 0.056).

Conclusion: Among symptomatic adults referred for PSG, HCT showed a more robust association with severe OSA. IG% showed an exploratory association, but its incremental AUC contribution was not statistically significant and its estimate was attenuated after multiple imputation. External validation, recalibration, and prospective impact assessment are required before clinical implementation.

Keywords: Obstructive sleep apnea, immature granulocytes, hematocrit; prediction model, polysomnography, decision curve analysis

sürdürdü (OR: 1,09; %95 GA: 1,03-1,15; p = 0,004); buna karşılık IG% tahmini zayıfladı (OR: 1,87; %95 GA: 0,98-3,54; p = 0,056).

Sonuç: Semptomatik olup PSG için yönlendirilmiş erişkinlerde HCT, şiddetli OUA ile daha sağlam bir ilişki gösterdi. IG% keşifsel bir ilişki sinyali gösterse de AUC'ye ek katkısı istatistiksel olarak anlamlı değildi ve çoklu atama analizi sonrasında anlamlılığı zayıfladı. Klinik uygulama öncesinde dış doğrulama, yeniden kalibrasyon ve prospektif etki değerlendirmesi gereklidir.

Anahtar Kelimeler: Obstrüktif uyku apnesi, immatür granülositler, hematokrit, öngörü modeli, polisomnografi, karar eğrisi analizi

Introduction

Obstructive sleep apnea (OSA) is increasingly recognized as a multisystem disorder in which chronic intermittent hypoxia promotes oxidative stress and systemic inflammation (1). Patients with OSA also have a high burden of metabolic and cardiovascular comorbidity. Continuous positive airway pressure remains the gold-standard treatment and reduces recurrent hypoxia by preventing upper airway collapse (2).

Traditional markers such as C-reactive protein are influenced by adiposity and comorbid conditions, which can confound their relationship with OSA severity (3). Consequently, there is growing interest in complete blood count (CBC)-derived inflammatory indices such as the neutrophil-to-lymphocyte ratio, systemic immune-inflammation index, and systemic inflammation response index, which reflect both innate and adaptive immune activity (4).

Immature granulocytes (IGs), which include promyelocytes, myelocytes, and metamyelocytes, are usually retained in the bone marrow and appear in peripheral blood when granulopoiesis is accelerated. Automated hematology analyzers can quantify IGs as an absolute count and as a percentage (IG%), enabling rapid and standardized assessment within routine CBC testing (5).

Hematocrit (HCT), defined as the proportion of circulating blood volume occupied by erythrocytes, may reflect a chronic hematologic response to recurrent hypoxemia, whereas IG% may capture stress-related granulopoiesis and systemic inflammatory activation. These markers therefore represent complementary biological pathways rather than interchangeable measures. IG% has shown early discriminative value in acute inflammatory conditions, and a recent study reported higher IG count and IG% values in patients with OSA than in controls (6,7).

The present study was conducted among symptomatic patients referred for polysomnography (PSG), the diagnostic reference standard for OSA. The primary objective was to determine whether HCT and IG% were independently associated with severe OSA [apnea-hypopnea index (AHI) ≥30 events/hour]. A prespecified secondary objective was to quantify whether adding IG% improved discrimination beyond age, body mass index (BMI), neck circumference, and HCT within this referred population. The model was evaluated for discrimination, calibration, internal validity, and exploratory potential net benefit; incremental performance claims were based on direct comparison of the reduced and full models.

Materials and Methods

Study Design and Participants

The Scientific Research Ethics Committee of Erzurum Faculty of Medicine, University of Health Sciences Türkiye approved this retrospective study (decision no: 2024/03-46; approval date: March 13, 2024). The requirement for informed consent was waived because de-identified retrospective data were used. The study was conducted at a tertiary referral center in eastern Türkiye, located approximately 1,900 m above sea level. Adult patients referred for attended PSG between January 2019 and July 2020 for snoring, witnessed apnea, or excessive daytime sleepiness were screened. Demographic and clinical variables, including age, sex, BMI, neck circumference, and comorbidities (diabetes mellitus and cardiovascular disease), were extracted from medical records. Biochemical and CBC parameters were obtained from blood samples collected on the same day as PSG or clinical evaluation according to routine hospital practice. All included participants had completed PSG before retrospective data extraction; therefore, there was no prospective loss to follow-up. The overall descriptive cohort comprised 275 participants. Participants with one or more missing prespecified model predictors were retained in descriptive analyses but were not included in the primary complete-case multivariable analysis (n = 238).

OSA severity was classified directly from recorded AHI values as no OSA (<5.0 events/hour), mild OSA (5.0-14.9 events/hour), moderate OSA (15.0-29.9 events/hour), and severe OSA (≥30 events/hour). For the primary binary prediction analysis, participants were grouped as severe OSA (n = 84) versus non-severe (no, mild, or moderate) OSA (n = 191).

Clinical exclusion criteria were age <18 years, incomplete PSG data preventing AHI classification, active infection or an acute inflammatory condition at blood sampling, hematologic disorders, active malignancy, advanced chronic kidney disease (stage 4-5) or dialysis, chronic liver failure, chronic hypoxemic lung disease requiring long-term oxygen therapy, pregnancy, documented exogenous testosterone or erythropoiesis-stimulating agent use, or predominant central sleep apnea. Missing HCT, IG%, age, BMI, or neck circumference was treated as predictor-level missingness rather than as a clinical exclusion from the descriptive cohort.

Polysomnography and Clinical Definitions

Overnight attended PSG was performed under baseline conditions. Recorded signals included electroencephalography, electro-oculography, electromyography, thoracoabdominal respiratory effort, body position, snoring, nasal airflow, pulse oximetry, and electrocardiography. Sleep stages and respiratory events were scored by an experienced physician according to the American Academy of Sleep Medicine criteria applicable at the time of each examination (8).

Laboratory Measurements

CBC parameters were measured using a Sysmex XN-9000 automated hematology analyzer (Sysmex, Japan). Variables of interest included HCT, IG% (Sysmex), platelet distribution width, platelet-large cell ratio (P-LCR), and other routine hematologic indices.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 31.0.1.0, R software through RStudio, and Python 3.13.5. Continuous variables were summarized as mean ± SD or median and interquartile range according to distribution, and categorical variables as frequency and percentage. Normality was assessed with histograms, Q-Q plots, and the Shapiro-Wilk test; homogeneity of variance was evaluated with Levene's test. All tests were two-sided and $p<0.05$ was considered statistically significant.

For the primary comparison of severe versus non-severe OSA, continuous variables were compared using the Mann-Whitney U test when non-normally distributed. To evaluate comorbidity-related differences while controlling for confounding, univariate analysis of covariance (ANCOVA) models (Type III sums of squares) was fitted for HCT, IG%, red cell distribution width (RDW), and P-LCR, with comorbidity group as the fixed factor and age, BMI, and neck circumference as prespecified covariates. AHI (continuous) was additionally included where appropriate. Adjusted pairwise comparisons used Bonferroni correction, and effect size was reported as partial eta (2).

Receiver operating characteristic (ROC) analyses were used to assess the discriminative performance of HCT alone, IG% alone, a reduced model containing age, BMI, neck circumference, and HCT, and the full model additionally containing IG%. Area under the ROC curve (AUC) values with 95% confidence intervals were calculated using non-parametric estimates. The paired AUC difference between the reduced and full models was formally tested using DeLong's method. Precision-recall AUC and Brier score changes were reported descriptively to complement the AUC comparison. Optimal thresholds for the full model were identified using Youden's index.

A multivariable binary logistic regression model was fitted with severe OSA (AHI ≥30 events/hour) as the dependent variable. The five candidate predictors were prespecified before model fitting: HCT and IG% were the biomarkers of primary interest, while BMI, age, and neck circumference were selected as established clinical correlates of OSA. All predictors were entered simultaneously. No stepwise procedures or selection based on univariable p values were used. The predictor set was intentionally limited to five variables to reduce overfitting relative to the number of severe-OSA events. Predicted probabilities were used for ROC and precision-recall analyses, calibration, and threshold-based performance metrics.

Predictor-level missingness was summarized for each of the five prespecified variables. Participants included in the complete-case analysis were compared with those excluded because of missing predictor data using the Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables. Differential missingness by severe-OSA status was also examined. Multiple imputation by chained equations was implemented with scikit-learn's IterativeImputer using BayesianRidge, posterior sampling, 20 iterations, and 50 datasets generated with random seeds 1-50. Severe-OSA status and all model predictors were included in the imputation procedure. IG% was transformed as ln(IG%+1) before imputation and back-transformed before model fitting. Logistic-regression estimates were combined using Rubin's rules. The missing-data, DeLong, decision curve analysis (DCA), and clinical-impact analyses were performed in Python 3.13.5 using scikit-learn 1.8.0 and statsmodels 0.14.6; calibration and bootstrap internal validation were performed using R software.

Model calibration was assessed using calibration-in-the-large (intercept), calibration slope, and the Brier score. A calibration plot was generated using deciles of predicted risk. Internal validation was performed with 1,000 bootstrap resamples to estimate optimism and obtain optimism-corrected performance. Multicollinearity was assessed with variance inflation factors (VIFs).

Exploratory potential clinical utility was evaluated using DCA over threshold probabilities from 0.05 to 0.80. Net benefit was compared with the default strategies of treating all and treating none, and nested models containing clinical variables only (age, BMI, and neck circumference), clinical variables plus HCT, and clinical variables plus HCT and IG% were compared. DCA and the clinical impact curve were interpreted as model-based indications of potential utility rather than evidence of actual clinical benefit.

To address information loss from dichotomizing AHI, two secondary analyses were performed in the same complete-case sample. First, ln(AHI+1) was modeled as a continuous outcome using multivariable linear regression with HC3 robust standard errors. Second, OSA severity was modeled ordinally (no, mild, moderate, severe OSA) using a proportional-odds logistic regression model. The same five prespecified predictors were entered simultaneously in both analyses. These analyses were considered supportive and did not replace the primary binary endpoint of severe versus non-severe OSA.

Results

Participant Characteristics and Group Comparisons

A total of 275 PSG-referred individuals were analyzed, including 84 with severe OSA and 191 without severe OSA. All participants had completed PSG before retrospective data extraction.

Compared with the non-severe group, the severe OSA group had higher BMI [34.5 (30.4-38.8) vs. 31.2 (28.1-35.8) kg/m^2; p<0.001], neck circumference [40.0 (38.0-42.6) vs. 37.5 (36.0-40.0) cm; p<0.001], HCT [47.0 (42.6-50.2)% vs. 44.6 (41.0-47.8)%; p<0.001], and IG% [0.4 (0.3-0.5)% vs. 0.3 (0.2-0.4)%; p = 0.045]. Results for the remaining variables are summarized in Table 1. Variable-specific sample sizes differed because descriptive analyses used available observations.

Within the OSA cohort, comorbidity-group differences (Group 0, no comorbidity; Group 1, cardiac disease; Group 2, diabetes mellitus; Group 3, cardiac disease + diabetes mellitus) were evaluated using ANCOVA with age, BMI, neck circumference, and AHI as covariates. After adjustment, comorbidity status was not associated with HCT (F(3,177) = 0.782, p = 0.506, partial eta^2 = 0.013), IG% (F(3,162) = 0.612, p = 0.608, partial eta^2 = 0.011), or RDW (F(3,177) = 2.124, p = 0.099, partial eta^2 = 0.035). In contrast, comorbidity group remained significantly associated with P-LCR (F(3,177) = 3.601, p = 0.015, partial eta^2 = 0.058).

Bonferroni-adjusted pairwise comparisons showed higher P-LCR values in Group 2 (diabetes mellitus) than in Group 0 (p = 0.013), Group 1 (p = 0.026), and Group 3 (p = 0.038), while other pairwise comparisons were not significant. No significant pairwise differences were observed for HCT, IG%, or RDW after adjustment.

Neck circumference and AHI were independently associated with HCT (neck circumference: F(1,177) = 13.180, p<0.001, partial eta^2 = 0.069; AHI: F(1,177) = 6.608, p = 0.011, partial eta^2 = 0.036). For IG%, AHI remained an independent predictor (F(1,162) = 6.599, p = 0.011, partial eta^2 = 0.039), whereas for RDW, BMI was independently associated (F(1,177) = 4.463, p = 0.036, partial eta^2 = 0.025). The selective elevation of P-LCR in the diabetes group may reflect diabetes-related platelet activation/turnover rather than OSA severity itself (Supplementary Table S1).

Missing-Data Analysis

Thirty-seven participants were not included in the complete-case model because of missing IG% (n = 23), neck circumference (n = 13), or BMI (n = 1). No patient had overlapping missingness among these three variables, and no participant was missing HCT or age. The exclusion proportion was 8.3% among participants with severe OSA and 15.7% among those without severe OSA (Fisher's exact p = 0.125). IG% was missing in 3.6% of severe OSA cases and 10.5% of non-severe cases (p = 0.061). Complete-case participants were older, had higher BMI, and more frequently had cardiovascular disease than excluded participants (54.2% vs. 32.4%; Fisher's exact p = 0.021). Diabetes mellitus was numerically more frequent in complete cases (17.6% vs. 5.4%) but the difference was not statistically significant (p = 0.088). There were also no significant differences in sex distribution (male: 61.3% vs. 73.0%; Fisher's exact p = 0.203), HCT, AHI, or severe OSA prevalence between complete and non-complete cases (Table 2).

Table 1. Comparison between participants with and without severe obstructive sleep apnea.

Variable	Severe OSA, available observations from n = 84	Non-severe OSA, available observations from n = 191	p-value
BMI	34.5 (30.4-38.8)	31.2 (28.1-35.8)	<0.001
Neck circumference (cm)	40 (38-42.6)	37.5 (36-40)	<0.001
HCT (%)	47 (42.6-50.2)	44.6 (41-47.8)	<0.001
MCV (fL)	84.9 (80.8-87.7)	85.5 (82.5-88.6)	0.111
MCH (pg)	28.6 (27.2-30.1)	29.1 (27.7-29.9)	0.183
PLT (10^3/uL)	262 (227-310)	259 (214-304)	0.320
MCHC (g/dL)	33.3 (32.1-34.5)	33.4 (32.4-34.7)	0.557
PCT (%)	0.26 (0.22-0.31)	0.27 (0.22-0.3)	0.771
MPV (fL)	9.9 (9.5-10.4)	10.2 (9.6-10.8)	0.048
N/L	1.72 (1.25-2.25)	1.91 (1.41-2.61)	0.099
Eosinophils (%)	0.15 (0.08-0.22)	0.14 (0.09-0.24)	0.855
CRP (mg/L)	5.54 (1.79-11.8)	5 (1.4-8.9)	0.452
ALB (g/L)	43.5 (41-45)	44 (41-46)	0.481
RDW (%)	13.2 (12.8-13.9)	13.2 (12.7-13.8)	0.437
PDW (fL)	11.5 (10.7-12.7)	11.3 (10.4-12.6)	0.448
IG (%)	0.4 (0.3-0.5)	0.3 (0.2-0.4)	0.045
Age (years)	57 (50-64)	54 (46-62)	0.089
AHI (events/h)	53.9 (39-78)	7.4 (2.7-19.4)	<0.001

OSA: Obstructive sleep apnea, BMI: Body mass index, HCT: Hematocrit, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, PLT: Platelet count, MCHC: Mean corpuscular hemoglobin concentration, PCT: Plateletcrit, MPV: Mean platelet volume, N/L: Neutrophil-to-lymphocyte ratio, CRP: C-reactive protein, ALB: Albumin, RDW: Red cell distribution width, PDW: Platelet distribution width, IG%: Immature granulocyte percentage, AHI: Apnea-hypopnea index.

Table 2. Comparison of participants included in and excluded from the complete-case multivariable analysis.

Variable	Complete-case analysis (n = 238)	Excluded because of missing predictor data (n = 37)	p-value
Age, years	56.0 (48.0-64.0)	52.0 (40.0-57.0)	0.032
Male sex, n (%)	146/238 (61.3%)	27/37 (73.0%)	0.203
Cardiovascular disease, n (%)	129/238 (54.2%)	12/37 (32.4%)	0.021
Diabetes mellitus, n (%)	42/238 (17.6%)	2/37 (5.4%)	0.088
BMI, kg/m^2	32.4 (28.7-37.5)	30.5 (27.7-34.2)	0.027
Neck circumference, cm	38.0 (36.0-41.0)	38.8 (36.0-40.6), n = 24	0.861
HCT, %	45.3 (41.4-48.7)	45.9 (41.2-47.7)	0.646
IG%, available observations	0.30 (0.20-0.50)	0.35 (0.30-0.48), n = 14	0.734
AHI, events/h	19.5 (3.9-38.7)	10.7 (4.5-27.0)	0.139
Severe OSA	77/238 (32.4%)	7/37 (18.9%)	0.125

BMI: Body mass index, HCT: Hematocrit, IG%: Immature granulocyte percentage, AHI: Apnea-hypopnea index, OSA: Obstructive sleep apnea. Continuous variables are presented as median (interquartile range, Mann-Whitney U test), and categorical variables were compared using Fisher's exact test. Other excluded-group variables used available observations as indicated. HCT and age were complete, missing predictors were IG% (n = 23), neck circumference (n = 13), and BMI (n = 1).

Multivariable Model for Prediction of Severe OSA

The multivariable model included 238 complete cases (77 with severe OSA and 161 with non-severe OSA). HCT, IG%, and neck circumference were independently associated with severe OSA. Each 1-percentage-point increase in HCT was associated with an [odds ratio (OR) of 1.09 (95% confidence interval (CI): 1.03-1.16; p = 0.003]; each 1-percentage-point increase in IG% was associated with an OR of 2.11 (95% CI: 1.05-4.24; p = 0.035); and each 1-cm increase in neck circumference was associated with an OR of 1.09 (95% CI 1.01-1.18; p = 0.030). BMI and age were not statistically significant (Supplementary Table S2). No relevant multicollinearity was observed (all VIFs <1.3; Supplementary Table S3).

Discrimination and Threshold-Based Clinical Performance

The full prediction model (HCT, IG%, BMI, age, and neck circumference) had an AUC of 0.731 (95% CI: 0.661-0.802), compared with 0.715 (95% CI: 0.644-0.787) for the reduced model containing age, BMI, neck circumference, and HCT. The absolute AUC increase after adding IG% was 0.016 (95% CI: -0.013 to 0.045) and was not statistically significant according to the paired DeLong test (p = 0.282). The precision-recall AUC (PR-AUC) increased numerically from 0.539 to 0.580 and the Brier score decreased from 0.192 to 0.187. HCT alone had an AUC of 0.643 (95% CI: 0.567-0.719), and IG% alone had an AUC of 0.586 (95% CI: 0.508-0.664) (Figure 1 and Table 3).

At the Youden-optimal probability threshold (0.267), the model achieved 79.2% sensitivity and 59.0% specificity [positive predictive value (PPV) 48.0%; negative predictive value (NPV) 85.6%; positive likelihood ratio (LR+) 1.93; negative likelihood ratio (LR-) 0.35; accuracy 65.5%). At a higher rule-in threshold (0.479), specificity was 90.1% and sensitivity was 40.3% (PPV 66.0%, NPV 75.9%, LR+ 4.05, LR- 0.66; accuracy 73.9%). These threshold profiles describe possible operating points within a PSG-referred population and should not be treated as validated clinical decision rules (Table 4).

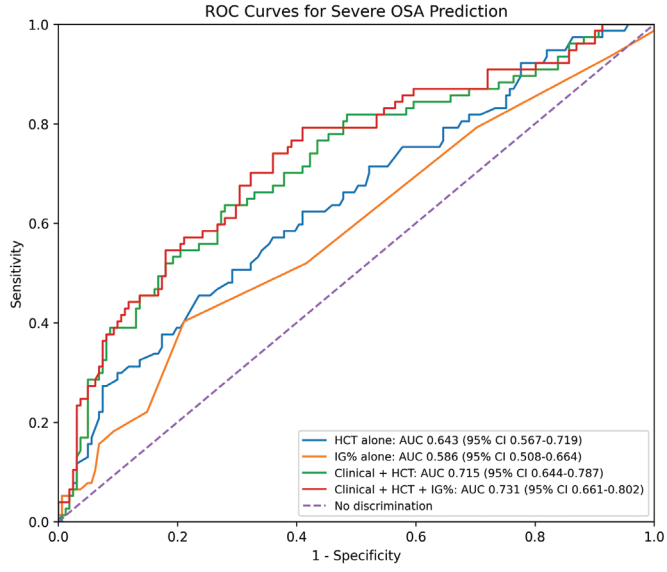

Figure 1. ROC curves for HCT alone, IG% alone, the reduced model (age, body mass index, neck circumference, and HCT), and the full model additionally containing IG% for prediction of severe OSA. The AUC difference between the reduced and full models was 0.016 (95% CI -0.013 to 0.045; paired DeLong p = 0.282). The diagonal line represents no discrimination.
ROC: Receiver operating characteristic, HCT: Hematocrit, IG%: Immature granulocyte percentage, OSA: Obstructive sleep apnea, AUC: Area under the curve.

Precision-recall analysis yielded a PR-AUC of 0.580 against an event-prevalence baseline of 0.324 (Figure 2A). The apparent Brier score was 0.187, and the decile-based calibration plot is shown in Figure 2B.

DCA suggested threshold-dependent potential net benefit, but differences between the clinical-only, clinical+HCT, and clinical+HCT+IG% models were modest and not uniform.

At thresholds of 0.10 and 0.20, the full model had the highest estimated net benefit (0.254 and 0.173), compared with 0.252 and 0.163 for the clinical+HCT model. At 0.30, the clinical-only and full models had similar net benefit (both 0.124), while at 0.40 the clinical+HCT model was marginally highest (0.087 vs. 0.085 for the full model). At 0.50, the full model was highest (0.067 vs. 0.050 for clinical+HCT). These findings are exploratory and demonstrate only potential utility under the modeled threshold assumptions; they do not establish clinical benefit in the absence of external validation and prospective impact assessment (Figure 3A). The clinical impact curve (Figure 3B) displays, per 1,000 referred individuals, the number classified as high risk and the number with severe OSA among those classified as high risk.

Multiple-Imputation Sensitivity Analysis

Across 50 multiply imputed datasets, HCT remained associated with severe OSA (pooled OR: 1.09, 95% CI: 1.03-1.15; p = 0.004), as did neck circumference (pooled OR: 1.10, 95% CI: 1.01-1.19; p = 0.023). The pooled IG% estimate was attenuated and did not meet the conventional significance threshold (OR: 1.87, 95% CI: 0.98-3.54; p = 0.056). Mean AUC across imputed datasets was 0.720 (SD 0.004; range 0.714-0.731), with a mean PR-AUC of 0.549 and mean Brier score of 0.184 (Table 3).

Calibration and Internal Validation

In 1,000 bootstrap resamples, the optimism-corrected AUC was 0.711. The optimism-corrected calibration intercept was -0.103 and the optimism-corrected calibration slope was 0.846, indicating modest overfitting and supporting the need for external validation and recalibration.

Secondary Analyses Using Continuous and Ordinal AHI

In the complete-case sample (n = 238), HCT and IG% remained associated with AHI when information across the full outcome distribution was retained. In the ln(AHI+1) linear model, HCT (beta = 0.040, 95% CI: 0.013-0.067; p = 0.003) and IG% (beta = 0.411, 95% CI: 0.017-0.805; p = 0.041) were positively associated with AHI. In the ordinal model, HCT (common OR: 1.06, 95% CI: 1.01-1.11; p = 0.010) and IG% (common OR: 2.30, 95% CI: 1.18-4.49; p = 0.014) were associated with higher OSA severity categories. Age and neck circumference were also associated with higher ordinal severity, whereas BMI was not (Table 5).

Table 3. Incremental discrimination of IG% and multiple-imputation sensitivity analysis.

Analysis	Model/Predictor	Estimate	95% CI	p-value	Additional performance
AUC comparison	Reduced model: age + BMI + neck circumference + HCT	AUC 0.715	0.644-0.787	-	PR-AUC 0.539; Brier 0.192
AUC comparison	Full model: reduced model + IG%	AUC 0.731	0.661-0.802	-	PR-AUC 0.580; Brier 0.187
AUC comparison	Full minus reduced model	Delta AUC 0.016	-0.013 to 0.045	0.282	Paired DeLong test
Multiple imputation (50 datasets)	HCT, per 1%	OR 1.09	1.03-1.15	0.004	
Multiple imputation (50 datasets)	IG%, per 1%	OR 1.87	0.98-3.54	0.056	
Multiple imputation (50 datasets)	BMI, per kg/m^2	OR 1.03	0.99-1.07	0.176	
Multiple imputation (50 datasets)	Age, per year	OR 1.02	1.00-1.05	0.073	
Multiple imputation (50 datasets)	Neck circumference, per cm	OR 1.10	1.01-1.19	0.023	
Multiple imputation (50 datasets)	Model performance	Mean AUC 0.720	SD 0.004; range 0.714-0.731	-	Mean PR-AUC 0.549; mean Brier 0.184

AUC: Area under the curve, BMI: Body mass index, HCT: Hematocrit, PR-AUC: Precision-recall area under the curve, IG%: Immature granulocyte percentage, OR: Odds ratio. The reduced and full models were based on the same 238 complete cases. Multiple-imputation estimates were pooled across 50 imputed datasets using Rubin's rules, and IG% was imputed on the ln(IG% + 1) scale.

Table 4. Threshold-based performance of the multivariable prediction model.

Strategy	Cut-off	Se (%)	Sp (%)	PPV (%)	NPV (%)	LR+	LR-	Acc. (%)	Bal. acc. (%)	F1 score	Youden J
Youden-optimal	0.267	79.2	59.0	48.0	85.6	1.93	0.35	65.5	69.1	0.598	0.382
Rule-in (Sp ≥90%)	0.479	40.3	90.1	66.0	75.9	4.05	0.66	73.9	65.2	0.500	0.303
Rule-out (Se ≥95%)	0.123	96.1	13.0	34.6	87.5	1.11	0.30	39.9	54.6	0.509	0.091

PPV: Positive predictive value, NPV: Negative predictive value, LR+: Positive likelihood ratio, LR-: Negative likelihood ratio. Thresholds were defined as follows: Youden-optimal threshold (maximum Youden J), rule-in threshold (specificity ≥90%), and rule-out threshold (sensitivity ≥95%). These operating points are descriptive and require external validation before clinical use.

Table 5. Secondary analyses treating AHI as a continuous and ordinal outcome.

Predictor	Continuous model beta	95% CI	p value	Ordinal common OR	95% CI	p-value
HCT	0.040	0.013 to 0.067	0.003	1.06	1.01 to 1.11	0.010
IG%	0.411	0.017 to 0.805	0.041	2.30	1.18 to 4.49	0.014
BMI	0.005	-0.055 to 0.066	0.862	1.01	0.98 to 1.05	0.449
Age	0.017	0.002 to 0.032	0.022	1.03	1.01 to 1.05	0.004
Neck circumference	0.043	-0.007 to 0.094	0.093	1.08	1.01 to 1.15	0.026

AHI: Apnea-hypopnea index, HCT: Hematocrit, IG%: Immature granulocyte percentage, BMI: Body mass index, OR: Odds ratio. The continuous model used ln(AHI + 1) as the dependent variable with HC3 robust standard errors. The ordinal proportional-odds model used four ordered categories: no OSA (<5), mild OSA (5.0–14.9), moderate OSA (15.0–29.9), and severe OSA (≥30 events/hour). Both models included HCT, IG%, BMI, age, and neck circumference simultaneously and used the same complete-case sample (n = 238).

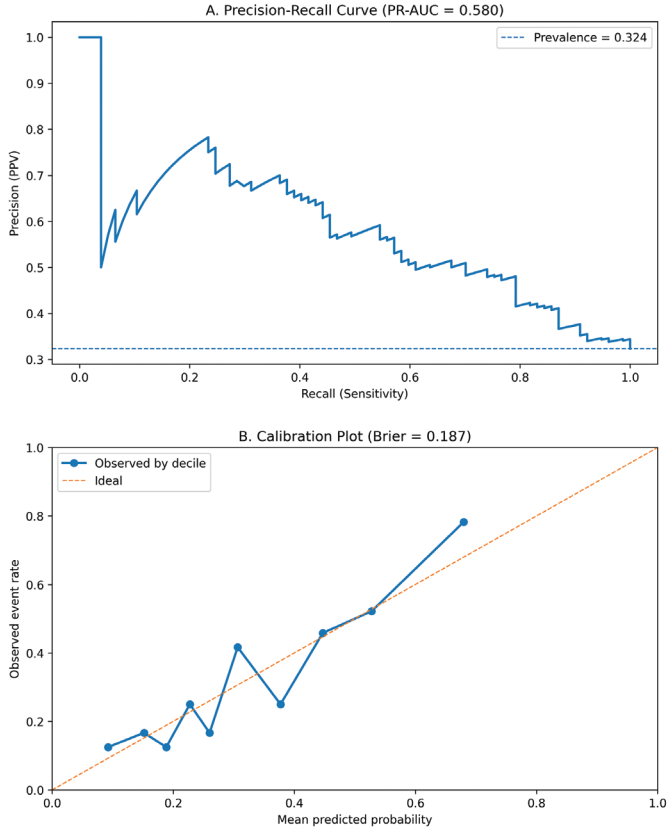

Figure 2. Performance of the full prediction model. (A) Precision-recall curve with the event-prevalence reference line. (B) Decile-based calibration plot comparing mean predicted probabilities with observed severe OSA frequencies. The diagonal line represents perfect calibration.

PR-AUC: Precision-recall area under the curve, PPV: Positive predictive value, OSA: Obstructive sleep apnea.

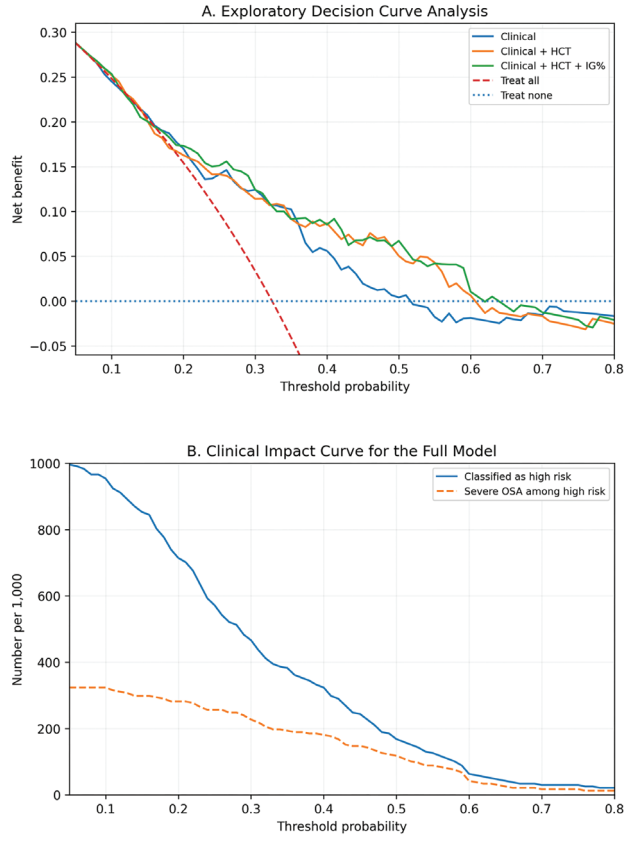

Figure 3. Exploratory assessment of potential clinical utility. (A) Decision curve analysis comparing the clinical-only model (age, body mass index, and neck circumference), the clinical+HCT model, and the clinical+HCT+IG% model with treat-all and treat-none strategies. (B) Clinical impact curve for the full model showing the number classified as high risk and the number with severe OSA among those classified as high risk per 1,000 referred individuals. These plots indicate potential utility under modeled assumptions and do not establish clinical benefit.

HCT: Hematocrit, IG%: Immature granulocyte percentage, OSA: Obstructive sleep apnea.

Discussion

In this single-center retrospective study of symptomatic adults referred for PSG, HCT showed the most robust hematologic association with severe OSA. IG% was independently associated with severe OSA in the complete-case model, but adding IG% to age, BMI, neck circumference, and HCT produced only a small, statistically non-significant increase in the AUC. The IG% estimate was also attenuated after multiple imputation. IG% should therefore be interpreted as an exploratory biomarker signal rather than an established incremental predictor.

The DCA findings should be interpreted cautiously. Although the full model showed the highest estimated net benefit at several threshold probabilities, DCA quantifies potential benefit under specified assumptions and does not demonstrate that use of the model improves waiting-list management, treatment timing, or patient outcomes. The optimism-corrected calibration slope of 0.846 further indicates modest overfitting. Accordingly, the DCA and clinical impact curve are hypothesis-generating and should not be used to justify implementation before independent validation, recalibration, and prospective impact evaluation.

A biological link between intermittent hypoxia and hematopoietic activation is plausible but remains incompletely established in humans. Repetitive hypoxia, sympathetic activation, oxidative stress, and inflammatory cytokine signaling may alter the bone marrow microenvironment and promote stress-related or emergency granulopoiesis (9-11). However, these mechanisms do not prove that OSA itself increases the peripheral blood IG%. Although OSA-specific evidence remains limited, a recent Turkish single-center study also reported higher IG count and IG% in patients with OSA (7). The present findings extend that observation to severity modeling, but causal interpretation is not warranted.

Our comorbidity-stratified analyses indicate that not all hematologic signals are OSA-specific. P-LCR was selectively elevated in the diabetes group after adjustment. Studies in type 2 diabetes have reported higher platelet volume indices, including P-LCR, and have related these changes to enhanced platelet reactivity, altered platelet turnover, and vascular risk (12). In contrast, IG% did not differ significantly across the recorded comorbidity groups. This asymmetry should not be interpreted as evidence that IG% is unaffected by comorbid conditions or is specific to OSA. IG% reflects accelerated granulopoiesis in response to a broad range of infectious, inflammatory, and physiologic stressors rather than a diabetes-specific pathway (5,10). Moreover, the comorbidity subgroups were relatively small, and unrecorded inflammatory conditions, medication use, glycemic control, or other residual confounders may have reduced our ability to detect comorbidity-related differences in IG%. Analyzer-related measurement variability is also relevant, because Sysmex XN IG% values can show systematic differences from manual microscopy, including at low concentrations (13). The observed P-LCR-IG% asymmetry should therefore be regarded as hypothesis-generating rather than evidence of biomarker specificity.

HCT has a well-established mechanistic relationship with chronic hypoxemia, but it is also influenced by smoking, hydration status, ambient altitude, and unrecognized secondary erythrocytosis. Smoking and hydration data were not systematically available in the retrospective records and could not be incorporated into the model. Ambient altitude may influence absolute HCT values; however, individual residential-altitude data and duration of residence were not available.

The secondary analyses addressed the information loss inherent in a binary AHI threshold. HCT and IG% remained associated with higher AHI when AHI was modeled continuously and when OSA severity was modeled ordinally. These results support the direction of the primary findings across the AHI distribution, although they do not remove the clinical heterogeneity within the non-severe group or establish causality.

Compared with questionnaire-based screening tools such as STOP-Bang (14), the present study evaluated an AHI-based prediction framework within a PSG-referred population. The model integrates BMI, age, neck circumference, HCT, and IG% and was evaluated using complementary metrics (ROC, precision-recall, calibration, DCA, and the clinical impact curve). HCT provided a consistent signal, whereas the incremental value of IG% was modest and uncertain. Direct comparisons with established questionnaires and external validation are required before any clinical role can be defined.

The model uses routinely available objective markers alongside simple clinical variables. At a probability threshold of approximately 0.48, it showed a high-specificity profile (specificity 90.1%; LR+ 4.05). This operating point may be of interest for future validation studies focused on prioritization within PSG pathways, but it should not be considered a validated rule-in threshold or used for clinical decisions in its current form.

Study Limitations

This study has several limitations. First, it was conducted in a single-center, clinically referred PSG cohort, so its estimates are not directly generalizable to community or primary-care populations. Second, 37 of 275 participants were not included in the primary complete-case model. Included participants were older, had higher BMI, and more frequently had cardiovascular disease than excluded participants, and the IG% association was attenuated after multiple imputation, indicating that the IG% result is sensitive to the missing-data approach. Third, smoking status, hydration status, individual residential-altitude data, duration of residence, and occult causes of secondary erythrocytosis were not systematically available. Therefore, residual confounding of HCT and IG% cannot be excluded. Fourth, IG% values may vary by analyzer platform and reporting conventions, requiring cross-platform standardization. Fifth, the primary binary endpoint combines no, mild, and moderate OSA into a heterogeneous non-severe group. Continuous and ordinal secondary analyses reduced but did not eliminate this limitation. Finally, DCA and the clinical impact curve estimate potential net benefit only and do not demonstrate actual clinical benefit.

Another limitation of this study is the absence of additional polysomnographic hypoxemia-related parameters e.g., oxygen desaturation index, minimum oxygen saturation, and time spent below 90% saturationin the analysis. Therefore, the present model should be interpreted as an AHI-based clinical prediction model rather than a comprehensive physiological model of OSA severity. Future studies should incorporate hypoxemia burden metrics and arousal-related indices to improve model calibration and clinical applicability.

Conclusion

Future work should include (i) external validation and recalibration in independent PSG-referred cohorts, (ii) prospective comparison with established screening tools such as STOP-Bang, (iii) incorporation of hypoxemia-burden and arousal-related PSG metrics, and (iv) formal impact studies assessing whether model-guided prioritization improves waiting times, time to treatment, or patient outcomes.

Ethics

Ethics Committee Approval: The Scientific Research Ethics Committee of Erzurum Faculty of Medicine, University of Health Sciences Türkiye approved this retrospective study (decision no: 2024/03-46; approval date: March 13, 2024).
Informed Consent: The requirement for informed consent was waived because de-identified retrospective data were used.

Footnotes

Authorship Contributions

Concept: O.Ç., Design: O.Ç., Data Collection or Processing: O.Ç., A.F.K., Analysis or Interpretation: A.F.K., Literature Search: O.Ç.,Writing: O.Ç.
Conflict of Interest: No conflict of interest was declared by the authors.
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Supplementary Tables Link: https://d2v96fxpocvxx.cloudfront.net/f6118de3-f656-440d-95f2-50c620149951/content-images/3a037bba-0b0d-431e-8912-e434c1788bc6.pdf

References

1. Qi Y, Li T, Zhao Y, et al. Correlation between peripheral blood inflammatory markers and obstructive sleep apnea severity. J Otolaryngol Head Neck Surg. 2026;55:19160216251407939.
2. Gabryelska A, Łukasik ZM, Makowska JS, Białasiewicz P. Obstructive sleep apnea: from intermittent hypoxia to cardiovascular complications via blood platelets. Front Neurol. 2018;9:635.
3. Lundetræ RS, Lehmann S, Saxvig IW, et al. Severity of obstructive sleep apnea is related to C-reactive protein levels: the influence of comorbidities and self-reported sleep duration. Sleep Med. 2025;131:106529.
4. Ucar Y, Yonar A. Evaluation of inflammatory markers in obstructive sleep apnea syndrome. Sci Prog. 2025;108(3):368504251365874.
5. Senthilnayagam B, Kumar T, Sukumaran J, M J, Rao K R. Automated measurement of immature granulocytes: performance characteristics and utility in routine clinical practice. Patholog Res Int. 2012;2012:483670.
6. Bhansaly P, Mehta S, Sharma N, Gupta E, Mehta S, Gupta S. Evaluation of immature granulocyte count as the earliest biomarker for sepsis. Indian J Crit Care Med. 2022;26(2):216-223.
7. Gencdal IY, Kabeloglu V, Koseoglu M, Sahin B, Baydili KN. Can immature granulocyte count be a new biomarker for the evaluation of inflammation in patients with obstructive sleep apnea syndrome? A single-centre study. Neurology Asia. 2025;30(3):861-869.
8. American Academy of Sleep Medicine. The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications. Versions 2.5 and 2.6. Darien, IL: American Academy of Sleep Medicine; 2018-2020.
9. Kohutek ZA, Caslin HL, Fehrenbach DJ, et al. Bone marrow niche in cardiometabolic disease: mechanisms and therapeutic potential. Circ Res. 2025;136(3):325-353.
10. Manz MG, Boettcher S. Emergency granulopoiesis. Nat Rev Immunol. 2014;14(5):302-314.
11. Alvarez-Martins I, Remedio L, Matias I, Diogo LN, Monteiro EC, Dias S. The impact of chronic intermittent hypoxia on hematopoiesis and the bone marrow microenvironment. Pflugers Arch. 2016;468(5):919-932.
12. Shilpi K, Potekar RM. A study of platelet indices in type 2 diabetes mellitus patients. Indian J Hematol Blood Transfus. 2018;34(1):115-120.
13. Linko-Parvinen AM, Kurvinen K, Tienhaara A. Accuracy of sysmex XN immature granulocyte percentage compared to manual microscopy. J Lab Precis Med. 2021;6:27.
14. Pivetta B, Chen L, Nagappa M, et al. Use and performance of the STOP-bang questionnaire for obstructive sleep apnea screening across geographic regions: a systematic review and meta-analysis. JAMA Netw Open. 2021;4(3):e211009.