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Research Article

Systemic inflammatory and immunonutritional profile in women with low anti-Müllerian hormone levels

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Abstract

Objectives: Anti-Müllerian hormone (AMH) is widely used as a biomarker of ovarian reserve. Although systemic inflammation and nutritional status may be associated with ovarian function, the relationships of composite inflammatory and nutrition-related indices with low AMH remain incompletely characterized. This study aimed to evaluate systemic inflammatory and nutrition-related indices in women with low AMH levels.

Methods: A total of 150 women were included, comprising 75 women with low AMH and 75 with high AMH. The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), aggregate index of systemic inflammation (AISI), prognostic nutritional index (PNI), and hemoglobin–albumin–lymphocyte–platelet (HALP) index were evaluated. Associations between continuous AMH concentrations and these indices were assessed using Spearman correlation analysis. Age- and body mass index (BMI)-adjusted logistic regression models were used to evaluate associations with low AMH.

Results: Women with low AMH were older than those with high AMH (33.0 [29.5–36.5] vs. 27.0 [24.0–31.0] years; $q<0.001$), whereas BMI did not differ significantly between the groups. AISI, SIRI, PLR, NLR, and SII were significantly higher, whereas PNI and HALP were significantly lower, in the low AMH group, with all differences remaining significant after multiple-comparison correction. AMH was inversely correlated with AISI ($\rho=-0.282$), SIRI ($\rho=-0.266$), PLR ($\rho=-0.257$), NLR ($\rho=-0.314$), and SII ($\rho=-0.324$), and positively correlated with PNI ($\rho=0.466$) and HALP ($\rho=0.366$) (all $p\leq0.001$). After adjustment for age and BMI, higher NLR was associated with greater odds of low AMH (adjusted OR=2.03, 95% CI: 1.34–3.06; $p<0.001$), whereas higher PNI was associated with lower odds (adjusted OR=0.31, 95% CI: 0.19–0.51; $p<0.001$).

Conclusion: Low AMH was associated with a profile of higher systemic inflammatory indices and lower nutrition-related indices. These associations remained significant after adjustment for age and BMI, supporting an association between low AMH and a distinct systemic inflammatory and immunonutritional profile. Further prospective, multicenter studies are needed to confirm these associations and clarify their biological and potential clinical significance.

Keywords: Anti-Müllerian hormone, HALP, neutrophil-to-lymphocyte ratio, ovarian reserve, prognostic nutritional index, systemic inflammation

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Ovarian reserve represents the quantity of the remaining follicular pool and is a major determinant of female reproductive potential. Anti-Müllerian hormone (AMH), a glycoprotein produced predominantly by granulosa cells of preantral and small antral follicles, is widely used as a biomarker of functional ovarian reserve because circulating AMH concentrations are closely related to the number of growing follicles [1, 2]. In contrast to several other reproductive hormones, AMH shows relatively limited intra-cycle variation and is clinically useful for assessing ovarian response, particularly in

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women undergoing assisted reproductive treatment [1]. Nevertheless, AMH primarily reflects follicle quantity rather than oocyte quality or the probability of spontaneous conception, and its concentration is strongly influenced by age and may also vary according to biological and clinical factors [1, 2].

Ovarian aging is a complex biological process characterized not only by progressive follicular depletion but also by alterations in the ovarian microenvironment. Accumulating evidence suggests that chronic low-grade inflammation, oxidative stress, mitochondrial dysfunction, cellular senescence, and immune dysregulation may contribute to age-related deterioration of ovarian function [3, 4]. Chronic inflammation may adversely affect folliculogenesis through changes in cytokine signaling, immune-cell activity, stromal fibrosis, oxidative stress, and follicular-cell survival, potentially linking systemic inflammatory status with ovarian reserve [3]. However, whether systemic inflammation is a cause, consequence, or merely a correlate of declining ovarian function remains unresolved, particularly in women without a defined inflammatory or reproductive disorder.

Several readily available hematological indices have therefore been investigated as surrogate markers of systemic inflammatory activity in reproductive medicine. The neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII) integrate different components of innate and adaptive immune responses and may provide broader information than individual blood-cell counts. Previous findings, however, have not been entirely consistent. Ilhan et al. [5] reported higher NLR values in women with premature ovarian insufficiency and demonstrated an inverse relationship between NLR and AMH. In contrast, a more recent study of women with diminished ovarian reserve found no significant association between NLR, PLR, or the red cell distribution width-to-platelet ratio and diminished ovarian reserve after considering other clinical factors [6]. More recently, a large retrospective cohort of 19,282 women undergoing assisted reproductive treatment showed that higher SII, PLR, and NLR were associated with lower AMH concentrations, lower antral follicle counts, and reduced ovarian response [7]. Collectively, these findings suggest a possible relationship between systemic inflammatory status and ovarian reserve while also highlighting the need for studies evaluating multiple inflammatory indices within the same population.

Beyond inflammation alone, nutritional and immunological status may also be relevant to reproductive physiology. The prognostic nutritional index (PNI), calculated from serum albumin concentration and lymphocyte count, is a simple composite measure integrating nutritional and immune-related information [8]. Similarly, the hemoglobin–albumin–lymphocyte–platelet (HALP) score incorporates hematological, nutritional, and inflammatory components and can be calculated from routinely available laboratory parameters [9]. Although PNI and HALP have been increasingly evaluated as immunonutritional markers in various clinical settings, their relationship with ovarian reserve has received substantially less attention than conventional inflammatory indices. Moreover, the combined assessment of nutrition-related indices together with broader systemic inflammatory markers such as the systemic inflammation response index (SIRI) and aggregate index of systemic inflammation (AISI) in women with low AMH remains limited.

The present study was not designed to identify alternatives to established ovarian reserve markers such as AMH or AFC or to predict reproductive outcomes. Rather, we hypothesized that women with low AMH may exhibit a distinct systemic inflammatory and immunonutritional phenotype. Accordingly, we investigated whether routinely derived inflammatory and immunonutritional indices differed according to AMH status, correlated with continuous AMH concentrations, and remained associated with low AMH after adjustment for age and BMI.

Therefore, the present study aimed to evaluate systemic inflammatory and nutrition-related indices in women with low AMH levels compared with women with higher AMH levels. Specifically, we investigated NLR, PLR, SII, SIRI, AISI, PNI, and HALP; examined their correlations with continuous serum AMH concentrations; and assessed their associations with low AMH after adjustment for age and BMI.

Materials and Methods

Ethical considerations

The requirement for written informed consent was waived by the Ethics Committee because of the retrospective study design and use of previously collected clinical and laboratory data. All data were analyzed in anonymized form." Please give the complete ethics approval number as E-22686390-200-102527 (29 June 2026).

Study design and participants

This retrospective cross-sectional study included 150 women of reproductive age who were evaluated at the Department of Obstetrics and Gynecology of Istanbul Atlas University Hospital between 15 June 2025 and 15 June 2026. Clinical, anthropometric, hormonal, biochemical, and hematological data were obtained from the participants' medical records and laboratory results.

The study population was divided into two groups according to serum AMH concentrations: the low AMH group (n=75) and the high AMH group (n=75). The AMH threshold used for group allocation was defined before the statistical analyses in accordance with the study protocol. Age, body mass index (BMI), reproductive history, menstrual characteristics, antral follicle count (AFC), hormonal measurements, metabolic parameters, serum proteins, and complete blood count variables were evaluated.

Women of reproductive age who underwent serum AMH assessment and had complete clinical and laboratory data required for the study were considered eligible. Women with conditions or treatments potentially affecting serum AMH

concentrations or systemic inflammatory, metabolic, hematological, or immunonutritional parameters were excluded. Specifically, women with polycystic ovary syndrome (PCOS), endometriosis or endometrioma, previous ovarian surgery, premature ovarian insufficiency, autoimmune disease, acute or chronic infection, obesity, smoking, metabolic disease, systemic inflammatory disease, or current use of hormonal contraceptives were excluded. These eligibility criteria were applied before group allocation.

Eligible women were evaluated consecutively during the study period. After application of the predefined inclusion and exclusion criteria, the first 75 eligible women with complete clinical and laboratory data in the low AMH group and the first 75 eligible women with complete clinical and laboratory data in the high AMH group were included in the final analysis. The same selection procedure was applied to both groups.

Participants were classified into low AMH and high AMH groups using a prespecified serum AMH threshold of 1.1 ng/mL. This threshold was selected based on previously published criteria in which AMH values within approximately 0.5–1.1 ng/mL have been considered indicative of an abnormal ovarian reserve test [10]. In the present study, however, the threshold was used solely to define AMH-based study groups and was not intended to establish a clinical diagnosis of diminished ovarian reserve.

Clinical and ultrasonographic assessment

Age, BMI, gravida, parity, age at menarche, and menstrual cycle length were recorded for each participant. BMI was calculated by dividing body weight in kilograms by the square of height in meters.

AFC was assessed using transvaginal ultrasonography during the early follicular phase of the menstrual cycle. AFC was defined as the total number of follicles measuring 2–10 mm in diameter in both ovaries. To reduce interobserver variability, ultrasonographic examinations were performed by an experienced gynecologist using a standardized assessment protocol.

Blood sampling and laboratory measurements

Venous blood samples were collected in the morning after an overnight fast. Serum samples were separated by centrifugation and analyzed according to the routine procedures of the clinical biochemistry laboratory.

Complete blood count (CBC) results were generated using an automated hematology analyzer (Sysmex XN-1000; Sysmex, Norderstedt, Germany).

Routine biochemical measurements were performed in the hospital's central laboratory using enzymatic assay techniques on an automated COBAS 8000 clinical chemistry system (Roche Diagnostics, Tokyo, Japan).

Routine hormonal parameters, including AMH, FSH, LH, estradiol (E2), prolactin, and insulin levels, were measured using a Cobas e601 immunoassay analyzer (Roche Diagnostics, Basel, Switzerland).

Insulin resistance was estimated using the homeostasis model assessment of insulin resistance:

HOMA-IR = [fasting insulin (μIU/mL) × fasting glucose (mg/dL)]/405

All measurements were performed in accordance with the manufacturers' instructions and the laboratory's internal quality-control procedures.

Calculation of inflammatory and nutritional indices

Inflammatory and nutritional indices were derived from complete blood count and serum albumin measurements using the following equations:

NLR=neutrophil count / lymphocyte count

PLR=platelet count / lymphocyte count

SII=(platelet count × neutrophil count) / lymphocyte count

SIRI=(neutrophil count×monocyte count) / lymphocyte count

AISI=(platelet count × neutrophil count × monocyte count) / lymphocyte count

PNI=[10 × serum albumin (g/dL)] + [0.005 × total lymphocyte count (/mm^3)]

HALP=(hemoglobin × albumin × lymphocyte count) / platelet count

Unit conversion was applied where necessary to ensure consistency between absolute blood cell counts and the calculated index values. All derived indices were independently recalculated and compared with the values recorded in the dataset. No discrepancy exceeding an absolute tolerance of 1×10^{-6} was detected.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 27.0 (IBM Corp., Armonk, NY, USA). Continuous variables were examined separately in each AMH group using the Shapiro-Wilk test. Variables satisfying the normality assumption were summarized as mean±standard deviation, whereas non-normally distributed variables were expressed as median and interquartile range.

Normally distributed variables were compared between the low AMH and high AMH groups using Welch's independent-samples t-test, which does not require equality of variances. Variables with non-normal distributions were evaluated using the Mann-Whitney U test. All comparisons were two-sided.

Cohen's d was calculated as the effect-size measure for parametric comparisons. Rank-biserial correlation was used for comparisons performed with the Mann-Whitney U test. To limit the false-positive rate resulting from multiple comparisons, p-values obtained from the group analyses were additionally adjusted using the Benjamini-Hochberg false discovery rate procedure. Both unadjusted p-values and adjusted q-values were reported.

Associations between serum AMH concentration and AISI, SIRI, PLR, NLR, SII, PNI, and HALP were examined using Spearman's rank correlation analysis.

Binary logistic regression analyses were performed with low AMH status coded as 1 and high AMH status coded as 0. Each inflammatory or nutritional index was evaluated in a separate model to avoid multicollinearity arising from their shared hematological components. All models were adjusted for age and BMI. Continuous predictors were standardized, and adjusted odds ratios were reported for each one-standard-deviation increase, together with their 95% confidence intervals.

To further account for the potential confounding effects of age and BMI, partial Spearman correlation analyses were performed between continuous serum AMH concentrations and each inflammatory or immunonutritional index while controlling for age and BMI. Two-sided p-values were reported, and statistical significance was defined as $p<0.05$.

Results

A total of 150 women were included in the study, with 75 participants in the low AMH group and 75 in the high AMH group. Women in the low AMH group were significantly older than those in the high AMH group (33.0 [29.5–36.5] vs. 27.0 [24.0–31.0] years; $p<0.001$, BH-$q<0.001$). In contrast, there were no significant differences between the groups in body mass index (BMI), gravidity, parity, age at menarche, or cycle length (all $q>0.05$).

As expected, serum AMH concentration and AFC were markedly lower in the low AMH group (both $p<0.001$, BH-$q<0.001$). Women with low AMH had significantly higher FSH and LH levels and lower estradiol (E2) levels than those with high AMH (all $p<0.001$, BH-$q<0.001$). No significant between-group differences were observed in TSH or prolactin levels. Similarly, glucose, insulin, and HOMA-IR did not differ significantly between the groups.

Regarding biochemical and hematological parameters, total protein and albumin concentrations were significantly lower in the low AMH group (both $p<0.001$, BH-$q<0.001$). Neutrophil counts were significantly higher ($p=0.001$, BH-$q=0.003$), whereas lymphocyte counts were significantly lower ($p=0.002$, BH-$q=0.003$) in women with low AMH. No significant differences were detected in hemoglobin, hematocrit, monocyte count, or platelet count.

Systemic inflammatory and nutrition-related indices

All evaluated systemic inflammatory indices were significantly higher in the low AMH group than in the high AMH group. AISI was 299 [238–354] versus 227 [181–298] ($p<0.001$), SIRI was 1.08 [0.90–1.33] versus 0.89 [0.68–1.08] ($p<0.001$), PLR was 141.41±29.93 versus 127.17±27.18 ($p=0.003$), NLR was 2.26±0.48 versus 1.92±0.53 ($p<0.001$), and SII was 596 [500–692] versus 465 [398–602] ($p<0.001$). All of these differences remained statistically significant after Benjamini-Hochberg correction for multiple comparisons.

In contrast, nutrition-related indices were significantly lower in women with low AMH. PNI was 51.36±2.23 in the low AMH group compared with 53.91±2.38 in the high AMH group ($p<0.001$), while HALP was 39.49 [31.78–44.81] versus 45.35 [38.42–50.79], respectively ($p<0.001$). Both differences remained significant after false-discovery-rate correction (BH-$q<0.001$) (Table 1).

Correlations between AMH concentration and inflammatory/nutritional indices

Spearman correlation analysis demonstrated significant inverse correlations between continuous serum AMH concentration and AISI ($\rho=-0.282$, $p<0.001$), SIRI ($\rho=-0.266$, $p=0.001$), PLR ($\rho=-0.257$, $p=0.001$), NLR ($\rho=-0.314$, $p<0.001$), and SII ($\rho=-0.324$, $p<0.001$). In contrast, AMH concentration was positively correlated with PNI ($\rho=0.466$, $p<0.001$) and HALP ($\rho=0.366$, $p<0.001$). Among the evaluated indices, the strongest correlation with AMH was observed for PNI (Table 2).

Age- and BMI-adjusted associations with low AMH

In separate binary logistic regression models adjusted for age and BMI, higher levels of all systemic inflammatory indices were significantly associated with greater odds of low AMH. For each 1-standard-deviation increase, the adjusted odds ratio (OR) was 1.78 for AISI (95% CI: 1.18–2.69; $p=0.006$), 1.90 for SIRI (95% CI: 1.26–2.89; $p=0.002$), 1.68 for PLR (95% CI: 1.14–2.49; $p=0.009$), 2.03 for NLR (95% CI: 1.34–3.06; $p<0.001$), and 1.87 for SII (95% CI: 1.25–2.81; $p=0.002$).

Conversely, higher PNI and HALP values were independently associated with lower odds of low AMH. The adjusted OR was 0.31 for PNI (95% CI: 0.19–0.51; $p<0.001$) and 0.52 for HALP (95% CI: 0.34–0.79; $p=0.002$). Among the evaluated models, the PNI model had the lowest Akaike information criterion value (AIC=159.3) (Table 3).

After adjustment for age and BMI, the associations between continuous AMH concentrations and all investigated indices remained statistically significant. AMH was inversely associated with AISI (partial $\rho=-0.261$, $p=0.001$), SIRI (partial $\rho=-0.254$, $p=0.002$), PLR (partial $\rho=-0.234$, $p=0.004$), NLR (partial $\rho=-0.273$, $p<0.001$), and SII (partial $\rho=-0.282$, $p<0.001$). In contrast, AMH remained positively associated with PNI (partial $\rho=0.385$, $p<0.001$) and HALP (partial $\rho=0.321$, $p<0.001$). These findings indicate that the observed relationships were attenuated only modestly after adjustment for age and BMI.

Discussion

The most important finding of the present study is that women with low AMH exhibited a consistent systemic inflammatory and immunonutritional profile characterized by higher AISI, SIRI, PLR, NLR, and SII and lower PNI and HALP levels. Importantly, although women in the low AMH group were significantly older, each of these indices remained significantly associated with low AMH when evaluated in separate models adjusted for age and BMI. Among the inflammatory indices, NLR showed the strongest positive association with low AMH, with a 1-SD increase corresponding to approximately twofold higher odds of low AMH (adjusted OR 2.03). In con-

Table 1. Participant characteristics according to AMH group

Variable	Low AMH (n=75)	High AMH (n=75)	p	BH q	Effect size
Age (years)	33.00 [29.50–36.50]	27.00 [24.00–31.00]	<0.001	<0.001	0.51
AMH (ng/mL)	0.55 [0.17–0.83]	3.39 [2.58–4.79]	<0.001	<0.001	-1.00
BMI (kg/m^2)	24.86 [22.72–28.09]	25.54 [23.19–27.57]	0.774	0.799	0.03
Gravida (n)	2.00 [0.00–3.00]	2.00 [1.00–3.00]	0.131	0.203	-0.14
Parity (n)	1.00 [0.00–1.00]	1.00 [0.00–2.00]	0.203	0.286	-0.11
Age at menarche (years)	12.00 [12.00–14.00]	13.00 [11.00–14.00]	0.991	0.991	0.00
Cycle length (days)	30.00 [28.00–31.00]	29.00 [28.00–31.00]	0.516	0.593	0.06
FSH (mIU/mL)	13.46 [10.86–15.79]	6.49 [5.37–7.88]	<0.001	<0.001	1.00
LH (mIU/mL)	8.29 [5.84–9.63]	5.74 [4.33–7.53]	<0.001	<0.001	0.50
E2 (pg/mL)	70 [52–81]	91 [69–104]	<0.001	<0.001	-0.50
AFC (n)	3.00 [2.00–4.00]	13.00 [11.00–16.00]	<0.001	<0.001	-1.00
TSH (mIU/L)	2.01 [1.16–2.67]	2.10 [1.56–2.72]	0.346	0.444	-0.09
Prolactin (ng/mL)	15.06 [9.78–19.55]	14.23 [10.36–18.77]	0.666	0.711	0.04
Glucose (mg/dL)	91 [87–96]	90 [86–95]	0.492	0.586	0.07
Insulin (µIU/mL)	10.06 [7.54–12.05]	10.53 [8.38–12.52]	0.090	0.154	-0.16
HOMA-IR	2.22 [1.67–2.64]	2.38 [1.85–2.84]	0.096	0.157	-0.16
Total protein (g/dL)	6.91±0.21	7.07±0.26	<0.001	<0.001	-0.69
Albumin (g/dL)	4.16±0.15	4.33±0.17	<0.001	<0.001	-1.08
Hb (g/dL)	12.80 [12.34–13.09]	12.88 [12.27–13.17]	0.358	0.444	-0.09
Hct (%)	38.40±1.86	38.55±1.83	0.615	0.681	-0.08
Monocyte (10^3/µL)	0.50 [0.46–0.54]	0.49 [0.41–0.54]	0.176	0.259	0.13
Platelet (10^3/µL)	269.04±33.70	262.87±31.03	0.245	0.330	0.19
Neutrophil (10^3/µL)	4.31±0.65	3.94±0.73	0.001	0.003	0.54
Lymphocyte (10^3/µL)	1.95 [1.71–2.15]	2.07 [1.87–2.39]	0.002	0.003	-0.30
AISI (index)	299 [238–354]	227 [181–298]	<0.001	<0.001	0.34
SIRI	1.08 [0.90–1.33]	0.89 [0.68–1.08]	<0.001	<0.001	0.35
PLR	141.41±29.93	127.17±27.18	0.003	0.005	0.50
NLR	2.26±0.48	1.92±0.53	<0.001	<0.001	0.67
SII	596 [500–692]	465 [398–602]	<0.001	<0.001	0.37
PNI	51.36±2.23	53.91±2.38	<0.001	<0.001	-1.11
HALP	39.49 [31.78–44.81]	45.35 [38.42–50.79]	<0.001	<0.001	-0.39

Data are presented as mean±standard deviation (SD) or median [interquartile range (IQR)], according to the distribution. Between-group comparisons were performed using Welch's independent-samples t-test or the Mann–Whitney U test, as appropriate. BH q denotes the Benjamini–Hochberg false-discovery-rate-adjusted p value. Effect sizes are reported as Cohen's d for parametric comparisons and rank-biserial r for non-parametric comparisons; positive values indicate higher levels in the low AMH group. Composite indices are expressed in calculated index units. AFC: Antral follicle count; AISI: Aggregate index of systemic inflammation; AMH: Anti-Müllerian hormone; BMI: Body mass index; E2: Estradiol; FSH: Follicle-stimulating hormone; HALP: Hemoglobin–albumin–lymphocyte–platelet index; HOMA-IR: Homeostasis model assessment of insulin resistance; LH: Luteinizing hormone; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; PNI: Prognostic nutritional index; SII: Systemic immune-inflammation index; SIRI: Systemic inflammation response index; TSH: Thyroid-stimulating hormone.

trast, PNI showed the strongest inverse association (adjusted OR 0.31). Furthermore, continuous AMH concentrations were inversely correlated with all inflammatory indices and positively correlated with PNI and HALP. Collectively, these findings suggest that low AMH is accompanied by a broader pattern of increased systemic inflammatory activity and an altered immunonutritional profile rather than by changes in a single inflammatory marker.

Our findings regarding systemic inflammatory indices are supported by emerging evidence linking peripheral inflammatory activity to ovarian reserve. In a large retrospective cohort of 19,282 women undergoing assisted reproductive treatment, Yao et al. [7] reported that higher SII, PLR, and NLR were associated with lower AMH levels, lower AFC, and fewer retrieved oocytes. These associations persisted in adjusted analyses, and dose–response relationships were observed across inflammatory-marker categories. Notably, the reported relationship was not significantly modified by age or BMI, lending support to the possibility that systemic inflammatory status may provide information beyond these major determinants of ovarian reserve. The concordance between that large cohort and the present findings is particularly relevant because our study similarly demonstrated higher SII, PLR, and NLR in women with low AMH and significant inverse correlations of these indices with continuous AMH levels.

The association observed for NLR is also consistent with earlier findings in women with impaired ovarian function. Ilhan et al. [5] reported significantly higher NLR values in women with

Table 2. Spearman and age- and BMI-adjusted partial correlations between continuous AMH concentrations and inflammatory/immunonutritional indices

Index	Spearman ρ	p	Age- and BMI-adjusted partial ρ	p
AISI	-0.282	<0.001	-0.261	0.001
SIRI	-0.266	0.001	-0.254	0.002
PLR	-0.257	0.001	-0.234	0.004
NLR	-0.314	<0.001	-0.273	<0.001
SII	-0.324	<0.001	-0.282	<0.001
PNI	0.466	<0.001	0.385	<0.001
HALP	0.366	<0.001	0.321	<0.001

Values are Spearman's rank correlation coefficients (ρ) and age- and BMI-adjusted partial Spearman correlation coefficients with two-sided p values. Partial correlations were calculated while controlling for age and BMI. Negative coefficients indicate inverse associations with AMH, whereas positive coefficients indicate direct associations. AISI: Aggregate index of systemic inflammation; AMH: Anti-Müllerian hormone; HALP: Hemoglobin–albumin–lymphocyte–platelet index; NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio; PNI: Prognostic nutritional index; SII: Systemic immune-inflammation index; SIRI: Systemic inflammation response index; BMI: Body mass index.

Table 3. Age- and BMI-adjusted associations with low AMH

Predictor	Adjusted OR (per 1 SD)	95% CI	p	AIC
AISI	1.78	1.18–2.69	0.006	179.1
SIRI	1.90	1.26–2.89	0.002	177.0
PLR	1.68	1.14–2.49	0.009	180.3
NLR	2.03	1.34–3.06	<0.001	174.7
SII	1.87	1.25–2.81	0.002	177.4
PNI	0.31	0.19–0.51	<0.001	159.3
HALP	0.52	0.34–0.79	0.002	177.2

Each index was evaluated in a separate binary logistic regression model with low AMH coded as 1 and High AMH coded as 0. Models were adjusted for age and BMI. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) are reported per 1-standard-deviation (SD) increase in the predictor. Indices were not entered simultaneously because they share hematological components. AMH: Anti-Müllerian hormone; AIC: Akaike information criterion; AISI: Aggregate index of systemic inflammation; BMI: Body mass index; CI: Confidence interval; HALP: Hemoglobin–albumin–lymphocyte–platelet index; NLR: Neutrophil-to-lymphocyte ratio; OR: Odds ratio; PLR: Platelet-to-lymphocyte ratio; PNI: Prognostic nutritional index; SII: Systemic immune-inflammation index; SIRI: Systemic inflammation response index.

premature ovarian insufficiency and found a negative correlation between NLR and AMH (r=-0.27). NLR demonstrated an AUC of 0.66 for premature ovarian insufficiency in that study [5]. In the present study, NLR was similarly inversely correlated with AMH (ρ=-0.314) and remained significantly associated with low AMH after adjustment for age and BMI. Although premature ovarian insufficiency and low AMH are clinically distinct entities and should not be considered interchangeable, the consistency in the direction of these associations supports a potential relationship between altered systemic immune-cell balance and low AMH.

Not all studies, however, have demonstrated an association between systemic inflammatory markers and ovarian reserve. Shoarishoar et al. [6] evaluated 174 women classified according to AMH concentrations above or below 1.1 ng/mL and found no significant associations between diminished ovarian reserve and NLR, PLR, or the red cell distribution width-to-platelet ratio; age and FSH were the principal variables associated with diminished ovarian reserve. Similarly, Long et al. [11], in an analysis of 703 reproductive-aged women, found no significant association between circulating C-reactive protein and AMH or the odds of diminished ovarian reserve after adjustment. Previous studies evaluating routine inflammatory indices in premature ovarian insufficiency (POI) have yielded heterogeneous findings [12–15]. Sanverdi et al. [12] reported higher NLR in women with POI, while Baki Erin demonstrated higher NLR, PLR, and SII and inverse correlations of these indices with AMH and antral follicle count. In contrast, Demir et al. [13] found no significant differences in NLR or PLR between women with POI and controls, and Yldrm et al. [15] unexpectedly reported lower NLR in POI. These discrepant findings may reflect differences in study populations, definitions of ovarian dysfunction, and inflammatory markers evaluated. Our results, showing higher NLR, PLR, SII, SIRI, and AISI and inverse correlations of these indices with AMH, add to the evidence supporting an association between reduced ovarian reserve and a systemic inflammatory profile. These differences may reflect heterogeneity in study populations, definitions of reduced ovarian reserve, inflammatory markers examined, timing of blood collection, comorbidities, and statistical adjustment. They may also indicate that different inflammatory biomarkers capture distinct components of immune activation. Unlike a single acute-phase protein such as CRP, cell-derived composite indices integrate neutrophil, lymphocyte, monocyte, and platelet compartments and therefore may characterize systemic inflammatory balance differently.

Similar findings have recently been reported in women with endometriosis. Ulger et al. [16] evaluated 91 women with surgically confirmed endometriomas and demonstrated significant inverse correlations between serum AMH concentrations and PLR, SII, and the monocyte-to-lymphocyte ratio. Moreover, age and PLR remained independently associated with AMH levels in multivariable analysis. These findings are consistent with our results, in which AMH was inversely correlated with PLR, SII, NLR, SIRI, and AISI, while higher inflammatory indices were associated with greater odds of low AMH after adjustment for age and BMI. The concordant findings support an association between systemic inflammatory status and ovarian reserve. However, because the study by Ulger et al. [16] was restricted to women with endometriomas, in whom local and systemic inflammation is an established component of the underlying disease, its findings cannot be directly generalized to women with low AMH without endometriosis. Similarly, Cui et al. [17] reported lower serum AMH concentrations in women with bilateral tubal occlusion used as a clinical model of chronic pelvic inflammation, with the difference remaining significant after BMI adjustment. Further clinical evidence supporting the relationship between inflammation and ovarian reserve has recently been provid-

ed by Griffiths et al. [18]. In women undergoing diagnostic laparoscopy, serum AMH concentrations were significantly lower in those with superficial peritoneal endometriosis, both with and without concomitant ovarian endometriosis, compared with women without endometriosis, even after accounting for age. Importantly, reduced AMH in women with superficial peritoneal endometriosis was accompanied by an elevated inflammatory profile, including increased serum IL-17 and TNF-α and increased peritoneal fluid IL-23 [18]. These observations are consistent with our findings demonstrating higher systemic inflammatory indices in women with low AMH and inverse correlations of AMH with NLR, PLR, SII, SIRI, and AISI. Although the inflammatory milieu associated with endometriosis represents a specific disease context and therefore cannot be directly extrapolated to women with low AMH in general, the findings strengthen the concept that reduced ovarian reserve may coexist with enhanced systemic and local inflammatory activity. These findings are consistent with the concept that both localized and systemic inflammatory environments may accompany impaired ovarian reserve. Nevertheless, studies in endometriosis or chronic pelvic inflammatory conditions cannot be directly extrapolated to otherwise unselected women with low AMH because the underlying inflammatory burden and mechanisms may differ substantially.

However, not all studies have demonstrated an independent association between peripheral inflammatory markers and AMH. In a recent retrospective cross-sectional study of 819 reproductive-age women, Karalök et al. [19] found that neither NLR nor CRP was independently associated with serum AMH after adjustment for chronological age. In particular, NLR showed no significant age-adjusted association with AMH, suggesting that the relationship observed in unselected reproductive-age populations may be largely influenced by age or may not be adequately captured by routine peripheral inflammatory markers [18]. This contrasts with our findings, in which NLR was inversely correlated with continuous AMH concentrations and remained significantly associated with low AMH after adjustment for both age and BMI. Moreover, our study demonstrated consistent associations across several complementary inflammatory indices, including AISI, SIRI, PLR, and SII. Differences in study design, participant characteristics, definition of ovarian reserve, statistical modeling, and the spectrum of inflammatory indices evaluated may partly account for these discrepant findings. Importantly, the absence of an association with isolated NLR or CRP does not necessarily exclude a relationship between ovarian reserve and broader systemic inflammatory or immunonutritional profiles.

A biological relationship between inflammation and ovarian aging is plausible, although the present findings cannot establish causality. Ovarian aging is a multifactorial process, and previous studies have described age-related alterations in inflammatory and immune pathways within the ovarian microenvironment [3, 4, 20]. Zeng et al. [3] highlighted chronic inflammation as a potentially important component of ovarian aging, while Seyhanli et al. [20] described age-related increases in ovarian inflammatory mediators and immune-cell accumulation. These observations provide biological context for the inverse associations between AMH and AISI, SIRI, NLR, PLR, and SII observed in the present study. However, our cross-sectional data cannot determine whether systemic inflammation contributes to declining ovarian reserve, develops in parallel with reproductive aging, or reflects shared age-related biological processes. Accordingly, these findings should be interpreted primarily as an association between lower AMH and a more pronounced systemic inflammatory profile rather than evidence of a causal mechanism.

An important and relatively novel aspect of the present study is the simultaneous evaluation of nutrition-related composite indices. Compared with conventional inflammatory markers such as NLR, PLR, and SII, PNI and HALP have been considerably less studied in relation to ovarian reserve. PNI combines serum albumin and lymphocyte count and therefore reflects both nutritional and immune-inflammatory components, whereas HALP integrates hemoglobin, albumin, lymphocyte, and platelet values [8, 9]. Both indices have increasingly been used as composite immunonutritional markers in different clinical settings, including reproductive and obstetric populations [20]. In the present study, both PNI and HALP were significantly lower in women with low AMH and were positively correlated with continuous AMH concentrations. Moreover, both remained inversely associated with low AMH after adjustment for age and BMI, with PNI demonstrating the strongest association and lowest AIC among the evaluated models. These findings extend the concept of altered systemic status in women with low AMH from inflammation alone toward a broader immunonutritional phenotype.

The PNI finding warrants particular attention. AMH showed its strongest correlation among the investigated indices with PNI (ρ=0.466), and each 1-SD increase in PNI was associated with 69% lower odds of low AMH after adjustment for age and BMI. However, PNI should not be interpreted as a direct measure of dietary intake or clinical malnutrition. Albumin is influenced by inflammatory and metabolic processes in addition to nutritional status, and lymphocyte counts reflect immune status. Thus, in this setting, PNI may be better regarded as an integrated immunonutritional marker rather than a specific measure of nutritional deficiency. Similarly, the lower HALP values may partly reflect the lower albumin and lymphocyte levels because these variables are mathematical components of the index.

The present findings should be interpreted as demonstrating an association between low AMH and a systemic inflammatory–immunonutritional phenotype rather than as evidence that the evaluated indices improve ovarian reserve assessment beyond established measures such as AMH and AFC. Because the study groups were defined according to AMH concentration, the present data cannot establish incremental diagnostic utility. Similarly, reproductive outcomes were not evaluated, and no prognostic inference can be made.

Strengths and limitations

The present study has several strengths. A broad panel of routinely available systemic inflammatory and immunonutritional indices was evaluated within the same population, allowing their associations with AMH status and continuous AMH concentrations to be compared directly. AMH was assessed both as a categorical and continuous variable, and the analytical approach included correlation analysis, age- and BMI-adjusted partial correlation analysis using continuous AMH, and age- and BMI-adjusted logistic regression. In addition, Benjamini–Hochberg correction was applied to baseline comparisons to reduce the risk of false-positive findings due to multiple testing.

Nevertheless, several limitations should be acknowledged. First, the retrospective cross-sectional design precludes determination of temporal or causal relationships between systemic inflammation, immunonutritional status, and low AMH. Second, women with low AMH were significantly older than those with high AMH. Although the associations between continuous AMH and all investigated inflammatory and immunonutritional indices remained statistically significant after adjustment for age and BMI, residual confounding related to reproductive aging cannot be completely excluded. Therefore, these findings should be interpreted as age- and BMI-adjusted associations rather than evidence that the observed systemic alterations are fully independent of reproductive aging. Third, inflammatory and nutritional indices and AMH were evaluated at a single time point; therefore, potential intra-individual changes over time could not be assessed. Fourth, the adjusted models included age and BMI, but residual confounding from other factors that may influence systemic inflammation or AMH, including lifestyle factors, unmeasured medication use, and underlying comorbidities, cannot be excluded. Furthermore, several of the evaluated indices share common hematological components and are therefore not biologically independent. Accordingly, the indices were examined in separate regression models, limiting assessment of their independent contributions when considered simultaneously. Finally, because the study population was defined according to AMH concentration and reproductive outcomes were not assessed, the present findings cannot establish incremental diagnostic or prognostic utility. Further prospective, multicenter studies are needed to confirm these associations and clarify their biological and clinical significance.

Clinical implications/future directions

The evaluated indices are inexpensive and readily derived from routine complete blood count and biochemical parameters. However, the present findings should be interpreted as reflecting the systemic inflammatory and immunonutritional context associated with low AMH rather than as evidence of diagnostic utility. In particular, PNI may warrant further investigation because it showed the strongest correlation with AMH and the strongest adjusted inverse association with low AMH. Prospective multicenter studies with longitudinal measurements are needed to confirm these associations and clarify their biological and potential clinical significance.

Conclusion

Women with low AMH exhibited a systemic profile characterized by higher inflammatory indices and lower nutrition-related indices. AMH was inversely associated with AISI, SIRI, PLR, NLR, and SII and positively associated with PNI and HALP. Importantly, these associations remained significant after adjustment for age and BMI. These findings support an association between low AMH and a distinct systemic inflammatory–immunonutritional phenotype but do not establish that these indices improve ovarian reserve assessment beyond established markers such as AMH and AFC. Prospective studies are needed to determine the biological and potential clinical significance of these associations.

Disclosures

Ethics Committee Approval: The study was approved by the Istanbul Atlas University Non-Interventional Scientific Research Clinical Research Ethics Committee (no: E-22686390-200-102527, date: 29/06/2026).

Informed Consent: The requirement for written informed consent was waived by the Ethics Committee because of the retrospective study design and use of previously collected clinical and laboratory data. All data were analyzed in anonymized form.

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