E-ISSN: 2147-2688

The Medical Bulletin of Haseki

2026
Volume 64
Issue
June 3

www.hasekidergisi.com

The Medical Bulletin of Haseki

Editorial Board

Publisher Contact
Address: Molla Gurani Mah. Kacamak Sk. No: 21/1 34093 Istanbul, Türkiye
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E-mail: info@galenos.com.tr/yayin@galenos.com.tr
Web: www.galenos.com.tr
Publisher Certificate Number: 14521

Online Publishing Date: June 2026
E-ISSN: 2147-2688
International scientific journal published quarterly.

The Medical Bulletin of Haseki

Scientific Advisory Board

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The Medical Bulletin of Haseki

Contents

Original Articles

Letter to the Editor

Original Article

DOI: 10.4274/haseki.galenos.2026.99608
Med Bull Haseki 2026;64(3):155-164

Regional tau Burden and Multidomain Cognitive Function in Clinically Unimpaired Older Adults: Evidence from the A4 Study

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Abstract

Aim: We aimed to evaluate how modifiable risk factors influence these relationships and to better understand the drivers of early cognitive changes in regional tau burden in the medial temporal lobe (MTL) versus the neocortex (NEO) during the preclinical stages of Alzheimer's disease (AD).

Methods: In this cross-sectional study, 447 participants in the A4 study (anti-amyloid treatment in asymptomatic AD) underwent tau-positron emission tomography-standardized uptake value ratio evaluations. Cognitive abilities were assessed using the Preclinical Alzheimer's Cognitive Composite (PACC). Depression, anxiety, and lifestyle factors were analyzed using t-tests, chi-square tests, and multiple linear regression models.

Results: The tau-positive cohort was notably older ($p=0.002$) and significantly more likely to carry APOE4 ($p<0.001$). Tau-positive groups demonstrated poorer cognitive performance. Negative correlations between tau accumulation and cognitive performance for PACC and its components, with tauMTL/tauNEO associated with worse outcomes. Females were associated with better objective performance but worse informant-reported function, suggesting an early loss of self-awareness. Higher education was protective; depression was linked to decreased memory and executive function, whereas anxiety showed no association.

Conclusion: Regional tau pathology is robustly associated with functional decline detectable by informants prior to clinical emergence. The significant interaction between tau and modifiable factors such as depressive symptoms underscores the importance of multifaceted, informant-based assessments in preclinical AD screening.

Keywords: Cognitive dysfunction, Alzheimer's disease, tau proteins, temporal lobe, depression, risk factors

Introduction

Cognitive decline (CD) is a significant concern in age-related diseases, especially in neurodegenerative disorders such as Alzheimer's disease (AD) related dementias (ADRDs) (1). Individuals experiencing CD often report higher levels of depression and anxiety, which further exacerbate reductions in their perceived quality of life (2). Multiple studies indicate that demographic and lifestyle factors influence subjective CD (SCD), a self-reported cognitive difficulty. Cognitive lifestyle factors, such as education, career, and social engagement, are associated with slower CD and offer protective benefits (3,4). Additionally, demographic factors such as age and sex may influence the onset and progression of SCD, thereby affecting the risk of developing AD (5).

The medial temporal lobe (MTL), particularly the hippocampus, is often among the earliest regions affected by AD (6,7). Studies indicate that individuals with SCD may exhibit reduced MTL volumes, which correlate with AD pathology (8). The neocortex (NEO), involved in higher cognitive functions, also exhibits atrophy in individuals with

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Received: 09.08.2025 **Accepted:** 26.02.2026 **Epub:** 31.03.2026 **Publication Date:** 01.06.2026

Cite this article as: Demirsoy I, Ozge A. Regional tau burden and multidomain cognitive function in clinically unimpaired older adults: evidence from the A4 study. Med Bull Haseki. 2026;64(3):155-164

CD, further supporting the view that SCD may precede more pronounced cognitive deficits (9). Elevated tau levels in cerebrospinal fluid are associated with AD, and the N-224 tau fragment has shown promise in differentiating AD from SCD, suggesting its potential as an early biomarker (10,11). Lifestyle choices also play a critical role in modulating CD. Regular exercise is associated with improved cognitive function and may delay the onset of dementia; physical activity is also linked to better cognitive outcomes (12). Conversely, alcohol consumption negatively impacts cognitive health, contributing to neuroinflammation and cognitive impairments, particularly in older adults.

In this study, we hypothesized that tau accumulation in the tau accumulation in the neocortex (tau_{NEO}) and tau accumulation in the medial temporal lobe (tau_{MTL}) would be associated with CD in individuals at risk for neurodegenerative diseases. This study represents one of the limited analyses within the A4 cohort that simultaneously evaluates regional tau burden (MTL vs. NEO) using both objective cognitive assessments and informant-based functional measures. Participants from the A4 study were stratified according to neuroimaging findings into groups with positive and negative tau accumulation in each region. In addition, we investigated the potential influence of demographic characteristics, health-related variables, and lifestyle factors on tau accumulation and their associations with cognitive outcomes across multiple assessment domains. By examining the relationship between regional tau pathology and cognitive performance, this study aims to provide a more comprehensive understanding of how tau accumulation contributes to early changes in memory and functional abilities. Furthermore, we explored whether demographic and lifestyle factors may act as potential moderators of this relationship, thereby offering further insights into the complicated interaction between biological mechanisms and modifiable risk factors in cognitive health.

Materials and Methods

Study Design

This study was designed as a cross-sectional secondary analysis of the A4 study dataset. The analysis did not require additional Institutional Review Board (IRB) approval because it used previously collected and fully de-identified data from a study that had already received IRB approval. The dataset used in this analysis was fully de-identified and contained no direct or indirect personal identifiers. As the researchers had no interaction with human subjects and no access to identifiable private information, the study does not meet the regulatory definition of human subjects research. It is therefore exempt from additional IRB review.

Participants

The A4 study, which began in 2014, was conducted at 67 sites across the United States, Japan, Australia, and Canada, and participant randomization was completed by the end of 2017. All locations obtained approval from their IRBs. Before joining the trial, participants provided informed consent. The Alzheimer's Therapeutic Research Institute at University of Southern California handled the management of the A4/LEARN Study, with data sourced from the university's Laboratory for Neuro Imaging (13). The study followed the ethical principles outlined in the Declaration of Helsinki, and all individuals gave written informed consent before participating. The analysis used previously deidentified individual-level data.

A total of 6,763 cognitively healthy participants aged between 65 and 85 years entered the study. To be eligible, participants needed to show no cognitive impairment. They must meet specific standards, including a score of 0 on the clinical dementia rating, a mini-mental state examination (MMSE) score ranging from 25 to 30, and a delayed paragraph recall (LM-IIa) subscale score on the Wechsler Memory Scale-Revised ranging from 6 to 18 (14). The A4 study was open to participants who had a significant amyloid burden, as demonstrated by positron emission tomography (PET) imaging. Those without high amyloid levels who were eligible for the A4 Study were referred to the LEARN Study. Subsequently, ^{18}F-florbetapir PET scans were conducted on 4,486 individuals (15,16).

Additionally, some participants in the research underwent ^{18}F-flortaucipir PET scans for tau PET imaging. A total of 447 individuals who received PET tau assessments were included in this study. Participants were divided into positive and negative groups for each region based on their tau standardized uptake value ratio (SUVr) values, which referred to tau SUVr in the tau_{MTL} and in the tau_{NEO} (Figure 1).

Magnetic Resonance Imaging

Throughout the study, volumetric magnetic resonance imaging scans and functional connectivity assessments were conducted. To assess the effects of fibrillar amyloid buildup, ^{18}F-florbetapir PET amyloid imaging was performed at the trial's conclusion. The PET data for tau and amyloid are analyzed using FreeSurfer (17).

Amyloid and tau Status

^{18}F-florbetapir was performed 50 to 70 minutes following the administration of 10 mCi of the tracer to obtain Amyloid PET imaging (18). The presence of amyloid deposits, classified as either high (Aß+) or low (Aß-), was assessed by the SUVr and by visual assessment at a leading research laboratory. Non-elevated amyloid status (Aß-) was defined using an average cortical SUVr,

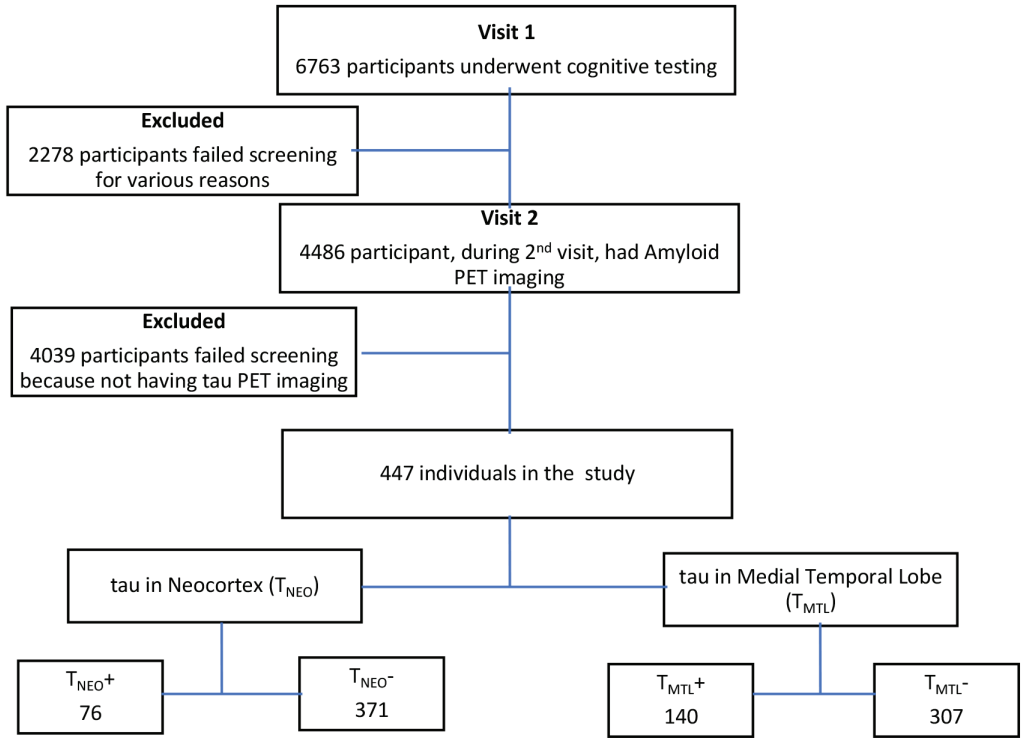

Figure 1. Participant selection flowchart and tau PET results. Of 6,763 initially tested, 447 met all criteria. Tables show number of participants with tau burden (SUVr*) in neocortex (left) and medial temporal lobe (right)
PET: Positron emission tomography, SUVr: Standardized uptake value ratio

with the entire cerebellum as the reference region and a threshold of <1.15 applied. This is considered a highly effective technique for detecting early amyloid deposits in the preclinical stage of AD (19).

In the A4 study, some participants underwent 18F-flortaucipir PET scans, performed 90 to 110 minutes after injection. The assessment of tau SUVr levels focused on the tau_{MTL}, a region encompassing the amygdala and entorhinal cortex bilaterally (20). Although the entorhinal cortex is smaller than the amygdala, it plays a critical role in the early stages of tau accumulation (7) for these two structures. The MTL region was defined based on an established temporal meta-region of interest that captures the typical pattern of tau spread (21,22). The criteria for grouping tau status in the MTL as positive or negative were established based on the mean tau level plus 2 standard deviations observed among all Aß-negative participants in the A4 study (20). For tau deposition in the tau_{MTL} and in the tau_{NEO}, the cut-off values were found to be 1.25 and 1.28, respectively.

Self-Assessment of Lifestyle Habits

The A4 study's self-report questionnaire consists of 8 questions. It was designed to assess participants' current lifestyle habits. It covers physical activity, sleep patterns, and substance use. It asks about the frequency of aerobic exercise (average hours spent swimming, jogging, or cycling per week), the average sleep duration per night, and the average daily alcohol consumption. However, no dietary questions were included (23,24).

Geriatric Depression Scale and State Anxiety Inventory

The GDS is a self-reported tool designed to examine depression among older adults. It consists of 15 questions with dichotomous (yes/no) answers and focuses primarily on the emotional and psychological symptoms of depression, making it an effective tool for identifying depressive symptoms in older adults (25). A higher score on the scale indicates more significant concerns (24).

The State Anxiety Inventory (STAI) is a widely used instrument for measuring anxiety levels (26). The 6-item version of STAI is designed to measure state anxiety, which refers to the temporary feelings of anxiety or nervousness that a person may experience in a particular situation (27).

Cognitive Assessments and Outcome Measures

This study compared various cognitive assessments and their relationships with regional and composite measures. They are used as outcome measures in regression analysis.

The following tests were included:

The main objective of the Preclinical Alzheimer's Cognitive Composite (PACC) is to measure outcomes in the first preclinical AD trial (13). It includes four key components designed to assess different aspects of cognitive function (28):

- Free and cued selective reminding test (FCSRT): A memory test that assesses associations through visual and semantic prompts. It yields two scores: free recall (items remembered independently) and total recall (a combination of free and cued recall), with higher scores (0-96) indicating better memory performance.

- Mini-mental state examination: The MMSE is a test comprising 30 items that evaluates overall cognitive function, covering orientation, attention, memory, naming, and simple drawing tasks. A score of 23 or below suggests cognitive impairment.

- Digit symbol substitution (DSS): A task in which participants match symbols with numbers to evaluate cognitive speed, memory recall, and executive functioning. Higher scores (0 to 91) signify improved cognitive abilities.

- Delayed logical memory (DLM): This test measures episodic memory by asking participants to recall a short story immediately, followed by a delayed recall 20–30 minutes later. Higher scores (0-25) indicate better memory retention.

The cognitive function index: Cognitive function index (CFI), developed by the Alzheimer's Disease Cooperative Study, is used to monitor changes in cognitive function over 1 year (29-31). To participate, individuals must be proficient in English, Japanese, or Spanish and have adequate hearing and vision for the assessments. Each participant needs a study partner to provide weekly insights into their cognitive function via phone, email, or in person.

The CFI has two editions: One for the participant to assess their own cognitive skills and another for the study partner to share their viewpoint (19). Both versions are mailed four weeks before the annual evaluation, with clear instructions for independent completion. Study partners are prohibited from discussing the questionnaire with the participant, though they may consult others if necessary. The CFI comprises 14 questions, which are the same for both the participant and study-partner versions, plus one additional question in the A4 study asking whether the participant has consulted a doctor regarding memory issues (29). Responses are scored as "Yes" (2), "Maybe" (1), or "No" (0) (19), and a higher score indicates more deleted significant severe subjective cognitive complaints (32). A "not applicable" option is provided for questions about driving, money, or job performance; when this option is chosen, the average of the other answers is used (16).

Statistical Analysis

Demographic data from all participants were compiled for the overall sample. Continuous variables were characterized using means and standard deviations, and Independent Samples t-tests were used to evaluate group differences in age, education, cognitive scores (e.g., PACC, FCRST96), and the difference between tau_{MTL} (negative/positive) and tau_{NEO} (negative/positive) groups. For categorical variables, analyses were performed using the chi-square test and Fisher's exact test. Chi-square tests were used to examine differences in amyloid eligibility, APOE ε4 status, and sex distribution between the tau_{MTL} and tau_{NEO} groups. We also assessed the independent relationships between tau_{MTL}, tau_{NEO}, and cognitive scores overall. We used multiple regression analysis across various models to test our hypotheses regarding the effects of demographics and habits and their interactions with tau_{MTL} and tau_{NEO} on cognitive function. R version 4.3.2 was used in the study (33).

Results

Demographics and Group Comparisons

Total 447 participants were included in the study, divided into tau_{NEO} and tau_{MTL} groups based on tau PET SUVr from neuroimaging. Regarding demographic characteristics, there were no significant differences in age between the tau-positive and tau-negative groups in the TNEO region. However, the tau_{MTL} positive group was significantly older than the comparison group [72.88 (4.83) vs. 71.36 (4.78), p=0.002]. Sex distribution was similar across all groups, with no significant differences observed for either the tau_{NEO} (p=0.756) or TMTL (p=0.557) groups. The prevalence of the APOE4 allele was significantly higher in tau-positive groups than in their respective tau-negative groups in both regions. Tau deposition was markedly elevated in the tau-positive groups across both regions, as indicated in Table 1.

The scores on the STAI and the GDS showed no discernible differences between the groups. Even if alcohol consumption was higher among TNEO+ participants, there were no significant differences. Similarly, weekly hours of aerobic activity were lower in tau-positive groups, but this difference was not statistically significant. Similarly, the proportion of participants living with a study partner was comparable across groups, with no significant differences observed.

Cognitive performance was significantly worse in the tau-positive groups at both levels. Participants with higher tau accumulation had significantly lower scores on several cognitive assessments. The PACC score was significantly lower in the tau-positive groups in both the TNEO and TMTL levels (p<0.001 for both). Likewise, MMSE scores

Table 1. The characteristics of the sample and subgroups							
		Stratified by tau_{NEO} Status			Stratified by tau_{MTL} Status		
Variables	**Full Dataset**	**Negative**	**Positive**	**p-value**	**Negative**	**Positive**	**p-value**
N	447	371	76		307	140	
Age (yrs), mean (SD)	71.84 (4.84)	71.65 (4.77)	72.76 (5.11)	0.067	71.36 (4.78)	72.88 (4.83)	**0.002**
Sex (F)	257 (57.5%)	211 (56.9%)	46 (60.5%)	0.557	175 (57.0%)	82 (58.6%)	0.756
Race - white (%)	409 (91.5%)	337 (90.8%)	72 (94.7%)	0.622	281 (91.5%)	128 (91.4%)	0.967
Education (yrs), mean (SD)	16.22 (2.84)	16.18 (2.88)	16.42 (2.59)	0.496	16.13 (2.91)	16.42 (2.67)	0.309
APOE4 - N (%)	234 (53.2%)	181 (49.5%)	53 (71.6%)	**<0.001**	141 (46.1%)	93 (69.4%)	**<0.001**
Amyloid (Aß)	1.28 (0.20)	1.25 (0.18)	1.41 (0.22)	**<0.001**	1.23 (0.18)	1.38 (0.20)	**<0.001**
tau_{MTL}	1.21 (0.15)	1.17 (0.11)	1.41 (0.18)	**<0.001**	1.13 (0.07)	1.39 (0.14)	**<0.001**
tau_{NEO}	1.20 (0.12)	1.16 (0.06)	1.39 (0.13)	**<0.001**	1.16 (0.08)	1.29 (0.13)	**<0.001**
Alcohol (day)	0.76 (0.93)	0.75 (0.95)	0.78 (0.86)	0.836	0.79 (0.98)	0.69 (0.80)	0.332
Aerobic (week)	2.90 (3.48)	2.92 (3.53)	2.82 (3.24)	0.814	3.04 (3.62)	2.60 (3.13)	0.216
Depression (total)	1.05 (1.44)	1.04 (1.47)	1.11 (1.33)	0.722	1.06 (1.51)	1.04 (1.28)	0.932
Anxiety (total)	10.17 (3.04)	10.17 (3.00)	10.18 (3.22)	0.976	10.13 (3.08)	10.28 (2.96)	0.625
CFI_p - mean (SD)	0.16 (0.15)	0.15 (0.14)	0.22 (0.18)	**<0.001**	0.14 (0.13)	0.19 (0.17)	**<0.001**
CFI_{sp} - mean (SD)	0.10 (0.13)	0.09 (0.12)	0.17 (0.18)	**<0.001**	0.10 (0.12)	0.12 (0.16)	**0.039**
PACC	-0.42 (2.79)	-0.16 (2.68)	-1.70 (3.00)	**<0.001**	-0.02 (2.76)	-1.29 (2.67)	**<0.001**
MMSE	28.64 (1.31)	28.71 (1.27)	28.26 (1.42)	**0.006**	28.74 (1.28)	28.41 (1.34)	**0.015**
LMD	11.59 (3.38)	11.83 (3.37)	10.38 (3.16)	**<0.001**	11.98 (3.40)	10.71 (3.16)	**<0.001**
DSS	42.56 (9.39)	43.12 (9.36)	39.82 (9.09)	**0.005**	43.17 (9.23)	41.22 (9.63)	**0.042**
FCSRT	75.69 (6.28)	76.05 (6.09)	73.96 (6.92)	**0.008**	76.40 (5.94)	74.13 (6.72)	**<0.001**

Bold values indicate statistically significant results (p<0.05).
Note: Using t-tests or continuous variables and chi-square test for categorical variables.
GDS: Geriatric Depression Scale (15 items), STAI: State Anxiety Inventory (6 items), CFI_p: Cognitive function index-participant, CFI_{sp}: Cognitive function index-study partner, PACC: Preclinical Alzheimer Cognitive Composite, MMSE: Mini-mental state examination, LMD: Logical Memory Delayed, DSS: Digit symbol substitution, FCSRT: Free and cued selective reminding test, SD: standard deviation, tau_{NEO}: Tau SUVr in neocortex, tau_{MTL}: Tau SUVr in medial temporal lobe

were lower in tau-positive groups (TNEO: p=0.006, TMTL: p=0.015). On the Logical Memory Delayed (LMD) test, which assesses verbal memory, the tau-positive groups also performed worse (p<0.001 for both groups). Additionally, tau-positive participants had significantly lower FCSRT scores, indicating impaired memory performance (TNEO: p=0.008; TMTL: p<0.001). Furthermore, the functional decline was more pronounced in the tau-positive groups. The DSS scores were significantly lower in the tau-positive groups, reflecting more significant functional impairment in those with higher tau levels (TNEO: p=0.005; TMTL: p=0.042). Finally, Tau-positive groups had higher CFI scores not only for participants but also for study partners for TNEO (p<0.001; p<0.001) and TMTL (p<0.001; p=0.039) groups (Table 1).

Factors Influencing tau Accumulation

To investigate the impact of lifestyle, health, and demographic variables on tau_{MTL} and tau_{NEO} and their correlation with cognitive function, we used multiple linear regression analyses. Separate regression models were employed for tau_{MTL} and tau_{NEO} (Tables 2 and 3), with an additional model assessing the interaction between tau_{MTL} and tau_{NEO} (Table S1). This allowed a comparison of how each form of tau deposition and its combined effect relate to cognitive outcomes.

Associations Between tau_{MTL} & Cognitive Function and tau_{NEO} & Cognitive Function

Higher tauMTL deposition was associated with poorer performance on the PACC (ß=-0.224, p<0.001), FCSRT (ß=-0.210, p<0.001), LMD (ß=-0.220, p<0.001), and MMSE (ß=-0.099, p=0.066) and with higher (worse) scores on the CFI participant and study-partner reports (ß=0.024 & 0.023, both p<0.001). It was not associated with DSS. Older individuals performed worse on the PACC, FCSRT, LMD, and MMSE (all p≤0.003). Female participants were associated with better performance on the PACC, FCSRT, DSS, and MMSE (all p<0.001), but with worse study-partner ratings on the CFI (ß=-0.043, p=0.004). Higher education was associated with better performance on the PACC (ß=0.161, p<0.001) and the LMD (ß=0.128, p=0.016). Geriatric Depression Scale were associated with worse PACC and FCSRT performance (ß=-0.099, p_FDR=0.061 & ß=-0.127, p=0.017) and worse CFI ratings (both p≤0.03),

but not with DSS, LMD, or MMSE. Neither the STAI, daily alcohol use, nor weekly aerobic activity showed significant associations with any cognitive measure (Table 2).

Similarly, Higher tau_{NEO} deposition was associated with poorer performance on the PACC (ß=-0.192, p<0.001), FCSRT (ß=-0.109, p=0.033), LMD (ß=-0.150, p=0.004), DSS (ß=-0.102, p=0.047), and MMSE (ß=-0.145, p=0.005), but with higher scores on the CFI participant and study-partner reports (ß=0.019, p=0.011 & ß=0.024, p<0.001). Older age was negatively associated with PACC, FCSRT, LMD, and MMSE performance (all p≤0.005). Females performed better on the PACC, FCSRT, DSS, and CFI study partner (all p<0.002). Higher education was associated with better performance on the PACC (ß=0.154, p<0.001), LMD (ß=0.121, p=0.027), and MMSE (ß=0.152, p=0.004). Geriatric Depression Scalewere associated with worse PACC and FCSRT performance (ß=-0.098, p=0.066; ß=-0.126, p=0.023) and worse CFI ratings (both p≤0.031). Daily alcohol use showed a minor negative association with PACC performance (ß=-0.087, p=0.084). However, no significant correlation was found between any cognitive measure and either weekly aerobic exercise or STAI. Every p-value has been corrected for false discovery rate (FDR) (Table 3).

Tau Region Interaction and Relation to Cognitive Performance

When examining the interaction between tau_{MTL} and tau_{NEO}, we found that tau_{MTL} retained significant negative associations with PACC (ß=-0.150, p=0.026), FCSRT (ß=-0.224, p<0.001), and LMD (ß=-0.200, p=0.007), whereas tau_{NEO} lost significance across cognitive measures. Notably, the interaction between tau_{MTL} and tau_{NEO} was slightly associated with performance on PACC (ß=-0.067, p=0.080) and FCSRT (ß=-0.062, p=0.109), indicating that the joint influence of both tau types may exacerbate CD in some domains. All p-values are FDR-adjusted (Table S1).

Age, sex, and education showed similarly significant associations with cognitive outcomes. Average daily alcohol use remains substantial only with respect to the global cognitive measure (PACC).

Discussion

This study is one of the rare A4 analyses that simultaneously evaluates regional tau burden (MTL vs. NEO) using both objective cognitive tests and informant-based functional measures. Notably, tau pathology in the tau_{MTL} was strongly linked to cognitive functioning, emphasizing its critical role in AD progression (20,34). Additionally, differences in cognitive functioning by sex highlighted the importance of considering self- and informant-reported measures (35). The protective effect of education on cognitive function was evident (36), and

Table 2. Associations between cognitive function and covariates with tau_{MTL} for the whole sample

	CFIp		CFIsp		PACC		FCSRT		LMD		DSS		MMSE	
Variables	**Coefficients**	**FDR p-value**	**Coefficients**	**FDR p-value**	**Coefficients**	**FDR p-value**	**Coefficients**	**FDR p-value**	**Coefficients**	**FDR p-value**	**Coefficients**	**FDR p-value**	**Coefficients**	**FDR p-value**
(Intercept)	0.167	**<0.001**	0.129	**<0.001**	-0.238	**0.001**	-0.266	**<0.001**	0.031	0.708	-0.225	**0.004**	-0.167	**0.050**
Sex-female	-0.012	0.491	-0.043	**0.004**	0.414	**<0.001**	0.462	**<0.001**	-0.054	0.635	0.392	**<0.001**	0.290	**0.008**
Age (yrs)	0.008	0.366	0.005	0.563	-0.304	**<0.001**	-0.209	**<0.001**	-0.140	**0.008**	-0.283	**<0.001**	-0.171	**0.001**
Education (yrs)	-0.004	0.635	0.010	0.168	0.161	**0.001**	0.061	0.252	0.128	**0.016**	0.081	0.138	0.153	**0.004**
tau_{MTL}	0.024	**0.001**	0.023	**<0.001**	-0.224	**<0.001**	-0.210	**<0.001**	-0.220	**<0.001**	-0.061	0.252	-0.099	0.066
Alcohol	0.006	0.450	0.013	0.080	-0.093	0.061	-0.063	0.236	-0.085	0.127	-0.028	0.626	-0.067	0.236
Aerobic	0.000	0.957	0.000	0.957	-0.014	0.779	-0.034	0.552	-0.043	0.479	-0.002	0.957	0.042	0.481
STAI	0.010	0.246	0.004	0.635	0.082	0.132	0.034	0.564	0.072	0.236	0.036	0.563	0.074	0.235
GDS	0.047	**<0.001**	0.017	**0.030**	-0.099	0.061	-0.127	**0.017**	-0.084	0.159	-0.028	0.635	-0.023	0.705

Bold values indicate statistically significant results (p<0.05)
Associations were examined using multiple linear regression models adjusted for relevant covariates. Bonferroni correction was applied to account for multiple comparisons. Coefficients represent standardized beta estimates.
GDS: Geriatric Depression Scale (15 items), STAI: State Anxiety Inventory (6 items), CFI_p: Cognitive function index-participant, CFI_{sp}: Cognitive function index-study partner, PACC: Preclinical Alzheimer Cognitive Composite, MMSE: Mini-mental state examination, LMD: Logical Memory Delayed, DSS: Digit symbol substitution, FCSRT: Free and cued selective reminding test, SD: Standard deviation, tau_{NEO}: Tau SUVr in neocortex, tau_{MTL}: Tau SUVr in medial temporal lobe

Table 3. Associations between cognitive function and covariates with tauNEO for the whole sample

	CFI_p		CFI_{sp}		PACC		FCSRT		LMD		DSS		MMSE	
Variables	**Coefficients**	**FDR p-value**	**Coefficients**	**FDR p-value**	**Coefficients**	**FDR p-value**	**Coefficients**	**FDR p-value**	**Coefficients**	**FDR p-value**	**Coefficients**	**FDR p-value**	**Coefficients**	**FDR p-value**
(Intercept)	0.167	**<0.001**	0.131	**<0.001**	-0.248	**<0.001**	-0.265	**<0.001**	0.027	0.712	-0.235	**0.001**	-0.179	**0.013**
Sex - female	-0.014	0.326	-0.045	**0.001**	0.431	**<0.001**	0.461	**<0.001**	-0.047	0.635	0.408	**<0.001**	0.311	**0.001**
Age (yrs)	0.009	0.183	0.005	0.384	-0.315	**<0.001**	-0.227	**<0.001**	-0.154	**0.001**	-0.281	**<0.001**	-0.169	**<0.001**
Education (yrs)	-0.003	0.653	0.011	0.077	0.154	**<0.001**	0.052	0.245	0.121	**0.011**	0.081	0.074	0.152	**0.001**
tau_{NEO}	0.019	**0.004**	0.024	**<0.001**	-0.192	**<0.001**	-0.109	**0.015**	-0.150	**0.001**	-0.102	**0.022**	-0.145	**0.002**
Alcohol	0.006	0.371	0.012	**0.050**	-0.087	**0.041**	-0.057	0.201	-0.079	0.090	-0.027	0.545	-0.064	0.162
Aerobic	0.001	0.892	0.000	0.990	-0.018	0.671	-0.039	0.385	-0.047	0.311	-0.003	0.94	0.041	0.374
STAI	0.011	0.132	0.005	0.484	0.074	0.104	0.028	0.555	0.064	0.198	0.033	0.496	0.069	0.163
GDS	0.047	**<0.001**	0.016	**0.013**	-0.098	**0.031**	-0.126	**0.009**	-0.083	0.097	-0.027	0.568	-0.022	0.655

Bold values indicate statistically significant results (p<0.05)
GDS: Geriatric Depression Scale (15 items), STAI: State Anxiety Inventory (6 items), CFI_p: Cognitive function index-participant, CFI_{sp}: Cognitive function index-study partner, PACC: Preclinical Alzheimer Cognitive Composite, MMSE: Mini-mental state examination, LMD: Logical memory delayed, DSS: Digit symbol substitution, FCSRT: Free and cued selective reminding test, SD: Standard deviation, tau_{NEO}: Tau SUVr in neocortex, tau_{MTL}: Tau SUVr in medial temporal lobe

the sensitivity of PACC in detecting cognitive changes across multiple domains was underscored by its numerous significant associations (13). The intriguing finding that alcohol consumption was significantly associated with PACC and study-partner-reported CFI, but not with other cognitive measures, suggests that its impact on cognition might be more subtle and better perceived by external observers (14,24).

Our finding that tau_{MTL} deposition shows a robust, specific association with informant-reported functional decline (CFI study partner) more than with global cognitive screens like the MMSE carries significant clinical implications. First, it indicates that functional changes in daily life emerge as an early and sensitive consequence of pathology, potentially preceding detectable impairment on standard cognitive tests. This positions the study partner not as a secondary source but as a primary sensor of early disease impact, leveraging a continuous, real-world observational perspective and an 'external observer advantage' rooted in social perception. Second, the notable discrepancy we observed—where female participants demonstrated better objective test performance but partners reported greater functional concerns—suggests a critical early clinical phenomenon. This divergence may represent a prodromal or subclinical form of anosognosia (loss of self-awareness). Affected individuals may lose the subtle metacognitive ability to monitor their functional lapses in daily life, even while retaining the capacity to perform well on focused cognitive tests. The study-partner CFI therefore may capture the earliest behavioral signature of this evolving lack of insight, marking a key transition from preclinical pathology to prodromal clinical disease.

Among the cognitive tests used in this study, FCSRT, MMSE, DLM, and DSS did not show any association between alcohol consumption and cognitive performance, whereas the PACC and CFI revealed a key relationship between alcohol consumption and cognitive performance. This implies that alcohol's effects on cognitive function could be more intricate and less straightforward for outside observers to detect. The findings could mean that alcohol's effect is more pronounced in everyday functioning and social contexts, which are captured by the PACC and the CFI study partner. Additionally, the PACC is a composite measure specifically designed to detect subtle changes in cognitive functioning in the early stages of AD and other neurodegenerative conditions (37). It includes tests that assess episodic memory, processing speed, and executive function, all of which are cognitive domains that are highly susceptible to disruption by alcohol use, particularly with chronic or daily consumption (38). Alcohol affects these domains early in its use, impairing episodic memory (especially recall), attention, and executive function (including decision-making and processing speed) (38).

On the other hand, the CFI might place more emphasis on global cognitive scores or a broader range of domains. In contrast, alcohol's impact might be more pronounced in certain cognitive functions (such as episodic memory or executive function), which are better captured by measures such as PACC (14).

The MTL plays a crucial role in memory formation, particularly in episodic memory. The MTL is also highly sensitive to alcohol-related neurodegeneration, which can impair memory (39). Tau deposition in the neocortex (NEO), on the other hand, may reflect more widespread cognitive involvement that affects multiple cognitive domains (40). Alcohol may influence these broader functions in a more diffuse or complex manner. This could explain why tau deposition in the MTL was significantly associated with cognitive performance measures such as PACC, whereas tau in the NEO showed a less pronounced association. Study partners are often more attuned to subtle changes in mental functioning because they observe the participant in everyday settings and may notice memory lapses, impaired judgment, or slower processing speed that the participant might not report. As other studies have shown, the CFI study partner captures these external observations and may be more sensitive to the early effects of daily alcohol use because study partners may report cognitive changes that participants do not recognize (16,24). This might explain why alcohol was significant for the CFI study partner but not for the CFI participant.

Study Limitations

One limitation of this study is its cross-sectional design, which provides only a snapshot of cognitive function and tau deposition, thereby limiting the ability to establish causal relationships. The exact role of alcohol use was unclear, since the study evaluated it without explicitly measuring its effects on tau accumulation or CD. Because the sample was drawn from a secondary prevention study and included older individuals without cognitive impairment, it might not be representative of larger groups, particularly those with severe cognitive impairment or other medical issues. Although tau PET imaging helps identify tau accumulation, it cannot distinguish between tau associated with Alzheimer's disease and that related to other neurodegenerative diseases (20). Potential confounding factors, such as comorbidities, could not be accounted for in the analysis, which may lead to skewed results and limit the generalizability of the findings to populations with varying health conditions. Another limitation is its low ethnic diversity and high educational attainment. These limitations highlight the necessity for extended research involving a more diverse participant pool and comprehensive methodologies to assess tau accumulation, cognitive function, and lifestyle factors.

Despite these limitations, the use of high-fidelity PET imaging in a large, well-characterized cohort of clinically normal individuals provides powerful evidence for the role of regional tau. By incorporating both objective and informant-based metrics, this study captures a more holistic view of early CD than traditional clinical assessments alone provide.

Conclusion

Our study provides compelling evidence that regional tau pathology, particularly in the MTL, may represent an early neurobiological correlate of cognitive and functional decline in asymptomatic older adults. While traditional screening often relies on global cognitive tests or self-reports, our findings demonstrate a clear "informant advantage" whereby study partners are more sensitive to the early functional effects of tau pathology than participants themselves. This discrepancy suggests that subclinical anosognosia may be an early behavioral marker of preclinical AD (41). From a clinical perspective, these results underscore the need to move beyond global cognitive screens, such as the MMSE, in the initial work-up of older adults. Clinicians ought to prioritize informant-based functional assessments (e.g., the CFI study partner) in conjunction with regional tau-PET imaging to ascertain individuals at the highest risk for progression.

Furthermore, the significant association between depressive symptoms and cognitive performance suggests that mood assessments must be carefully integrated into the diagnostic process, as depression may mimic or exacerbate the earliest stages of neurodegeneration. These findings emphasize the need for longitudinal studies that track how the interplay between regional tau accumulation and modifiable lifestyle factors, such as alcohol use and education, influences the rate of decline. Shifting toward a multimodal assessment framework that incorporates biological markers, mood profiles, and external observations will be essential for developing the precision screening tools required for early intervention and targeted clinical trials.

Ethics

Ethics Committee Approval: This study was designed as a cross-sectional secondary analysis of the A4 study dataset. The analysis did not require additional Institutional Review Board (IRB) approval because it used previously collected and fully de-identified data from a study that had already received IRB approval. The dataset used in this analysis was fully de-identified and contained no direct or indirect personal identifiers. As the researchers had no interaction with human subjects and no access to identifiable private information, the study does not meet the regulatory definition of human subjects research. It is therefore exempt from additional IRB review.

Informed Consent: All individuals gave written informed consent before participating.

Footnotes

Authorship Contributions

Concept: I.D., Design: I.D., A.O., Data Collection or Processing: I.D., Analysis or Interpretation: I.D., A.O., Literature Search: I.D., A.O., Writing: I.D., A.O.

Conflict of interests: The authors declare that they have no conflict of interest related to this study.

Financial Disclosure: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data Availability: The data is freely available on https://ida.loni.usc.edu/login.jsp.

Supplementary Table Link: https://d2v96fxpocvxx.cloudfront.net/66b874bd-7aaa-4f61-9199-52f558d61c0d/content-images/b1e3c8ab-5e64-468e-919c-0b8bd6aac622.pdf

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Original Article

DOI: 10.4274/haseki.galenos.2026.30301
Med Bull Haseki 2026;64(3):165-169

Immunohistochemical Assessment of YAP1 Expression in Endometrial Hyperplasia with and without Atypia

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Abstract

Aim: Endometrial hyperplasia, particularly when accompanied by atypia, is considered a well-established precursor of endometrial carcinoma. Yes-associated protein 1 (YAP1), a key effector of the Hippo signaling pathway, plays a crucial role in the regulation of cell proliferation, apoptosis, and tissue homeostasis and has been implicated in tumorigenesis. The present study aimed to investigate whether YAP1 protein expression in endometrial hyperplasia with and without atypia differs from that in normal endometrial tissue.

Methods: This retrospective observational case-control study included 122 patients: 41 cases of endometrial hyperplasia with atypia, 41 cases of endometrial hyperplasia without atypia, and 40 controls with normal endometrial histology. Immunohistochemical analysis was performed on formalin-fixed, paraffin-embedded tissue sections using a YAP1 polyclonal antibody. Staining localization (nuclear and/or cytoplasmic), intensity, and distribution were evaluated semi-quantitatively. Statistical comparisons among the three groups were performed using parametric or nonparametric tests according to the distribution characteristics of the variables.

Results: No statistically significant differences were observed among the study groups in terms of YAP1 staining localization, intensity, or distribution. Both nuclear and cytoplasmic expression patterns were comparable in endometrial hyperplasia with and without atypia and in control tissues.

Conclusion: Yes-associated protein 1 protein expression did not differ significantly between precancerous endometrial lesions and normal endometrium. These findings suggest that YAP1 activation may represent a later molecular event in endometrial carcinogenesis rather than an early alteration during precursor stages. Further prospective studies integrating molecular and functional analyses are warranted to clarify the precise role of YAP1 in the progression from benign to malignant endometrial pathology.

Keywords: Endometrial hyperplasia, endometrial neoplasms, immunohistochemistry, hippo signaling pathway

Introduction

Endometrial hyperplasia (EH) comprises a heterogeneous spectrum of pathologic lesions ranging from mild glandular proliferation to direct precursors of endometrial carcinoma, with atypical forms conferring the highest risk of progression to endometrioid adenocarcinoma (1). EH is driven primarily by chronic exposure to unopposed estrogen, resulting in abnormal

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Received: 19.09.2025 **Accepted:** 26.02.2026 **Epub:** 31.03.2026 **Publication Date:** 01.06.2026

Cite this article as: Kinter AK, Oztekin O, Yalcın N, et al. Immunohistochemical assessment of YAP1 expression in endometrial hyperplasia with and without atypia. Med Bull Haseki. 2026;64(3):165-169

proliferation of endometrial glands relative to the stroma; risk factors include obesity, anovulation, estrogen-producing tumors, and exogenous estrogen exposure (2). The Hippo signaling pathway, a conserved regulator of tissue growth and organ size, controls cellular proliferation and apoptosis and has been increasingly recognized for its role in tumorigenesis across multiple organ systems (3). Yes-associated protein 1 (YAP1), a core downstream effector of the Hippo pathway, acts as a transcriptional co-activator that promotes proliferation and inhibits apoptosis when it is translocated to the nucleus; aberrant YAP1 activity has been implicated in various cancers, including endometrial carcinoma (3). In endometrial cancer, dysregulated Hippo signaling and increased nuclear YAP/TAZ activity correlate with tumor progression, poor prognosis, and resistance to therapy, suggesting a functional role in malignant transformation (3). Nevertheless, existing evidence concerning YAP1 expression in precancerous endometrial lesions is scarce, with the majority of studies predominantly concentrating on endometrial carcinoma rather than hyperplasia subtypes (4).

We hypothesized that YAP1 expression patterns differ between normal endometrium and subtypes of endometrial hyperplasia, particularly in the presence of atypia, reflecting its potential involvement in early endometrial carcinogenesis. Therefore, the present study aimed to evaluate the immunohistochemical expression of YAP1 in endometrial hyperplasia with atypia, endometrial hyperplasia without atypia, and normal endometrial tissue. By elucidating whether YAP1 expression changes at the precancerous stage, this study seeks to clarify the temporal role of Hippo-YAP signaling in the continuum from benign proliferation to malignancy, potentially identifying a biomarker for early detection or risk stratification. The findings may help determine whether YAP1 represents an early biomarker of malignant transformation or a molecular event occurring later in the progression toward endometrial cancer, thereby providing clinically relevant insight for future diagnostic or therapeutic strategies.

Materials and Methods

Compliance with Ethical Standards

This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki. Ethical approval was obtained from the Pamukkale University Local Ethics Committee (approval number: 12, date: 19.10.2017). Written informed consent was obtained from all participants prior to enrollment. All clinical data were anonymized to ensure patient confidentiality.

Study Design

This study was designed as a retrospective, observational, case-control study conducted at a tertiary gynecologic oncology center. The study population consisted of three distinct groups: patients with endometrial hyperplasia with atypia, patients with endometrial hyperplasia without atypia, and a control group of individuals with normal endometrial histology. The study included 122 patients: 41 with endometrial hyperplasia with atypia, 41 with endometrial hyperplasia without atypia, and 40 control subjects. Clinical records, ultrasonographic findings, and histopathological reports were retrospectively reviewed. All pathological diagnoses were re-evaluated and confirmed prior to immunohistochemical analysis.

Patients histopathologically diagnosed with endometrial hyperplasia, with or without atypia, following endometrial biopsy or hysterectomy were eligible for inclusion. The control group consisted of patients who underwent endometrial sampling for abnormal uterine bleeding and who demonstrated normal endometrial histology. Patients with a current or previous diagnosis of malignancy, systemic inflammatory or metabolic disorders (including hypertension, diabetes mellitus, and thyroid disease), active infections, or prior hormonal or systemic drug use were excluded. Cases with inadequate tissue samples or suboptimal fixation were also excluded. Formalin-fixed, paraffin-embedded tissue blocks were sectioned at a thickness of 3 µm and mounted on electrostatically charged slides. All staining procedures, including deparaffinization, antigen retrieval, and immunostaining, were performed using a fully automated immunohistochemistry system (Ventana BenchMark LT, Roche Diagnostics, Tucson, AZ, USA).

Immunohistochemical staining was carried out using a polyclonal anti-YAP1 antibody according to the manufacturer's protocol. Positive staining was defined as brown granular staining observed in the cytoplasm and/or nucleus of endometrial epithelial cells. Staining distribution and intensity were evaluated independently by a single experienced pathologist who was blinded to clinical data. Staining intensity was semiquantitatively graded as weak (+), moderate (++), or strong (+++) (Figures 1a, 1b, and 1c). The percentage of positively stained cells was categorized as <50%, 50-79%, or 80-100% (Figures 2a, 2b, and 2c).

Statistical Analysis

Statistical analyses were performed using SPSS software version 20.0 (IBM Corp., Armonk, NY, USA). The normality of continuous variables was evaluated using the Shapiro-Wilk test and visual inspection of histograms. Continuous variables were presented as mean ± standard deviation for normally distributed data or as median (interquartile range) for non-normally distributed data. Categorical variables were expressed as frequencies and percentages. The Kruskal-Wallis test was used for non-normally distributed continuous variables, while one-way analysis

of variance (ANOVA) was applied for normally distributed variables. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. All tests were two-tailed, and a p-value <0.05 was considered statistically significant.

Results

A total of 122 patients were included in the study: 41 with endometrial hyperplasia without atypia, 41 with endometrial hyperplasia with atypia, and 40 control subjects.

Baseline demographic and clinical characteristics of the study groups were comparable, with no significant differences in age or clinical indications for endometrial sampling. The distributions of nuclear and cytoplasmic YAP1 staining patterns were comparable across the three groups, with no statistically significant differences observed. Immunohistochemical evaluation demonstrated that both cytoplasmic and combined nuclear-cytoplasmic staining patterns were similarly distributed across endometrial hyperplasia with atypia, endometrial hyperplasia without atypia, and control tissues. Comparative analysis revealed no significant differences in staining localization among the groups.

Similarly, semi-quantitative assessment of staining intensity showed comparable proportions of weak, moderate, and strong YAP1 expression across all study cohorts, with no statistically significant differences between groups. The distribution of staining percentages (<50%, 50-79%, and 80-100%) also did not differ significantly between groups.

Overall, YAP1 expression patterns did not differ significantly between precancerous endometrial lesions and normal endometrial tissue. Detailed quantitative results are presented in Table 1.

Discussion

We investigated the immunohistochemical expression patterns of YAP1 in endometrial hyperplasia with and without atypia and in normal endometrial tissue. Our results demonstrated that YAP1 expression, evaluated in terms of localization, staining intensity, and distribution, did not differ significantly among the three groups. These findings suggest that YAP1 protein expression is not altered at the stage of endometrial hyperplasia, regardless of the presence of atypia.

Recent evidence increasingly supports the involvement of YAP1 signaling in endometrial pathophysiology. Yu et al. (4) conducted a prospective immunohistochemical study in China, including 35 patients with endometrial polyps and 35 healthy controls, and demonstrated significantly increased nuclear YAP1 expression in hyperproliferative endometrial tissue compared with normal endometrium. Their study highlighted that YAP1 activation is associated with progesterone resistance and excessive cellular proliferation, consistent with our observation of elevated

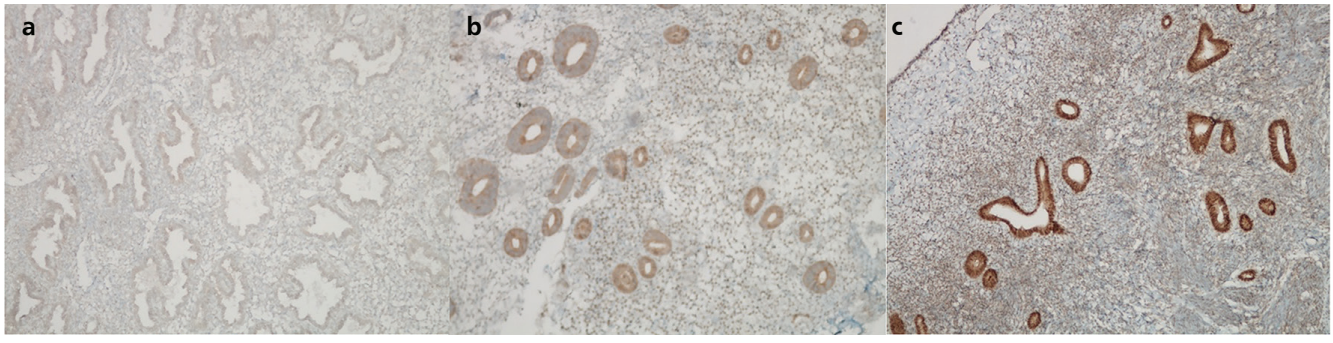

Figure 1. a. Weak staining intensity, **b.** Moderate staining intensity , **c.** Strong staining intensity

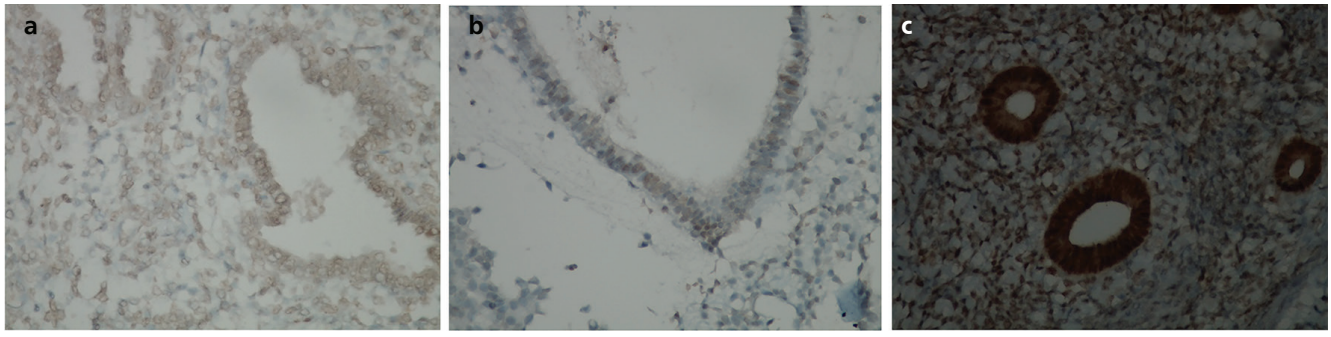

Figure 2. a. Cytoplasmic staining, **b.** Nuclear staining, **c.** Nuclear and cytoplasmic staining

YAP1 expression in endometrial hyperplasia. Importantly, while Yu et al. (4) focused on endometrial polyps, our study extends these findings to endometrial hyperplasia, a recognized precursor lesion of endometrial carcinoma, thereby expanding the clinical relevance of YAP1 dysregulation (4).

Similarly, Lin et al. (5) investigated the molecular mechanisms underlying progesterone resistance in endometriosis by analyzing human tissue samples (n=42) and an in vivo mouse model. Their work revealed that YAP1 overexpression suppresses progesterone receptor expression through upregulation of miR-21-5p, leading to impaired decidualization and sustained cellular proliferation. Although the study was conducted in the context of endometriosis, these findings strongly support our results, suggesting that YAP1-mediated progesterone resistance may represent a common pathogenic mechanism across various endometrial proliferative disorders, including endometrial hyperplasia (5).

Using a mechanistic animal model, Zhou et al. (6) investigated the role of YAP1 in bovine endometrial epithelial cells and demonstrated that upregulation of YAP1 significantly enhanced epithelial proliferation, migration, and invasion, whereas its knockdown reversed these effects. Their experimental findings provide strong biological plausibility for our clinical observations, reinforcing the role of YAP1 as a central regulator of endometrial epithelial growth. Unlike our human-based retrospective design, their controlled in vitro and in vivo approach provides mechanistic insight, complementing our translational findings (6).

Further supporting evidence comes from transcriptomic analyses by Chen et al. (7), who, using a rat model of intrauterine adhesions, demonstrated that YAP-Smad7 signaling modulates fibrotic remodeling in endometrial tissue. Their findings underscore the regulatory capacity of YAP1 across a broad spectrum of endometrial pathologies, including fibrosis, hyperplasia, and neoplastic transformation. While their focus was on fibrosis rather than hyperplasia, both studies highlight YAP1 as a critical molecular hub governing abnormal endometrial tissue remodeling (7).

From an oncologic perspective, multiple large-scale studies have demonstrated that YAP1 overexpression correlates with tumor aggressiveness, increased proliferative index, and unfavorable prognosis across diverse malignancies. Marx et al. (8) analyzed over 17,000 prostate cancer specimens and identified high YAP1 expression as an independent predictor of early biochemical recurrence and poor clinical outcome. Although these studies were performed in prostate cancer, their results emphasize the universal oncogenic potential of YAP1-driven signaling pathways, supporting the concept that sustained YAP1 activation in endometrial hyperplasia may represent an early oncogenic event (8).

Collectively, these studies highlight YAP1 as a critical molecular determinant of abnormal endometrial proliferation and tumorigenesis. However, in contrast to reports demonstrating increased YAP1 activity in hyperproliferative or malignant endometrial conditions, our findings did not reveal a significant difference in YAP1 expression between endometrial hyperplasia (with or without atypia) and normal endometrium. This discrepancy may suggest that YAP1 activation represents a later molecular event in the progression toward endometrial carcinoma rather than an early alteration occurring at the hyperplasia stage. Our study, therefore, contributes important clinical data indicating that YAP1 overexpression may not be a distinguishing feature of precancerous endometrial lesions.

Table 1. Comparison of groups in terms of staining status, staining density, and percentage of staining

	Endometrial hyperplasia without atypia (n=41)	EIN (n=41)	Normal endometrium (n=40)	p
Staining status Nuclear Cytoplasmic Nuclear and cytoplasmic	 0 (0%) 21 (51.2%) 20 (48.8%)	 1 (2.4%) 21 (51.2%) 19 (46.3%)	 0 (0%) 20 (50%) 20 (50%)	0.87
Staining density Weak Moderate Strong	 12 (29.3%) 24 (58.5%) 5 (12.2%)	 14 (34.1%) 19 (46.3%) 8 (19.5%)	 9 (22.5%) 26 (65%) 5 (12.5%)	0.61
Percentage of staining <50% 50-79% 80-100%	 7 (17.1%) 2 (4.9%) 32 (78.0%)	 3 (7.3%) 3 (7.3%) 35 (85.4%)	 3 (7.5%) 2 (5.0%) 35 (87.5%)	0.53

Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate. A p-value <0.05 was considered statistically significant
EIN: Endometrial intraepithelial neoplasia

Study Limitations

This study has several limitations. First, it was conducted retrospectively at a single center, which may limit the generalizability of the findings. Second, the sample size, although calculated to achieve sufficient statistical power, may still be insufficient to detect subtle differences in YAP1 expression among subgroups. Third, a single pathologist performed the immunohistochemical evaluation, which may have introduced observer bias. Lastly, molecular analyses, such as mRNA or protein quantification, were not performed, which could have provided additional insight into YAP1 expression dynamics. In addition to these factors, technical issues inherent to immunohistochemical analysis may have influenced the results. Variations in antibody specificity, antigen retrieval procedures, or fixation time can alter staining intensity and sensitivity. Although a standardized automated staining protocol was used, pre-analytical variability cannot be entirely excluded. An additional limitation of this study is the absence of comprehensive data on hormonal status, menopausal condition, and exogenous hormone exposure, preventing analysis of their potential impact on YAP1 expression patterns. All these factors might have contributed to the absence of statistically significant differences in YAP1 expression between study groups.

Despite these limitations, our study benefits from strict histopathological confirmation, standardized immunohistochemical evaluation, and well-defined patient selection criteria, thereby strengthening the reliability of our findings. Moreover, the relatively homogeneous patient population minimizes confounding and enhances internal validity.

Conclusion

Overexpression of the YAP1 protein, which has been recognized as an important factor in cancer pathogenesis, was not observed in endometrial hyperplasia, with or without atypia, compared with normal endometrial tissue. This suggests that YAP1 activation may occur later in malignant transformation than in precursor lesions. Despite the lack of differential expression, the present study provides valuable preliminary data on early molecular events in endometrial carcinogenesis. The results emphasize the potential role of YAP1 and the Hippo signaling pathway as promising molecular targets for future diagnostic and therapeutic research. Further prospective, multicenter studies integrating hormonal and molecular analyses are warranted to clarify the role of YAP1 in the transition from benign to malignant endometrial pathology.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Pamukkale University Local Ethics Committee (approval number: 12, date: 19.10.2017).

Informed Consent: Written informed consent was obtained from all participants prior to enrollment.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.K.K., N.Y., Concept: A.K.K., O.O., Design: A.K.K., O.O., Data Collection or Processing: A.K.K., R.S., A.K., Analysis or Interpretation: A.K.K., S.O., A.K., Literature Search: A.K.K., G.T., Writing: A.K.K., G.T.

Conflict of interests: No conflict of interest was declared by the authors.

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

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Original Article

DOI: 10.4274/haseki.galenos.2026.06977
Med Bull Haseki 2026;64(3):170-175

Effect of Wet Cupping Therapy on Cardiac Autonomic Function Assessed by 24-hour Holter Monitoring in Healthy Individuals

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Abstract

Aim: Despite increasing interest in wet cupping therapy (WCT), its effects on cardiac autonomic regulation have not been sufficiently investigated. In this context, we aimed to investigate whether WCT affects cardiac autonomic function in healthy individuals.

Methods: This study was designed as a prospective single-arm interventional pre-post study in which 24-hour rhythm Holter (RH) recordings were obtained before and after WCT between August 2, 2022, and December 31, 2022. Time-domain measures were used to assess heart rate variability (HRV). 50 healthy volunteers were included in the study. Before the WCT, nurses in the cardiology outpatient clinic Holter room attached 24-hour RHs to the participants; the RHs were removed after 24 hours, before the WCT was applied in the traditional and complementary medicine department. After the WCT procedure, the 24-hour RH was immediately reattached to the healthy participants in the Holter room and removed 24 hours later.

Results: No statistical difference was found between the two groups in the following parameters: standard deviation of NN intervals (SDNN) [95% Confidence interval (CI): -8.912-5.434, t=-0.487, p=0.628], SDANN (95% CI: -9.515-4.776, t=-0.666, p=0.508), SDNN index (95% CI: -2.815-2.245, t=-0.226, p=0.822), SDSD (z=-1.238, p=0.216), NN50 (z=-1.725, p=0.085), RMSSD (z=-1.048, p=0.295), pNN50 (z=-0.104, p=0.917) and triangular index (z=-1.355, p=0.176).

Conclusion: To the best of our knowledge, studies evaluating HRV parameters using 24-hour Holter monitoring before and after WCT are limited. When HRV parameters were compared before and after WCT, no statistically significant differences were observed between the two groups. More studies are needed with a larger number of healthy volunteers and with repeated WCT procedures.

Keywords: Heart rate variability, cupping therapy, autonomic nervous system, holter monitoring, complementary therapies

Introduction

Cupping therapy (CT) is one of the oldest traditional medicine practices, with a history spanning thousands of years (1). Although it is applied using different methods across cultures, the essence of CT is the idea of purification and activation of energy. The most common classification of cupping distinguishes procedures in which an incision is made [wet CT, or wet cupping therapy (WCT)] from those in which it is not (dry CT). In the dry cup application, no blood is taken from the body. When the cup is applied, the air inside the cup is evacuated and the skin swells due to negative pressure. WCT starts like the dry cup application, but superficial incisions are made on the skin to drain the blood from the skin in the area where the application is made (2). The autonomic nervous system consists of sympathetic and parasympathetic components that regulate body functions. Dysfunction in sympathetic and

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Received: 19.06.2025 **Accepted:** 09.03.2026 **Epub:** 31.03.2026 **Publication Date:** 01.06.2026

Cite this article as: Aydin G, Ciftci MM. Effect of wet cupping therapy on cardiac autonomic function assessed by 24-hour holter monitoring in healthy ınıdıvıduals. Med Bull Haseki. 2026;64(3):170-175

parasympathetic components can lead to cardiovascular disease. Heart rate variability (HRV) has evolved as a non-invasive indicator of cardiac autonomic modulation (3). According to cutivisceral reflex theory, the heart segment is defined as between the first and fifth thoracic vertebrae (4).

In traditional Chinese medicine, the body possesses energy channels called meridians that belong to the organs and these channels have acupuncture points with various features (5). In traditional Chinese medicine, GV-14, bilateral BL-15, and bilateral BL-18 points are associated with the heart. (6,7). While circadian rhythms triggered by sunlight in humans are well-defined, fewer clinical studies have been conducted on the effects of lunar gravity and light. In some traditional practices, the timing of WCT may align with specific lunar calendar days; however, the physiological significance of this practice is unclear. This view holds that the human body is subject to the Moon's gravitational effect, as liquids on Earth rise due to this effect during the full-moon phase. In prophetic traditions, WCT is recommended to be performed on the 17th, 19th, or 21st days of the lunar month, which coincide with peak gravitational influence during the full moon (8).

In this study, WCT application points were determined by considering segmental CT and mechanisms of traditional Chinese medicine. Wet cupping therapy practice was performed on the 17th, 19th, and 21st days of the lunar months. Nurses attached 24-hour rhythm Holter (RHs) to the participants; the RHs were removed after 24 hours and before WCT was applied in the traditional and complementary medicine departments. After the WCT procedure, 24-hour RH was immediately reattached to the participants in the Holter room and was again removed. We hypothesized, according to the cutivisceral reflex theory, that stimulating the heart meridians results in positive changes in HRV parameters.

Therefore, the present study aimed to evaluate the effect of WCT on cardiac autonomic regulation by comparing HRV parameters obtained from 24-hour Holter recordings before and after the intervention in healthy individuals. This will help determine whether WCT, which is commonly used in daily practice, affects cardiac autonomic function.

Materials and Methods

Compliance with Ethical Standards

Approval was obtained from the University of Health Sciences Türkiye, Sultan Abdulhamid II Educational and Research Hospital Traditional and Complementary Medicine Clinical Research Ethics Committee (approval number: SBUSAH-GETAT 2022- 024, date: 25.02.2022). The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from the patients who agreed to take part in the study.

Study Design and Patient Selection

This study was designed as a prospective single-arm interventional pre–post study between August 2, 2022, and December 31, 2022. The 50 consecutive healthy participants over the age of 18 who presented to the hospital for WCT were included in the study.

The basic demographic characteristics and examination results of the participants were recorded. Individuals with active diseases at the time of application (e.g., acute tonsillitis, acute sinusitis, pneumonia, coronavirus disease-19, acute urinary tract infection, acute renal failure, acute liver failure, active cancer, acute decompensated heart failure, or acute coronary syndrome) were excluded. Participants with chronic anemia [women with hemoglobin (Hb) <11 g/dL and men with Hb <12 g/dL), bleeding diathesis, antithrombotic or antiaggregant therapy, platelet counts <50,000 × 10^3/μL, or concomitant chronic diseases (including chronic coronary syndrome, diabetes mellitus, hyperlipidemia, chronic liver failure, hypertension, chronic renal failure, psoriasis, chronic heart failure, and rheumatological diseases such as familial Mediterranean fever) were also excluded. Individuals who had received WCT within the past three months, those menstruating women, and pregnant women were additionally excluded. Participants were asked to restrict caffeine intake and physical activity before and after WCT.

Prior to WCT, all participants underwent blood tests conducted by the biochemistry laboratory. The laboratory findings were recorded in the standard electronic medical records at the same hospital. All participants were also evaluated at the cardiology outpatient clinic of the same hospital one day before the WCT. A 12-lead surface electrocardiogram (ECG) was performed at rest by nurses in the cardiology outpatient clinic. Transthoracic echocardiographic examinations in the left lateral recumbent position were performed using the ultrasound imaging system. The flowchart of the study is shown in Figure 1.

WCT Application and RH Monitoring

Wet cupping therapy sessions last approximately 20 minutes. Various cup materials, such as bamboo, glass, and plastic, can be used in practice. Disposable plastic cups were used in the study. In our patients, the area to be treated was first cleaned with a disinfectant, and then a dry cup was applied for 5 minutes. The cup was then removed, and superficial (0.2-0.5 millimeter) incisions were made in the skin with a number 15 scalpel. The cup

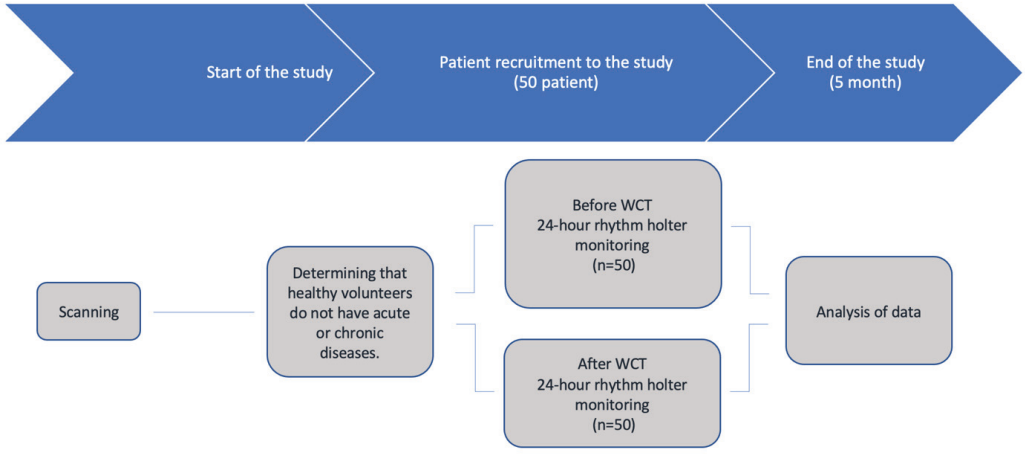

Figure 1. Flow chart of the study
WCT: Wet cupping therapy

was then reapplied to the incision site. After 10 minutes of blood collection, the application area was cleaned and dressed.

Before the WCT, nurses in the cardiology outpatient clinic Holter room attached 24-hour RHs to the participants; the RHs were removed after 24 hours, and the WCT was subsequently applied in the traditional and complementary medicine department. After the WCT procedure, 24-hour RH was again attached immediately to the healthy participants in the Holter room and again removed 24 hours later. The Holter recordings were analyzed using ABP analysis software (version 2.00.001, P1). Time-domain measures were used to measure the following HRV parameters: standard deviation of NN intervals (SDNN), standard deviation of the average NN intervals for each 5 min segment of a 24 h HRV recording (SDANN), mean of the standard deviations of all the NN intervals for each 5 min segment of a 24 h HRV recording (SDNN index), standard deviation of the differences between successive NN intervals (SDSD), number of pairs of successive NN intervals that differed by more than 50 ms (NN50), root mean square of successive NN interval differences (RMSSD), percentage of successive NN intervals that differed by more than 50 ms (pNN50) and integral of the density of the NN interval histogram divided by its height (triangular index).

The primary endpoint was the change in HRV parameters measured by 24-hour Holter monitoring before and after WCT.

Statistical Analysis

Statistical analyses were performed using SPSS software (version 26.0, SPSS Inc., Chicago, IL, USA). The normality of data distribution was assessed using the Kolmogorov-Smirnov test. Continuous variables were presented as mean ± standard deviation or median (interquartile range) as appropriate, while categorical variables were expressed as numbers and percentages. Comparisons between measurements obtained before and after wet CT were performed using the paired t-test for normally distributed variables and the Wilcoxon signed-rank test for non-normally distributed variables. Bonferroni correction was applied to adjust for multiple comparisons. A two-tailed p-value <0.05 was considered statistically significant.

Results

In this study, we consecutively enrolled 50 healthy volunteers who presented to our hospital for WCT. Of the participants, 25 (50%) were women and 25 (50%) were men. The mean age was 43.46 (10.93) years. The participants' basic clinical characteristics, including age, gender, and laboratory findings, are listed in Table 1. Impaired fasting plasma glucose is used when fasting plasma glucose is between 106 and 126 mg/dL. Impaired fasting plasma glucose was detected in 5 (10%) of the healthy participants. Hyperlipidemia was detected in 29 participants (58%). Lifestyle changes, diet, and exercise were recommended to the participants with impaired fasting glucose and hyperlipidemia. Neither deep vein thrombosis nor pulmonary embolism was detected in any participant. No abnormal findings were observed in the other laboratory tests.

The mean resting heart rate was 70.26 (8.91) beats per minute, and all participants had a normal sinus rhythm. Sinus bradycardia was detected in 5 (10%) of the participants, and a premature atrial complex was found on the resting ECG of 1 (2%) participant.

Data from the 24-hour RH monitoring before and after WCT are shown in Table 2. Comparison of HRV

Table 1. The demographic and laboratory findings of the patients		
Parameters	**Results**	**Normal range**
Gender (female/male) n (%)	25/25 (50/50)	
Age (years) mean ± SD	43.46 (10.93)	
Fasting plasma glucose (mg/dL) mean ± SD	92.06 (13.25)	74-106
Glomerular filtration rate (mL/min/1.73 m2) mean ± SD	105.76 (15.35)	-
Alanine aminotransferase (U/L) median (IQR)	19.00 (13.75-26.00)	0-50
Aspartate transaminase (U/L) median (IQR)	19.00 (16.00-23.00)	0-50
Triglyceride (mg/dL) median (IQR)	112.00 (84.75-168.00)	<150
Total cholesterol (mg/dL) mean ± SD	197.22 (43.59)	<200
High density lipoprotein (mg/dL) mean ± SD	48.38 (10.94)	>50
Low density lipoprotein (mg/dL) mean ± SD	118.92 (37.24)	<130
C reactive protein (mg/L) median (IQR)	2.40 (2.00-3.95)	0-5
Calcium (mg/dL) mean ± SD	9.41 (0.44)	8.8-10.60
Magnesium (mg/dL) median (IQR)	2.00 (1.81-2.10)	1.8-2.60
Sodium (mmol/L) mean ± SD	138.46 (2.01)	135-148
Potassium (mmol/L) mean ± SD	4.27 (0.31)	3.5-5.10
Thyroid stimulating hormone (mIU/L) median (IQR)	1.48 (0.95-2.07)	0.35-4.94
Thyroxine (T4) (ng/dL) mean ± SD	0.95 (0.10)	0.70-1.48
White blood cell count (10^3/mL) mean ± SD	7.04 (1.49)	3.98-10.04
Hemoglobin (g/dL) mean ± SD	14.20 (1.67)	11.7-16.00
Hematocrit (%) mean ± SD	41.14 (4.27)	38-50
Platelet (10^3/µl) mean ± SD	243.32 (46.05)	150-360
Cardiac troponin I (ng/L) median (IQR)	1.00 (1.00-1.00)	0-34
D-dimer (ug/mL) median (IQR)	0.27 (0.27-0.33)	0-0.5
Pro BNP (pg/mL) median (IQR)	10.10 (10.00-16.70)	0-100

IQR: Inter quantile range, n: Number, SD: Standard deviation, mg/dL: Milligram/deciliter, mmol/L: Millimole/liter, IU/mL: Micro international unit/milliliter, g/mL: Microgram/ milliliter, L: Microliter, mg/L: Milligram/liter, pg/mL: Picogram/ milliliter, ng/L: Nanogram/liter, U/L: Unit/liter, Pro BNP: Pro B type natriuretic peptid

parameters before and after WCT revealed no statistically significant differences between the two groups in terms of SDNN [95% confidence interval (CI): -8.912-5.434, t=-0.48, p=0.628], SDANN (95% CI: -9.515-4.776, t=-0.666, p=0.508), SDNN index (95% CI: -2.815-2.245, t=-0.226, p=0.822), SDSD (z=-1.238, p=0.216), NN50 (z=-1.725, p=0.085), RMSSD (z=-1.048, p=0.295), pNN50 (z=-0.104, p=0.917) or triangular index (z=-1.355, p=0.176). When the other 24-hour RH parameters were compared, there were no statistically significant differences between the two groups in average heart rate (95% CI: -1.806-1.886, t=0.044, p=.965), minimum heart rate (z=-0.453, p=.651), or maximum heart rate (z=-1.826, p=.068) (Table 2).

Discussion

In this prospective pre–post study including 50 healthy volunteers, HRV parameters obtained from 24-hour Holter recordings were compared before and after WCT. The results demonstrated no statistically significant changes in HRV indices or other Holter-derived cardiac parameters following the intervention.

Several studies have examined the benefits of WCT. For example, in a pilot study, post-exercise WCT was applied to martial arts athletes. After WCT, the inflammatory markers (e.g., interleukin-6 and -tumor necrosis factor) were found to be significantly reduced. It has been argued that taking WCT immediately after exercise can alleviate the inflammatory response to exercise in martial arts athletes (9). It has also been reported that WCT can increase endogenous NO production; NO acts as a vasodilator. Thus, enlarged blood vessels will provide better delivery of nutrients and oxygen to the muscles. Therefore, it can contribute to improving physical performance (10). A randomized controlled study compared WCT with acupuncture in patients with migraine. migraine disability assessment scale and visual analog scale pain scores decreased significantly in both treatment groups after WCT, while they remained at similar levels in the control

Table 2. Comparison of heart rate variability and other 24-hour holter parameters before and after WCT			
Variables	**Before wet cupping**	**After wet cupping**	**p-value**
*SDNN ms mean ± SD	144.44 (34.84)	146.18 (37.31)	0.628
*SDSD ms median (IQR)	33.21 (26.12-48.47)	33.20 (25.13-47.94)	0.216
*SDANN ms mean ± SD	129.95 (35.11)	132.31(36.89)	0.508
*NN50 median (IQR)	8351.00 (4122.75-15024.00)	7936.00 (3840.00-14342.50)	0.085
*RMSSD ms median (IQR)	32.46 (26.12-46.02)	33.20 (25.13-47.94)	0.295
*pNN50 median (IQR)	8.55 (4.28-16.65)	9.65 (4.05-16.78)	0.917
*SDNN index mean ± SD	62.17 (16.12)	62.45 (16.53)	0.822
*Triangular index median (IQR)	19.18 (17.60-25.04)	19.78 (16.64-24.03)	0.176
*Average heart rate (bpm) mean ± SD	74.90 (5.84)	74.86 (6.26)	0.965
*Minimum heart rate (bpm) median (IQR)	50.00 (40.00-55.00)	50.00 (38.00-53.00)	0.651
*Maximum heart rate (bpm) median (IQR)	130.00 (108.00-141.75)	135.00 (112.00-148.75)	0.068

*Significance values have been adjusted by the Bonferroni correction for multiple tests
IQR: Inter quantile range, n: Number, SD: Standard deviation, SDNN: Standard deviation of NN intervals, SDSD: Standard deviation of the differences between succesive NN intervals, SDANN: Standard deviation of the average NN intervals for each 5 min segment of a 24 h HRV recording, SDNN index: Mean of the standard deviations of all the NN intervals for each 5 min segment of a 24 h HRV recording, pNN50: Percentage of successive RR intervals that differ by more than 50 ms, RMSSD: Root mean square of successive RR interval differences, Triangular index: Integral of the density of the RR interval histogram divided by its height

group over the same period (11). A systematic review was conducted to investigate the effect of CT on metabolic outcomes (blood sugar, blood pressure, and lipid profiles) in women. The results of this study showed that CT had a positive effect on various metabolic parameters. Significant correlations were observed between CT and improvements in blood pressure, blood sugar levels, and lipid profiles (12).

We found studies examining the effect of WCT on cardiac autonomic function. Arslan et al. (13) conducted a study that applied WCT to 40 healthy participants (13). They recorded ECGs one hour before and one hour after WCT, and found that WCT corrected sympathovagal imbalances by stimulating the peripheral nervous system. The number of patients in our study was higher, and our Holter wearing time was longer than in their study. Contrary to their findings, our study found no increase in HRV parameters after WCT. This difference may be due to the fact that the effect of WCT is greatest immediately after application and decreases over time. During WCT, the heart meridians are stimulated for approximately 15 minutes. WCT stimulates the peripheral nervous system by acting on the sympathovagal system. This effect disappears when the stimulation is removed. During WCT, a small amount of blood is removed from the body. To investigate whether this has long-term effects on the sympathovagal system, we administered RH for 24 hours.

Çelik et al. (14) investigated the effect of WCT on ventricular repolarization in 120 participants (14). Electrocardiogram strips were recorded from each participant one hour before and one hour after WCT. They found no statistically significant change in the average heart rate, QT interval, or QTc interval before and after the procedure. Similarly, in our study, no statistically significant difference was observed in the mean heart rate before and after the procedure in 24-hour RH recordings.

Study Limitations

This study has several limitations. First, it was conducted at a single center with a relatively small sample size. Second, only a single session of WCT was performed; therefore, potential effects of repeated or longer-term applications may not have been fully captured in the 24-hour rhythm Holter recordings. Investigating the cumulative effects of WCT would require multiple treatment sessions. However, participation in this study required volunteers to commit approximately 48 hours and attend the hospital for prolonged monitoring, which posed practical challenges. Because the participants were healthy adults who were mostly actively employed, obtaining time away from work made recruitment for repeated WCT sessions difficult. In addition, the Holter device used in this study did not allow frequency-domain HRV analysis. Finally, the absence of a control group limits the ability to draw causal inferences from the observed findings. Despite these limitations, this study contributes valuable data to the limited literature evaluating HRV parameters before and after the WCT procedure.

Conclusion

In this study, cardiac autonomic function was evaluated using 24-hour rhythm Holter recordings before and after WCT. No significant changes were observed in

HRV parameters following the intervention. Future studies with larger populations and repeated WCT sessions are warranted to further elucidate the potential effects of WCT on cardiac autonomic regulation.

Ethics

Ethics Committee Approval: Approval was obtained from the Sultan Abdulhamid II Educational and Research Hospital Traditional and Complementary Medicine Clinical Research Ethics Committee (approval number: SBUSAH-GETAT 2022- 024, date: 25.02.2022).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Acknowledgment

We would like to express our endless gratitude to Professor Ebru Golcuk, who contributed to the completion of the article.

Footnotes

Authorship Contributions

Surgical and Medical Practices: G.A., M.M.C., Concept: G.A., M.M.C., Design: G.A., M.M.C., Data Collection or Processing: G.A., M.M.C., Analysis or Interpretation: G.A., M.M.C., Literature Search: G.A., M.M.C., Writing: G.A., M.M.C.

Conflict of interests: No conflict of interest was declared by the authors.

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

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Original Article

DOI: 10.4274/haseki.galenos.2026.72692
Med Bull Haseki 2026;64(3):176-185

Side Effects and Treatment Discontinuation in Women Receiving Oral Iron Therapy: A Cross-Sectional Study

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Abstract

Aim: Iron deficiency anemia remains a common global health problem, particularly affecting women owing to reproductive and nutritional factors. This study aims to assess the use of iron preparations, their side-effect profiles, and their impact on treatment adherence among women in Türkiye.

Methods: This study was designed as a cross-sectional analytical study between October 1 and November 30, 2023. A total of 270 female patients receiving iron replacement therapy for at least one month were included in the study. A structured 20-item questionnaire was used to collect data on demographic characteristics, iron preparations, side effects, and treatment adherence. Data were analyzed using descriptive statistics, chi-square tests, t-tests, and binary logistic regression to identify predictors of treatment discontinuation.

Results: Nausea was the most frequently reported cause of medication discontinuation (84.0%) and of switching (73.4%). Iron (III) polymaltose complex was associated with the highest rates of side effects (55.6% reported dyspeptic complaints) and treatment discontinuation (88.9%). The tablet formulation substantially increased the risk of treatment discontinuation by approximately ninefold overall and by about 5.6 fold due to side effects. Each additional year of age increased the odds of discontinuation by 10.4% (odds ratio 1.104; 95% confidence interval 1.062-1.146; p<0.001). Non pregnant women experienced higher rates of side effects, treatment discontinuation (47.2% vs. 30.9%), and medication changes (38.9% vs. 25.3%) than pregnant women (p=0,007; p=0.018).

Conclusion: These findings support the need for personalized treatment strategies that consider factors such as age, pregnancy status, and formulation type to improve adherence and minimize treatment discontinuation.

Keywords: Anemia, iron-deficiency, iron, medication adherence, pregnancy, treatment outcome

Introduction

Iron deficiency anemia (IDA) affects more than 1.2 billion people worldwide (1). Due to factors such as pregnancy and related conditions, menstrual blood loss, insufficient dietary intake, and nutritional imbalance, women are at particularly high risk (2). During pregnancy, the demand for iron increases with fetal growth and peaks in the third trimester, a physiological period often associated with IDA (3).

The primary goals in the management of IDA anemia are to identify and eliminate the underlying cause, administer an effective treatment for an adequate duration, and monitor the response to therapy. Oral iron therapy remains the basis of treatment for most patients with IDA. However, both patient- and supplement-related factors must be considered to ensure optimal iron replacement. These include underlying pathological conditions, severity of anemia, urgency for hemoglobin increase, tolerance to previous treatments, treatment

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Received: 04.09.2025 **Accepted:** 24.01.2026 **Epub:** 31.03.2026 **Publication Date:** 01.06.2026

Cite this article as: Altun Bozkurt Z, Kinaci Gumuscubuk Y, Simsek E, Dagcioglu BF, Yilmaz Cakmak N. Side effects and treatment discontinuation in women receiving oral ıron therapy: a cross-sectional study. Med Bull Haseki. 2026;64(3):176-185

resistance, history of allergic reactions, cost of medication, and potential side effects (4). For patients who cannot tolerate or do not respond to oral iron or in certain clinical situations, intravenous (IV) administration is the preferred route (5). However, IV iron therapy is associated with higher costs, the need for infusion facilities, and a low risk of hypersensitivity reactions. These factors limit its widespread use, particularly in low-income countries (6).

Although ferrous sulfate is considered the gold standard for oral iron therapy, iron preparations commonly contain one of three iron salts: ferrous sulfate, ferrous gluconate, or ferrous fumarate (7). The bioavailability of ferric iron salts is lower than that of ferrous iron salts, limiting their oral use (8). These advantages are considered when prescribing iron preparations.

One of the greatest challenges of oral iron therapy is nausea and epigastric discomfort that appears within one to two hours after ingestion. These symptoms contribute to poor patient compliance and can trigger complaints such as indigestion, nausea, vomiting, abdominal pain, constipation, and diarrhea, which are due to the oxidative effects of iron on the GI mucosa (9). These side effects are generally dose-dependent and reflect inherent properties of the iron regulatory system, which prevents long-term iron overload (9,10). Gastrointestinal (GI) side effects caused by iron therapy adversely affect the patient's health, disrupting both physiological and psychological well-being. Consequently, patients often discontinue oral iron treatment prematurely or continue therapy with a different medication or a modified treatment regimen.

We hypothesized that, in women receiving iron therapy, particularly those using tablet formulations, side effects and discontinuation rates would differ by drug formulation and that factors such as age and pregnancy status would significantly influence treatment adherence.

Despite awareness of the prevalence of IDA, which adversely affects women's health, it is believed that insufficient attention is paid to monitoring treatment in patients and pregnant women who receive prophylactic iron. Therefore, this study aimed to evaluate the use of iron preparations among female patients, determine the frequency and types of side effects, identify reasons for drug discontinuation or switching, and examine factors affecting treatment adherence.

Materials and Methods

Compliance with Ethical Standards

The local ethics committee approval was obtained from the Ankara Bilkent City Hospital Clinical Research Ethics Committee No. 1 (approval no.: E1/4009/2023, date: 12.09.2023). This study was prepared in accordance with the principles of the Declaration of Helsinki.

Study Design

This study was designed as a cross-sectional analytical study between October 1 and November 30, 2023, and included female volunteers who had used iron supplements for at least one month. The study was reported in accordance with the STROBE guidelines for cross-sectional studies. Participants were recruited from the General Internal Medicine and Obstetrics and Gynecology outpatient clinics. A total of 270 women, both pregnant and non-pregnant, were included. Participation was voluntary, and data were collected through face-to-face interviews using a structured questionnaire. Informed consent was obtained from all participants. Exclusion criteria included refusal to participate, age under 18 years, male sex, and use of iron supplements for less than one month (Figure 1).

The researcher developed a 20-item questionnaire covering the participants' sociodemographic characteristics, reasons for iron supplement use, duration of use, habits, method of supplement use, experienced side effects, reasons for discontinuing treatment, and changes in medication. Treatment discontinuation was characterized as the patient-reported cessation of iron therapy prior to the physician-recommended duration. Discontinuation owing to side effects was defined as cessation explicitly linked to adverse consequences.

Statistical Analysis

Data were analyzed using SPSS version 24.0 (IBM Corp., Armonk, NY, USA). For descriptive statistics, frequencies, percentages, mean ± standard deviation, minimum and maximum, median, and interquartile range (Q1-Q3) were reported. The normality of continuous data was evaluated using the Kolmogorov-Smirnov test, supplemented by visual examination of histograms and Q-Q plots. Student's t-test was used to compare continuous data. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate.

Binary logistic regression analysis was used to determine factors influencing drug discontinuation in patients receiving iron therapy and to predict which individuals would discontinue treatment because of side effects. In the first analysis, the dependent variable was treatment discontinuation (dropout), coded as 0= not discontinued and 1= discontinued. Variables with $p<0.10$ in univariate analysis were included in the multivariate model. Independent variables included age, education level (ordinal), drug form, and active-ingredient group. Multicollinearity was assessed using variance inflation factor (VIF); variables with VIF >5 were excluded.

In the second analysis, the dependent variable was whether the patient discontinued iron therapy due to side effects. The independent variables were the same as those

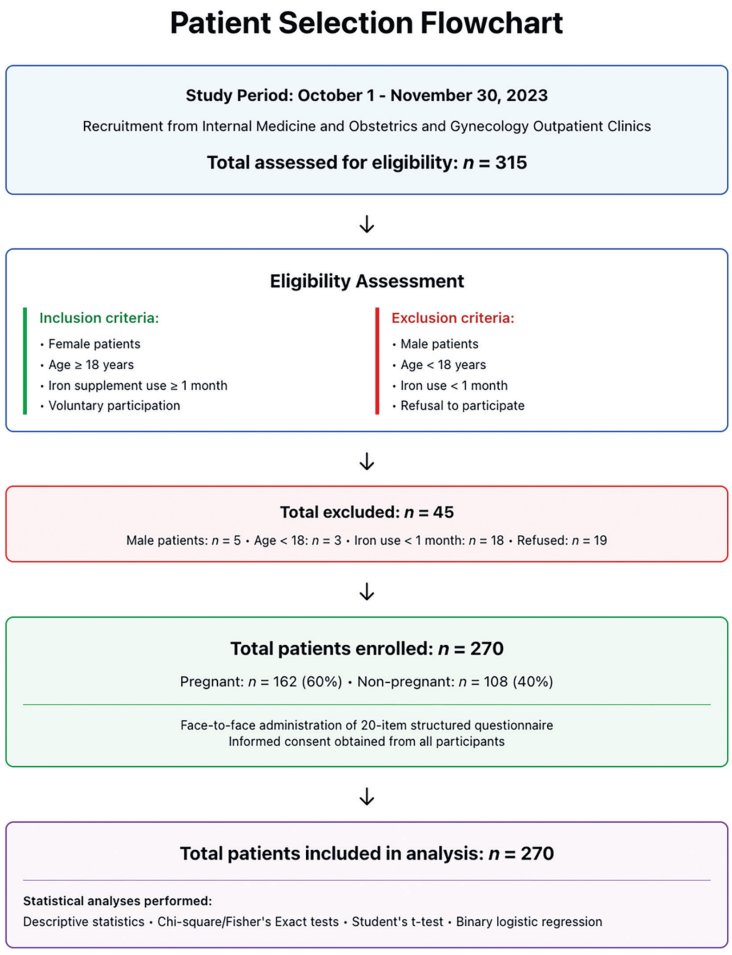

Figure 1. Flowchart of study

used in the previous analysis. Model validity was assessed using the Hosmer-Lemeshow goodness-of-fit test; explanatory power was evaluated using the Nagelkerke R-squared; and effects of variables were estimated using odds ratios (ORs) [Exp(B)] with 95% confidence intervals (CIs). Statistical significance was set at $p<0.05$.

Results

A total of 270 female patients receiving iron replacement therapy were included in the study. On average, patients used iron supplements for 3.59±1.78 months. The vast majority of the participants (95.6%) used the supplement in tablet form. The distribution of sociodemographic characteristics and selected features related to iron supplement use among the patients is summarized in Table 1.

When asked about the side effects of the iron supplements they used, the most commonly reported side effect was nausea (35.9%), followed by constipation (19.6%) (Table 2).

37.0% of patients reported discontinuing their iron medication, and 34.8% reported changing their iron treatment. Nausea was the most common reason for both medication change (73.4%) and discontinuation (84.0%). Additionally, 68.1% of patients reported side effects even after changing their medication. Details are summarized in Tables 2 and 3.

In patients who changed their medications, the rate of side effects from their previous medications was significantly higher ($p<0.001$). The medication discontinuation rate (88.9%) among iron (III) polymaltose complex users was significantly higher than that among other complex users ($p=0.004$). When side-effect distribution by type of iron supplement was examined, the rate of dyspeptic complaints among patients using iron (III) polymaltose complex (55.6%) was significantly higher than that for other iron preparations ($p=0.04$). Details are summarized in Table 4.

The mean duration of medication use was higher among pregnant women (4.40) than among non-

Table 1. Distribution of sociodemographic data of patients		
Category	**Variables**	**Results**
1. Sociodemographic characteristics	Patient age (year) **Mean ± SD (min-max)**	31.36±7.74 (19-58)
	Educational status, n (%) Primary school and below Secondary school High school University Master's/doctorate	 8 (3.0) 35 (13.0) 96 (35.6) 117 (43.3) 14 (5.2)
	Occupation, n (%) Housewife Healthcare worker Teacher Student Engineer Private sector Other	 134 (49.6) 32 (11.8) 35 (12.9) 14 (5.1) 5 (1.8) 29 (10.7) 21 (7.7)
2. Iron supplement usage specifications	**Duration of use (months)** (**Mean ± SD (min-max)**	3.59±1.78 (1-11)
	Drug form n (%) Intravenous (IV) Tablet Drop Syrup/suspension	 0 258 (95.6) 1 (0.4) 11 (4.1)
	Type of iron supplement n (%) Ferric pyrophosphate Ferrous fumarate Iron (II) sulfate Iron (II) glycine Iron (III) hydroxide polymaltose complex Iron (III) polymaltose complex	 2 (0.7) 67 (24.8) 49 (18.1) 69 (25.6) 74 (27.4) 9 (3.3)
	How the medication is obtained, n (%) By prescription From a pharmacy (paid)	 266 (98.5) 4 (1.5)
	Prescribing physician, n (%) Family physician Internal medicine Obstetrics and gynecology Other	 85 (31.5) 72 (26.7) 111(41.1) 2 (0.7)
	Reason for using medication, n (%) Anemia Pregnancy Weakness Hair loss Nail deformity	 103 (38.1) 162 (60.0) 3 (1.1) 1 (0.4) 1 (0.4)
	Directions for use, n (%) In the morning on an empty stomach Independent of meals On a full stomach Before bedtime 2 hours after meals	 162 (60.0) 41 (15.2) 29 (10.3) 25 (9.3) 11 (4.1)
Exploratory and frequency tests were used. Data are presented as mean ± SD, median (min-max), or n (%) n: Number of participants, %: Percentage, SD: Standard deviation, min-max: Minimum-maximum		

Table 2. Distribution of side effects and related treatment outcomes

Side effect type	Side effects (n=270)	Reason for treatment discontinuation (n=100)	Reason for changing medication (n=94)	Side effects after change (n=60)
Nausea	97 (35.9%)	84 (84.0%)	69 (73.4%)	42 (70.0%)
Constipation	52 (19.2%)	24 (24.0%)	22 (23.4%)	14 (23.3%)
Diarrhea	34 (12.5%)	14 (14.0%)	10 (10.6%)	11 (18.3%)
Vomiting	14 (5.1%)	15 (15.0%)	15 (15.9%)	9 (15.0%)
Heartburn	41 (15.1%)	8 (8.0%)	5 (5.3%)	5 (8.3%)
Abdominal pain	21 (7.7%)	14 (14.0%)	8 (8.5%)	5 (8.3%)
Dyspeptic complaints	41 (15.1%)	9 (9.0%)	10 (10.6%)	9 (15.0%)
Surgery	-	1 (1.0%)	1 (1.0%)	-
Forgetfulness	-	1 (1.0%)	-	-
No results from treatment	-	-	11 (11.6%)	-

Explore and frequency test were used. Data are presented as n (%)
n: Number of participants, %: Percentage

Table 3. Medication preference, change status, and post-change side effects

Category	Subcategory/option	n	Percentage (%)
Reason for preference	Because a doctor prescribes it	217	80.4%
	Fewer side effects	47	17.4%
	Habit	2	0.7%
	No special preference	1	0.4%
	Other	3	1.1%
Medication change status	Yes	94	34.8%
	No	173	65.1%
Post-change medication form	Tablet	59	63.4%
	Intravenous (IV)	25	26.8%
	Syrup/suspension	9	9.6%
Post-change side effect status	Yes	60	68.1%
	No	28	31.8%

Explore and frequency test were used. Data are presented as n (%)
n: Number of participants

Table 4. Comparison of side effects and discontinuation rates among different iron preparations

Side effects	Assessment type	Ferric pyrophosphate	Ferrous fumarate	Iron (II) sulfate	Iron (II) glycine	Iron (III) hydroxide polymaltose	Iron (III) polymaltose	p-value
Constipation	Seen	0	9 (13.4)	5 (11.9)	20 (29.0)	17 (23.0)	1 (11.1)	0.082
	Dropout	1 (50.0)	4 (6.0)	6 (12.2)	5 (7.2)	7 (9.5)	1 (11.1)	0.319
Diarrhea	Seen	0	6 (9.0)	6 (12.2)	12 (17.4)	10 (13.5)	0	0.564
	Dropout	0	3 (4.5)	3 (6.1)	6 (8.7)	3 (4.1)	0	0.785
Nausea	Seen	1 (50.0)	26 (38.8)	19 (38.8)	16 (23.2)	30 (40.5)	5 (55.6)	0.177
	Dropout	1 (50.0)	17 (25.4)	19 (38.8)	19 (27.5)	21 (28.4)	8 (88.9)	0.004
Vomiting	Seen	0	1 (1.5)	4 (8.2)	2 (2.9)	7 (9.5)	0	0.234
	Dropout	0	2 (3.0)	2 (4.8)	5 (7.2)	6 (8.1)	2 (22.2)	0.290
Heartburn	Seen	0	11 (16.4)	7 (14.3)	11 (15.9)	12 (16.2)	0	0.825
	Dropout	0	0	1 (2.0)	5 (7.2)	1 (1.4)	2 (22.2)	0.005
Abdominal pain	Seen	0	3 (4.5)	2 (4.1)	10 (14.5)	5 (6.8)	2 (22.2)	0.119
	Dropout	1 (50.0)	3 (4.5)	3 (6.1)	3 (4.3)	3 (4.1)	1 (11.1)	0.099
Dyspepsia	Seen	0	10 (14.9)	6 (12.2)	16 (23.2)	6 (8.1)	5 (55.6)	0.004
	Dropout	1 (50.0)	2 (3.0)	2 (4.1)	2 (2.9)	2 (2.7)	0	0.115
Failure to respond to treatment	Dropout	0	3 (4.5)	3 (6.1)	3 (4.3)	6 (8.1)	0	0.858

A chi-square test or Fisher's exact test was used for categorical comparisons. $p<0.05$ was considered statistically significant

pregnant women (2.98) (p<0.001). A higher proportion of pregnant women (35.2%) than non-pregnant women (18.5%) reported no side effects (p=0.003). Medication changes were more common in non-pregnant patients (38.9%) than in pregnant patients (25.3%) (p=0.018). The details are shown in Tables 5 and 6.

To examine the effects of independent variables, two logistic regression models were fitted. In the overall discontinuation model, a positive association was observed between age and discontinuation, with each one-year increase corresponding to a 10.4% higher likelihood of discontinuation (OR=1.104; 95% CI: 1.062-1.146; p<0.001). In the overall treatment discontinuation model, tablet formulation was also associated with a markedly increased risk (OR=9.033; 95% CI: 1.791-45.560; p=0.008). Education level showed a borderline association (OR=1.356, p=0.056), whereas the active ingredient group was not significantly associated.

In the side-effect discontinuation model, age remained significant (OR=1.082; 95% CI: 1.041-1.123; p<0.001), and tablet formulation was again associated with a higher risk (OR=5.599; 95% CI: 1.581-19.829; p=0.008). Education level and active ingredient group were not statistically significant (p=0.056). The details are shown in Tables 7a and 7b.

Table 5. Medication use, changes, and outcomes by pregnancy status

Category	Subtitle	Non-pregnant (n=108)	Pregnant (n=162)	p-value
Drug form	Tablet/syrup/drops/IV	103 tablet (95.4%)	155 tablet (95.7%)	0.458
Prescribing department	Family physician/internal medicine/gynecology and obstetrics/other	Different	Different	**<0.001**
Medication usage	Eating/on a full day/other	68.5% hungry	55.3% hungry	0.067
Discontinuation status	Yes	47.2%	30.9%	**0.007**
Drug change status	Yes	38.9%	25.3%	**0.018**
Drug form after change	IV/tablet/syrup	IV 46.2%	IV 2.4%	**<0.001**
Side effects after change	Yes	84%	73.7%	0.235

Either the chi-square test or Fisher's exact test was used for categorical variables. Student's t-test was used for continuous variables. p<0.05 was considered statistically significant
n: Number of participants, IV: Intravenous

Table 6. Analysis of side effects, discontinuation, and treatment switch by pregnancy status

Side effect type	Side effects non-pregnant/pregnant	p-value	Reason for discontinuing non-pregnant/pregnant	p-value	Reason for change non-pregnant/ pregnant	p-value
Nausea	47 (43.5%)/50 (30.9%)	0.034	43 (39.8%)/42 (25.9%)	0.016	35 (32.4%)/34 (21%)	0.035
Constipation	20 (18.5%)/32 (19.8%)	0.801	16 (14.8%)/8 (4.9%)	0.005	13 (12%)/9 (5.6%)	0.056
Diarrhea	13 (12%)/21 (13%)	0.822	7 (6.5%)/8 (4.9%)	0.588	4 (3.7%)/6 (3.7%)	1.000
Vomiting	5 (5.6%)/8 (4.9%)	0.823	9 (8.3%)/8 (4.9%)	0.261	9 (8.3%)/6 (3.7%)	0.104
Heartburn	17 (15.7%)/24 (14.8%)	0.835	4 (3.7%)/5 (3.1%)	1.000	2 (1.9%)/3 (1.9%)	1.000
Abdominal pain	10 (9.3%)/12 (7.4%)	0.586	9 (8.3%)/5 (3.1%)	0.057	4 (3.7%)/4 (2.5%)	0.717
Dyspepsia	16 (14.8%)/27 (16.7%)	0.684	7 (6.5%)/2 (1.2%)	0.032	8 (7.4%)/2 (1.2%)	0.016
No side effects	20 (18.5%)/57 (35.2%)	0.003	-	-	-	-

Chi-square test or Fisher's exact test was used for categorical comparisons. p<0.05 was considered statistically significant

Table 7a. Multivariate analysis of predictors for overall treatment discontinuation

Variables	OR	95% CI (lower)	95% CI (upper)	p-value
Age	1.104	1.062	1.146	<0.001
Education level	1.356	0.992	1.853	0.056
Form (oral form vs other)	9.033	1.791	45.560	0.008
Active ingredient (Fe2+ vs. other)	1.172	0.252	5.444	0.839
Active ingredient (Fe3+ vs. other)	0.835	0.475	1.467	0.530

Binary logistic regression analysis was used. p<0.05 was considered statistically significant
OR: Odds ratio, CI: Confidence interval, Fe2+: Iron (II) ion, Fe3+: Iron (III) ion

Table 7b. Multivariate analysis of predictors for discontinuation due to side effects				
Variables	**OR**	**95% CI (lower)**	**95% CI (upper)**	**p-value**
Age	1.082	1.041	1.123	<0.001
Education level	1.310	0.929	1.846	0.124
Form (oral form vs other)	5.599	1.581	19.829	0.008
Active ingredient (Fe2+ vs. other)	0.632	0.103	3.856	0.619
Active ingredient (Fe3+ vs. other)	0.643	0.343	1.204	0.168
Binary logistic regression analysis was used. p<0.05 was considered statistically significant OR: Odds ratio, CI: Confidence interval, Fe2+: Iron (II) ion, Fe3+: Iron (III) ion				

Discussion

According to World Health Organization data for 2023, an estimated 37% of pregnant women and 30% of women aged 15-49 years are anemic (11). Various studies conducted in Türkiye have reported anemia prevalence rates of 40-50% among women of reproductive age and 14-49% among pregnant women, with iron deficiency being the primary cause (2). These findings reveal that IDA is an important public health problem, especially among women. Therefore, in our study, we targeted women, the group most affected by IDA, and investigated their use of iron supplements.

In our study, iron supplements were most commonly used during pregnancy and for anemia. Pregnant women were better informed about iron supplementation, had a more positive attitude toward treatment for iron deficiency, and demonstrated better adherence to therapy. Data obtained from the Turkey Demographic and Health Survey (TDHS) showed that 81% of women used iron supplements during their pregnancy. According to the 2018 THDS report, 75% of women had completed at least primary school, and 26% had completed at least high school (12). In our study, 43.3% of participants were university graduates, while 35.6% were high school graduates. The distribution of education levels and employment status of women in our study was compatible with that reported in the 2018 THDS data. Moreover, the education level variable showed borderline significance in our study (p=0.056), indicating a tendency for higher education levels to be associated with an increased risk of discontinuation (OR=1.343).

Oral iron therapy should be attempted first when initiating treatment. Parenteral iron may be administered in cases of significant blood loss, malabsorption, or intolerance to oral iron (9,13). In our study, the vast majority of patients (95.6%) used the medication orally (tablet form). Oral treatment is preferred over other therapies due to high patient compliance, greater accessibility, and cost-effectiveness (14). Previous studies generally recommend ferrous sulfate as the first-line treatment for iron deficiency (4,9,15). In our study, when participants were asked which iron formulation they used, the three most commonly reported formulations among both pregnant and non-pregnant individuals were iron (III)-hydroxide polymaltose complex (27.4%), iron (II)-glycine (25.6%), and ferrous fumarate (24.8%). In our sample, 41.2% of iron (III) formulations were prescribed by family physicians. The high prescription rate of iron (III) preparations in this group may indicate patients' trust in primary care and in the effective functioning of the primary healthcare system. Although side effects and treatment adherence may also play a role, further comprehensive studies are needed to clarify these findings.

Gastrointestinal side effects are the most commonly reported adverse effects of treatment. GI side effects are known to occur more frequently in patients receiving oral iron therapy compared to those receiving IV formulations. The most commonly reported side effects are GI-related, including nausea, bloating, abdominal pain, diarrhea, constipation, and black or tarry stools (11). In our study, adverse effects during treatment were observed in 79.7% of patients receiving iron (III)-hydroxide polymaltose complex, 73.9% of those receiving iron (II)-glycine, 71.4% of those receiving iron (II)-sulfate, 64.2% of those receiving ferrous fumarate, and 44.4% of those receiving iron (III)-polymaltose complex. These findings indicate that GI side effects are common among individuals receiving oral iron therapy and that the frequency of these side effects varies depending on the formulation used. When researchers attempt to determine the true incidence of GI side effects associated with oral iron therapy, limitations and inconsistencies across studies make it difficult to draw definitive conclusions (9).

One review examined data on adverse events from studies of oral iron supplementation in patients without GI disease and reported an overall incidence of adverse events of 32.3% for ferrous sulfate, 47% for ferrous fumarate, and 30.9% for ferrous gluconate (16). In a study conducted by Aydin et al. (17), they compared +2 and +3 iron preparations and found no significant differences in side effects between the two preparations. In another study conducted in our country, no difference

was observed with respect to side effects between women with IDA who were treated with iron glycine sulfate (ferrous group) and those treated with iron protein succinate (ferric group) (18). Studies also show that the polymaltose complex is better tolerated than +2 iron preparations (19,20). Unlike previous studies, in our study the rate of treatment discontinuation due to nausea was significantly higher among patients using iron (III) polymaltose complex (88.9%) than among those using other formulations. When divalent (+2) and trivalent (+3) iron preparations were compared, nausea was reported more frequently among patients receiving trivalent formulations. This finding may reflect differences in tolerability between Iron(III) hydroxide polymaltose complex and +2 formulations; however, no causal inference can be drawn. Additionally, factors such as patients' previous experiences, social background, genetic characteristics, and nutritional patterns may have influenced these results, although no causal inferences can be drawn.

In studies investigating the individual side effects of IDA treatment, the most frequently reported symptoms were constipation (12%), nausea (11%), and diarrhea (8%) (9,10). When patients in our study were asked about the side effects of iron supplements, nausea was the most common response (35.9%), followed by constipation (19.6%). When participants were categorized by pregnancy status, a higher proportion of pregnant individuals (35.2%) reported no drug-related side effects than non-pregnant individuals (18.5%).

When we examined side effects, only nausea was observed significantly more frequently in the non-pregnant group. Nausea was detected more frequently than other side effects in our study, differing from previous studies; this may be explained by the fact that 60% of the participants used iron medication on an empty stomach and that a high proportion of patients in the side-effect group (approximately 60%) were taking iron for pregnancy prophylaxis. In our study, it was not possible to determine whether the high rate of nausea was pregnancy-related or a side effect of IDA treatment. Additionally, medication changes were more frequent among non-pregnant patients (38.9%) than among pregnant patients (25.3%). In both groups, nausea was the most common side effect after medication changes (70%). Although nausea is a common complaint during pregnancy, pregnant individuals may have tolerated nausea better, or iron supplements may have aggravated pre-existing nausea. However, it is not clear whether nausea was primarily pregnancy-related or caused by treatment. Further studies in pregnant populations are needed to clarify this.

In a previous study involving 96 women with iron-deficiency anemia, 40% discontinued treatment due to side effects, the most common being GI intolerance (21). Similarly, in our study, 37% of participants interrupted treatment; nausea was again the leading reason for interruption (84%), followed by constipation (24%) and vomiting (15%). While constipation has been reported more frequently in earlier studies, our findings suggest that patients may have been more willing to tolerate constipation than nausea (10,22). Since not all side effects led to treatment discontinuation, larger sample sizes may better identify the symptoms that most strongly influence adherence.

The GI side effects of oral iron administration are dose-related. These side effects increase when the drug is administered on an empty stomach and decrease when the drug is administered on a full stomach (4). In our study, contrary to the literature, no statistically significant association was found between side effects and patients' fasting or feeding status or the time of day (morning versus evening) of iron administration. This result may be attributed to the fact that this study was not conducted as a field survey, that the evaluation was limited to patients presenting to the outpatient clinic, and that 60% of the participants were pregnant women. Additionally, patient compliance with treatment may influence the incidence of side effects.

Previous studies suggest that elderly patients may be more sensitive to dose-dependent side effects (23). In our study, older age was associated with lower adherence and some formulations appeared less well-tolerated, which was correlated with reduced treatment compliance. Therefore, the patient's age and drug formulation should be considered in treatment planning, and better-tolerated formulations should be preferred. Additionally, recent studies report that intermittent iron administration is as effective as and better tolerated than daily administration. With this approach, treatment should be individualized, taking into account the patient's tolerability and adherence to medication (24,25).

While oral iron therapy has traditionally been the mainstay of iron deficiency treatment, its effectiveness is often compromised by poor GI absorption, adverse effects, and low treatment adherence. Consequently, IV iron is recognized as a potentially more effective and safer alternative for the treatment of IDA (26,27). In this study, age and medication form were found to be significant factors influencing the discontinuation of iron therapy. In the overall discontinuation model, tablet formulation was associated with ninefold higher odds of discontinuation (OR=9.033). In the side-effect discontinuation model, tablet formulation was also associated with an increased risk (OR=5.599). These parallel findings suggest that tablet formulations were associated with higher discontinuation rates, both overall and those driven by side effects. From

a clinical perspective, these data indicate that choosing more tolerable formulations and exploring other dosing techniques, such as alternate-day administration, may improve treatment adherence in real-world practice.

Study Limitations

This study also has several important limitations. First, the cross-sectional design only allows us to describe associations at a single point in time, and no causal inferences can be made. Second, the study was conducted in a single tertiary hospital, which may limit the generalizability of the findings to other populations. Third, subgroup sizes were particularly small for some categories, such as non-pregnant women who switched to IV treatment, thereby reducing the statistical power of the analyses. Additionally, the vast majority of participants were tablet users, meaning that the study could not provide balanced comparisons across different formulations. Moreover, data were collected using self-reported questionnaires, which may introduce recall bias. Finally, information about long-term adherence, repeated interruptions, or subsequent treatment modifications could not be obtained. These limitations should be considered when interpreting the findings, and they may partly explain differences compared with previous studies. Future research should therefore employ prospective, multicenter designs with larger and more diverse populations to better capture treatment patterns and adherence factors. Despite limitations, our study provides valuable real-world data on iron therapy in women and highlights important factors influencing treatment adherence.

Conclusion

This study makes several contributions to the existing literature. First, it provides real-world data from Türkiye, focusing specifically on women who use iron supplements, a population that is disproportionately affected by IDA. Unlike many previous reports, the present study analyzed pregnant and non-pregnant women separately, revealing distinct patterns of side effects, discontinuations, and treatment switching between these groups. Moreover, the observation that family physicians were more likely to prescribe ferric formulations provides additional insight into prescribing behaviors in primary care settings. Finally, by relying on patient-reported experiences collected through face-to-face interviews, this study highlights practical challenges to treatment adherence that may not always be captured in randomized clinical trials. To our knowledge, this is the first study from Türkiye to systematically compare pregnant and non-pregnant women in this context, thereby filling an important gap in the existing literature.

The findings indicate that both age and tablet formulation were consistently linked to treatment discontinuation. These results show how important it is to think about both the patient's age and the type of iron supplement used when planning therapy. Adapting treatment to the unique characteristics of each patient and ensuring consistent follow-up can enhance adherence and decrease the probability of treatment discontinuation.

Ethics

Ethics Committee Approval: The local ethics committee approval was obtained from the Ankara Bilkent City Hospital Clinical Research Ethics Committee No. 1 (approval no.: E1/4009/2023, date: 12.09.2023).

Informed Consent: Informed consent was obtained from all participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Z.A.B., Concept: Z.A.B., E.Ş., B.F.D., N.Y.Ç., Design: Z.A.B., B.F.D., N.Y.Ç., Data Collection or Processing: Z.A.B., E.Ş., B.F.D., N.Y.Ç., Analysis or Interpretation: Z.A.B., Y.K.G., B.F.D., N.Y.Ç., Literature Search: Z.A.B., Y.K.G., Writing: Z.A.B., Y.K.G., N.Y.Ç.

Conflict of interests: The authors declare that they have no conflict of interest related to this study.

Financial Disclosure: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Original Article

DOI: 10.4274/haseki.galenos.2026.47955
Med Bull Haseki 2026;64(3):186-191

Clinical Utility of Systemic Immune-inflammatory Index and Systemic Immune Response Index in Symptomatic Patients with Hashimoto's Thyroiditis

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Abstract

Aim: Systemic immune-inflammatory indices have recently been investigated as potential biomarkers in several inflammatory and autoimmune diseases. This study aimed to investigate the symptom-based diagnostic value of the systemic immuno-inflammatory index (SII) and the systemic immunoresponsive index (SIRI) in patients with Hashimoto's thyroiditis (HT).

Methods: The medical records of 169 patients who presented to our clinic between January 2023 and June 2023 were retrospectively reviewed. Demographic and laboratory parameters including age, gender, drug use, thyroid-stimulating hormone (TSH), anti-thyroid peroxidase antibody (Anti-TPO), Anti-Tg, platelet (PLT), neutrophil, lymphocyte, monocyte, SIRI, and SII values were analyzed. SII and SIRI indices were calculated using standard formulas based on complete blood count parameters. The association between inflammatory indices and symptom status was evaluated using correlation and logistic regression analyses.

Results: Spearman's rho correlation analysis showed that the correlation between symptom positivity and Anti-TPO was significant ($r=0.203$; $p<0.01$). The correlation of symptom positivity with age, gender, drug usage, TSH, anti-Tg, PLT, neutrophil, lymphocyte, monocyte, SIRI, and SII was not statistically significant. Binary logistic regression analysis showed that the effects of gender, drug usage, age, SIRI, and SII on symptom positivity were not statistically significant. Although the effects of SIRI and SII on symptom positivity were not significant, the effect of Anti-TPO was significant ($B=0.002$; $p<0.01$).

Conclusion: Neither SIRI nor SII had diagnostic value in patients with HT based on symptoms. Therefore, clinical evaluations based on the SIRI and SII indicators for monitoring disease progression and morbidity in cases of HT may not provide reliable information for symptom-based clinical evaluation.

Keywords: Hashimoto's thyroiditis, systemic immune-inflammatory index, systemic immune response index, thyroid

Introduction

Hashimoto's thyroiditis (HT) is one of the most common autoimmune thyroid diseases and is a leading cause of hypothyroidism in iodine-poor regions (1). Hashimoto's thyroiditis has been associated with acquired hypothyroidism in children, adults, and adolescents (2). Hashimoto's thyroiditis is classified into four forms: juvenile form, fibrous form, painless thyroid, and fibrous variant (3). Risk factors include demographic characteristics such as genetics, gender, and age, as well as daily life factors such as environment and nutrition (4). Although there are no definitively distinct symptoms, weight gain, constipation, and excessive weakness and fatigue are prominent (5,6). While treatment is easier with early diagnosis, in advanced stages it can lead to many health problems ranging from mental health issues to diabetes, cholesterol problems, circulatory system problems, and cancer (7). Therefore, early diagnosis and treatment of the disease are important to prevent other comorbidities that it may cause. Therefore, both biomarker monitoring and symptom monitoring are important for early diagnosis.

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Received: 17.02.2025 **Accepted:** 05.03.2026 **Epub:** 31.03.2026 **Publication Date:** 01.06.2026

Cite this article as: Gunturk A, Eryilmaz M. Clinical utility of systemic immune-inflammatory index and systemic immune response index in symptomatic patients with Hashimoto's thyroiditis. Med Bull Haseki. 2026;64(3):186-191

Systemic immune-inflammatory index (SII) and systemic immune response index (SIRI) are two important biomarkers that have been the subject of recent studies. They are easily obtainable biomarkers that reflect systemic inflammatory status and have been investigated in various diseasesFDİAGNOS, especially those related to inflammation (8). Studies on SIRI and SII mostly highlight circulatory tract diseases (9,10).

Since cardiovascular diseases have been reported as comorbidities in patients with HT (5-7), SIRI and SII biomarkers may have value in the symptomatic evaluation of HT. To investigate this, we hypothesized that SII and SIRI values have symptomatic diagnostic value in patients with HT.

Materials and Methods

Compliance with Ethical Standards

Ethical approval was obtained for the study from the Demiroglu Science University Clinical Trials Ethical Committee (approval number: 2023-25-01, date: 05.12.2023). Informed patient consent was not applicable because of the retrospective nature of the study. The Declaration of Helsinki and Good Clinical Practice guidelines were followed in the research.

Study Design

This study was designed as a retrospective cross-sectional study. Clinical and laboratory data, including SIRI and SII indices, were obtained from the medical records of patients who presented to our clinic. The association between these indices and symptom status was evaluated using appropriate statistical analyses.

Research Data

In this study, the medical records of 168 patients who presented to our clinic between January and June 2023 were retrospectively reviewed. The patients' ages, gender, drug use, thyroid-stimulating hormone (TSH), anti-thyroid peroxidase antibody (Anti-TPO), Anti-Tg, platelet (PLT), neutrophil, lymphocyte, monocyte, SIRI, and SII were analyzed. Since our study was retrospective, the symptoms were based on the statements in the epicrisis. In our study, we performed SII and SIRI calculations as follows:

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

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

Sample Size

We did not find sufficient research examining the symptoms and the diagnostic value of SIRI and SII in HT. Sample size calculation was performed using G*Power software (version 3.1). Assuming an effect size of 0.50, α=0.05, and power of 95%, the minimum required sample size was calculated as 45 participants.

Inclusion and Exclusion Criteria

Being over 18 and under 75 years of age,
Having been diagnosed with HT,
Having complete data in their file,
Having no inconsistencies in their file data,
Having no comorbidities or medication use that could affect the research results,

71 patients without symptoms and 97 patients with symptoms were included in the study (Figure 1).

Statistical Analysis

Descriptive statistics were used to summarize the study variables. Continuous variables were expressed as mean ± standard deviation, median, and range, while categorical variables were presented as frequencies and percentages. The Kolmogorov-Smirnov test was used to assess the normality of the distribution of continuous variables. Since several variables did not meet the assumption of normal distribution, non-parametric methods were preferred. Spearman's rho correlation analysis was performed to evaluate the relationship between symptom status (coded as a dummy variable) and the study parameters. To determine the independent effects of clinical and inflammatory indices on symptom positivity, a generalized linear model with logit link function (binary logistic regression) was applied. Statistical analyses were conducted using SPSS version version 25.0 (IBM Inc., Armonk, NY, USA), and a p-value of <0.05 was considered statistically significant. To determine the independent effects of clinical and inflammatory indices on symptom positivity, a generalized linear model with logit link function (binary logistic regression) was applied (11).

Results

The mean age of the symptom-negative group was 43±10 years (range: 18-74), while the mean age of the symptom-positive group was also 43±10 years (range: 18-

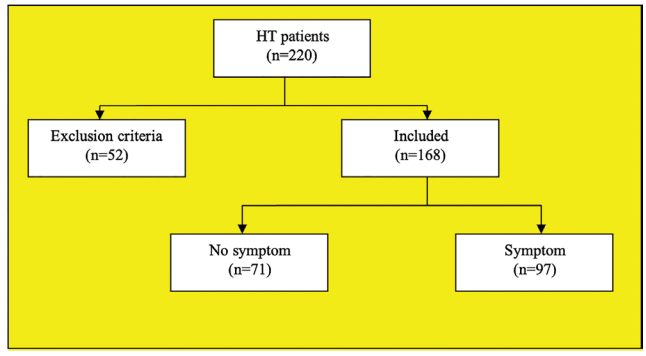

Figure 1. Research flowchart
HT: Hashimoto's thyroiditis

Table 1. Baseline characteristics of patient groups with difference analysis results			
	Symptom		p-value
	No (n=71)	Yes (n=97)	
Age, mean ± SD Median (min-max)	43±10 42 (18-74)	43±10 42 (18-70)	0.928[a]
Gender, n (%)			0.116[b]
Female	61 (85.9)	90 (92.8)	
Male	10 (14.1)	7 (7.2)	
Drug usage, n (%)	48 (66.7)	58 (59.8)	0.226[b]
TSH, mean ± SD Median (min-max)	2.35±4.72 1.44 (0.06-39.00)	2.38±3.06 1.50 (0.30-26.00)	0.220[a]
Anti-TPO, mean ± SD Median (min-max)	71.00±153.74 2.79 (0.12-857.14)	**303.36±789.33** **49.45 (0.02-6851.18**)	0.009[a]
Anti-Tg, mean ± SD Median (min-max)	28.85±79.89 2.44 (0.20-511.00)	67.85±245.85 5.99 (0.10-2276.15)	0.070[a]
PLT, mean ± SD Median (min-max)	247.54±51.93 242.00 (163.00-384.00)	261.09±59.37 253.00 (149.00-447.00)	0.122[a]
Neutrophil, mean ± SD Median (min-max)	3.66±1.12 3.65 (2.10-6.35)	3.78±1.34 3.60 (1.30-7.76)	0.777[a]
Lymphocyte, mean ± SD Median (min-max)	2.16±0.65 2.00 (0.60-4.91)	2.11±0.64 2.10 (0.61-5.04)	0.561[a]
Monocyte, mean ± SD Median (min-max)	0.50±0.14 0.50 (0.20-0.90)	0.55±0.72 0.50 (0.20-7.50)	0.445[a]
SIRI, mean ± SD Median (min-max)	0.90±0.46 0.80 (0.36-2.54)	1.05±1.15 0.85 (0.19-10.63)	0.736[a]
SII, mean ± SD Median (min-max)	441.32±184.17 380.80 (216.67-1076.67)	494.96±236.67 447.72 (173.91-1475.34)	0.170[a]

[a]Mann-Whitney U test, [b]Fisher's exact test
SD: Standard deviation, TSH: Thyroid-stimulating hormone, Anti-TPO: Anti-thyroid peroxidase antibody, Anti-Tg: Anti-thyroglobulin antibodies, PLT: Platelet, SIRI: Systemic immune response index, SII: Systemic immuno-inflammatory index

70). Female patients constituted 85.9% of the symptom-negative group and 92.8% of the symptom-positive group. 66.7% of the negative-symptom group and 59.8% of the positive-symptom group used drugs. The mean Anti-TPO level was significantly higher in the positive-symptom group. Differences in age, gender, drug usage, TSH, anti-Tg, PLT, neutrophil, lymphocyte, monocyte, SIRI and SII parameters between symptom groups were not statistically significant (Table 1).

Spearman's rho correlation analysis results showed that correlation of symptom positivity with Anti-TPO was significant (r=0.203; p<0.01). Correlations of symptom positivity with age, gender, drug usage, TSH, Anti-Tg, PLT, neutrophil, lymphocyte, monocyte, SIRI, and SII parameters were not statistically significant (Table 2).

Results of binary logistic regression analysis showed that the effects of gender, drug usage, age, SIRI, and SII on symptom positivity were statistically insignificant (Table 3).

Although the effects of SIRI and SII on symptom positivity were not significant, the effect of Anti-TPO was significant (B=0.002; p<0.01) (Table 4).

Table 2. Spearman's rho correlation analysis between symptom variable (dummy) and research parameters		
Symptom	**r**	**p**
Gender	-0.112	0.147
Drug	-0.070	0.364
Age	0.007	0.928
TSH	0.095	0.221
Anti-TPO	0.203**	0.008
Anti-Tg	0.140	0.070
PLT	0.119	0.122
Neutrophil	0.022	0.778
Lymphocyte	-0.045	0.563
Monocyte	-0.059	0.447
SIRI	0.026	0.740
SII	0.106	0.171

**p<0.01, TSH: Thyroid-stimulating hormone, Anti-TPO: Anti-thyroid peroxidase antibody, Anti-Tg: Anti-thyroglobulin antibodies, PLT: Platelet, SIRI: Systemic immune response index, SII: Systemic immuno-inflammatory index

Table 3. Binary logistic regression analysis for effects of SIRI, SII and baseline characteristics on symptom positivity								
	B	S.E.	Wald	df	p	OR	95% CI for OR	
							Lower	Upper
Gender	-0.746	0.534	1.949	1	0.163	0.474	0.166	1.352
Drug	-0.334	0.338	0.976	1	0.323	0.716	0.369	1.389
Age	0.001	0.016	0.000	1	0.990	1.000	0.969	1.033
SIRI	0.087	0.236	0.137	1	0.712	1.091	0.687	1.731
SII	0.001	0.001	1.041	1	0.308	1.001	0.999	1.003
Constant	0.815	1.062	0.589	1	0.443	2.259		
SIRI: Systemic immune response index, SII: Systemic immuno-inflammatory index, CI: Confidence interval, OR: Odds ratio								

Table 4. Binary logistic regression analysis for effects of SIRI, SII and Anti-TPO on symptom positivity								
	B	S.E.	Wald	df	p	OR	95% C.I.for OR	
							Lower	Upper
SIRI	0.037	0.214	0.030	1	0.862	1.038	0.682	1.580
SII	0.001	0.001	1.604	1	0.205	1.001	0.999	1.003
Anti-TPO	0.002	0.001	7.346	1	0.007	1.002	1.001	1.004
Constant	-0.591	0.407	2.105	1	0.147	0.554		
Anti-TPO: Anti-thyroid peroxidase antibody, SIRI: Systemic immune response index, SII: Systemic immuno-inflammatory index, CI: Confidence interval, OR: Odds ratio								

Although the mean SIRI was higher in the symptom-positive group, this difference was not statistically significant. One patient had the highest SIRI value in the symptom-positive group, and we reanalyzed the data after removing this patient. However, the difference remained non-significant (Figure 2).

Unlike SIRI means, SII mean differences were closer and distributions were more similar between patient groups; the differences were not statistically significant (Figure 3).

Discussion

This study aimed to evaluate the diagnostic value of the SII and SIR) for symptoms in patients with HT. Data from 169 patients who presented to our clinic were retrospectively analyzed. Our findings showed that neither SIRI nor SII had diagnostic value for symptoms in patients with HT.

Hashimoto's thyroiditis is one of the most common autoimmune thyroid disorders and represents a major cause of acquired hypothyroidism across all age groups (12-15). Because HT risk factors are similar to other disease risk factors (4-6) and its symptoms are limited, more biomarkers and parameters are needed for early diagnosis. The emergence of comorbidities and especially circulatory problems in advanced stages of HT (5-7) suggests that symptomatic circulatory indicators may also

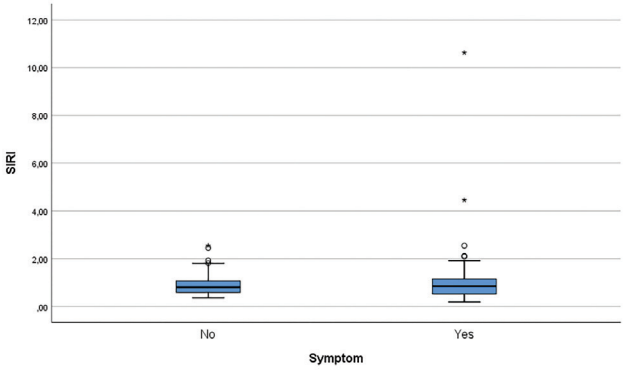

Figure 2. SIRI means and distributions according to symptom positivity
SIRI: Systemic immune response index

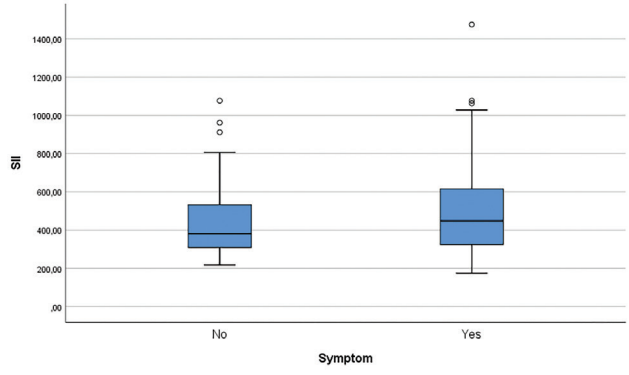

Figure 3. SII means and distributions according to symptom positivity
SII: Systemic immuno-inflammatory index

have diagnostic value for HT. Two commonly reported biomarkers of circulatory diseases are SIRI and SII (16-18). Based on this, in our study, we investigated the relationship between HT symptoms and SIRI and SII.

Studies on SIRI and SII biomarkers in thyroid diseases are limited. Among these, Wang et al. (19) reported that SIRI and SII parameters may have diagnostic value for treatment progression in thyroid cancer cases. Gu et al. (20) reported that the SII index may have diagnostic value in terms of lymph node positivity in elderly patients with papillary thyroid carcinoma. Yang and Yang (21) reported that SIRI and SII values were significantly higher in patients with differentiated thyroid carcinoma. Zhai et al. (22) examined the relationship between SIRI and thyroid function level and reported that inflammatory diseases and the SIRI index may be markers related to progression, but more evidence is needed. Although these studies suggest a potential relationship between thyroid-related diseases and SIRI and SII, available evidence remains limited.

In our study, neither SIRI nor SII had diagnostic value in patients with symptomatic HT. Although we designed our research to account for patients' cardiovascular disease or anti-inflammatory drug use, the evidence shows that the SIRI and SII indices do not have sufficient discriminatory power to detect HT at the symptom level.

Although HT is a significant health problem, early diagnosis may not be possible through routine blood tests. Early diagnosis significantly affects both the treatment process and disease progression. Our findings reveal that SIRI and SII do not have a value for symptom differentiation. Therefore, our findings suggest that HT patients may have pathophysiologies beyond those indicated by symptomatic blood values.

Study Limitations

The most significant limitation of the study is that it is a single-center study. Due to its single-center nature, the influence of environmental factors and differing demographic, social, and economic contexts on the research results was not sufficiently assessed. Therefore, multicenter studies and cross-comparisons are needed in future research. Another limitation is the absence of prospective clinical assessment of symptoms, as symptom status was determined retrospectively from medical records. The retrospective design also does not allow adequate inclusion of potential confounders in the study. For this reason, further prospective trials, especially those including other confounders who may be related to Anti-TPO, could be considered. Another significant limitation of the study is the small number of patients and the paucity of literature on symptoms specific to HT. Although our sample size (n=169) exceeds the required number by the power analysis, more comprehensive data on symptom diversity could be obtained with larger samples. Our study is retrospective, and the derivation of symptoms from statements in the medical records is another significant limitation.

Studies indicate that SIRI and SII have significant value. However, a substantial gap exists in the literature regarding symptoms of HT, necessitating the identification of meaningful indicators and further research. In this respect, the research is important because it examines the relationship between SIRI, SII, and symptoms of HT, which is one of the first questions that comes to mind in the literature. This research contributes to clinical practice by helping to prevent potential misassessments and misinterpretations in treatment through demonstrating that the potential effects of SIRI and SII indices are not applicable to HT. Our sample is not sufficient to definitively conclude that there is no relationship of SIRI and SII with HT, but it is important because it shows that these indicators are unreliable and may even yield misleading results.

Conclusion

Although some studies report the indicator value of SIRI and SII, our findings indicate that neither SIRI nor SII has diagnostic value in patients with HT when diagnosis is based on symptoms. Therefore, clinical evaluations based on SIRI and SII indicators for monitoring disease progression and morbidity in HT cases may not provide reliable information for symptom-based clinical evaluation. To improve the generalizability of the results obtained in our study, the research sample could be increased by enlarging the sample size and conducting multicenter studies.

Ethics

Ethics Committee Approval: Ethical approval was obtained for the study from the Demiroglu Science University Clinical Trials Ethical Committee (approval number: 2023-25-01, date: 05.12.2023).

Informed Consent: Informed patient consent was not applicable because of the retrospective nature of the study.

Acknowledgments

We thank Kadir Yılmaz, Istanbul Commerce University, for his valuable statistical support.

Footnotes

Authorship Contributions

Concept: A.G., Design: A.G., Data Collection or Processing: A.G., M.E., Analysis or Interpretation: A.G., M.E., Literature Search: A.G., M.E., Writing: A.G.

Conflict of Interest: No conflict of interest was declared by the authors.

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

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Original Article

DOI: 10.4274/haseki.galenos.2026.04696
Med Bull Haseki 2026;64(3):192-199

Clinical and Inflammatory Predictors of Sentinel Lymph Node Involvement in T1 Early-stage Breast Cancer with Unfavorable Histology

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Abstract

Aim: Despite advances in early detection and surgical de-escalation strategies in breast cancer, accurately predicting sentinel lymph node involvement (SLNI) among patients with T1 disease remains a clinical challenge, particularly in those with unfavorable histologic subtypes. In this context, this study aimed to examine clinical factors related to pathological SLNI among patients with T1 early-stage breast cancer (ESBC) and unfavorable histologic subtypes.

Methods: This retrospective analysis included 128 patients with clinically node-negative T1 ESBC and unfavorable histology who underwent surgery between January 2010 and December 2020. Clinicopathological and preoperative laboratory parameters were analyzed. To identify the independent risk factors associated with SLNI, logistic regression analyses were performed.

Results: Thirty-six (28.1%) patients were SLNI-positive, and 92 (71.9%) were SLNI-negative. In univariate analysis, the presence of lymph nodes with a thickened cortex on preoperative ultrasonography (p=0.016), lymphovascular invasion (LVI) (p=0.002), larger tumor size (p=0.002), and higher neutrophil levels (p=0.046) were significantly associated with SLNI positivity. SLNI-positive patients also demonstrated significantly lower serum albumin levels (p=0.002), while monocyte levels exhibited a tendency toward lower values (p=0.064). In multivariate analysis, serum albumin levels (p=0.015), neutrophil count (p=0.031), monocyte count (p=0.035), and LVI (p=0.040) remained independently associated with SLNI.

Conclusion: Selected clinicopathological and inflammatory parameters were independently associated with SLNI in patients with T1 ESBC and unfavorable histology and may help identify patients at higher risk of nodal involvement.

Keywords: Breast neoplasm, sentinel lymph node biopsy, inflammation, albumin, retrospective study

Introduction

In patients with clinically node-negative (cN0) early-stage breast cancer (ESBC), sentinel lymph node biopsy (SLNB) is currently used as the standard approach for axillary staging (1,2). Minimally invasive SLNB is still a surgical procedure (3). In the era of treatment de-escalation, the routine use of axillary staging has increasingly been debated, particularly in patients with small primary tumors (4-6). The prevalence of sentinel lymph node involvement (SLNI)

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Received: 15.08.2025 **Accepted:** 26.02.2026 **Epub:** 31.03.2026 **Publication Date:** 01.06.2026

Cite this article as: Cangoz K, Canlikarakaya F, Pehlevan Ozel H, et al. Clinical and inflammatory predictors of sentinel lymph node involvement in T1 early-stage breast cancer with unfavorable histology. Med Bull Haseki. Med Bull Haseki. 2026;64(3):192-199

in patients with T1 tumors has been reported to range from approximately 18% to 36% (2,3). Similarly, Wang et al. (4) reported SLNI rates of 2.8% in T1mic, 4.5% in T1a, 9.3% in T1b, and 21.0% in T1c tumors. This indicates that a considerable proportion of patients undergo axillary surgery without nodal disease. To address this issue, several prediction models based on clinicopathological characteristics and advanced imaging techniques have been developed to estimate the preoperative risk of SLNI in ESBC. However, none of them have been universally adopted as a standardized tool in routine practice (7,8). Recent randomized trials, including SOUND and INSEMA, have further suggested that omitting SLNB in carefully selected patients may be non-inferior to performing SLNB. This supports the concept of a more selective approach to axillary surgery in T1 ESBC with respect to oncological outcomes (5,6).

Tumor progression and prognosis have been associated with the systemic inflammatory (SI) response (9). In particular, lymphocyte-to-monocyte ratio (LMR) and neutrophil-to-lymphocyte ratio (NLR) have been reported as prognostic biomarkers in breast cancer (BC) patients (9). Fuji et al. (10) also stated that low serum albumin levels have been associated with poorer overall survival (OS) and recurrence-free survival (RFS) in ESBC patients. Several studies have evaluated the association between preoperative inflammatory markers and SLNI in cN0 T1 BC (2,3). However, the clinical utility of these inflammatory markers for guiding axillary surgery decision-making in T1 ESBC remains unclear.

We hypothesized that in patients with T1 BC and unfavorable histologic types, certain clinical factors are associated with an increased risk of pathological SLNI. Accordingly, the aim of this study was to evaluate the clinical factors associated with pathological SLNI in ESBC patients with T1 tumors and unfavorable histologic types. Improved preoperative identification of patients at increased risk of SLNI may help refine patient selection for SLNB and provide additional information for individualized axillary management in ESBC.

Materials and Methods

Compliance with Ethical Standards

This study was conducted in accordance with the principles of the Declaration of Helsinki. Ankara Bilkent City Hospital Clinical Research Ethics Committee No. 1 approved the study (approval no.: E1/2236/2020, date: 15.12.2021) and waived the requirement for informed consent due to its retrospective nature.

Study Rationale

The literature indicates that SLNI plays a more critical role in guiding adjuvant and neoadjuvant treatment decisions for T1 BC than for T2 tumors. Due to differences in neoadjuvant and adjuvant chemotherapy strategies between T1 and T2 disease, patients with T2 tumors were excluded from the present study. In addition, previous studies have indicated that the necessity of SLNB is controversial and that the incidence of SLNI is relatively low in small tumors with favorable histologic types. Therefore, these tumors were also excluded from the analysis.

Exclusion Criteria

Patients with isolated tumor cells or micrometastases in the sentinel lymph node (SLN), hematologic disorders, SI diseases, a history of other malignancies, active infections, or steroid use within the past month were excluded. Patients who received neoadjuvant therapy, had incomplete clinical or laboratory data, or demonstrated lymphocytic infiltration consistent with breast inflammation on histopathological examination were also excluded from the study.

Study Cohort

Patients with ESBC who underwent SLNB at Ankara Bilkent City Hospital between January 2010 and December 2020 were analyzed retrospectively. A total of 547 individuals who underwent SLNB for clinically ESBC were evaluated. Patients with favorable histological tumor types and those with tumors larger than pT1 were excluded. The study cohort consisted of 128 patients with pT1 and unfavorable tumors (Figure 1).

Patients were then grouped according to SLNI into Group 1 (SLNI negative) and Group 2 (SLNI positive). The association between clinical characteristics, preoperative inflammatory biochemical markers, and SLNI was then analyzed.

Preoperative Breast Imaging and Diagnostic Procedures

Bilateral breast ultrasonography (US) was performed preoperatively in all patients, while those aged ≥40 years also underwent bilateral mammography for diagnostic evaluation and the planning of BC treatment. Breast imaging was performed by radiologists specializing in breast imaging. Following imaging of a suspicious breast lesion, the diagnosis of BC was established using a core needle biopsy, stereotactic biopsy, or excisional biopsy, as appropriate.

Preoperative Axillary Evaluation

During preoperative axillary US, lymph nodes (LNs) that demonstrated a preserved hilum and a normal or mildly thickened cortex (<3 mm) were classified as cN0. Lymph nodes showing cortical thickening without loss of the hilum underwent fine-needle aspiration biopsy, and cases with negative cytology were also considered cN0. SLNB was performed in patients classified as cN0. Axillary

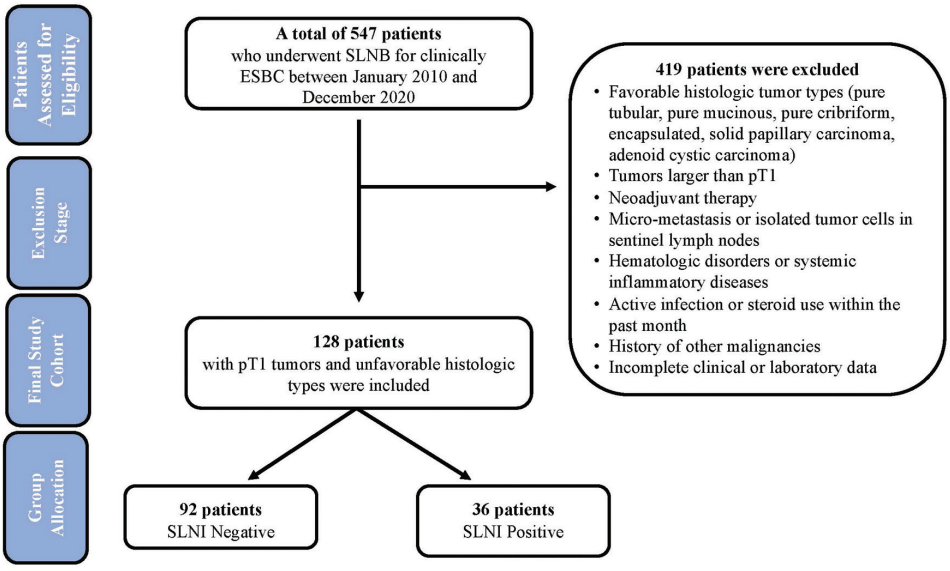

Figure 1. Study flow diagram
SLNB: Sentinel lymph node biopsy, ESBC: Early-stage breast cancer, SLNI: Sentinel lymph node involvement

LNs with cortical thickness greater than 3 mm and an absent hilum were classified as clinically node-positive and excluded from the study.

SLNB Procedure

After induction of general anesthesia, the procedure continued with the injection of 10 mL of blue dye into the subareolar region. The blue dyes used were patent blue, isosulfan blue, and methylene blue. A 12-minute massage was performed to facilitate lymphatic drainage. All blue-stained LNs were designated as sentinel lymph nodes (SLN) and were excised. Intraoperative pathological evaluation was performed using frozen section analysis, with hematoxylin and eosin staining of SLNs sectioned at 2-mm intervals.

Because a single-dye technique was used, patients with two or fewer identified SLNs underwent axillary dissection if at least one SLN was positive on frozen section analysis. Patients in whom no SLNs were identified also underwent axillary dissection. In patients with three or more identified SLNs, axillary dissection was performed only when more than two SLNs were found to be positive on frozen section analysis.

Data Collection and Reference Ranges

Patient and tumor parameters, including histologic type and grade, clinical and pathological tumor size, molecular subtype, presence of lymphovascular invasion (LVI), and Ki-67 score, were collected. Ultrasonography characteristics of axillary LN, SLNI, the total number of excised SLNBs, and preoperative levels of white blood cell count (WBC), lymphocytes, monocytes, neutrophils, red cell distribution width (RDW), albumin, and platelets were recorded. Reference ranges used in our biochemistry laboratory were as follows: WBC 3.9-10.2x10^9/L, lymphocytes 1.1-4.5x10^9/L, monocytes 0.1-0.9x10^9/L, neutrophils 1.5-7.7x10^9/L, RDW 11.5-16%, platelets 150-400x10^9/L, and albumin 3.2-4.8 g/dL. The LMR represents the ratio of total lymphocytes to total monocytes; the platelet-to-lymphocyte ratio (PLR) represents the ratio of total platelet count to total lymphocyte count; and the NLR represents the ratio of total neutrophils to total lymphocytes.

Study Outcomes

The primary outcome of this study was the identification of clinicopathological and preoperative SI parameters that were independently associated with SLNI in patients with T1 ESBC and unfavorable histologic types.

The secondary outcome was the identification of these parameters in order to provide additional information to support clinical decision-making in axillary management.

Statistical Analysis

All statistical analyses were conducted utilizing SPSS version 22.0 software (IBM Inc., Armonk, NY, USA). Data normality was examined with the Kolmogorov-Smirnov test, together with histogram and Q-Q plot inspection. Continuous data were summarized as mean ± standard deviation, the Independent Samples t-test was employed to evaluate differences between these variables for normally distributed data, while the Mann-Whitney U test was used for non-normally distributed variables. For categorical data, the chi-square test or Fisher's exact test was applied, as appropriate.

Statistical significance is defined as a p-value of less than 0.05. Variables that were statistically significant in univariate analysis were included in multivariate analyses. In logistic regression, a p-value of ≤0.05 was designated as the threshold for model inclusion, while a p-value of ≥0.10 was established for model exclusion. The results of the multivariable analysis were reported as odds ratios (OR) together with the corresponding 95% confidence intervals (CI).

Results

This study included 128 female patients with a mean age of 51.73±10.55 years (range: 35-84). The histological distribution of tumors was as follows: invasive ductal carcinoma (115 patients, 89.8%), invasive lobular carcinoma (4 patients, 3.1%), mixed-type carcinoma (1 patient, 0.8%), micropapillary carcinoma (1 patient, 0.8%), apocrine carcinoma (3 patients, 2.3%), and medullary-pattern ductal carcinoma (4 patients, 3.1%).

Patients were classified into Group 1 (SLNI negative), comprising 92 patients (71.9%), and Group 2 (SLNI positive), comprising 36 patients (28.1%). A mean of 3.07±1.59 SLNs (range 1-7) was excised overall. When analyzed according to SLNI status, the mean number of excised LNs was 2.98±1.55 in Group 1 and 3.27±1.71 in Group 2, with no statistically significant difference between the groups (p=0.36). For all patients included in the study, final pathology results were consistent with frozen section findings.

Assessment of the cortical thickness of axillary LNs on preoperative US revealed statistically significant differences among the groups. A thickened cortex was observed more frequently in the SLNI-positive group (Group 1: 79.3% normal cortex, 20.7% thickened cortex; Group 2: 58.3% normal cortex, 41.7% thickened cortex; p=0.016).

Similarly, the presence of LVI was significantly higher in the SLNI-positive group than in the SLNI-negative group (Group 1: 73.9% absent, 26.1% present; Group 2: 44.4% absent, 55.6% present; p=0.002).

Tumor size, serum albumin levels, and neutrophil counts showed statistically significant differences between Group 1 (SLNI negative) and Group 2 (SLNI positive). Compared with Group 1, the SLNI-positive group demonstrated lower serum albumin levels, larger tumor size, and higher neutrophil counts (Albumin: Group 1, 4.52±0.38 vs. Group 2, 4.28±0.36, p=0.002; Tumor size: Group 1, 13.30±4.90 vs. Group 2, 15.47±4.02, p=0.02; Neutrophil count: Group 1, 4.31±1.31 vs. Group 2, 4.90±1.89, p=0.046).

Comparisons of laboratory, demographic, and clinicopathological features between the groups are presented in Tables 1-3.

In univariate analysis, significant differences were observed between Group 1 (SLNI negative) and Group 2 (SLNI positive) with respect to tumor size, serum albumin levels, and neutrophil counts. Compared with the SLNI-negative group, patients with SLNI had lower serum albumin and monocyte levels, larger tumor size, a higher frequency of LVI, and higher neutrophil counts (p=0.002, p=0.064, p=0.02, p=0.002, and p=0.046, respectively).

In multivariate logistic regression analysis, LVI, serum albumin level, neutrophil count, and monocyte count were identified as independent variables associated with SLNI (Table 4).

Discussion

In invasive BC, SLNI is considered a critical prognostic indicator and has traditionally been evaluated together with tumor size when planning systemic and radiation therapy (6). Following the landmark studies by Giuliano et al. (11) and the ACOSOG Z0011 (Alliance) trial published in 2017 (12), routine axillary dissection has progressively been replaced by SLNB in cN0 patients with T1 and T2 BC.

Recent studies have increasingly evaluated the feasibility of omitting SLNB in selected subgroups of BC patients (13). In particular, the INSEMA and SOUND trials have demonstrated that omission of SLNB in carefully selected patients is non-inferior to standard SLNB with respect to oncological outcomes (5,6). These findings have not yet been fully integrated into existing clinical guidelines; however, they underscore the increasing significance of precisely predicting SLNI, particularly in patients with T1 ESBC. In this context, identifying clinicopathological characteristics and preoperative SI parameters associated with SLNI may support a more individualized approach to axillary management in patients with T1 ESBC and unfavorable histologic types.

Multiple clinical factors have been reported to influence disease progression and SLNI in patients with BC. In addition, accumulating evidence suggests that both disease progression and the likelihood of SLNI may be affected by the host's SI response (2,3,9,10,14,15). To more accurately evaluate the association between BC and preoperative factors potentially related to SLNI, it is important to focus on patient cohorts with homogeneous characteristics. Accordingly, the present study was restricted to patients with T1 tumors to minimize heterogeneity arising from differences in neoadjuvant and adjuvant treatment strategies for T1 versus T2 disease (16). In addition, favorable histologic subtypes, which have consistently been associated with lower rates of SLNI in the literature (17,18), were excluded from the analysis.

Low albumin levels in cancer patients have been attributed to malnutrition, increased metabolic demand, and suppressed albumin synthesis in the context of systemic inflammation. In addition, serum albumin has been proposed to function as an endogenous antioxidant

Table 1. Comparison of clinical characteristics between groups			
	Group 1 SLNI (-) (n=92)	**Group 2 SLNI (+) (n=36)**	**p-value**
Age (mean ± SD) (n=128)	52.58±10.98	49.55±9.16	0.145
Multifocality/multicentrity (n, %) (n=128)			0.295
Absent	72 (78.3%)	25 (69.4%)	
Present	20 (21.7%)	11 (30.6%)	
Lymph node characteristics (n, %) (n=128)			**0.016**
Normal finding	73 (79.3%)	21 (58.3%)	
Thick cortex	19 (20.7%)	15 (41.7%)	

Data are presented as mean±standard deviation or number (%). Continuous variables were compared using Independent Samples t-test or Mann-Whitney U test, as appropriate, and categorical variables were compared using the chi-square test.
Bold values in the table represent statistically significant parameters.
SLNI: Sentinel lymph node involvement, SD: Standard deviation

Table 2. Comparison of pathologic characteristics between groups			
	Group 1 (n=92) SLNI (-)	**Group 2 (n=36) SLNI (+)**	**p-value**
Tumor size (mean ± SD) (n=128)	13.30±4.90	15.47±4.02	**0.02**
Grade (n, %) (n=128)			0.269
I	34 (37.0%)	8 (22.2%)	
II	39 (42.4%)	18 (50.0%)	
III	19 (20.6%)	10 (27.8%)	
LVI (n, %) (n=128)			**0.002**
Absent	68 (73.9%)	16 (44.4%)	
Present	24 (26.1%)	20 (55.6%)	
Ki-67 score (%) (n=95)			0.90
≤15	43 (61.4%)	15 (60%)	
>15	27 (38.6%)	10 (40%)	
Molecular subtype (n, %) (n=128)			0.872
Luminal A	45 (49.0%)	18 (50.0%)	
Luminal B	36 (39.1%)	12 (33.4%)	
Her2 enriched	5 (5.4%)	3 (8.3%)	
Triple negative	6 (6.5%)	3 (8.3%)	
Total removed SLN (mean±SD) (n=128)	2.98±1.55	3.27±1.71	0.360

Data are presented as mean±standard deviation or number (%). Continuous variables were compared using Independent Samples t-test or Mann-Whitney U test, as appropriate, and categorical variables were compared using chi-square test.
Bold values in the table represent statistically significant parameters.
LVI: Lymphovascular invasion, SLNI: Sentinel lymph node involvement, SLN: Sentinel lymph node, SD: Standard deviation

and may play a role in reducing cancer-related risk (19). Several previous studies have demonstrated an association between decreased serum albumin levels and poorer prognosis across different malignancies, including BC (10,19,20).

In a large population-based cohort study, Yang et al. (19) investigated the association between pre-diagnostic serum albumin levels and overall cancer risk across multiple cancer types. No significant association was observed for BC, which the authors attributed to the limited number of BC cases and to the low proportion of female participants in the study. In contrast to these findings, the present study identified the preoperative serum albumin level as an independent predictor of SLNI in multivariate analysis among patients with T1 ESBC. We believe that this association becomes more apparent when the patient cohort is restricted to a clinically and pathologically homogeneous group, as described above.

Similarly, Fuji et al. (21) reported that reduced serum albumin levels were not associated with disease recurrence or SLNI in BC patients. However, in their subsequent study with longer follow-up, the same group demonstrated that OS and RFS were significantly shorter in patients with low serum albumin levels (10). These findings are consistent

Table 3. Comparison of systemic inflammatory blood parameters between groups			
Variables (mean ± SD)	**Group 1 (n=92) SLNI (-)**	**Group 2 (n=36) SLNI (+)**	**p-value**
Albumin (g/dL)	4.52±0.38	4.28±0.36	**0.002**
Lymphocyte (x10^9/L)	2.19±0.70	2.15±0.75	0.798
Monocyte (x10^9/L)	0.48±0.15	0.43±0.13	0.064
Neutrophil (x10^9/L)	4.31±1.31	4.90±1.89	**0.046**
Platelet (x10^9/L)	291.43±76.96	295.30±76.48	0.798
WBC (x10^9/L)	7.22±1.72	7.70±2.30	0.197
RDW (%)	13.91±1.44	14.28±1.56	0.209
LMR	4.75±1.61	5.25±2.06	0.147
NLR	2.19±1.10	2.51±1.36	0.167
PLR	148.34±67.87	154.86±72.49	0.663

Data are presented as mean±standard deviation. Continuous variables were compared using Independent Samples t-test or Mann-Whitney U test, as appropriate.
Bold values in the table represent statistically significant parameters.
SLNI: Sentinel lymph node involvement, SD: Standard deviation, WBC: White blood cell counts, RDW: Red cell distribution width, LMR: Lymphocyte to monocyte ratio, NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio

Table 4. Multivariate logistic regression analysis of factors associated with SLNI			
	OR	**95% CI**	**p-value**
Tumor size (mm)	1.071	0.970-1.183	0.177
Albumin (g/dL)	0.234	0.073-0.750	**0.015**
Neutrophil (x10^9/L)	1.381	1.030-1.853	**0.031**
Monocyte (x10^9/L)	0.020	0.001-0.764	**0.035**
Lymphovascular invasion	2.632	1.045-6.452	**0.040**
Lymph node characteristics	1.647	0.640-4.255	0.301

Multivariate logistic regression analysis was performed to identify independent factors associated with SLNI.
Bold values in the table represent statistically significant parameters.
OR: Odds ratio, CI: Confidence interval, SLNI: Sentinel lymph node involvement

with the prognostic trends observed in our cohort and support the potential clinical relevance of serum albumin in ESBC.

The literature presents inconsistent findings regarding preoperative inflammatory parameters. Several studies have reported an association between decreased lymphocyte counts, LMR and NLR; increased PLR; elevated monocyte and platelet counts; and unfavorable prognosis in patients with BC (14,15,22,23). In addition, some studies, including those with heterogeneous disease stages and ESBC populations, have demonstrated an association between PLR and SLNI (2,3,23).

In the present study, PLR values were higher in patients with SLNI, although this association did not reach statistical significance. This discrepancy may be related to the relatively small sample size of our cohort and to the inclusion of a more pathologically restricted population, specifically patients with unfavorable histologic subtypes of BC. In their meta-analysis, Hu et al. (14) reported that low LMR was not significantly associated with SLNI in BC patients, which is consistent with our findings. Similarly, Goto et al. (22) found no significant differences in SLNI when comparing low and high LMR and NLR levels in BC patients receiving neoadjuvant chemotherapy. In line with these studies, no significant association was observed among NLR, LMR, and SLNI in our cohort.

In our multivariate analysis, decreased monocyte levels and increased neutrophil counts were identified as independent predictors of SLNI. These findings suggest that alterations in specific components of the SI response may be associated with nodal involvement in ESBC. Monocytes play an important role in tumor-host interactions and have been associated with tumor progression and metastatic potential in various malignancies. Consequently, fluctuations in circulating monocyte levels may indicate a compromised antitumor immune response that promotes lymphatic dissemination (24).

Consistent with previous studies, our findings indicate that LVI is significantly associated with SLNI (25,26). LVI is regarded as a biological prerequisite for systemic dissemination and metastatic spread, and its presence has been consistently associated with a poorer prognosis in BC patients. Kuhn et al. (27) emphasized that LVI reflects an aggressive tumor phenotype and is closely associated with nodal involvement. Furthermore, Wei et al. (28) demonstrated that LVI is an independent predictor of non-SLN metastases in BC patients with one or two positive SLNs, highlighting its potential role in guiding adjuvant treatment decisions. In line with these data, our results confirm LVI as a significant predictor of SLNI within a pathologically homogeneous cohort.

In the literature, distinct cut-off values for serum albumin have been reported across different patient populations, largely reflecting tumor burden or the

presence of an SI tumor microenvironment. Albumin levels below 4 g/dL are generally considered markers of poor prognosis and malnutrition in various malignancies. However, in ESBC, systemic effects of the disease are often limited, and albumin levels are therefore expected to remain within normal reference ranges. This characteristic of ESBC limits the ability to establish reliable cutoff values for SI markers such as albumin, neutrophil, and monocyte levels, which were identified in our study as significant predictors of SLNI. Future studies involving larger and more homogeneous cohorts may help define more precise cut-off values and enhance the clinical applicability of these parameters.

Study Limitations

This study has several limitations. Due to the retrospective design, access to detailed information on certain preoperative variables that may influence SI markers was limited. In addition, the single-center setting may limit the generalizability of the findings. Furthermore, the relatively small sample size resulted in limited variability in monocyte and albumin levels between groups, which may have hindered the identification of definitive cut-off values for these parameters.

Despite these limitations, the present study has notable strengths. The analysis was restricted to a clinically and pathologically homogeneous cohort consisting exclusively of patients with T1 ESBC and unfavorable histologic subtypes. This approach minimized heterogeneity related to tumor biology. Additionally, the evaluation focused on objectively measured preoperative parameters and the pathological assessment of SLN, which may contribute to the consistency of findings and provide a basis for prospective studies.

Conclusion

This study demonstrated that LVI and selected preoperative SI markers, including albumin, are associated with SLNI in patients with T1 ESBC and unfavorable histologic subtypes. These findings were derived from a pathologically homogeneous cohort and specifically reflect early-stage disease. The result may contribute to future studies aimed at improving preoperative assessment of SLNB and supporting clinical decision-making in axillary management.

Ethics

Ethics Committee Approval: Ankara Bilkent City Hospital Clinical Research Ethics Committee No. 1 approved the study (approval no.: E1/2236/2020, date: 15.12.2021).

Informed Consent: Waived the requirement for informed consent due to its retrospective nature.

Acknowledgements

This research was presented as an oral presentation at the 23rd Turkish National Surgical Congress (April 2024, Antalya), and the abstract was included in the congress proceedings.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.G.D., E.M., Concept: E.G.D., E.M., Design: K.C., E.G.D., E.M., Data Collection or Processing: F.C., M.B.A., S.K.O., Analysis or Interpretation: H.P.O., E.M., Literature Search: K.C., H.P.O., E.M., Writing: K.C., H.P.O., E.M.

Conflict of interests: The authors declare that they have no conflict of interest related to this study.

Financial Disclosure: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Original Article

DOI: 10.4274/haseki.galenos.2026.58066
Med Bull Haseki 2026;64(3):200-204

Association Between C-reactive Protein/Albumin Ratio and Histopathological Severity of Gastritis in Children with *Helicobacter pylori* Infection

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Abstract

Aim: Considering that systemic inflammatory indicators may insufficiently represent localized gastric inflammation in juvenile populations, chronic *Helicobacter pylori (H. pylori)* infection is associated with persistent gastric inflammation, which may influence systemic inflammatory parameters in children. This study aimed to investigate whether the C-reactive protein/albumin ratio (CAR) was associated with the severity of histopathological gastritis and *H. pylori* colonization density in *H. pylori*-positive children.

Methods: This retrospective cross-sectional study included 121 children aged 1-18 years who underwent upper gastrointestinal endoscopy for dyspeptic symptoms and were diagnosed with *H. pylori* infection. Gastritis severity, activity, and *H. pylori* colonization density were graded according to the modified Sydney classification system. The association between the CAR and histopathological parameters was analyzed.

Results: The study included 121 pediatric patients (mean age ± standard deviation: 14.49±2.83 years), of whom 66% were female. No statistically significant association was observed between the CAR and chronic gastric inflammation grade, gastric inflammatory activity grade, or *H. pylori* colonization density grade (p=0.735, p=0.287, and p=0.318, respectively). Although the median CAR was higher in patients with severe *H. pylori* colonization than in those with mild or moderate colonization, this difference did not reach statistical significance (p=0.744).

Conclusion: The findings indicate that the CAR is not associated with histopathological severity or colonization density of *H. pylori* in children and does not reflect the histopathological severity in pediatric *H. pylori* gastritis.

Keywords: C-reactive protein, child, gastritis, *Helicobacter pylori*, inflammation

Introduction

Helicobacter pylori (*H. pylori*) infection remains a significant global health problem and is typically acquired during early childhood, often persisting throughout life in the absence of eradication therapy. Although the overall prevalence of *H. pylori* infection has declined in recent years, it continues to affect a substantial proportion of the pediatric population worldwide. In children, *H. pylori* infection is usually asymptomatic but is consistently associated with chronic gastric inflammation, whereas severe complications such as peptic ulcer disease or premalignant lesions are considerably less common than in adults (1). The prevalence of *H. pylori* infection varies according to geographical and socioeconomic factors, and previous studies from Türkiye have reported high

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Received: 25.03.2025 **Accepted:** 02.03.2026 **Epub:** 31.03.2026 **Publication Date:** 01.06.2026

Cite this article as: Kara H, Arslan M, Ozkececi CF, Basaran EG, Balamtekin N, Unay B. Association between C-reactive protein/albumin ratio and histopathological severity of gastritis in children with *Helicobacter pylori* infection. Med Bull Haseki. 2026;64(3):200-204

prevalence rates in children, ranging from approximately 50% to over 60%, with prevalence increasing with age (2,3).

C-reactive protein (CRP) is a positive acute-phase reactant synthesized by the liver that increases in response to systemic inflammation, whereas albumin is a negative acute-phase reactant that decreases during inflammatory states (4,5). Recent studies in the literature on these two inflammatory markers have shown that the CRP/albumin ratio (CAR) is closely associated with the prognosis and mortality in inflammatory diseases related to inflammation, such as acute pancreatitis, Crohn's disease, rheumatoid arthritis, and ulcerative colitis (6-9). H. pylori gastritis is associated with chronic inflammatory stress (10). It is therefore reasonable to investigate CAR in *H. pylori* gastritis. However, a comprehensive review of the literature did not identify any previous studies evaluating the relationship between CAR and histopathological features of gastritis or H. pylori colonization in children. We hypothesized that CAR might be associated with histopathological features of gastritis and the severity of *H. pylori* colonization in children.

The aim of the present study was to evaluate the association between the CAR and clinical, endoscopic, and histopathological features of gastritis, as well as *H. pylori* colonization density, in children with *H. pylori* infection. By elucidating this relationship, we aimed to determine whether readily available systemic inflammatory parameters reflect the severity of localized gastric histopathological changes in pediatric *H. pylori* gastritis, rather than to assess their diagnostic performance.

Materials and Methods

Compliance with Ethical Standards

The study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the University of Health Science Türkiye, Gulhane Scientific Research Ethics Committee (approval number: 2022-207, date: 26.05.2022).

Study Design and Patient Selection

This study was designed as a retrospective cross-sectional observational study including pediatric patients who underwent upper gastrointestinal endoscopy for dyspeptic complaints and were diagnosed with *H. pylori* gastritis based on histopathological examination. Patients with previous *H. pylori* eradication therapy, recent antibiotic or proton pump inhibitor use, chronic systemic inflammatory diseases, or incomplete clinical or laboratory data were excluded from the study. A total of 121 pediatric patients aged 1-18 years who met the inclusion criteria were enrolled. The patient selection process and study flow are summarized in Figure 1.

Endoscopic and Histopathological Evaluation

Esophagogastroduodenoscopy was performed by a single pediatric gastroenterologist using an Olympus X260 endoscope (Olympus, Japan) under deep sedation administered by an anesthesiologist. *H. pylori* diagnosis was based on five biopsy samples—two from the antrum, two from the corpus, and one for rapid urease testing (campylobacter-like organism test). The biopsy samples were processed, stained with hematoxylin-eosin, and examined via light microscopy. The severity of gastritis and *H. pylori* colonization density were graded according to the modified Sydney system (11).

Laboratory Parameters

Laboratory findings, including serum CRP and albumin levels obtained at the time of diagnosis, were retrieved from the hospital database. The reference ranges in our laboratory are 0-5 mg/L for CRP and 3.0-5.5 g/dL for albumin.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 26.0 (IBM Corporation, Armonk, NY, USA). Normality of continuous variables was assessed using the Kolmogorov-Smirnov test. Continuous variables were expressed as mean ± standard deviation or median (minimum-maximum), as appropriate. Non-parametric tests were used for group comparisons, including the Mann-Whitney U test for two-group comparisons and the Kruskal-Wallis test for comparisons involving more than

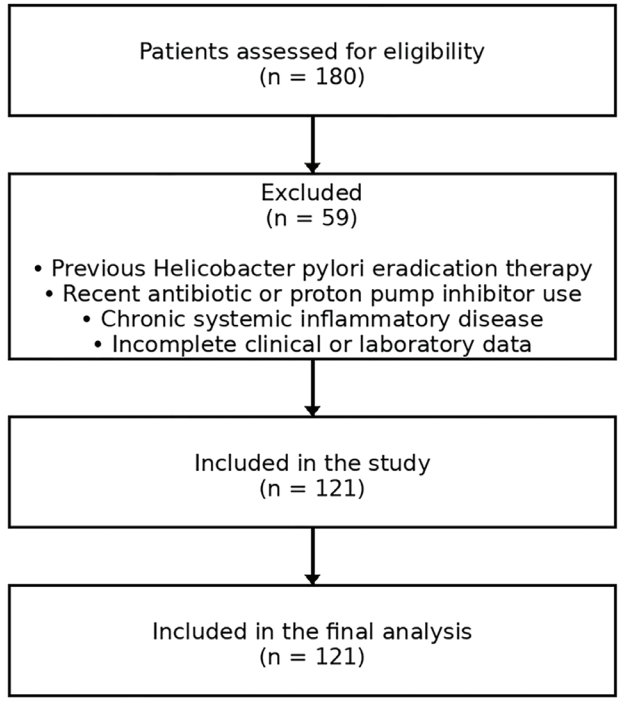

Figure 1. Flow diagram of patient selection and study population

two groups, with Bonferroni-adjusted post hoc analyses when applicable. Categorical variables were expressed as frequencies and percentages and compared using the chi-square test. Diagnostic performance analyses, including receiver operating characteristic analysis, were not performed. A p-value <0.05 was considered statistically significant.

Results

Descriptive analyses

A total of 121 pediatric patients were included (mean age: 14.49±2.83 years). The mean CRP level was 2.94±9.53 mg/L, the mean albumin was 4.46±0.47 g/dL, and the mean CAR was 0.72±2.26 (Table 1). Of the patients, 62.0% were aged ≥15 years and 66.6% were female. Endoscopic evaluation revealed antral gastritis in 43.8% of patients and pangastritis in 56.2%. Histopathologically, gastritis severity was classified as mild in 19.0%, moderate in 64.5%, and severe in 16.5% of patients. Similarly, *H. pylori* colonization density was mild in 31.4%, moderate in 46.3%, and severe in 22.3% of cases. Neither intestinal metaplasia nor atrophy was observed in any patient.

Relationship Between CAR and Clinical and Histopathological Parameters

No significant associations were identified between CAR and demographic, clinical, endoscopic, or histopathological parameters, including gastric inflammation grade, inflammatory activity, and *H. pylori* colonization density (all p>0.05) (Table 2). Although median CAR values tended to be higher in patients with severe *H. pylori* colonization compared with those with mild or moderate colonization, this difference did not reach statistical significance (p=0.74).

Table 1. Socio-demographic and clinical characteristics of the patients

Variable	Median (min-max)
Age (years)	15 (5-18)
CRP (mg/L)	0.64 (0.05-102)
Albumin (g/dL)	4.48 (1.5-5.5)
CRP/albumin	0.15 (0.01-23.08)

CRP: C-reactive protein

Table 2. Association between the C-reactive protein/albumin ratio and demographic, clinical, endoscopic, and histopathological characteristics

		CRP/albumin Median (min-max)	p
Gender	**Female (n=77)**	0.14 (0.01-23.08)	0.459*
	Male (n=44)	0.23 (0.02-3.47)	
Age (year)	**<15 (n=46)**	0.12 (0.02-23.08)	0.928*
	≥15 (n=75)	0.16 (0.01-4.81)	
Stomach pain	**No (n=17)**	0.25 (0.02-5.63)	0.153*
	Yes (n=104)	0.15 (0.01-23.08)	
Nausea/vomiting	**No (n=78)**	0.15 (0.01-23.08)	0.820*
	Yes (n=43)	0.14 (0.01-5.63)	
Retrosternal burning	**No (n=82)**	0.15 (0.01-23.08)	0.794*
	Yes (n=39)	0.15 (0.01-4.81)	
Regurgitation	**No (n=114)**	0.14 (0.01-23.08)	0.172*
	Yes (n=7)	0.2 (0.09-2.07)	
Endoscopic finding	**Antral gastritis (n=53)**	0.09 (0.02-23.08)	0.408*
	Pangastritis (n=68)	0.19 (0.01-4.68)	
Gastric inflammation grade	**Mild (n=23)**	0.15 (0.02-3.11)	0.735**
	Moderate (n=78)	0.14 (0.01-5.63)	
	Severe (n=20)	0.14 (0.01-23.08)	
Gastric inflammatory activity grade	**Mild (n=36)**	0.12 (0.02-3.11)	0.287**
	Moderate (n=56)	0.12 (0.01-5.63)	
	Severe (n=22)	0.16 (0.04-23.08)	
	Negative (n=7)	0.1 (0.04-1.82)	
Gastric *H. pylori* colonization density grade	**Mild (n=38)**	0.07 (0.02-5.63)	0.318**
	Moderate (n=56)	0.13 (0.01-3.47)	
	Severe (n=27)	0.22 (0.01-23.08)	

*Mann-Whitney U test
**Kruskal-Wallis test post-hoc: Bonferroni Mann-Whitney U test

Discussion

Helicobacter pylori infection remains the most common chronic bacterial infection worldwide and represents a significant public health burden, particularly in developing countries (1). A Turkish epidemiological study by Ertem et al. reported that the prevalence of *H. pylori* infection in children under 4 years old was 18.2%, increasing to 65% in adolescents (3). Consistent with previous epidemiological data, the majority of patients in the present cohort were adolescents, with a higher prevalence observed among individuals aged 15 years and older. Similar to prior reports, no significant gender-related differences were observed, supporting the notion that *H. pylori* infection affects male and female children equally.

Previous studies have demonstrated a close association between *H. pylori* colonization density and both chronic gastric inflammation and gastric inflammatory activity, with increasing bacterial burden being linked to more pronounced mucosal inflammation (12). Consistent with these reports, our findings indicate that gastric inflammatory activity increases in parallel with rising *H. pylori* colonization density, supporting the concept that bacterial load plays a key role in the severity of the local gastric inflammatory response in pediatric patients. The absence of gastric atrophy or intestinal metaplasia in this cohort is in line with existing pediatric literature, which indicates that H. pylori infection in childhood is more commonly associated with chronic gastritis and peptic ulcer disease rather than premalignant gastric lesions (13).

The primary aim of this study was to determine whether the CRP/CAR reflects histopathological severity in pediatric *H. pylori* gastritis. Despite clear histopathological evidence of gastric inflammation and inflammatory activity, no significant association was observed between the CAR and any of the following: chronic gastric inflammation grade, gastric inflammatory activity grade, or *H. pylori* colonization density grade. These findings suggest that this systemic inflammatory marker does not adequately reflect the degree of localized gastric inflammation in children with *H. pylori* infection.

The CRP/CAR is an inflammation-based prognostic marker linked to the severity of inflammatory conditions. The CAR has been widely investigated as an inflammation-based marker in pediatric and adult populations, particularly in conditions characterized by systemic and high-grade inflammatory responses. Previous studies have demonstrated its clinical utility in diseases such as complicated appendicitis, sepsis, inflammatory bowel disease, and advanced liver disease, where inflammation is diffuse, persistent, and associated with measurable alterations in circulating acute-phase reactants (14-17).

Helicobacter pylori infection has been shown to induce both localized gastric mucosal inflammation and low-grade systemic inflammatory responses, reflecting its role as a common cause of chronic gastritis. Previous pediatric studies have demonstrated that this low-grade systemic inflammation may be detected through cell-based inflammatory indices, such as neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios, which appear to correlate with the presence and severity of *H. pylori* infection (18).

In contrast, the C-reactive protein/albumin ratio represents a composite marker of the acute-phase response and may require a more pronounced or diffuse systemic inflammatory burden to show consistent alterations. Although *H. pylori* infection is associated with localized gastric inflammation and low-grade systemic inflammatory responses, this level of inflammation may be insufficient to induce measurable changes in serum acute-phase reactants in pediatric patients. This pathophysiological difference may explain the lack of association observed in the present study between the C-reactive protein/albumin ratio and gastric chronic inflammation grade, gastric inflammatory activity grade, or *H. pylori* colonization density.

Study Limitations

The limitations of this study include its retrospective design, a relatively small sample size, and the absence of an *H. pylori*-negative control group, which limit the evaluation of the diagnostic performance and the cut-off value of the C-reactive protein/albumin ratio. In addition, serum CRP and albumin levels are non-specific parameters that may be influenced by various clinical conditions unrelated to gastric inflammation. Despite these limitations, the study provides a detailed histopathological evaluation based on the standardized Sydney classification and offers novel insight into the relationship between a widely used systemic inflammatory marker and localized gastric inflammation in pediatric *H. pylori* gastritis.

Conclusion

Although median CAR values tended to be higher in children with significant *H. pylori* colonization than in those with mild or moderate colonization, the difference did not reach statistical significance. The findings of this study indicate that the CAR does not reliably reflect the severity of chronic gastric inflammation, gastric inflammatory activity, or *H. pylori* colonization density in pediatric patients. These results suggest that systemic acute-phase reactants may have limited utility in assessing localized gastric inflammation associated with *H. pylori* infection in children. Further large-scale prospective studies are needed to validate these findings.

Ethics

Ethics Committee Approval: The study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the University of Health Science Türkiye, Gulhane Scientific Research Ethics Committee (approval number: 2022-207, date: 26.05.2022).

Informed Consent: Written informed consent was waived due to the retrospective nature of the study; however, general consent for diagnostic procedures was obtained from all patients and/or their legal guardians.

Footnotes

Authorship Contributions

Surgical and Medical Practices: H.K., N.B., B.U., Concept: H.K., N.B., B.U., Design: H.K., N.B., B.U., Data Collection or Processing: H.K., M.A., C.F.O., E.G.B., N.B., Analysis or Interpretation: H.K., M.A., C.F.O., E.G.B., Literature Search: H.K., M.A., Writing: H.K., M.A., N.B.

Conflict of interests: No conflict of interest was declared by the authors.

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

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Original Article

DOI: 10.4274/haseki.galenos.2026.39358
Med Bull Haseki 2026;64(3):205-212

Association of Job Satisfaction and Sleep Quality with Psychological Symptom Severity among Hospital Security Personnel: A Cross-Sectional Study

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Abstract

Aim: Hospital security staff encounter specific occupational stressors, such as irregular work hours, exposure to violence, and crises, but research on their mental health remains limited. This study aimed to examine the association between psychological symptom severity and sleep quality, job satisfaction, work schedule, and psychiatric history among hospital security personnel.

Methods: A cross-sectional study was performed with 115 hospital security personnel from May 1, 2025, to July 1, 2025. All security workers completed structured questionnaires. The assessment tools included the Minnesota Satisfaction Questionnaire, the Pittsburgh Sleep Quality Index, and the Symptom Checklist-90-Revised (SCL-90-R). Participants' sociodemographic data were recorded. Spearman correlation analysis was used to examine associations between continuous variables. Multiple linear regression analysis was performed to determine variables that were independently associated with SCL-90-R scores.

Results: Significant differences in psychological symptoms were not found across demographic groups, work schedules, or psychiatric history. Correlation analysis revealed a significant negative association between job satisfaction and psychological distress (r=-0.253, p=0.006). Multiple linear regression analysis demonstrated that job satisfaction was independently associated with SCL-90-R scores (B=-0.004, 95% confidence interval: -0.007 to -0.001, p=0.031), whereas sleep quality (p=0.310), age (p=0.299), gender (p=0.130), and work schedule (p=0.965) showed no statistically significant association. Sleep quality, age, gender, work schedule, and other variables showed no significant predictive value.

Conclusion: Job satisfaction was the only variable independently associated with psychological well-being among hospital security personnel, independent of traditional occupational stressors such as shift work and sleep quality. These findings suggest that organizational interventions targeting job satisfaction may be associated with improved mental health outcomes in this population.

Keywords: Health personnel, job satisfaction, psychological distress, shift work, sleep quality

Introduction

Hospitals and other healthcare centers are workplaces that can impose a significant psychosocial burden on support staff and healthcare workers. In this setting, security guards are a professional group at high risk of violence and frequent crises, and they play a vital role in patient-caregiver interactions. Research on the mental health of hospital security personnel is lacking.

Security officers in healthcare centers face a unique confluence of stressors: irregular work hours, sleep disruption, limited institutional support, and chronic exposure to crises. These stressors are known risk factors for psychological symptoms such as depression, anxiety, hostility, and somatization (1,2). The main factors affecting psychological symptom severity include sleep quality, work schedule, and job satisfaction. Psychopathological conditions, particularly depressive and anxiety symptoms, have been linked to poor sleep quality (3). Similarly, low job satisfaction may cause burnout, somatization, and depression (4). Shift work can interfere with the circadian

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Received: 09.09.2025 **Accepted:** 09.03.2026 **Epub:** 31.03.2026 **Publication Date:** 01.06.2026

Cite this article as: Hoca SC, Senturk Pehlivan K. Association of job satisfaction and sleep quality with psychological symptom severity among hospital security personnel: a cross-sectional study. Med Bull Haseki. 2026;64(3):205-212

rhythm, which can negatively impact sleep and mental well-being (5). However, despite the well-documented associations among nurses, paramedics, and other clinical personnel, there is a dearth of research on the mental health of hospital security staff (6-12). Given their unique exposure to occupational risks and their integral role in maintaining hospital safety, it is crucial to examine the psychological outcomes in this population.

We hypothesized that lower job satisfaction and poorer sleep quality would be associated with higher levels of psychological symptom severity among hospital security personnel. Therefore, this study aimed to examine the association of sleep quality, job satisfaction, work schedule, and psychiatric history with psychological symptom severity in hospital security staff. By identifying modifiable occupational factors associated with psychological distress, such as job satisfaction and sleep quality, this study may contribute to the development of organizational strategies aimed at improving mental well-being among hospital security personnel.

Materials and Methods

Compliance with Ethical Standards

This study was conducted between 01 May 2025 and 01 July 2025 at the University of Health Sciences Türkiye, Umraniye Training and Research Hospital, Istanbul, Türkiye. The University of Health Sciences Türkiye, Umraniye Training and Research Hospital Scientific Research Ethics Committee approved the study protocol (approval no.: 70, date: 10.04.2025). All study procedures adhered to the principles of the Declaration of Helsinki. Prior to enrollment, written informed consent was obtained from each participant.

Study Design

The study was designed as prospective and cross-sectional. The study population comprised security personnel employed at the University of Health Sciences Türkiye, Umraniye Training and Research Hospital. Individuals aged 18-65 who agreed to participate in the study and did not have an active psychiatric diagnosis, neurological disorder, or history of serious medical illness were included. Participants were excluded if they had an active psychiatric diagnosis at the time of evaluation, a known neurological disorder, a history of severe medical illness that could affect psychological functioning, or incomplete questionnaire data. In addition, personnel assigned to external units were not eligible for participation due to limited access during the study period. A history of psychiatric diagnoses in remission was not considered an exclusion criterion and was recorded as a separate variable. At the time of the study, 140 hospital security personnel were employed by our institution. A total of 115 personnel, representing 82% of the hospital security workforce, met the inclusion criteria, provided informed consent, and were included in the study. The participant selection and inclusion process is presented in the study flow diagram (Figure 1). Data were collected through face-to-face interviews using structured questionnaires administered during participants' annual psychiatric examinations. After completion of all procedures, data from all patients were anonymized.

Working Conditions and Employment Characteristics

All hospital security personnel were employed under standardized institutional contracts with fixed monthly salaries and full social insurance coverage in accordance with national labor regulations. Personnel were entitled to standard employment rights, including regulated working hours, annual leave, and occupational health protections. These institutional working conditions were uniform across participants and not performance-based.

Sociodemographic and Occupational Characteristics

A structured questionnaire collected data on demographics, work characteristics (shift type, years in the security sector, tenure at the current workplace), and psychiatric history.

Psychological Symptoms

The Turkish version of the Symptom Checklist-90-Revised (SCL-90-R) assessed psychological symptom severity. Derogatis and Cleary (13) developed the scale in 1977. The validity and reliability of the Turkish version were established in 1991 (14). The SCL-90-R, a 90-item self-report scale, assesses psychological symptoms across nine domains (depression, anxiety, phobic anxiety, hostility, paranoid ideation, psychoticism, somatization, obsessive-compulsive, and interpersonal sensitivity). Items are rated on a 5-point Likert scale (0-4). The Global Severity Index, reflecting overall distress, was computed as the mean of all items.

Sleep Quality

Buysse et al. (15) developed the Pittsburgh Sleep Quality Index (PSQI) in 1989 to assess subjective sleep quality over the last month. The Turkish validity and reliability of the scale were established by Agargün et al. (16) in 1996. The PSQI comprises 19 self-report items that assess seven domains of sleep: daytime dysfunction, use of sleeping medication, sleep disturbances, sleep efficiency, sleep latency, sleep duration, and subjective sleep quality. The total score (0-21) reflects overall sleep quality, with higher scores denoting greater impairment.

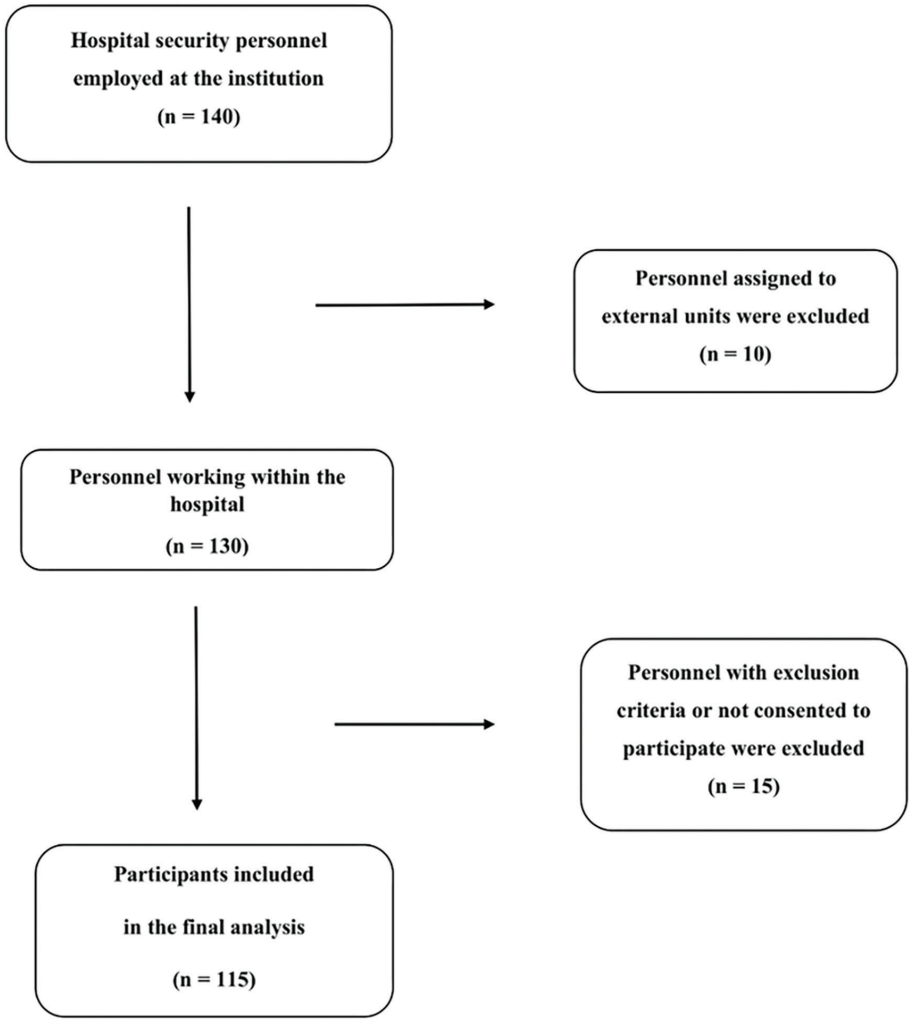

Figure 1. Flow diagram of participant recruitment and inclusion process

Job Satisfaction

In 1967, Weiss et al. (17) developed the Minnesota Satisfaction Questionnaire (MSQ). The validity and reliability studies were conducted, and this questionnaire was translated into Turkish by Baycan (18) in 1985. The MSQ short form contains 20 items rated on a 5-point Likert scale (1= very dissatisfied, 5= very satisfied), yielding intrinsic, extrinsic, and general satisfaction scores. The total score ranges from 20 to 100, with higher scores indicating greater job satisfaction.

Statistical Analysis

Statistical analyses were conducted with IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics included means±standard deviations for continuous variables and frequencies (percentages) for categorical variables. We used the Kolmogorov-Smirnov test to assess the normality of continuous variables. Skewness and Kurtosis values and visual inspection of histograms were used to assess normality. Since the SCL-90-R scores showed a non-normal distribution based on these assessments, non-parametric statistical tests were employed for group comparisons. Mann-Whitney U tests were used to compare SCL-90-R scores between groups for categorical variables with two levels (gender, work schedule, and psychiatric history). Kruskal-Wallis tests were conducted on categorical variables with more than two categories to examine differences in SCL-90-R scores across the following groups: education level, marital status, experience in the security sector, and experience in the current workplace. In cases where significant differences emerged, post-hoc pairwise analyses were performed via Dunn's test, incorporating Bonferroni correction to control for multiple comparisons. Associations between continuous

variables were examined using Spearman's rank-order correlation coefficient due to the non-normal distribution of SCL-90-R scores. Correlation analyses were conducted to assess the relationships between SCL-90-R scores and age, MSQ scores, and PSQI scores. A multiple linear regression model was constructed to evaluate variables independently associated with SCL-90-R scores. All independent variables (job satisfaction, sleep quality, psychiatric history, marital status, gender, age, education level, work schedule, years of experience in the security sector, and tenure at the current workplace) were entered into the model simultaneously using the enter method. The threshold for statistical significance was established at $p<0.05$.

Results

Participant Characteristics

A total of 115 hospital security personnel were included in the study. The mean age of the participants was 37.99±7.17 years, and the majority were male. Most participants were high school graduates and were married. Rotating shift work was the most common working pattern. Most participants had 6–10 years of experience in the security sector and a similar duration of employment at the current institution.

The mean SCL-90-R score was 0.24±0.19, the mean PSQI score was 3.72±2.55, and the mean MSQ score was 74.31±10.77. A history of psychiatric diagnosis or treatment was reported by a minority of participants. Detailed descriptive characteristics are presented in Table 1.

Group Comparisons

Non-parametric analyses were conducted to compare SCL-90-R scores across demographic and occupational variables. No statistically significant differences in psychological symptom severity were observed according to gender, education level, marital status, work schedule, work experience, or psychiatric history. Detailed group comparisons are presented in Table 2.

Correlation Analysis

Correlation analysis revealed a significant negative association between job satisfaction and psychological symptom severity ($r=-0.253$, $p=0.006$). No significant correlations were found between SCL-90-R scores and age or sleep quality. The full correlation matrix is presented in Table 3.

Regression Analysis

Multiple linear regression was performed to determine the factors associated with psychological symptom severity. The regression model explained a modest proportion of the variance in SCL-90-R scores ($R^2=0.110$, adjusted $R^2=0.021$). Multicollinearity diagnostics indicated no significant multicollinearity among the independent variables, with variance inflation factor (VIF) values ranging between 1.15 and 2.86.

Job satisfaction was the only variable independently associated with SCL-90-R scores (B=-0.004, 95% confidence interval: -0.007 to -0.0004, $p=0.031$), while age, gender, education level, marital status, work schedule, work experience, psychiatric history, and sleep quality were not significantly associated with SCL-90-R scores. Full regression results are presented in Table 4.

Table 1. Descriptive characteristics and sociodemographic findings of all patients

Characteristics	n (%) or Mean ± SD
Age (years)	37.99±7.17
Gender	
Male	79 (68.7)
Female	36 (31.3)
Education	
High school	72 (62.6)
Vocational school	18 (15.7)
University	25 (21.7)
Marital status	
Married	78 (67.8)
Single	29 (25.2)
Divorced/Widowed	8 (7.0)
Work schedule	
Day shift only	43 (37.4)
Rotating shifts	72 (62.6)
Experience in security sector	
<1 year	4 (3.5)
1-5 years	15 (13.0)
6-10 years	52 (45.2)
11-15 years	21 (18.3)
>15 years	23 (20.0)
Experience in current workplace	
<1 year	11 (9.6)
1-5 years	15 (13)
6-10 years	60 (52.2)
11-15 years	19 (16.5)
>15 years	10 (8.7)
Psychiatric history	
Present	14 (12.2)
Not present	101 (87.8)
SCL-90-R	0.24±0.19
MSQ	74.31±10.77
PSQI	3.72±2.55

N: Number of patients, SD: Standard deviation, SCL-90-R: Symptom Checklist-90-Revised, MSQ: Minnesota Satisfaction Questionnaire, PSQI: Pittsburgh Sleep Quality Index

Table 2. SCL-90-R scores by demographic and occupational characteristics

	SCL-90-R (Mean ± SD)	p-value
Gender		
Female	0.26±0.18	0.098
Male	0.22±0.19	
Education		
High school	0.26±0.21	0.432
Vocational school	0.23±0.15	
University	0.18±0.12	
Marital status		
Married	0.24±0.20	0.905
Single	0.23±0.18	
Divorced/Widowed	0.23±0.16	
Work schedule		
Day shift only	0.25±0.18	0.350
Rotating shifts	0.23±0.19	
Experience in security sector		
<1 year	0.37±0.10	0.302
1-5 years	0.21±0.21	
6-10 years	0.23±0.15	
11-15 years	0.24±0.24	
>15 years	0.24±0.21	
Experience in current workplace		
<1 year	0.28±0.23	0.966
1-5 years	0.20±0.12	
6-10 years	0.22±0.17	
11-15 years	0.26±0.25	
>15 years	0.25±0.21	
Psychiatric history		
Present	0.24±0.19	0.617
Not present	0.20±0.16	

The Mann-Whitney U test and the Kruskal-Wallis test were used for group comparisons. Statistical significance was set at p<0.05.
SD: Standard deviation, SCL-90-R: Symptom Checklist-90-Revised

Table 3. Correlations of different variables with SCL-90-R scores

Age	**r**	0.042
	p	0.660
MSQ	**r**	-0.253
	p	**0.006**
PSQI	**r**	0.126
	p	0.179

Spearman's rank correlation coefficient was used for correlation analysis. Statistically significant p-values (<0.05) were shown in bold.
SCL-90-R: Symptom Checklist-90-Revised, MSQ: Minnesota Satisfaction Questionnaire, PSQI: Pittsburgh Sleep Quality Index

Table 4. Regression model for determining factors independently affecting SCL-90-R scores

Variable	B	Std. error	Lower bound	Upper bound	p-value
Constant	0.538	0.202	0.137	0.938	0.009
Age	0.003	0.003	-0.003	0.009	0.299
Gender	-0.068	0.045	-0.157	0.020	0.130
Education level	-0.024	0.023	-0.07	0.022	0.297
Marital status	-0.027	0.037	-0.099	0.046	0.465
Work schedule	-0.002	0.046	-0.093	0.089	0.965
Experience in security sector	-0.013	0.028	-0.068	0.041	0.626
Experience in current workplace	0.017	0.028	-0.039	0.073	0.544
Psychiatric history	-0.049	0.057	-0.162	0.065	0.395
MSQ	-0.004	0.002	-0.007	-0.0004	**0.031**
PSQI	0.008	0.008	-0.008	0.023	0.310

Multiple linear regression analysis using the enter method was performed. Confidence intervals are presented at the 95% level. Statistically significant p-values (<0.05) were expressed in bold.
SCL-90-R: Symptom Checklist-90-Revised, MSQ: Minnesota Satisfaction Questionnaire, PSQI: Pittsburgh Sleep Quality Index

Discussion

This research analyzed the association between psychological symptom severity and factors including job satisfaction, sleep quality, and shift arrangements among hospital security personnel. Our findings indicate that job satisfaction was the only variable independently associated with psychological symptom severity in the regression analysis. In contrast, gender, age, work modality, psychiatric history, and sleep quality did not show a statistically significant association with distress levels.

The inverse relationship between job satisfaction and psychological distress found in this study is consistent with prior research showing that lower satisfaction is associated with increased depression, anxiety, and burnout (1,4,19). Lack of job satisfaction may increase perceived job distress, reduce resilience, and exacerbate the psychological burden experienced in high-stress work environments, such as hospitals, where security staff are frequently exposed to aggression, unpredictable emergencies, and interpersonal conflict. A study of Chinese army officers found that higher job satisfaction was linked to a stronger sense of calling. This link was made stronger by how meaningful they thought their work and life were (20). Such findings suggest that organizational strategies enhancing these dimensions indirectly support mental health by increasing job satisfaction.

Our findings can be interpreted through the perspective of the Job Demands-Resources (JD-R) model, which suggests that workplace factors include job demands (stressors requiring sustained effort) and job resources (factors that facilitate goal achievement and reduce distress) (21). Interestingly, traditional job demands like shift work and poor sleep quality did not show a significant association with psychological symptoms in our sample, despite being commonly recognized as major factors affecting mental health in shift workers (22,23). In contrast, job satisfaction—a crucial job resource—emerged as the only significant predictor. This unexpected pattern may be explained by an adaptive phenomenon among our experienced security personnel (mean experience >6 years), who appear to have habituated to the chronic, unchangeable demands inherent in security work. When job demands become fixed aspects of the occupational role that cannot be modified (such as mandatory shift rotations and exposure to workplace violence), workers may psychologically adapt to these stressors, rendering them invisible to well-being assessments. Consequently, job resources, particularly satisfaction, become the primary determinants of psychological health. This suggests that for hospital security personnel, the traditional dual-process JD-R model may collapse into a resource-dominant model in which variations in job satisfaction may be associated with differences in psychological outcomes. This interpretation has important practical implications: rather than attempting to modify unchangeable job demands through costly structural changes to shift systems, interventions should focus on enhancing modifiable job resources through recognition programs, professional development opportunities, and initiatives that strengthen a sense of organizational belonging—approaches that are both more feasible and potentially more effective in this population.

We found no significant differences in psychological distress across gender, marital status, or education level. Neither rotating shift work nor sleep quality was significantly associated with the severity of psychological symptoms among hospital security staff. This finding contrasts with some studies on healthcare professionals and paramedics, where rotating shifts were linked to higher stress, poorer sleep, and increased depressive symptoms (2,10,11,24-26). The absence of such an effect in our data may reflect occupational adaptation among experienced security personnel—indeed, most of our participants had more than six years of sector experience—or the influence of institutional policies mitigating shift-related distress. Nonetheless, certain studies involving different occupational groups, in which shift patterns and perceived sleep quality were not consistently associated with mental health outcomes, corroborate our findings (27). For example, among Icelandic nurses, Sveinsdóttir (28) reported no significant differences in job satisfaction, illness experience, or sleep quality across different shift types. Similarly, a study of healthcare workers in Egypt and Saudi Arabia during the coronavirus disease-2019 pandemic found no association between night-shift schedules and increased anxiety or depression. Although poor sleep quality was prevalent, it did not independently predict mental health outcomes in multivariate analysis. The study's authors further suggested that the absence of a direct effect may be due to different variables, such as individual or institutional coping strategies, which can play a decisive role in shaping psychological well-being in shift-working populations (29). Aside from shift work, other independent variables (age, gender, and sleep quality) were not significantly associated with psychological symptom severity in our analysis. While occupational adaptation may partly explain the absence of an association between shift-related factors and psychological distress, it is less likely to account for the non-significant findings observed for demographic variables. One possible explanation is that the study population was relatively homogeneous in terms of sociodemographic characteristics and occupational roles, potentially limiting variability across these factors. Furthermore, the relatively stable employment conditions and standardized working environment within the hospital security unit may have attenuated the influence of individual-level differences on psychological outcomes.

The absence of a significant association between shift work and psychological symptom severity in our study may be related to the institutional characteristics of the shift scheduling system. In our hospital, security personnel do not work under extended 24-hour duty schedules; instead, shorter and more ergonomically structured rotating shifts are implemented. Emerging evidence suggests that transitioning from prolonged 24-hour shifts to shorter and safer scheduling systems may reduce fatigue, circadian disruption, and psychological distress among healthcare personnel. For example, Cerela-Boltunova and Klavina (30) reported that replacing extended 24-hour shifts with shorter duty periods for healthcare staff was associated with improved occupational safety and reduced mental distress. Therefore, the relatively ergonomic shift structure in our institution may have mitigated the adverse psychological effects typically attributed to shift work in previous studies. These results, together with our findings, suggest that other factors may moderate the impact of shift work and sleep quality on psychological well-being. Occupational role, individual coping strategies, and organizational support systems underscore the need for multifactorial approaches when assessing mental health risks in shift-working populations. From a practical perspective, these results underscore the importance of

managerial strategies aimed at enhancing job satisfaction and promoting the mental health of hospital security staff. Interventions include improving working conditions, offering opportunities for professional development, and fostering a supportive workplace climate.

Study Limitations

The study has limitations, particularly its cross-sectional design, which restricts causal interpretation of the link between job satisfaction and psychological symptoms. The single-center setting and specific cultural context may limit generalizability to other healthcare institutions or countries. All measures were self-reported, potentially introducing response bias and social desirability effects. The modest sample size may have reduced the statistical power to detect small effects, especially in subgroup analyses. Additionally, an a priori sample size or statistical power calculation was not performed because the study aimed to include all accessible hospital security personnel at the institution. Although a large proportion of the workforce participated (82%), the absence of a formal power analysis should be considered a methodological limitation.

Despite these limitations, the study has several strengths. The study aimed to include the entire accessible population of the hospital security unit, thereby reducing selection bias. Moreover, the use of validated psychometric instruments and the consideration of both occupational and psychological variables provide a comprehensive evaluation of factors associated with psychological symptom severity in this understudied occupational group.

Conclusion

Our findings indicate that job satisfaction is associated with psychological symptom severity among hospital security personnel, independent of demographic characteristics and sleep quality. These findings suggest that organizational interventions that focus on increasing job satisfaction may be more effective in improving mental health outcomes among healthcare security workers than interventions that address structural work demands. Longitudinal research is needed to clarify causal links and explore mediators such as coping styles and institutional support.

Ethics

Ethics Committee Approval: The University of Health Sciences Türkiye, Umraniye Training and Research Hospital Scientific Research Ethics Committee approved the study protocol (approval no.: 70, date: 10.04.2025).

Informed Consent: Prior to enrollment, written informed consent was obtained from each participant.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.C.H., K.S.P., Concept: S.C.H., Design: S.C.H., Data Collection or Processing: S.C.H., K.S.P., Analysis or Interpretation: S.C.H., Literature Search: S.C.H., Writing: S.C.H.

Conflict of interests: The authors declare that they have no conflict of interest related to this study.

Financial Disclosure: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Original Article

DOI: 10.4274/haseki.galenos.2026.24633
Med Bull Haseki 2026;64(3):213-219

Comparison of Anxiety Levels and Satisfaction of Patients Who Underwent CABG Surgery in a PPP Hospital and in a Public Hospital

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Abstract

Aim: Public-private partnership (PPP) hospitals have been increasingly implemented in Türkiye to improve healthcare infrastructure and patient comfort. Coronary artery bypass grafting (CABG) is a high-risk surgical procedure frequently associated with significant preoperative anxiety, which may influence perioperative outcomes. This study aimed to compare preoperative anxiety levels and patient satisfaction among CABG patients treated at both a public hospital and a PPP-operated hospital with similar clinical capacity.

Methods: A total of 2,201 patients who underwent isolated CABG between April 2016 and July 2024 were included in a retrospective analysis. Patients were divided into two groups: alethe [public hospital group (PHG), n=1.110] and the [PPP hospital group (PPPHG), n=1.091]. Patients using antidepressant or anxiolytic medications or whith known psychiatric disorders were excluded. Preoperative anxiety was assessed using the Beck Anxiety Inventory (BAI), and patient satisfaction was evaluated using the Patient Satisfaction Questionnaire Short Form (PSQ-18) and patient satisfaction were assessed using the BAI and the PSQ-18, respectively. Continuous and categorical variables were compared using Student's t-test and χ^2 test, respectively.

Results: Overall patient satisfaction scores did not differ significantly between the two groups. However, preoperative anxiety levels were significantly lower in the PPPHG compared with the PHG (BAI: 9.3±4.1 vs. 17.8±6.4; p<0.001). Higher anxiety levels were associated with previous percutaneous coronary intervention, chronic obstructive pulmonary disease, divorced or widowed marital status, and lower socioeconomic status.

Conclusion: While patient satisfaction with medical care was similar in both hospital models, CABG patients treated in the PPP hospital experienced significantly lower preoperative anxiety. Hospital environment and organizational characteristics may influence psychological well-being independently of clinical care quality.

Keywords: Public-private partnership, coronary artery bypass grafting, anxiety, patient satisfaction, Beck Anxiety Inventory

Introduction

A routine visit to an ordinary hospital for a serious medical condition is often stressful and uncomfortable (1). Healthcare institutions, no matter how good they are, are usually insufficient to break the tie between trust and anxiety (1,2). Technological innovations in the healthcare field should be implemented to create more reliable impressions among patients but they fail to demonstrate their potential benefits for many reasons. According to the 2023 budget discussion in the Turkish Grand National Assembly, Türkiye has spent approximately 1.6 trillion over the last two decades on building new hospitals, including project costs for new public-private partnership (PPP) hospitals (3,4). Despite this total outlay, Türkiye has the lowest healthcare expenditure in Europe, at most 6.4% of gross domestic product per year [3-6] (1-3). PPP hospitals were built over the last 10 years in Türkiye to improve the effectiveness of care delivery, patient safety, and comfort (5). Moreover, these new institutions aim to reduce patient and family anxiety, thereby improving overall outcomes

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Received: 02.02.2025 **Accepted:** 26.02.2026 **Epub:** 31.03.2026 **Publication Date:** 01.06.2026

Cite this article as: Onar LC. Comparison of anxiety levels and satisfaction of patients who underwent CABG surgery in a PPP hospital and in a public hospital. Med Bull Haseki. 2026;64(3):213-219

and quality of service (5,6). The PPP model has introduced a new horizon in hospital design for Turkish architects and contractors (7). This new pattern of hospital design provided good indoor views, spaciousness, and brightness. In addition to the current literature, patients reported that accessible, well-resourced, and comfortable facilities build trust and prevent a sense of impending threat or doom, particularly for patients scheduled to undergo major surgery and those with type D personality (8-11). In Türkiye, cardiovascular diseases remain the primary cause of mortality (35.4%) (12). The fear of death is a natural consequence of acute cardiovascular events occurring in hospitals (13). These new facilities may improve patient comfort and reduce anxiety (14,15). This theory forms the basis of this study. In medical schools, it is always taught that evidence-based medicine is essential for clinical practice; similarly, evidence-based hospital design makes hospitals safer, more conducive to curative care, and a better place to work and may be essential for better clinical outcomes in the near future.

Symptoms of anxiety are common among surgical patients, especially before coronary artery bypass grafting (CABG) surgery (16). Coronary bypass patients usually spend more than 3-4 days in the hospital before surgery. They are generally referred by another physician after the diagnostic period, or they are admitted to the emergency department with acute coronary syndromes. The period before referral for surgery generally provides them with an opportunity to observe the advantages and disadvantages of the hospital facilities, the in-hospital routines of healthcare workers, and sometimes adverse events, which may evoke mixed feelings in them. Therefore, the coronary bypass patients are suitable subjects for observing the mood-affecting features of the institutions.

The Patient Satisfaction Questionnaire Short Form (PSQ-18) is a validated tool to determine and improve the weaknesses in the health system and to compare patient satisfaction scores across different health-care organizations, departments, or hospitals (17). The Beck Anxiety Inventory (BAI) questionnaire has been widely used in cardiac patients and has been found to be a good scale for evaluating the psychometric properties of different individuals (18). Hospitals with futuristic and well-designed environments play a unique role in patients' psychological status (19). It has long been a tradition among Turkish people, to build resplendent, peaceful spaces that incorporate symbolic environmental features, creating relaxing atmospheres, such as ornamental pools with burbling water and the sound of traditional flutes (20,21). Wide corridors, high ceilings, and soft, cool spaces are other reassuring, anxiety-preventing structural features (19).

The patients in Turkish city hospitals experience convenience and confidence in designated social spaces where they can reduce stress and arousal. Earlier studies of anxiety in patients with heart disease have both strongly assumed and demonstrated that high levels of preoperative anxiety are positively associated with longer hospitalization, postoperative readmission, and recurrent cardiac events, which may be detectable and preventable (22).

This study aims to show the impact of the Turkish model of the "city hospital concept" on anxiety and patients' positive psychological responses before the CABG procedures.

Materials and Methods

Compliance with Ethical Standards

Ethical approval for this study was obtained from the Dr. Ismail Fehmi Cumalioglu City Hospital Clinical Trials Ethics Committee (approval no: 105, date: 19.04.2024). Due to the retrospective design of the study, the requirement for informed consent was waived by the committee. All data were fully anonymized prior to analysis. This study was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki.

Study Design

After approval by the local ethics committee, data collection was initiated in two hospitals with comparable capacity. Cardiac surgery in these two institutions was not available until the author started working in them. Cardiac surgery in the non-PPP hospital (hereafter referred to as Hospital 1) began in April 2016; the patients' psychological status and anxiety levels (BAI) were recorded with the future objective of improving and retrofitting the design of the cardiovascular surgery clinic. The PPP hospital (which will be referred to as Hospital 2) began admitting cardiac surgery patients in January 2021.

The 1,110 patients from hospital 1 (will be referred to as the public hospital group (PHG), and 1,091 patients from hospital 2 [will be referred to as the PPP Group, PPP hospital group (PPPHG)] have been included in the study.

Inclusion and Exclusion Criteria

The two cohorts were selected to maximize clinical homogeneity with respect to chronic comorbidities and angiographic coronary disease severity. Exclusion criteria were:

1. Current or past use of monoaminergic antidepressants or anxiolytic medications (e.g., selective serotonin reuptake ınhibitors/serotonin-norepinephrine reuptake ınhibitors),
2. Previous diagnosis of major depressive or psychotic disorders,
3. History of prior CABG surgery,
4. Emergent indication for CABG,

5. Minimally invasive direct coronary artery bypass procedures.

Psychological and Satisfaction Measures

Two validated instruments were administered during the preoperative period:

Beck Anxiety Inventory for anxiety levels,

-Patient Satisfaction Questionnaire Short Form for overall satisfaction with medical care (17).

The BAI consists of 21 items, each scored 0-3, with established severity thresholds: 0-7 (minimal), 8-15 (mild), 16-25 (moderate), and 26-63 (severe). Patient Satisfaction Questionnaire Short Form evaluates multiple subdomains of satisfaction, including general satisfaction, technical quality, interpersonal manner, communication, accessibility, and time spent with physicians (23,24). Financial subdomains of the original PSQ-III were excluded due to the standardized Turkish Social Security reimbursement system.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation and compared using Student's t-tests. Categorical variables were expressed as proportions and compared using χ^2 tests. Univariable analyses were performed to identify factors associated with anxiety and satisfaction outcomes. A p-value <0.05 was considered statistically significant. Statistical analyses were performed using the SPSS software, version 20.0 (IBM Corp., Armonk, NY, USA).

Results

Baseline and Operative Characteristics

A comprehensive overview of demographic variables, comorbid conditions, New York Heart Association (NYHA) classification, socio-economic and marital status, prior cardiac interventions, and insurance coverage for both groups is provided in Table 1. The distributions of age, sex, and major cardiovascular risk factors were similar across both institutions, with expected variations across comorbidity clusters.

Operative characteristics were also comparable. Cross-clamp time did not differ significantly between groups (PHG 89.4±12.6 min vs. PPPHG 87.8±13.1 min; p=0.214), nor did cardiopulmonary bypass duration (117.2±18.5 min vs. 115.6±17.9 min; p=0.301). Intensive care unit and total hospital stays were equivalent (p>0.05 for both).

Patient Satisfaction

Patient Satisfaction Questionnaire Short Form analysis demonstrated no significant differences in overall satisfaction or in subdomains, including technical quality, interpersonal manner, communication, accessibility, and time spent with physicians (all p>0.05). These results are summarized in Table 2.

Univariable analyses identified poorer NYHA functional class (p<0.001) and impaired renal function (p=0.000) as predictors of higher satisfaction, suggesting that patients with greater clinical acuity perceived care as more responsive.

Preoperative Anxiety

In contrast, BAI scores revealed significantly lower anxiety levels in the PPPHG compared with the PHG (9.3±4.1 vs. 17.8±6.4; p<0.001). Beck Anxiety Inventory severity categorization showed that PHG patients were more frequently in moderate/severe categories, whereas PPPHG patients were predominantly in minimal/mild categories (Table 3).

Higher anxiety scores were associated with prior percutaneous coronary intervention (PCI) (p<0.001), chronic obstructive pulmonary disease (COPD) (p<0.001), atrial fibrillation (p<0.001), divorced or widowed marital status (p=0.000), and lower socioeconomic status (p=0.000).

Postoperative Outcomes

Early mortality was similar (PHG 0.7% vs. PPPHG 0.5%; p=0.612). Postoperative complications—including acute renal failure, major hemorrhage, prolonged ventilation, and transfusion requirements—did not differ significantly between groups. Although psychological parameters differed, perioperative morbidity and mortality outcomes remained clinically equivalent.

Discussion

The purpose of this study was to examine the influence of hospital management models—specifically the PPP model—on patient satisfaction and preoperative anxiety levels in individuals undergoing CABG surgery. By comparing two hospitals operating under different management models within the same city, we aimed to minimize regional and demographic variability. The findings demonstrate that although overall patient satisfaction was similar between the two institutions, patients treated in the PPP hospital experienced significantly lower levels of preoperative anxiety.

Patient satisfaction, assessed using the PSQ-18, did not differ significantly between the public and PPP hospitals. This suggests that core components of clinical care, such as physician competence, communication, and treatment effectiveness, were perceived similarly across both settings. In contrast, anxiety levels measured by the BAI were substantially lower among patients at the PPP hospital, indicating that psychological outcomes may be influenced by factors beyond clinical care.

The reduced anxiety observed in the PPP group may be attributed to characteristics inherent to the PPP framework, including improved hospital infrastructure, maintenance quality, and environmental design. Previous studies have shown that hospital environments with better room design, access to natural light, reduced noise, and enhanced privacy can positively influence patients' psychological well-being and reduce stress, particularly in

Table 1. Demographic findings of the study group

Variable n		PHG (Group 1, n=1110)		PPPHG (Group 2, n=1091)	
		%	n	%	
Gender	Female	586	52	607	55
	Male	524	48	484	45
Age		Mean	SD	Mean	SD
		61.4	0.54	58.6	0.86
		n	%	n	%
Body mass index (BMI, kg/m²)	Underweight	11	1.12	21	1.19
	Normal	618	55.6	654	59.9
	Overweight	467	42	387	35.4
	Obese	14	1.26	29	2.65
Diabetes		451	40.6	474	43.4
Hypertension		420	37.9	491	45
Hyperlipidemia		371	33.4	391	36.2
COPD		121	10.9	91	8.3
NYHA functional classification	Class 1	465	41.8	521	47.7
	Class 2	346	31.1	398	36.4
	Class 3	213	19.1	98	8.9
	Class 4	86	7.7	74	6.7
Chronic renal insufficiency	Stage 3	127	8.7	161	14.7
	Stage 4	51	4.5	74	6.7
	Stage 5	19	1.7	30	2.7
Smoking status	Non-smoker	396	35.6	427	39.1
	Smoker	635	57.2	554	50.7
	Electronic smoker	79	7.2	110	10.2
History of previous cardiac intervention	Diagnostic CAG	101	9	126	11.5
	Primer PCI	316	28.4	271	24.8
	PCI	206	18.5	180	16.4
	No history	587	52.8	514	47.1
Marital status	Married	729	65.6	761	69.7
	Single	210	18.9	211	19.3
	Divorced/widow	171	15.4	119	10.9
Socioeconomic status	High	691	62.2	511	46.8
	Middle	310	27.9	420	38.4
	Low	109	9.8	160	14.6
Insurance status	Social security institution (SSI, SGK)	911	82	859	78.7
	Green card	141	12	186	17.1
	No insurance	46	4.1	21	1.9
	Foreign insurance	12	1.1	25	2.2

PHG: Public hospital group, COPD: Chronic obstructive pulmonary disease, NYHA: New York Heart Association, CAG: Coronary angiography, PCI: Percutaneous coronary intervention, SSI: Social security institution, PPPHG: Public-private partnership hospital group

high-risk surgical populations. In this context, the physical setting and overall hospital experience in the PPP hospital may have mitigated the psychological distress commonly associated with major cardiac surgery.

Conversely, public hospitals are often characterized by higher patient volumes, limited physical space, and fewer opportunities for environmental optimization. Overcrowded waiting areas, reduced privacy, and longer waiting times may contribute to increased psychological stress, especially in patients undergoing complex procedures such as CABG. In our study, higher anxiety levels were associated with a history of PCI and COPD, as well as lower socio-economic status, supporting the notion that patients with greater medical complexity and social vulnerability are particularly susceptible to anxiety in hospital settings.

In addition to anxiety outcomes, the study identified factors influencing patient satisfaction. Patients with a worse NYHA functional class and impaired renal function reported higher satisfaction with medical care. This finding may reflect increased attention, monitoring, and perceived support provided to patients with more severe clinical conditions. More frequent interactions with healthcare professionals and heightened clinical vigilance may positively affect patients' perceptions of care quality, even in the presence of significant disease burden.

The absence of significant differences in satisfaction, despite differing anxiety levels, suggests that satisfaction and anxiety represent distinct dimensions of patient experience. While satisfaction appears to be closely linked to clinical competence and interpersonal aspects of care, anxiety may be more sensitive to environmental and organizational factors. This distinction is particularly relevant in the perioperative period, during which psychological stress can influence recovery, length of hospitalization, and overall patient well-being.

Table 2. The univariate aanalysis of PSQ-18 survey for the Group 1 (PHG) and the Group 2 (PPPHG)

Subscale and item	Category	PHG		PPPHG		Statistical significance
		Mean	SD±	Mean	SD±	p-value
Doctors are good about explaining the reason for medical tests	Communication	4.0	0.7	4.1	0.1	p>0.05
I think my doctor's office has everything needed to provide complete care.	Technical quality	3.0	0.6	4.8	0.2	p<0.001
The medical care I have been receiving is just about perfect	General satisfaction	4.4	0.2	4.8	0.2	p>0.05
Sometimes doctors make me wonder if their diagnosis is correct	Technical quality	2.9	0.2	4.6	0.2	p<0.001
I feel confident that I can get the medical care I need without being set back financially	Financial aspects	3.9	0.7	4.2	0.1	p>0.05
When I go for medical care, they are careful to check everything when treating and examining me	Technical quality	3.3	0.4	4.6	0.2	p<0.001
I have to pay for more of my medical care than I can afford	Financial aspects (N/A)	3.4	0.6	4.4	0.2	p>0.05,
I have easy access to the medical specialists I need	Accessibility and convenience	4.0	0.7	4.6	0.6	p<0.001
Where I get medical care, people have to wait too long for emergency treatment	Accessibility and convenience	3.4	0.2	4.0	0.7	p<0.001
Doctors act too businesslike and impersonal toward to me	Interpersonal manner	4.3	0.4	4.4	0.4	p>0.05
My doctors treat me in a very friendly and courteous manner	Interpersonal manner	4.4	0.5	4.5	0.2	p>0.05
Those who provide my medical care sometimes hurry too much when they treat me	Time spent with doctor	3.9	0.6	4.1	0.2	p=0.00
Doctors sometimes ignore what I tell them	Communication	4.0	0.1	4.1	0.5	p>0.05
Doctors usually spend plenty of time with me	Time spent with doctor	3.6	0.2	4.6	0.2	
I find it hard to get an appointment for medical care right away	Accessibility and convenience	4.0	0.7	4.0	0.2	p>0.05
I am dissatisfied with some things about the medical care I receive	General satisfaction	4.5	0.7	4.5	0.6	p>0.05
I am able to get medical care whenever I need it	Accessibility and convenience	4.5	0.5	4.8	0.1	p>0.05

PHG: Public hospital group, PPPHG: Public-private partnership hospital group, SD: Standard deviation, PSQ-18: Patient Satisfaction Questionnaire Short Form

Table 3. The standardized BAI results of the two groups			
Variable	**PHG**	**PPPHG**	**p-value**
Continuous BAI score (mean ± SD)	17.8±6.4	9.3±4.1	<0.001
Minimal (0-7)	144 (13.0%)	491 (45.0%)	<0.001
Mild (8-15)	367 (33.1%)	358 (32.8%)	0.882
Moderate (16-25)	413 (37.2%)	202 (18.5%)	<0.001
Severe (≥26)	186 (16.8%)	40 (3.7%)	<0.001
BAI: Beck Anxiety Inventory, PHG: Public hospital group, PPPHG: Public-private partnership hospital group, SD: Standard deviation			

Several mechanisms may explain the lower anxiety levels observed in PPP hospitals. A well-designed hospital environment can promote a sense of safety, comfort, and privacy, all of which are essential for patients undergoing major surgery. Features such as single or less-crowded rooms, improved wayfinding, reduced noise, and aesthetically pleasing interiors may contribute to psychological reassurance. In addition, PPP hospitals often benefit from structured facility management, efficient service delivery, and patient-centered amenities, all of which may reduce stress during hospitalization (25-27).

The psychological benefits observed in the PPP group cannot be attributed solely to the hospital management model. Patient-related factors such as socio-economic status, marital status, and comorbid conditions were also significant determinants of anxiety. Lower socioeconomic status and being divorced or widowed were associated with higher anxiety levels, underscoring the complex interaction between social, psychological, and clinical factors in shaping patient experiences. These findings highlight the need for comprehensive perioperative care strategies that address both medical and psychosocial needs, regardless of hospital type (28).

Notably, early postoperative outcomes and complication rates were similar between the two hospitals, suggesting that the observed differences in anxiety were not related to variations in surgical performance or immediate clinical outcomes. This supports the interpretation that the hospital environment and organizational characteristics primarily influence psychological outcomes, rather than short-term surgical results. Addressing preoperative anxiety may therefore represent an additional opportunity to improve patient-centered care without altering established clinical protocols.

Study Limitations

This study has several limitations that should be considered. First, its observational design limits the ability to establish causal relationships between hospital management models and patient outcomes, and the lack of randomization may have introduced selection bias. Second, although the study was conducted in two hospitals within a single metropolitan region, which may limit generalizability to other geographic or healthcare settings, this design ensured a high degree of homogeneity in referral patterns, socioeconomic characteristics, and cultural context. Such homogeneity reduces environmental and demographic variability that would otherwise confound psychological and satisfaction measures, thereby strengthening internal validity while constraining external applicability. In addition, anxiety and patient satisfaction were assessed using self-reported instruments, which may be subject to response bias. While major psychiatric disorders were excluded, subclinical psychological conditions and unmeasured psychosocial factors may still have influenced the results. Finally, the study did not directly assess specific environmental or infrastructural characteristics of the hospitals, thereby limiting the ability to identify the elements that most strongly contributed to differences in anxiety levels. Future multicenter and prospective studies incorporating objective environmental measures are warranted. Despite these limitations, the study provides valuable insights into the role of hospital management models in shaping patients' psychological experiences. While perceived clinical care satisfaction appeared comparable between public and PPP institutions, preoperative anxiety may be differentially shaped by higher-order institutional features, including environmental affordances, spatial ergonomics, and patient-centric service infrastructures. In complex surgical populations, such contextual variables have been implicated in modulating cognitive appraisal processes and stress responses, suggesting that the perioperative psychological trajectory is influenced not only by the competence of medical care but also by the built environment in which care is delivered (29).

Conclusion

This study shows that, while overall patient satisfaction with medical care was similar between public and public-private partnership hospitals, patients undergoing CABG in PPP hospitals experienced significantly lower levels of preoperative anxiety. These findings suggest that the hospital environment and organizational characteristics may influence psychological outcomes independently of the quality of clinical care. Addressing preoperative anxiety

may represent an important component of patient-centered cardiac care. Further multicenter and prospective studies are needed to clarify the mechanisms underlying these observations.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from the Dr. Ismail Fehmi Cumalioglu City Hospital Clinical Trials Ethics Committee (approval no: 105, date: 19.04.2024).

Informed Consent: Due to the retrospective design of the study, the requirement for informed consent was waived by the committee.

Footnotes

Financial Disclosure: The author declared that this study received no financial support.

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Letter to the Editor

DOI: 10.4274/haseki.galenos.2026.19480
Med Bull Haseki 2026;64(3):220-221

The Novel Metabolic Bridges Extending from Liver to the Bone: The Liver-Bone Axis

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To the editor,

We read with great interest the article by Ayyildiz et al. (1). We believe this study is valuable in terms of investigating the role of non-alcoholic fatty liver disease (NAFLD) in osteoporosis clinical practice. However, we have several suggestions to strengthen the study.

In this study, the presence of advanced hepatic steatosis was determined by ultrasonography, which has several limitations. Ultrasonography provides a subjective classification that depends on the evaluator and is, therefore, not recommended for grading hepatic steatosis in international NAFLD guidelines. Furthermore, in NAFLD, the severity of steatohepatitis and fibrosis, rather than the mere presence of steatosis, is more important for clinical progression (2). It is recommended that fibrosis risk assessment be performed to determine the clinical course, particularly when evaluating disease severity. In addition, international guidelines recommend that fibrosis risk be determined primarily by the Fibrosis-4 score and that further investigation be carried out in high-risk individuals (2). In light of these data, we believe that comparing patients with and without NAFLD within the current patient cohort, and subsequently evaluating individuals with NAFLD according to their fibrosis levels, will increase the study's power (3).

Secondly, the presence of steatosis in patients with NAFLD is directly related to metabolic syndrome and associated diseases. Many metabolic disorders, primarily obesity and type 2 diabetes mellitus (T2DM), increase the severity of hepatic steatosis during the progression of NAFLD (4). Furthermore, obesity and diabetes mellitus are known to be associated with the development and progression of osteoporosis. These clinical data demonstrate that multiple metabolic disorders affect the severity of osteoporosis; therefore, examining the direct impact of these diseases is important (4). The present study did not investigate the relationship between obesity, T2DM, and clinical outcomes among the patient groups. Therefore, it could not be determined whether the current results are attributable to NAFLD itself or to NAFLD-related obesity and T2DM (5). We believe that the clinical evaluation of obesity and diabetes mellitus, which are directly related to both osteoporosis and NAFLD, will increase the study's statistical power.

Lastly, osteoporosis is a multisystem disease resulting from interactions among multiple factors. Predisposing factors such as smoking, long-term use of glucocorticoids, body weight, and physical activity levels are important in the development and progression of osteoporosis (5). However, the effects of these factors were not evaluated in the clinical analysis comparing the groups in the present study. We believe that examining the relationship between these predisposing factors especially body weight and smoking and clinical disease severity, and comparing these data with the presence of NAFLD, will increase the study's power.

In summary, the relationship between NAFLD and osteoporosis is not fully understood, and clinical evaluation based on the presence of steatosis and fibrosis is critically important. Additionally, factors such as obesity, T2DM, smoking, and physical activity should be considered to better elucidate this relationship.

Footnotes

Financial Disclosure: The author declared that this study received no financial support.

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Received: 18.01.2026 **Accepted:** 21.01.2026 **Epub:** 31.03.2026 **Publication Date:** 01.06.2026

Cite this article as: Ali Kirik. The novel metabolic bridges extending from liver to the bone: the liver-bone axis. Med Bull Haseki.2026;64(3):220-221

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