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Editor in Chief

Dear Readers and Esteemed Authors,

We are delighted to present the first issue of the *Gülhane Medical Journal* in 2026 during the cold and rainy days of winter. In this season, when nature rests, the earth is nourished by rain, and life appears to slow down, the continuity of scientific production becomes even more evident. Winter is a season of patience, reflection, and preparation. Likewise, scientific research requires dedication, discipline, and continuity.

The original research articles, reviews, and case reports submitted to our journal over the past year have made significant contributions to maintaining and further enhancing our academic quality. The studies included in this issue provide current and practical insights into both the basic sciences and clinical disciplines and offer valuable data aimed at improving the quality of healthcare services.

The sustainability of scientific publishing depends not only on the meticulousness of editorial processes but also on the productivity and commitment of researchers to scientific advancement. On this occasion, we would like to express our sincere gratitude to all authors who contribute to the regular and high-quality publication of our journal. The dedication of our colleagues—who share their scientific work with us despite demanding clinical responsibilities, educational commitments, and research obligations—remains one of the strongest pillars of our journal.

We would also like to extend our sincere appreciation to our reviewers and editorial board members for their valuable contributions to the peer-review process. Their commitment to upholding scientific objectivity and ethical principles forms the foundation of our journal's academic credibility.

We once again thank all contributors for bringing the warmth of scientific endeavor to these cold and rainy winter days, and we wish 2026 to be a year filled with health, success, and productive work. As the *Gülhane Medical Journal*, we remain committed to working resolutely toward our goal of increasing our scientific impact at both national and international levels.

Sincerely,

M. Ali Gülçelik, M.D., Prof.
Editor-in-Chief

GÜLHANE MEDICAL JOURNAL
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Relationship between bronchial hyperreactivity and complete blood count derived inflammatory biomarkers

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ABSTRACT

Aims: Studies specifically linking bronchoprovocation test (BPT) positivity with complete blood count (CBC)-derived biomarkers are limited. We investigated the relationship between CBC-derived biomarkers and BPT positivity in this study.

Methods: We retrospectively evaluated patients who underwent methacholine BPT and simultaneous CBC from May 2017 to March 2020. Non-smoker patients without a prior diagnosis or treatment of asthma were selected. We investigated the relationship between bronchial hyperreactivity and CBC parameters white blood cell (WBC), neutrophil (NEU), lymphocyte (LYM), eosinophil (EOS), platelet counts (PLTs), mean platelet volume (MPV), neutrophil-to-lymphocyte ratio (NLR), eosinophil-to-lymphocyte ratio (ELR), platelet-tolymphocyte ratio (PLR), and the systemic immune-inflammation index (SII).

Results: The study population consisted of 246 adult patients (69.1% female, mean age 40.5±13.1 years) evaluated for asthma-like symptoms. The BPT was negative in 156 (63.4%) patients and positive in 90 patients (36.6%). A relationship was found between EOS count and BPT positivity [135 (interquartile range (IQR) 167) vs 119 (IQR: 99 p=0.04)]. However, no statistically significant relationship was found between BPT positivity and other parameters, WBC, NEU, LYM, PLT, MPV, NLR, ELR, PLR, and the SII.

Conclusions: We identified an association between BPT positivity and EOS count among CBC parameters. However, we found no relationship between BPT positivity and WBC, NEU, LYM, EOS, PLT, MPV, and CBC-derived inflammatory biomarkers such as NLR, ELR, PLR, and SII. In asthmatic patients, a relationship between asthma and CBCderived biomarkers may emerge after inflammation persists for a period of time.

Introduction

Chronic inflammation is the basis of asthma pathogenesis (1). This inflammatory process contributes to bronchial hyperreactivity (BHR), which leads to recurrent symptoms and signs of airway obstruction. One of the diagnostic tools used to demonstrate BHR is the bronchial provocation test (BPT). Non-specific bronchial provocation using methacholine is performed as supporting evidence in the diagnosis of asthma (2). Nevertheless, its routine clinical use remains restricted.

The complete blood count (CBC) represents a basic and universally performed laboratory assessment, available in nearly all clinical settings. Parameters obtained from the CBC can provide insights into systemic inflammation and assist in identifying inflammatory phenotypes of asthma. The link between CBC parameters and diverse inflammatory subtypes of asthma has been assessed in numerous studies (3,4). Moreover, a number of older and recent studies have explored the relevance of hemogram parameters in BHR and asthma (5,6). In recent years, data indicating systemic inflammation in asthma have accumulated increasingly (7). The systemic immune-inflammation index (SII) has been studied as a marker in both inflammatory conditions and malignancies (8-10). However, current evidence exploring the association between SII and BHR remains limited.

In the present research, we sought to explore the relationship between BHR and CBC-derived parameters, including white blood cell (WBC) count, neutrophil (NEU), lymphocyte (LYM), eosinophil (EOS), and platelet (PLT) counts; mean platelet volume (MPV); neutrophil-to-lymphocyte ratio (NLR); eosinophil-to-lymphocyte ratio (ELR); platelet-to-lymphocyte ratio (PLR); and the SII, calculated as (NEUs×PLTs)/LYMs.

Methods

Study design and participants

This study retrospectively enrolled patients presenting to the outpatient department with asthma-like symptoms who underwent non-specific BPT with methacholine for asthma diagnosis between May 2017 and March 2020. Inclusion criteria were age ≥18 years, non-smoker status, no prior diagnosis or treatment for asthma, and availability of CBC results obtained concurrently with the BPT. Exclusion criteria were age <18, smoking, former smoker, diagnosis of asthma, and lack of a CBC simultaneously with BPT. CBC analyses were performed using the Mindray BC-6000 automated hematology analyzer (Mindray Bio-Medical Electronica Co., Ltd., Shenzhen, China). The Ethics Committee of the University of Health Sciences Türkiye, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital Institution provided formal approval for this research (approval no.: 244, date: 13.12.2023).

Data collection

Data collected included demographic characteristics, BPT results, provocative concentration 20 (PC20) values, atopy status, and CBC parameters (WBC, NEU, LYM, EOS, PLT, MPV, NLR, ELR, PLR, and SII). The study population was divided into four categories based on PC20 values: Group I: PC20 <1 mg/mL. Group II: PC20 1–<4 mg/mL. Group III: PC20 4–<16 mg/mL. Group IV: Negative BPT result (PC20 ≥16 mg/mL). Additionally, comparisons were made between patients with a positive BPT (Groups I-III) and those with a negative result (Group IV).

Bronchial provocation test

One approach to assess airway reactivity is the application of methacholine challenge testing. Methacholine bronchial challenge tests were performed and interpreted following the recommendations of the American Thoracic Society. Five methacholine chloride concentrations (0.0625, 0.25, 1, 4, and 16 mg/mL) were prepared in sterile vials using normal saline as diluent, placed in a labeled holder, and stored at 2-8 °C until use. The solutions were administered in quadrupling concentrations (every other dilution) according to the standard bronchial challenge protocol (11). Baseline spirometry was performed, and the target forced expiratory volume in one second (FEV_1) was calculated, which indicates a 20% fall in FEV_1 [baseline (or diluent) FEV_1 x 0.8].

Outcomes

The primary outcome is to evaluate the relationship between BPT and CBC-derived inflammatory markers. The secondary outcome is to evaluate the difference between groups, according to the degree of BPT positivity.

Statistical Analysis

All statistical analyses were carried out with IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, NY, USA). Data were summarized using descriptive measures including mean, standard deviation, median, interquartile range (IQR), number and percentages. The Shapiro-Wilk test and graphical methods were applied to assess the normality of distribution for quantitative variables. When the variables did not follow a normal distribution, two-group comparisons were performed using the Mann-Whitney U test, whereas comparisons among more than two groups were carried out with the Kruskal-Wallis test. One-Way Analysis of Variance was applied for normally distributed quantitative variables involving more than two groups. Categorical variables were examined using the Pearson chi-square test, with statistical significance defined as $p<0.05$.

Results

This investigation involved 246 adult subjects as the study population. Participants (69.1% female, mean age 40.5±13.1 years) were evaluated for asthma-like symptoms. BPT positivity was identified in 36.6% of the cases. In the BPT-negative group, the patients' mean age was 40.7±12.1 years, whereas in the BPT-positive group it was 40.2±14.8 years.

No statistically significant differences were observed between the BPT-positive and BPT-negative groups with respect to age, sex, atopy, or body mass index. Median total immunoglobulin E (IgE) levels were significantly elevated in the BPT-positive group (52.7 IU/mL) compared with the BPT-negative group (25.0 IU/mL) (p=0.027). However, no significant association was found between the extent of BPT positivity and total IgE levels (p=0.13) (Table 1).

No statistically significant relationship was observed between BPT positivity and CBC-derived parameters such as WBC count, NEU count, LYM count, PLT count, MPV, NLR, ELR, PLR, or SII. Peripheral blood EOS counts were significantly greater in the BPT-positive group (median 135 cells/μL; IQR 167) than in the BPT-negative group (median 119 cells/μL; IQR 99) (p=0.040). A comprehensive summary of the results is provided in Table 2. When evaluating the four PC20-based groups (Group I, Group II, Group III, and Group IV), no statistically significant differences were observed in parameters such as WBC, NEU, LYM, or PLT counts; MPV; NLR; ELR; PLR; SII; or EOS counts among the subgroups.

Discussion

This investigation revealed that peripheral EOS levels were markedly higher among patients with positive BPT results, suggesting a potential link between EOS inflammation and BHR. Although leukocyte counts appeared elevated in BPT-positive individuals, this difference did not reach statistical significance. These findings highlight EOS count as the most sensitive CBC parameter in distinguishing patients with BPT positivity.

Annesi et al. (5) examined the association between WBC count and BHR using methacholine in a population-based sample of 324 men. They demonstrated that elevated WBC counts (≥8.000 cells/mm³) were associated with BPT positivity; however, the study included smokers and male patients only (5). According to another report, impaired lung function was associated with increased WBC counts in a negative direction (12). In contrast, our study included both male and female non-smokers and found no statistically significant relationship between WBC count and either BPT positivity or degree of BHR. The discrepancy may stem from differences in study populations regarding smoking status.

In our study, LYM counts did not show a statistically significant association with BPT positivity or the severity of BHR, aligning with findings from a previous study that also reported no such relationship (13). However, some studies have indicated that LYM percentages may be significantly reduced in patients with asthma (14).

Table 1. Comparison of demographic characteristics, BMI, and total IgE levels between BPT-positive and BPT-negative groups

		BPT positive			BPT negative	Total	p-value
		Group I 13 (5.3)	Group II 26 (10.6)	Group III 51 (20.7)	Group IV		
			90 (36.6)		156 (63.4)	246 (100)	
Gender	Female, n (%)	9 (3.6)	18 (7.3)	40 (16.3)	103 (41.9)	170 (69.1)	0.42[a]
			67 (27.2)				
	Male, n (%)	4 (1.6)	8 (3.3)	11 (4.5)	53 (21.5)	76 (30.9)	
			23 (9.4)				
Atopy presence	Yes, n (%)	6 (2.4)	14 (5.7)	17 (6.9)	58 (23.6)	95 (38.6)	0.30[a]
			37 (41.1)				
	No, n (%)	7 (2.8)	12 (4.9)	34 (13.8)	98 (39.9)	151 (61.4)	
			53 (21.5)				
Age, years, mean ± SD		41.4±16.4	40.4±16.0	39.8±14.0	40.7±12.1	40.5±13.1	0.97[b]
			40.2±14.8				0.80[c]
Body mass index, median, (IQR)		31.0 (9.5)	25.45 (9.8)	26.8 (7.8)	27.6 (7.25)	27.2 (7.55)	0.25[d]
			26.6 (8.02)				0.75[e]
Total IgE (IU/mL), median, (IQR)		51.3 (65.9)	134.6 (190.59)	36.7 (74.15)	25.0 (60.98)	30.9 (72.14)	0.13[d]
			52.7 (152.01)				0.027[e]

[a]: Pearson chi-square test, b: One-Way ANOVA test, c: Independent sample t test, d: Kruskal-Wallis, eMann-Whitney U test
BMI: Body mass index, IgE: Immunoglobulin E, BPT: Bronchoprovocation test, SD: Standard deviation, IQR: Interquartile range

Table 2. Comparison of CBC parameters and CBC-derived inflammatory biomarker findings of BPT-positive and BPT-negative groups

	PC20-16 (2 Groups)	Mean	SD	Median	IQR	p-value
Leukocyte (x10^9/L)	Negative	7.36	2.32	6.95	2.70	0.454[a]
	Positive	7.41	1.89	7.10	2.33	
Neutrophil (x10^9/L)	Negative	4.54	2.04	4.20	2.10	0.749[a]
	Positive	4.43	1.51	4.20	1.13	
Lymphocyte (x10^9/L)	Negative	2.12	0.57	2.10	0.80	0.068[a]
	Positive	2.24	0.53	2.30	0.83	
Eosinophil (x10^9/L)	Negative	142	113	119	99	**0.040**[a]
	Positive	185	157	135	167	
Thrombocyte (x10^9/L)	Negative	264.40	67.72	254.00	84.00	0.617[b]
	Positive	259.93	67.10	250.50	86.50	
MPV (fL)	Negative	8.93	1.03	8.80	1.30	0.784[a]
	Positive	9.03	1.27	8.85	1.23	
NLR	Negative	2.29	1.49	2.02	1.04	0.326[a]
	Positive	2.04	0.77	1.92	0.84	
ELR	Negative	0.07	0.06	0.05	0.04	0.118[a]
	Positive	0.09	0.09	0.06	0.09	
PLR	Negative	133.74	53.44	123.03	51.69	0.121[a]
	Positive	120.72	36.32	115.52	49.5	
SII	Negative	634.03	630.47	514.56	297.25	0.349[a]
	Positive	533.43	254.28	493.40	266.98	

[a]: Mann-Whitney U test, b: Independent Sample t-test
CBC: Complete blood count, BPT: Bronchoprovocation test, MPV: Mean platelet volume, NLR: Neutrophil-to-lymphocyte ratio, ELR: Eosinophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, SII: Systemic immune-inflammation index, PC20: Provocative concentration 20, SD: Standard deviation, IQR: Interquartile range

The link between peripheral EOS counts and BHR has already been documented in earlier studies. In one study, a peripheral EOS cut-off of ≥226 cells/μL was associated with modest sensitivity but high specificity in predicting BHR (15). Consistent with this, our study also revealed a significant elevation in EOS counts among patients with BPT positivity, supporting the role of EOSs as a relevant marker in the assessment of BHR.

In their study, Bedolla-Barajas et al. (16) assessed peripheral leukocyte distributions among asthmatic and non-asthmatic patients, reporting no notable differences in either WBC or LYM counts and percentages. Their study included patients with established asthma diagnoses, while our cohort consisted of individuals undergoing BPT as part of the diagnostic work-up for asthma. Another report indicated that, once confounding factors were considered, significant associations with asthma prevalence remained only for WBC and NEU counts (17).

Evidence from various studies supports the notion that PLTs may participate in allergic inflammation as well as in asthma (18). MPV has been studied as a possible marker of systemic inflammation and PLT activation in asthma (19). In our study, no relationship was found between BPT positivity and PLT count or MPV. In contrast, other studies demonstrated a relationship between MPV and asthma, reporting lower MPV values in patients with asthma (6).

A study evaluating CBC-based inflammatory markers reported that NLR, PLR, and SII were linked to higher mortality from respiratory and other causes in adults with asthma (17). In contrast, our findings did not demonstrate any significant association between BPT positivity and CBC-derived indices, including NLR, ELR, PLR, and SII.

NLR has been associated with chronic inflammatory conditions (20). Elevated NLR levels have been reported in children with asthma and allergic asthma (21). However, in our study involving adult patients, no relationship was observed between BPT positivity and NLR. The literature shows inconsistency on this subject, with some studies reporting no association between NLR and asthma (16). In another study, NLR was investigated as an objective biomarker to assess exacerbation severity in asthma and the need for hospitalization in children (22). However, findings remain inconclusive.

ELR has been found to be elevated in asthma and has been correlated with the response to omalizumab in severe asthma (16,23). Additionally, ELR levels have been shown to be higher

in both allergic and non-allergic rhinitis compared to healthy controls (24). Our findings showed that ELR values did not differ significantly between patients with positive and negative BPT results.

Our findings are in line with earlier reports indicating no meaningful differences in PLR between subjects diagnosed with asthma and those without disease (16). In contrast, Tahseen et al. (25) reported significantly elevated PLR values in asthmatic patients compared with healthy controls.

SII has demonstrated prognostic value in various diseases (26,27), and its correlation with asthma has been reported (17). Nevertheless, no significant association was identified between BPT positivity and SII in our study.

Asthma-related inflammation is a chronic process, and various phenotypes and endotypes of asthma have been identified (28). Among the inflammatory phenotypes, the paucigranulocytic type is the most common, followed by the EOS type (4). An overlap between different inflammatory phenotypes may occur. These phenotypic variations may explain the absence of associations between BPT results and CBC-based inflammatory markers in the initial diagnostic evaluation in our study.

Study Limitations

There are a number of limitations to this study. It was a single-center, retrospective study. Nevertheless, it provides valuable clinical insights due to its sample size and specific patient population. Moreover, it was conducted in a tertiary care hospital, which serves as the largest referral center in the region. Data collection was performed electronically through the hospital's online database, minimizing the risk of incorrect or missing data. Second, the study included only patients with asthma-like symptoms who underwent non-specific BPT with methacholine and had available CBC results. Therefore, the findings may not be generalizable to the broader population. However, the results may aid clinicians in managing patients with BHR or those presenting with asthma symptoms during follow-up.

Conclusion

Among CBC parameters, EOS count demonstrated a significant association with BPT positivity, highlighting its potential role as an accessible and clinically useful biomarker in patients with asthma-like symptoms. In contrast, our analysis did not demonstrate significant associations between BPT positivity and other variables, including WBC, neutrophil and lymphocyte counts, EOS percentage, platelet number, MPV, or CBC-based inflammatory indices such as NLR, ELR, PLR, and SII. Given the practical limitations of performing bronchial provocation testing in routine clinical settings, the identification of elevated eosinophil levels, readily obtained from a simple CBC, may serve as a valuable adjunct in both the diagnostic evaluation and longitudinal management of this patient population. Considering that asthma represents a long-standing inflammatory disorder characterized by dynamic clinical features, these associations may become even more pronounced over time.

Ethics

Ethics Committee Approval: The ethics committee of the University of Health Sciences Türkiye, Sancaktepe Şehit Prof. Dr. İlhan Varank Training and Research Hospital institution provided formal approval for this research (approval no.: 244, date: 13.12.2023).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: M.K., Concept: M.K., E.T., F.D., Design: M.K., E.T., F.D., Data Collection or Processing: M.K., E.T., F.D., Analysis or Interpretation: M.K., E.T., F.D., Literature Search: M.K., E.T., F.D., Writing: M.K., E.T., F.D.

Conflict of Interest: The authors declared no conflict of interest.

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The impact of antenatal education on mode of delivery and postpartum depression: a retrospective analysis

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ABSTRACT

Aims: This study aimed to evaluate the impact of antenatal education on childbirth-related anxiety, mode of delivery, and the risk of postpartum depression (PPD). A secondary aim was to assess the relationship between antenatal education, obstetric outcomes, social support, and demographic characteristics.

Methods: This retrospective observational study included postpartum women who received antenatal care and delivered at the same tertiary center. Participants were categorized according to whether they attended an antenatal education program. Demographic characteristics, obstetric outcomes, and Edinburgh Postnatal Depression Scale (EPDS) scores were obtained from routine postpartum assessments. The primary endpoint was the effect of antenatal education on PPD risk (EPDS ≥13). Secondary endpoints included mode of delivery, social support, and factors associated with EPDS scores.

Results: The study included 265 women (mean age: 28.72±5.42 years). The rate of spontaneous vaginal delivery was higher among women who attended antenatal education (54.13%; p=0.021), while cesarean section was more common among those who did not attend (60.26%; p=0.021). Attendees had higher educational levels and more frequent support with infant care (p<0.05). The mean EPDS score was 6.22±5.04, and there was no significant difference in EPDS scores between attendees and non-attendees (6.83 and 5.81; p=0.095). Higher gravida, parity, and number of living children were associated with lower EPDS scores (p<0.001). The proportion of women classified as high risk for PPD (EPDS ≥13) was similar between the two groups (12.15% and 9.62%; p=0.513).

Conclusions: Antenatal education was associated with higher rates of vaginal delivery and increased social support, but it did not significantly reduce PPD risk. Increasing gravida, parity, and number of living children were associated with lower EPDS scores. While antenatal education contributed positively to obstetric outcomes, it may be insufficient alone to reduce the likelihood of PPD.

Introduction

Pregnancy and the postpartum period are essential stages in a woman's life, during which profound physiological, hormonal, and emotional alterations occur. Although these processes are considered natural, concerns regarding miscarriage, fetal abnormalities, fear of childbirth, and doubts about maternal competence can significantly increase maternal anxiety as pregnancy advances. Anxiety about labor pain and delivery mode often peaks in the third trimester, particularly when access to information and emotional support is limited (1,2).

Based on data from the World Health Organization, caesarean section rates above 10-15% are not associated with improved maternal or neonatal outcomes. Unnecessarily high rates, however, may lead to increased risks for both mothers and newborns (3). Therefore, reducing unnecessary cesarean sections and promoting informed birth choices have become critical goals in modern obstetric care.

During this period, the mental health of the mother is also important. The hormonal changes and physical demands of pregnancy and childbirth can increase psychological vulnerability and raise the risk of postpartum depression (PPD). PPD negatively impacts not only the psychological health of mothers but also mother-infant bonding and infant development (4).

Antenatal education programs have been developed to address concerns related to childbirth and postpartum psychological risks. These programs provide evidence-based information, emotional support, and coping strategies that can help pregnant women manage their fears about childbirth and make informed decisions about the mode of delivery. Consequently, their preference for cesarean section is reduced (5,6). Furthermore, these programs can strengthen psychological resilience during the postpartum period and protect maternal mental health.

Social support and psychological guidance during pregnancy are also pivotal in facilitating a healthy transition to parenthood (6). Antenatal education programs, delivered by multidisciplinary teams including obstetricians, midwives, physiotherapists, dietitians, and psychologists, are structured to enhance maternal self-efficacy, alleviate childbirth-related fears, and encourage positive birth experiences, including promoting vaginal delivery when appropriate.

In our country, "antenatal education classes" were established in state hospitals by a circular issued by the Turkish Public Health Institution of the Ministry of Health in 2014 (7). According to the circular, these classes are led by a multidisciplinary team consisting of an obstetrician, a midwife, a physical therapist, a dietitian, and a psychologist. These programs are designed to promote positive birth experiences by enhancing mothers' self-efficacy, alleviating fears related to childbirth, and encouraging vaginal birth when appropriate.

Current research indicates that prenatal education programs significantly reduce fear of childbirth and enhance awareness of childbirth preferences (8,9). Participation in these programs has also been associated with lower rates of cesarean delivery (10,11). However, the impact of these programs on PPD is still debated. While some studies report that women who attend prenatal education classes have significantly lower PPD scores than those who do not, other studies suggest that these programs do not substantially reduce the risk of PPD (8,9-12,13).

This study aimed to investigate the effect of antenatal education on mode of delivery and PPD risk, as well as its relationship with social support, childbirth-related anxiety, and maternal demographic characteristics.

Methods

Study design and participants

This cross-sectional, descriptive study included 265 patients who were assessed for PPD using the Edinburgh Postnatal Depression Scale (EPDS) as part of standard postpartum care provided by the Turkish Ministry of Health and who received follow-up at the University of Health Sciences Türkiye, Gülhane Training and Research Hospital, Clinic of Obstetrics and Gynecology between May 2023 and May 2024. All patients received prenatal care and gave birth at the same clinic. Participation was voluntary and began four weeks after childbirth.

All eligible participants were included without applying exclusion criteria. Participants were then divided into two groups based on their participation in the antenatal education programme: participants in the programme (n=109) and those who did not (n=156, the control group). Figure 1 shows the participant inclusion process and group allocation. Participants' antenatal follow-up results, mode of delivery, and participation in the antenatal education programme were obtained from hospital records.

Ethical considerations

The study protocol complied with the ethical guidelines outlined in the 1975 Declaration of Helsinki and its revisions (most recently in 2013).

Ethical approval for the study was granted by the University of Health Sciences, Türkiye, Gülhane Training and Research Hospital Non-interventional Scientific Research Ethics Committee (approval no.: 2024/11, date: 11.07.2024).

Inclusion criteria

Volunteers were included in the study if they met the following criteria: aged between 17 and 45 years, undergoing antenatal care, delivery, and postpartum controls in our clinic, voluntarily agreed to participate in the study, and had a sufficient level of education to complete the assessment scales.

Participants with a history of psychiatric disorders or severe pregnancy complications were excluded from the study. Patients who had undergone a planned caesarean section for obstetric reasons (such as previous caesarean section, history of uterine surgery, malpresentation, placental implantation abnormalities) were also excluded from the study.

Data collection

Socio-demographic and obstetric data were collected from participants using a data form developed based on those used in other studies on this topic. Demographic variables included

age, body mass index, level of education, occupation, presence of comorbidities, parity, number of living children, availability of support for infant care, difficulties with postnatal infant care, the mother's perception of her family's financial situation, and participation in an antenatal education programme.

Obstetric outcomes of participants (mode of delivery, indication for caesarean section, birth weight, admission to neonatal intensive care unit (NICU), development of postpartum maternal complications, etc.) were obtained from hospital records.

Antenatal education program

The antenatal education program of the University of Health Sciences Türkiye, Gülhane Training and Research Hospital, Clinic of Obstetrics and Gynecology is implemented in accordance with the regulations (14) published by the Ministry of Health in 2018. The programme is conducted by a multidisciplinary team consisting of obstetricians, midwives, dietitians, physiotherapists, and psychologists. The structured education programme provides comprehensive information on healthy lifestyle habits during pregnancy, routine prenatal care, and early recognition of warning signs. It also covers nutrition and exercise recommendations during pregnancy, childbirth, and the postpartum period, as well as topics related to motherhood and parenting. The programme aims to increase mothers' awareness, encourage their active participation in care processes, and provide integrated physical, nutritional, and psychological support. Participation in antenatal education programmes for pregnant women is voluntary.

PPD assessment

To evaluate PPD symptoms, all participants were assessed using the EPDS between the 4th and 8th weeks postpartum. The EPDS was originally developed by Cox et al. (15) in 1987 and was later adapted into Turkish with validation and reliability studies conducted by Engindeniz et al. (11).

The EPDS is a 10-item, 4-point Likert-type scale, with each item scored between 0 and 3, resulting in a total score ranging from 0 to 30. The cut-off score for identifying women at risk of PPD is (15-19). Women scoring 13 or higher on the scale are considered at increased risk for PPD. The scale has been reported to have a sensitivity of 0.84 and a specificity of 0.88.

In this study, a cut-off score of ≥13 was used, and participants exceeding this threshold were classified as at risk for PPD and referred for further psychological evaluation.

Statistical Analysis

Data evaluation was conducted with SPSS (IBM Corp., Armonk, NY, USA), version 25.0. The distribution of the variables was examined for normality using the Kolmogorov-Smirnov and Shapiro-Wilk tests. For descriptive purposes, continuous variables are summarized by median, minimum,

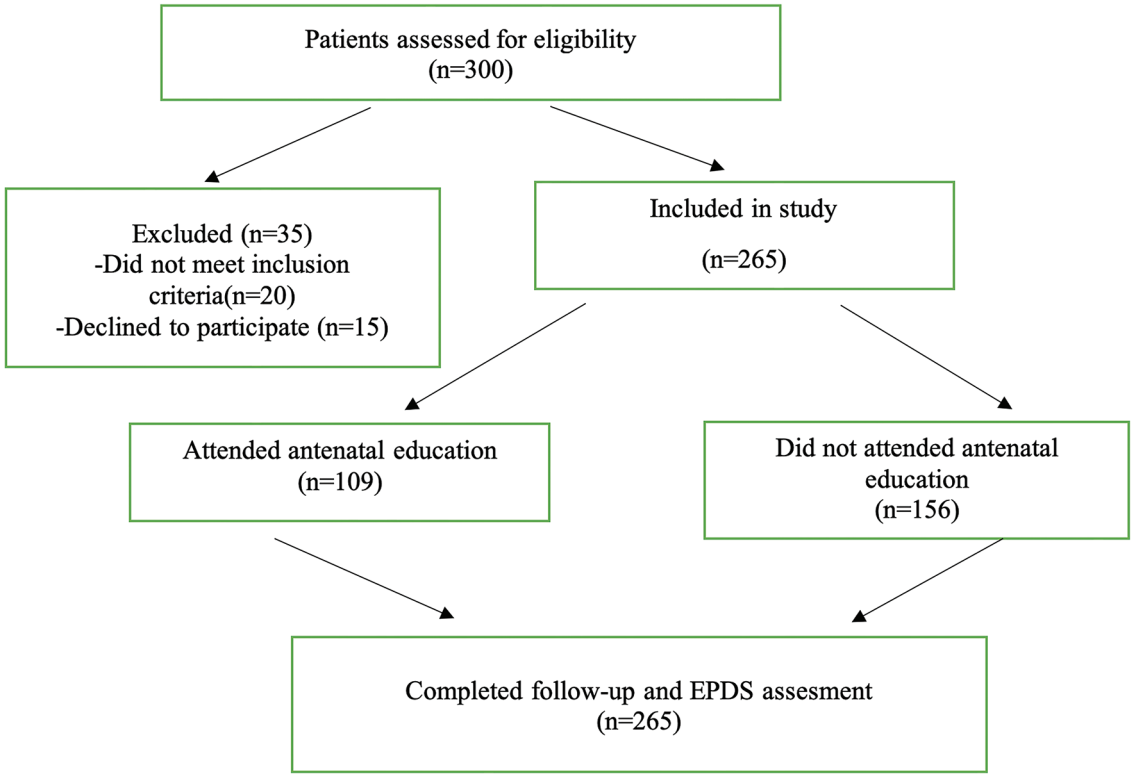

Figure 1. Participant flow diagram illustrating enrollment, group allocation, and follow-up

maximum, mean, and standard deviation, while categorical variables are expressed as counts and percentages. Because most continuous data deviated from a normal distribution, the Mann-Whitney U test was employed for comparisons between two independent groups, whereas the Kruskal-Wallis test was applied when more than two groups were compared. For categorical comparisons, Pearson's chi-square or Fisher's exact test was selected depending on data suitability. Associations between EPDS scores and other continuous variables were evaluated with Spearman's rank correlation. Statistical significance was accepted at a threshold of $p<0.05$. Multivariate logistic regression was also conducted to identify independent predictors of higher risk for postnatal depression (EPDS ≥13). Variables showing significance in univariate analyses were entered into the model, and the findings are presented as odds ratios with 95% confidence intervals and corresponding p-values. To ensure sufficient statistical power, an a priori sample size calculation was conducted using G*Power software (version 3.1.9.7). The target power was set at 1-β, with β representing the probability of Type II error. Assuming an anticipated effect size (Cohen's d) of 0.45, it was estimated that at least 212 participants (106 per group) would be required to achieve 95% power at a significance level of $\alpha=0.05$.

Results

A total of 265 participants who underwent antenatal follow-up and delivery at University of Health Sciences, Türkiye, between 2023 and 2024, were included in the study. Among them, 41.13% (n=109) attended the antenatal education program, while 58.87% (n=156) did not participate.

Socio-demographic factors, participant characteristics, EPDS scores, and antenatal education attendance.

The mean age of the participants was 28.72 years (±5.42), and the mean EPDS score was 6.22 (±5.04), with a median score of 5 (range: 0-23). The number of participants classified as high risk for PPD (EPDS score ≥13) was 28 (10.65%). Table 1 summarizes the remaining socio-demographic data.

Participants who attended the antenatal education program had a significantly higher educational level (high school or above) compared to those who did not attend (p=0.043). Additionally, the presence of an individual providing support in infant care was significantly more frequent among those who attended antenatal education than those who did not (p=0.003) (Table 1).

Obstetric outcomes and EPDS classification

No statistically significant association was found between planned pregnancy status (p=0.272), infant sex (p=0.625), term or preterm birth (p=0.561), NICU admission (p=0.498), or postnatal follow-up difficulties (p=0.807) and EPDS classification or antenatal education attendance (Table 1). A significant difference was observed between the groups in terms of mode of delivery. The rate of spontaneous vaginal delivery was higher among those who attended antenatal education, compared to those who did not (54.13% vs. 39.74%, p=0.021). Conversely, the cesarean section rate was significantly higher in the non-attendee group than in those who attended the program (60.26% vs. 45.87%, p=0.021) (Table 1).

The mean EPDS score was 6.22 (±5.04), and no significant difference was found between antenatal education attendees and non-attendees (6.83 vs. 5.81, p=0.095) (Table 1).

Although the proportion of participants classified as high risk for PPD (EPDS ≥13) was higher among those who attended antenatal education, this difference was not statistically significant (12.15% vs. 9.62%, p=0.513) (Table 1).

In the study, gravida ($p<0.001$), parity ($p<0.001$), and the number of living children ($p<0.001$), were found to be higher in those who did not attend the pregnancy school compared to those who did. Additionally, the age gap between the youngest sibling and the newborn was lower in the non-attending group (p=0.037) (Table 2).

In addition, no statistically significant differences were found between groups according to EPDS risk classification when comparing socio-demographic characteristics, medical history, obstetric outcomes, neonatal parameters, and postnatal infant health concerns ($p>0.05$ for all) (Table 3).

After adjustment for potential confounders, the multivariate logistic regression model did not identify any of the examined variables—including perceived financial status (p=0.289), mode of delivery (p=0.254), infant care assistance (p=0.251), and postnatal infant health concerns (p=0.118)—as independent predictors of PPD. This outcome implies that inter-variable interactions may partly explain the non-significant associations observed in the univariate analyses (Table 4).

Discussion

The findings revealed that participation in antenatal education was associated with a significantly higher rate of vaginal delivery. However, no significant difference was observed in EPDS scores between the groups, suggesting that the antenatal education program alone may not be sufficient to reduce the risk of PPD. Additionally, while a higher level of perceived social support was observed in the antenatal education group, the difference did not reach statistical significance.

However, a study by Gürkan and Ekşi (13) found no significant effect of antenatal education on reducing PPD risk, which aligns with our results (20). PPD is influenced by multiple biological and psychosocial factors, including hormonal fluctuations, psychological vulnerability, limited social support, and economic hardship (21), suggesting that no single intervention alone is sufficient for its prevention. Although participation in antenatal education was more common among women with higher

Table 1. Comparison of socio-demographic factors, participant characteristics, obstetric outcomes, and EPDS scores based on participation in the antenatal education

Variables		Antenatal education programme			p
			Attended (n=109)	Did not attended (n=156)	
			n (%)	n (%)	
Maternal educational level	Less than high school education	84 (31.69)	57 (36.54)	27 (24.77)	**0.043***
	High school graduate or higher	181 (68.3)	99 (63.46)	82 (75.23)	
Maternal employment status	Unemployed	220 (82.09)	134 (85.9)	86 (78.9)	0.135
	Employed	48 (17.91)	22 (14.1)	23 (21.1)	
Maternal perception of financial status (according to mother)	No	88 (33.33)	50 (32.26)	38 (34.86)	0.659
	Yes	176 (66.67)	105 (67.74)	71 (65.14)	
Presence of chronic disease	No	161 (60.75)	101 (64.74)	60 (55.05)	0.112
	Yes	104 (39.25)	55 (35.26)	49 (44.95)	
Use of medication	No	190 (71.7)	117 (75)	73 (66.97)	0.153
	Yes	75 (28.3)	39 (25)	36 (33.03)	
Assistance in infant care	No	173 (65.28)	113 (72.44)	60 (55.05)	**0.003***
	Yes	92 (34.72)	43 (27.56)	49 (44.95)	
Planned pregnancy	No	170 (64.66)	96 (61.94)	74 (68.52)	0.272
	Yes	93 (35.36)	59 (38.06)	34 (31.48)	
Mode of delivery	Vaginal delivery	121 (45.66)	62 (39.74)	59 (54.13)	**0.021***
	Cesarean section	144 (54.34)	94 (60.26)	50 (45.87)	
Newborn gender	Female	128 (48.67)	73 (47.4)	55 (50.46)	0.625
	Male	135 (51.33)	81 (52.6)	54 (49.54)	
Gestational age at birth (weeks)	Preterm (<37)	38 (14.34)	24 (15.38)	14 (12.84)	0.561
	Term (≥37)	227 (85.66)	132 (84.62)	95 (87.16)	
Neonatal hospitalization history	No	191 (72.08)	110 (70.51)	81 (74.31)	0.498
	Yes	74 (27.92)	46 (29.49)	28 (25.69)	
Postnatal follow-up issues	No	211 (79.62)	125 (80.13)	86 (78.9)	0.807
	Yes	54 (20.38)	31 (19.87)	23 (21.1)	
EPDS risk classification	Low risk	235 (89.35)	141 (90.38)	94 (87.85)	0.513
	High risk	28 (10.65)	15 (9.62)	13 (12.15)	

*: p<0.05, statistically significant. Data are presented as n (%) or mean ± standard deviation
EPDS: Edinburgh Postpartum Depression Scale

Table 2. Comparison of continuous variables based on antenatal education programme participation

Variables	Antenatal education programme				p
	Attended		Did not attended		
	Median (min-max)	Mean ± SD	Median (min-max)	Mean ± SD	
Maternal age (years)	29 (17-44)	29.13±5.73	28 (18-41)	28.14±4.92	0.18
Body mass index (kg/m²)	26.3 (16.61-43.82)	26.93±4.21	25.15 (19.53-40.27)	26.08±4.23	**0.016***
Gravida	2 (1-7)	2.33±1.26	1 (1-6)	1.74±1.07	**<0.001***
Parity	1 (0-4)	0.99±0.89	0 (0-3)	0.5±0.74	**<0.001***
Number of living children	1 (0-4)	0.94±0.85	0 (0-3)	0.46±0.69	**<0.001***
Number of abortions	0 (0-4)	0.35±0.76	0 (0-5)	0.25±0.68	0.263
Age gap with the youngest sibling (years)	4 (1-12)	4.79±2.72	5 (2-16)	6.12±3.31	**0.037***
EPDS	5 (0-23)	5.81±4.84	6 (0-22)	6.83±5.28	0.095

*: p<0.05, statistically significant. Data are presented as n (%) or mean ± SD
SD: Standard deviation, EPDS: Edinburgh Postpartum Depression Scale

Table 3. Comparison of EPDS scores based on socio-demographic and medical history according to antenatal education programme participation

Antenatal education program			EPDS classification		p
			Low risk (≤12)	High risk (≥13)	
			n (%)	n (%)	
Educational level	Less than high school education	Did not attended	53 (92.98)	4 (7.02)	1.00
		Attended	24 (92.31)	2 (7.69)	
	High school graduate or higher	Did not attended	88 (88.89)	11 (11.11)	0.615
		Attended	70 (86.42)	11 (13.58)	
Employment status	Unemployed	Did not attended	121 (90.3)	13 (9.7)	0.301
		Attended	72 (85.71)	12 (14.29)	
	Employed	Did not attended	20 (90.91)	2 (9.09)	0.608
		Attended	22 (95.65)	1 (4.35)	
Perceived financial status (according to mother)	None	Did not attended	48 (96)	2 (4)	0.395
		Attended	33 (89.19)	4 (10.81)	
	Yes	Did not attended	92 (87.62)	13 (12.38)	0.926
		Attended	61 (87.14)	9 (12.86)	
Presence of chronic disease	None	Did not attended	94 (93.07)	7 (6.93)	0.083
		Attended	49 (84.48)	9 (15.52)	
	Present	Did not attended	47 (85.45)	8 (14.55)	0.309
		Attended	45 (91.84)	4 (8.16)	
Medication use	None	Did not attended	107 (91.45)	10 (8.55)	0.363
		Attended	62 (87.32)	9 (12.68)	
	Present	Did not attended	34 (87.18)	5 (12.82)	1.00
		Attended	32 (88.89)	4 (11.11)	
Availability of assistance in infant care	None	Did not attended	104 (92.04)	9 (7.96)	0.627
		Attended	53 (89.83)	6 (10.17)	
	Present	Did not attended	37 (86.05)	6 (13.95)	0.932
		Attended	41 (85.42)	7 (14.58)	
Planned pregnancy	Yes	Did not attended	52 (88.14)	7 (11.86)	1.00
		Attended	29 (87.88)	4 (12.12)	
	No	Did not attended	88 (91.67)	8 (8.33)	0.392
		Attended	64 (87.67)	9 (12.33)	
Mode of delivery	Vaginal delivery	Did not attended	54 (87.1)	8 (12.9)	0.886
		Attended	50 (86.21)	8 (13.79)	
	Cesarean section	Did not attended	87 (92.55)	7 (7.45)	0.545
		Attended	44 (89.8)	5 (10.2)	
Gestational age at delivery	Preterm	Did not attended	19 (79.17)	5 (20.83)	0.137
		Attended	14 (100)	0 (0)	
	Term	Did not attended	122 (92.42)	10 (7.58)	0.818
		Attended	80 (86.02)	13 (13.98)	
Infant sex	Female	Did not attended	64 (87.67)	9 (12.33)	0.610
		Attended	48 (90.57)	5 (9.43)	
	Male	Did not attended	75 (92.59)	6 (7.41)	0.167
		Attended	46 (85.19)	8 (14.81)	

Table 3. Continued

Antenatal education program			EPDS classification		p
			Low risk (≤12)	High risk (≥13)	
			n (%)	n (%)	
Neonatal intensive care unit admission	None	Did not attended	100 (90.91)	10 (9.09)	0.312
		Attended	69 (86.25)	11 (13.75)	
	Present	Did not attended	41 (89.13)	5 (10.87)	1.00
		Attended	25 (92.59)	2 (7.41)	
Postnatal infant health concerns	None	Did not attended	110 (88)	15 (12)	0.839
		Attended	74 (87.06)	11 (12.94)	
	Present	Did not attended	31 (100)	0 (0)	0.168
		Attended	20 (90.91)	2 (9.09)	

AEP: Antenatal education program, EPDS: Edinburgh Postnatal Depression Scale

Table 4. Effect of independent risk factors on high depression risk: logistic regression analysis

Risk factors	B	Standard error	p	OR	95% Confidence interval	
					Lower	Upper
Perceived financial status (insufficient)	-0.519	0.490	0.289	0.595	0.228	1.554
Mode of delivery (CS)	-0.467	0.409	0.254	0.627	0.281	1.398
Presence of assistance in infant care (no)	-0.473	0.412	0.251	0.623	0.278	1.397
Postnatal infant health concerns (present)	-1.180	0.755	0.118	0.307	0.070	1.350

CS: Cesarean section, OR: Odds ratio, CI: Confidence interval

education, it did not significantly affect EPDS scores across socio-demographic variables such as chronic illness, medication use, financial status, or support in infant care.

The high educational level of participants in both groups may be one of the possible reasons why no significant association was found between participation in antenatal education classes and the risk of PPD.

This finding is consistent with studies by Leung et al. (21) and McLearn et al. (22), while other studies in the literature indicate that a low level of education is a risk factor for PPD (23).

The results suggest that mothers who participated in the antenatal education programme had stronger social support systems and were more likely to receive help with infant care. Social support has been identified in the literature as one of the most critical protective factors against PPD (24). A study conducted in Japan demonstrated that maternal self-efficacy is shaped by environmental support, which plays a crucial role in reducing the risk of PPD (21). However, despite the stronger social support systems observed in our study, no significant effect on EPDS scores was detected. This suggests that social support alone may not be sufficient and further reinforces the multifactorial nature of PPD.

It has been suggested that unplanned pregnancies negatively affect maternal psychological well-being and reduce mothers' ability to cope with postpartum challenges (25,26). Similarly, a study by Durukan et al. (20) emphasized that unplanned pregnancies increase the risk of PPD and that planned pregnancies have a positive effect on maternal psychological well-being. Likewise, Brockington et al. (27) reported that mothers with unwanted pregnancies may exhibit a lack of interest or even negative emotions toward their newborns in the postpartum period, thereby increasing the likelihood of PPD. However, contradictory findings also exist in the literature. Similar to our study, Ulusoy (28) and Demir et al. (29) did not find a significant relationship between pregnancy planning status and the risk of PPD. Additionally, studies by Gonidakis et al. (30) and Efe et al. (25) reported that whether a pregnancy was planned or unplanned had no statistically significant impact on the frequency of PPD symptoms.

The literature highlights that antenatal education programmes, particularly those that include individualised counselling, provide significant benefits to mothers and parents during pregnancy and the postpartum period (29-31).

The literature suggests that childbirth preparation courses support women's preference for vaginal delivery and reduce cesarean section rates (10). This finding indicates that educational programs play an important role in preparing women for childbirth and alleviating fear related to labor. The preparation facilitated through education may enable women to approach the childbirth process more positively and contribute to a reduction in cesarean rates (32). The increase in awareness

and reduction in fear among educated participants could be a crucial factor in supporting vaginal delivery. This aligns with the perspective that education enhances women's sense of control over their own bodies, thereby influencing their birth preferences (33).

In our country, antenatal education programs are promoted nationwide through initiatives led by the Ministry of Health, aiming to reach every pregnant woman (13). New regulations are currently under development to enhance and standardize these programs.

Although the antenatal education program in our study was designed to be structured and multidisciplinary, certain limitations should be acknowledged. The relatively brief duration of the sessions (6-8 hours) may have been insufficient to yield lasting behavioral or psychological outcomes, particularly in postpartum adjustment and anxiety reduction. As this was a single-center study conducted at a tertiary care hospital, the antenatal education group primarily included women with higher educational attainment, the findings may not be generalizable to the broader pregnant population.

Moreover, the lack of nationwide standardization in antenatal education programs—regarding content, educator qualifications, and delivery methods—may have affected the consistency and comparability of outcomes. The absence of systematic pre- and post-intervention evaluations, as noted in the literature, also limits the robustness of conclusions regarding their effectiveness.

Despite these limitations, this study provides valuable insights as one of the few retrospective analyses in Türkiye evaluating both obstetric and psychological outcomes related to antenatal education. The study, conducted in a real-world clinical setting with a multidisciplinary team, reflects routine tertiary care practice. An adequate sample size, determined through power analysis, enhances the reliability of the findings and contributes to national strategies for maternal health education.

Conclusion

This study reinforces the role of antenatal education in improving maternal health, particularly by increasing vaginal delivery rates and reducing unnecessary cesarean sections. Although a clear reduction in PPD was not observed, this finding highlights the need for more comprehensive and longitudinal educational approaches. Structured and standardized antenatal education programs hold promise as an effective public health strategy to enhance maternal and neonatal outcomes. National expansion of these programs, inclusion of both parents, and evaluation across diverse populations may further strengthen their impact. Moreover, larger multicenter studies with standardized program content and long-term follow-up are required to clarify the true effect of antenatal education on postpartum psychological outcomes.

Ethics

Ethics Committee Approval: Ethical approval for the study was granted by the Scientific Research Ethics Committee of Gülhane Health Application and Research Center (approval no: 2024/11, date: 11.07.2024).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: P.K.T., S.A.Ç.,A.F.T., Concept: P.K.T., A.T.A., A.F.T., Ö.Ö., Design: P.K.T., A.F.T., Ö.Ö., Data Collection or Processing: P.K.T., S.A.Ç.,Analysis or Interpretation: P.K.T., A.T.A., S.A.Ç.,Ö.Ö., Literature Search: P.K.T., A.T.A., S.A.Ç.,A.F.T., Ö.Ö., Writing: P.K.T., A.F.T.

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The correlation of ASAS Health Index and scales assessing general health status, disease activity, functional capacity, spinal mobility, and quality of life in Turkish patients with ankylosing spondylitis

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ABSTRACT

Aims: We aimed to investigate whether the Assessment of SpondyloArthritis International Society Health Index (ASAS HI) correlates with scales assessing overall health status, disease activity, spinal mobility, quality of life, and functional capacity in individuals with ankylosing spondylitis (AS).

Methods: This cross-sectional study included patients with AS diagnosed according to the 2010 ASAS classification criteria. ASAS HI, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Ankylosing Spondylitis Disease Activity Score-C-Reactive Protein (ASDAS-CRP), Bath Ankylosing Spondylitis Functional Index (BASFI), Dougados Functional Index (DFI), Bath Ankylosing Spondylitis Metrology Index, Bath Ankylosing Spondylitis Patient Global Score (BAS-G), Visual Analog Scale (VAS) for pain and morning stiffness scores, Ankylosing Spondylitis Quality of Life (ASQoL), EuroQol-5D (EQ-5D), and EQ VAS were measured. Statistical analyses were conducted to examine correlations between the ASAS HI and other measurement instruments.

Results: A cohort of 141 patients (84 males and 57 females) with a mean age of 39.02±12.16 years was included in the study. ASAS HI was positively correlated with BASDAI, ASDAS-CRP, and ASDAS-ESR ($p<0.001$, $r=0.63$, $r=0.61$, $r=0.64$). ASAS HI demonstrated strong positive correlations with BASFI and DFI ($p<0.001$, $r=0.71$, $r=0.72$), and a significant negative correlation with EQ-5D ($p<0.001$, $r=-0.67$). Additionally, notable positive associations were observed with ASQoL ($p<0.001$, $r=0.79$) and BAS-G ($p<0.001$, $r=0.63$).

Conclusions: The ASAS HI may serve as a measure of overall health in patients with AS, provide additional insights alongside assessments of disease severity, functional ability, and well-being, and facilitate longitudinal monitoring of treatment outcomes.

Introduction

Ankylosing spondylitis (AS) is a chronic rheumatologic condition characterized by inflammation mainly of the spine, sacroiliac joints, and entheses, and occasionally of the peripheral joints (1). The reported prevalence varies between 0.1% and 1.4%, and it is observed approximately twice as often in men compared to women (2). AS is marked by persistent inflammation, which plays a central role in driving both disability and increased mortality among affected individuals. The evaluation of inflammation using reliable markers in AS plays a key role in predicting patients' long-term prognosis (3). There is no standardized laboratory test to be used as a diagnostic and follow-up tool specific to AS. Currently, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are routinely employed as biochemical indicators of inflammation (4).

Over time, AS can cause significant disability in patients. Therefore, monitoring disease activity and function, selection of the optimal treatment, and the evaluation of therapeutic response play a vital role. The Assessment of SpondyloArthritis International Society Health Index (ASAS HI), developed by Kiltz et al. (5), is an ASAS instrument for measuring health status in patients across all spondyloarthritis (SpA) categories, including radiographic and non-radiographic axial and peripheral manifestations of SpA, based on the International Classification of Functioning, Disability and Health (ICF) categories (5). The instrument has been translated and culturally adapted into 15 languages, including Turkish (6). The reliability and validity of the Turkish version were established by Duruöz et al (7). The ASAS HI provides a comprehensive assessment of health status by addressing key domains derived from the ICF framework, including pain, emotional well-being, sleep quality, sexual health, mobility, personal care, and social participation. Importantly, the ASAS HI is intended as a general measure of health status rather than a health-related quality-of-life tool for AS. In contrast, most existing instruments for patients with SpA concentrate on individual health domains, such as pain, disease severity, or physical function, and aim to evaluate specific aspects such as functional performance or health-related quality of life. Nonetheless, the overall effect of AS on patients' functional ability and social engagement has not been comprehensively captured by questionnaires specifically designed for SpA.

Our primary aim was to investigate whether the ASAS HI correlates with measures of pain, disease activity, functional capacity, health status, spinal mobility, and quality of life in patients with AS.

Methods

Research design, study population, and ethical considerations

This cross-sectional study was undertaken between October 4, 2018, and October 8, 2018, in the Rheumatology Division of the Department of Physical Medicine and Rehabilitation at Cumhuriyet University Faculty of Medicine. The eligibility criteria for participation included: a diagnosis of AS according to the 2010 ASAS criteria (8); AS patients aged 18 years or older; patients willing and competent to provide written informed consent; and participants capable of adhering to study procedures. Patients with active inflammatory bowel disease, poorly controlled diabetes, recently active coronary artery disease, heart failure, a history of cancer or lymphoproliferative disease, gout, calcium pyrophosphate dihydrate crystal deposition, other concomitant inflammatory rheumatic diseases, hepatitis, active tuberculosis, concomitant fibromyalgia, mental health disorders, and pregnancy were excluded. The study included 141 patients.

Ethics Committee approval was obtained from the Clinical Research Ethics Committee of Cumhuriyet University (approval no.: 2018-03/04; date: 26.03.2018). In accordance with the Declaration of Helsinki, all participants provided written informed consent after receiving appropriate study information.

Data collection and instruments

A predesigned data collection form was used to record the patients' socio-demographic and clinical characteristics. This form consisted of questions regarding demographic and clinical parameters such as gender identity, age of patients, level of education, civil status, work status, disease duration, concurrent chronic disorders, smoking status, body mass index (BMI), certain laboratory findings [such as CRP, ESR, human leukocyte antigen-B27 (HLA-B27)], and medications used.

Patient-reported outcome measures assessing pain, disease activity, functional capacity, duration of morning stiffness, health status, quality of life, and general condition were completed by the patients themselves, with explanatory assistance provided when necessary. Spinal mobility measurements and BMI were assessed by the investigator.

Laboratory data

CRP and ESR values were obtained from routine tests. Normal reference ranges were 0-8 mg/L for CRP and 0-20 mm/h for ESR. HLA-B27 test results were obtained from patients' medical records.

Pain and morning stiffness

Visual Analog Scale (VAS) is accepted as an appropriate and practical method for assessing the severity of the most common complaints of pain and stiffness among patients with AS. In this study, pain intensity was assessed with VAS. The scale is composed of a 10 cm (100 mm) line, which can be oriented horizontally or vertically. The beginning of the line denotes "no pain or stiffness," and the end denotes "the most severe pain or stiffness imaginable." Patients are informed that pain intensity increases from the left to the right end of the line and are asked to indicate the point that corresponds most closely to their current

level of pain. The point marked by the patient is measured in cm or mm (9). The duration of morning stiffness was measured in minutes, and severity was assessed using VAS.

Disease activity

To assess disease activity, the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Ankylosing Spondylitis Disease Activity Score (ASDAS)-CRP, and ASDAS-ESR were employed (10-12).

The BASDAI assesses fatigue, spinal pain, localized tenderness in enthesitis areas, and the duration and intensity of morning stiffness. For this purpose, the patient is asked to answer 6 questions and to provide a score between 0 and 10 on the VAS. The answers in questions 5-6 are summed and divided by two, the result is summed with the other scores, and the result is divided by 5. If the score obtained is between 0 and 3, it is classified as mild; between 3.1 and 5, as moderate; between 5.1 and 7, as severe; and between 7.1 and 10, as very severe. In general practice, patients with a score of 4 or higher are considered active, and those with a score below 4 are considered inactive (10,12).

The parameters used in the ASDAS Score are: (1) total back pain (BASDAI question 2), (2) patient global assessment (VAS), (3) peripheral pain/swelling (BASDAI question 3), (4) duration of morning stiffness (BASDAI question 6), and (5) CRP or ESR levels. In the calculation, CRP is expressed in mg/L and ESR in mm/h. The VAS scores and the CRP values are included in the ASDAS formula. The evaluation of the results is presented as follows: above 3.5 is very high disease activity, 2.1-3.5 is high disease activity, 2.1-1.3 is moderate disease activity, and values below 1.3 are inactive disease status. A change greater than 1.1 in the ASDAS-CRP, which is useful for treatment follow-up, is classified as clinically meaningful, while a change greater than 2 points represents a substantial improvement (12).

Functional status

Bath Ankylosing Spondylitis Functional Index (BASFI) and Dougados Functional Index (DFI) were used to assess the functional status of the patient with AS (13,14).

The BASFI includes 10 questions about activities related to the patient's functional anatomy and day-to-day living activities. The patient is asked to rate each activity on a VAS from 0 to 10 according to the degree of difficulty. The marks are measured in cm, and the result is divided by 10. Higher scores are interpreted as indicating greater limitation in physical function (13).

The DFI includes 20 questions related to functional capacity and daily living tasks. Patients answer these questions using three response categories: 0= able to do without difficulty; 1= able to do with difficulty; and 2= unable to do. The overall score ranges from 0 to 40. A higher score indicates greater functional limitations (14).

Quality of life

The EuroQol-5D (EQ-5D) index assesses five health dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (15). Each dimension is rated on three levels: no problems, some problems, and severe problems, yielding a total of 243 possible health states. From these responses, an index score ranging from -0.59 to 1 is derived, where 0 represents a state equivalent to death, 1 represents optimal health, and negative scores correspond to severely impaired states, such as unconsciousness or a completely bedridden state. The EQ VAS complements this by allowing individuals to self-rate their current health status on a 0-100 scale, visually represented like a thermometer, producing a health-related quality of life score (15).

AsQoL was used to assess quality of life in patients with AS (16). This scale, used by AS patients, comprises 18 statement-based items rather than questions. There are yes/no options for each sentence. Patients are asked to provide the most appropriate response based on their current situation. These items are related to the patients' daily life functions, social relations, mental state, the severity of pain they feel, and how it affects their daily life. The statements in the questionnaire are negatively worded. Each "yes" answer is scored as 1 point. Elevated scores on the scale indicate diminished QoL. This QoL measure is quick, simple, and easy for patients to understand.

General condition

Bath Ankylosing Spondylitis Patient Global Score (BAS-G) is a practical measure of the general effects of the disease on the patient's overall health status, whereby the patient evaluates his/her own condition in recent days using VAS (17,18). This measure is a simple but highly reflective assessment of disease activity, in which the patient evaluates himself/herself with respect to general aspects such as symptoms, functional status, and QoL. It consists of two questions: "How have you felt in the last week?" and "How have you felt in the last six months?" Patients are requested to respond to these questions using the VAS. A total score is calculated by averaging these two VAS values.

Spinal mobility

Spinal mobility was evaluated using the Bath Ankylosing Spondylitis Metrology Index (BASMI) (19). This index comprises five clinical assessment measures: tragus-to-wall distance, lateral spinal flexion, modified lumbar Schober, cervical rotation, and intermalleolar distance. The results for right and left lateral lumbar flexions, cervical rotations, and tragus-wall distance are averaged. Each measurement is evaluated separately; scores of zero, one, and two are assigned according to specific measurement intervals. The scores of the five measurements are summed. A total score ranging from 0 to 10 is calculated. The increased score, the greater the limitation of mobility due to AS (20).

Health status

The ASAS HI was established to assess health status across all SpA subtypes, including radiographic and non-radiographic axial SpA as well as peripheral manifestations (5). It is a self-reported questionnaire comprising 17 items covering domains such as pain, emotional functioning, sleep, sexual health, physical movement, personal care, and social engagement. Each item is phrased in the first person and present tense, with two possible responses: "agree" or "disagree." A value of 1 is assigned to each "agree" answer and 0 to each "disagree" answer, resulting in an overall score ranging from 0 to 17. Increased scores denote more pronounced impairment, and lower scores indicate better health.

Outcomes

The primary outcome of this study was the correlation between the ASAS HI and disease activity (BASDAI, ASDAS-CRP, ASDAS-ESR), functional status (BASFI, DFI), spinal mobility (BASMI), quality of life (ASQoL, EQ-5D, EQ-VAS), and patient global assessment (BAS-G). The secondary outcome was the comparison of ASAS HI scores among disease activity groups based on BASDAI and ASDAS-CRP.

Statistical Analysis

All statistical procedures were executed using SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). Descriptive data were expressed as mean ± standard deviation, median (min-max), and percentage. An a priori power analysis was conducted using G*Power 3.1. Given a medium effect size (f=0.25), an alpha error probability of 0.05, and a desired power of 0.90, the required sample size was calculated to be 128. Our study included 141 patients, exceeding this requirement and thus providing adequate statistical power. The Kolmogorov-Smirnov test was used to assess the normality of quantitative data. Since the parametric test assumptions could not be fulfilled in the evaluation of the data, Kruskall-Wallis test was used in the comparison of ASAS HI scores with BASDAI and ASDAS-CRP Group scores. Pairwise post-hoc comparisons were performed using the Mann-Whitney U test. To account for multiple testing in post-hoc comparisons, the Bonferroni correction was applied, and $p<0.0125$ was considered statistically significant. The chi-square test or Fisher's exact test was applied to examine categorical data, and the results are presented as frequency and percentage [n (%)]. The relationship between the variables was evaluated using Spearman correlation analysis. Correlations ≤0.30 were considered as low, >0.30 and ≤0.50 moderate, between 0.50 and 0.80 as strong, ≥80 as very strong. Two-tailed statistical tests were used, and statistical significance was set at $p\leq0.05$.

Results

A cohort of 141 patients (84 males and 57 females) with a mean age of 39.02±12.16 years was included in the study. The patients' socio-demographic data are presented in Table 1. The median CRP was 3.37 mg/L (0.60-35), and the median ESR was 8 mm/h (1-48). The ASAS HI had a median of 8 (0-17). Disease activity scores were BASDAI: 4.8 (0-11.1), ASDAS-CRP: 2.8 (0-5), and ASDAS-ESR: 2.6 (0.6-4.8). The Functional indices were BASFI: 4.5 (0-9.5) and DFI: 11 (0-25). Patients' clinical profiles and laboratory findings are presented in Table 2.

When ASAS HI values were compared across BASDAI groups, a statistically significant difference was observed ($p<0.001$). In pairwise comparisons, statistically significant differences were observed between the mild disease activity group and all other groups and between the moderate disease activity group and all other groups ($p<0.001$). However, the analysis revealed no statistically significant differences between the severe and very severe disease activity groups ($p>0.05$) (Table 3).

When ASAS HI scores were compared across ASDAS-CRP groups, a statistically significant difference was observed ($p<0.001$). In pairwise comparisons, marked differences were found between the following pairs of groups: inactive vs. high disease activity, inactive vs. very high disease activity, moderate vs. high disease activity, moderate vs. very high disease activity, and high vs. very high disease activity (all $p<0.001$). However, the difference between the inactive and moderate disease activity groups was not significant ($p>0.05$) (Table 3).

The analyses revealed no statistically significant correlation between ASAS HI scores and CRP values ($p>0.05$). However, ASAS HI scores demonstrated a modest positive correlation with ESR values ($p<0.016$, $r=0.20$). Additionally, significant positive correlations were noted between ASAS HI scores and pain, morning stiffness severity ($p<0.001$, r values: 0.59, 0.55, respectively), and significant positive moderate correlations was founded between ASAS HI and the morning stiffness ($p<0.001$, r values: 0.33). Furthermore, high-strength significant positive correlations were identified between ASAS HI scores and ASDAS-CRP, ASDAS-ESR, and BASDAI scores ($p<0.001$, r values: 0.61, 0.64, 0.63, respectively).

We also observed strong, positive, and significant correlations between ASAS HI scores and BASFI scores, and between ASAS HI scores and DFI scores ($p<0.001$; $r=0.71$ and 0.72, respectively). However, there was no statistically significant correlation between ASAS HI scores and disease duration (Table 4).

Discussion

In this study, ASAS HI scores were meaningfully correlated with multiple clinical parameters, including parameters of disease activity (BASDAI, ASDAS-CRP, ASDAS-ESR), functional measures (BASFI, DFI), spinal mobility (BASMI), patient global assessment (BAS-G), and quality-of-life scales (ASQoL, EQ-5D). Strong correlations were observed, particularly with disease

Table 1. Socio-demographic data, medication use, clinical features, and HLA-B27 status of AS patients

Characteristics	Values
Age, years, mean ± SD (min-max)	39.02±12.16 (18-68)
Male/female, n (%)	84 (59.6)/57 (40.4)
Disease duration, months, mean ± SD (min-max)	78.41±96.86 (5-480)
BMI (kg/m²), mean ± SD	27.40±5.63
BMI group (kg/m²), n (%)	
<18.5	3 (2.1)
18.5-24.9	44 (31.2)
25-29.9	55 (39)
≥30	39 (27.7)
Background, n (%)	
No features	107 (75.9)
HT	12 (8.5)
DM	2 (1.4)
HT and DM	1 (0.7)
CAD and DM	1 (0.7)
Thyroid disease	5 (3.5)
Others	13 (9.2)
Education status, n (%)	
Illiterate	2 (1.4)
Literate	7 (5)
Primary school	54 (38.3)
High school	32 (22.7)
University	46 (32.6)
Marital status, n (%)	
Married	103 (73)
Single	37 (26.2)
Widowed	1 (0.7)
Smoking status, n (%)	
Non-smoker	101 (71.6)
Smoker	35 (24.8)
Former-smoker	5 (3.5)
Medications used, n (%)	
Non-medication	4 (2.8)
NSAIDs	43 (30.5)
Sulfasalazine	5 (3.5)
NSAIDs and sulfasalazine	9 (6.4)
Biological agents	80 (56.7)
HLA-B27	
Positive	38 (27)
Negative	59 (41.8)
Not obtained	44 (31.2)

HLA-B27: Human leukocyte antigen B27, AS: Ankylosing spondylitis, SD: Standard deviation, Min-max: Minimum-maximum, BMI: Body mass index, HT: Hypertension, DM: Diabetes mellitus, CAD: Coronary artery disease, NSAIDs: Non-steroidal anti-inflammatory drugs

Table 2. Clinical and laboratory characteristics of AS patients

Characteristics	Values*
CRP (mg/L)	3.37 (0.60-35)
ESR (mm/h)	8 (1-48)
Pain (VAS, 0-10 cm)	7 (0-10)
Severity of morning stiffness (VAS, 0-10 cm)	5 (0-10)
Duration of morning stiffness (minutes)	30 (0-180)
ASAS HI	8 (0-17)
BASDAI	4.8 (0-11.1)
ASDAS-CRP	2.8 (0-5)
ASDAS-ESH	2.6 (0.6-4.80)
BASFI	4.5 (0-9.5)
DFI	11 (0-25)
BAS-G	6.5 (0-10)
BASMI	1 (0-10)
ASQoL	9 (0-18)
EQ-5D Index	0.507 (0.04-1)

*Data are presented as median (minimum-maximum)
AS: Ankylosing spondylitis, CRP: C-reactive protein, ESR: Erytrocyte sedimentation rate, VAS: Visual Analogue Scale, ASAS HI: Assessment of SponyloArthritis International Society Health Index, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, ASDAS: Ankylosing Sponylitis Disease Activity Score, BASFI: Bath Ankylosing Spondylitis Functional Index, DFI: Dougadas Functional Index, BAS-G: Bath Ankylosing Spondylitis Patient Global Score, BASMI: Bath Ankylosing Spondylitis Metrology Index, ASQoL: Ankylosing Spondylitis Quality of Life EQ-5D: EuroQoL-5 Dimension Index

activity, functional capacity, and quality-of-life measures, while weaker associations were found with inflammatory markers such as CRP. The observed outcomes provide new perspectives on the applicability of ASAS HI and its potential role in clinical practice.

The ASAS HI was designed to evaluate health status in patients with all types of SpA (6). Although various scales exist to monitor disease activity, quality of life, and functional capacity in AS, research on the ASAS HI remains limited, as it is a newly developed index.

In patients with AS, pain intensity and the degree and duration of morning stiffness are important parameters for disease follow-up (21). In the current investigation, a statistically marked positive correlation was observed with pain scores in relation to ASAS HI scores. In addition, our study revealed a meaningful positive correlation of morning stiffness duration and intensity with ASAS HI scores. Our findings were consistent with the literature (19-22). Based on this significant correlation between pain, morning stiffness duration, morning stiffness intensity, and ASAS HI scores, ASAS HI may provide additional benefit in assesesing activity of disease in patients diagnosed with AS.

CRP and ESR are widely employed as markers of inflammation in AS and may provide additional value in

Table 3. Comparison of ASAS HI scores according to BASDAI and ASDAS-CRP groups

BASDAI groups	n	ASAS HI Scores				
		Median	Minimum	Maximum	p-value	Post-hoc**
0-3 (Mild disease activity between, I)	32	2.56	0	11.68	<0.001*	I vs. II, III, IV
3.1-5 (Moderate disease activity, II)	43	7.43	0	15		II vs. I, III, IV
5.1-7 (High disease activity, III)	40	9.31	3.40	17		
7.1-10 (Very high disease activity, IV)	26	10.62	5	17		
ASDAS-CRP groups						
<1.3 (Inactive disease activity, I)	3	2.00	0	2	<0.001*	I vs. III, IV
1.3-2.1 (Moderate disease activity, II)	31	3.18	0	13.80		II vs. III, IV
2.1-3.5 (High disease activity, III)	67	7.90	0	17		III vs. IV
≥3.5 (Very high disease activity, IV)	40	11.11	5	17		

*: Kruskal-Wallis test, **: Mann-Whitney U testt
ASAS HI: Assessment of SponyloArthritis International Society Health Index, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, ASDAS: Ankylosing Spondylitis Disease Score, CRP: C-reactive protein

Table 4. Correlation coefficient between ASAS HI and clinical features

	ASAS HI	
	r	p-value
CRP (mg/L)	0.10	0.217
ESR (mm/h)	0.20	**0.016**
Pain (VAS)	0.59	**<0.001**
Severity of morning stiffness (VAS)	0.55	**<0.001**
Duration of morning stiffness (minute)	0.33	**<0.001**
ASDAS-CRP	0.61	**<0.001**
ASDAS-ESR	0.64	**<0.001**
BASDAI	0.63	**<0.001**
BASFI	0.71	**<0.001**
DFI	0.72	**<0.001**
EQ-5D index	-0.67	**<0.001**
EQ-VAS	-0.44	**<0.001**
ASQoL	0.79	**<0.001**
BASMI	0.23	0.006
BAS-G	0.63	**<0.001**
Disease duration (months)	0.19	0.825

ASAS HI: Assessment of SpondyloArthritis International Society Health Index, CRP: C-reactive protein, ESH: Eryhtrocyte sedimentation rate, VAS: Visual Analogue Scale, ASDAS: Ankylosing Spondylitis Disease Activity Score, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index, DFI: Dougadas Functional Index, BAS-G: Bath Ankylosing Spondylitis Patient Global Score, BASMI: Bath Ankylosing Spondylitis Metrology Index, ASQoL: Ankylosing Spondylitis Quality of Life, EQ-5D: EuroQoL-5 Dimension, EQ-VAS: EuroQoL Visual Analogue Scale

assessing disease activity; however, their use is controversial (21). In patients with AS, a 50-70% increase in ESR and CRP has been observed in clinical studies. However, it has been reported that this elevation is not consistently correlated with disease activity and should be evaluated in conjunction with other parameters (4). In our study, there was no correlation between ASAS HI scores and CRP values. There was a statistically significant positive correlation between ASAS HI scores and ESR; however, the strength of the correlation was weak. Min et al. (22) observed a robust correlation between ASAS HI and CRP values. The observed discrepancy could be attributed to variations in sample size and patient characteristics, particularly in disease duration and treatment exposure.

BASDAI and ASDAS-CRP are commonly used scales to evaluate disease activity in patients with AS. A statistically significant positive correlation was observed between these two disease activity scales and ASAS HI scores, though ASAS HI is not a tool for evaluating disease activity. Similar to this study, other studies have reported robust positive correlations between ASAS HI scores and both ASDAS-CRP and BASDAI scores (22-33). Different cut-off values were determined in three previous studies (27,29,30).

The statistical significance of BASDAI and ASDAS, compared with ASAS HI, across disease activity groups suggests that ASAS HI can serve as an easy-to-use and effective tool in daily practice for assessing disease activity, in addition to its use as a health status scale.

ASAS HI is not traditionally considered a tool for functional assessment. In this study, we observed a statistically significant positive correlation between ASAS HI scores and BASFI and DFI scores. In the literature, a strong statistical correlation was found between ASAS HI scores and BASFI scores (22-34). However, these studies did not investigate whether a correlation exists between ASAS HI and DFI. This correlation suggests that it can be used in routine practice to assess functional status in patients with AS.

In this study, we observed a statistically significant but weak positive correlation between ASAS HI and BASMI scores. Consistent with our findings, Di Carlo et al. (24) obtained a statistically significant but weak correlation between ASAS HI and BASMI scores. Choi et al. (25) and Qu et al. (28) also

found statistically significant moderate and strong correlations, respectively, between ASAS HI scores and BASMI scores. This difference may be due to disparities in patient clinical and demographic features, disease severity, and structural damage, as well as to the broader health dimensions captured by ASAS-HI, compared with the more specific metrological scope of BASMI.

In this study, the ASAS HI demonstrated a strong positive correlation with ASQoL, a widely recognized health-related quality of life scale (HRQoL), and a strong correlation with EQ-VAS, an instrument reflecting general health preceptions and a strong negative correlation with EQ-5D, which emphasizes functional and mobility dimensions in HRQoL. Min et al. (22) and Di Carlo et al. (24) demonstrated a marked correlation with ASAS HI scores and ASQoL scores in a study conducted in axial SpA patients, a negative correlation with ASAS HI scores and EQ-5D index scores in axial SpA patients; the correlation strength was moderate, a negative correlation with ASAS HI scores and EQ-VAS scores in axial SpA patients; the correlation strength was moderate. In line with our study, Choi et al. (25) observed a strong negative correlation between ASAS HI scores and EQ-VAS scores. Although the ASAS HI is not a quality-of-life scale, these findings highlight the multidimensional nature of ASAS HI, encompassing aspects of general health and well-being beyond its original purpose.

We investigated the relationship between the BAS-G and the ASAS HI scores. A statistically high correlation between ASAS HI scores and BAS-G scores was observed. Li et al. (31) also obtained a statistically significant high correlation with the ASAS HI and BAS-G scores. The overlap between BAS-G and ASAS HI reinforces the importance of integrating patient-reported outcomes into clinical assessment, particularly in diseases like AS, where subjective and objective disease measures often complement one another.

Study Limitations

ASAS HI score cut-off values were not examined, and ASDAS-CRP and BASDAI were not compared across disease activity groups. This can be attributed to the study's use of an alternative methodological approach. This lack of evaluation might be attributed to the limited number of existing studies, and addressing this gap in future research would help clarify the utility of ASAS HI in classifying disease activity and in integrating it more effectively into clinical decision-making processes.

Although the assessment of the ASAS HI in correlation with several AS activity of disease, pain severity, overall health, functional capacity, metrological index, and quality of life allows the evaluation of all aspects that may affect AS patients, the cross-sectional nature of this study, lack of long-term follow-up, and limited patient group seem to be the shortcomings of this study.

Conclusion

In this study, the ASAS HI showed marked correlations with disease activity indices (ASDAS-CRP/ESR), functional indices (BASFI and DFI), quality-of-life scales (EQ-5D and ASQoL), and the metrology index (BASMI). Therefore, the ASAS HI appears to be a useful instrument for assessing health status and may provide additional benefit in the evaluation of disease severity, functional capacity, and well-being in individuals diagnosed with AS.

Ethics

Ethics Committee Approval: Ethics Committee approval was obtained from the Clinical Research Ethics Committee of Cumhuriyet University (approval no.: 2018-03/04; date: 26.03.2018).

Informed Consent: In accordance with the Declaration of Helsinki, all participants provided written informed consent after receiving appropriate study information.

Footnotes

Authorship Contributions

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

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How prenatal attachment relates to breastfeeding self-efficacy in mothers during the transition to motherhood: a descriptive study

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ABSTRACT

Aims: Prenatal attachment and breastfeeding self-efficacy are two important psychosocial factors that influence the health of mothers and infants. These factors play a pivotal role in shaping maternal caregiving behaviors during the transition to motherhood. This study aimed to examine the relationship between prenatal attachment and breastfeeding self-efficacy among mothers during the transition to motherhood.

Methods: A descriptive study design was used to examine the experiences of mothers during the transition to motherhood. The participants included were mothers aged 18 years and older who were in any trimester of the prenatal period and without communication impairments. To ensure the safety of the participants and data integrity, individuals with high-risk pregnancies or diagnosed psychiatric disorders were excluded from the study. The primary outcomes were the levels of prenatal attachment and prenatal breastfeeding self-efficacy. The secondary outcome was the relationship between prenatal attachment and prenatal breastfeeding self-efficacy. Both outcomes were assessed using the Prenatal Attachment Scale and the Prenatal Breastfeeding Self-Efficacy Scale.

Results: A total of 306 mothers during the transition to motherhood were included in the study (mean age: 28.4±5.2 years). The mean prenatal breastfeeding self-efficacy score was 86.27±6.52, which indicated a high level of self-efficacy among the mothers. The mean prenatal attachment score was 93.19±4.84. Prenatal attachment explained 29.8% of the variance in breastfeeding self-efficacy (R^2=0.298, p<0.001), demonstrating a significant positive association between these variables.

Conclusions: Prenatal attachment is significantly related to breastfeeding self-efficacy in mothers during the transition to motherhood.

Introduction

The prenatal period is a critical window of physical and psychological transformation that profoundly influences maternal health and the development of infants (1). Prenatal attachment serves as the foundational emotional bond that shapes maternal identity and supports positive postnatal interactions. It is defined as the emotional connection a mother develops with her fetus in the prenatal period and encompasses affectionate feelings, thoughts, and behaviors such as talking to the fetus, naming it, stroking the abdomen, and preparing for childbirth (1,2-8). Prenatal attachment is essential for establishing initial cognitive (recognizing the fetus as an individual and attributing personality), emotional (forming a bond), and behavioral (interacting and role-playing) relationships between the mother

and fetus (2-5). Positive prenatal attachment supports maternal psychological adaptation and the development of maternal identity and improves the interaction between the mother and the infant after childbirth (1,6,9). Moreover, stronger prenatal attachment is associated with lower prenatal anxiety and depression, contributing to better mental health outcomes of the mother (1,10). Early formation of this bond is also crucial for postnatal interaction and the mother's willingness to breastfeed (2,7).

Breastfeeding self-efficacy reflects a mother's confidence and emotional readiness, directly affecting breastfeeding success and the well-being of infants (8). Rooted in Bandura's self-efficacy theory, breastfeeding self-efficacy encompasses a mother's belief in her ability to breastfeed successfully, her emotional preparedness, and strategies to overcome breastfeeding challenges (7,11-14). Breastfeeding is not just a biological function but also a relational act that strengthens the emotional bond between mothers and their infants during the transition to motherhood (7). This sense of efficacy significantly influences both the initiation and duration of breastfeeding; mothers with higher self-efficacy are more likely to persist through difficulties, whereas those with lower confidence tend to discontinue breastfeeding prematurely (15). Moreover, high breastfeeding self-efficacy is associated with greater maternal satisfaction and a lower risk of early breastfeeding cessation (12,15,16). Improving prenatal attachment and breastfeeding self-efficacy benefits not only individual mother-infant dyads but also broader public health outcomes by fostering healthy family bonds (8,16-19).

Supporting prenatal attachment and breastfeeding self-efficacy during the prenatal period positively affects the biological and emotional well-being of mothers and infants, facilitates the development of maternal identity, and contributes to successful breastfeeding outcomes (8,16-19). This period involves not only physical changes but also a transformative journey toward motherhood, during which strengthening the emotional bond with the infant and increasing confidence in breastfeeding help mothers internalize their caregiving roles (1,3,8,9,16). Such psychosocial preparation is essential for mother-infant bonding and nurturing, enabling healthcare professionals, including pediatric nurses, to provide holistic, family-centered care. Studies have shown a positive relationship between prenatal attachment and breastfeeding self-efficacy; mothers with strong emotional bonds to their fetuses internalize their maternal role more effectively, increasing their confidence and motivation in breastfeeding (13,18). Therefore, prenatal attachment improves the self-efficacy of breastfeeding by fostering maternal identity and emotional readiness, both of which strongly promote breastfeeding and the well-being of the mother and infant (7,9,10).

Although several studies have independently examined prenatal attachment (1,10,18) and prenatal breastfeeding self-efficacy (13), a notable gap remains in the literature regarding the interplay between these two essential components during the transition to motherhood. Addressing this relationship is crucial, as it may provide valuable insights into the emotional bonding and caregiving processes that shape maternal experiences throughout the prenatal period. Therefore, the aim of this study was to examine the levels of prenatal attachment and prenatal breastfeeding self-efficacy among mothers during the transition to motherhood and to investigate the relationship between these two variables.

Methods

Study design, setting, and participants

This descriptive study was conducted at the antenatal clinic of a maternity and child hospital located in the Western Black Sea region of Türkiye between June 2022 and June 2023. The hospital offers a comprehensive range of maternal and child health services, including antenatal care, breastfeeding and lactation counseling, delivery units, neonatal intensive care, pediatric surgery, and general pediatric services. This makes it a suitable setting for assessing the experiences of mothers during the transition to motherhood from a multidisciplinary perspective, including pediatric nursing.

A non-probability convenience sampling method was used to recruit eligible mothers during the transition to motherhood. This method involves selecting mothers during the transition to motherhood based on their availability and willingness rather than through random sampling. The sample size was determined to be 306 participants using the known population sample formula, which is based on a population of 1,500 individuals who applied within one year (20). Initially, 333 individuals meeting the preliminary eligibility criteria were screened. Of these, 16 individuals were excluded for not meeting the inclusion criteria, and 11 individuals declined to participate. Consequently, the final sample consisted of 306 women in the prenatal period.

This study included women who were in the transition to motherhood, aged 18 years or older, had no communication difficulties, and were in the prenatal period. All individuals voluntarily participated in this study. To ensure participant safety and maintain data integrity, individuals with high-risk conditions during the prenatal period or who were diagnosed with psychiatric disorders were excluded from the study.

Instruments

Parental information form

This form was developed by researchers based on relevant studies (19,21,22). It consists of eight questions addressing socio-demographic characteristics (e.g., age, education status, employment) and maternal information, including the number of previous children, whether the pregnancy was

planned, pregnancy status (such as normal pregnancy versus pregnancy under treatment), preparation for motherhood, and participation in educational sessions related to motherhood and breastfeeding.

Prenatal Breastfeeding Self-Efficacy Scale (PBSES)

This scale was developed by Wells et al. (23) and consists of 20 items. It assesses various breastfeeding-related situations, such as obtaining information and support about breastfeeding during the prenatal period, managing planning-related concerns, preparing expressed milk for others to feed the infant, breastfeeding and discussing it in the presence of others, and deciding to breastfeed despite others' disapproval. The responses are rated on a five-point Likert scale ranging from 1 (not at all confident) to 5 (completely confident). The total score ranges from 20 to 100, with no specific cut-off point; higher scores indicate greater breastfeeding self-efficacy. The scale includes four sub-dimensions. The Turkish adaptation and validation of the scale were conducted by Hazar and Akça (24). In the Turkish version, the scale comprises 19 items, with total scores ranging from 19 to 95. Cronbach's alpha coefficient for the Turkish version was reported as 0.86. In this study, Cronbach's alpha was calculated as 0.79, indicating acceptable internal consistency.

Prenatal Attachment Scale (PAS)

This scale was developed by Kurnaz and Türkmen Çevik (25). It comprises 33 items divided into three sub-groups: curiosity, excitement, and planning (13 items); acceptance and enthusiasm (9 items); and hope (11 items). Each item offers three response options: "strongly agree", "partially agree", and "strongly disagree". Individuals scoring high on the scale are considered to have a high level of prenatal attachment. The total possible score ranges from 33 to 99. Cronbach's alpha coefficients for the scale range between 0.88 and 0.94 (25). In this study, Cronbach's alpha was calculated as 0.79.

Data collection

In this study, a non-probability convenience sampling method was used to recruit eligible mothers during the transition to motherhood. All individuals who met the inclusion criteria were invited to participate after the study purpose was explained and written informed consent had been obtained. The data were collected through face-to-face interviews using data collection forms, with each session lasting about 15 minutes. During the interviews, mothers transitioning to motherhood completed the forms under the supervision of the same researcher throughout the data collection process. They were encouraged to ask questions and received clarifications when needed. The data were collected in a private room in the antenatal outpatient clinic while the mothers waited for their appointments, ensuring privacy throughout the process.

Outcomes

The primary outcomes of this study were the levels of prenatal attachment and prenatal breastfeeding self-efficacy among mothers during the transition to motherhood.

The secondary outcome was the relationship between prenatal attachment and prenatal breastfeeding self-efficacy.

Ethical considerations

Ethical approval for the study was obtained from the Bartın University Social and Human Sciences Ethics Committee (approval no: 2022-SBB-0156; date: 12.05.2022). Written permission was obtained from the institution, and consent was obtained from the owners of the scales used in data collection via email correspondence. Before completing the data collection forms, information about the study was provided to mothers during their transition to motherhood, and participation was voluntary. Written informed consent was obtained from each participant. The study was conducted following the principles of the Declaration of Helsinki. Mothers were free to withdraw from the study at any time without any consequences.

Statistical Analysis

The data were analysed using SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics, including frequency, percentage, mean, standard deviation, median, and minimum and maximum values, were calculated. Normality was assumed for variables with skewness and kurtosis coefficients within the ±1.5 range (26). The relationships between the scores of the mothers on the PBSES and the PAS were examined by conducting Pearson's correlation analysis. Simple linear regression analysis was performed to evaluate the effect of prenatal attachment on prenatal breastfeeding self-efficacy. A 95% confidence level was applied, with statistical significance set at $p<0.05$.

Results

In this study, 72.9% of mothers were 25-34 years old, with the majority (34.0%) holding a bachelor's degree or higher. About 55.2% of mothers were unemployed. Among them, 60.1% had experienced only one childbirth, and 82.4% reported their pregnancies as planned. Most mothers (43.8%) were in the second trimester, and 7.2% of pregnancies occurred through medical intervention. Additionally, 53.6% of the mothers received breastfeeding education (Table 1).

The mean total scores of the PBSES and the PAS were compared based on socio-demographic characteristics (Table 2). Statistically significant differences were observed in the mean scores across age groups, income levels, and pregnancy status ($p<0.05$). Additionally, a significant difference was found in the mean PAS score depending on whether the pregnancy was planned ($p<0.05$).

Table 1. Socio-demographic and obstetric characteristics of mothers during the transition to motherhood (n=306)

		n	%
Age (years)	18-24	47	15.3
	25-34	223	72.9
	35-44	36	11.8
Educational level	Primary school	17	5.6
	Secondary school	69	22.5
	High school	94	30.7
	Associate degree	22	7.2
	Bachelor's degree and above	104	34.0
Employment status	Employed	137	44.8
	Unemployed	169	55.2
Number of births	Single birth	184	60.1
	Multiple birth	122	39.9
Planned/desired nature of pregnancy	Yes	252	82.4
	No	54	17.6
Pregnancy status	Naturally	284	92.8
	Medical treatment	22	7.2
Prenatal period	First trimester	61	19.9
	Second trimester	134	43.8
	Third trimester	111	36.3
Breastfeeding education status	Yes	164	53.6
	No	142	46.4

The mean total scores of the PBSES and the PAS, along with the relationships between these scores among mothers, are presented in Table 3. The mean total scores for both the PBSES (86.27±6.52) and the PAS (93.19±4.84) were high. The results of the Pearson correlation analysis revealed a significant positive correlation between the total PBSES score and the PAS score ($r=0.546$, $p<0.001$).

The relationships between prenatal attachment and prenatal breastfeeding self-efficacy are presented in Table 4. Prenatal attachment was significantly associated with prenatal breastfeeding self-efficacy ($p<0.001$). Prenatal attachment accounted for 29.8% of the variance in prenatal breastfeeding self-efficacy scores (adjusted $R^2=0.298$) and was associated with an increase in prenatal breastfeeding self-efficacy.

Discussion

This study demonstrated that mothers transitioning to motherhood had high levels of prenatal attachment and prenatal breastfeeding self-efficacy. Importantly, prenatal attachment was significantly associated with breastfeeding self-efficacy. These findings highlight the critical role of maternal-infant bonding in supporting breastfeeding confidence and underscore the importance of nurses, particularly pediatric nurses, in promoting maternal and infant well-being during the transition to motherhood.

The evaluation of prenatal attachment helps nurses manage the care process, providing early and healthy interaction data between the mother and the infant (2). While studies have reported that the number of births does not directly affect prenatal attachment (8), it has also been reported that during the transition to motherhood (i.e., first-time mothers), women have higher total prenatal attachment scores (2,27-29). Research findings on the effect of maternal education level on prenatal attachment are inconsistent; certain studies have found minimal influence (8,30), whereas others have shown a positive correlation between education level and attachment score (18,31,32). In this study, no proportional increase in attachment scores was found with maternal education, nor was there an inverse relationship with the number of births. These findings align with studies indicating that maternal education level and parity do not directly affect prenatal attachment. In contrast, this study revealed that prenatal attachment scores decreased as maternal age increased. While other studies suggest that maternal age has a limited effect on prenatal attachment (30), studies also report, consistent with our findings, a decrease in attachment scores with increasing age (31,33), possibly due to a decrease in focus on the parenting process in older mothers. Regarding income level, the literature presents mixed findings, including slight effects on prenatal attachment (30), positive correlations with higher income (34), and no significant relationship (18). In

Table 2. Comparison of scale scores according to socio-demographic characteristics (n=306)

Characteristics	n	Prenatal breastfeeding self-efficacy level			Prenatal attachment level		
		Mean	SD	Median (IQR)	Mean	SD	Median (IQR)
Age (years)							
18-24	47	89.30	5.27		95.65	3.58	
25-34	223	85.37	6.46		92.76	4.83	
35-44	36	87.89	7.01		92.66	5.44	
		F=8.713; p<0.00[1a.c]			F=7.481 p<0.001[a.b]		
Educational level							
Primary school	17	90.18	4.94		94.05	4.08	
Secondary school	69	86.33	5.67		93.39	4.75	
High school	94	85.95	6.65		93.27	4.61	
Associate degree	22	87.73	6.62		94.77	4.81	
Bachelor's degree and above	104	85.57	6.97		92.52	5.17	
		F=2.190; p=0.070			F=1.251; p=0.290		
Income status							
Income more than expenses	93	85.08	7.11	84.00 (79.50-92.50)	92.17	5.12	92.00 (88.00-97.00)
Income equals expense	156	87.49	6.06	88.00 (82.25-93.00)	94.01	4.51	95.00 (91.00-98.00)
Income less than expenses	57	84.86	6.20	84.00 (80.00-90.00)	92.64	4.93	93.00 (89.50-97.50)
		X^2=10.916; p=0.004[d.e]			X^2=8.646; p=0.013[f]		
Number of birth							
Single birth	184	85.80	6.81		93.08	4.95	
Multiple birth	122	86.97	6.03		93.36	4.67	
		t=-1.567; p=0.118			t=-0.498; p=0.619		
Planned/desired nature of pregnancy							
Yes	252	86.42	6.63		93.55	4.76	
No	54	85.56	6.02		91.55	4.91	
		t=0.940; p=0.350			t=2.780; p=0.006		
Pregnancy status							
Naturally	284	86.00	6.42		92.95	4.84	
Medical treatment	22	89.73	6.95		96.36	3.52	
		t=-2.605; p=0.010			t=-4.236; p<0.001		
Breastfeeding education status							
Yes	164	86.00	6.45		93.26	4.57	
No	142	86.58	6.61		93.11	5.14	
		t=-0.771; p=0.441			t=0.267; p=0.789		

IQR: Interquartile range, SD: Standard deviation, F: One way ANOVA test, X^2: Kruskal-Wallis test, t: Student's t-test, p<0.05 was considered significant. [a]: Comparison between age groups 18-24 and 25-34, [b]: Comparison between age groups 18-24 and 35-44, c: Comparison between age groups 25-34 and 35-44, [d]: Comparison between income more than expenses and income equal to expenses, [e]: Comparison between income equal to expenses and income less than expenses, [f]: Comparison between income more than expenses and income equal to expenses

Table 3. Relationship between prenatal breastfeeding self-efficacy and prenatal attachment in mothers during the transition to motherhood (n=306)

Scale scores (possible score range)	Mean ± SD	Min (score)	Max (score)
Prenatal breastfeeding self-efficacy (19-95)	86.27±6.52	71.00	95.00
Prenatal attachment (33-99)	93.19±4.84	79.00	99.00
Scales	**Prenatal attachment level**		
	r	**p**	
Prenatal breastfeeding self-efficacy level	0.546	**0.001**	

SD: Standard deviation, Min: Minimum, Max: Maximum, r: Pearson correlation analysis

Table 4. How prenatal attachment relates to breastfeeding self-efficacy in individuals in the transition to motherhood (n=306)

Independent variable	B	Standard error	β	t	p	F	Model (p)	Adjusted R^2
Constant	17.711	6.048	-	2.928	**0.004**	128.831	**<0.001**	0.298
Prenatal attachment	0.736	0.065	0.546	11.350	**0.001**			

B: Unstandardized coefficient, β: Standardized coefficient, t: t-value, p: P-value; F: F-value, Model (p): Significance of the model, Adjusted R^2: Adjusted coefficient of determination

this study, mothers with a moderate income level had the highest prenatal attachment scores, indicating that attachment may vary with socio-economic conditions. Whether pregnancy was planned was also a significant factor. The literature presents conflicting results, including studies that report no significant relationship between pregnancy planning and attachment (18,35) and those that demonstrate significantly higher attachment scores in planned pregnancies (29,31). This study supports the latter finding, reflecting more positive thoughts and emotions toward the infant among mothers with planned pregnancies. Regarding the mode of conception, the literature presents mixed findings: certain studies suggest no significant of natural versus assisted reproductive technology conception on attachment (36), whereas others report higher prenatal attachment scores among mothers who conceived through treatment (26). Similarly, this study found higher scores among mothers who conceived through assisted reproductive treatments, which may be explained by the emotional investment and greater expectations associated with the parenting journey in such cases.

Evaluating prenatal breastfeeding self-efficacy is a critical component in supporting mothers during the transition to motherhood, benefiting both the mothers and the nurses who guide them through this process (21). The mean prenatal breastfeeding self-efficacy score in this study (86.3) reflects a high level of confidence, aligning with previous research findings. While existing literature often suggests that breastfeeding self-efficacy increases with maternal age (37,38), this study found higher self-efficacy scores among mothers who were under the age of 25 and those aged 35 and above during the transition to motherhood. These results may be influenced by factors such as the enthusiasm of first-time motherhood, accumulated life experience, and prior positive breastfeeding experiences.

The relationship between income level and prenatal breastfeeding self-efficacy has been reported inconsistently in the literature. While some studies have associated higher socio-economic status with more favorable breastfeeding outcomes (13,36,37), others have identified an inverse relationship, with greater self-efficacy observed among low-income mothers (39). In the present study, lower-income was associated with higher prenatal breastfeeding self-efficacy. This finding may reflect several factors: increased motivation to breastfeed due to financial constraints, limited access to alternative feeding options, the perception of breastfeeding as a more economical choice, and stronger familial or community support networks that encourage breastfeeding. Cultural beliefs and targeted breastfeeding promotion programs for low-income populations may also contribute to enhanced maternal confidence and commitment to breastfeeding (7,12,13,17). These factors, including “financial constraints, limited alternative feeding options, cultural and community support, and the perception of breastfeeding as an economical choice”, help explain why lower-income mothers might report higher prenatal breastfeeding self-efficacy. Overall, the findings highlight that the association between income and breastfeeding self-efficacy is complex and influenced by contextual, psychosocial, and environmental variables that require further investigation.

A moderate positive correlation was identified between prenatal attachment and breastfeeding self-efficacy, which is consistent with previous studies reporting different degrees of association (13,22,40). This finding highlights the importance of the mother-infant bond in shaping breastfeeding outcomes. Prompt initiation and continued breastfeeding after birth are essential for the health and well-being of mothers and infants (39). The results of this study suggest that prenatal attachment is a strong predictor of breastfeeding self-efficacy, reinforcing the need for pediatric nurses and other healthcare professionals to actively foster prenatal bonding to support positive parenting and breastfeeding experiences among mothers during the transition to motherhood.

The strength of this study lies in its contribution to the limited body of research on prenatal attachment and prenatal breastfeeding self-efficacy among mothers during the transition to motherhood. The findings provide valuable scientific insights into prenatal attachment and prenatal breastfeeding self-efficacy. However, the study has several limitations. First, a convenience sampling method was used. Second, the results are based on self-reported data from mothers at a single hospital, which may limit the generalizability of our findings. Additionally, including women at various stages of the prenatal period (first, second, or third trimester) constitutes another limitation, as the specific trimester may affect prenatal attachment and breastfeeding self-efficacy. This variability might have influenced the findings of the study. Future studies can benefit from focusing on a more homogeneous sample in terms of the prenatal stage to gain a clearer understanding of these concepts.

Conclusion

This study demonstrated that prenatal attachment significantly influences breastfeeding self-efficacy among mothers during the transition to motherhood. Strengthening prenatal attachment can enhance maternal confidence, breastfeeding success, and mother-infant bonding. Pediatric nurses and midwives should collaborate in antenatal care to provide education and counseling programs that promote prenatal attachment and breastfeeding self-efficacy. Future studies with larger and more homogeneous samples are recommended to confirm and extend these findings.

Ethics

Ethics Committee Approval: Ethical approval for the study was obtained from the Bartın University Social and Human Sciences Ethics Committee (approval no: 2022-SBB-0156; date: 12.05.2022).

Informed Consent: All individuals who met the inclusion criteria were invited to participate after the study purpose was explained and written informed consent had been obtained.

Footnotes

Authorship Contributions

Concept: E.B.A., F.D., D.Y., Design: E.B.A., F.D., D.Y., Data Collection or Processing: E.B.A., F.D., Analysis or Interpretation: E.B.A., F.D., Literature Search: E.B.A., F.D., Writing: E.B.A., F.D., DY.

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Association of epidermal growth factor receptor with hormone receptor and molecular subtypes in breast cancer patients from South India

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ABSTRACT

Aims: Breast cancer (BC) remains a major global health challenge, characterized by molecular heterogeneity and a complex interplay of risk factors. Epidermal growth factor receptors (EGFRs) role in BC underscores the importance of targeted therapies and the need for personalized treatment approaches. This study aimed to examine EGFR expression in tumor samples from BC patients and assess its relationship with molecular subtypes and receptor status.

Methods: This cross-sectional study involved female BC patients with confirmed diagnoses. Core-cut biopsy specimens were formalin-fixed, paraffin-embedded, and assessed for EGFR expression using immunohistochemistry (IHC). A chi-square test was performed to assess its association. The patients' records were reviewed for demographic data, and receptor status was determined using IHC as part of routine clinical evaluation.

Results: A total of 62 BC patients were included in the study, with ages ranging from 25 to 70 years (mean ± standard deviation: 49.9±10.8 years). EGFR expression showed predominantly weak staining intensity (61.3%), followed by moderate staining (17.7%), no staining (17.7%), and strong staining (3.3%). Regarding receptor status, weak EGFR expression was prevalent in estrogen receptor (ER)-positive (57.9%) and progesterone receptor (PR)-negative (65.8%) patients, whereas strong EGFR expression was observed in the ER-negative, PR-negative, and human epidermal growth factor receptor 2 (HER2)/neu-negative subgroups (2 cases each). Assessment by molecular subtype showed a prevalence of weak and moderate EGFR staining in the Luminal B subtype, whereas strong EGFR expression was observed only in triple-negative BC patients (2 cases, 100%). However, there was no statistically significant association between EGFR expression and molecular subtypes or hormone receptor status.

Conclusions: EGFR expression was more common in aggressive subtypes, such as HER2-positive and Luminal B, highlighting its potential role in tumor progression. However, the lack of a significant association suggests that the relevance may be subtype-specific.

Introduction

Breast cancer (BC) remains one of the most prevalent and challenging health issues worldwide, affecting millions of women annually. It is the most common cancer and the leading cause of cancer-related deaths in women (1,2). Despite significant advancements in early detection and treatment, the incidence of BC continues to rise. Early detection methods have significantly contributed to earlier diagnoses and improved patient outcomes. However, the complex interplay of various risk factors, including genetics, age, lifestyle habits, and environmental influences, contributes to its increased prevalence (3). BC is a heterogeneous group of malignancies with distinct histological, molecular, and clinical characteristics. The molecular landscape of BC is highly diverse, with several key biomarkers and molecular targets playing crucial roles in its progression and treatment response (4). This heterogeneity requires a tailored treatment approach because subtypes of BC respond differently to therapeutic strategies. The primary treatment modalities for BC include surgery, chemotherapy, radiation therapy, hormone therapy, targeted therapy, and immunotherapy. Despite these advancements, challenges such as the development of treatment resistance, side effects, and disparities in access to care continue to impact patient outcomes (5,6).

Epidermal growth factor receptor (EGFR), a member of the ErbB family of transmembrane receptor tyrosine kinases, has garnered significant attention as both a biomarker and a therapeutic target. It regulates cell proliferation, differentiation, and survival (7). The dysregulation of EGFR in BC leads to oncogenesis and tumor progression. The overexpression of EGFR in BC is associated with several adverse clinical outcomes, including larger tumor size, poor differentiation, and an increased risk of relapse (8,9). Studies have shown that the expressions of EGFR and human epidermal growth factor receptor 2 (HER2) (another member of the ErbB family) are often inversely correlated with estrogen receptor (ER) status. BC patients who are positive for EGFR and HER2 generally have a higher risk of relapse and a worse prognosis compared to those who are negative for these receptors (10,11). In ER-positive BC, EGFR overexpression has been linked to resistance to endocrine therapy, posing a significant challenge in treatment. Endocrine therapies, such as tamoxifen and aromatase inhibitors, effectively manage hormone receptor-positive BC. However, EGFR can interfere with these therapies, necessitating alternative or combination treatments to overcome resistance (12-14). This interplay between EGFR and hormone receptors underscores the complexity of BC treatment and the need for personalized therapeutic strategies. The present study aimed to investigate EGFR expression in a cohort of BC patients and to explore its association with molecular subtypes and receptor status.

Methods

Study design, patient selection, settings, and sample size

This cross-sectional study was conducted in the Department of General Surgery at a tertiary care hospital in Mangalore, India, from April 2021 to September 2022. The study included consenting female patients with a confirmed BC diagnosis; patients with recurrent BC and those who had received post-neoadjuvant therapy were excluded. Ethical approval was obtained from the institutional Ethics Committee of the KS Hegde Medical Academy (which has university status) and written informed consent was obtained from all patients (approval no.: EC/066/2021-22, date: 05.02.2021).

The sample size for this study was calculated using G*Power software (v. 3.1.9.4) with the following criteria: effect size =0.5, a 5% level of significance, 95% power, and degrees of freedom =2. The initial target sample size for the study, according to the sample size calculation, as per the sample size calculation, for the study was 100. However, due to the loss of some samples during standardization and challenges related to clinical relevance, the final sample consisted of 62 confirmed cases of BC patients.

Data collection

Clinical and demographic data were extracted from the patient's case records. The hormone receptor status and molecular subtypes were assessed by pathologists as part of routine diagnostic procedures. The hormone receptor expression was first determined using immunohistochemistry (IHC), as described below. Based on the presence or absence of ER, progesterone receptor (PR), and HER2 receptors, the samples were classified into molecular subtypes. The carcinomas were classified and graded according to the World Health Organization 2012 (15) and the Nottingham classification system (16).

Tissue preparation

The core cut biopsy specimens were fixed overnight in 10% buffered formalin, processed, and embedded in paraffin. These samples were then sectioned at 3-µm thickness using the rotary microtome (Leica RM2125 RTS, India) and mounted on positively charged slides. IHC was performed using the PolyExcel HRP/DAB Detection System (PEH002) Universal Kit (PathnSitu Biotechnologies, India). Firstly, the slides were heated on the hot plate at 90 ºC for 20 mins to remove the paraffin and were rehydrated through graded alcohols.

Antigen retrieval

The antigen was retrieved using a preheated sodium citrate buffer (pH 6) at 90 °C in a water bath. The slides were then cooled and washed with distilled water.

Immunostaining procedure

After antigen retrieval, the slides were treated with a peroxidase quencher, "Peroxidase Block," to inhibit endogenous peroxidase activity, followed by a 1% bovine serum albumin (BSA) blocking solution to prevent nonspecific binding. Then, the primary antibody (sc-374607, mouse monoclonal, lot no. A1514, Santa Cruz Biotechnology, TX, USA, diluted 1:100 in 1% BSA) against the target antigen, EGFR, was applied to the sections and incubated overnight at 4 °C. Similarly, for hormone receptors, their respective primary antibodies were used (ER: PR042; PR: PR068; and HER2: PR047), all of which are rabbit monoclonal. The next day, slides were washed with Tris-NaCl wash buffer (pH 7), incubated with the poly-HRP-conjugated secondary antibody "Target Binder" for 30 mins at 37 °C in the dark, and washed again with the wash buffer.

Staining and counterstaining

The slides were incubated with horseradish peroxidase, "Poly HRP," for 20 min and washed before adding the chromogen diaminobenzidine (DAB) to visualize immunostaining. The unstained DAB was removed using a wash buffer, and the haematoxylin counterstain was applied to the sections for 5 seconds. Finally, the slides were rinsed in tap water, dehydrated with graded alcohols, cleared with xylene, and mounted on the coverslip with distrene, plasticizer, xylene mountant. Appropriate positive and negative control slides were included in each batch to ensure the reliability of the results. The expression of EGFR in the patient cohort was categorized based on staining intensity as follows: 0 (no staining), 1+ (weak staining intensity), 2+ (moderate staining intensity), and 3+ (strong staining intensity) (17).

Statistical Analysis

Statistical analyses were conducted using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp., Armonk, NY, USA). A chi-square test was used to assess the association between EGFR expression and molecular subtypes and receptor status in BC. A p-value <0.05 was considered statistically significant. The results were presented as frequencies for tumor grade, ER/PR status, and HER2 expression.

Results

Patient demographic characteristics

The patients' ages ranged from 25 to 70 years, with a mean ± standard deviation of 49.9±10.8 years. The age distribution indicated that most patients (53.2%) were aged between 46 and 60 years, while 17.7% were older than 60 years. Tumor size classification revealed T2 tumors as the most prevalent (33.9%), and the lymph node involvement assessment showed N1 status in 45.2% of patients. Regarding hormone receptor status, 56.5% of patients were ER-positive, 33.9% were PR-positive, and 61.3% were HER2/neu-positive. The distribution of BC subtypes identified Luminal B as the most common (50.0%), followed by triple-negative BC (TNBC) (30.6%) (Table 1).

Intensity of EGFR staining among the patients

The EGFR expression with weak, moderate, and strong staining intensities was observed in 55 patients (82.2%) of the cohort. The weak staining intensity was the most common observation, occurring in 38 patients (61.3%), suggesting lower levels of EGFR expression (Figure 1). Moderate or no staining intensity was observed in 11 patients (17.7%). Only two patients (3.2%) exhibited strong staining intensity, indicating higher levels of EGFR expression.

Table 1. Characteristics of breast cancer patients (n=62)

Variables	Value
Age (in years)	
30-45	18 (29.0)
46-60	33 (53.2)
>60	11 (17.7)
Mean age (years) mean ± SD	49.9±10.8
Tumor grade	
T1	8 (12.9)
T2	21 (33.9)
T3	16 (25.8)
T4	17 (27.4)
Lymph node status, n (%)	
N0	19 (30.6)
N1	28 (45.2)
N2	7 (9.7)
N3	8 (11.3)
Molecular subtypes, n (%)	
Luminal A	4 (6.5)
Luminal B	31 (50.0)
HER2	8 (12.9)
TNBC	19 (30.6)
Hormone receptor status, n (%)	
ER positive	35 (56.5)
ER negative	27 (43.5)
PR positive	21 (33.9)
PR negative	41 (66.1)
Her2Neu positive	20 (32.3)
Her2Neu negative	38 (61.3)
Her2Neu Equivocal	4 (6.4)

*: Lymph node status refers to the presence or absence of cancer in the lymph nodes. N0: No cancer found in nearby lymph nodes; N1: Cancer has metastasised to 1-3 lymph nodes; N2: Cancer found in 4-6 lymph nodes; N3: Cancer has metastasised to 10 or more lymph nodes, or to lymph nodes near the collarbone or internal mammary nodes.
SD: Standard deviation, TNBC: Triple-negative breast cancer, ER: Estrogen receptor, PR: Progesterone receptor, HER2: Human epidermal growth factor receptor 2.

Association of EGFR with hormone receptors

The analysis of EGFR staining intensity concerning hormone receptor status and HER2/neu receptor status in BC patients revealed distinct patterns within the studied cohort (Table 2). Among the 62 patients, the distribution of EGFR staining varied notably between ER-positive and ER-negative cases (Table 3). Weak EGFR staining was seen in 22 cases (57.9%) of ER-positive patients and in 16 cases (42.1%) of ER-negative patients. Moderate staining was more frequent in ER-positive patients (7 cases, 63%) than in ER-negative ones (4 cases, 36.4%).

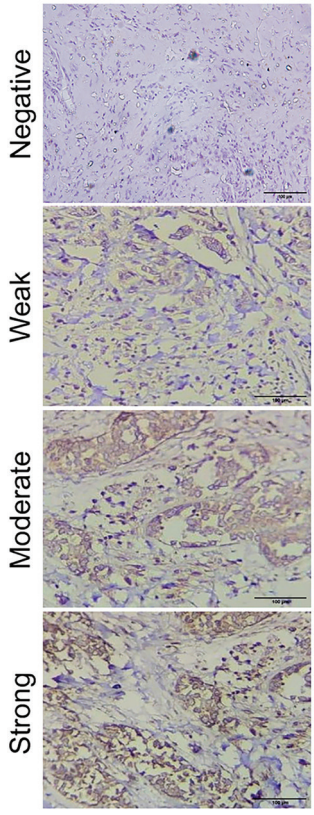

Figure 1. Representation of epidermal growth factor receptor staining intensity

No EGFR staining was observed in 6 ER-positive patients (54.5%) and in 4 ER-negative patients (45.5%). However, strong EGFR staining was exclusive to the ER-negative subgroup (2 cases, 100%).

Regarding PR status, weak EGFR staining was notably more frequent in PR-negative patients (25 cases, 65.8%) compared with PR-positive patients (13 cases, 34.2%). Moderate and no staining intensities were each observed in 7 PR-negative patients (63.6%), compared with 4 PR-positive patients (36.4%). Strong EGFR staining was observed exclusively in PR-negative cases (2 cases, 100%).

In contrast to the ER and PR findings, EGFR staining intensity differed markedly among HER2/neu groups. Weak EGFR staining was observed in 23 HER2/neu-negative cases (62.2%), 12 HER2/neu-positive cases (32.4%), and 2 equivocal cases (5.3%). EGFR staining intensity was absent in HER2/neu-negative patients (7 cases, 63.6%), HER2/neu-positive patients (3 cases, 27.3%), and equivocal patients (1 case, 9.1%). Moderate EGFR intensity was noted in 6 HER2/neu-negative patients (50%), 5 HER2/neu-positive patients (41.7%), and 1 equivocal patient (8.3%). As in ER and PR subgroups, strong EGFR staining was found exclusively in HER2/neu-negative cases (2 cases, 100%).

Association of EGFR with molecular subtypes

EGFR staining intensity and the molecular subtypes of BC showed no significant association in the current cohort (Table 3). The distribution of molecular subtypes among patients with weak EGFR staining was as follows: Luminal B (52.6%), TNBC (28.9%), HER2 (13.2%), and Luminal A (5.3%); for patients with no staining, the distribution was Luminal B (45.5%), TNBC (36.4%), Luminal A (9.1%), and HER2 (9.1%). Moderate EGFR staining was prevalent in the Luminal B group (54.5%), followed by HER2-enriched (18.2%), TNBC (18.2%), and Luminal A (9.1%). Furthermore, strong EGFR staining was exhibited only in the TNBC group (100% of patients).

Table 2. Association of EGFR expression with hormonal receptor status in breast cancer patients (n=62)

Hormone receptor	Status	EGFR expression						
		No, n (%)	Weak, n (%)	Moderate, n (%)	Strong, n (%)	χ2 value	df	p-value
ER	Negative	5 (45.5)	16 (42.1)	4 (36.4)	2 (100.0)	2.87	3	0.412
	Positive	6 (54.5)	22 (57.9)	7 (63.6)	0 (0.0)			
PR	Negative	7 (63.6)	25 (65.8)	7 (63.6)	2 (100.0)	1.09	3	0.780
	Positive	4 (36.4)	11 (34.2)	4 (36.4)	0 (0.0)			
HER2	Negative	7 (63.6)	23 (62.2)	6 (50.0)	2 (100.0)	4.81	9	0.851
	Positive	3 (27.3)	12 (32.4)	5 (41.7)	0 (0.0)			
	Equivocal	1 (9.1)	2 (5.4)	1 (8.3)	0 (0.0)			

EGFR: Epidermal growth factor receptor, ER: Estrogen receptor, df: Degrees of freedom, PR: Progesterone receptor, HER2: Human epidermal growth factor receptor 2.

Table 3. Association of EGFR expression with molecular subtypes of breast cancer

Molecular subtypes	EGFR expression				χ^2 value	df	p-value
	No	Weak	Moderate	Strong			
HER2, n (%)	1 (9.1)	5 (13.2)	2 (18.2)	0 (0.0)	6.06	9	0.733
Luminal A, n (%)	1 (9.1)	2 (5.3)	1 (9.1)	0 (0.0)			
Luminal B, n (%)	5 (45.5)	20 (52.6)	6 (54.5)	0 (0.0)			
TNBC, n (%)	4 (36.4)	11 (28.9)	2 (18.2)	2 (100.0)			

EGFR: Epidermal growth factor receptor, HER2: Human epidermal growth factor receptor 2, TNBC: Triple-negative breast cancer, df: Degrees of freedom

Discussion

EGFR expression exhibited predominantly weak staining intensity (61.3%). Regarding receptor status, weak EGFR expression was prevalent in ER-positive patients (57.9%) and PR-negative patients (65.8%), whereas strong EGFR expression was observed in ER/PR/HER2/neu-negative subgroups. Assessment of molecular subtype showed a prevalence of weak and moderate EGFR staining in the Luminal B subtype, while strong EGFR expression was observed only in TNBC patients. However, there was no statistically significant association between EGFR expression and either molecular subtypes or hormone receptor status.

EGFR expression is a well-studied biomarker in BC, with positivity rates ranging from 14% to 91% across various studies (18). The present study found EGFR expression in 82.2% of the patient cohort. A study by Choccalingam et al. (19), observed high EGFR expression in HER2-positive patients. However, differences in Luminal B and TNBC subtypes between studies highlight variability in EGFR expression across populations and in study methodologies. For instance, Hashmi et al. (20) reported significantly lower EGFR expression (18.7%) in TNBC patients compared to our findings (78.9%). Such variations may be due to differences in patient demographics, sample sizes, and detection methodologies.

Regarding hormonal receptors, EGFR expression was observed in 46.7% of ER-positive cases, 54.8% of PR-negative cases, and 50% of HER2-negative cases. These findings did not show a significant association between EGFR expression and hormone receptor status, corroborating Choccalingam et al. (19), except for ER-positive cases with an inverse correlation. The lack of a strong association between EGFR and hormone receptor status suggests that EGFR expression might be independent of hormone receptor pathways. This is crucial for understanding the pathways that influence BC progression and treatment resistance.

HER2 expression is a critical biomarker in BC, impacting its prognosis and treatment strategies. In ductal carcinoma *in situ* (DCIS), HER2 positivity is prevalent in up to 50% of cases, particularly in high-grade lesions, and is associated with aggressive disease features, such as larger tumor size, high nuclear grade, and elevated proliferation indices (21). HER2-positive DCIS has an increased risk of recurrence compared to HER2-negative DCIS (22). Targeted therapies like trastuzumab can improve outcomes for HER2-positive patients, emphasizing the importance of accurate HER2 status assessment for personalized treatment (22). However, the role of HER2 in the progression from DCIS to invasive BC remains complex. Despite its association with aggressive features and higher recurrence rates, HER2-positive DCIS may not be the primary driver of progression to invasive disease (23). HER2 overexpression is more common in DCIS than in invasive BC, suggesting it may be more crucial in the initiation rather than the progression of DCIS (21). Invasive cancers may arise from HER2-negative precursor lesions or HER2-negative subclones within DCIS (21). Further research is needed to clarify the intricate relationship between HER2 expression, disease progression, and treatment response (21-23).

The present study assessed EGFR expression in 62 patients and found that most exhibited low EGFR expression. However, higher EGFR expression was observed in the Luminal B and TNBC subtypes. These findings suggest that EGFR may play a critical role in the pathogenesis and progression of these subtypes. EGFR overexpression has been associated with larger tumor size, higher proliferation rates, genomic instability, and a higher likelihood of HER2 overexpression and lower hormone receptor levels (23,24). Furthermore, preclinical studies have demonstrated that EGFR overexpression leads to malignant transformation, increased proliferation, and resistance to apoptosis in BC models (24). EGFR has also been implicated in resistance to hormone therapy through crosstalk with ER (25-27). The activated form of EGFR, phosphorylated EGFR (pEGFR), has been associated with an antiapoptotic effect through the PI3K pathway and is correlated with poor prognosis in lung cancer (28,29). In BC, simultaneous expression of EGFR and pEGFR has emerged as a more promising prognostic marker in invasive carcinomas (30).

Invasive micropapillary carcinoma (IMPC) is a rare and distinct histological subtype of BC, comprising approximately 0.9-2% of all BC cases (31). It is characterized by an aggressive clinical course, a high likelihood of lymph node involvement, and a unique histopathological architecture (31). Despite its

aggressive features, survival rates for IMPC are comparable to those of other BC subtypes (32). Accurate recognition of IMPC is essential for guiding clinical management, particularly concerning axillary assessment and surgical planning (32). A case report by Verras et al. (33), highlights the challenges in managing IMPC due to its unique histological characteristics. It underscores the need for clinical awareness to optimize treatment strategies. The report details the case of a woman diagnosed with IMPC who underwent tumor and lymph node marking, primary systemic therapy, and oncoplastic surgery with sentinel lymph node biopsy. Despite the imaging suggesting a complete radiological response to neoadjuvant chemotherapy, pathology revealed multiple areas of high-grade micropapillary DCIS. One of the five sentinel lymph nodes removed showed micro-metastatic infiltration with extranodal extension (33).

Our study also highlights the predictive value of EGFR expression. The correlation between EGFR and poor prognosis and aggressive tumor characteristics, such as higher proliferation rates and genomic instability, emphasizes its role as a marker of disease progression. However, the inconsistency in its prognostic significance across studies, potentially due to small sample sizes and varying methodologies, calls for more standardized and large-scale studies to validate these associations.

Overall, the high rate of EGFR expression observed in the present study, particularly in HER2-positive and TNBC subtypes, highlights the potential clinical significance of this biomarker in BC. EGFR may serve as a therapeutic target and a prognostic marker, especially in aggressive BC subtypes. However, further research is needed to establish the clinical utility of EGFR assessment in routine practice and to develop targeted therapies that effectively inhibit EGFR signaling in BC.

Study Limitations

Though our study provides insights into EGFR in BC, it has certain limitations. The main limitation of our study is the relatively small sample size and single-institution recruitment, which may limit the generalizability of our findings. Larger, multi-center studies are necessary to confirm the patterns of EGFR expression and its clinical implications across diverse populations. Further research should focus on molecular mechanisms underlying EGFR-mediated resistance pathways and on developing combination therapies targeting EGFR and other pathways involved in BC progression.

Conclusion

In conclusion, while most patients exhibited low EGFR expression, no significant association was found between EGFR expression and BC subtypes or hormone receptor status, suggesting that EGFR alone may have limited value as a marker for BC classification. This underscores the importance of comprehensive molecular profiling for more accurate prognosis and tailored treatment strategies.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the institutional Ethics Committee of the KS Hegde Medical Academy (which has university status) (approval no.: EC/066/2021-22, date: 05.02.2021).

Informed Consent: Written informed consent was obtained from all patients.

Footnotes

Authorship Contributions

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

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Duodenogastric reflux does not influence *Helicobacter pylori* colonization in children

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ABSTRACT

Aims: Duodenogastric reflux (DGR) and *Helicobacter pylori (H. pylori)* infection are two common etiologies implicated in gastric mucosal injury during childhood. However, their interplay remains poorly understood. This study aimed to investigate the relationship between DGR and *H.pylori* colonization through comprehensive endoscopic and histopathological evaluation in a pediatric cohort.

Methods: In this retrospective study, the medical records of 698 children who underwent esophagogastroduodenoscopy between January 2024 and March 2025 were reviewed. Patients were classified into DGR and non-DGR groups, based on the presence or absence of bile residues in the stomach during endoscopy. Histopathological assessments were conducted using the modified Sydney classification to evaluate *H.pylori* presence and density. Demographic, endoscopic, and histological parameters were compared across groups.

Results: DGR was identified in 21.6% of patients and was significantly associated with older age and female sex ($p<0.001$ and $p=0.017$, respectively). However, no significant differences were observed between the DGR and non-DGR groups regarding the frequency or density of *H.pylori* colonization ($p=0.647$ and $p=0.731$). Both DGR and *H.pylori* positivity were independently associated with increased endoscopic abnormalities ($p<0.001$ for both) and gastric mucosal inflammation ($p=0.047$, and $p<0.001$ respectively).

Conclusions: DGR and *H.pylori* infection independently contribute to gastric mucosal pathology in children. However, DGR does not appear to influence *H.pylori* colonization significantly. These findings underscore the need for further prospective and molecular studies to elucidate the mechanistic interactions between bile reflux and *H.pylori* in pediatric populations.

Introduction

Duodenogastric reflux (DGR) is characterized by the backward flow of duodenal contents into the gastric lumen, typically resulting from pyloric sphincter dysfunction. Although the exact cause of DGR remains unclear, factors such as gastroduodenal dysmotility, hormonal disturbances, dietary habits, and *Helicobacter pylori (H. pylori)* infection have been implicated. Gastrointestinal hormones, including gastrin, cholecystokinin, and secretin, may increase the risk of DGR by influencing gastric acid secretion and regulating gastric motility. In addition, *H. pylori* infection may further impair motility and contribute to the development of DGR. Pyloric dysfunction, however, is considered the primary underlying cause. It can occur primarily or develop secondarily to upper gastrointestinal surgeries such as cholecystectomy or gastrectomy.

DGR can cause irritation, inflammation, and various histopathological changes in the gastric mucosa in both adults and children. Recent pediatric esophagogastroduodenoscopy (EGD) studies have reported an increasing frequency of DGR, likely due to changes in dietary patterns, the more frequent use of EGD in children, and a higher prevalence of gastric surgery (1-5).

H. pylori is capable of establishing long-term colonization within the gastric mucosa, which may result in chronic gastritis, peptic ulceration, and, in progressive cases, the development of gastric adenocarcinoma. The development of *H. pylori* infection is influenced by host-related factors, environmental conditions, and bacterial virulence mechanisms (1,6-8).

The relationship between DGR and *H. pylori* remains uncertain. Only a limited number of studies have investigated this association in the pediatric population, and it is still debated whether the chemical gastritis environment caused by bile acids in DGR affects *H. pylori* colonization. Some studies suggest that DGR may reduce *H. pylori* colonization, while others report no significant effect (1,4,9-11).

This study investigates the association between DGR and *H. pylori* in children by combining endoscopic findings with histopathological analyses. The results are expected to clarify whether DGR has a reducing effect or no effect on *H. pylori*, thereby informing diagnostic and therapeutic strategies in pediatric patients.

Methods

Research design and setting

This retrospective analysis was conducted in the Pediatric Gastroenterology Department of a university-based tertiary care hospital and included the clinical records of 1,168 pediatric patients who underwent EGD between January 1, 2024, and March 31, 2025.

Children aged 1-18 years who underwent EGD during the study period for symptoms such as nausea, weight loss, dyspepsia, vomiting, chronic diarrhea, abdominal pain, malnutrition, or gastroesophageal reflux, and who had gastric biopsies obtained, were included. Written informed consent was obtained from their legal guardians. Patients were excluded if they had Crohn's disease, celiac disease, ulcerative colitis, eosinophilic esophagitis, immunodeficiency, a history of gastrointestinal surgery, chronic liver disease, a gastrostomy or nasogastric tube, or required EGD for foreign body retrieval. Patients with a history of antibiotic use targeting *H. pylori* before EGD were also excluded. After applying these criteria, a total of 698 pediatric cases were included in the final analysis.

Patients in whom bile residues were observed upon initial entry into the stomach during EGD and who also had evidence of gastritis, either endoscopically or histopathologically, were classified into the DGR group. Patients without bile residue at initial entry, as well as those in whom bile was observed later during the procedure, were assigned to the non-DGR group. (1,4,10,11). In addition, the characteristics of patients with confirmed *H. pylori* colonization (*H. pylori*-positive) and those without (*H. pylori*-negative) were analyzed. The same inclusion and exclusion criteria were applied across all groups. A power calculation was performed to determine the minimum number of participants required to achieve sufficient statistical power for the study's main objective.

Data collection and EGD

Patient data, including age, sex, presenting symptoms, EGD indications, endoscopic findings, and histopathological results, were retrospectively collected from the hospital information management system. EGD procedures were performed by an experienced pediatric gastroenterologist using the FUJINON ELUXEO VP-7000 endoscopy system, under deep sedation administered by an anesthesiologist. During the procedure, findings such as hyperemia, edema, nodularity, friability, bleeding, erosion, ulceration, and the presence of bile in the stomach were recorded for the esophageal, gastric, and duodenal mucosa. In accordance with European Society for Paediatric Gastroenterology, Hepatology and Nutrition guidelines, at least two biopsy samples were obtained from the corpus, antrum, and duodenum of each patient during EGD, regardless of whether any visible lesions were present (12).

Histopathological evaluation

The detection and colonization density of *H. pylori* were assessed using the criteria outlined in the modified Sydney system. In this context, the degree of inflammation was determined based on the infiltration of mononuclear cells in the lamina propria, while the level of activity was assessed by the extent of neutrophil infiltration. The severity of inflammation and *H. pylori* colonization density were graded as "none", "mild", "moderate", and "severe" (13).

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA). Normality of continuous variables was assessed with histograms, quantile-quantile plots, and the Kolmogorov-Smirnov test. Group comparisons were conducted using the independent samples t-test for normally distributed variables and the Pearson chi-square test for categorical data. All tests were two-sided, with $p<0.05$ considered significant. Sample size, determined by prior power analysis, was sufficient for statistical validity.

A binary logistic regression was performed to evaluate the effects of DGR, age, and gender on *H. pylori* infection, with *H. pylori* positivity as the dependent variable. Model fit was assessed using Nagelkerke R^2 and the Hosmer-Lemeshow test, and results included β coefficients, odds ratios [Exp(β)], Wald test, and p-values, with significance set at $p<0.05$.

An ordinal logistic regression was conducted to identify factors associated with gastric inflammation severity, using *H. pylori* positivity, age, DGR, and gender as independent variables. Results included β coefficients and odds ratios Exp(β) for interpreting the effects of each variable.

Ethical approval

The study received ethical approval from the Scientific Research Ethics Committee of the University of Health Sciences Türkiye, Gülhane (decision no: 2025-320, date: 03.06.2025). All procedures were conducted in accordance with the ethical principles outlined in the Declaration of Helsinki.

Results

This study included 698 pediatric patients, and DGR was identified in 151 of them (21.6%). The mean age of patients in the DGR group (13.88±2.81 years) was significantly higher than that of the non-DGR group (11.79±4.27 years) (p<0.001). Female patients were more frequently represented in the DGR group (p=0.017). There was no statistically significant variation in *H. pylori* detection or colonization intensity between the DGR and non-DGR groups (p>0.05) (Table 1).

The frequency of pathological findings on gastric endoscopy was 97.4% in the DGR group and 84.3% in the non-DGR group (p<0.001). In histopathological examination of the stomach, the severity of inflammation was significantly greater in the DGR group (p=0.047). This difference corresponded to a Cramér's V of 0.106, indicating a weak effect size. Neutrophil activity was similar between the two groups (p>0.05) (Table 2).

When evaluated in terms of *H. pylori* colonization, 184 patients (26.4%) constituted the *H. pylori*-positive group. This group had a higher mean age, while the gender distribution was similar to that of the *H. pylori*-negative group (p=0.03 and p>0.05, respectively). Abnormal findings on gastric endoscopy were more frequent in the *H. pylori*-positive group (95.1%) compared to the *H. pylori*-negative group (84.4%) (p<0.001). Histopathological examination of the stomach revealed significantly higher degrees of inflammation and neutrophil activity in the *H. pylori*-positive group (p<0.001) (Table 3).

According to the results of the binary logistic regression analysis, the β value for age was calculated as 0.069, and Exp(β)=1.072. This means that each increase in age is associated with a 7.2% increase in the likelihood of *H. pylori* positivity. The p-value for the significance test was found to be 0.03.

The gender variable was found to have no significant effect on *H. pylori* positivity. The β value for gender was 0.068, Exp(β)=1.071, and the p-value was 0.705. This indicates that the effect of gender on *H. pylori* positivity is minimal and not statistically significant. This result suggests that gender is not a determining factor in the development of *H. pylori* infection. Similarly, the relationship between DGR and *H. pylori* positivity was not statistically significant. The β value for DGR was 0.029, Exp(β)=1.029, and the p-value was 0.892. This result indicates that DGR does not have a significant effect on *H. pylori* positivity.

The overall model fit was calculated as Nagelkerke R^2=0.20. Additionally, the Hosmer-Lemeshow test used to assess the model's fit yielded a p-value of 0.076, indicating that the model fits the data well but does not provide statistically significant alignment.

The ordinal logistic regression analysis demonstrated that *H. pylori* positivity had the strongest impact on gastric inflammation (β=1.64). Additionally, age was identified as an important factor in increasing inflammation (β=0.35). DGR contributed very little to gastric inflammation (β=0.09). Gender did not have a significant effect on inflammation.

When patients with both DGR and *H. pylori* were compared to those with either DGR or *H. pylori* alone, a significant difference was observed between the groups in terms of histopathological inflammation (p=0.023) and activity (p=0.001). The DGR and *H. pylori* group had markedly higher rates of moderate-to-severe inflammation (73.8%) and moderate-to-severe activity (61.9%). No statistically significant difference was found in endoscopic gastric findings (p=0.062); however, the DGR and *H. pylori* group showed a higher tendency for erosion (14.3%) and ulcer (11.9%) (Table 4).

Table 1. Distribution of age, gender, and *H. pylori* colonization in the DGR and non-DGR groups

Variable	Category	Non-DGR group (n=547)	DGR group (n=151)	p-value
Age (mean ± SD)	Years	11.79±4.27	13.88±2.81	**<0.001***
		n (%)	**n (%)**	
Gender	Male	218 (39.8)	44 (29.1)	**0.017****
	Female	329 (60.2)	107 (70.9)	
***H. pylori* colonization**	Absent	405 (74.0)	109 (72.2)	0.647**
	Present	142 (25.9)	42 (27.8)	
***H. pylori* colonization density**	Mild	41 (7.5)	15 (9.9)	0.731**
	Moderate	66 (12.1)	16 (10.6)	
	Severe	35 (6.4)	11 (7.3)	

*Independent samples t-test, **Pearson chi-square test
H. pylori: Helicobacter pylori, DGR: Duodenogastric reflux, SD: Standard deviation

Table 2. **Endoscopic and histopathological gastric evaluation in non-DGR and DGR groups**

Variable	Category	Non-DGR group (n=547) n (%)	DGR group (n=151) n (%)	p-value*
Gastric endoscopic evaluation	Normal	86 (15.7)	4 (2.6)	**0.001**
	Hyperemia/edema	315 (57.5)	109 (72.2)	
	Nodularity	74 (13.5)	18 (11.9)	
	Erosion	44 (8.0)	9 (6.0)	
	Ulcer	28 (5.1)	11 (7.3)	
Gastric inflammation severity	Normal	59 (10.7)	6 (4.0)	**0.047**
	Mild	362 (66.1)	105 (69.5)	
	Moderate	83 (15.1)	30 (19.9)	
	Severe	43 (7.8)	10 (6.6)	
Gastric neutrophil activity	Normal	396 (72.3)	108 (71.5)	0.971
	Mild	51 (9.3)	15 (9.9)	
	Moderate	71 (12.9)	21 (13.9)	
	Severe	29 (5.3)	7 (4.6)	

*Pearson chi-square test
DGR: Duodenogastric reflux

Table 3. **Age, gender, gastric endoscopic and histopathological evaluation of *H. pylori*-positive and *H. pylori*-negative groups**

Variable	Category	*H. pylori*-negative (n=514)	*H. pylori*-positive (n=184)	p-value
Age (mean ± SD)	Years	11.98±4.29	13.02±3.35	**0.030***
		n (%)	**n (%)**	
Gender	Male	193 (37.5)	69 (37.5)	0.091**
	Female	321 (62.5)	115 (62.5)	
Gastric endoscopic evaluation	Normal	80 (15.6)	9 (4.9)	**<0.001****
	Hyperemia/edema	352 (68.5)	73 (39.7)	
	Nodularity	21 (4.1)	71 (38.6)	
	Erosion	33 (6.4)	20 (10.9)	
	Ulcer	28 (5.4)	11 (6.0)	
Gastric inflammation severity	Normal	65 (12.6)	0 (0.0)	**<0.001****
	Mild	427 (83.1)	40 (21.7)	
	Moderate	18 (3.5)	95 (51.6)	
	Severe	4 (0.8)	49 (26.6)	
Gastric neutrophil activity	Normal	491 (95.5)	13 (7.1)	**<0.001****
	Mild	15 (2.9)	51 (27.7)	
	Moderate	6 (1.2)	86 (46.7)	
	Severe	2 (0.4)	34 (18.5)	

*Independent samples t-test, **Pearson chi-square test
H. pylori: Helicobacter pylori, SD: Standard deviation

Table 4. Endoscopic and histopathological gastric evaluation in patients with both DGR and *H. pylori* vs. those with either DGR or *H. pylori* alone

Variable	Category	DGR and *H. pylori* group (n=42) n (%)	DGR or *H. pylori* alone group (n=251) n (%)	p-value*
Gastric endoscopic evaluation	Normal	0 (0.0)	13 (5.2)	0.062
	Hyperemia/edema	19 (45.2)	144 (57.4)	
	Nodularity	12 (28.6)	65 (25.9)	
	Erosion	6 (14.3)	17 (6.8)	
	Ulcer	5 (11.9)	12 (4.8)	
Gastric inflammation severity	Normal	0 (0.0)	6 (2.4)	**0.023**
	Mild	11 (26.2)	123 (49.0)	
	Moderate	21 (50.0)	83 (33.1)	
	Severe	10 (23.8)	39 (15.5)	
Gastric neutrophil activity	Normal	5 (11.9)	111 (44.2)	**0.001**
	Mild	11 (26.2)	44 (17.5)	
	Moderate	19 (45.2)	69 (27.5)	
	Severe	7 (16.7)	27 (10.8)	

*Pearson chi-square test
H. pylori: Helicobacter pylori, DGR: Duodenogastric reflux

Discussion

This study investigated the association between DGR and *H. pylori* in children by integrating both endoscopic and histopathological assessments. Our findings indicate that the presence of DGR was associated with older age and female sex, yet it had no significant impact on the frequency or density of *H. pylori* colonization. Importantly, both conditions were independently linked to abnormal endoscopic findings and increased gastric mucosal inflammation. These results suggest that each contributes to the pathogenesis of gastric disorders in the pediatric population.

In our study, no significant difference was detected in *H. pylori* positivity between children with and without DGR (27.8% vs. 25.9%). Colonization density was also comparable across groups. These findings suggest that DGR does not exert a marked suppressive effect on *H. pylori* in children. However, any potential influence might be offset by the bacterium's adaptive mechanisms. The high environmental adaptability of *H. pylori* and its ecological advantage within the gastric microbiota may allow it to maintain colonization despite bile exposure.

Previous studies have examined the relationship between these two conditions, but results remain inconsistent. Some pediatric studies have reported lower rates of *H. pylori* gastritis in children with DGR, attributing this to the possible bactericidal effects of bile acids (10,11). In contrast, some studies suggested that DGR did not influence *H. pylori* colonization rates in children (1,4).

A recent study demonstrated that the presence of DGR is associated with distinct alterations in the gastric mucosal microbiota, marked by an increase in non-*H. pylori* species (14). Supporting this, two prospective investigations showed a substantial reduction in the relative abundance of commensal taxa in both the duodenal bulb and gastric mucosa of *H. pylori*-infected children, alongside a predominance of the *Helicobacter* genus (15,16). These observations suggest that *H. pylori* may activate adaptive responses to maintain a competitive edge within a dynamically shifting microbial environment. Our findings appear to support this hypothesis, suggesting that despite exposure to hostile conditions such as bile acids, *H. pylori* might influence competing microbiota and contribute to the establishment of a more favorable ecological niche for its persistence.

The interaction between bile acids and *H. pylori* is influenced by factors such as the type, concentration, and duration of exposure. Conjugated bile acids may damage bacterial membranes and inhibit adaptive mechanisms, while bile-induced epithelial injury may reduce bacterial adherence. Certain bile acids have been reported to suppress metabolism and virulence gene expression, potentially limiting colonization. Despite these effects, *H. pylori* has genetic adaptations that may provide resistance to prolonged bile exposure (14,17). This multifaceted interplay may help explain the inconsistencies observed across studies examining the bile and *H. pylori* interaction, including our study.

In our cohort, gastric mucosal lesions such as hyperemia, edema, and ulceration were significantly more common among children with DGR compared to the non-DGR group, supporting the notion of direct mucosal injury by bile acids, as previously

reported in the literature (2,18,19). Histopathologically, inflammation severity was also higher in the DGR group, suggesting an elevated risk of chemically induced gastritis. Notably, no significant difference was observed in neutrophil activity, potentially indicating a stronger association of DGR with chronic rather than acute inflammation.

Meanwhile, in children with *H. pylori* infection, gastric endoscopy revealed more extensive pathology, and histological analysis showed significantly elevated inflammation and neutrophil activity scores. These findings reaffirm *H. pylori* as a principal driver of gastric inflammation and highlight its critical role in the extent of mucosal damage.

Regression analyses indicated that both DGR and *H. pylori* independently contribute to gastric mucosal inflammation (β=1.64 and β=0.35, respectively). Each condition was associated with higher rates of hyperemia, edema, and ulceration. The coexistence of conditions may further increase the risk of gastritis. Clinically, this highlights the importance of considering both entities in therapeutic strategies. However, the combination of DGR and *H. pylori* may negatively impact treatment outcomes, potentially necessitating longer durations of acid-suppressive therapy in these patients. In addition, dietary modifications to minimize mucosal irritation remain important in affected children. Comprehensive education and structured follow-up plans should also be provided to families to support treatment adherence.

One of the notable strengths of our study lies in the inclusion of a large, systematically evaluated pediatric cohort, in which the relationship between DGR and *H. pylori* infection was assessed using both endoscopic and histopathological criteria. While few pediatric studies have addressed this interaction, our findings provide valuable insights into this underexplored area. The detailed evaluation of multi-site biopsy specimens based on the modified Sydney classification further enhances the reliability of our results.

Nonetheless, the retrospective nature of our study posed certain limitations in accessing complete clinical data. As in previous studies, the diagnosis of DGR was based on the visual detection of bile residues in the stomach and was supported by endoscopic or histopathological evidence of gastritis (1,4,10,11). Although DGR was assessed upon initial entry into the stomach to minimize the effects of sedation and the endoscopic procedure, only patients with bile residues were classified as having chronic DGR, and this approach may still have influenced the accuracy of diagnosis. In addition, as with any visually based assessment, the diagnosis of DGR is subject to observer variability, which represents another limitation of our study.

In future research, prospective studies using more objective methods such as intragastric bile acid quantification or pH monitoring could help improve diagnostic precision. Likewise, directly measuring bile acid concentrations could provide a more detailed understanding of the effect of DGR on *H. pylori* colonization.

Conclusion

In conclusion, our findings suggest that, contrary to common assumptions, DGR may not significantly influence the frequency or intensity of *H. pylori* colonization in children, indicating that the presumed antibacterial effects of bile may be counteracted by the bacterium's strong adaptive mechanisms. Importantly, we demonstrated that DGR and *H. pylori* each independently contribute to mucosal inflammation, and that their coexistence may amplify bile-induced chemical gastritis. This study is among the first to systematically evaluate the independent and combined effects of DGR and *H. pylori* in a large pediatric cohort. These results advance current understanding in pediatric gastroenterology by emphasizing the need for an integrated diagnostic and therapeutic approach in children presenting with gastrointestinal symptoms, and may guide future strategies aimed at improving management and outcomes.

Ethics

Ethics Committee Approval: The study received ethical approval from the Scientific Research Ethics Committee of the University of Health Sciences Türkiye, Gülhane (decision no: 2025-320, date: 03.06.2025).

Informed Consent: Written informed consent was obtained from their legal guardians.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.T., Y.M.E., Concept: S.T., Design: S.T., Data Collection or Processing: S.T., Y.M.E., Analysis or Interpretation: S.T., Y.M.E., Literature Search: S.T., Y.M.E., Writing: S.T.

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Low-vision at a tertiary eye care centre in Western India: a five-year retrospective study

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ABSTRACT

Aims: To examine (1) the etiological patterns of low vision across pediatric, working-age, and geriatric populations; (2) the severity distribution of visual impairment; and (3) the prescription trends of low-vision devices (LVDs) at a single tertiary eye care centre in western India.

Methods: This single-center retrospective study reviewed the records of 1,039 patients who visited a low-vision clinic between January 2019 and April 2024. Demographic details, ocular diagnoses, visual acuity [classified per International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10)], and LVD prescriptions were analysed.

Results: The cohort consisted predominantly of male patients (70.0%), with the following age distribution: working-age adults (45.0%; mean age 38.9±16.1 years), children (40.2%; mean age 10.2±3.3 years), and geriatric patients (14.7%; mean age 76.0±6.6 years). Retinal disorders (57.8%) were the leading cause of low vision, with age-specific variations: nystagmus (17.9%) and congenital cataracts (20.3%) in children; retinitis pigmentosa (25.0%) and diabetic retinopathy (25.6%) in working-age adults; and age-related macular degeneration (37.9%) and cataracts (55.6%) in the geriatric population. Moderate visual impairment was most common (48.8%), followed by blindness (25.9%). Telescopes were the most frequently prescribed LVDs (72.9%), and spectacle magnifiers were the most common near-vision aid (83.4%).

Conclusions: The findings highlight distinct age-related patterns in the etiology of low vision and assistive device needs within this patient population. Although limited by its single-centre scope, this study offers valuable baseline data to guide age-specific rehabilitation strategies.

Introduction

Low vision is widely recognized as a significant public health concern (1). Evidence suggests that individuals with functionally impaired vision often experience permanent sight loss, which can hinder their ability to perform daily activities such as reading, recognizing faces, writing, and participating in social interactions (2). Additionally, accidents, loss of independence, and feelings of loneliness or grief may further exacerbate these challenges. Such difficulties may adversely affect physical and emotional well-being (3). From a clinical perspective, two primary approaches are commonly used to manage low vision: low-vision rehabilitation and low-vision devices (LVDs). LVDs—including optical, non-optical, and electronic tools—may enhance patients' performance by maximizing their remaining vision (4).

Comprehensive rehabilitation and low-vision services may provide individuals with tools to optimize their residual eyesight, potentially enabling them to engage in meaningful activities and maintain a degree of personal independence. These services may also alleviate some of the challenges associated with visual impairment (3).

Understanding the causes of low vision plays a critical role in assessing the need for treatment and rehabilitation services, supporting blindness prevention efforts, informing eye health policies, and guiding research priorities for diverse populations. While studies have examined trends in low-vision rehabilitation services and causes of low vision in southern and northern India, comparable reports from the western region remain limited (5). This region, comprising 1,866 villages with a population of 7.4 million, has received relatively little attention in the literature. Given the limited data on low-vision care in western India, this study seeks to address a critical gap in the literature by investigating the causes and management of low vision. Previous studies suggest that regional differences may influence both the underlying causes of visual impairment and the availability of vision rehabilitation resources (6). By examining these factors, the study aims to inform targeted interventions and health policies to address this important public health concern. The primary goal of this study was to explore potential factors contributing to low vision among patients from three age groups attending a hospital-affiliated low-vision rehabilitation clinic. Additionally, the study examined patient characteristics such as the severity of visual impairment and the types of LVDs prescribed to them.

Methods

Study design and participants

This study employed a retrospective design to analyze secondary data from patients treated at the low-vision clinic of a tertiary eye care hospital located in Pune, Western India, from January 2019 to April 2024. The Dr. D. Y. Patil Medical College, Hospital and Research Centre, Pune Ethics Committee approved this research (reference no.: DYPV/EC/489/2020, date: 04.02.2020), and all procedures followed the ethical guidelines outlined in the Declaration of Helsinki.

Participants were diagnosed with visual impairment attributable to various ocular conditions. All participants underwent a low-vision assessment and were deemed to require rehabilitation. Participants were included if they had a confirmed diagnosis of visual impairment and complete medical records. Those with incomplete datasets or missing follow-up data were excluded to ensure the reliability of the analysis.

Data collection and measurements

Certified ophthalmologists and optometrists examined patients over a specific period to gather relevant data. Variables such as age, gender, ocular conditions causing low vision, visual acuity (VA), and types of prescribed LVDs were recorded. VA was assessed binocularly using a Snellen chart to determine best-corrected VA. Visual impairment was classified according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10, World Health Organization, 2016) criteria. According to ICD-10 criteria (Category H54), visual impairment was classified into four stages: mild (VA 6/18), moderate (VA 6/18-6/60), severe (VA 6/60-3/60), and blindness (VA <3/60) (7).

Availability of LVDs

The clinic maintained a fixed and comprehensive inventory of optical, non-optical, and electronic LVDs throughout the study period (January 2019 to April 2024). This standard inventory, which included the full range of devices reported in the results, was consistently available. The prescription of specific devices was based solely on the individual patient's visual needs, task requirements, and functional goals as assessed by the certified low-vision optometrist and ophthalmologist. The stability of the inventory ensures that the prescribing patterns analyzed in this study reflect genuine clinical practice and patient requirements rather than temporal variations in device availability.

Statistical Analysis

Microsoft Excel 365 and IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA) were used for data collection and analysis. Descriptive statistics, including means, standard deviations, and frequencies (percentages), were generated to summarize demographic factors, the degree of visual impairment, and the types of LVDs prescribed across different age groups. Inferential statistical analyses were also performed. Chi-square (χ^2) tests were used to examine the associations between (i) age group and severity of visual impairment, (ii) age group and primary etiology, (iii) gender and severity of visual impairment, and (iv) gender and primary

etiology. A one-way analysis of variance was conducted to assess whether the mean age differed across the categories of visual impairment severity (mild, moderate, severe, blind). A p-value <0.05 was considered statistically significant.

Results

Demographic characteristics of the study population

The study involved 1,039 patients, of whom 727 (70.0%) were male, and 312 (30.0%) were female. The low-vision clinic primarily served working-age individuals (n=468, 45.0%), followed by children (n=418, 40.2%) and geriatric patients (n=153, 14.7%).

Mean ages for each group were: pediatric patients, 10.2±3.3 years (range 2-16 years); working-age patients, 38.9±16.1 years (range 17-65 years); and geriatric patients, 76.0±6.6 years (range 66-91 years). There was no statistically significant difference in the mean age across the mild, moderate, severe, and blindness categories [F (3, 1035)=0.99, p=0.40]. This indicates that the severity of visual impairment was not associated with a specific age group within this patient population. These demographic details are summarized in Table 1.

We further investigated associations between gender and clinical characteristics. While no significant association was found between gender and the severity of visual impairment [χ^2 (3)=2.77, p=0.43], a highly significant association was identified between gender and the underlying etiology of low vision [χ^2 (5)=138.57, p<0.001].

Comorbidities

Comorbidities were identified through a retrospective review of medical records and diagnostic evaluations. In the pediatric group, the most common comorbidities were congenital cataracts (20.3%) and retinopathy of prematurity (14.8%). Among working-age patients, diabetic retinopathy (DR) (25.6%) and glaucoma (20.3%) were the most frequently observed. Age-related macular degeneration (AMD) (58.8%) and cataracts (55.6%) were the leading comorbidities in geriatric patients. The mean number of comorbidities varied across age groups: 1.5±0.8 in the pediatric group, 2.1±1.2 in the working-age group, and 2.8±1.5 in the geriatric group.

Etiological analysis of low vision across age groups

The causes of low vision across the three age groups are summarized in Table 2. The retina was the most commonly affected anatomical site, with 597 (57.8%) of the 1,039 patients presenting with retinal disorders. In the pediatric age group, the most frequently observed ocular pathologies were nystagmus (n=75, 17.9%), retinitis pigmentosa [(RP); n=45, 10.8%], and macular dystrophy (n=35, 8.4%). In the working-age group, RP (117, 25.0%), myopic macular degeneration (50, 10.6%), and nystagmus (36, 7.7%) were the primary causes. In the geriatric group, the leading causes were AMD (n=58, 37.9%), DR (n=17, 11.1%), and glaucoma (n=15, 9.8%). Among documented cases of optic atrophy, the likely etiologies were heterogeneous. In pediatric patients, causes were often congenital or hereditary (e.g., related to perinatal events or genetic disorders). In adults, etiologies were typically acquired and included glaucomatous, ischemic, inflammatory (e.g., post-optic neuritis), and compressive causes (6). Statistical analysis confirmed a highly significant association between age group and the primary etiology of low vision [χ^2 (10)=487.80, p<0.001]. This supports the observed clinical pattern in which specific conditions, such as nystagmus and congenital disorders, are prevalent among children, whereas age-related conditions, such as AMD and cataracts, predominate among older adults.

Severity of visual impairment across age groups

Among the 1,039 patients, 77 (7.4%) had mild visual impairment, 507 (48.8%) had moderate impairment, 186 (17.9%) had severe impairment, and 269 (25.9%) were blind. In the pediatric age group (n=418), visual impairment was

Table 1. Demographic characteristics of the study population (n=1.039)

Characteristics	Category	Frequency (n)	Percentage (%)
Gender	Male	727	70.0
Male distribution by age	Pediatric	270	64.6*
	Working adults	334	71.4*
	Geriatric	123	80.4*
	Female	312	30.0
Female distribution by age	Pediatric	148	35.4*
	Working adults	134	28.6*
	Geriatric	30	19.6*
Age group	Pediatric (0-16 years)	418	40.2
	Working adults (17-65 years)	468	45.0
	Geriatric (≥66 years)	153	14.7

Percentages marked with an asterisk (*) indicate the proportions of males and females in each age group

Table 2. Causes of low vision in pediatrics, working adults and geriatrics

Causes of low vision in pediatrics	Frequency (n)	Percentage (%)	Causes of low vision in working adults	Frequency (n)	Percentage (%)	Causes of low vision in geriatrics	Frequency (n)	Percentage (%)
Nystagmus	75	17.9	Retinitis pigmentosa	117	25.0	ARMD	58	37.9
Retinitis pigmentosa	45	10.8	MMD	50	10.7	Diabetic retinopathy	17	11.1
Macular dystrophy	35	8.4	Nystagmus	36	7.7	Glaucoma	15	9.8
Coloboma	34	8.1	Macular dystrophy	33	7.1	Myopic macular degeneration	15	9.8
Microcornea	30	7.2	Diabetic retinopathy	32	6.8	Optic atrophy	10	6.5
Optic atrophy	27	6.5	Optic atrophy	30	6.4	Macular scar	8	5.2
MMD	21	5.0	Coloboma	17	3.6	Retinitis pigmentosa	6	3.9
Microphthalmos	20	4.8	Microcornea	16	3.4	Macular dystrophy	4	2.6
Albinism	17	4.1	Glaucoma	15	3.2	BRVO	3	2.0
ROP	14	3.4	ARMD	14	3.0	Coloboma	3	2.0
Cone dystrophy	14	3.4	Retinal detachment	13	2.8	RD	3	2.0
Stargardt's disease	13	3.1	Macular scar	11	2.4	Corneal opacity	3	2.0
Amblyopia	13	3.1	Stargardt's disease	11	2.4	Others	8	5.2
Glaucoma	12	2.9	Microphthalmos	11	2.4			
Aniridia	7	1.7	Maculopathy	11	2.4			
Cone rod dystrophy	6	1.4	Toxoplasmosis	8	1.7			
Toxoplasmosis	5	1.2	Albinism	6	1.3			
Retinal hypoplasia	5	1.2	Corneal opacity	6	1.3			
Others	25	6.0	Cone dystrophy	6	1.3			
			Amblyopia	5	1.1			
			Aphakia	5	1.1			
			Others	15	3.2			
Total	**418**	**100.0**	**Total**	**468**	**100.0**	**Total**	**153**	**100**

Percentages reflect the proportion of each cause within the respective age groups. "Others" includes less frequent conditions, such as aphakia, maculopathy, retinal detachment, corneal opacity, dislocated lens, and optic neuritis as detailed below. The pediatric group "Others" includes aphakia (n=4), maculopathy (n=4), retinal detachment (n=4), corneal opacity (n=4), dislocated lens (n=3), corneal scar (n=3), macular scar (n=2), and optic neuritis (n=1). The working-age group "Others" includes: retinal hypoplasia (n=3), uveitis (n=3), cone rod dystrophy (n=2), corneal scar (n=2), vitelliform macular dystrophy (n=1), aniridia (n=1), macular hole (n=1), and BRVO (n=1). The geriatric group "Others" includes macular hole (n=2), toxoplasmosis (n=2), aphakia (n=2), and albinism (n=2). Association between age group and primary etiology (chi-square test): χ^2 (10)=487.80, p<0.001

MMD: Myopic macular degeneration, ARMD: Age-related macular degeneration, RD: Retinal detachment, ROP: Retinopathy of prematurity, BRVO: Branch retinal vein occlusion

distributed as follows: moderate in 209 patients (50.0%), blindness in 107 patients (25.6%), severe visual impairment in 75 patients (17.9%), and mild visual impairment in 27 patients (6.5%). Similarly, among working-age adults (n=468), 231 (49.4%) had moderate impairment; blindness was noted in 121 (25.9%), severe impairment in 82 (17.5%), and mild impairment in 34 (7.3%). A comparable trend was observed in the geriatric age group (n=153), in which the majority had moderate impairment: 67 (43.8%), followed by blindness: 41 (26.8%), severe impairment: 29 (19.0%), and mild impairment: 16 (10.5%). There was no statistically significant association between age group and visual-impairment severity [χ^2 (6)=3.58, p=0.73], indicating that the distribution of mild, moderate, and severe visual impairment and blindness was similar across pediatric, working-age, and geriatric populations. Table 3 provides a detailed breakdown of VA and severity classifications across all age groups. Figure 1 illustrates the distribution of visual impairment severity across the three major age groups, demonstrating that moderate visual impairment was the most frequent category across all groups.

Prescription patterns of LVDs

Among the 1,039 patients, telescopes were most frequently prescribed as distance optical devices (757, 72.9%), followed by near optical devices (457, 44.0%), and non-optical devices (329, 31.7%). Additionally, 31 electronic devices (3.0%) were prescribed based on the specific needs of the patients. Among the optical LVDs prescribed for close-up tasks, spectacle magnifiers (381, 36.7%), reading stands (159, 15.3%), and overhead reading lamps (116, 11.2%) were the most commonly recommended. Binocular telescopes were prescribed to 413

Table 3. Severity of visual impairment across age groups

Age group (n)	Visual acuity range*	Severity classification (ICD-10)	Frequency (n)	Percentage (%)
Pediatrics (418)	≥6/18	Mild	27	6.5
	<6/18-6/60	Moderate	209	50.0
	<6/60-3/60	Severe	75	17.9
	<3/60-1/60	Blindness	70	16.8
	<1/60-LP†	Blindness	37	8.9
Working adults (468)	≥6/18	Mild	34	7.3
	<6/18-6/60	Moderate	231	49.4
	<6/60-3/60	Severe	82	17.5
	<3/60-1/60	Blindness	72	15.4
	<1/60-LP†	Blindness	49	10.5
Geriatrics (153)	≥6/18	Mild	16	10.5
	<6/18-6/60	Moderate	67	43.8
	<6/60-3/60	Severe	29	19.0
	<3/60-1/60	Blindness	24	15.7
	<1/60-LP†	Blindness	17	11.1

*Visual acuity ranges are based on the ICD-10 classification of the World Health Organization.
†LP: Light perception, ICD: International Statistical Classification of Diseases and Related Health Problems, 10th Revision
Association between age group and severity of visual impairment (chi-square test): χ^2 (6)=3.58, p=0.73

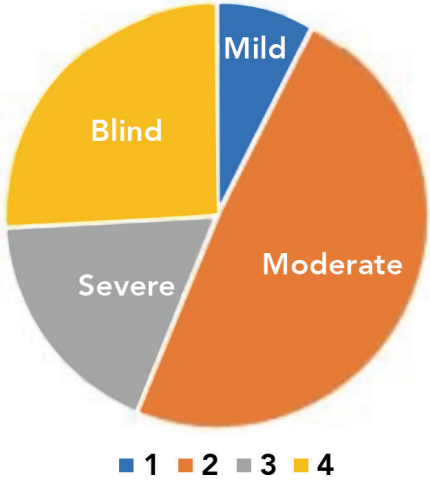

Figure 1. Severity of visual impairment in all age groups
1: Mild (≥6/18), 2: Moderate (<6/18-6/60), 3: Severe (<6/60-3/60), 4: Blindness (<3/60-1/60 to <1/60-PL)

patients (39.7%), and 344 patients (33.1%) were provided with monocular telescopes. Of the 329 non-optical devices (31.7%), canes (19; 5.8%) and flashlights (18; 5.5%) were offered to assist with orientation and mobility, while filters and tinted lenses (17; 5.2%) were prescribed to reduce glare-related discomfort. Table 4 summarizes the number of LVDs prescribed across all age groups.

Discussion

Retinal disorders were the leading cause of visual impairment in this study, accounting for 57.8% cases and demonstrating distinct age-specific patterns. This finding aligns with the growing burden of retinal diseases as a leading cause of low vision globally, but reveals critical age-specific variations: nystagmus and congenital cataracts were most common in children, whereas AMD and DR were most common in older adults. Furthermore, moderate visual impairment was the most prevalent severity category (48.8%), and telescopes were the most frequently prescribed LVDs (72.9%). These results underscore the heterogeneous etiology and functional demands across age groups within this population, highlighting the imperative for customized, evidence-driven rehabilitation strategies. The distinct patterns observed, particularly the high prevalence of retinal pathologies, provide valuable baseline data for the western region of India and emphasize the need for targeted public health and clinical interventions.

Key contributors to vision loss in pediatric populations

In the pediatric cohort of our study, nystagmus, RP, and macular dystrophy were the most frequently observed causes of low vision, consistent with prior findings from South Asia and other developing regions. For instance, Sapkota and Kim (8) reported similar trends, with nystagmus, refractive errors (RE), and congenital cataracts emerging as dominant causes in Nepalese children, while Uprety et al. (9) found refractive error and amblyopia, RP, and macular dystrophy to be the most common causes of pediatric visual impairment in the same region. Gao et al. (10), who studied a comparable cohort in China, found high rates of congenital cataracts and optic atrophy. These shared aetiologies point to underlying patterns of inherited and congenital visual disorders among younger populations. However, notable regional variations remain, such

Table 4. Low vision devices prescribed across age groups

Device category	Specific device	Pediatric group (n=418), n (%)	Working age group (n=468), n (%)	Geriatric group (n=153), n (%)	Total (n=1,039), n (%)
Near optical devices	-	103	243	110	457
	Spectacle magnifiers	94 (91.3)	195 (80.3)	91 (82.7)	381 (83.4)
	Hand-held magnifiers	7 (6.8)	25 (10.3)	8 (7.3)	40 (8.8)
	Stand magnifiers	2 (1.9)	23 (9.5)	11 (10.0)	36 (7.9)
Distance optical devices	-	315	346	96	757
	Binocular telescope	158 (50.2)	176 (50.7)	79 (82.3)	413 (54.6)
	Monocular telescope	157 (49.8)	170 (49.0)	17 (17.7)	344 (45.4)
Non-optical devices	-	139	145	45	329
	Reading stand	70 (49.7)	65 (44.8)	24 (53.3)	159 (48.3)
	Overhead lamp	54 (37.6)	44 (30.3)	18 (40.0)	116 (35.3)
	Filters/tinted lenses	8 (5.0)*	9 (6.2)	-	17 (5.2)
	Canes	4 (3.6)	13 (9.0)	2 (4.4)	19 (5.8)
	Flashlight	3 (2.2)	14 (9.7)	1 (2.2)	18 (5.5)
Electronic devices	Video magnifier	6 (19.4)**	14 (45.2)**	11(35.5)**	31

*: Percentage discrepancy noted (original showed 5.0% but 8/139=5.8%)
**: Percentages calculated against total electronic devices (n=31) rather than group totals

as higher rates of RE and amblyopia reported by Verma et al. (11) in urban Indian schoolchildren and elevated prevalence of albinism and optic atrophy reported by Olusanya et al. (12) in low-resource Nigerian settings (13). These discrepancies likely stem from genetic, environmental, and healthcare access factors. Our findings contribute to this global landscape by reinforcing the need for early pediatric screening and diagnosis, particularly for nystagmus and hereditary retinal conditions.

Common causes of vision impairment in working-age adults

Among working-age adults in our study, visual impairment was most commonly associated with myopic macular degeneration, nystagmus, optic atrophy, macular dystrophy, and DR. This spectrum aligns with observations from regional and international studies. For instance, Chotikavanich et al. (14) in Thailand noted a similar burden of degenerative and systemic conditions among adults attending low-vision clinics. Likewise, Z Alotaibi (15) from Saudi Arabia identified optic atrophy, RP, DR, and AMD as the common causes of low vision in adults, while Zeried et al. (16) found DR, glaucoma, and cataracts to be the prevalent contributors to vision loss. The recurring presence of DR across studies reinforces the growing impact of systemic diseases on ocular health, particularly in middle-aged populations. These findings emphasize the importance of integrating ophthalmologic screening into chronic disease management programs, especially for conditions such as diabetes and high myopia, to address preventable vision loss in economically active age groups.

Primary causes of vision impairment in elderly adults

In the geriatric cohort, our study identified cataracts, AMD, and DR as major causes of visual impairment—highlighting a complex interplay of age-related degenerative and metabolic conditions. While AMD is widely recognized globally as a leading cause, our data emphasize the continued burden of treatable conditions such as cataracts in the elderly population in India. This pattern mirrors findings from Malaysia, where Chew et al. (17) reported high rates of untreated cataracts and DR in older adults, and from Haryana, where Malhotra et al. (18) reported that uncorrected RE and cataracts contributed substantially. These variations across regions likely reflect differences in healthcare access, surgical coverage, and population health-seeking behavior. Such observations reinforce the importance of local epidemiological surveillance and targeted outreach programs, particularly those aimed at improving surgical uptake and diabetes control among elderly individuals.

Gender-based barriers to eye care access

The gender distribution in our study revealed that male patients constituted nearly 70% of low-vision service users—a pattern that aligns with prior epidemiological studies across diverse healthcare settings (9,12,17,18,19). While this disparity may partly reflect demographic factors, it is more likely to underscore deeper systemic issues, such as gender-based differences in health literacy and access to care, and cultural norms that influence healthcare-seeking behaviour. Limited autonomy in travel, financial dependence, and lower awareness of available rehabilitation services may also disproportionately affect women in certain regions. These findings highlight the urgent need for gender-sensitive outreach strategies and community education programs to ensure equitable access to low-vision care. Further research using mixed-methods approaches can help unpack these barriers more deeply and inform context-specific interventions aimed at addressing gender inequities in vision rehabilitation.

Barriers to low-vision services among different age groups

Our study found that working-age adults (17-65 years) constituted the largest user group of low-vision services, consistent with observations from other developing countries (20,21). In contrast, the relatively lower representation of geriatric patients may reflect access-related barriers such as limited referrals, inadequate transportation, and reduced awareness of rehabilitative care. These challenges, often exacerbated by physical frailty and social dependency, can hinder service utilization among older adults despite their high burden of visual impairment. Addressing these disparities requires community-based screening, enhanced referral pathways, and geriatric-friendly service models to improve access to and utilization of low-vision rehabilitation among older adults.

Availability and prescription trends of LVDs

The predominance of telescopes for distance vision in our clinic reflects not only patients' needs but also the limited availability of alternatives. Near-vision rehabilitation relied largely on spectacle, hand, and stand magnifiers, suggesting a preference for simple, cost-effective optical solutions. Bakkar et al. (22) and Gao et al. (23) observed comparable patterns, reporting similar reliance on basic magnification tools in low-resource settings. These trends may be shaped by both institutional inventories and practitioner training, as the availability and familiarity with advanced electronic or customizable low-vision aids remain limited in many clinical environments. Enhancing optometric training and expanding device availability—particularly for pediatric and elderly users—could improve individualized rehabilitation outcomes.

Prescription patterns must be viewed in light of patients' functional visual abilities. The high prevalence (72.9%) of telescopes used for distance vision reflects the need for improved acuity in tasks such as face recognition and television viewing. However, the absence of visual field data in our study limits a more detailed analysis of the device's suitability for specific visual field defects. For instance, patients with peripheral field loss (e.g., from RP) may find high-power magnifiers less effective for navigation despite their utility in spot reading. Similarly, the widespread use of spectacle magnifiers (36.7%) may not accommodate the functional challenges faced by patients, such as children with nystagmus, who experience unstable fixation and may have difficulty maintaining precise alignment. These patients may benefit more from hand-held or stand-mounted devices. These functional considerations, which were not fully explored in retrospective analyses, are essential for tailoring rehabilitation strategies and underscore that device selection is influenced by a complex interplay among acuity, field loss, and oculomotor control.

Study Limitations

Our investigation provides important clinical observations on the etiology and management of low vision; however, several limitations warrant consideration. The retrospective methodology carries an inherent risk of information bias in both data recording and interpretation. Furthermore, because this is a single-institution study conducted in urban Pune, our results may not fully represent the diverse patient populations and practice patterns across Western India, particularly in rural communities, where access to vision rehabilitation services often differs substantially. Therefore, while the findings offer important clinical insights, they primarily reflect the experiences of this institution's patient population and should be interpreted cautiously when considering broader applications across Western India, given regional differences in healthcare infrastructure and disease patterns. The restricted inventory of assistive devices available during the study period may have influenced prescribing trends and the assessment of outcomes.

Additionally, visual field data, a critical functional parameter, particularly in conditions such as RP, glaucoma, and nystagmus, were not consistently available for analysis in this retrospective review. The lack of this functional measure limits our ability to make more nuanced interpretations of device selection, especially for patients with conditions where visual field loss plays a key role in determining rehabilitation strategies. For example, visual field loss is often a critical factor in prescribing LVDs such as bioptic telescopes for patients with glaucoma or prism lenses for patients with certain forms of nystagmus. Without this information, it is difficult to fully assess how patients' functional vision loss influenced prescription trends for assistive devices.

Notably, our study found no cases in which trauma was the primary etiology; this may reflect unique population characteristics or specific referral patterns at our tertiary center, where trauma cases are typically managed by surgical services rather than low-vision rehabilitation.

Furthermore, our etiological classification was based on ophthalmologic records. For patients with nystagmus—a sign of underlying pathology rather than a final diagnosis—a standardized neurological evaluation was not included in the routine protocol. Therefore, the potential contribution of underlying neurological conditions to vision loss in this subgroup may not be fully captured.

We recommend that future studies include visual field measurements to better understand their impact on device selection and rehabilitation strategies, which would provide a more comprehensive view of low vision rehabilitation in these conditions.

Conclusion

This study identifies retinal disorders as the leading cause of low vision (57.8%) across age groups in a Western Indian cohort, with distinct patterns of severity of visual impairment and prescriptions for assistive devices. The findings highlight (1) the need for age-specific rehabilitation strategies and (2) regional disparities in low-vision etiology compared with other

Indian states. While the single-centre retrospective design limits the generalizability of our findings, this study provides valuable baseline evidence to inform low-vision rehabilitation policies in Western India. To strengthen the applicability of these insights across diverse populations and settings, broader multi-centre research—particularly involving rural and underserved regions—is recommended.

Ethics

Ethics Committee Approval: The Dr. D. Y. Patil Medical College, Hospital and Research Centre, Pune Ethics Committee approved this research (reference no.: DYPV/EC/489/2020, date: 04.02.2020), and all procedures followed the ethical guidelines outlined in the Declaration of Helsinki.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

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

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Evaluation of the efficacy of reirradiation therapy in patients with refractory bilateral heel spur

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Keywords: Calcaneal spur, heel spur, plantar fasciitis, reirradiation, recurrent pain management

ABSTRACT

Aims: Calcaneal spurs and plantar fasciitis cause intractable plantar pain amenable to radiation therapy (RT). However, because of individual variations in neural capillaries within the spurs, reirradiation may be needed to relieve recurrent pain from irradiated heel spurs and thereby achieve a better quality of life. The aim of this study is to document the benefit of reirradiation for recurrent heel spur pain.

Methods: This single-center retrospective study included patients who underwent reirradiation between November 2016 and December 2024 for recurrent calcaneal spur pain after the first radiotherapy course. Patient inclusion criteria included a previous history of irradiation with recurrent pain; patients younger than 35 years or weighing more than 120 kg were excluded. A total RT dose of 8 Gy was delivered over 2 consecutive days. Treatment response was assessed at the eighth week after completion of reirradiation. The primary endpoint was pain relief for recurrent calcaneal spur, assessed using the Numeric Rating Scale pain intensity score at 6 months post-irradiation.

Results: A total of 103 patients with calcaneal spur who were irradiated for recurrent pain were included in the study. The ages of the study group ranged from 36 to 77 years with a median age of 52 years (range 36-77, interquartile range: 14) and male to female ratio was 1:4. Most patients with a spur size of 6 mm or greater required reirradiation for recurrent pain. Reirradiation resulted in a complete response in 58 patients (56%), a partial response in 31 patients (30%), and no response in 14 patients (14%); no radiation-related adverse effects were observed.

Conclusions: Reirradiation for recurrent calcaneal spur pain is an effective treatment option to relieve pain in selected patients where other treatment options do not work.

Introduction

Painful benign lesions have been intensively treated with low-dose radiotherapy since the 1950s. A better understanding of the mechanism of low-dose radiotherapy has been facilitated by advances in radiobiology related to radiotherapy. Currently, low-dose radiotherapy applied to benign target tissues in the management of refractory pain produces an effective anti-inflammatory response (1).

The German surgeon Plettner first described the calcaneal spur in 1900 as an abnormal plantar bony formation that can be visualized radiologically on the medial surface of the calcaneus. Chronic microtrauma and damage caused by pressure from

the spur on the sural and posterior tibial nerves induce pain (2). Its incidence varies between 8% and 88% in the general population (3,4). Obesity, female gender, and advanced age are major risk factors associated with increased incidence (5). Its typical symptom is a localized stinging pain in the heel region, increasing in intensity, especially in the morning when walking or standing. Although it is often asymptomatic, surgical treatment is occasionally used in cases of severe pain that do not respond to physiotherapy, steroid injections, or radiotherapy. Laser, ultrasound, and microwave treatments are alternative methods (6).

Reirradiation of heel spurs may be necessary when the capillaries supplying the sural and posterior tibial nerves are not adequately damaged during the initial irradiation to achieve complete neural blockade and pain relief. In this study, we aimed to document the benefit of reirradiation for recurrent heel spur pain.

Methods

Study design, participants and ethics

This single-center retrospective study included patients who underwent reirradiation between November 2016 and December 2024 for recurrent calcaneal spur pain after completion of the first radiotherapy course. Patients with a previous history of irradiation who developed recurrent pain and had at least 6 months of follow-up after the initial treatment were included. Patients younger than 35 years or weighing more than 120 kg were excluded.

The study was conducted in accordance with the Declaration of Helsinki, the World Medical Association's Code of Ethics, and the Uniform Requirements for Manuscripts Submitted to Biomedical Journals. The study was approved by the University of Health Sciences Türkiye Institutional Ethics Committee (decision no.: 2025-409, dated: 19.08.2025). All patients were provided with detailed treatment information, and informed consent was obtained from all patients.

Data collection

Among 1949 patients who underwent reirradiation for recurrent heel spur pain during the study period, 103 met the eligibility criteira and were included in the analysis. Recorded variables included, age, gender, the time between two radiotherapy treatments, pre- and post-treatment Numeric Rating Scale (NRS) scores for pain, and spur size. The distribution of patients by heel spur size is shown in Figure 1.

Radiotherapy protocol

Based on two-dimensional (2D) simulation, both calcaneal spurs were included in the treatment field and 8 Gy was delivered in two consecutive daily fractions via anteroposterior and posteroanterior portals using a Co-60 unit (Theratronics-Theratron 780-E serial nr: 672-1, Co-60 Teletherapy Machine). A pre-treatment radiograph of a patient diagnosed with a heel spur who received radiotherapy is shown in Figure 2. Figure 3 shows a 2D simulation image on the 2D simulator scopy screen in which the treatment portal covers bilateral heel spurs. Treatment response was assessed at the eighth week after completion of reirradiation.

Outcome assessment

NRS scores were recorded by questioning patients before reirradiation treatment and at two and six months after treatment, using a pain intensity scale ranging from 0 to 10. The primary endpoint was pain relief at 6 months following reirradiation.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences for Windows, version 20 (IBM Corp., Armonk, NY, USA). Pre- and post-treatment 6-month NRS scores were compared using the non-parametric Wilcoxon signed-rank test. Multivariate logistic regression analysis was performed to determine independent predictors of a complete pain response

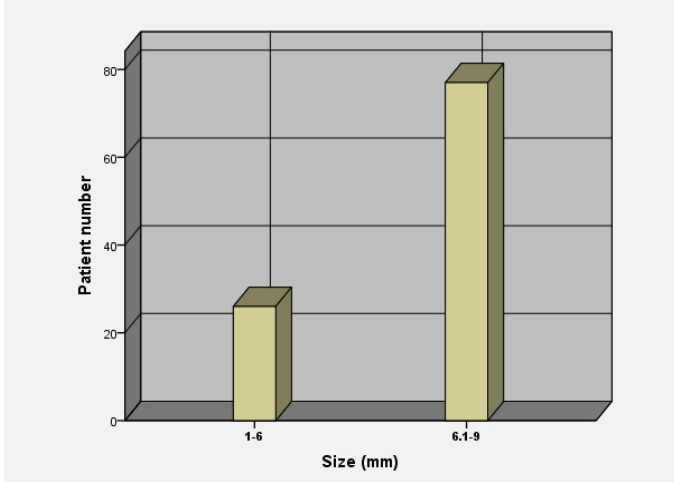

Figure 1. Distribution of patients by heel spur size

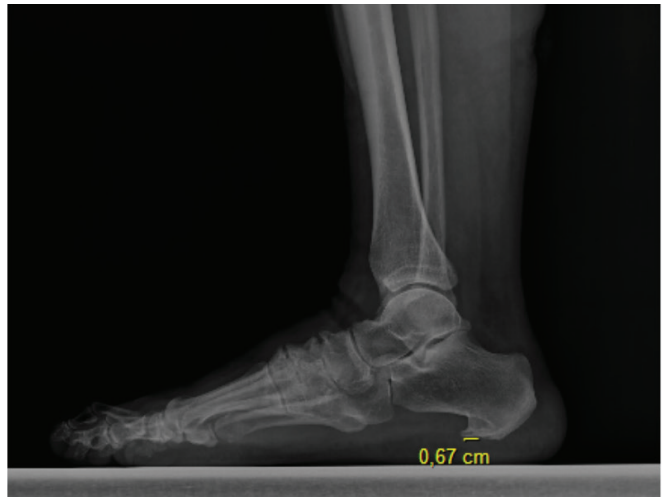

Figure 2. Plantar heel spur of a patient shown on radiograph

at 6 months. Variables with p<0.05 in univariate analyses were included in the model. Odds ratios (OR) and 95% confidence intervals (CI) were calculated. Correlations between pre-treatment NRS scores, heel spur size, and pain duration were assessed using Spearman's correlation test. A chi-square test was used to evaluate the association of heel spur size, pre-treatment pain intensity, and pain duration with response rate. A two-sided p-value less than 0.05 was considered statistically significant.

Results

A total of 1949 patients were treated with radiotherapy for a heel spur between 2016 and 2024; 103 of these patients (5.2%) required reirradiation for recurrence.

The median follow-up of the 103 recurrent patients was 24 months (range, 6-99 months). Of the 103 patients, 83 (80.6%) were female and 20 (19.4%) were male, with a F/M ratio of 4.2:1. Median age was 52 years (range, 36-77 years). Other details about patient characteristics are shown in Table 1. Adequate pain relief was achieved in 89 patients (86.4%). The median NRS score decreased from 6 (range 3-9) before reirradiation to 4 (range 2-7) at 2 months post-treatment and to 2 (range 1-5) at 6 months post-treatment. Changes in NRS scores before and after the second RT are shown in Figure 4.

A statistically significant difference in pain relief was observed between pre-reirradiation and 6-month post-treatment pain levels (Z=-8.854, p<0.001). No statistically significant correlation was observed between heel spur size and pre-treatment pain intensity (p>0.05). By contrast, analysis of response rates revealed a statistically significant association between pre-reirradiation pain intensity and complete response [χ^2 (2)=10.692, p=0.005)] (Table 2). The results show that patients with mild to moderate pain before reirradiation had a higher rate of complete pain relief compared with patients with severe pain (66.7% vs. 41.9%), and patients before reirradiation had a higher "no response" rate than those with mild to moderate pain (25.6% vs. 5.0%). Additionally, variables that were significant in the univariate analysis [pre-treatment pain intensity and pain recurrence interval from first radioation therapy (RT)] were entered into the multivariate logistic regression model, which showed that both pre-treatment pain intensity (OR=0.35, 95% CI: 0.15-0.80, p=0.013) and pain recurrence interval from first RT (OR=0.31, 95% CI: 0.13-0.77, p=0.011) were independent predictors of complete response (Figure 5). Patients with severe pre-treatment pain and those with a recurrence interval longer than 24 months were significantly less likely to achieve a complete response. No patient-reported acute or late toxicities were recorded in the patient files according to the Common Terminology Criteria for Adverse Events v5.0 toxicity assessment method.

Table 1. Characteristics of the reirradiated patients

Characteristics	Category	n (%)
Sex	Female	83 (80.6)
	Male	20 (19.4)
Age, years	≤50	45 (43.7)
	>50	58 (56.3)
	Median (range)	52 (36-77)
Pain duration before 2nd RT, months	≤12	69 (67.0)
	>12	34 (33.0)
Relapse duration, months	≤12	43 (41.7)
	>12	60 (58.3)
Spur size, millimeters	≤6	26 (25.2)
	>6	77 (74.8)

RT: Radiation therapy

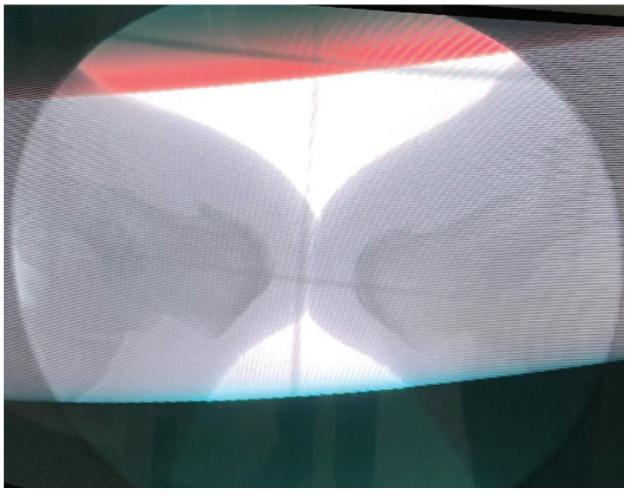

Figure 3. 2D simulation image showing treatment portal covering bilateral heel spur on 2D Simulator Scopy Screen
2D: Two-dimensional

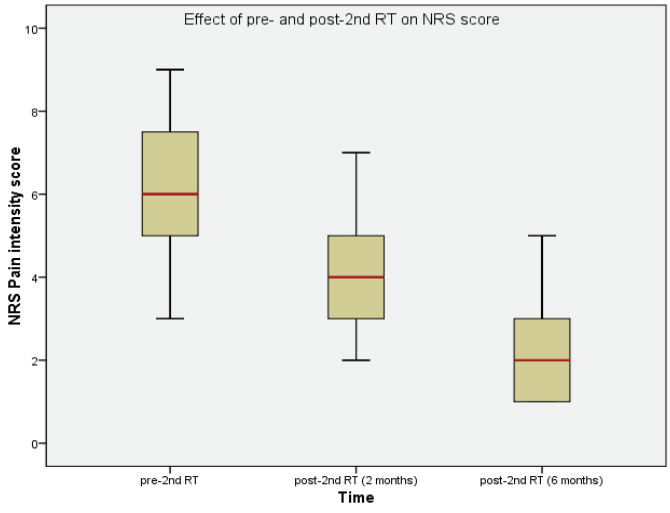

Figure 4. Comparison of NRS scores before and after the second radiotherapy
RT: Radiation therapy, NRS: Numeric Rating Scale

Table 2. Association between pre-2nd RT pain intensity and response to treatment

Response rate	Mild-moderate pain (n=60)	Severe pain (n=43)	p-value	Total (n=103)
Complete response, n (%)	40 (66.7)	18 (41.9)	0.005	58 (56.3)
Partial response, n (%)	17 (28.3)	14 (32.6)	0.645	31 (30.1)
No response, n (%)	3 (5.0)	11 (25.6)	0.07	14 (13.6)

RT: Radiation therapy

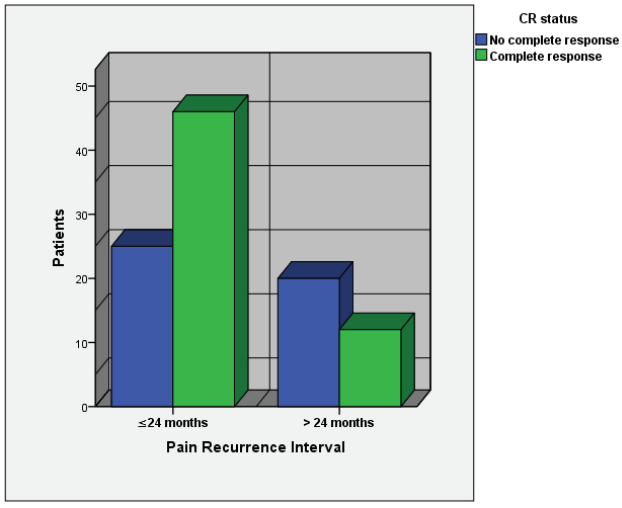

Figure 5. Distribution of complete response by pain recurrence interval
CR: Complete response

Discussion

Reirradiation for recurrent calcaneal spur pain demonstrated favorable clinical outcomes in this study. More than half of the patients achieved complete response, with additional patients experiencing partial improvement, and no radiation-related adverse effects were observed. The need for reirradiation was more common in patients with spur size ≥6 mm, suggesting a possible association between larger spur size and recurrent symptoms.

Non-malignant diseases do not always exhibit clinically benign features and may cause dysfunction and significant symptoms. The initial use of ionizing radiation for non-malignant diseases dates back centuries and was directed at traditional benign lesions amenable to radiotherapy, which were classified as hyperproliferative, degenerative, inflammatory, and functional. However, acute and late effects of radiotherapy have changed treatment concepts and indications. Achieving lasting pain relief and improved quality of life may justify the use of low-dose ionizing radiation for analgesic and anti-inflammatory effects. RT is a non-invasive option for patients with painful calcaneal spurs. Although the mechanism of pain relief after radiotherapy is not yet clearly defined, it has been suggested that radiation may exert analgesic effects through damage to small nerve endings or capillaries, thereby reducing nociceptive signaling. However, this explanation is not yet fully supported by experimental data (7). Sural and posterior tibial blockade achieved by radiation-induced occlusion of nourishing capillaries may result in partial or complete pain relief.

Numerous studies support the efficacy of low-dose irradiation in relieving pain from calcaneal spurs. In the study by Heyd et al. (7) evaluating two groups that received total doses of 3 Gy and 6 Gy, the pain response rate exceeded 80%, and there was no statistically significant difference in analgesic effect between the dose groups at the 6-month follow-up. In the large-scale study by Hermann et al. (8), which included 250 patients, the subgroup with the most pronounced analgesic effect was identified among patients with a spur size of ≤6.5 mm and those reporting pain for more than 12 months before treatment.

Data on reirradiation for recurrent calcaneal spur pain are limited (9,10). As reported in Hermann et al.'s (8) study, most refractory patients requiring reirradiation in our study had spur sizes of 6 mm or greater, while we did not observe a statistical correlation between spur size and pain intensity.

Radiation exerts its effect through endothelial damage, causing capillary microthrombosis and activating the coagulation system, which leads to hypoxia and ischemia in the capillaries. Radiation can also trigger endothelial cell death and cause thrombus formation on the exposed matrix, resulting in small vessel occlusion. Microangiopathy after radiation can lead to vascular insufficiency and infarction. The primary targets for pain relief are the nerves that transmit pain signals (11,12). The rationale for pain relief in heel spur patients may involve occlusion of the capillaries supplying the sural and posterior tibial nerves, thereby producing neural blockade of these nerves and alleviating pain (13,14). However, larger spurs measuring 6 mm or greater may have neural vasculature irregularities, such that occlusion of nerve-nurturing capillaries may not be achieved completely with the initial application of radiotherapy for nerve blockade to relieve pain, necessitating reirradiation for recurrence (12-14).

This study has several limitations. Firstly; due to its retrospective nature, there is a risk of selection bias in patient selection and data collection. Secondly; the study is single-center, which may limit the generalizability of the results. Thirdly; NRS scoring was used for pain assessment,as the primary endpoint; which is based on patients' subjective perceptions and is not supported by an objective biomarker. Furthermore, while a 6-month follow-up period is sufficient to assess the

effectiveness of radiotherapy, longer follow-up periods are needed to determine lengthy long-term recurrence rates and other late radiation-related side effects. Future prospective and randomized controlled trials will contribute to the validation of these findings.

Conclusion

Reirradiation with a total dose of 8 Gy delivered over two consecutive days appears to be an effective and well-tolerated approach for managing recurrent calcaneal spur pain. It offers a reliable, non-invasive treatment alternative for patients who do not respond adequately to conventional medical therapies.

Ethics

Ethics Committee Approval: This study was approved by the Gülhane Scientific Research Ethics Committee of the University of Health Sciences Türkiye (decision number: 2025/409, dated: 19.08.2025).

Informed Consent: Informed consent was obtained from all patients.

Footnotes

Authorship Contributions

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

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Successful treatment of an older patient with delayed neurological sequelae and delirium after carbon monoxide poisoning with memantine

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Keywords: CO poisoning, geriatrics, memantine, delayed neurological sequelae, delirium

ABSTRACT

Carbon monoxide (CO) poisoning can cause delayed neurological sequelae (DNS), a condition with no effective treatment. We report a 66-year-old male patient who recovered from acute CO poisoning but developed DNS and delirium one week later. He showed akinetic mutism, parkinsonism, rigidity, and cognitive impairment. Non-pharmacological approaches and donepezil were tried, but due to side effects, memantine (20 mg/day) was started. Over the course of one year, the patient showed significant improvement in neurological and functional status, with improvements in cognitive function (Mini-Mental State Examination: 26) and brain magnetic resonance imaging findings. This case suggests memantine may contribute to DNS recovery.

Introduction

Carbon monoxide (CO) poisoning is a major cause of death and illness worldwide, with an incidence and mortality rate of 137 and 4.6 per million individuals, respectively (1). Brain, heart muscles, kidneys, and skeletal muscles are among the most affected tissues (2). CO poisoning can lead to delayed neuropsychiatric sequelae (DNS), which refers to brain damage that emerges after a period ranging from a few days to six weeks following recovery from hypoxic injury (3). DNS occurs in 1-47% of individuals affected by CO poisoning. The clinical manifestations of DNS include motor dysfunction, gait abnormalities, autonomic dysfunction, seizures, and blindness (4). Currently, there is no effective treatment for DNS and the precise pathophysiological mechanisms remain to be elucidated.

This case report presents a patient who recovered from acute CO poisoning. Significant improvements in long-term neurological deficits were achieved with memantine treatment.

Case Presentation

Written informed consent was obtained from the patient for publication of this case report. A 66-year-old male patient was found unconscious by his relatives in a room in his house, which was heated with a coal stove and permeated by a strong smell of smoke. The patient had no history of chronic illness, regular medication use, smoking, or alcohol consumption. Upon arrival at the emergency department, his Glasgow Coma Score (GCS) was 3. Following reservoir oxygen therapy, GCS score increased to 11 (E4-M5-V2).

Analysis of the arterial blood gas sample revealed a pH of 7.35, lactate of 5.7 mmol/L, and carboxyhemoglobin level of 29.8%. Hyperbaric oxygen therapy (HBOT) was not administered because air trapping was detected in the upper lobe of the right lung on thoracic computed tomography (CT). The cranial CT findings of the patient, who had no previous cranial imaging, were normal when performed in the emergency department. He was hospitalized in the intensive care unit and high-flow normobaric 100% oxygen was administered (Figure 1a). After 12 days, the patient was discharged with normal neurological and general examination findings. Seven days after discharge, he was brought back to the hospital with complaints of inability to communicate, urinary incontinence, muscle stiffness, and inability to walk. On examination, akinetic mutism, parkinsonism, widespread trunk and extremity muscle stiffness, and a hypomimetic face were observed. Activity of daily living (ADL) score was 0 out of 6 (totally dependent), instrumental activities of daily living (IADL) score was 0 out of 5 (totally dependent), and the Mini-Mental State Examination (MMSE) score was 0 out of 30 (Table 1). Brain magnetic resonance imaging (MRI) T2-weighted images revealed diffuse hyperintensity in the bilateral hemispheric white matter, consistent with delayed leukoencephalopathy secondary to prior CO exposure. Additionally, hyperintense changes were observed in the bilateral globus pallidus regions (Figure 1b*). An electroencephalogram revealed bitemporal slowing of brain activity.

Based on these findings, the diagnosis of DNS and delirium after CO intoxication was considered. Non-pharmacological approaches were implemented. Plans for exercises to be performed at home were created by a physiotherapist. After one week, his diffuse rigidity had slightly lessened. His efforts to form sentences increased, and he began to recognize his relatives and indicate his need to urinate. At this visit, donepezil treatment was attempted for prolonged delirium; however, due to the development of insomnia and hallucination side effects, the medication was switched to memantine at a dose of 20 mg/day (Figure 1a). One month later, his rigidity decreased, he began to walk without assistance, and was able to eat by himself (Table 1). At the end of one year, ADL and IADL were independent

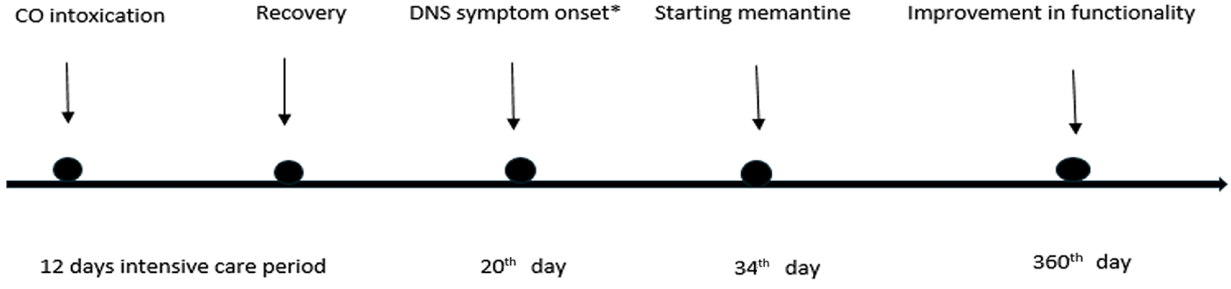

Figure 1a. The patient's course after acute CO poisoning
CO: Carbon monoxide, *DNS: Delayed neurological sequelae

Table 1. Detailed cognitive and functional evaluation on the day the patient presented with DNS symptoms and at the follow-ups

Time after exposure (days)	20	30	40	50	100	180	360
ADL (0-6)	0	0	1	2	6	6	6
IADL (0-8)	0	0	0	0	1	4	8
MMSE (0-30)	0	1	3	5	14	20	26
Clock drawing test (0-6)	0	0	0	2	2	4	5
Word fluency semantics*	-	-	-	-	-	6	14
Trail making test -A*	-	-	-	-	-	188	147
Trail making test -B*	-	-	-	-	-	Not completed	Not completed
Immediate recall short story*	-	-	-	-	-	3	5

*: These tests could not be performed on days 20, 30, 40, 50, and 100 due to the patient's developing cognitive dysfunction.
DNS: Delayed neurological sequelae, ADL: Activities of daily living, IADL: Instrumental activities of daily living, MMSE: Mini-Mental State Examination

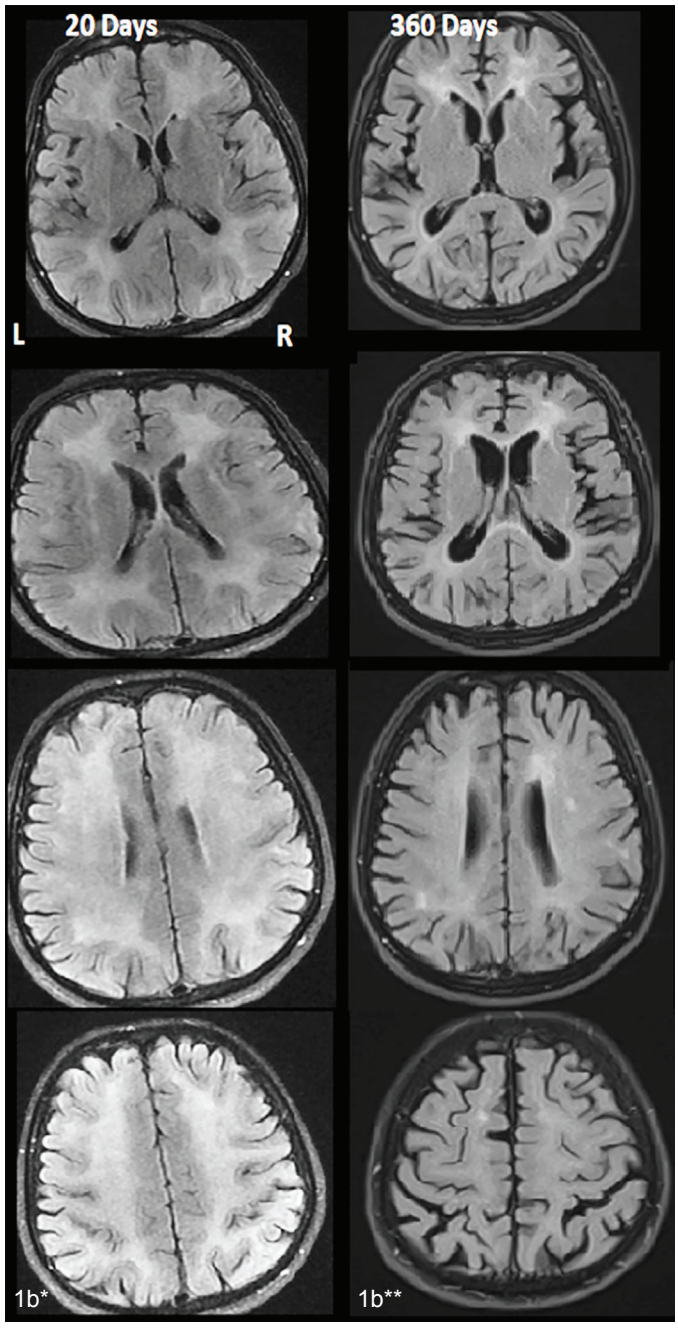

Figure 1b. Bilateral globus pallidus lesions, periventricular and deep white matter hyperintensities were seen on MRI 20 days after the first event (**Figure 1b***) and regressed after 1 year (**Figure 1b****)

L: Left, R: Right, MRI: Magnetic resonance imaging

(Figure 1a). Considering further detailed cognitive tests, the MMSE scores increased to 26 points after one year (Table 1). He was able to continue his work as a farmer and maintain his daily life. Follow-up brain MRI findings after one year showed that the diffuse hyperintensities had decreased (Figure 1b**).

Discussion

We showed for the first time that memantine hydrochloride treatment administered when DNS symptoms developed in an older adult following a recovery period after CO intoxication alleviated the neurological disorder and improved clinical status.

White matter demyelination is observed in the pathology of DNS, a rare complication that develops following a recovery period after CO intoxication. The mechanisms underlying this pathology are not well understood. Perivascular changes caused by N-methyl-D-aspartate activation and neuronal nitric oxide synthase overactivity, along with post-CO poisoning inflammation, sequester and activate neutrophils (5). Memantine may reduce this activated inflammatory response through its anti-inflammatory, neuroprotective, and hemodynamic effects mediated by glutamate receptor blockade (6). Experimental studies that found that memantine alleviated edema and infarction in rats with focal cerebral ischemia and reperfusion injury support this mechanism (7). To our knowledge, there is only one middle-aged case of DNS in which memantine was given (8).

DNS symptoms might be preventable or treatable. HBOT is considered a promising method for the prevention and treatment of DNS; however, there is no consensus on its effectiveness (9). In our case, HBOT could not be performed because of the risk of lung barotrauma. Other experimental treatments, including anti-inflammatory and immunomodulatory drugs, such as immunoglobulin, interferon, glatiramer acetate, and steroids, have been studied in clinical trials, but their success has been limited (10). The exact mechanism of CO toxicity remains unclear; however, because oxidative stress, neuronal injury, and ischemia-reperfusion-related damage contribute to the development of delayed symptoms, antioxidant therapies may offer a promising alternative treatment strategy (11,12).

As a result, successful clinical recovery from DNS in an older adult whom we monitored with detailed cognitive and functional tests and MRI during a long follow-up period, could be attributable to memantine treatment. Further clinical studies on this beneficial effect are required.

Conclusion

Our findings suggest that memantine treatment may have contributed to the significant neurological and functional improvement observed in an elderly patient with DNS following CO poisoning. While spontaneous recovery cannot be completely ruled out, the rapid improvement in cognitive and motor functions, as well as radiological findings, highlights the potential role of memantine in the management of DNS.

Ethics

Informed Consent: Written informed consent was obtained from the patient for publication of this case report.

Footnotes

Authorship Contributions

Concept: H.T.Y., Z.S.D., M.İ.N., Design: H.T.Y., Z.S.D., M.İ.N., Data Collection or Processing: H.T.Y., Z.S.D., C.A., Analysis or Interpretation: H.T.Y., Z.S.D., C.A., M.İ.N., Literature Search: H.T.Y., C.A., Writing: H.T.Y., Z.S.D., M.İ.N.

Conflict of Interest: All the authors declare that they have no conflicts of interest regarding this study.

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A diagnosis confused with hereditary angioedema: nephrotic syndrome

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Keywords: Hereditary angioedema, lupus nephritis, nephrotic syndrome

ABSTRACT

Hereditary angioedema (HAE) is a rare, autosomal dominant disease that primarily affects the skin, upper respiratory tract, and gastrointestinal system. Nephrotic syndrome (NS) is defined by the presence of severe proteinuria, low serum albumin levels, and generalized edema. Periorbital edema seen in NS can be confused with allergic edema or HAE. Accurate differential diagnosis is essential for appropriate treatment. This report presents a case of NS initially misdiagnosed as HAE.

Introduction

Hereditary angioedema (HAE) is an uncommon autosomal dominant condition that mainly involves the skin, upper airways, and gastrointestinal tract. Impaired C1 inhibitor (C1-INH) function or deficiency leads to excessive bradykinin generation, which increases vascular permeability and causes angioedema (AE) (1). Bradykinin-mediated AE does not respond to antihistamines (AH), corticosteroids (CST), or adrenaline. Attacks of AE typically last 2-5 days. Unlike mast cell-mediated AE, HAE-related AE is usually not accompanied by urticaria (2).

Nephrotic syndrome (NS) is defined by the presence of severe proteinuria, low serum albumin levels, and generalized edema. NS should be considered in the differential diagnosis of newly developed periorbital edema, which can resemble AE caused by allergies or other conditions (3,4).

We present a case of NS misdiagnosed as HAE.

Case Presentation

A 36-year-old male with a medical history of rheumatoid arthritis (RA) and chronic kidney disease presented to the emergency department with swelling in his hands and feet for one week, progressing to facial and periorbital edema over the past two days. He had been taking upadacitinib for RA and had undergone the right nephrolithiasis surgery 30 years ago. There were no similar past episodes, no abdominal pain, and no family history.

On physical examination, asymmetric edema was observed in the eyes, lips, and face (Figure 1A). There was no uvular edema or urticaria. Vital signs and systemic examination were normal. He received intravenous pheniramine 45.5 mg and dexamethasone 8 mg, without improvement. Due to unresponsive AE, he was administered 1000 international units (IU) plasma-derived C1-INH, (pdC1-INH), followed by 30 mg icatibant without clinical improvement.

Laboratory tests revealed hypoalbuminemia, proteinuria, and low C3 and C4 levels. Liver and thyroid functions, and C-reactive protein were normal. Complete blood count showed anemia and leukocytosis (Table 1). Anemia of chronic disease was considered. Consumption-related hypocomplementemia was considered due to low C3, C4, and C1q levels. In this case, the low level of C3, along with C4, normal determination of C1-INH level and function (Table 1), and the presence of edema that does not respond to pdC1-INH and icatibant treatment exclude the diagnosis of HAE. Nephrology consultation was obtained, diuretics were initiated, and the edema regressed (Figure 1B). A kidney biopsy was planned for the patient to investigate the causes of NS and for treatment planning.

Rheumatology consultation revealed antinuclear antibody, anti-double-stranded deoxyribonucleic acid, anti-Smith D1, lupus anticoagulant positivity, and hypocomplementemia, consistent with systemic lupus erythematosus (SLE). Kidney biopsy confirmed class IV lupus nephritis (diffuse proliferative necrotizing glomerulonephritis). Upadacitinib was discontinued, and pulse steroid therapy was started. During the service follow-up, the patient was intubated due to a sudden loss of consciousness, and brain computed tomography revealed findings consistent with subarachnoid hemorrhage. The patient underwent endovascular treatment of the intracranial aneurysm. The patient was transferred to intensive care and was pronounced deceased during follow-up.

Discussion

Bradykinin-mediated AE in HAE is not associated with allergies or urticaria. It presents with recurrent, spontaneously resolving edema. Patients with HAE frequently experience skin swelling and abdominal pain, with laryngeal edema being a potentially life-threatening manifestation (5,6). HAE can be fatal if not treated, due to laryngeal involvement. In cases of AH, CST, and adrenaline-unresponsive AE, HAE should be considered, and treatment should be initiated immediately (7). First-line treatment in acute attacks includes pdC1-INH and icatibant. pdC1-INH is administered via slow intravenous infusion. If the body weight is less than 25 kg between the ages of 2-11, 500 IU is administered; if the body weight is more than 25 kg, 1000 IU is administered. In adults, 1000 IU is administered. Icatibant, a bradykinin B2 receptor antagonist, is delivered via subcutaneous injection at 30 mg/3 mL. It is a ready-to-use product that does not require dilution (8-10).

This is a case report of an NS patient who was misdiagnosed as having HAE. Although HAE may be confused with NS, clinicians have to keep in mind laboratory parameters and systemic edema. In patients with persistent, bilateral, pitting edema unresponsive to AH and CST, clinicians should consider NS, particularly when accompanied by proteinuria and hypoalbuminemia. NS-related edema is influenced by gravity, unlike HAE.

Figure 1. (A) There is bilateral asymmetric edema in the eyes, lips, and face. (B) It is seen that the patients edema regressed following diuretic treatment

Table 1. Blood parameters

	Laboratory results	Reference range
Blood biochemistry		
Glucose (mg/dL)	90	70-107
Urea (mg/dL)	144	19-44
Creatinine (mg/dL)	2.48	0.7-1.2
ALT (u/L)	40	0-40
AST (u/L)	36	0-40
Total protein (g/dL)	5.4	6-8.3
Albumin (g/dL)	2.6	3.5-5.2
CRP (mg/dL)	18.5	0-5
Complete blood count		
Hemoglobin (g/dL)	9.4	13.4-17.6
Leukocyte count (x10^3/mm^3)	13.28	4.01-9.75
Platelet count (x10^3/mm^3)	315	151-387
Hormones		
TSH (mU/L)	6.01	0.4-4.2
Free T4 (ng/dL)	1.01	0.8-1.7
Rheumatological markers		
Rheumatoid factor (u/mL)	24.1	0-14
Anti-CCP IgG (u/mL)	6.7	<20
C3 (mg/dL)	43	90-180
C4 (mg/dL)	5	10-40
C1 esterase inhibitor (mg/dL)	42.2	18-40
C1 esterase inhibitor function (%)	>130	70-130
Complement C1q (mg/dL)	2.13	15.7-30.6
IgG (mg/dL)	1604	700-1600
IgA (mg/dL)	20.3	70-400
IgM (mg/dL)	196.2	40-230
PR3-ANCA (u/mL)	2.6	<10
MPO-ANCA (u/mL)	1	<5
Anti-dsDNA (u/mL)	>200	<20
Lupus anticoagulant	54.4	31-44
Antinuclear antibody	++++ (1/10000) Nuclear speckles and a cytoplasmic dense fine speckle pattern	
Anti-SS-A	+++	
Anti-SS-B	Negative	
Anti-SCL	Negative	
Anti-Jo-1	Negative	
Anti-RNP	+++	
Anti-ribosomal P	+++	
Anti-histon	++	
Anti-Sm D1	+++	
Serum amyloid A (mg/dL)	>30	<1
Urine analysis		
Protein (full urinalysis)	+++	
Protein (spot urine) (mg/dL)	234.5	0-30
Creatinine (spot urine) (mg/dL)	71.9	22-392
Protein/creatinine (spot urine) (mg/g)	3261.47	0-150

ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, CRP: C-reactive protein, TSH: Thyroid stimulan hormone, Anti-CCP: Anti cyclic citrullinated peptide, C3: Complement 3, C4: Complement 4, IgG: Immunoglobulin G, IgA: Immunoglobulin A, IgM: Immunoglobulin M, PR3-ANCA: Proteinase 3 anti-neutrophil cytoplasm antibodies, MPO-ANCA: Myeloperoxiase anti-neutrophil cytoplasm antibodies, Anti-dsDNA: Anti-double stranded deoxyribonucleic acid, Anti-SS-A, Anti Sjogren's syndrome-A, Anti-SS-B: Anti Sjogren's syndrome-B, Anti-SCL: Anti-scleroderma antibody, Anti-RNP: Anti-ribonucleoprotein, Anti-Sm D1: Anti Smith antigen

A thorough clinical history is essential, including pruritus, urticaria, triggering factors (food, insect bites, medication, exercise, stress, infections), concomitant diseases, family history, previous attacks, and treatment responses. AE can be histamine- or bradykinin-mediated. Histamine-mediated AE responds to AH and CST treatments, is symmetrical, and is usually accompanied by urticaria (9). Our case does not have these features. It has the features of bradykinin-mediated AE. Bradykinin-mediated AE types include HAE, acquired C1-INH deficiency, and AE due to angiotensin-converting enzyme inhibitor use. Acquired C1-INH deficiency can arise in patients with underlying disorders, including lymphoproliferative or autoimmune diseases, or in conditions that either reduce C1-INH levels or trigger the production of antibodies that neutralize C1-INH (7,9).

The following diseases should be considered in the differential diagnosis of AE: autoimmune diseases, thyroid diseases, superior vena cava syndrome, subcutaneous emphysema, and hypocomplementemic urticarial vasculitis (7,9).

In our case, other causes were considered because of the lack of response to HAE treatment, and the C1-INH level and function were also found to be normal. Thyroid and liver function tests were normal. There was renal dysfunction and proteinuria. Low complement and positive lupus autoantibodies suggested the diagnosis of SLE, and a kidney biopsy was performed.

Moreover, multiple studies have reported a higher prevalence of autoimmune disorders, particularly SLE, in patients with HAE, likely due to the chronic activation of early components of the classical complement pathway. Acquired C1-INH deficiency, however, is more frequently linked to lymphoma or monoclonal gammopathy of undetermined significance than to autoimmune conditions, including SLE, even in the presence of anti-C1-INH antibodies (11). The mechanisms by which the C1-INH enzyme is depleted or autoantibodies against C1-INH play a role are still being investigated. The therapeutic approach for acquired C1-INH deficiency centers on treating the underlying disorder (9).

Conclusion

This case emphasizes the importance of distinguishing NS from HAE. Clinical judgment, response to treatment, and laboratory parameters are essential for correct diagnosis.

There are several limitations in our case report. In our case, the low levels of C3 together with C4, the presence of SLE autoantibodies, normal C1-INH level and function; and the lack of response to HAE treatment excluded the diagnosis of HAE. Genetic evaluation can be conducted to identify HAE. This was not needed because there was no response to HAE treatment in our case. Anti-C1 antibodies should be checked for the diagnosis of SLE-associated acquired C1-INH deficiency, but could not be tested because the test was not available in our hospital. However, the treatment remains focused on addressing the underlying disease, obviating the need for additional diagnostic procedures.

Ethics

Informed Consent:

Footnotes

Authorship Contributions

Surgical Medical Practices: Ö.Ü., E.Ç.B., B.H., Consept: Ö.Ü., S.Y., Ö.K., Design: Ö.Ü., S.Y., Ö.K., Data Collection or Processing: Ö.Ü., E.Ç.B., Analysis or Interpretation: Ö.Ü., Ö.K., Literature Search: Ö.Ü., E.Ç.B., Writing: Ö.Ü.

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Augmentation of sertraline with aripiprazole in a case of treatment-resistant skin picking disorder

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ABSTRACT

Skin picking disorder (SPD) is a chronic psychiatric condition characterized by recurrent self-excoriation behaviors that often lead to marked psychosocial and functional impairment. Although the disorder is relatively prevalent and substantially disabling, therapeutic options for persistent and treatment-resistant cases remain scarce. The present case report discusses a 54-year-old woman with a three-decade history of SPD and coexisting depressive disorder who exhibited significant clinical improvement following combined treatment with sertraline and aripiprazole. This case underscores the potential clinical value of integrating selective serotonin reuptake inhibitors with atypical antipsychotics in addressing refractory forms of SPD.

Introduction

Skin picking disorder (SPD), which is among the obsessive-compulsive and related disorders in the Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5), is characterized by repetitive skin picking behavior and causes serious functional impairments (1). The prevalence of SPD varies between 1.4% and 5.4% (2). The disorder typically begins in adolescence and can persist throughout life. Studies have shown that SPD behaviors often involve multiple body parts (3). Skin picking triggers vary widely between individuals. Psychosocial factors such as stress, anxiety, boredom, fatigue, and anger often initiate the behavior, and the resulting scars worsen anxiety, contributing to a vicious cycle that negatively impacts social and occupational functioning (4).

Neuroimaging and neurobiological evidence point toward dysfunctions in cortico-striatal and limbic circuitry, implicating regions responsible for mood modulation, inhibitory control, and habit learning. Abnormalities in white matter connectivity and altered dopaminergic reward responses have been proposed as contributory mechanisms (5).

The course of SPD is usually chronic, and treatment-resistant cases are common. Early diagnosis and treatment are

critical to prevent functional impairments associated with SPD (6). However, Grant and Chamberlain (7) reported that 87.1% of individuals diagnosed with SPD never receive treatment. There is currently no accepted first-line pharmacotherapy for SPD. Similarly, no randomized controlled trials are investigating the effectiveness of augmentation strategies in treatment-resistant cases. Nonetheless, several case reports have indicated that combining selective serotonin reuptake inhibitors (SSRIs) with atypical antipsychotics such as aripiprazole, olanzapine, or paliperidone may lead to a marked reduction in skin-picking symptoms (8). This case report presents the significant clinical improvement of a female patient who had been followed for more than 30 years with a diagnosis of SPD and who had previously failed numerous pharmacological interventions.

Case Presentation

A 54-year-old, married, female patient presented with depressive symptoms including pessimism, lack of motivation, fatigue, and loss of interest and pleasure. The patient provided written consent for the publication of this case.

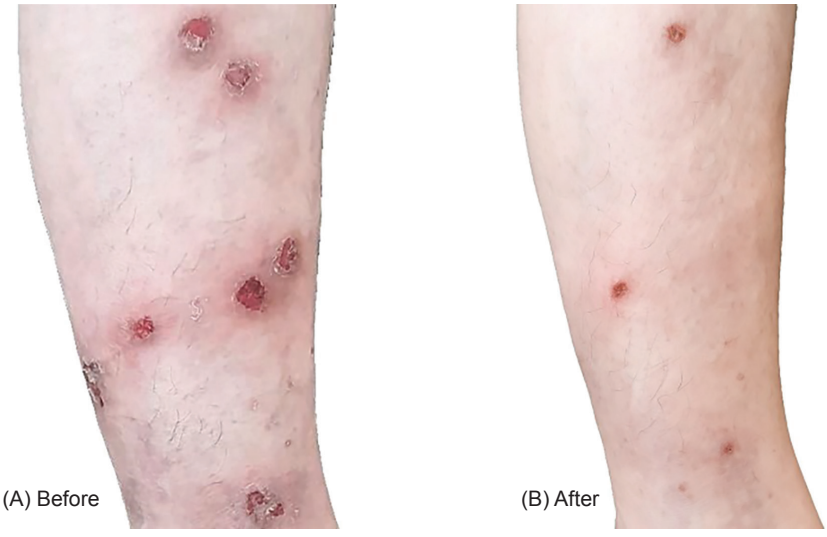
Over the past three decades, the patient experienced several recurrent episodes of depression and had undergone multiple pharmacological treatments, including clomipramine, citalopram, paroxetine, and risperidone. However, she had remained without psychiatric medication for approximately three years before presentation. Based on DSM-5 diagnostic criteria, she met the conditions for both depressive disorder and SPD (1). She exhibited obsessive-compulsive personality traits, including marked perfectionism, meticulousness, and strict adherence to rules. No criteria were met for a specific diagnosis of obsessive-compulsive disorder (Figure 1).

At the time of the interview, the patient reported no complaints of skin picking behavior. However, physical examination revealed skin-picking on multiple sites on her arms, legs, and abdomen. A detailed interview indicated that these lesions had been present for approximately 30 years, with their severity fluctuating over time but never fully resolving. She stated that she engaged in skin-picking behavior involuntarily, particularly during stressful and challenging situations. When asked about the behavior, she responded, “I don’t even realize I’m doing it until someone points it out”.

The patient denied any history of substance use. There was likewise no familial predisposition to dermatological conditions, and dermatologic evaluation revealed no primary dermatosis that could account for the observed lesions. Neurological assessment and standard laboratory investigations yielded results within normal ranges.

Treatment process

Sertraline therapy was initiated at a daily dose of 50 mg and gradually increased to 100 mg/day. After eight weeks of follow-up, a marked amelioration in depressive symptomatology was noted. However, no improvement was noted in skin-picking behavior, and new lesions had developed. Following a comprehensive evaluation, the same dose of sertraline was continued, and off-label augmentation with aripiprazole at a dose of 5 mg/day was initiated. The rationale for the combination therapy was explained to the patient, and written informed consent was obtained. After the addition of aripiprazole, a noticeable reduction in skin-picking behavior was observed starting from the fourth week. By the twelfth week, the patient’s score on the skin-picking-adapted version of the Yale-Brown Obsessive Compulsive Scale modified for Neurotic Excoriation (NE-YBOCS) (9) had decreased from 24 to 9, corresponding to an approximate clinical improvement of 62.5%.



(A) Before (B) After

Figure 1. The lesions on the arms, abdominal area, and legs caused by skin picking significantly improved with the sertraline + aripiprazole combination [appearance of the lesions on the patient's right leg before (A), and after treatment (B)]

Discussion

This case is noteworthy in demonstrating that significant clinical improvement can be achieved in the course of chronic and treatment-resistant SPD through an appropriate pharmacological strategy.

The neurobiological basis of SPD involves dysfunctions in the serotonergic and dopaminergic systems (10,11). Within this framework, SSRIs are considered the primary pharmacologic option. Evidence from a double-blind, placebo-controlled clinical trial evaluating fluoxetine in patients with neurotic excoriation demonstrated its therapeutic efficacy. Similarly, sertraline and escitalopram have also been shown to be effective in the management of SPD (2).

However, in cases where SSRI monotherapy fails to produce an adequate clinical response, the addition of atypical antipsychotics is considered a viable augmentation strategy (12,13). Moreover, several case reports have suggested that dopaminergic reward pathways may serve as important pharmacological targets in SPD, thereby making antipsychotics a particularly suitable class of agents (14,15). Aripiprazole functions as a partial agonist at 5-hydroxytryptamine (5-HT)1A receptors, an antagonist at 5-HT2A receptors, and a partial agonist at dopamine D2 receptors. Through its modulatory action on D2 receptors, it exerts therapeutic benefits, particularly in disorders characterized by impaired impulse control. Consistent with this pharmacodynamic profile, a previous case of treatment-resistant SPD reported that adjunctive aripiprazole with venlafaxine,a serotonin-norepinephrine reuptake inhibitor used for anxiety and depressive disorders-resulted in complete remission of the picking behavior (15).

This case highlights that the combination of sertraline and aripiprazole may be an effective pharmacological treatment option, particularly in chronic and treatment-resistant cases of SPD. However, this case report is uncontrolled in nature and the observed improvement may partly reflect a placebo effect. Additionally, while the NE-YBOCS provides a structured measure for skin picking symptoms, depressive symptoms were not assessed with a structured-standardized scale. Future case reports and clinical studies should integrate such validated tools to strengthen clinical rigor.

Ethics

Informed Consent: The patient provided written consent for the publication of this case.

Footnotes

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ERRATUM

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