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Review

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Nigella Sativa in the Prevention and Treatment of COVID-19 and Respiratory System Diseases: A Systematic Review and Meta-analysis

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Abstract

This systematic review and meta-analysis aimed to determine the effects of Nigella sativa (NS) on respiratory diseases and COVID-19. The identified search terms were used to search PubMed, Scopus, and Web of Science, the Cochrane Library, Ovid, Google Scholar, and EBSCO CINAHL databases through 18 June 2022. The risk of bias was assessed using Cochrane's ROB2 and ROBINS scales. The meta-analysis and systematic review included 16 studies with a total of 1991 participants. Among the publications included in the study, 11 were randomized controlled trials, 2 were non-randomized clinical trials, 1 was a single-group clinical trial, 1 was a case/placebo study, and 1 was a non-randomized survey study. Nigella sativa was found to have a positive effect on COVID-19 [odds ratio =1.80, 95% confidence interval (CI) =0.21-3.28]. The mean effect size of NS supplementation in respiratory diseases was 1.25, and Cohen's d (95% CI) ranged from 0.25 to 2.24. As a result, sufficient evidence was found to conclude that the intervention had a positive effect on the experimental group (z=2.46, p=0.01). In people with COVID-19, the group receiving NS supplementation had a higher recovery rate and a lower hospitalization rate. Fewer patients were infected in the group that received NS supplements for protection against COVID-19. Adverse effects reported include insomnia, daytime lethargy (when administered orally), excessive nasal dryness, stomach upset, and headache. There was insufficient evidence that prophylactic use of NS has a positive effect for COVID-19 or respiratory diseases.

Keywords: Nigella sativa, COVID-19, respiratory tract diseases, meta-analysis as topic, systematic review

Introduction

Diseases of the respiratory system are a serious global health problem (1). Chronic respiratory diseases pose significant global health challenges and impose severe socio-economic burdens on individuals and society. Chronic respiratory diseases cause significant problems worldwide and impose substantial socio-economic burdens on individuals and society. Chronic obstructive pulmonary disease (COPD) affected approximately 213 million people in 2021 (2).

The COVID-19 pandemic caused 5.7 million deaths over a two-year period, and non-COVID-19 lower respiratory tract infections (LRTIs) led to 344 million cases and 2.18 million deaths in 2021 (3,4). Although no effective treatment for COVID-19 infection is known, the recommended general measures are supportive (5). The inability to fully treat some respiratory diseases, patients' desire for rapid recovery, or economic inadequacies direct people to traditional and complementary medicine (6).

Nigella sativa (NS), which has been used for thousands of years as a spice and food preservative, to cure various ailments, and to protect against diseases, is a flowering plant that grows in Southern Europe and some parts of Asia. Nigella sativa is nutrient-rich and is considered one of the most valuable plants in world history. Nigella sativa seeds contain significant levels of calcium, iron,

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phosphorus, zinc, copper, pyridoxine, thiamine, niacin, and folic acid (7). Studies have reported that NS can be used as an anti-inflammatory and antiviral agent (8). Nigella sativa contains pharmacologically active constituents, such as thymoquinone, dithymoquinone, and nigellin, and has been associated with airway relaxation and reduced airway hyperresponsiveness in preclinical asthma models (9). In a clinical study in which NS was applied to patients with rhinitis and nasal mucosal congestion, NS reduced itching, rhinorrhea, sneezing episodes, turbinate hypertrophy, and mucosal pallor (10).

No meta-analyses or systematic literature reviews on the effect of NS on respiratory diseases, including COVID-19 were found. Researchers note the high prevalence of respiratory diseases in the population and the wide range of effects of NS, despite the absence of an effective treatment for COVID-19. The potential role of NS in preventing or treating respiratory diseases and COVID-19 has not yet been clearly established. Therefore, this systematic review and meta-analysis was designed to determine the effect of NS on respiratory diseases and COVID-19. It will be the first systematic review and meta-analysis to evaluate the effectiveness of NS in COVID-19 and respiratory diseases, and its results are expected to fill a gap in the literature.

Materials and Methods

Study Registration

Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed in this systematic review. The study protocol was uploaded to PROSPERO. PROSPERO ID: CRD4202125aldwi80 (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021254480). Details of the systematic review were developed in accordance with the Cochrane Handbook for Systematic Reviews of Interventions (11).

Design and Search Strategy

The PICOS approach was followed in designing the study, comprising participants, intervention, comparison, outcomes, and study design. These details were explained as subheadings. Based on the PICOS strategy, the following research question was formulated: "Do NS and NS derivatives affect the disease process when used in the prevention and treatment of respiratory diseases and infections, including COVID-19?"

No date or age restrictions were applied in the systematic literature review. All academic publications in English to date were included. PubMed, Scopus, Web of Science, Cochrane Library, OVID, Google Scholar, and EBSCO CINAHL databases were. Search terms were derived from MeSH terms (Supplemental file). The databases were searched for the specified terms in the title, abstract, and keywords. The first searches were conducted between 20 December 2021 and 15 April 2022. Second searches were conducted on 18 June 2022 before the meta-analysis was performed. The search was carried out by two independent researchers (S.T. and P.I.), and all titles and abstracts were examined according to inclusion and exclusion criteria by the same two independent researchers. Prior to analysis, a second search was conducted and newly identified publications were included in the study. Data extraction and risk of bias assessments were also performed independently by two authors (S.T. and P.I.). A third investigator (H.S.) checked the extracted data. The following extracted data were recorded in Excel format for each study: respiratory disease studied, authors, title, date, country where the study was conducted, study objective, treatment duration, sample size, mean age of participants, study design, outcomes examined, intervention content, control methods, and results. The Template for Intervention Description and Replication (12) guideline was used to report the details of the intervention. The following were summarized: what the intervention was; how and where it was applied, the duration and dose of application; the method of application, and to whom it was administered. Mean and standard deviation were used to report age (Table 1).

Inclusion criteria: Related to the respiratory system or COVID-19 and the use of NS and its products. Randomized controlled studies (RCTs), clinical controlled studies, case-control studies, and non-randomized survey studies were included.

Exclusion criteria: In vitro studies, studies on animal models, in silico drug trials, protocol studies, studies using other herbal mixtures with NS, and studies not in English.

Population/Participants and Interventions/Comparison

To maximize study capacity, no exclusions were made based on participant type. Participants diagnosed with COVID-19 and other respiratory diseases were included regardless of age, gender, or ethnicity.

Supplementation with NS and its derivatives constituted the intervention. The comparison group consisted of those who did not receive NS supplements and instead received a placebo, routine control, or standard care. Since this study investigated the treatment and preventive effects of NS, studies without a comparison group were also included. Only one of the studies included in the meta-analysis was a non-randomized questionnaire study; however, because it included both a control and an experimental group, it was retained in the meta-analysis.

Outcome

The primary outcomes were the resolution rate of respiratory diseases and COVID-19 symptoms, hospitalization and length of stay, and infection status. No restrictions were placed on additional results. Clinical measurements included hematological parameters, respiratory function tests, including forced vital capacity (FVC), blood eosinophil levels, immunoglobulin E (IgE) level, serum cytokine levels, respiratory rate, wheezing, oxygen saturation, asthma symptom scores, interferon-gamma (IFN-g) interleukin-4 (IL-4) levels, and disease-specific clinical findings (fever, cough, anosmia, fatigue, headache, myalgia).

Risk of Bias

Two independent researchers (ST and PI) evaluated the studies included in the study for the risk of bias. To evaluate the risk of bias, the Cochrane Handbook for Systematic Reviews of Interventions guidelines were used (11). The Risk of Bias Scale (RoB2), was used for randomized controlled studies, and the ROBINS-I scale was used for non-randomized studies. Risk of bias assessment for randomized trials includes a randomization process, deviation from intended intervention, missing outcome data, measurement of outcomes, and selection of outcome reports. For non-randomized studies, domains include confounding, selection of participants, classification of interventions, deviation from the intended intervention, missing outcome data, measurement of outcomes, and selection of outcome reports. As a result of the evaluation of each category, RCTs were defined as Low, High, and Of Some Concern, and non-RCTs were defined as Serious, Moderate, and Low.

Statistical Analysis

The RevMan program was used for the meta-analysis. When comparing effects measured by continuous quantitative data, the effect size was calculated as the mean difference (MD) between groups. The statistical significance level was set at α=0.05 and the results were reported with a 95% confidence interval (CI). It is critical to assess heterogeneity when examining the differences between the studies included in the research, i.e., whether the studies show effects in the same direction and of similar magnitude. Although heterogeneity can be assessed using the traditional Cochrane Q statistic (χ^2, p<0.10), as well as measures such as Tau² and I², this study primarily relied on the I² statistic. This approach quantifies the proportion of total between-study variation attributable to true heterogeneity, facilitating clearer interpretation of the consistency of meta-analysis findings. Accordingly, I² values were presented alongside effect sizes and CIs, enabling a comprehensive assessment of both the statistical significance of the results and the consistency across studies.

Results

Study Selection

A total of 3342 publications were identified as a result of database searches. After removing 756 duplications, 2,586 publications remained. The titles and abstracts of these publications were examined in line with the inclusion/exclusion criteria. Studies using other herbal supplements in conjunction with NS were also excluded. A total of 2,385 publications that did not meet the criteria were excluded. After evaluating the remaining 201 full texts, 185 publications were excluded because the necessary data could not be obtained and the results were unsuitable for the purposes of this study; the remaining 16 publications were included in the systematic review and meta-analysis. Among the publications included in the study, 11 were RCTs, two were non-randomized clinical trials, one was a single-group clinical trial, one was a case-placebo study, and one was a non-randomized survey study. The flowchart illustrating study selection is presented in Figure 1.

Description of Included Studies

This analysis included 16 studies involving patients with respiratory tract diseases or COVID-19, conducted between 2007 and 2021, comprising a total of 1,991 patients. The studies were conducted in Indonesia (n=2), Iran (n=4), Iraq (n=2), India (n=1), Egypt (n=1), Saudi Arabia (n=4), Pakistan (n=1), and Türkiye (n=1). The clinical areas examined were asthma (n=6), COPD (n=1), LRTI (n=1), COVID-19 (n=3), rhinosinusitis (n=1), and

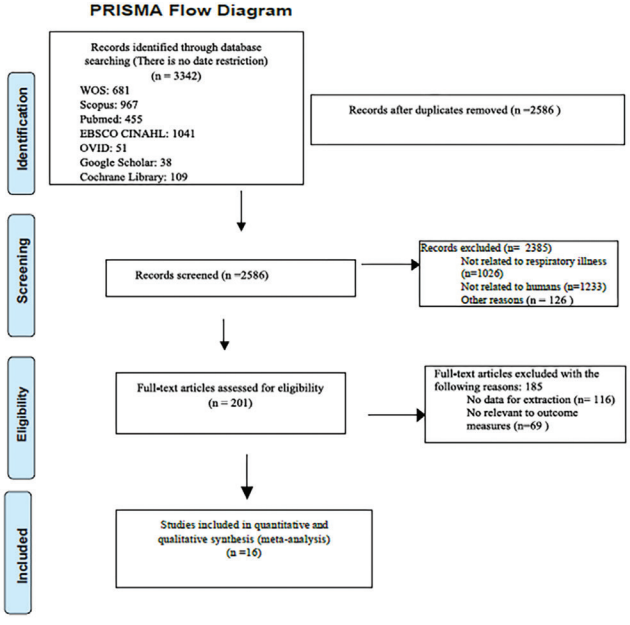

Figure 1. PRISMA flow diagram for study selection

PRISMA: Preferred Reporting Items for Systematic reviews and Meta-analyses

allergic rhinitis (n=4). Nigella sativa was administered in different forms and doses, and its efficacy was evaluated using condition-specific criteria: nasal mucosal eosinophils and IgE levels, symptom scores, hematological parameters (polymorphonuclear leukocyte functions and lymphocyte counts), blood eosinophilia, symptom severity, and vital signs in allergic rhinitis; endoscopic evaluation and Sino-Nasal Outcome Test-22 (SNOT-22) scores in rhinosinusitis; Asthma Control Test scores, pulmonary function tests, blood eosinophilia, serum IgE and cytokine levels, FVC, Th1/Th2 balance, and IFN-g/IL-4 levels in asthma; respiratory rate, wheezing, inspiratory-to-expiratory ratio, use of accessory muscles, and oxygen saturation in LRTI; hematological and biochemical parameters in COPD; and clinical symptoms and hospitalization outcomes in COVID-19. Detailed characteristics of the publications included in the study are presented in Table 1.

Risk of Bias

According to the Cochrane RoB2, one study (13) demonstrated a low risk of bias across all five domains. Appropriate random sequence generation and allocation concealment procedures were implemented in five studies during the randomization process (13-17). Three studies were rated as having "some concern" due to insufficient information regarding allocation concealment (18-20). Three studies were judged to have a high risk of bias because of inadequate concealment of allocation (21-23).

Four studies were rated as having a low risk of bias related to deviations from intended interventions (13,16,19,23). Six studies were classified as having "some concern" because healthcare providers were aware of the assigned interventions (14,17,18,20-22). One study was rated as having a high risk of bias due to uncertainty regarding baseline group balance (15). All studies with missing outcome data were assessed as having a low risk of bias. In the fourth domain, one study was judged to be at risk of bias because outcome assessors were aware of the intervention assignment (23). Six studies were assessed as having "some concern" due to insufficient information regarding whether outcome selection adhered to a pre-specified analysis plan (15,16,18-20,22).

In the ROBINS-I assessment of non-randomized studies, all were judged to have a low risk of bias with respect to participant selection, intervention classification, and selection of reported outcomes. However, one study was rated as having a serious risk of bias because it excluded participants with missing intervention status data (10). Risk-of-bias summary tables for the included publications are presented in Figures 2 and 3.

Outcome

The results of the studies included in the systematic review are presented in narrative form.

Effect of Nigella Sativa on Respiratory Disease

Asthma: Several studies have reported improvements in pulmonary function and immune parameters in patients with asthma receiving NS. Boskabady et al. (24) observed significant increases in forced expiratory volume in 1 second (FEV_1), maximum mid-expiratory flow, and peak expiratory flow (PEF) after administration of 100 mg/kg of NS extract, although the improvements were smaller than those observed with theophylline. Another study using 15 mL/kg of a 0.1% boiled NS extract in combination with standard therapy reported a decrease in FEV_1 at the end of the study period (15). Nigella sativa supplementation as an adjunct therapy showed 1-4% improvements in predicted FEV_1; however, these changes were not statistically significant (16). Salem et al. (17) reported significant increases in FEV_1 and PEF with 1-2 g/day of NS administered over 6-12 weeks. Nigella sativa supplementation also reduced peripheral eosinophil counts and IgE levels and modulated immune responses by increasing the Th1/Th2 ratio, reducing the proportion of Th17 cells, and increasing IFN levels in some studies (16-19).

Lower Respiratory Tract Infection (LRTI): Nigella sativa inhalation (0.1 mL/kg/day) combined with standard therapy improved peak expiratory flow rate (PEFR); however, the differences were not statistically significant (21).

In patients with COPD, daily supplementation with 2 g of NS for three months significantly improved all respiratory function parameters compared with controls, with greater percentage changes observed in FEV_1%, FVC%, FEV_1/FVC%, PEF, and forced expiratory flow 25-75% (14).

Nigella sativa supplementation or topical application significantly alleviated symptoms of rhinitis and rhinosinusitis. Nikakhlagh et al. (10) reported decreases in severe rhinorrhea, nasal itching, and sneezing by day 30. Ansari et al. (25) observed reductions in daytime symptom scores from 23.86 to 2.9 by day 14. Alsamarai et al. (22) reported improvements in rhinorrhea (100%), sneezing (89.7%), nasal itching (90%), and nasal obstruction (73.5%). Işik et al. (20) demonstrated enhanced polymorphonuclear leukocyte phagocytosis and intracellular killing. Patients with chronic rhinosinusitis using NS nasal spray showed significantly lower SNOT-22 scores compared with controls (NS: 14.87±5.01; controls: 23.15±5.01) (13).

Effect of Nigella Sativa on COVID-19

Three studies evaluating NS and COVID-19 were included. Al-Haidari et al. (26) conducted a study assessing the protective effects of NS against COVID-19, in which participants received an oral dose of 40 mg/kg NS once daily. The study reported a lower incidence of infection in the NS group [68 (36.2%)] compared with the

control group [180 (95.7%)]. Aldwihi et al. (27) examined the association between dietary supplement use and hospitalization rates among individuals with COVID-19 before and during infection. Their findings indicated that hospitalization rates were lower among individuals classified as NS users [85 (24.6%)] compared with those who did not use dietary supplements [152 (38.7%)], and this difference was statistically significant. Koshak et al. (23) administered 500 mg of NS supplements twice daily for 10 days to evaluate the effect of NS on recovery in patients diagnosed with COVID-19. The study reported a higher recovery rate in the NS group [57 (63%)] compared with the control group [32 (35%)].

Meta-Analysis

Effect of Nigella Sativa Supplementation on COVID-19

Two studies evaluated the effect of NS supplementation on COVID-19. The pooled data analysis indicated that NS supplementation was associated with a positive effect size on COVID-19 outcomes (Figure 4). In a meta-analysis of two studies including 551 patients with COVID-19, NS was shown to be effective in improving COVID-19-related symptoms odds ratio [odds ratio (OR)=10.07, 95% CI: 6.55-15.49; p<0.001; I^2=98%)]. In study (26), the effect of NS was substantial (OR=37.94; 95% CI=17.59-81.84), accounting for 19.9% of the total weight of the analysis. The other study (23) reported a lower, but still significant, (OR=3.14; 95% CI=1.72-5.75) and contributed 80.1% of the total analysis weight. Significant heterogeneity between studies was observed (I^2=96%; p<0.00001), indicating high variability among the results.

Effect of Nigella Sativa Supplementation on Asthma

To determine the effect of Nigella sativa in asthma patients, meta-analyses were conducted on three different parameters: Asthma Control Test (ACT) score, IFN-gamma, and IL-4.

ACT Score

In the analysis of 3 studies and 158 patients examining the effect of asthma patients on ACT score, NS increased ACT scores and improved asthma control. [Mean difference (MD): 1.22 (CI 95%: 0.42-2.03; p=0.003; I^2=0%)]. No significant heterogeneity was found among the studies included in the analysis (I^2=0%; p=0.76), indicating that the results of the studies were consistent with each other (Figure 5).

IFN-Gama

In two studies examining IFN-γ levels in asthma patients and in an analysis of 78 patients, NS significantly increased IFN-γ levels [MD: 5.46 (95% CI: 3.04-7.88); p< 0.001; I^2=91%] (Figure 6).

In two studies examining IL-4 levels in asthma patients (n=78), NS significantly reduced IL-4 levels [MD: -0.32 (CI 95%: -0.61-0.03); p=0.03; I^2=0%] (Figure 7).

Effect of Nigella Sativa Supplementation on Rhinitis

In two studies and in an analysis of 127 patients, NS was significantly effective in improving rhinitis symptoms [OR: 26.12 (CI 95%: 7.87-86.66); p<0.001; I^2=0%] (Figure 8).

Safety

The meta-analysis focused on the effect of NS on COVID-19 and respiratory diseases, while safety data on the treatment were also analyzed. Only three studies reported adverse events. In a report of 23 patients with allergic rhinitis who received NS, insomnia occurred in one patient (4.3%), and daytime lethargy after oral administration occurred in two patients (8.6%) (25). Excessive nasal dryness (17.8%) has been reported after 5-12 days of topical NS use in patients with allergic rhinitis, and nasal dryness and diarrhea have been reported after systemic use (22). Adverse events (stomach upset, headache, and insomnia) were reported in three patients in total: two of 40 in the experimental group and one of 40 in the placebo group among asthma patients administered NS (16). In general, adverse events were reported to be mild. In the analysis of three studies reporting side effects of NS, there was no significant difference in side effects between NS and the control group (OR=0.88, 95% CI: 0.39-1.96; p=0.75; I^2= 67%) (Figure 9).

Discussion

Respiratory diseases have high mortality and morbidity rates worldwide, and COVID-19 is among them (4,28). Considering the high morbidity and mortality of these diseases, alternative and complementary medicine practices have become increasingly adopted for prevention and treatment; NS has become one of the most widely used medicinal plants (29). Thymoquinone has been reported to inhibit nuclear factor kappa-B signaling pathways by suppressing proinflammatory cytokines (IL-6, TNF-α, and IL-1β), and it has also been found to potentially bind to the spike protein and the main protease of severe acute respiratory syndrome coronavirus 2 (30). Nigella sativa has antiviral, antibacterial, antifungal, antiparasitic, antioxidant, anti-inflammatory, immunomodulatory, anticancer, antidiabetic, anti-obesity, hypolipidemic, neuroprotective, cardioprotective, hepatoprotective, antihypertensive, pulmonary-protective, nephroprotective, and gastroprotective effects, as well as effects on fertility and reproduction. It has also been scientifically shown to have skin-protective, anti-osteoporotic, bone-regenerative, and anti-arthritic effects (31,32). Due to these properties, this study was designed to determine the effect of NS on respiratory diseases and COVID-19.

Table 1: Characteristics of the studies included in the systematic review

Disease	Author Year, Country	Title of the study	Objective	Sample Size (I:Intervention, C:Control Group)	Age (Mean±SD)
Asthma	Boskabady et al. 2007, (15) Iran	The possible prophylactic effect of Nigella sativa seed extract in asthmatic patients	Prophylactic effect of boiled N.Sativa extract on asthma.	29 I: 15 C:14	C: 48.20±11.91 I: 35.87±12.79
Asthma	Koshak et al.(16) 2017, Saudi Arabia	Nigella sativa Supplementation Improves Asthma Control and Biomarkers: A Randomized, Double-Blind, Placebo-Controlled Trial	To determine the clinical and inflammatory effects of Nigella Sativa in asthmatic patients.	80 I:40 C: 40	I:39±13 C:42±15
Asthma	Salem et al. (17) 2017, Saudi Arabia	Effect of Nigella sativa supplementation on lung function and inflammatory mediators in partly controlled asthma: a randomized controlled trial	Effect on airway inflammation and airflow limitation in partially controlled asthma patients.	76	C: 37.1 Group Nigella Sativa-1: 37.5 Group Nigella Sativa-2: 39.2
Asthma	Barlianto et al.(18) 2017, Indonesia	Effects of Nigella sativa oil on Th1/Th2, cytokine balance, and improvement of asthma control in children	To investigate the potential anti-asthmatic effect of Nigella sativa oil on Th1/Th2 cells, IFN-g/IL-4 cytokines, and improvement of asthma control	28 C:14 I: 14	I:8.79±2.940 C:8.71±3.771
Asthma	Barlianto et al.(19) 2018, Indonesia	Improvement of Th17/Treg balance and Asthma Control Test score by Nigella sativa supplementation in asthmatic children: a new approach to managing asthma	To investigate the impact of Nigella sativa on Th17/Treg balance and asthma control in children with asthma.	28 C :14 I: 14	C: 8.71±3.771 I: 8.79±2.940
Asthma	Boskabady et al.(24) 2010, Iran	Antiasthmatic effect of Nigella sativa in airways of asthmatic patients	To investigate the antiasthmatic effect of Nigella Sativa extract in asthmatic patients.	15	42.80±11.42

Table 1: Continued

Study Type	Analyzed Findings	Duration of Treatment /Intervention	Control	Outcome Measures
Randomized Controlled Study	Asthma symptom score, Pulmonary function test. Forced vital capacity	12 Weeks Patients with a previous diagnosis of asthma and two or more of the following symptoms were included: recurrent wheeze, recurrent cough or tightness at rest; wheeze, cough or tightness during the night or early morning; wheeze or cough during exercise, having forced expiratory volume in 1 s (FEV1) and peak expiratory flow (PEF) less than 80% of predicted values, had no history or symptoms of cardiovascular or other respiratory diseases that required treatment Standard asthma treatment + 15 mL/kg of 0.1% g boiled extract daily.	Standard asthma treatment + placebo glucose solution	Nigella Sativa was found to have a positive effect on Asthma.
Randomized Controlled Double blind	Primary outcome: Asthma Control Test (ACT) score Secondary outcome: SFT, blood eosinophils, serum IgE results	4 Weeks 2*500 mg Nigella Sativa Capsules (oral) Patients diagnosed with asthma according to the Global Initiative for Asthma Guidelines	2*500 mg capsules of olive oil in the same image	It showed that Nigella Sativa supplementation improved asthma control with a tendency to improve respiratory function.
One Blind Placebo Randomized Controlled Trial	Clinical evaluation, spirometry, fractional exhaled nitric oxide (FeNO), and serum (IgE) measurements were performed. Blood samples were taken to measure serum cytokine levels only during visit 0 and visit 2.	12 Weeks Patients with partially controlled asthma, according to the Global Initiative for Asthma guidelines NS-1 group: 2x500mg N.Sativa capsules per day. NS-2 group: 2 g N.Sativa 2 Capsulesx500 mg capsules per day Weeks 6 and 12 were evaluated twice. All medications were taken for 12 weeks in addition to maintenance inhaler therapy.	Control Group: Received placebo one capsule two times a day.	Inhaled Nigella Sativa maintenance therapy improves measures of pulmonary function and inflammation in asthma.
Clinical Single Blind Randomize	Asthma Control Test (ACT) Scale Th1/Th2 IFN-g/IL-4	8 Weeks Patients with a diagnosis of asthma, according to the Global Initiative for Asthma (GINA) guideline, were included. All patients received routine asthma medication. Nigella Sativa Oil was given as adjunctive therapy at a dose of 15-30 mg/kg/day for eight weeks.	Routine asthma medication	Nigella sativa oil supplementation improves IFN-g/IL-4 balance and asthma control in children.
Randomize single blind	Asthma Control Test (ACT) Scale Th17/Treg cell Peripheral Blood Mononuclear Cells(PBMCs)	8 Weeks All patients received routine asthma medication. In addition, they received N. Sativa Oil at a dose of 15-30 mg/kg/day for eight weeks.	Routine asthma medication	Nigella sativa oil improves Th17/Treg balance and clinical signs in asthmatic children.
Clinical Trial Prospective Double blind	Pulmonary Function Test	2 Weeks Patients with a previous diagnosis of asthma and two or more of the specified symptoms were included. Patients on regular asthma medication: 1-oral theophylline syrup, 6mg/kg 2- N.Sativa 50 mg/kg-oral 3- N.Sativa 100 mg/kg orally 4- 200 mg inhaled salbutamol Pulmonary Function Test was performed at 30-60-90-120-150-180 minutes before drug administration.	No control group	Nigella Sativa has been found to have a relatively strong antiasthmatic effect on the airways in asthma patients, with the boiled extract having less effect than theophylline.

Table 1: Continued

Disease	Author Year, Country	Title of the study	Objective	Sample Size (I:Intervention, C:Control Group)	Age (Mean±SD)
COPD	Al-Azzawi et al.(14) 2020, Egypt	Therapeutic effects of black seed oil supplementation on chronic obstructive pulmonary disease patients: A randomized controlled double blind clinical trial	The aim of this study was to investigate whether Nigella sativa oil supplementation can improve lung function tests, reduce inflammation and lower levels of oxidant and antioxidant markers in patients with COPD.	91 C:44 I: 47	C:55.18±4.27 I:53.74 ±4.68
COVID-19	Koshak et al. (23) 2021, Saudi Arabia	Nigella sativa for the treatment of COVID-19: An open-label randomized controlled clinical trial	To investigate the effect of Nigella sativa oil supplementation on reducing the duration of symptoms and complications in mildly symptomatic COVID-19 patients.	183 I:91 C :92	I:35±10 C:36±12
COVID-19	Al-Haidari et al.(26) 2021, Iraq	Preventive Value of Black Seed in People at Risk of Infection with COVID – 19	To evaluate the preventive effects of Nigella Sativa in reducing the incidence of COVID-19 infection.	376 C: 188 I: 188	No information is available.
COVID-19	Aldwihi et al.(27) 2021,Saudi Arabia	Patients' Behavior Regarding Dietary or Herbal Supplements before and during COVID-19 in Saudi Arabia	To examine the hospitalisation status of individuals who use black seed.	738	36,5
Lower respiratory tract infection	Ahmad et al.(21) 2010, India	A study of Nigella sativa oil in the management of wheeze associated lower respiratory tract illness in children	To investigate the impact of Nigella sativa oil on Wheeze-associated Lower Respiratory Tract Infection.	84 I:43 C: 41	No information is available.
Rhinitis	Nikakhlagh et al.(10) 2010,Iran	Herbal treatment of allergic rhinitis: the use of Nigella sativa	To examine the anti-inflammatory properties of N. Sativa in individuals experiencing symptoms of allergic rhinitis.	66 (59 Completed with patients)	20.81±7.27

Table 1: Continued

Study Type	Analyzed Findings	Duration of Treatment /Intervention	Control	Outcome Measures
Randomised Controlled Trial	Full medical history, complete clinical examination, haematological and biochemical parameters oxidative stress markers, antioxidant markers, inflammatory markers	12 Weeks Patients with mild to moderate COPD were enrolled in the study and received 2x1 g daily of oral Nigella Sativa oil capsules, in addition to their COPD treatment.	only routine Standard COPD treatment	Supplementation with black seed oil may be an effective complementary therapy to improve lung function and correct antioxidant imbalances in people with COPD.
Randomised Controlled Trial	COVID-19 Symptoms	10 days Mild COVID-19 patients presenting to the emergency department and outpatient clinics were enrolled and received	Standard maintenance implemented.	Nigella Sativa Oil supplementation was found to lead to faster symptom improvement than traditional care alone for patients with mild COVID-19 infection.
Clinical controlled study non randomize	The clinical symptoms were assessed.	No information is available. Participants with varying levels of risk for COVID-19, including high, medium, and low, were recruited for the study. They received oral administration of 40 mg/kg. per day of Nigella Sativa.	There was no supply of Nigella sativa.	It has been concluded that Nigella Sativa has the capability of lowering the rates of COVID-19 infections in individuals who are vulnerable.
Survey Descriptive	Status of Black seed use before and during infection and hospitalisation during COVID.	none 2*500 mg oral Nigella Sativa oil daily for 10 days.	None	The utilization of black cumin in COVID-19 infection escalated by 27% within the overall populace. Whilst the outcomes showed a minor decrease in hospitalization necessity among black cumin users, this observation was not considered significant in multivariable logistic regression.
Randomised Controlled Trial	Respiratory rate, Wheezing, Inspiratory-Expiratory Ratio, Accessory Muscle Use and Oxygen Saturation. Peak expiratory flow rate (PEFR)	2 Weeks Patients with wheezing on auscultation who were admitted to the Paediatric Clinic as outpatients or inpatients were enrolled for the study. The intervention included administering standard treatment in conjunction with N. Sativa oil at a dose of 0.1 ml/kg per day for a period of 14 days. Patients were assessed and monitored on days 0, 3, 7, 10, and 14 post-intervention.	Standard Treatment (Salbutamol nebule)	Nigella Sativa oil reduced the pulmonary index and increased the peak expiratory flow rate.
Prospective, descriptive analytical double-blind case-placebo	Measurements of eosinophil count in the nasal mucosa epithelium and IgE levels in the nasal mucosa were taken before and after the study.	4 Weeks Patients with allergic rhinitis attending the Otorhinolaryngology Clinic were enrolled. A symptom scale (including nasal itching, congestion, sneezing, rhinorrhoea, turbinate hypertrophy, and mucosal pallor) was administered to patients with rhinitis on days 0-15 and 30.	Plesebo not defined.	The results provide evidence that N. sativa is effective in reducing nasal mucosal congestion, nasal itching, runny nose, sneezing attacks, turbinate hypertrophy and mucosal pallor within the initial 2 weeks (by the 15th day).

Table 1: Continued

Disease	Author Year, Country	Title of the study	Objective	Sample Size (I:Intervention, C:Control Group)	Age (Mean±SD)
Rhinitis	Işik et al.(20) 2010, Turkey	Potential adjuvant effects of Nigella sativa seeds to improve specific immunotherapy in allergic rhinitis patients	To examine the impact of Nigella sativa seed supplementation on symptoms, PMN functions, lymphocyte subsets, and haematological parameters in individuals with allergic rhinitis.	I: 24 C:8	I: 34 C:23
Rhinitis	Alsamarai et al.(22) 2014, Iraq	Evaluation of Topical Black Seed Oil in the Treatment of Allergic Rhinitis	To assess the therapeutic effectiveness of N.sativa extract as a treatment modality for allergic rhinitis.	68 C: 30 I: 38	No information is available.
Rhinitis	Ansari et al.(25) 2010, Pakistan	Montelukast versus nigella sativa for management of seasonal allergic rhinitis: a single blind comparative clinical trial	To compare the therapeutic efficacy of montelukast with Nigella sativa seeds in patients presenting symptoms of seasonal allergic rhinitis.	47 Montelukast Group: 24 Nigella Sativa Group: 23	31.6±1.9
Rhinosinusitis	Rezaeian et al.(13) 2018, Iran	Effect of Nigella sativa Nasal Spray on the Treatment of Chronic RhinosinusitisWithout a Nasal Polyp	Evaluation of N. sativa efficacy in chronic rhinosinusitis patients without nasal polyps.	65 C:34 I: 31	I: 44.12±13.03 C: 45.50±12.57

Table 1: Continued

Study Type	Analyzed Findings	Duration of Treatment /Intervention	Control	Outcome Measures
Randomised Controlled Trial	Symptom scores, functions of polymorphonuclear leukocytes, subsets of lymphocytes and other parameters related to haematology	8 Weeks After one month of immunotherapy, 12 patients as well as all healthy volunteers were administered N. sativa seed supplementation (2 g/day orally) for 30 days. The remaining 12 patients continued to receive only immunotherapy during the seed supplementation period.	A group consisting of seven patients were administered 0.1 ml saline solution subcutaneously once per week as a placebo for a duration of 2 months.	Nigella sativa seed supplementation could be considered as a potential adjuvant therapy for specific immunotherapy in allergic rhinitis.
Randomised Controlled Trial double blind	Clinical examination vital signs day and night symptoms	6 Weeks Participants with indications of mild, moderate, and severe allergic rhinitis were selected. 2 drops (one in each nostril) intranasally three times a day for 6 weeks.	Food oil for 6 weeks.	Topical application of black seed oil has been found to be an effective treatment for allergic rhinitis, with minimal side effects.
Single Blind Non-randomize	Symptoms experienced during the day, symptoms related to the eyes, symptoms experienced at night, vital signs, and the level of eosinophils in the blood. Symptom severity on day 0-7-14	2 Weeks Patients attending as outpatients for seasonal allergic rhinitis were enrolled. A daily dosage of 250 mg Nigella Sativa was administered.	Montelukast 10mg per day for a duration of two weeks.	Nigella Sativa proves to be a dependable alternative therapy for seasonal allergic rhinitis without any negative impacts.
Randomised Controlled Trial	Endoscopic evaluation score with modified Lund-Kennedy CT scoring with Lund-McKay SNOT-22 survey	8 Weeks Nigella sativa was administered as two nasal sprays per day for a duration of eight weeks. All patients received a daily dosage of 10 mg of cetirizine tablets and 500 mg of azithromycin tablets for a period of 12 weeks. (Every 12 hours on the first day and then 1 tablet daily should be taken for azithromycin.)	Sodium chloride as a nasal spray 2 sprays a day	The administration of Nigella Sativa intranasal spray was identified as having a positive impact on alleviating symptoms in cases of chronic rhinosinusitis.

IgE: Immunoglobulin E, IFN-g: IL-4: Interleukin 4, COPD: Chronic obstructive pulmonary disease CT: Computed tomography, SNOT-22: Sino-Nasal Outcome Test-22, SD: Standard deviation

This systematic review and meta-analysis demonstrated that NS supplementation affected diseases of the respiratory system and the treatment and prophylaxis of COVID-19. Few studies on this subject were identified in the literature. Eleven of these studies were RCTs, and five were non-RCT studies. Respiratory system diseases examined in the study included asthma, COPD, LRTIs, rhinitis, rhinosinusitis, and COVID-19. According to the results of the systematic review and meta-analysis, asthma patients receiving NS supplements showed improvements in respiratory function tests (15-17), Asthma Control Test scores (16,17), blood eosinophil levels, serum IgE levels (16), serum cytokine levels (17), blood Th1/Th2 and IFN levels (18), and blood Th17 levels (19). In patients with COPD, respiratory function tests showed more favorable results in the group receiving NS (14). In patients with LRTI, PEFR increased in the NS group (21). Symptoms assessed in patients with rhinitis decreased in the NS group (10,22,25). In patients with rhinosinusitis, symptom questionnaire scores were also lower in the group receiving NS supplements (13). When clinicians evaluated recovery status in patients with COVID-19, an infectious viral disease, the recovery rate was higher in the NS group (23), and hospitalization

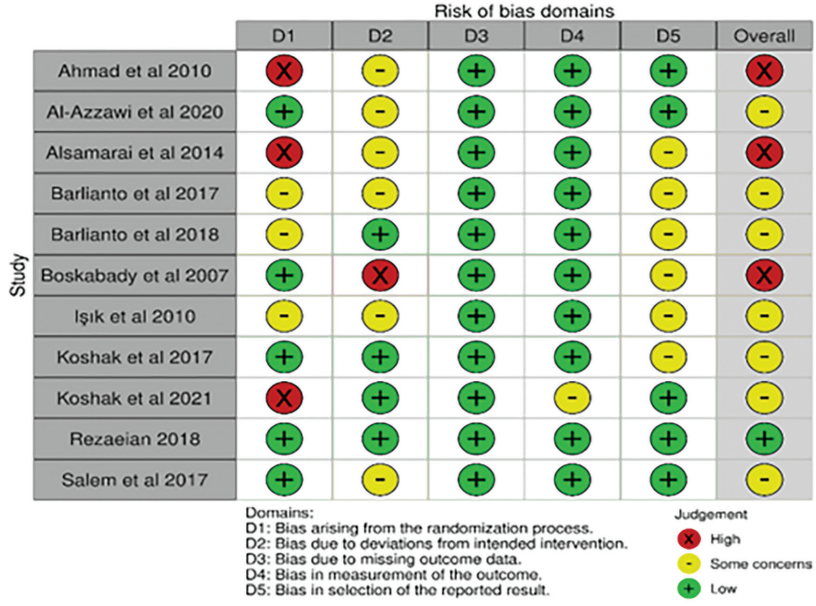

Figure 2. Risk of bias assessment for RCT
RCT: Randomized controlled study

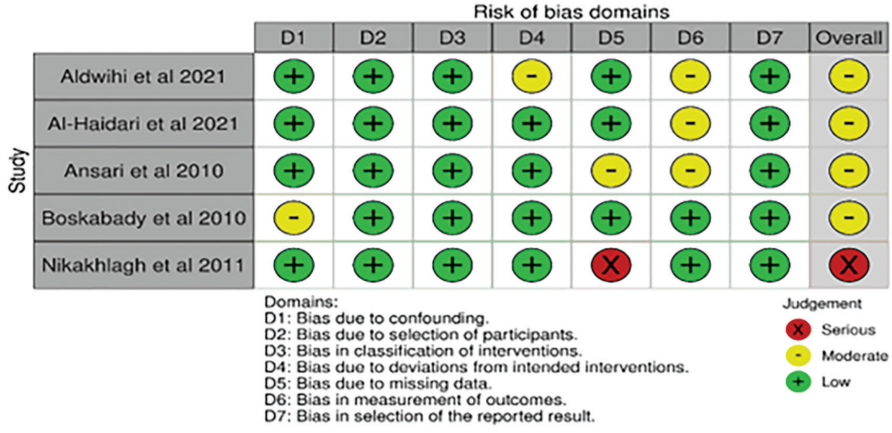

Figure 3. Risk of bias assessment for non-RCT
RCT: Randomized controlled study

(27) and infection (26) rates were lower in the NS group (Table 1). A study in which NS was supplemented for 12 weeks reported a significant and clinically relevant increase in both ACT scores and FEV_1/FVC compared with standard therapy in adolescent patients with asthma (33). This result, consistent with findings in the literature, confirms the potential of NS to reduce symptom burden and support clinical and functional improvement in respiratory diseases.

A systematic review and meta-analysis found that treatment durations of NS ranged from 2 to 12 weeks. These studies covered up to 12 weeks of use; however, no data were available regarding the effects of longer-term use. Although the herbal supplement NS appears to have short-term effects, randomized controlled trials are required to determine its long-term efficacy. In a systematic review and meta-analysis investigating different herbal supplement treatments for COVID-19, the duration of herbal supplement use was similar to that reported in our study (34). Another systematic review examining dietary supplements and herbal medicines for COVID-19 reported that the duration of herbal supplement use was at most two weeks (35). In a systematic review evaluating the effects of NS in patients with rhinosinusitis, the authors reported that the duration of application in humans ranged from 2 weeks to 2 months (36). In these studies, in which NS was administered for short periods, recovery rates were high, mortality rates were low, and NS was effective against dyspnea and myalgia. It was also observed to shorten the duration of olfactory impairment (34,35). Similarly, in the studies included in this systematic review and meta-analysis, patients receiving short-term NS supplementation showed higher recovery rates from anosmia (23), lower hospitalization rates (27), and lower rates of COVID-19 infection (26). A systematic review of traditional formulations in the management of COVID-19 found that integrative or stand-alone traditional formulations may represent inexpensive, preventive, and therapeutic options for preventing SARS-CoV-2 infection and its clinical symptoms (37). Possible sources of heterogeneity among studies include differences in study design, population characteristics, and interventions. Subgroup analyses could not be performed due to an insufficient number of studies. The high heterogeneity observed cannot be attributed to publication bias. Differences in dose and mode of NS administration may have contributed to the observed heterogeneity. This variability suggests that, although NS is promising, its effects may vary depending on specific study conditions, and caution should be exercised when generalizing the results.

Three studies reported side effects, whereas no information on adverse effects was provided in the remaining studies. More comprehensive studies are needed to determine the safety and reliability of NS.

This study aimed to investigate the effect of NS on the prevention and treatment of respiratory system diseases and COVID-19. One study on COVID-19 prevention was identified (29); however, there was insufficient evidence to support prophylactic use. Other studies primarily examined the therapeutic effects of NS. Nigella sativa was found to be effective in relieving symptoms and supporting the clinical management of chronic respiratory diseases.

Study Limitations

The use of NS in different forms and formulations (inhalation, extract, tablet, topical application), the lack of detailed explanations regarding its mechanisms of action, and the inclusion of diverse outcome parameters in the meta-analysis may affect the assessment of the overall effect of the intervention. As the included studies were conducted predominantly in Asian and Middle Eastern countries, the results may not be generalizable to the global population. Additional limitations include the fact that not all studies included in the systematic review and meta-analysis were assessed as having a low risk of bias and that only studies published in English were included. The studies included in this meta-analysis had follow-up periods ranging from 2 to 12 weeks; therefore, long-term safety and efficacy data for NS are unavailable, and the findings reflect only short-term effects. Furthermore, some studies compared NS with placebo, whereas others used standard care as the control group. This heterogeneity in control interventions may have influenced the pooled estimates. Despite these limitations, this meta-analysis

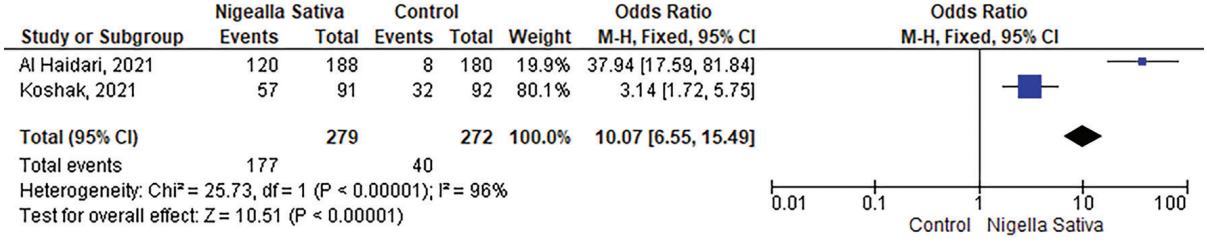

Figure 4. The meta-analysis results of the effect of Nigella sativa on COVID-19
CI: Confidence interval

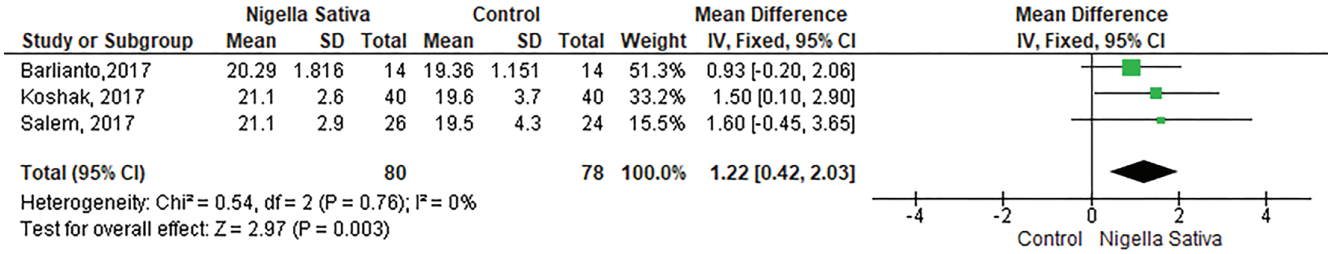

Figure 5. The meta-analysis results of the effect of Nigella sativa on Asthma (ACT Score)
ACT: Asthma Control Test, CI: Confidence interval, SD: Standard deviation

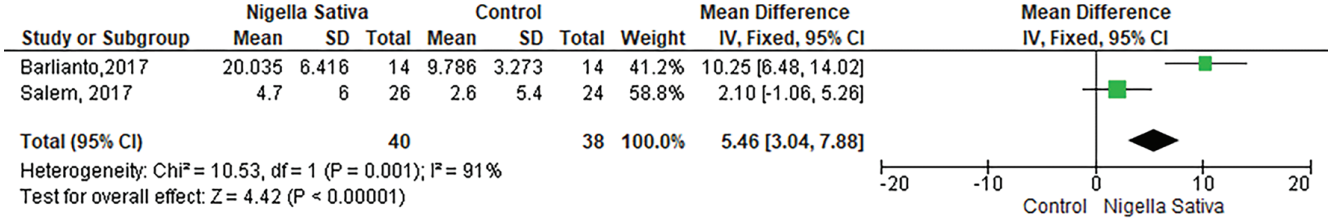

Figure 6. The meta-analysis results of the effect of Nigella sativa on astma (IFN-gama)
CI: Confidence interval, SD: Standard deviation, IFN-gama: Interferon-gamma

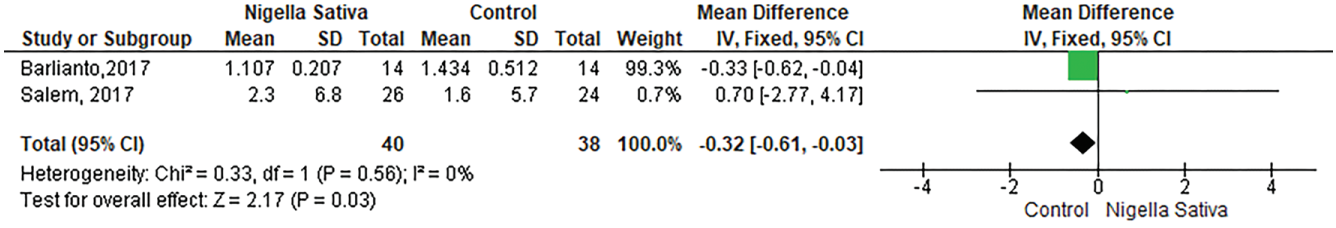

Figure 7. The meta-analysis results of the effect of Nigella sativa on astma (IL-4)
CI: Confidence interval, SD: Standard deviation, IL-: Interleukin 4

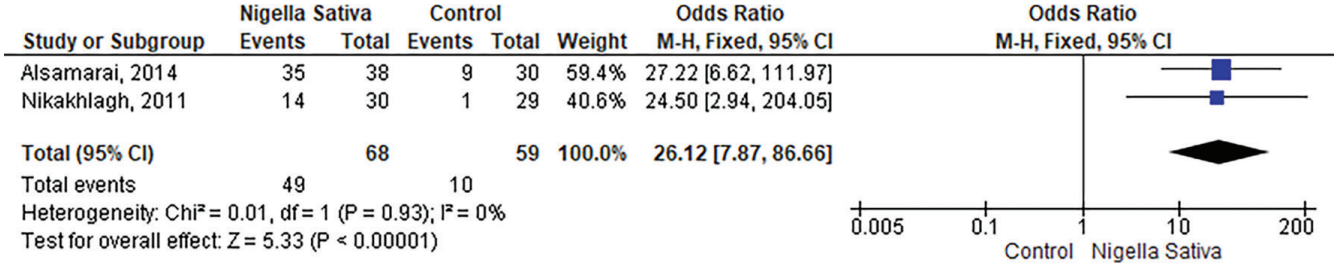

Figure 8. The meta-analysis results of the effect of Nigella sativa on rhinitis symptom improvement
CI: Confidence interval

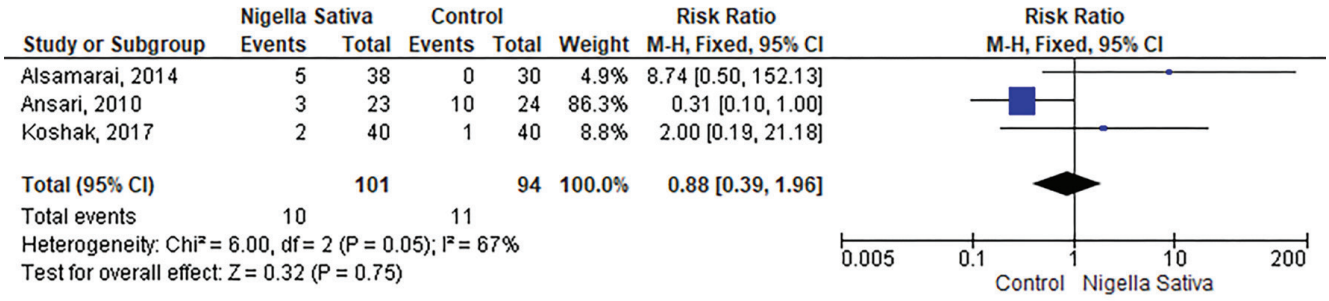

Figure 9. The meta-analysis results of the effect of Nigella sativa on adverse events
CI: Confidence interval

provides a comprehensive and up-to-date synthesis of the available evidence regarding the effects of NS on COVID-19 and various respiratory diseases. The analysis incorporated both clinical and immunological outcomes, applied rigorous methodological quality assessments (ROB2 and ROBINS-I), and quantitatively combined data to enhance the robustness of the findings. These strengths support the reliability of the observed beneficial effects of NS on respiratory health.

Clinical Implications

Nigella sativa reduces symptoms of respiratory diseases such as asthma, LRTI, rhinitis, rhinosinusitis, and COPD, and has a positive effect on disease treatment when used alone or in combination with standard therapy. It has also been shown to be effective in the prevention and treatment of COVID-19. Nigella sativa may represent a suitable alternative approach to improve disease management and enhance treatment efficacy.

Conclusion

This study synthesizes existing research and provides insights into alternative treatment options. The results of the meta-analysis indicate that NS has a positive effect in the prevention and treatment of respiratory diseases, including asthma, COPD, rhinitis, rhinosinusitis, LRTI, and COVID-19. However, these findings are derived from a limited number of studies and therefore have inherent limitations. High-quality clinical trials are required to further substantiate these results.

Acknowledgments

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Footnotes

Authorship Contributions

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

Conflict of Interest: There is no conflict of interest between the authors.

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Supplemental file	
Search strategy for all database	
Number	**Search items**
1	"Coronavirus"
2	Coronavirus* OR coronovirus* OR Coronavirus* OR Coronovirus* OR "2019-nCoV" OR "2019nCoV" OR "nCoV2019" OR "nCoV-2019" OR "COVID-19" OR "COVID19" OR "2019 novel*" OR "SARS-CoV-2" OR "SARSCoV-2" OR "SARSCoV2" OR "SARSCov19" OR "SARS-Cov19" OR "SARSCov-19" OR "SARS-Cov-19" OR "SARS" OR "SARS-nCoV" OR "MERS" OR "MERS-CoV" OR "HCoV-229E" OR "HCoV-OC43" OR "HCoV-NL63" OR "HCoV-HKU1" OR "middle east respiratory syndrome coronavirus" OR "severe acute respiratory syndrome"
3	Outbreak* OR pandemic* OR epidemic*
4	"Antiviral" OR "herbal treatment" OR "prophylaxis" OR "supplement" OR "supplements" OR "supplementation" OR "supplementations"
5	"Respiratory system" OR "respiratory" OR "Respiratory Infections" OR "respiratory tract infections" OR "respiratory system infections" OR "acute respiratory tract infections" OR "upper respiratory tract infections" OR "Upper Respiratory Infections" OR "lower respiratory tract infections" OR "common cold" OR "Severe Acute Respiratory Syndrome-Related Coronavirus" OR "Acute Febrile Respiratory Syndrome" OR "Viral Respiratory Infection" OR "Pneumonia" OR "Flu-Like Illness" OR "Common Cold" OR "Pulmonary Inflammation" OR "Lung Diseases" OR "Bronchitis" OR "Bronchiolitis" OR "Chronic Bronchitis" OR "Human Influenza" OR "laryngitis" OR "pharyngitis" OR "nasopharyngitis" OR "tonsillitis" OR "bronchopneumonia" OR "rhinitis" OR "sinusitis" OR "tracheitis" OR "tuberculosis" OR "cough" OR "asthma" OR "Chronic Obstructive Pulmonary Disease" OR "COPD" OR "apnea" OR "dyspnea" OR "hyperventilation"
6	#1 OR #2 OR #3 OR #4 OR #5
7	"Nigella sativa" OR "Nigella sativas" OR "sativa, Nigella" OR "Cumin, Black" OR "Kalonji" OR "Kalonjus" OR "Black Cumin" OR "Black Cumins" OR "Cumins, Black" OR "Nigella sativa oil" OR "black caraway" OR "black seed" OR "thymoquinone"
8	"Nigella sativa" OR "Nigella sativas" OR "sativa, Nigella" OR "Cumin, Black" OR "Kalonji" OR "Kalonjus" OR "Black Cumin" OR "Black Cumins" OR "Cumins, Black" OR "Nigella sativa oil" OR "black caraway" OR "black seed" OR "thymoquinone"
9	#7 OR #8
10	#9 AND #6

Original Article

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Flexible Cystoscopy Patient Experience: Comparative Effects of Irrigation Techniques on Comfort and Satisfaction

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Abstract

Aim: Flexible cystoscopy under local anesthesia is frequently associated with pain and discomfort, and irrigation delivery may influence patient experience. The aim of this study was to compare three irrigation techniques with respect to pain, patient satisfaction, and willingness to repeat (WtR) during flexible cystoscopy.

Methods: This single-center retrospective comparative cohort study included 283 men who underwent flexible cystoscopy under local anesthesia between October 2023 and June 2024. Patients were allocated to patient-controlled pressurized irrigation with a sphygmomanometer cuff (Group 1, n=73), operator-controlled manual pressurized irrigation (Group 2, n=126), or non-squeeze irrigation (Group 3, n=84). The primary outcome was intraoperative pain assessed by a 0-10 visual analog scale (VAS). Secondary outcomes were postprocedural VAS, WtR (0-10), satisfaction (5-point Likert scale), and complications. Groups were compared using Kruskal-Wallis and chi-square or Fisher's exact tests (two-sided; $p<0.05$).

Results: Age and body mass index were similar across groups. Intraoperative VAS differed significantly across groups (Group 1: 3.07±1.07; Group 2: 3.64±1.26; Group 3: 4.88±1.58; $p<0.001$), with both pressurized techniques associated with less pain than non-squeeze irrigation. Postprocedural VAS scores were also lower with pressurized irrigation (2.63±0.96 and 2.98±1.32 vs. 3.73±1.20; $p<0.001$). Willingness to repeat was highest in Group 2 and lowest in Group 3 (7.79±1.63 vs. 6.71±1.74; $p<0.001$). Satisfaction was higher in the pressurized groups (4.34±0.58 and 4.30±0.68 vs. 3.71±0.84; $p<0.001$). Complication rates were low and comparable (6.8%, 6.3%, and 3.6%; $p=0.610$).

Conclusion: Pressurized irrigation during flexible cystoscopy under local anesthesia was associated with less pain and greater patient satisfaction than non-squeeze irrigation, without an increase in complications. Operator-controlled pressurization showed a modest advantage in WtR.

Keywords: Cystoscopy, pain, patient satisfaction, irrigation, urology

Introduction

Flexible cystoscopy is one of the most frequently performed diagnostic and follow-up procedures in urologic practice, used for bladder cancer surveillance, evaluation of hematuria, and assessment of lower urinary tract symptoms (1). Although it is generally better tolerated than rigid cystoscopy and can be performed under local anesthesia in an office setting, a considerable proportion of patients still report pain or discomfort—most commonly during passage through the external urethral sphincter—which may negatively affect satisfaction and adherence to follow-up (2-5).

Multiple approaches have been investigated to reduce discomfort during cystoscopy, including pharmacological measures (e.g., intraurethral lidocaine gel) and non-pharmacological interventions (6-8). Pre-procedural strategies, such as adequate patient information and

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scheduling (immediate vs. scheduled cystoscopy), may also affect patient-reported pain and anxiety (9). Beyond these, procedural modifications—such as increasing irrigation pressure—have recently been proposed to facilitate urethral passage and reduce pain (10). In a randomized trial, manual bag-squeeze pressurization significantly lowered visual analog scale (VAS) pain scores compared with non-squeeze irrigation (10); however, this method may be operator-dependent and less standardized in routine practice (5,10). Patient-controlled pressurization using a sphygmomanometer cuff could improve standardization and autonomy; however, no study has directly compared patient-controlled pressurization, operator-controlled manual pressurization, and non-squeeze irrigation and simultaneously incorporated patient-centered outcomes such as satisfaction and willingness to repeat (WtR) the procedure.

We hypothesized that pressurized irrigation would be associated with lower pain scores and higher rates of WtR than with non-pressurized irrigation during flexible cystoscopy performed under local anesthesia. Therefore, this study aimed to compare the effects of the three aforementioned irrigation techniques on pain intensity, patient satisfaction, WtR the procedure, and complication rates during flexible cystoscopy under local anesthesia to identify the optimal irrigation strategy.

Materials and Methods

Study Design and Ethical Approval

This single-center, retrospective, comparative cohort study included 283 men who underwent flexible cystoscopy under local anesthesia from October 2023 to June 2024. Ethical approval was obtained from the University of Health Sciences Türkiye, Umraniye Training and Research Hospital Scientific Research Ethics Committee prior to data collection (approval number: 287, date: 30.09.2024). The study was performed in accordance with the principles of the Declaration of Helsinki.

Patient Selection and Grouping

A total of 283 male patients who met the inclusion criteria and underwent flexible cystoscopy under local anesthesia were enrolled in the study. During the eligibility assessment, 21 patients were excluded due to regular analgesic use (n=7), use of psychiatric medication, or analgesic intake within 24 hours before the procedure (n=10) (Figure 1). The reviewed procedures were performed by various urologists, and the irrigation method was chosen according to each operator's preference. Irrigation was performed by manual bag compression by the urologist, by patient-controlled pressurization using a sphygmomanometer cuff, or by non-squeeze irrigation.

Accordingly, patients were divided into three groups:

- Group 1 (n=73): Patient-controlled pressurized irrigation using a sphygmomanometer cuff,
- Group 2 (n=126): Operator-controlled manual pressurized irrigation,
- Group 3 (n=84): Control group- non-squeeze irrigation (gravity-driven flow).

Inclusion Criteria

Patients were included if they:

- were male and aged ≥18 years,
- had no history of neurological disease,
- had not previously undergone cystoscopy under local anesthesia,
- had complete data for intraoperative VAS pain scores and post-procedural VAS and WtR scores.

Exclusion Criteria

The following were excluded from the study:

- regular use of analgesics,
- use of psychiatric medication,
- intake of any analgesic within 24 hours before the procedure.

Procedure

All procedures were performed under local anesthesia following the same clinical protocol. Each examination was conducted using a flexible cystoscope. Before the procedure, all patients received 10 mL of 2% lidocaine gel for intraurethral anesthesia, followed by a 10-minute waiting period. This approach was consistent with current guideline recommendations and standard clinical practice (5,11). Sterile saline was used as the irrigation solution, and the delivery method depended on the assigned group. The procedure time was recorded as the interval from insertion of the cystoscope into the urethra to its withdrawal.

Primary Endpoint: Pain intensity during the procedure (VAS 0-10).

Secondary Endpoints:

- Post-procedural pain (VAS 0-10)
- Willingness to repeat the procedure (WtR, 0-10 scale)
- Patient satisfaction (5-point Likert scale)
- Presence of complications (hematuria, dysuria, postvoid burning)

Demographic and procedural variables such as age, body mass index (BMI), and procedure duration were also recorded for all patients.

Statistical Analysis

Data were analyzed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Normality of continuous variables was assessed using the Kolmogorov-Smirnov test. Continuous variables were presented as median (interquartile range)

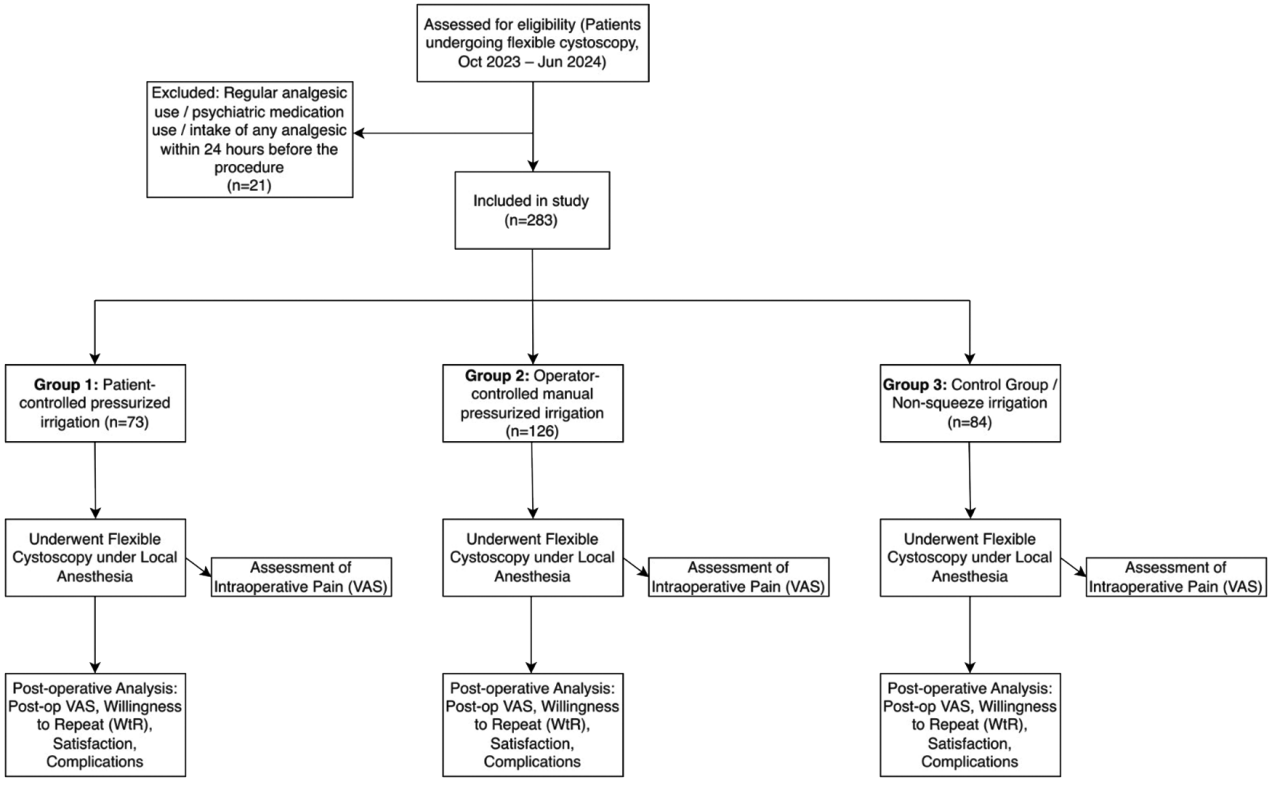

Figure 1. Study flowchart: Comparison of irrigation methods in flexible cystoscopy
VAS: Visual analog scale

or mean ± standard deviation, as appropriate, and were compared among the three groups using the Kruskal-Wallis test. When a significant overall difference was detected, post-hoc pairwise comparisons were performed with Bonferroni-adjusted p-values. Categorical variables are presented as n and compared using the chi-square test or Fisher's exact test, as appropriate. All tests were two-sided, and a p-value <0.05 was considered statistically significant.

Results

Demographic and Clinical Characteristics

Age and BMI were similar across groups (Table 1). Procedure time was longer in the non-squeeze group than in either pressurized group (Group 1 vs. Group 3, p=0.027; Group 2 vs. Group 3, p<0.001), with no difference between the two pressurized groups (Table 1).

Primary Endpoint: Intraoperative Pain

Intraoperative VAS scores differed significantly among the three groups (p<0.001) (Table 2). Post-hoc comparisons showed lower pain scores in both pressurized groups compared with the non-squeeze group (Group 1 vs Group 3, p<0.001; Group 2 vs Group 3, p<0.001), with no difference between Groups 1 and 2 (p=0.235) (Table 2).

Post-Procedural Pain

Post-procedural VAS differed among groups (p<0.001), with no significant difference between the two pressurized groups (p=0.123) (Table 2).

Table 1. Demographic and clinical characteristics

	Group 1 (n=73)	Group 2 (n=126)	Group 3 (n=84)	p-value*
Age, median (IQR)	63 (14)	63 (10)	62 (11)	0.699
BMI (kg/m^2), mean ± SD	26.5±3.1	27.0±3.4	26.2±3.0	0.453
Procedure time (min), median (IQR)	8 (2)	7 (2)	8 (4)	**<0.001**

*Kruskal Wallis test
BMI: Body mass index, SD: Standard deviation, IQR: Interquartile range

Willingness to Repeat the Procedure (WtR)

Willingness to repeat scores differed among groups (p<0.001). Both pressurized groups had higher WtR than the non-squeeze group (Group 2 vs. Group 3, p<0.001; Group 1 vs. Group 3, p=0.016), while Groups 1 and 2 were similar (p=0.743) (Table 2, Figure 2).

Patient Satisfaction

Satisfaction differed among groups (p<0.001).The non-squeeze group reported lower satisfaction than both pressurized groups (each p<0.001), with no difference between Groups 1 and 2 (p=0.999) (Table 2).

Complication Rates

Complication rates were low and comparable across groups (p=0.610; Table 2; Figure 3). No serious adverse events occurred; all complications were mild and transient (temporary hematuria, mild dysuria, or post-void burning).

Discussion

This study is among the first to systematically compare the effects of different irrigation techniques on patient comfort, satisfaction, and safety during flexible cystoscopy under local anesthesia.

Our findings demonstrate that pressurized irrigation methods, whether patient-controlled or operator-controlled, are associated with significantly lower pain scores, higher satisfaction, and greater willingness to undergo repeat procedures than with non-squeeze irrigation. Importantly, complication rates were comparable across the three methods, indicating that pressurized techniques can be safely implemented.

A notable within-study observation was that the irrigation strategy appeared to influence procedural flow and efficiency. Although median procedure times were similar, the distribution differed significantly, with longer and more variable durations in the non-squeeze group. This pattern is consistent with the practical notion that suboptimal flow may impair visualization and necessitate additional maneuvers or intermittent irrigation adjustments, potentially prolonging urethral manipulation. While our retrospective dataset does not allow a formal mediation analysis, the concordant directionality—higher pain, lower satisfaction/WtR, and longer procedure times in the non-squeeze group—supports a plausible mechanical pathway by which improved, steadier irrigation can reduce procedural friction and shorten exposure to discomfort, thereby enhancing overall patient experience.

Pain Management and the Role of Irrigation Pressure

The primary finding of reduced intraoperative pain supports the clinical efficacy of pressurized irrigation. Group 1 (patient-controlled, VAS =3.07) and Group 2 (operator-controlled, VAS =3.64) showed 37-24% lower pain scores

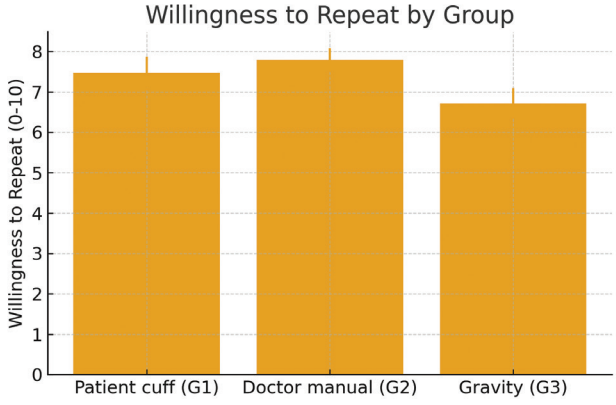

Figure 2. Willingness to repeat scores by group

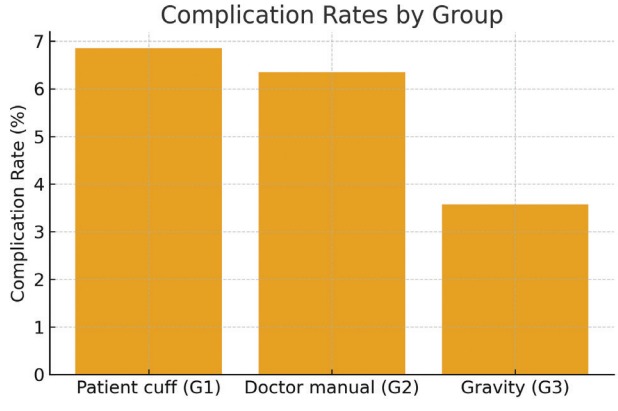

Figure 3. Complication rates by group

Table 2. Outcome measures				
	Group 1 (n=73)	**Group 2 (n=126)**	**Group 3 (n=84)**	**p-value***
VAS (intraoperative)	3.07±1.07	3.64±1.26	4.88±1.58	**<0.001**
VAS (post-procedural)	2.63±0.96	2.98±1.32	3.73±1.20	**<0.001**
WtR (0-10)	7.47±1.78	7.79±1.63	6.71±1.74	**<0.001**
Satisfaction (1-5)	4.34±0.58	4.30±0.68	3.71±0.84	**<0.001**
Complications (%)	6.8	6.3	3.6	0.610

*Kruskal Wallis test, significance values have been adjusted by the Bonferroni correction for multiple tests
VAS: Visual analog scale, WtR: Willingness to repeat

compared with Group 3 (non-squeeze, VAS =4.88). These results are consistent with the randomized controlled trial by Gunendran et al. (10), which reported that manual bag-squeeze irrigation reduced VAS scores from 3 to 1.38. The slightly higher VAS values in our study may be explained by differences in patient demographics, lidocaine dwell times, or operator experience.

The mechanisms by which increased irrigation pressure reduces pain are likely multifactorial. Physiologically, elevated pressure increases bladder hydrodistention and widens the urethra (12).

This expansion minimizes mucosal contact during scope advancement, particularly at the external urethral sphincter, the narrowest and most sensitive region of the urethra (3,13). Taghizadeh et al. (3) showed that up to 70% of pain during cystoscopy occurs as the scope passes through the membranous urethra. Therefore, reducing resistance at this critical segment can substantially improve overall procedural comfort.

From a physical standpoint, Chang et al. (12) emphasized the importance of independently controlling irrigation pressure and flow rate in endoscopic systems. The authors proposed that controlled-pressure systems be considered an alternative for cystoscopy. Our results provide clinical evidence supporting this view, confirming that both patient- and operator-controlled pressurizations are effective.

Patient-controlled vs. Operator-controlled Pressurization

There was no significant difference in pain scores between patient-controlled and operator-controlled groups (p=0.235), indicating no detectable difference in analgesic efficacy; however, this does not establish equivalence. Although not statistically significant, WtR was slightly higher in the operator-controlled group (7.79 vs. 7.47; p=0.743). This may be due to the operator's ability to maintain more consistent, flow-optimized pressure throughout the procedure.

From an implementation perspective, the absence of a significant pain difference between patient- versus operator-controlled pressurization suggests that the key determinant is achieving adequate and sustained irrigation performance rather than who applies the pressure. Accordingly, centers may select the approach that best fits their workflow: patient-controlled pressurization may be attractive in resource-constrained settings by preserving staff time and enhancing perceived patient control, whereas operator-controlled pressurization may facilitate more consistent titration across procedural phases. The modest, not statistically significant, numerical advantage in WtR observed under operator control may reflect greater stability of flow and pressure during critical transitions (e.g., passage through the external sphincter). Prospective studies could standardize and objectively record pressure profiles to clarify whether consistency of pressurization—rather than peak pressure—best explains the patient-centered benefits observed in our cohort. It is also important to avoid over-interpreting the lack of statistical difference between the two pressurized strategies as "true equivalence." Our analysis was not designed as an equivalence or non-inferiority comparison, and adjustment for multiple testing may have reduced the sensitivity for detecting small differences between techniques. Therefore, the most conservative interpretation is that both approaches yield broadly comparable patient-reported comfort in routine practice, while any incremental differences—if present—are likely modest and dependent on how consistently pressure and flow are maintained. Prospective studies with prespecified equivalence margins and objective pressure profiling would be needed to determine whether small differences carry practical relevance.

The patient-controlled technique offers distinct advantages, including enhanced autonomy, psychological reassurance through perceived control (14), and no need for additional personnel. However, individual variations in pain thresholds and anxiety levels may lead to inconsistent applied pressure, thereby limiting standardization. Indeed, Armany et al. (15) proposed using standardized pressure bags (350 mmHg) to minimize such variability.

Conversely, the operator-controlled method allows experienced clinicians to modulate pressure dynamically across procedural stages (e.g., urethral entry, bulbar, prostatic, and bladder neck passages). This adaptability may optimize both visualization and comfort. Nevertheless, as Gunendran et al. (10) noted, manual pressurization introduces inter- and intra-operator variability.

Patient Satisfaction and Willingness to Repeat

Patient satisfaction and WtR are increasingly recognized as key indicators of quality in patient-centered care. In our study, satisfaction scores were high in both pressurized irrigation groups (4.34 and 4.30 out of 5), consistent with prior research (16,17). The lower satisfaction score in the non-squeeze group (3.71) may reflect its higher pain levels and slightly longer procedure times.

Willingness to repeat is particularly relevant in long-term surveillance settings, such as bladder cancer follow-up. Koo et al. (18) highlighted the psychological burden of repeated cystoscopy and its negative impact on compliance. The higher WtR scores observed in our pressurized groups (7.47 and 7.79 out of 10) suggest that these methods may enhance long-term adherence to surveillance protocols.

Similarly, Casteleijn et al. (19) reported that pain during cystoscopy reduces female patients' willingness to return

for future procedures. Our results reinforce the notion that effective pain control improves not only immediate comfort but also future compliance.

Safety Profile and Complications

Complication rates were similar among groups (3.6-6.8%; p=0.610), supporting the safety of pressurized irrigation. All reported events (temporary hematuria, mild dysuria, and post-void burning) were minor and self-limited (20,21).

Theoretically, increased irrigation pressure could pose risks, such as upper urinary tract reflux, bladder perforation, or infection (22,23). However, no serious complications were observed in our series.

Jung and Osther (24) demonstrated that controlled irrigation during flexible ureteroscopy remains within safe pressure thresholds. Given the bladder's larger capacity and urethral valvular mechanisms, it is likely more tolerant of transient pressure elevations compared with the upper urinary tract.

Local Anesthesia and Multimodal Analgesia

All patients received 10 mL of 2% lidocaine gel with a 10-minute dwell time. Although lidocaine gel is widely used, the efficacy of lidocaine gel remains controversial. A meta-analysis by Patel et al. (7) found a statistically significant but clinically minimal benefit compared with that of plain lubricant gel (mean VAS reduction =0.6). Razdan et al. (25) further reported that cooled lidocaine gel (4 °C) improved patient satisfaction.

Our design specifically assessed the additive analgesic effect of irrigation pressure in addition to standard lidocaine anesthesia, aligning with the principles of multimodal pain control. As Xie et al. (13) suggested, combining different analgesic modalities may provide synergistic benefits. Future studies should compare different lidocaine concentrations, dwell times, and combinations of pressurized irrigation techniques.

Non-Pharmacological Approaches

Beyond irrigation pressure, several non-pharmacological methods have been evaluated for cystoscopy-related pain reduction. Several studies have reported that allowing patients to watch the procedure on a monitor reduced patients' discomfort (6,26,27), although Koenig et al. (28) failed to confirm this finding. Distraction techniques, such as listening to music (29-31) or using stress balls (32), show mixed efficacy. However, music may shift attention by recruiting the cingulo-frontal cortex, periaqueductal gray, and posterior thalamus (31).

Unlike these approaches, pressurized irrigation acts through direct physiological mechanisms rather than psychological ones, and its efficacy is therefore less influenced by factors such as anxiety, education, or cultural background. Nevertheless, integrating psychological support or distraction techniques into a multimodal protocol may yield synergistic benefits.

Clinical Implications and Cost-effectiveness

Both pressurized irrigation methods are simple, low-cost, and easy to implement. The patient-controlled technique is labor-efficient, requires no additional personnel, and can be applied with a standard blood pressure cuff or an inexpensive pressure bag. In Armany et al.'s (15) protocol, Infu-Surg standard-pressure infusion bags were shown to be cost-effective and widely available.

The operator-controlled technique typically requires a second staff member (physician, nurse, or technician), but this is already standard practice in most endoscopy units. Overall, the minimal additional cost of pressurized irrigation is likely offset by higher patient satisfaction and potentially reduced complication-related expenses.

Study Limitations

Certain limitations should be acknowledged. Due to its retrospective design, randomization was not possible, introducing a potential selection bias. However, the groups were demographically and clinically comparable, minimizing this risk. Second, the single-center design may limit external validity. Third, irrigation pressure in the operator-controlled group was not objectively measured, and future studies using pressure sensors could standardize this variable. Fourth, pain was assessed using a VAS, a subjective measure influenced by psychological and cultural factors (33,34). Nevertheless, VAS remains the most widely validated tool for cystoscopy-related pain assessment. Lastly, the inclusion of only male patients limits generalizability, as anatomical differences may influence irrigation effects in females. Despite these limitations, this study provides real-world comparative data from a relatively large cohort and evaluates clinically relevant patient-centered outcomes (pain, satisfaction, and WtR) using standardized measures, while reporting low complication rates across all techniques.

Future Directions

Validation through prospective randomized controlled trials. Dose-response studies should be conducted to determine the optimal irrigation pressure, including validation of the proposed 350 mmHg level (10). Evaluation of combinations of pressurized irrigation with pharmacologic and non-pharmacologic analgesic methods. Replication in female cohorts to assess anatomical influences. Assessment of long-term outcomes, such as pain perception and compliance in repeated cystoscopies. Cost-effectiveness analyses identify economically optimal strategies. Comparative evaluations from the operator's perspective included visualization quality and procedural

ease. Investigation of specific patient subgroups (elderly, BPH, urethral stricture) to determine tailored safety and efficacy profiles.

Conclusion

This study demonstrates that pressurized irrigation techniques, whether patient- or operator-controlled, significantly reduce pain and improve satisfaction compared with non-squeeze (gravity-driven) irrigation during flexible cystoscopy under local anesthesia. Both methods exhibit comparable efficacy and safety, with the operator-controlled approach showing a slight advantage in WtR.

These results suggest that integrating pressurized irrigation into routine flexible cystoscopy practice may enhance patient-centered outcomes. The patient-controlled technique, offering autonomy and requiring no additional personnel, presents a practical advantage for clinical implementation. However, prospective randomized studies are warranted to confirm these findings and to determine optimal pressure parameters for routine use.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the University of Health Sciences Türkiye, Umraniye Training and Research Hospital Scientific Research Ethics Committee prior to data collection (approval number: 287, date: 30.09.2024).

Informed Consent: Written consent was obtained from all participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.I., R.S., E.V.K., Concept: M.B., H.S.G., A.T., Design: M.B., A.T., Data Collection or Processing: R.S., M.U.E., E.V.K., Analysis or Interpretation: A.I., M.U.E., Literature Search: M.B., H.S.G., Writing: M.B., H.S.G.

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

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Original Article

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Clinical Outcomes and Management Challenges of Pediatric Uveitis Associated with Systemic Rheumatic Diseases

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Abstract

Aim: Pediatric uveitis is a sight-threatening condition associated with various systemic diseases. The prognosis depends on both the etiology and multidisciplinary management. This study evaluates the etiology, clinical characteristics, and outcomes of pediatric uveitis managed through a coordinated rheumatology-ophthalmology approach.

Methods: This retrospective cross-sectional study included patients diagnosed before age 16 who were followed jointly for ≥6 months. Demographics, clinical presentations, underlying diseases, treatments, and outcomes were extracted from medical records. The primary endpoint of this study was to identify the systemic etiological spectrum of pediatric uveitis. The secondary endpoints were to evaluate clinical characteristics and the efficacy of various treatment modalities with respect to disease course and achievement of ocular remission (complete or partial) during follow-up.

Results: Of the 109 enrolled patients, 73 patients with systemic disease-related uveitis were analyzed; 51% were female. Juvenile idiopathic arthritis (JIA) was the leading cause (70% of cases), followed by probable sarcoidosis (17.6%) and Behçet's disease (BD) (11%). The mean age was 11.1±4.2 years. Juvenile idiopathic arthritis was more prevalent in younger children; BD was more prevalent in older age groups. Anterior uveitis (71.2%), chronic course (74%), and bilateral involvement (75.3%) predominated. Antinuclear antibodies positivity was 64.4%. Treatment included systemic steroids (71%) and methotrexate/biologics (65.7%). Both sarcoidosis and BD groups demonstrated favorable outcomes: clinical remission was achieved in 12 of 13 (92.3%) sarcoidosis patients and 8 of 8 (100%) BD patients. Relapse rates were lower in sarcoidosis (7.7%) and BD (12.5%) than in the JIA group (55%). Complications were observed in 38.5% of sarcoidosis patients and 12.5% of BD patients.

Conclusion: Pediatric uveitis requires aggressive immunosuppressive therapy. Juvenile idiopathic arthritis-associated uveitis is associated with a higher risk of relapse. Etiology influences outcomes.

Keywords: Autoimmune disease, biological therapy, prognosis, uveitis

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Introduction

Uveitis is an umbrella term for more than 30 distinct conditions characterized by intraocular inflammation. Although it primarily affects the densely vascularized and pigmented uveal tract of the eye, inflammation may spread to neighboring structures, including the vitreous, retina, and retinal vessels. Without appropriate and timely intervention, these conditions may progress collectively to cause irreversible vision loss (1).

Pediatric uveitis accounts for 2-14% of all uveitis cases, with an estimated incidence of 4.3 per 100,000 people and a prevalence of 27.9 per 100,000 people (2). The etiological diagnosis of childhood uveitis varies according to geographical, ethnic, and genetic factors, as well as referral patterns in the study population. The condition may manifest independently, as in idiopathic uveitis, or in connection with infectious and non-infectious (immune-mediated) causes. Non-infectious pediatric uveitis is an inflammatory condition that can lead to visual impairment (3). It occurs idiopathically in approximately half of cases or in association with systemic diseases such as juvenile idiopathic arthritis (JIA), Behçet's disease (BD), sarcoidosis, vasculitis, and tubulointerstitial nephritis and uveitis (TINU) syndrome (2,4,5). Given the complexity of intraocular inflammation, accurate diagnosis and effective treatment of rheumatic diseases require close collaboration between ophthalmologists and pediatric rheumatologists. While the existing literature provides insights into childhood uveitis, there is a lack of comprehensive data on the long-term outcomes of patients managed through such dedicated multidisciplinary partnerships.

We hypothesized that a coordinated, multidisciplinary approach in a tertiary-referral setting would enable more precise identification of the cause of disease and optimize clinical outcomes for complex, non-infectious pediatric uveitis cases. To address this gap, the present study evaluates our twelve-year institutional experience, focusing on patient demographics, disease subtypes, therapeutic strategies, and long-term prognosis.

Materials and Methods

Compliance with Ethical Standards

The study was approved by the Istanbul University Istanbul Faculty of Medicine Clinical Research Ethics Committee (no.: 1774366, date: 23.05.2023). The study was conducted in accordance with the principles of the Declaration of Helsinki, local regulations and written informed consent were obtained from the responsible adult for each patient.

Study Design and Patient Enrollment

This retrospective cross-sectional cohort study enrolled patients diagnosed with uveitis who had been under the care of tertiary pediatric rheumatology and ophthalmology clinics for at least six months, with enrollment between November 2011 and March 2023. Inclusion criteria included a confirmed diagnosis of uveitis before the age of 16, regular follow-up visits for at least six months, and the availability of complete medical records. Cases of uveitis associated with primary ophthalmological conditions clearly attributed to infectious etiologies (e.g., herpes virus, syphilis, or toxoplasmosis), as well as idiopathic uveitis without underlying or suspected rheumatological conditions, were excluded from the study. Data on patients, including demographic characteristics, clinical presentations, underlying diseases, laboratory results, uveitis manifestations, therapeutic interventions, and outcomes, were extracted from medical charts. The primary endpoint of this study was to identify the systemic etiological spectrum of pediatric uveitis. The secondary endpoints were to evaluate clinical characteristics and the efficacy of various treatment modalities with respect to disease course and achievement of ocular remission (complete or partial) during follow-up.

Uveitis Classification

Ophthalmologists classified uveitis in accordance with the guidelines established by the International Uveitis Working Group. Patients are categorized based on the anatomical location of the inflammation: anterior uveitis—inflammation primarily affecting the anterior chamber (including iritis, iridocyclitis, and anterior cyclitis); intermediate uveitis—inflammation primarily involving the vitreous (including pars planitis, posterior cyclitis, and hyalitis); posterior uveitis: inflammation primarily involving the retina/choroid (including choroiditis, chorioretinitis, retinitis, and neuroretinitis) and panuveitis: inflammation affecting all ocular regions. Regarding the clinical course, cases were classified as acute (characterized by an abrupt onset and limited duration), recurrent (characterized by repetitive episodes separated by inactive periods of at least three months without therapy), or chronic (characterized by reactivation occurring within three months of treatment cessation) (6).

Uveitis Outcomes

Uveitis outcomes, as assessed by ophthalmologists, were defined as follows: complete remission (with or without treatment): inactive ocular inflammation (no anterior chamber cells, no papilledema, no macular edema, no vitreous opacity, no floaters, or other complications) for at least six months following completion of therapy or anti-inflammatory treatments; partial remission—defined as the presence of anterior chamber cells up to 1+ grade, provided there were no new inflammatory complications; non-remission is defined as being refractory to treatment (6,7).

Diagnosis of Systemic Diseases

Patients who underwent a comprehensive diagnostic evaluation but for whom neither a definitive cause could be identified nor a specific diagnosis could be established were categorized as having "idiopathic uveitis" (8). The following standardized criteria were applied to the diagnosis of systemic diseases: JIA was diagnosed according to the International League of Associations for Rheumatology classification (9); BD was diagnosed according to the International Study Group criteria (10); sarcoidosis was diagnosed according to criteria established by the International Workshop on Ocular Sarcoidosis; probable sarcoidosis was diagnosed when a biopsy could not be performed (11). Tubulointerstitial nephritis and uveitis syndrome was diagnosed based on compatible clinical and laboratory findings in the absence of other identifiable causes (12).

Statistical Analysis

Descriptive statistics were used to summarize the demographic and clinical characteristics of the study cohort, including means and standard deviations for continuous variables and percentages for categorical variables. The distribution of anatomical locations, clinical course, and outcomes of uveitis was described using frequency counts and percentages.

For the analysis of follow-up duration and time to remission, median values with interquartile ranges (IQR) were reported, as the data were not normally distributed. All statistical analyses were performed using IBM SPSS for Windows, version 26.0 (New York, USA). Results were considered statistically significant at $p<0.05$.

Results

Patient Recruitment and Demographics

A total of 109 patients presenting to our department were initially enrolled in the study. Of these, 36 were excluded due to a diagnosis of idiopathic uveitis. The final analysis, therefore, included 73 patients with systemic disease-related uveitis (Figure 1). Female respondents constituted 51% of the total. The mean age of the cohort was 14.8±4.1 years, with a median follow-up period of 28 months (range 7-82 months). The mean age at uveitis diagnosis was 11.1±4.2 years. Underlying systemic conditions included JIA in 51 patients (70%), probable sarcoidosis in 13 patients (17.8%), BD in 8 patients (11%), and TINU in 1 patient (1.4%). Regarding the temporal sequence of diagnoses, 46 patients (63%) were diagnosed with a rheumatological condition before the onset of uveitis, 9 (12.3%) developed uveitis before receiving a rheumatological diagnosis, and 18 (24.6%) were diagnosed with both conditions simultaneously.

Anatomical classification revealed anterior uveitis in 52 patients (71.2%), intermediate uveitis in 3 patients (4.1%), posterior uveitis in 2 patients (3%), and panuveitis in 16 patients (22%). Regarding duration and disease course, the majority had chronic uveitis (54 patients, 74%) and a limited disease course (42 patients, 57.5%); 38 patients (52%) were symptomatic at presentation. Bilateral involvement was observed in 55 patients (75.3%) (Table 1).

At the initial uveitis visit, antinuclear antibody (ANA) positivity was detected in 64.4% of patients (38 out of 59 tested), primarily in the JIA-associated uveitis (JIAU) group (73.9%) (Table 1).

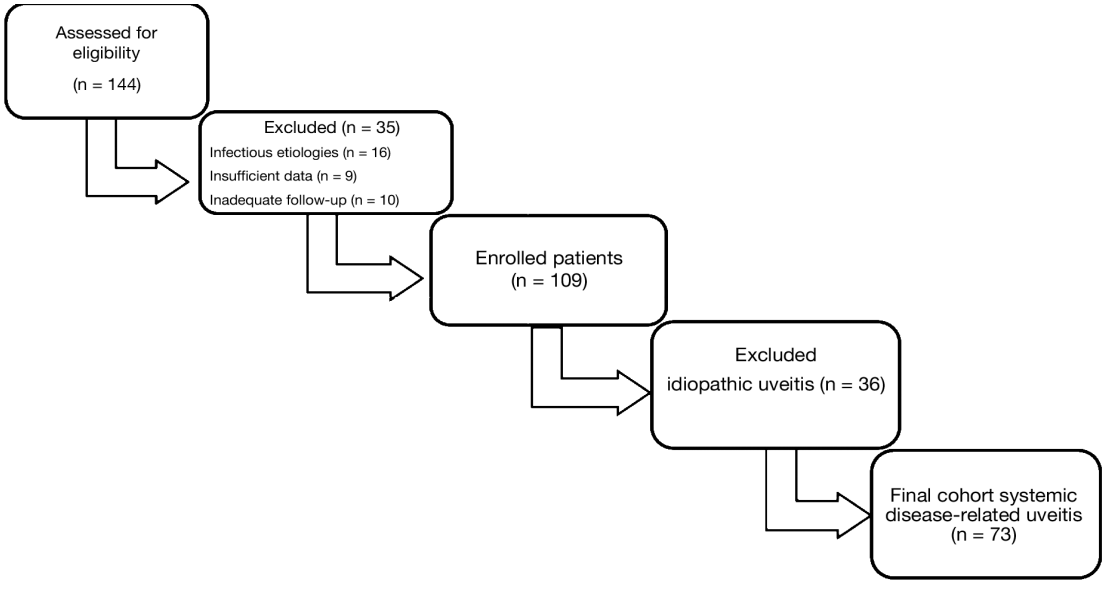

Figure 1. Flowchart for the selection of the study population

Table 1. Demographic, clinical and laboratory features of the patients with uveitis

	JIA	Sarcoidosis	Behçet	TINU
Number of patients, n (%)	51 (70%)	13 (17.6%)	8 (11%)	1 (1.4%)
Gender (Female), n (%)	30/51 (58.8%)	5/13 (38.5%)	2/8 (25%)	0/1 (0%)
Median age (years), (IQR 25-75)	5 (IQR: 4-8)	8.5 (6.7-11)	14.5 (13.0-17.2)	11
Initial diagnosis, n (%) Initially diagnosed with RD Concurrently diagnosed with RD and uveitis Initially diagnosed with uveitis	 41 (50%) 6 (11.8%) 4 (7.8%)	 2 (15.4%) 9 (69%) 2 (15.4%)	 3 (37.5%) 2 (25%) 3 (37.5%)	1 (100%)
Localization of uveitis, n (%) Anterior uveitis Intermediate uveitis Posterior uveitis Panuveitis uveitis	 47 (92.2%) 2 (3.9%) 1 (2%) 1 (2%)	 3 (23%) 0 1 (7.7%) 9 (69%)	 2 (25%) 0 0 6 (75%)	1 (100%)
Duration of uveitis, n (%) Limited Persistent	 33 (65%) 18 (35%)	 4 (18.2%) 9 (69%)	 5 (62.5%) 3 (37.5%)	1 (100%)
Course of uveitis, n (%) Acute Recurrent Chronic	 5 (9.9%) 7 (13.7%) 39 (76.5%)	 2 (15.4%) 0 11 (84.6%)	 4 (50%) 1 (12.5%) 3 (37.5%)	1 (100%)
Bilateral involvement, n (%)	37 (72.5%)	10 (77%)	7 (87.5%)	1 (100%)
Symptomatic, n (%)	18 (35%)	12 (92.3%)	7 (87.5%)	1 (100%)
ANA positivity, n/N (%)	34/46 (73.9%)	3/10 (33.3%)	1/3 (33.3%)	0
CRP positivity, n (%)	30 (58.8%)	9 (69%)	1 (12.5%)	0
ESR positivity, n (%)	26 (51%)	5 (38.5%)	1 (12.5%)	0

JIA: Juvenile idiopathic arthritis, TINU: Tubulointerstitial nephritis and uveitis, RD: Rheumatologic disease, ANA: Antinuclear antibody, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, IQR: Interquartile range

All patients received topical glucocorticosteroids and cycloplegic drops. Systemic steroids were administered to 52 patients (71%), beginning at 1-2 mg/kg/day, with doses tapered after two weeks. The most commonly used immunosuppressive treatments were methotrexate (MTX) and biologic disease-modifying antirheumatic drugs (bDMARDs) (65.7% each).

Complete remission was achieved in 32 patients (44%), partial remission in 26 patients (36%), and remission was not achieved in 15 patients (21%) (Table 2). Regarding disease progression, nine patients (12.3%) required surgical intervention. Complications were observed in 23 patients (31.5%), and relapses in 30 patients (41%) (Table 2).

Data of Patients with JIAU

Among the 51 patients with JIA, the subtype distribution was as follows: thirty (58.8%) were classified as persistent, six (11.8%) as extended oligoarticular, eight (15.7%) as rheumatoid factor-negative polyarticular, four (7.8%) as enthesitis-related, two (3.9%) as psoriatic, and one (2.0%) as systemic.

The median age at uveitis diagnosis was 5 years (IQR 4-8 years), with a median follow-up of 30 months (IQR 13.9-75.7 months). When JIA preceded uveitis, the median interval from JIA diagnosis to uveitis onset was 28 months (IQR 13-48 months). When uveitis preceded JIA, the median interval from uveitis diagnosis to JIA onset was 37 months (IQR 8-78 months) (Table 1).

All patients received topical therapy, and 35 patients (68.6%) received systemic steroids. At the onset of uveitis, among the 51 JIA patients, 16 (31.4%) were not receiving treatment, 19 (37.3%) were receiving MTX monotherapy, 6 (11.7%) were receiving disease-modifying antirheumatic drugs (DMARDs) alone, and 10 (19.6%) were receiving combination therapy. Following diagnosis, treatment was intensified: 36 patients (70.6%) ultimately received conventional DMARDs (35 received MTX and one received sulfasalazine), and 32 patients (62.7%) received bDMARDs. Specifically, 14 of 16 patients not receiving treatment initiated MTX therapy, and 14 of 19 patients already receiving MTX added adalimumab. Importantly, all 11 patients who were receiving etanercept (as monotherapy or in combination with other drugs) at the time of diagnosis were promptly switched to adalimumab (n=9) or tocilizumab (n=2). By the final follow-up, the bDMARDs administered included adalimumab (n=27), tocilizumab (n=2), etanercept (n=2 for arthritis alone), and infliximab (n=1); 25 patients (49%) were managed with combination therapy (Table 2).

Table 2. Treatment characteristics and clinical outcomes of uveitis

	JIA	Sarcoidosis	Behçet	TINU
Local treatment	51 (100%)	13 (100%)	8 (100%)	1 (100%)
Systemic steroid, n (%)	35 (68.6%)	12 (92%)	4 (50%)	1 (100%)
MTX, n (%)	35 (68.6%)	13 (100%)	0	0
SZP, n (%)	1 (2%)	0	0	0
bDMARD, n (%)	32 (63%)	13 (100%)	2 (25%)	1 (100%)
MMF, n (%)	0	2 (15.4%)	0	0
AZT, n (%)	0	0	7 (87.5%)	0
Surgery intervention	5 (9.8%)	3 (23%)	1 (12.5%)	0
Complication	16 (31.6%)	5 (38.4%)	1 (12.5%)	1 (100%)
Recurrence	28 (55%)	1 (8%)	1 (12.5%)	0
Outcome Complete remission Partial remission Non-remission	 20 (39.2%) 19 (37.2%) 12 (23.5%)	 7 (54%) 4 (31%) 2 (15%)	 5 (62.5%) 3 (37.5%) 0	1 (100%)

JIA: Juvenile idiopathic arthritis, TINU: Tubulointerstitial nephritis and uveitis, MTX: Methotrexate, SZP: Sulfasalazine, bDMARDs: Biological disease-modifying antirheumatic drugs, MMF: Mycophenolate mofetil, AZT: Azathioprine

Surgical intervention was required for only five patients (9.8%). Complications were observed in 16 patients (31.6%), including cataracts (n=6), band keratopathy (n=2), glaucoma (n=2), posterior synechiae (n=3), and visual impairment (n=3). Relapse occurred in 28 patients (55%). No cases of legal blindness were recorded during the follow-up period.

At the final follow-up visit, 20 patients (39.2%) had achieved complete remission (Table 2).

Data of Patients with Sarcoidosis-related Uveitis

The median age of the 13 patients with probable sarcoidosis-related uveitis was 8.5 years (IQR 6.7-11 years); the median follow-up period was 34.8 months (23.9-48.1 months). Uveitis was diagnosed concurrently with sarcoidosis in 69% of patients. Panuveitis was present in 69% of patients and was chronic in 84.6% of cases had a chronic active course. The ocular condition affected both eyes in 77% of cases; 92.3% of patients presented with clinical manifestations, including conjunctival hyperemia, decreased vision, eye pain, and blurred vision.

All patients received topical therapy, and 12 (92%) were treated with systemic steroids. Combination therapy with MTX and adalimumab was initiated in 10 patients (77%), of whom two had discontinued MTX and added mycophenolate mofetil to adalimumab after a uveitis relapse; one had stopped MTX due to gastrointestinal side effects and continued adalimumab monotherapy; and one had replaced adalimumab with infliximab due to worsening arthritic symptoms. One patient was initially treated with MTX and infliximab. Two patients (15.4%) who received MTX monotherapy were subsequently treated with adalimumab monotherapy.

Surgical intervention was necessary for three patients. Complications arose in five patients (two with cataracts, two with band keratopathy, and one with glaucoma). Only one patient experienced a recurrence of the disease, while two patients did not respond to treatment at the last follow-up.

Data of Patients with Behçet's Uveitis

The median age of the eight patients with Behçet-related uveitis was 14.5 years (IQR 13.0-17.2 years), with a median follow-up period of 26 months (range 4.5-82 months). Three patients (37.5%) were diagnosed with BD prior to uveitis, while two patients (25%) received both diagnoses simultaneously. The remaining three patients (37.5%) were diagnosed with uveitis before BD was identified. The majority (75%) of patients presented with panuveitis, and four patients (50%) presented with acute uveitis. Ocular involvement was bilateral in 87.5% of patients and was symptomatic; a limited clinical course was observed in 62.5% of cases.

A review of the treatment protocols revealed that all patients received topical therapy. Systemic corticosteroids were administered to four patients (50%). Two patients (25%) were treated with colchicine, and five patients (62.5%) were treated with a combination of azathioprine (AZT) and colchicine. Due to disease progression, the treatment for one of these patients was changed to infliximab and cyclosporine. In another case, initial therapy with cyclosporine and AZT for six months was switched to infliximab because of persistent uveitis. After the patient had achieved two years of remission, infliximab was discontinued and AZT was reintroduced.

Surgical intervention was required for one patient. One patient developed retinitis as a complication, and another patient experienced a disease relapse. At the final follow-up, five patients were in complete remission and three were in partial remission.

Data of Patients with TINU Syndrome

An 11-year-old male patient with TINU syndrome was followed for 7 months. The initial presentation included bilateral ocular hyperaemia and intermediate, chronic, and persistent uveitis. Treatment initially comprised topical and systemic steroid therapy, but adalimumab was introduced after three months. The patient achieved partial remission at the final follow-up.

Discussion

This retrospective cohort study provides comprehensive data on patients with chronic uveitis of pediatric onset that is non-infectious and associated with systemic disease. The study offers insight into the condition's clinical features, treatment approaches, and outcomes. Uveitis was predominantly anterior and bilateral and was most frequently associated with ANA-positive oligoarticular JIA. Despite the difficulties of treating pediatric uveitis, more than half of our patients went into complete remission, and none of them went blind. This shows how well MTX and biologic therapy work for this group of patients.

In our cohort, JIAU was the leading etiology, followed by sarcoidosis. While idiopathic uveitis is commonly reported as the most frequent cause worldwide (3,13), JIA remains the most important systemic association in Europe and North America. Our JIA rate was higher than in most international series (16-25%) (14-18). We attribute this difference to our study design, which included only patients with suspected rheumatological conditions and excluded those with idiopathic uveitis. By contrast, the BUST Registry reported JIA in only 12.4% of pediatric uveitis cases (19); studies from Japan reported almost no JIA cases, with BD predominating (20).

In line with data from endemic regions along the Silk Road, BD was the third most frequent systemic cause. In Türkiye, pediatric studies have reported the prevalence of Behçet's uveitis ranging from 9.3% to 19.7%, thereby ranking it among the two most common systemic associations (21-24). Studies from Israel, where BD is also endemic, have documented Behçet's uveitis in 4.6-26.3% of pediatric patients (25-27). The etiological distribution of uveitis due to BD varies considerably with geographic, genetic, and demographic factors, as well as institutional referral patterns. Additionally, the use of different definitions of the pediatric age range can lead to discrepancies in etiology, resulting in notable variations even among studies from the same geographical region (19). Therefore, our data highlight that in endemic regions, BD remains a critical differential diagnosis in pediatric uveitis, even when JIA is the primary systemic association.

In our study, the mean age at uveitis diagnosis was 11.1±4.2 years. Juvenile idiopathic arthritis tended to present in younger children, whereas BD was more prevalent in older age groups. Similarly, when analyzed by age group, Altınel et al. (28) found that JIAU was most frequently observed in the preschool-age group, while BD was most frequently observed in the late-school-age group. The BUST Study Group's National Registry Report also found that JIA was the most common systemic disease in kids under 10 years old, while BD was the most common systemic disease in kids 10 years old and older (19). This pattern likely reflects the distinct pathophysiological mechanisms and immune system maturation processes underlying these conditions. This age-stratified distribution has important clinical implications, as it can help clinicians develop age-appropriate diagnostic algorithms and screening protocols.

The majority of uveitis cases in our cohort presented with an anterior localization, a chronic course, and bilateral involvement. These findings are consistent with those reported in the existing literature (3,13,15,17,28,29). However, the anatomical distribution varied significantly according to the underlying cause: anterior uveitis predominated in most JIA patients, whereas panuveitis predominated in approximately three-quarters of patients with sarcoidosis or BD. The predominance of anterior uveitis in our cohort largely reflects the high proportion of JIA patients, who typically present with chronic bilateral anterior uveitis. Our findings are consistent with previous reports demonstrating that anterior uveitis is the most common type among pediatric patients, affecting approximately 80% of cases (16,17,30). Similarly, the pattern of panuveitis observed in most of our BD patients confirms existing knowledge and mirrors the findings of Koru et al. (17), who reported panuveitis in all BD patients.

In line with previous reports, the majority of cases showed chronic bilateral involvement, highlighting the severe nature of the disease (3,8,16,17,30,31). Although the majority of JIA patients were asymptomatic, only 35% exhibited symptoms, highlighting the asymptomatic nature of JIAU. Another study found that approximately 40% of patients with BD reported no symptoms (17). This may be due to children's limited ability to recognize or report ocular problems, compared with adults who have the same disease. Therefore, we believe that uveitis screening is crucial to identify these asymptomatic cases, even in the absence of ocular complaints.

Consistent with the existing literature, our study confirmed that the oligoarticular subtype and ANA positivity are key risk factors for the development of uveitis

in JIA patients (32). Of our JIA patients with uveitis, 64.4% were ANA positive and 70.6% had oligoarticular disease. This is consistent with previous studies demonstrating that these features are risk factors for JIAU (2-4,32-34).

Our treatment approach produced inconsistent results among various uveitis etiologies, highlighting the challenges of managing the condition in pediatric patients. The overall treatment strategy involved a step-up approach: topical corticosteroids and cycloplegic agents were administered to all patients initially, followed by systemic interventions based on disease severity and response. The high utilization of systemic corticosteroids aligns with current guidelines, which recommend early, aggressive treatment to prevent complications (35,36). The successful tapering protocol after two weeks helped minimize steroid-related side effects while maintaining therapeutic efficacy. Methotrexate was the most frequently used immunosuppressive agent, consistent with its established role as a first-line, steroid-sparing therapy for pediatric uveitis (35-37). Biologic therapy was required for 65.7% of our patients. According to current treatment guidelines (35-38), anti-tumor necrosis factor agents were the most commonly used biologic treatments. The significant proportion of patients requiring biologic DMARDs highlights the refractory nature of pediatric uveitis and the shift toward earlier biologic intervention.

Among patients with JIAU in our cohort, the primary treatment consisted of conventional DMARDs, predominantly MTX, which has been used at similar rates in previous studies (60-82%) (15,19,37). Adalimumab was the most frequently used biologic agent, reflecting findings from the SYCAMORE trial, which demonstrated the superiority of adalimumab in combination with MTX over MTX monotherapy (38). Similarly, another study reported MTX use in 87% of patients, with bDMARDs added in 73.9% of treatment-resistant cases. This regimen achieved a treatment response in 26.1% of patients at the final visit (15).

The management of sarcoidosis-associated uveitis proved particularly challenging, as all patients required systemic immunosuppression, often as combination therapy with MTX and adalimumab, due to the predominance of panuveitis. The frequent need to modify treatment reflected the severe course of the disease, as also reported in pediatric sarcoid uveitis studies (39-41). In our cohort, the most aggressive regimens were required for uveitis associated with both JIA and probable sarcoidosis, characterized by substantial systemic treatment requirements and early use of biologics. This highlights the chronic, severe inflammatory nature of these conditions and their resistance to conventional therapy.

Complications occurred in 31.5% of the cohort, relapses occurred in 41% of the cohort, and surgical intervention was required in only 12.3% of the cohort. Recent pediatric uveitis series have reported variable complication rates, ranging from 11.4% to 69% across studies (42-44). Yalçındağ et al. (21) reported complications in 26.1% of cases, with surgical intervention in 2.8%, while other studies showed complication rates ranging from 34% to 76.1% and surgical intervention rates of 8-46% (15,22). By comparison, our lower complication rate and surgical intervention rate may reflect earlier use of biologics, rigorous screening protocols, and effective multidisciplinary collaboration between the rheumatology and ophthalmology departments. We achieved favorable outcomes that support the validity of our therapeutic approach with 44% complete remission and 36% partial remission at the final follow-up. A notable finding was that, despite JIA patients demonstrating the complication and recurrence rates, only 23.5% remained non-remissive at the final visit and no cases of blindness were observed, which contrasts with previous studies (39,45).

It was similarly noteworthy that patients with sarcoidosis and BD, despite presenting with chronic panuveitis, achieved remission by the final follow-up appointment, with no progression to blindness. We attribute this outcome to our earlier escalation strategy, which aligns with current guidelines that advocate prompt treatment intensification.

Study Limitations

Our study has several limitations. Primarily, it is retrospective and single-center; follow-up durations are variable, which may affect the assessment of long-term outcomes. The relatively small sample sizes in certain subgroups, such as those with BD or TINU, mean that these findings should be interpreted with caution. Retrospective constraints also limited the uniformity of diagnostic procedures and the availability of advanced genetic testing and ocular imaging. Furthermore, diagnosing systemic diseases in children is challenging, as symptoms may emerge long after the onset of uveitis. Despite these limitations, a key strength of our study is the longitudinal evaluation of a broad spectrum of causes managed within a dedicated multidisciplinary model.

Conclusion

Our data suggest that the early use of biologics, particularly in ANA-positive JIA and sarcoidosis-associated uveitis, when combined with close collaboration between rheumatologists and ophthalmologists, reduces complications and improves visual outcomes. This multidisciplinary approach allows for timely screening, early diagnosis, and intensified treatment before irreversible damage occurs.

Ethics

Ethics Committee Approval: The study was approved by the Istanbul University Istanbul Faculty of Medicine Clinical Research Ethics Committee (no.: 1774366, date: 23.05.2023).

Informed Consent: Written informed consent were obtained from the responsible adult for each patient.

Footnotes

Authorship Contributions

Concept: V.G., F.G.D., M.C., T.O., M.E., N.A.A., Design: V.G., F.G.D., M.C., T.O., M.E., N.A.A., Data Collection or Processing: V.G., F.G.D., O.C., M.C., T.O., M.E., N.A.A., Analysis or Interpretation: V.G., F.G.D., T.O., M.E., N.A.A., Literature Search: V.G., F.G.D., M.C., T.O., M.E., N.A.A., Writing: V.G., F.G.D., M.C., M.E., N.A.A.

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Original Article

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Magnetic Resonance Imaging in the Evaluation of Sinusitis Related Complications in Children

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Abstract

Aim: Acute sinusitis in children can occasionally lead to orbital or intracranial complications as a result of contiguous spread of infection. We aimed to evaluate the magnetic resonance imaging (MRI) features and distribution patterns of these complications in pediatric patients with acute paranasal sinusitis.

Methods: This retrospective analytical study included 32 pediatric patients (aged 0-18 years) who underwent contrast-enhanced brain and diffusion-weighted MRI between May 2017 and April 2024 for suspected sinusitis-related complications. Demographic data (age, sex), sinus involvement, and MRI findings were evaluated. Statistical analyses were performed using chi-square tests and Student's t-tests; a p-value of <0.05 was considered significant. All MR images were reviewed by a pediatric neuroradiologist with ten years of experience.

Results: Among the 32 pediatric patients, the most frequent complication was subperiosteal abscess (n=15, 46.9%), followed by preseptal cellulitis (n=13, 40.6%). Less common findings included epidural empyema (n=2, 6.3%), venous sinus thrombosis (n=1, 3.1%), cerebral abscess (n=1, 3.1%), and cerebral infarction (n=1, 3.1%). Involvement of the ethmoid and maxillary sinuses was significantly more frequent in younger children (p<0.01), whereas involvement of the sphenoid and frontal sinuses was more common in older patients (p=0.03). When evaluated by complication type, orbital complications predominated in younger patients, while intracranial complications were more frequent in older age groups (p=0.02). This indicates a statistically significant age-related shift in the patterns of sinus involvement and distribution of complications.

Conclusion: Magnetic resonance imaging plays a critical role in detecting and characterizing sinusitis-related complications in pediatric patients. Beyond confirming a diagnosis, it provides valuable information for clinical decision-making and surgical planning. Recognizing age-dependent sinus involvement patterns helps predict the potential routes and severity of the spread of complications, ultimately improving outcomes and reducing morbidity.

Keywords: Child, sinusitis, complications, magnetic resonance imaging

Introduction

Sinusitis is common in children and is usually associated with upper respiratory tract infections. Acute sinusitis typically occurs due to viral agents and follows a self-limited course. However, bacterial superinfections may develop in some cases, increasing the risk of complications (1). Although sinusitis is a significant health problem in pediatric patients, it can lead to serious complications if not diagnosed and treated promptly.

Symptoms of sinusitis in children may include nasal congestion, mucopurulent nasal discharge, cough, fever, and facial pain (2). Although radiographic imaging is usually unnecessary, it can be used to confirm the diagnosis in selected cases. However, plain radiography

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in children may be misleading; therefore, more advanced imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) are preferred (3,4). While CT provides high sensitivity in evaluating bony structures, MRI offers superior soft-tissue resolution and, importantly, does not involve ionizing radiation—an advantage in pediatric patients (5). Complications of sinusitis include preseptal and postseptal cellulitis, subperiosteal abscess, meningitis, cerebritis, epidural and subdural empyema, cavernous sinus thrombosis, and cerebral venous sinus thrombosis (6). Ethmoid and maxillary sinus infections are more frequent in younger children, whereas sphenoid and frontal sinus infections are more common in older age groups (7). Magnetic resonance imaging allows clear visualization of soft tissue and intracranial structures, making it particularly valuable in detecting the extension and nature of sinusitis-related complications (8,9). Recent studies highlight the importance of a multidisciplinary approach to the management of pediatric sinusitis complications (10). Diffusion-weighted MRI sequences, particularly for early detection of intracranial involvement, have been shown to enhance diagnostic accuracy (11). Moreover, combining surgical and medical management strategies provides optimal outcomes for these patients (12). We hypothesized that MRI could effectively demonstrate both orbital and intracranial complications related to acute sinusitis in pediatric patients, thereby improving diagnostic confidence and clinical management.

This study aimed to investigate the MRI findings of complications resulting from the local spread of acute paranasal sinusitis in pediatric patients. By defining the characteristic MRI features of these complications, the study seeks to improve diagnostic accuracy and promote the earlier recognition of serious disease extension. This, in turn, is expected to facilitate timely clinical management and multidisciplinary decision-making, thereby contributing to better patient outcomes and advancing the diagnostic approach in pediatric radiology.

Materials and Methods

Compliance with Ethical Standards

This retrospective study was approved by the Selcuk University Rectorate Local Ethics Committee (approval no.: 2024/447, date: 18.09.2024). The research was conducted in accordance with the principles of the Declaration of Helsinki (2013 revision). Patient confidentiality was maintained throughout the study, and all data were anonymized prior to analysis. Due to the retrospective design, obtaining informed consent from individual participants was deemed unnecessary by the ethics committee.

Study Design and Population

The step-by-step process for selecting patients included in this retrospective cohort study is illustrated in the flowchart below (Figure 1). This study had a retrospective cohort design. Pediatric patients aged 0-18 years who underwent contrast-enhanced brain MRI and diffusion-weighted MRI between May 2017 and April 2024 for suspected sinusitis-related complications were included. The hospital's Radiology Information System and Picture Archiving and Communication System were searched using the keywords "sinusitis," "orbital cellulitis," "subperiosteal abscess," "intracranial complication," and "paranasal sinus infection."

Inclusion and Exclusion Criteria

Inclusion criteria were (1) age 0-18 years; (2) clinical diagnosis of sinusitis; and (3) availability of contrast-enhanced brain MRI and diffusion MRI with diagnostic image quality. Exclusion criteria included history of trauma, congenital craniofacial anomalies, known malignancy, prior sinus surgery, or non-diagnostic or artifactual images.

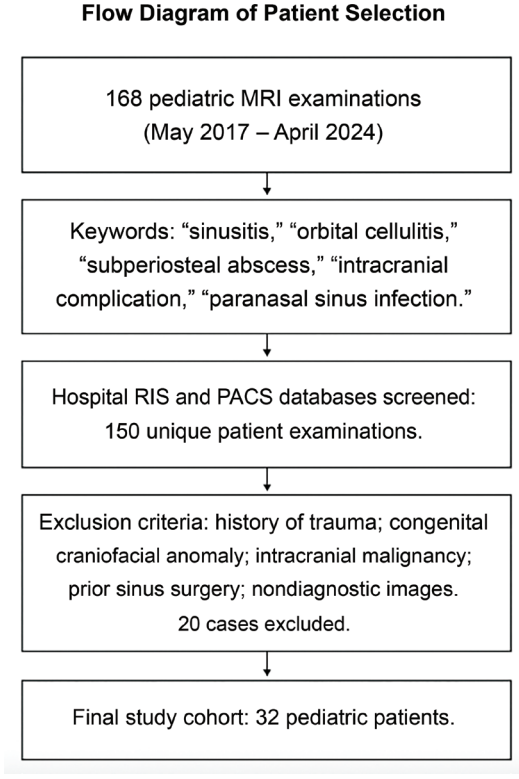

Figure 1. Flow diagram illustrating the step-by-step selection process of pediatric patients included in the retrospective cohort study. The diagram summarizes the total number of MRI examinations reviewed, applied inclusion and exclusion criteria, and the final study cohort of 32 patients

MRI: Magnetic resonance imaging, RIS: Radiology information system, PACS: Picture archiving and communication system

Based on these criteria, 32 pediatric patients were included.

MRI Protocol

All MRI examinations were performed on a 1.5-Tesla system (Siemens Magnetom Aera, Erlangen, Germany) using a standardized pediatric brain protocol optimized to evaluate complications of sinusitis. The sequences included an axial T1-weighted spin-echo sequence (TR/TE =500/10 ms; slice thickness =4 mm; interslice gap =1 mm; matrix =256 × 256; field of view =220 × 220 mm). Axial T2-weighted turbo spin-echo (TR/TE: 4000/100 ms, echo train length: 15, same slice parameters). Axial and coronal FLAIR (TR/TE/TI: 9000/90/2500 ms, slice thickness: 4 mm, FOV: 220 × 220 mm). Axial diffusion-weighted imaging (b-values: 0 and 1000 s/mm², TR/TE: 3500/90 ms, slice thickness: 4 mm, matrix: 192 × 192). Post-contrast T1-weighted sequences were acquired in axial, coronal, and sagittal planes following intravenous administration of 0.1 mmoL/kg gadolinium-based contrast agent, using acquisition parameters identical to those of the pre-contrast T1-weighted imaging. Fat-suppressed sequences were used in the orbital and paranasal sinus regions to enhance soft-tissue contrast. All images were interpreted by a pediatric neuroradiologist with 10 years of experience.

Image Analysis

Evaluated parameters included the involved sinuses (maxillary, ethmoid, frontal, and sphenoid); orbital complications (preseptal/postseptal cellulitis, subperiosteal abscess); intracranial complications (meningitis, cerebritis, epidural/subdural empyema, abscess, sinus vein thrombosis, and cavernous sinus thrombosis); and bone changes (osteomyelitis and erosion). Preseptal cellulitis was defined as anterior orbital septum edema or enhancement, postseptal cellulitis as posterior orbital septum inflammation, and subperiosteal abscess as a fluid collection between the periosteum and the underlying bone.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics, version 25.0 (IBM Corp., Armonk, NY, USA). The normality of data distribution was evaluated using the Shapiro-Wilk test. Continuous variables were expressed as mean ± standard deviation for normally distributed data or as median (interquartile range) for non-normally distributed data; categorical variables were presented as frequencies and percentages. For comparisons between groups, the Student's t-test and the Mann-Whitney U test were used for parametric and non-parametric data, respectively. Categorical variables were analyzed using the chi-square test or Fisher's exact test, as appropriate. To enhance the analytical rigor of the study, inferential and correlational analyses were incorporated. Specifically, the relationship between age and type of complication (orbital vs. intracranial) was analyzed using the Spearman's rank correlation coefficient.

The association between frontal sinus involvement and the presence of intracranial complications was evaluated using the chi-square test. Additionally, the co-occurrence of orbital and intracranial complications was assessed to compare the age distribution and clinical characteristics between groups. All statistical analyses were two-tailed, and a p-value <0.05 was considered statistically significant.

Results

The mean age of the 32 pediatric patients included in the study was 8.7±3.4 years (range: 2-17 years). Of these patients, 19 (59.4%) were male and 13 (40.6%) were female, yielding a male-to-female ratio of 1.46:1 (p=0.41, not statistically significant).

On MRI, ethmoid sinus involvement was identified in 28 patients (87.5%) and was the most frequently affected paranasal sinus. This rate was significantly higher than those for maxillary (81.3%), frontal (53.1%), and sphenoid (28.1%) sinus involvement (p<0.01). Involvement of multiple sinuses was present in 22 patients (68.8%), and the most frequent combination was the concurrent involvement of the ethmoid and maxillary sinuses (n=18, 56.3%).

Sinusitis-related complications were classified into two major categories: orbital and intracranial. Orbital complications were identified in 28 patients (87.5%), whereas intracranial complications occurred in 7 patients (21.9%). Both orbital and intracranial complications coexisted in 3 patients (9.4%). The mean age of patients with orbital complications was significantly lower than that of those with intracranial complications (p=0.02).

Among orbital complications, subperiosteal abscesses were the most common finding, detected in 15 patients (46.9%). Most of these abscesses were localized to the periorbital region (n=10, 31.3%; Figure 2), whereas frontal subperiosteal abscesses occurred in five patients (n=5, 15.6%; Figure 3). All periorbital subperiosteal abscesses were confined to the medial orbital wall (p<0.01). Preseptal cellulitis occurred in 13 patients (40.6%) and was the second most common orbital pathology, followed by postseptal cellulitis in 5 patients (15.6%). Notably, all cases of postseptal cellulitis also demonstrated concomitant preseptal cellulitis (n=5; 100%), supporting the progressive spread of infection from the preseptal to the postseptal compartment (p<0.01).

Regarding intracranial complications, subdural empyema was identified in 2 patients (6.3%; Figure 4), whereas epidural empyema, sinus vein thrombosis, cerebral abscess, cerebral infarction, and transient callosal

lesion were each observed in 1 patient (3.1%; Figure 5). The majority of intracranial complications (n=5, 71.4%) were associated with frontal sinusitis; this association was statistically significant (p=0.03).

A single complication was detected in 19 patients (59.4%), whereas multiple complications were present in 13 patients (40.6%) (p=0.27; not statistically significant). The most frequent combination was preseptal cellulitis with periorbital subperiosteal abscess (n=7, 21.9%).

When stratified by age group, orbital complications were predominant in the 0-5-year age group (n=8; 87.5%), while both orbital and intracranial complications were most common in the 6-12-year age group (n=15; 73.3% orbital, 26.7% intracranial). Intracranial complications were more frequently observed in the 13-17-year age group (33.3%), and this age-related increasing trend was statistically significant (p=0.04).

Correlation analyses further supported these findings. A significant positive correlation (r=0.38, p=0.04) was identified between age and complication type (orbital vs. intracranial), indicating that intracranial complications were more likely to occur in older children. The association between frontal sinus involvement and intracranial complications was also statistically significant (p=0.03). Additionally, patients with orbital complications were found to be significantly younger than those with intracranial involvement (p=0.02).

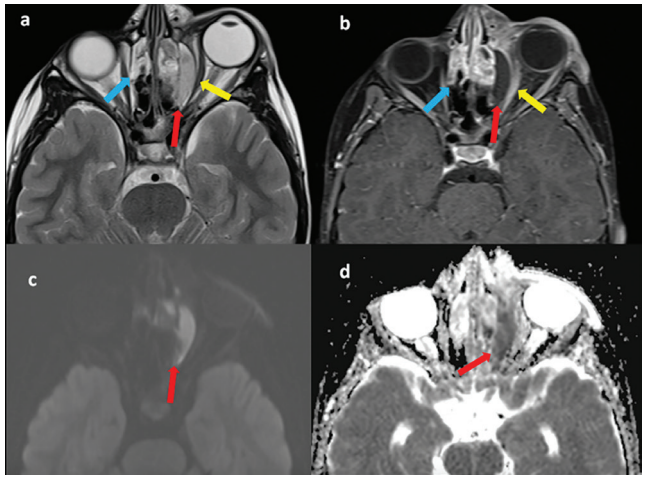

Figure 2. Thirteen-year-old female with ethmoidal sinusitis complicated by orbital subperiosteal abscess. Contrast-enhanced brain MRI (a, b) and diffusion-weighted imaging (c, d) show ethmoidal sinusitis with erosion of the lamina papyracea (blue arrow) and a rim-enhancing, loculated retro-orbital subperiosteal collection exhibiting diffusion restriction (red arrow), consistent with an abscess. The medial rectus muscle appears thickened and displaced laterally (yellow arrow), indicating inflammatory involvement and mass effect from the adjacent abscess. These findings highlight the typical pathway of infection spread from the ethmoid sinus through the lamina papyracea into the orbital compartment

MRI: Magnetic resonance imaging

Discussion

This study provides a detailed analysis of MRI findings in pediatric patients with acute paranasal sinusitis and its complications, emphasizing data specific to our cohort. The results indicate that ethmoid sinus involvement was the most frequent finding, while frontal sinus involvement was significantly associated with intracranial complications, underscoring a potential anatomical pathway for the spread of infection. Moreover, the significant positive correlation between age and the occurrence of intracranial complications indicates that the type and severity of complications vary across age groups. These findings not only align with existing literature but also extend current knowledge by defining MRI-based diagnostic patterns and risk associations specific to the pediatric population evaluated in this study.

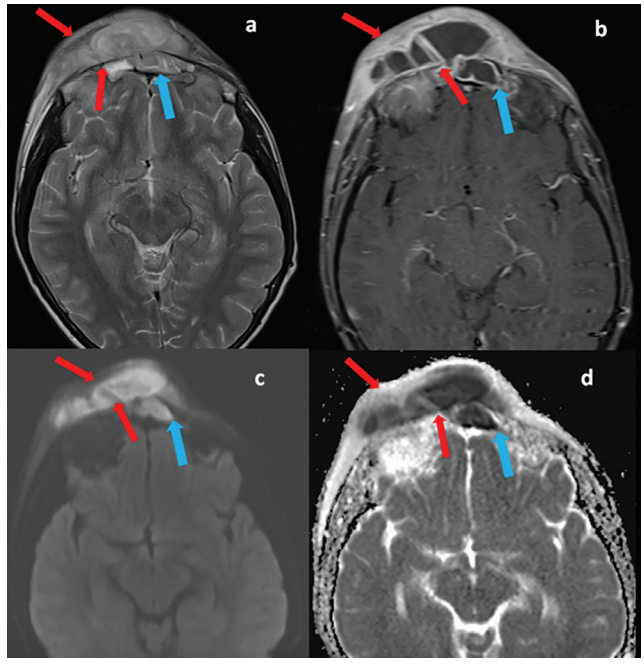

Figure 3. Twelve-year-old male with frontal sinusitis complicated by subperiosteal abscess formation. Contrast-enhanced brain MRI (a, b) and diffusion-weighted imaging (c, d) demonstrate frontal sinusitis with erosion of the anterior sinus wall and a rimenhancing, loculated subperiosteal collection along the frontal bone (red arrow), showing diffusion restriction consistent with an abscess. The affected frontal sinus exhibits mucosal thickening and fluid accumulation (blue arrow), indicating active inflammation. Adjacent subgaleal soft tissue edema and enhancement are also evident, supporting the diagnosis of Pott's puffy tumor secondary to frontal sinusitis

MRI: Magnetic resonance imaging

The most common complication in our study was subperiosteal abscess, consistent with studies reporting that it is among the most common complications in pediatric sinusitis (1). The anatomical proximity of the ethmoid sinuses to the orbital periosteum explains the high incidence of subperiosteal abscesses. The direct spread of ethmoid sinus infections across the lamina papyracea into the periorbital tissues facilitates abscess formation. Notably, all periorbital subperiosteal abscesses in our cohort were localized to the medial orbital wall, supporting the view that the most frequent route by which infection spreads from the ethmoid sinus to the orbit is through the lamina papyracea (12). Additionally, the proportion of frontal subperiosteal abscesses among all subperiosteal abscesses in our series (33.3%) was comparable to the 25% rate reported in the literature (13). The high frequencies of preseptal (40.6%) cellulitis and postseptal cellulitis (15.6%) align with reports identifying preseptal cellulitis as a common early-stage orbital complication in pediatric sinusitis (3). The observation that all postseptal cellulitis cases were accompanied by preseptal cellulitis supports the notion of stepwise infectious progression through the orbital septum. Although postseptal cellulitis is less common, it remains clinically important because it can progress to severe complications, such as orbital abscess or cavernous sinus thrombosis (4). In addition to these literature-supported observations, our findings emphasize that localization to the medial orbital wall and combined ethmoid and maxillary sinus involvement were particularly distinctive features of this cohort, suggesting that the anatomical configuration of the pediatric paranasal sinuses may predispose to this characteristic pattern of spread. Furthermore, the relatively higher incidence of frontal subperiosteal abscesses in our study may indicate an age-related increase in frontal sinus aeration and susceptibility to infection, thereby providing

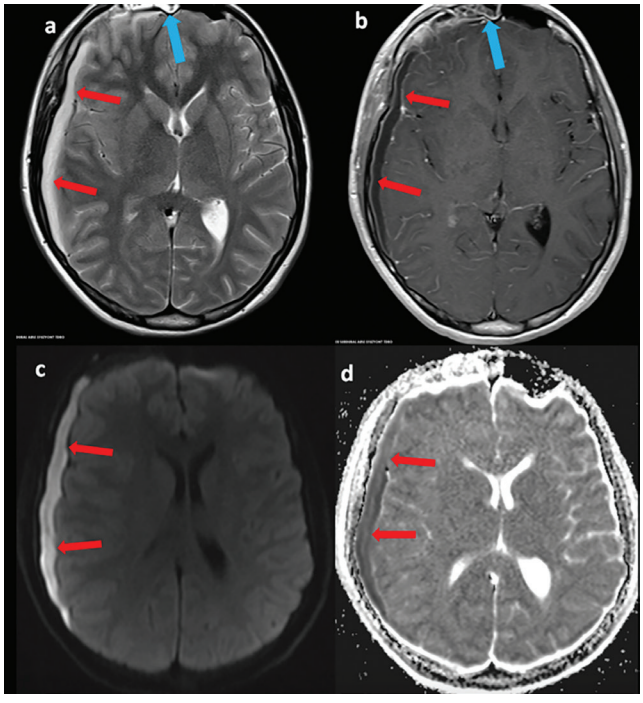

Figure 4. Nine-year-old male with frontal sinusitis complicated by subdural empyema. Contrast-enhanced brain MRI (a, b) and diffusion-weighted imaging (c, d) demonstrate right frontal sinusitis with mucosal thickening and enhancement (blue arrow). In the adjacent right frontotemporal region, a crescent-shaped extra-axial collection with peripheral enhancement and marked diffusion restriction is seen (red arrow), consistent with subdural empyema. Associated dural thickening and enhancement are evident, indicating inflammatory spread from the frontal sinus. Mild adjacent cortical edema and mass effect on the frontal lobe further support the diagnosis of intracranial extension secondary to sinusitis

MRI: Magnetic resonance imaging

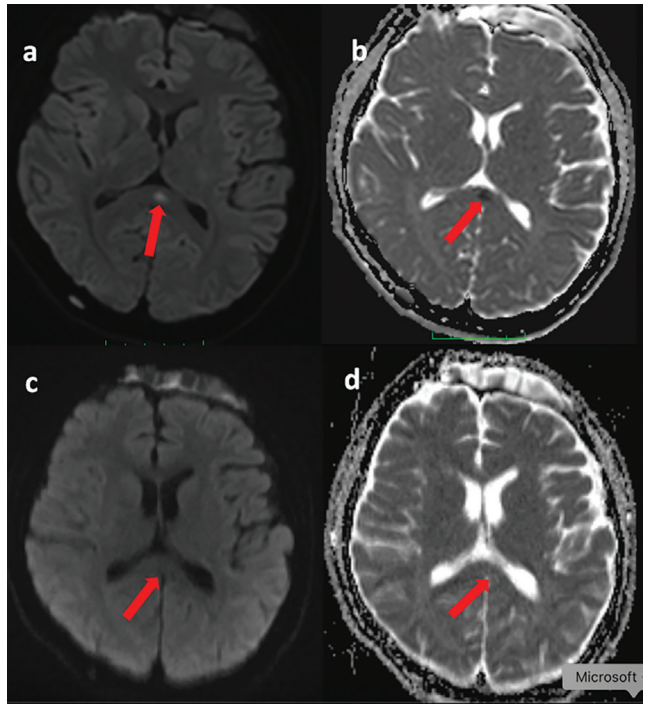

Figure 5. Fourteen-year-old male with pansinusitis and transient splenial lesion of the corpus callosum. Diffusion-weighted MRI obtained on admission (a, b) demonstrates a well-defined focus of restricted diffusion in the splenium of the corpus callosum (red arrow), without corresponding contrast enhancement, consistent with a transient cytotoxic lesion. Follow-up MRI performed 16 days later (c, d) shows complete resolution of the diffusion abnormality, confirming its reversible nature. This transient splenial lesion likely represents a secondary inflammatory or metabolic response associated with systemic infection and sinusitis, rather than direct infectious involvement of the corpus callosum

MRI: Magnetic resonance imaging

a pathophysiological explanation specific to the pediatric population evaluated.

Intracranial complications, including meningitis, cerebral abscess, epidural empyema, subdural empyema, and venous sinus thrombosis, were observed in 21.9% of patients in our cohort, underscoring the considerable prevalence of these severe outcomes. This rate is comparable to the 15-20% incidence reported in previous studies (14). The detected intracranial complications included subdural empyema (6.3%), epidural empyema (3.1%), venous sinus thrombosis (3.1%), cerebral abscess (3.1%), and cerebral infarction (3.1%). Notably, 71.4% of these cases were associated with frontal sinusitis, indicating that frontal sinus involvement represents a significant anatomical and clinical risk factor for intracranial spread. In our cohort, both patients who developed neurological sequelae had intracranial complications, further emphasizing their clinical significance and potential for long-term morbidity. Moreover, the single case of cerebral abscess required surgical drainage and prolonged antibiotic therapy, which confirms the aggressive clinical course of this complication despite early recognition and management (7). These findings indicate that although the frequency of intracranial complications parallels previous reports, their clinical presentation and treatment requirements in our study underscore the importance of early MRI evaluation for timely detection and intervention, particularly in cases related to frontal sinusitis.

The results of our study demonstrated that the distribution of complications varied significantly among age groups, revealing characteristic patterns at different developmental stages. Orbital complications predominated in younger children (0-5 years, 87.5%), whereas intracranial complications were more frequent in adolescents (13-17 years, 33.3%). This age-related shift in complication patterns corresponds to the progressive pneumatization and anatomical maturation of the frontal sinuses, which facilitates the superior and posterior spread of infection in older patients. These findings are consistent with reports indicating an increased risk of intracranial complications in adolescents due to greater frontal sinus development and increased venous drainage complexity (15). Furthermore, the meta-analysis conducted by Patel et al. (15) confirmed a higher incidence of intracranial complications in this age group. In our cohort, this correlation between age and type of complication ($r=0.38$, $p=0.04$) supports the pivotal role of anatomical maturation in the pathophysiological transition from orbital to intracranial involvement and represents a key age-dependent risk factor specific to pediatric sinusitis.

In our study, MRI proved highly effective in evaluating pediatric sinusitis complications due to its superior soft tissue contrast and absence of ionizing radiation. The combined use of diffusion-weighted and contrast-enhanced sequences enabled the accurate detection of abscesses and dural enhancement, and the differentiation between empyema and cellulitis (8). The consistent peripheral enhancement in all subperiosteal abscesses further underscored the diagnostic value of post-contrast imaging. Moreover, FLAIR and T2-weighted sequences effectively demonstrated meningeal inflammation and parenchymal edema, particularly in cases with intracranial extension (9). Our findings showed that subperiosteal abscess was the most frequent complication, and that frontal sinus involvement was significantly correlated with intracranial spread, confirming the strength of MRI in identifying patients at high risk. Based on these results, MRI stands as the cornerstone imaging modality for the early diagnosis and management of pediatric sinusitis complications. Prospective multicenter studies employing standardized protocols and advanced MRI techniques—including perfusion imaging, MR spectroscopy, and susceptibility-weighted imaging—are needed to validate and extend these findings for clinical practice (10).

Study Limitations

This study has several limitations that should be acknowledged. The retrospective design and limited sample size may restrict the generalizability of the findings. Additionally, being a single-center study limits the ability to compare diagnostic and management approaches across different institutions. Future multicenter, prospective studies with larger cohorts are needed to validate these results and better define institutional variability (10). Moreover, potential selection bias may have occurred because only patients who underwent MRI were included; individuals with milder forms of sinusitis complications who did not require MRI were therefore not represented. This could have influenced the observed incidence of complications. Furthermore, the absence of long-term follow-up data limits the evaluation of delayed or recurrent complications. Another limitation of the study is the lack of prognostic data on intracranial complications, which limits assessment of long-term neurological outcomes and recovery patterns in affected patients. Despite these limitations, this study provides a comprehensive MRI-based evaluation of sinusitis complications in pediatric patients. The inclusion of both contrast-enhanced and diffusion-weighted sequences, detailed clinical correlation, and age- and location-specific analyses enhances the scientific strength of the study and provides clinically meaningful insight into the diagnostic and prognostic value of MRI in this setting.

Conclusion

This study provides definitive evidence that MRI is an indispensable tool for diagnosing and managing

complications of pediatric sinusitis, revealing that subperiosteal abscesses predominate overall, while intracranial complications—more common in adolescents—are associated with more severe outcomes. MRI's superior soft-tissue contrast, multiplanar capabilities, and absence of ionizing radiation make it uniquely valuable for pediatric imaging; diffusion-weighted sequences are particularly effective at detecting abscesses and ischemic changes. Our age-stratified findings provide clinicians with critical guidance for risk assessment and intervention planning, emphasizing that early, accurate diagnosis through appropriate MRI protocols significantly reduces morbidity and mortality in these potentially serious conditions. Optimizing MRI techniques and protocols for complications of pediatric sinusitis is a crucial area for ongoing clinical research and development.

Ethics

Ethics Committee Approval: This retrospective study was approved by the Selcuk University Rectorate Local Ethics Committee (approval no.: 2024/447, date: 18.09.2024). The research was conducted in accordance with the principles of the Declaration of Helsinki (2013 revision).

Informed Consent: Due to the retrospective design, obtaining informed consent from individual participants was deemed unnecessary by the Ethics Committee.

Footnotes

Authorship Contributions

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

Conflict of Interest: No conflicts of interest were declared by the authors.

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Original Article

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Knowledge of Human Papillomavirus Among Students in Health- and Non-health-related Departments of a Private University

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Abstract

Aim: The knowledge of human papillomavirus (HPV) and related diseases plays a vital role in shaping individual perspectives on prevention. This study aimed to evaluate HPV infection and vaccination knowledge among university students based on their fields of study.

Methods: This cross-sectional study was conducted as part of the graduation project of two fifth-year students between April and May 2023 among undergraduate students from different departments at the university. The survey was administered online using Google Forms. Invitations to participate were sent to students via social media. Students' demographic data were collected using a structured form, and the Turkish validated HPV knowledge scale was used to assess their knowledge.

Results: A total of 100 students (mean age, 22.9 years; range, 18-29) completed the online questionnaire. The average score of the participants was 15.40. Students in health-related departments had higher knowledge scores ($p<0.05$). However, despite the relatively high scores, only 5% of the participants had undergone HPV screening, and only 7% had been vaccinated against HPV. Regular sexual activity was the main predictor of the knowledge score.

Conclusion: The average knowledge level of students was relatively high, but uptake of vaccination and screening was low.

Keywords: Human papillomavirus, HPV-knowledge score, HPV vaccination, HPV prevention, sexually transmitted diseases

Introduction

Human papillomavirus (HPV) is the name given to a group of 200 known sexually transmitted deoxyribonucleic acid (DNA) viruses (1). Human papillomavirus is common worldwide and is more prevalent among young adults under 25 years of age in most countries (2). High-risk HPV types are known to cause anogenital cancers, notably cervical cancer, whereas genital warts are generally caused by low-risk HPV types (1). Cervical cancer is the fourth most common cancer among women worldwide. Molecular epidemiological evidence demonstrates that certain types of HPV are the underlying cause of cervical intraepithelial neoplasia and invasive cervical cancer (2,3).

The exact prevalence of HPV in Türkiye is unknown, as reporting cases to the Ministry of Health is not mandatory. According to the most recent data obtained from 4 million women in the Turkish Cervical Cancer Screening Program, which has been ongoing since 2014, HPV DNA positivity was 4.39% as of 2020 (4).

The World Health Organization (WHO) recognizes HPV-related health problems as a global public health concern and recommends HPV vaccination and screening (5). The bivalent and quadrivalent vaccines are the two HPV vaccines approved by the Food and Drug Administration. The HPV vaccine elicits a greater systemic immune response than that induced by infection itself (6). The quadrivalent Gardasil vaccine can

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also be administered to men. Vaccinating both men and women is essential for reducing the risk of transmission (7). The WHO encourages vaccination of girls aged 9-14 years prior to sexual debut to optimize immune response and prevent viral transmission (2). In the long term, HPV vaccination plays a crucial role in the potential elimination of cervical cancer (3).

Significant decreases in the incidence of infection, precancerous lesions, anogenital warts, and cervical cancer lesions have been recorded in countries that have established efficient vaccination programs for adolescent females. In 2018, the WHO issued a circular recommending the global adaptation of vaccination programs to prevent cervical cancer and other HPV-related cancers. The HPV vaccine has been added to the national vaccination schedule of more than 100 countries, including the United States of America and some European countries (5). Given its proven efficacy, cost-effectiveness, and safety, universal HPV vaccination for early-adolescent females and, at minimum, for high-risk males in settings with sufficient resources should be prioritized in global health initiatives (7).

The HPV vaccine has not yet been adopted into the mandatory vaccination program in Türkiye. Awareness of HPV and its preventive measures among young adults who are at higher risk is vital for implementing adequate preventive strategies. The most common public health concerns regarding HPV vaccination in Türkiye, as reported in previous research, include a lack of understanding of vaccine protection, insufficient knowledge of HPV, widespread prejudice, and general attitudes toward health (8). An earlier study revealed that higher understanding of HPV and HPV vaccines was significantly associated with greater willingness to be vaccinated. Vaccine refusal was associated with inadequate knowledge of the vaccine and its potential side effects (9).

We hypothesized that undergraduate students with prior awareness of HPV would have significantly higher HPV knowledge scores compared with those who had not heard of HPV. Additionally, HPV knowledge scores will vary significantly by gender, department, and year of study. Our study aimed to evaluate awareness of HPV infection and vaccination among university students using a recently validated scale and to determine whether students' field of study affected knowledge levels.

Materials and Methods

Compliance with Ethical Standards

Ethical approval for this study was obtained from the Istanbul Medipol University Non-Interventional Clinical Research Ethics Committee (approval no.: 14, date: 05.01.2023). The study was conducted in accordance with the principles outlined in the Declaration of Helsinki.

Study Design and Participants

This cross-sectional study was conducted as part of the graduation project of two fifth-year students between April and May 2023 among undergraduate students from different departments at the university. The survey was administered online using Google Forms. Invitations to participate were sent to students via social media. Participants were required to approve the consent form before proceeding with the questionnaire (Figure 1).

Data Collection Tools

Socio-demographic data and the Turkish-validated HPV-Knowledge Scale (HPV-KS) (10) were integrated into Google Forms. The HPV-KS contains 33 items. Response choices are "True," "False," or "Don't know." One point is awarded for each correct answer, and zero points are awarded for incorrect and "Don't know" responses. A total score, with a maximum of 33, was calculated for each participant. Only participants who answered "YES" to the question "Have you heard of HPV before?" were allowed to continue with the questionnaire; those who answered "NO" scored 0 on the HPV-KS. Socio-demographic data and the summed scale scores were evaluated.

Statistical Analysis

SPSS Version 25.0 was used for statistical analysis. The distribution pattern was assessed using the Kolmogorov-Smirnov test. Normally distributed continuous variables were reported as mean ± standard deviation; non-normally distributed variables were reported as median and interquartile range. Ordinal and nominal data were expressed as n (%). Spearman's correlation analysis was used to assess the relationship between continuous variables. The Mann-Whitney U test was used to evaluate differences in HPV-Knowledge scores between groups. A backward multiple linear regression model was used to identify predictors of the HPV-KS score. A p-value <0.05 was considered statistically significant at the 95% confidence level.

Results

A total of 100 students (median age 23 years, range 18-29) completed the online questionnaire during the one-month study period. Among the participants, 72% were women, 92% were single, and 53% were studying in health-related departments. Demographic data are presented in Table 1. The educational status and occupations of the students' parents were also recorded. Most of the mothers (66%) did not have a university degree, and 70% of them were housewives. While 57% of the fathers had no university degree, 27% were traders.

Based on the responses, 86% of the students reported having heard of HPV, and 91% of them reported knowing about sexually transmitted diseases. Of the participants,

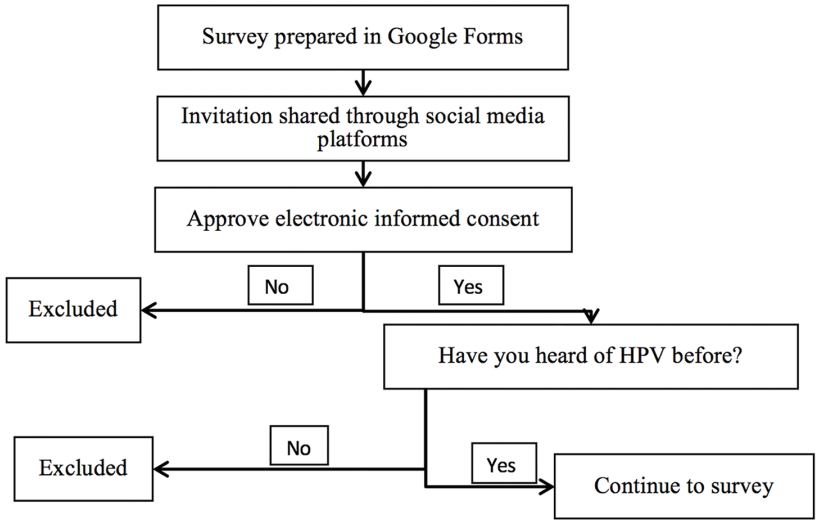

Figure 1. Flowchart of the study

HPV: Human papillomavirus

Table 1. Socio-demographic data of the students			
Demographic data		**Median**	**Min-max**
Age (year)		**23**	**18-29**
		Frequency (n)	**Percentage (%)**
Gender	Female	72	72
	Male	28	28
Marital status	Married	8	8
	Single	92	92
Field of study	Health-related	53	53
	Non-health related	47	47
Year in university	1st year	5	5
	2nd year	7	7
	3rd year	12	12
	4th year	41	41
	5th year	28	28
	6th year	7	7
Parents' socio-demographic data		**Mother (n)**	**Father (n)**
Educational level	No formal education	0	1
	Primary	18	14
	Secondary	48	42
	Under-graduate	30	33
	Post-graduate	4	10
Occupation	Housewife/unemployed	70	8
	Trader	2	27
	Civil servant	14	22
	Worker	7	26
	Retiree	1	15
	Other	6	2

35% reported having had at least one instance of sexual intercourse between the ages of 17 and 27 years, with 25 reporting a regular sex life. Only 5% of the participants had undergone at least one HPV test and only seven of them were vaccinated, four of whom were from non-health departments. Details are given in Table 2. Most of the students who had heard of HPV (p=0.048), had sexual intercourse (p<0.001), and had regular sex lives (p=0.01) were significantly more likely to be from the health-related departments.

When asked about the preferred method of sexually transmitted disease prevention, 16 students reported using condoms, the majority (75%) of whom were from the non-health departments. Only four students, all from health-related departments, stated a preference for vaccination.

The 86 participants who answered yes to "Have you ever heard of HPV?" continued with the HPV-KS. Details of their responses are given in Table 3. The majority (84%) of the participants correctly answered the items "Having many sexual partners increases the risk of getting HPV" and "HPV can be passed on during sexual intercourse," whereas only 3, 4, and 9 students, respectively, correctly answered the items "HPV usually doesn't need any treatment," "The HPV vaccine is licensed for women aged 30-45 years," and "The available HPV vaccines (Gardasil and Cervarix) protect against both genital warts and cervical cancer." The highest score obtained was 30 and the lowest was 0. The median (mean) score for all participants was 17 (15.40); that for students in health-related departments was 20 (18.32), and that for other students was 15 (12.11). Spearman's rho test was used to assess associations between factors and students' scores. Although their scores were correlated with their year of study (r=0.251, p=0.012), there was no correlation with their ages (p=0.208) or with age at first sexual encounter (p=0.382).

Human papillomavirus knowledge level scores were compared between groups using the Mann-Whitney U test (Table 4). There were statistically significant differences between genders (p=0.042) and, in particular, between fields of study (p<0.001). Significant differences by gender and in students' scores were primarily found in five items. Female participants provided significantly more appropriate responses to the items "Having more than one sexual partner increases the risk of HPV transmission," "HPV is very rare," "Girls who have been vaccinated with the HPV vaccine do not need to have a smear test at an advanced age," "HPV vaccines protect against many types of cervical cancer," and "The HPV vaccine should be given in three doses" with counts of 90 versus 69 (p=0.009), 78 versus 55 (p=0.026), 61 versus 28 (p=0.003), 72 versus 38 (p=0.002), and 56 versus 24 (p=0.003), respectively. There was no difference

Table 2. The distribution of participants with previous knowledge and experience regarding sexual health

Questions	Yes		No/don't know	
	n	HPV-KS median (IQR)	n	HPV-KS median (IQR)
Have you heard of HPV before?	86	18 (8)	14	0 (1)
Do you have information about STDs?	91	18 (11)	9	1 (13)
Have you ever had sexual intercourse?	35	16 (13)	65	18 (14)
Do you have a regular sex life	25	19 (8)	75	16 (15)
Have you ever been tested for HPV?	5	21 (6)	95	16 (14)
Have you had an illness related to your genitals?	12	16 (12)	88	17 (14)
Have you received any HPV vaccines?	7	22 (3)	93	16 (15)
What is your approach to preventing sexually transmitted diseases?				
Approach not specified	15			
Use of emergency contraceptive	1			
Having one sex partner	2			
Vaccination	4			
Nothing as I am not sexually active	4			
I pay attention to personal hygiene and cleanliness	7			
Use of condom	16			
Nothing	51			

HPV: Human papillomavirus, STD: Sexually transmitted diseases, IQR: Interquartile range, HPV-KS: Human Papillomavirus Knowledge scale

in students' scores between those who had sexual experience or engaged in regular sexual intercourse and those who had not. The Kruskal-Wallis test revealed no significant differences in students' HPV knowledge scores between parents' educational levels and occupations (p>0.05).

Linear regression analysis was performed to identify potential predictors of the HPV-KS score (Table 5). Numerical variables included in the analysis were students' ages, year of study, and age at first sexual experience. Categorical variables included department (health/non-health), gender, marital status, and parents' education level. Their responses to the questions "Have you heard of HPV before?," "Do you have information about STDs?," "Have you had an illness related to your genitals?," "Do you have a regular sex life?," "Have you ever been tested for HPV?," and "Have you received any HPV vaccines?" were recorded. Only two factors were identified as predictors of HPV-KS: previous knowledge of HPV and regular sexual activity. However, there was no statistically significant difference in HPV-KS between those having regular sexual intercourse and those who were not (p=0.342); the median scores were 19 and 16, respectively.

Table 3. Distribution of appropriate responses among participants based on their field of study

HPV-KS	Students in health-related departments (n=53)	Students in other departments (n=47)	Total	p-value
1. "HPV can cause cervical cancer" (T)	41	25	66	0.011*
2. "A person could have HPV for many years without knowing it" (T)	45	30	75	0.015*
3. "Having many sexual partners increases the risk of getting HPV" (T)	48	36	84	0.057
4. "HPV is very rare" (F)	40	31	71	0.295
5. "HPV can be passed on during sexual intercourse" (T)	47	37	84	0.175
6. "HPV always has visible signs or symptoms" (F)	39	26	65	0.056
7. "Using condoms reduces the risk of getting HPV" (T)	43	33	76	0.202
8. "HPV can cause HIV/AIDS" (F)	15	9	24	0.287
9. "HPV can be passed on by genital skin-to-skin contact" (T)	38	23	61	0.020*
10. "Men cannot get HPV" (F)	45	31	76	0.027*
11. "Having sex at an early age increases the risk of getting HPV" (T)	32	7	39	<0.001**
12. "There are many types of HPV" (T)	39	22	61	0.006*
13. "HPV can cause genital warts" (T)	42	27	69	0.019*
14. "HPV can be cured with antibiotics" (F)	34	13	47	<0.001*
15. "Most sexually active people will get HPV at some point in their lives" (T)	10	7	17	0.597
16. "HPV usually doesn't need any treatment" (T)	3	0	3	0.106
17. "If a woman tests positive for HPV, she will definitely get cervical cancer" (F)	37	22	59	0.020*
18. "An HPV test can be done at the same time as a Pap test" (T)	20	11	31	0.122
19. "An HPV test can tell you how long you have had an HPV infection" (F)	20	6	26	0.004*
20. "HPV testing is used to indicate if the HPV vaccine is needed" (F)	25	13	38	0.045*
21. "When you have an HPV test, you get their results the same day" (F)	15	8	23	0.181
22. "If an HPV test shows that a woman does not have HPV, her risk of cervical cancer is low" (T)	22	10	32	0.030*
23. "Girls who have had an HPV vaccine do not need a Pap test when they are older" (F)	35	16	51	0.001*
24. "One of the HPV vaccines offers protection against genital warts" (T)	28	16	44	0.005*
25. "The HPV vaccines offer protection against all sexually transmitted infections" (F)	33	15	48	0.002*

Table 3. Continued

HPV-KS	Students in health-related departments (n=53)	Students in other departments (n=47)	Total	p-value
26. "Someone who has an HPV vaccine cannot develop cervical cancer" (F)	33	16	49	0.005*
27. "HPV vaccines offer protection against most cervical cancers" (T)	36	26	62	0.195
28. "The HPV vaccine requires three doses" (T)	29	18	47	0.101
29. "The HPV vaccines are most effective if given to people who have never had sex" (T)	17	9	26	0.141
30. "HPV vaccine is recommended for all females aged 11-26 years" (T)	31	20	51	0.112
31. "HPV vaccine is licensed for women aged 30-45 years" (F)	3	1	4	0.368
32. "Both HPV vaccines that are available (Gardasil and Cervarix) protect against both genital warts and cervical cancer" (F)	6	3	9	0.389
33. "HPV vaccine is permitted for males aged 11-26 years" (T)	20	6	26	0.004*
Total HPV-KS, median (IQR)	20 (9)	15 (15)	17 (13)	<0.001**
Total HPV-KS, mean ± SD	18.32±7.35	12.11±8.19	15.40±8.32	<0.001**

Mann-Whitney U test, *p<0.05, **p<0.01
HPV-KS: Human Papillomavirus Knowledge scale, T: True, F: False, HPV: Human papillomavirus, AIDS: Acquired immune deficiency syndrome, SD: Standard deviation, HIV: Human immunodeficiency virus, AIDS: Acquired immune deficiency syndrome, IQR: Interquartile range

Table 4. The difference between median HPV scores according to gender and the field of study

p-value		<0.001*				
	Gender	Health field		Non-health field		p-value
		n=53	HPV-KS median (IQR)	n=47	HPV-KS median (IQR)	
0.042*[b]	Female (n=71)	40 (56%)	21.5	31 (44%)	16	0.002*[a]
	Male (n=29)	13 (45%)	19	16 (55%)	9.5	0.045*[a]
	p-value	0.373[a]		0.093[a]		

*p<0,05
[a]: Mann-Whitney U, [b]: Chi-square, HPV: Human papillomavirus, IQR: Interquartile range, HPV-KS: Human Papillomavirus Knowledge scale

Table 5. Predictive Factors of HPV-KS

	Unstandardized coefficients		Standardized coefficients	t	p-value
	B	Std. Error	Beta		
Factors	-2.552	1.502		-1.699	0.100
Having regular sexual intercourse	4.966	1.363	0.266	3.644	0.001*
Being vaccinated	4.759	2.523	0.137	1.886	0.069
Having previous knowledge of HPV	16.328	1.480	0.803	11.036	<0.001*

Dependent variable: Total HPV-KS

*p<0.05
HPV: Human papillomavirus, HPV-KS: Human Papillomavirus Knowledge scale, Std. Error: Standard error

Discussion

Human papillomavirus is a group of viruses known to cause various diseases in humans, including genital warts and cervical cancer (1). The WHO considers HPV-related health problems a global public health concern and recommends HPV vaccination and screening (5). The most recent data revealed that HPV DNA prevalence among Turkish women in 2020 was 4.39% (4). Awareness and attitudes regarding HPV and prevention strategies among the younger generation are critical for deterring HPV transmission and reducing HPV-related diseases.

In this study, conducted among university students, 100 participants (median age 23 years) completed the online questionnaire during the one-month study period. Most participants were female and unmarried. Our study population is similar to that reported by Ergün (11), which was conducted at the faculty of health sciences. They reported that 71.6% of the students were familiar with HPV, while 93.1% had not been vaccinated. While 86% of our participants had heard of HPV, 93% had not been vaccinated. A similar study involving 144 students (71.5 % female) from health sciences stated that 74.3% of their participants had heard of HPV. They reported higher HPV knowledge among females (12). A study in China, conducted only on male college students, showed HPV-related knowledge to be insufficient, and it negatively affected vaccine recommendations (13). In our study, a notable disparity existed between male and female students; most female participants were enrolled in health-related departments. A more detailed examination reveals that there is no difference between genders within the same field of study. Therefore, the discrepancy is attributable to the field of study. Consistent with our findings, a previous study in Türkiye among younger participants also found no sex-based differences in HPV knowledge.

A recent study in Türkiye reported generally low HPV knowledge scores (mean: 12.16) among students in health sciences (11). We recorded higher scores among students studying in health-related faculties (mean: 18.32). A previous study also reported higher HPV knowledge in nursing students (14). Higher awareness of HPV did not correspond to willingness to receive vaccination or undergo regular screening in their study. Likewise, in our study, only a few students had been vaccinated against or screened for HPV.

A study in 2010 reported a vaccination rate of 0.4% among 717 1st-year college students (15). Studies identified lack of information as the most significant barrier to vaccination (8,9,16). One study reported limited awareness of and knowledge about HPV, its link to cervical cancer, cervical cancer screening through Pap smears, and prevention through vaccination among Turkish female adolescents and young women (16). Our results show an increase in knowledge, but the attitude towards vaccination remains unchanged. A Turkish review reported the lowest and highest rates of HPV vaccination as 0.3% and 6.0%, respectively. However, parents' willingness to vaccinate their daughters with the HPV vaccine ranged from 14.4% to 68.0%, and their willingness to vaccinate their sons ranged from 11% to 62% (17). The overall vaccination rate among the Turkish population is low. Females are more likely than males to be vaccinated. Only one of the seven vaccinated participants in our study group was male. Aksoy et al. (12) reported that 21 participants, 16 of whom were female, had been vaccinated. This suggests that Türkiye is falling short of the WHO 2030 vaccination target of 90% vaccination coverage among girls (3).

Having had sexual intercourse and prior knowledge of HPV were found to be the main determinants of HPV awareness in our study. Durusoy et al. (15) also reported that similar factors affected their participants' knowledge. Oz et al. (9) also found that similar predictors influence vaccine decisions. They identified sexual experience, a history of sexually transmitted infections, sexual behavior, and knowledge of HPV and vaccines as the main predictors of willingness to be vaccinated. Another study among nursing students found that HPV infections and opinions about vaccination were affected by sexual behavior, culture, and religion (18). HPV awareness is still considerably low among the Turkish population, and concerns about vaccine effectiveness and side effects are common among patients attending vaccination programs (19). Public knowledge should be improved through the provision of socioculturally appropriate campaigns; health care professionals should address all patients' concerns to improve acceptance of screening and vaccination (18,19). Research by Yıldız et al. (20) reported that HPV vaccination was not readily recommended by different health care professionals, who cited a lack of knowledge about vaccines, concerns about side effects, and cost implications as the main reasons for abstaining from recommending vaccination. Improved training of healthcare professionals is also required.

Study Limitations

The study was limited to students at a single university who had similar socio-economic and educational backgrounds. The number of participants was low relative to the total number of students at the university. The study could yield results for different socio-demographic groups of students if conducted as a multicenter study across public and private universities. Despite these limitations, our study contributes valuable data to the limited body of literature assessing HPV knowledge among university students studying in health-related and non-health-related

departments; it also highlights the educational disparities and emphasizes the need for targeted awareness interventions.

Conclusion

Overall HPV knowledge among participants was high, but vaccination and screening rates were significantly low, even among students in health-related departments. Our study has made an additional contribution to the limited body of research on university students' knowledge of HPV. Notably, the comparison of students in health-related fields with those in other fields has demonstrated the relevance of this topic within university education. There is a need to improve attitudes toward vaccination and screening by increasing awareness and implementing more effective nationwide HPV vaccination and screening programs.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from the Istanbul Medipol University Non-Interventional Clinical Research Ethics Committee (approval no. 14; date: 05.01.2023).

Informed Consent: Participants were required to approve the consent form before proceeding with the questionnaire.

Footnotes

Authorship Contributions

Concept: B.N.C., Design: B.N.C., Data Collection or Processing: A.K., Analysis or Interpretation: B.N.C., R.M.U., A.K., Literature Search: B.N.C., R.M.U., A.K., Writing: B.N.C., R.M.U., A.K.

Conflict of Interest: No conflicts of interest were declared by the authors.

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Original Article

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Differential Associations Between Left Atrial Volume Parameters and Ischemic Stroke Subtypes

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Abstract

Aim: An increase in left atrial diameter (LAD) is commonly used to differentiate cardioembolic stroke from other ischemic stroke subtypes. We investigated whether echocardiographic volume-indexed parameters beyond the routinely used LAD could also be used to differentiate cardioembolic from atherothrombotic ischemic stroke.

Methods: In this single-center retrospective cross-sectional study, 74 patients with confirmed ischemic stroke were classified as having cardioembolic (n=33) or atherothrombotic stroke (n=41) based on neuroimaging, clinical assessment, and cardiac rhythm monitoring. Baseline demographics, National Institutes of Health Stroke Scale (NIHSS) scores, modified Rankin Scale (mRS) outcomes, and echocardiographic measurements—including left atrial diameter/height (LAD/H), left atrial diameter/body surface area (LAD/BSA), left atrial volume index (LAVi), interventricular septal thickness, and left ventricular (LV) posterior wall thickness—were recorded. Receiver operating characteristic curve analysis was conducted to assess the discriminative performance of left atrial (LA) parameters.

Results: The cardioembolic group demonstrated significantly higher NIHSS scores and worse follow-up mRS outcomes compared with the atherothrombotic group (p=0.011). Echocardiography revealed elevated values of LAD (p<0.001), LAD/H (p<0.001), LAD/BSA (p=0.004), and LAVi (p=0.004) in patients with cardioembolic stroke, while interventricular septum and LV posterior wall thicknesses showed no significant intergroup differences. Receiver operating characteristic analysis identified LAVi, LAD/H, LAD/BSA, and LAD as significant discriminators. Optimal thresholds included LAVi >42 mL/m², LAD/BSA >21.59 mm/m², and LAD/H >0.23 mm/cm. Pairwise comparisons showed no significant differences between LAD and these echocardiographic markers in discriminating cardioembolic from atherothrombotic stroke (p>0.05).

Conclusion: Indexed LA measurements, particularly LAVi, LAD/H, and LAD/BSA enhance discrimination between cardioembolic and atherothrombotic stroke and may improve routine echocardiographic evaluation.

Keywords: Stroke, cardioembolic, ischemic, echocardiography, left atrium, left atrial volume

Introduction

Ischemic stroke is a heterogeneous clinical entity comprising several subtypes, most prominently cardioembolic and atherothrombotic strokes, each with distinct pathophysiological mechanisms and therapeutic implications (1). Accurate identification of stroke subtype is essential, as secondary prevention strategies—particularly antithrombotic and anticoagulant therapies—are largely determined by the underlying etiology (1,2). Cardioembolic stroke is commonly related to structural or functional

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cardiac abnormalities, whereas atherothrombotic stroke is typically associated with advanced vascular stenosis. In recent years, the concept of atrial cardiomyopathy has emerged, emphasizing the role of atrial structural and functional remodeling as a potential contributor to ischemic stroke, independent of atrial fibrillation (AF) (3).

Left atrial (LA) enlargement, a hallmark of atrial remodeling, has been consistently associated with adverse cardiovascular outcomes, including stroke and all-cause mortality, independent of traditional vascular risk factors (2,3). Transthoracic echocardiography remains the most widely available imaging modality for the assessment of LA size in routine clinical practice (4,5). Although cardiovascular magnetic resonance is considered the gold standard for quantifying cardiac chamber volumes, echocardiographic indices, such as left atrial diameter (LAD) and left atrial volume index (LAVi), serve as readily identifiable and practical markers of atrial cardiomyopathy (6). Left atrial volume index, in particular, reflects the severity and chronicity of diastolic dysfunction and has been linked to increased risks of AF, heart failure, and ischemic stroke (7-10). However, the comparative value of indexed LA measurements—including left atrial diameter/height (LAD/H), left atrial diameter/body surface area (LAD/BSA)—in discriminating between ischemic stroke subtypes remains insufficiently defined. We hypothesized that indexed LA measurements, particularly increased LAVi, LAD/H, and LAD/BSA, would be more strongly associated with cardioembolic stroke than with atherothrombotic stroke.

Based on this hypothesis, the present study aimed to compare the most commonly used echocardiographic parameter, LAD with indexed LA parameters (LAD/H, LAD/BSA, and LAVi) in differentiating cardioembolic from atherothrombotic ischemic stroke and to evaluate their associations with stroke severity and prognosis. Elucidating the relationships between indexed LA measurements and stroke etiology may enable improved risk stratification and implementation of more targeted preventive strategies in clinical practice.

Materials and Methods

Compliance with Ethical Standards

This study was performed in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from every participant. Ethical approval for the study was granted by the University of Health Sciences Türkiye, Bakirkoy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (approval no.: 2023-21-23, date: 06.11.2023).

Study Design and Patient Selection

This retrospective cross-sectional study was conducted in the Clinic of Neurology at University of Health Sciences Türkiye, Bakirkoy Prof. Dr. Mazhar Osman Mental Health and Neurological Diseases Training and Research Hospital. A total of 74 patients diagnosed with acute ischemic stroke between September 2021 and September 2022 were enrolled. Patients with known coronary or congenital heart disease, left ventricular (LV) systolic dysfunction (ejection fraction <50%), acute heart failure, acute coronary syndrome, hepatic or renal failure, malignancy, or inadequate echocardiographic imaging windows were excluded. Patients with evidence of hemorrhagic stroke; those with hematologic, neoplastic, infectious, or inflammatory etiologies; and patients with stroke due to any other subtype (e.g., cryptogenic stroke, known hypercoagulable state, or arterial dissection) were also excluded.

Demographic data (age and gender), body mass index, comorbidities, smoking status, alcohol use, medical history, laboratory results, imaging findings, ultrasound parameters, and discharge medications were collected. Ischemic stroke etiologic subtypes were classified using the Trial of Org 10172 in Acute Stroke Treatment (11) criteria by two neurologists during routine clinical practice before study conception. The present study retrospectively analyzed these pre-existing classifications, with stroke subtype assignment performed independently of echocardiographic data. Patients were categorized as having cardioembolic or atherothrombotic stroke based on completed imaging studies and 24-72-hour Holter rhythm monitoring. Stroke severity and functional outcome were assessed at stroke onset and after at least three months' follow-up, respectively, using the National Institutes of Health Stroke Scale (NIHSS) and the modified Rankin Scale (mRS) (12). Based on their NIHSS scores, patients were classified as having a mild stroke (0-5) or a moderate-to-severe stroke (≥6). Based on the mRS scores, functional outcome was defined as good (0-2) or poor (>2) (Figure 1).

Echocardiography Measurements

Transthoracic echocardiography was performed on all participants during hospitalization by two experienced cardiologists who were blinded to the clinical information, using a GE Vivid 7 Dimension system. Standard imaging planes were obtained in the left lateral decubitus position, in accordance with the recommendations of the American Society of Echocardiography (13). Left atrial diameter was measured using two-dimensional echocardiography in the parasternal long-axis view at end-ventricular systole, extending from the posterior aortic wall to the posterior LA wall. Left atrial diameter was indexed to the patient's height and BSA (4,14).

Left ventricular ejection fraction was assessed using either the Teichholz method or the biplane Simpson

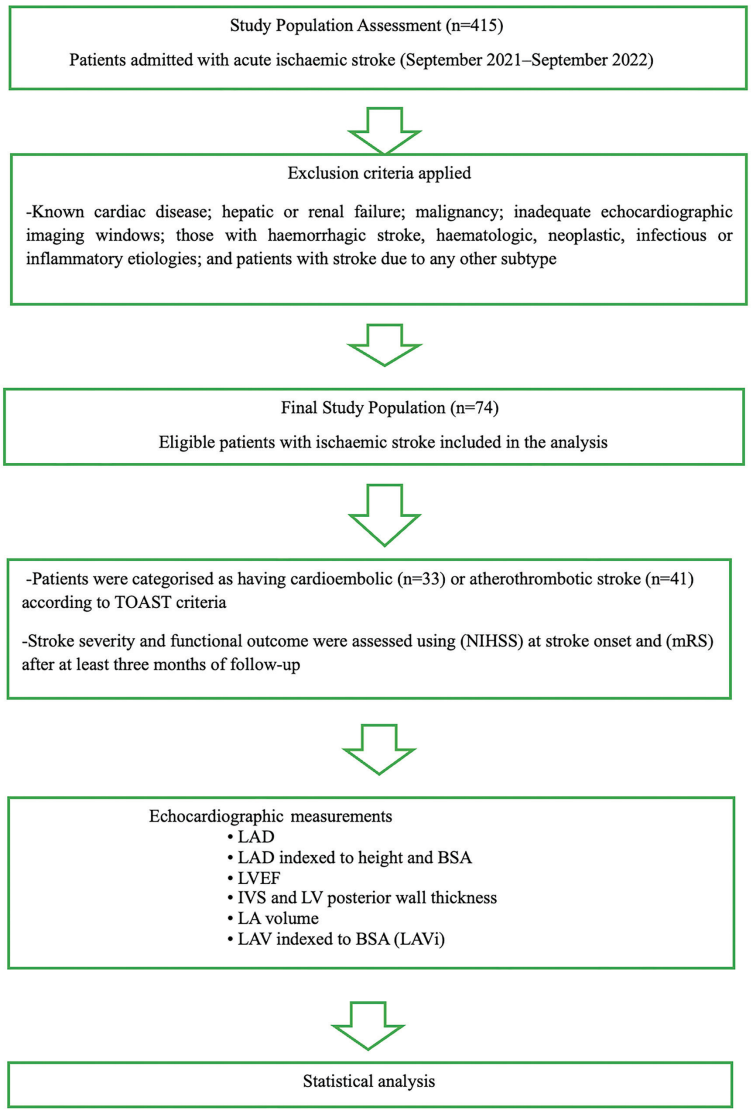

Figure 1. Flowchart of the study

BSA: Body surface area, LA: Left atrial, LAD: Left atrial diameter, LAVi: Left atrial volume index, LV: Left ventricular, LVEF: Left ventricular ejection fraction, IVS: Interventricular septum, TOAST: Trial of Org 10172 in Acute Stroke Treatment

method, depending on image quality. The interventricular septal thickness (IVS) and the LV posterior wall thickness were also recorded.

Given that a single linear LA dimension may be insufficient when atrial enlargement is non-uniform, additional volumetric assessment was performed. Left atrial volume was calculated using the area-length method with planimetry on apical four-chamber (A1) and two-chamber (A2) views at end-ventricular systole. Left atrial volume was obtained using the area-length method, calculated as 0.85 × (A1×A2) / L, and indexed to BSA to derive the LAVi (14,15).

Statistical Analysis

Data analysis was performed using IBM SPSS Statistics version 25. Categorical variables are reported as counts and percentages. The normality of continuous variables was examined with the Shapiro-Wilk test. Since these variables did not follow a normal distribution, they are summarized as median values with corresponding ranges (minimum-maximum). In comparisons of demographic, clinical, and echocardiographic variables between atherothrombotic and cardioembolic groups, the independent sample t-test was used if the data conformed to normal distribution,

and the Mann-Whitney U test was used if the data did not conform to normal distribution. The ability of echocardiographic measurements to discriminate cardioembolic stroke was evaluated through receiver operating characteristic (ROC) analysis. Parameters demonstrating statistically significant ROC curves were further subjected to pairwise comparisons. A two-tailed p-value <0.05 was considered statistically significant.

Results

The demographic and clinical characteristics of the study population are presented in Table 1. A total of 74 patients were included, including 49 males (66.2%) with a median age at stroke onset of 59 years (range, 31-76) and 25 females (33.8%) with a median age at stroke onset of 61 years (range, 37-76). There was no statistically significant difference in age between the groups (p>0.05). Of the 74 patients, 41 (55.4%) were categorized as having atherosclerotic ischemic stroke and 33 (44.6%) as having cardioembolic ischemic stroke. No significant differences were observed between groups with respect to age, age at stroke onset, or median follow-up duration.

The median NIHSS score was significantly higher in the cardioembolic group than in the atherosclerotic group [3 (1-16) vs. 2 (1-6), p<0.001]. During a median follow-up of 45.5 (34-50) months, recurrent ischemic stroke occurred in 10 (13.5%) patients, including 3 patients in the atherothrombotic group and 7 patients in the cardioembolic group. The two groups also differed significantly in follow-up mRS scores, with median mRS scores of 0 (0-3) and 1 (0-4) in the atherothrombotic and cardioembolic groups, respectively (p=0.011).

Baseline characteristics and echocardiographic parameters are summarized in Table 2. Patients in the cardioembolic group demonstrated significantly higher LAD values than those in the atherothrombotic group [38 (29-50) mm vs. 36 (26-42) mm, p<0.001]. Similarly, LAD/H was significantly elevated in the cardioembolic group [0.23 (0.18-0.31) mm/cm vs. 0.21 (0.15-0.26) mm/cm, p<0.001]. Left atrial diameter/body surface area was significantly higher in patients with cardioembolic stroke than in patients with atherothrombotic stroke [20.6 (16.2-31.5) mm/m² vs. 18.9 (13.46-26.8) mm/m², p=0.004].

Left atrial volume index values were likewise significantly higher in the cardioembolic group than in the atherothrombotic group [33.5 (17-62) mL/m² vs. 23 (16-59) mL/m²; p=0.004]. The two groups did not differ significantly in median IVS thickness [12 (10-17) mm vs. 10 (9-15) mm] or in LV posterior wall thickness [11 (9-18) mm vs. 10 (9-17) mm] (p>0.05 for both).

As shown in Table 3, ROC curve analysis demonstrated that LAD (p=0.001), LAD/BSA (p=0.004), LAD/H (p<0.001), and LAVi (p=0.004) were significant markers for distinguishing cardioembolic stroke. The risk of cardioembolic stroke increased with LAVi values above 42 mL/m², LAD/BSA above 21.59 mm/m², and LAD/H above 0.23 mm/cm.

Pairwise comparisons based on ROC curve analysis revealed no significant differences between LAD and

Table 1. Demographics and clinical characteristics of study patients

	n (%)
Gender	
Female	25 (33.8)
Male	49 (66.2)
Smoking	
No	63 (85.1)
Yes	11 (14.9)
Alcohol use	
No	72 (97.3)
Yes	2 (2.7)
Hypertension	
No	42 (56.8)
Yes	32 (43.2)
Diabetes	
No	53 (71.6)
Yes	21 (28.4)
History of stroke or TIA	
No	57 (77)
Yes	17 (23)
NIHSS	
<6	65 (87.8)
≥6	9 (12.2)
mRS	
<3	60 (81.1)
≥3	14 (18.9)
Recurrent ischemic stroke	
No	64 (86.5)
Yes	10 (13.5)
Treatment at baseline	
None	54 (73.0)
Antiplatelet	17(23.0)
Dual antiplatelet	3 (4.0)
Treatment at discharge	
Antiplatelet	14 (19)
Anticoagulant	28 (38)
Dual antiplatelet	27 (36)
Anticoagulant+antiplatelet	5 (7)

NIHSS: National Institutes of Health Stroke Scale, mRS: modified Rankin Score, TSI: Transient ischemic attack

LAD/BSA (p=0.393), between LAD and LAD/H (p=0.803), or between LAD and LAVi (p=0.464) in discriminating cardioembolic stroke from the atherothrombotic group, as shown in Table 4.

Discussion

The present study reinforces and expands the evidence linking LA structural remodelling with both the occurrence and prognosis of ischemic stroke across etiological subtypes. Consistent with prior research, we observed that, similar to LAD, left atrial enlargement (LAE) parameters, including LAD/BSA, LAD/H, and LAVi, were significantly higher in patients with cardioembolic stroke than in those with atherothrombotic stroke. These findings are consistent with earlier population-based and clinical cohort studies identifying LAE as an independent predictor of cardioembolic stroke and stroke recurrence (5,14,16-18).

In the cardioembolic group, our data further show that increased LA size and volume correlate with greater stroke severity, as reflected by higher NIHSS scores and poorer functional outcomes (mRS). This supports prior studies reporting that LAE is associated with more severe neurological deficits, particularly in embolic stroke subtypes (19-21). The pathophysiological mechanisms likely involve the close association between LAE and AF, a major embolic stroke risk factor, and structural changes in the LA appendage that promote thrombus formation by causing blood stasis and reduced appendage flow velocity (21-24). Recent imaging-based studies have provided further insight into these mechanisms. In a study it is demonstrated that impaired LA functional parameters predicted AF development independently of LA volume, highlighting the clinical relevance of atrial structural-functional coupling (25).

Importantly, the ROC curve analysis demonstrated that LAD, LAD/H, LAD/BSA, and LAVi were significant discriminators of cardioembolic stroke, with the established thresholds that support improved risk stratification. These indexed measurements showed prognostic utility comparable to LAD, corroborating findings from large cohorts, including the Atherosclerosis Risk in Communities Study (5,14,26,27). Because the left atrium is an asymmetrical cavity, volume-based measurements provide a more accurate assessment of its size compared to area or linear dimensions (28). While LAVi is widely regarded as a robust cardiovascular risk marker, in our study pairwise comparisons revealed no significant superiority of one echocardiographic parameter over another, suggesting

Table 2. Demographic and echocardiographic parameters of ischemic stroke patients

	Med (min-max)
Age	62 (34-79)
Follow-up period (months)	45.5 (34-50)
Age at stroke onset	59 (31-76)
BSA	1.82 (1.43-2.26)
LAD (mm)	36 (26-50)
LAD/BSA (mm/m²)	19.7982 (13.46-31.5)
LAD/H (mm/cm)	0.2174 (0.15-0.31)
IVS (mm)	10 (9-17)
LV posterior wall thickness (mm)	10 (9-18)
LAVi (mL/m²)	26.5 (16-62)
A1	16.6 (10.6-32.4)
A2	16.5 (12-30.7)

A1: Apical 4-chamber view, A2 and apical 2 chamber view
BSA: Body surface area, LAD: Left atrial diameter, LAD/H: Left atrial diameter/height, LAD/BSA: Left atrial diameter/body surface area, LAVi: Left atrial volume index, IVS: Interventricular septal wall thickness

Table 4. Pairwise comparisons between LAD and echocardiographic markers in discriminating cardioembolic from atherothrombotic stroke

	LAD p-value
LAD/BSA	0.393
LAD/H	0.803
LAVi	0.464

LAD: Left atrial diameter, LAD/H: Left atrial diameter/height, LAD/BSA: Left atrial diameter/body surface area, LAVi: Left atrial volume index
ROC curve analysis

Table 3. ROC curve analysis of echocardiographic parameters for discriminating cardioembolic from atherothrombotic stroke

	AUC	SE	p-value	95% CI	Cut-off	Sensitivity	Specificity
LAD	0.734	0.061	0.001*	0.614-0.854	>38	45.45	95.12
LAD/BSA	0.703	0.063	0.004*	0.579-0.827	>21.59	42.42	95.12
LAD/H	0.746	0.059	<0.001*	0.631-0.861	>0.23	42.42	95.12
LV posterior wall thickness	0.594	0.069	0.175	0.459-0.729	>11	48.39	70.00
LAVi	0.703	0.064	0.004	0.578-0.828	>42	36.36	97.56
IVS	0.618	0.068	0.091	0.485-0.75	>13	25.81	95.00

*p<0.05
ROC: Receiver operating characteristic, AUC: Area under the curve, SE: Standard error, CI: Confidence interval, LAD: Left atrial diameter, LAD/H: Left atrial diameter/height, LAD/BSA: Left atrial diameter/body surface area, LAVi: Left atrial volume index, IVS: Interventricular septal wall thickness

that these measures may be used interchangeably in clinical practice.

Our findings also support the emerging concept of atrial cardiopathy as an independent embolic substrate beyond clinically detected AF. Elevated LAVi, a marker of chronic diastolic dysfunction and atrial remodeling, was associated with more disabling strokes, including cryptogenic presentations, which indicates its utility in identifying subclinical atrial pathology and embolic risk (8,28,29). Zhang et al. (30) further demonstrated that LAE is associated with ischemic stroke severity even in the absence of overt AF, reinforcing the clinical value of LA indices in detecting subclinical atrial pathology.

However, therapeutic implications remain complex. The ARCADIA randomized clinical trial failed to demonstrate the superiority of apixaban over aspirin for secondary prevention of stroke in patients with cryptogenic stroke and atrial cardiopathy (31). These findings underscore that, while LA structural markers provide valuable risk stratification and etiologic insight, they may not yet be sufficient to serve as the sole determinants of anticoagulation strategies. Ongoing and future studies integrating LA structural, functional, and biomarker-based parameters may help refine patient selection and optimize secondary prevention.

Study Limitations

This single-center study had a limited sample size, which may affect the generalizability of the results. The retrospective design limited data availability, contributing to the absence of significant differences in pairwise comparisons of parameters. Additionally, the small sample size precluded multivariable modeling to evaluate combined echocardiographic predictors for cardioembolic stroke. Larger prospective multicenter studies are needed to confirm these findings.

Despite these limitations, a major strength of this study was the meticulous etiological evaluation performed for all participants, which enhanced the accuracy of stroke subtype classification. Additionally, extended Holter monitoring—prolonged up to 72 hours when clinically indicated—and a detailed echocardiographic examination allowed a more comprehensive assessment of occult arrhythmias and reduced the likelihood of missed paroxysmal AF.

Conclusion

Our findings suggest that, similar to LAD, LAVi and LAD adjusted for height and BSA may provide incremental value in the etiologic classification and risk stratification of patients with ischemic stroke. Systematic integration of these measures into routine echocardiographic reporting could improve clinical decision-making, facilitate more precise identification of cardioembolic risk, and support the implementation of targeted secondary prevention strategies, ultimately enhancing patient outcomes.

Ethics

Ethics Committee Approval: The study received ethical approval from the University of Health Sciences Türkiye, Bakirkoy Dr. Sadi Konuk Training and Research Hospital Clinical Research Ethics Committee (approval no.: 2023-21-23, date: 06.11.2023).

Informed Consent: Written consent was obtained from every participant.

Footnotes

Authorship Contributions

Surgical and Medical Practices: I.Y.G., E.O., A.K., K.N.B., D.A., A.Se., A.S., Concept: I.Y.G., E.O., A.K., K.N.B., D.A., A.Se., A.S., Design: I.Y.G., E.O., A.K., K.N.B., D.A., A.Se., A.S., Data Collection or Processing: I.Y.G., E.O., Analysis or Interpretation: I.Y.G., K.N.B., Literature Search: I.Y.G., E.O., A.K., K.N.B., D.A., A.Se., A.S., Writing: I.Y.G., E.O., A.K.

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Original Article

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Incidental Detection of Cardiac Arrhythmias during Routine Electroencephalography: Prevalence and Clinical Significance of Single-lead ECG Monitoring

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Abstract

Aim: Routine electroencephalography (EEG) recordings often include a single-lead electrocardiogram (ECG) channel, primarily to identify cardiac artifacts. However, incidental detection of cardiac arrhythmias during EEG may provide clinically relevant information. This study aimed to assess the prevalence and clinical relevance of arrhythmias detected during routine EEG.

Methods: This retrospective, descriptive, observational study included outpatient EEG recordings that were performed between April 2023 and December 2024. Routine and sleep EEGs recorded with simultaneous single-lead ECGs were analyzed. Reports were screened using arrhythmia-related keywords. Clinical, electrophysiological, and follow-up data were reviewed, and patients were compared by age group (<50 and ≥50 years).

Results: Arrhythmia-related findings were identified in 157 EEG reports (3.6%). Extrasystoles were the most frequent arrhythmia (35%), followed by atrial fibrillation (AF) (21%). Atrial fibrillation was observed exclusively in patients aged ≥50 years and showed a significant positive correlation with age ($r=0.413$, $p<0.001$). In six patients (3.8%), arrhythmias detected on EEG led to referral to cardiology and subsequent diagnosis of clinically significant cardiac conditions.

Conclusion: Single-lead ECG monitoring during routine EEG can reveal clinically important arrhythmias, including previously undiagnosed AF. Careful interpretation of ECG traces recorded during EEG may facilitate timely cardiology referral and improve patient management.

Keywords: EEG, ECG, arrhythmia, extrasystoles, atrial fibrillation, epilepsy

Introduction

Routine electroencephalography (EEG) recordings commonly include a simultaneously recorded, single-lead electrocardiography (ECG) channel. Current guidelines from the International Federation of Clinical Neurophysiology (IFCN) and the International League Against Epilepsy (ILAE) recommend routine ECG recording as the minimum recording standard for routine and sleep EEG recordings to facilitate accurate interpretation and patient safety (1). Although the ECG channel is primarily used to identify cardiac or pulse-related artifacts that may interfere with EEG interpretation, it also provides an opportunity for continuous cardiac rhythm monitoring during EEG recording. This additional information may be particularly valuable in patients evaluated for epilepsy or paroxysmal events, in whom cardiogenic conditions, such as syncope, may mimic epileptic seizures.

Misdiagnosis between epilepsy and cardiogenic syncope remains a significant clinical problem, with previous studies reporting that 20-30% of patients initially diagnosed with epilepsy ultimately have an underlying cardiovascular cause (2,3). The REVISE (Reveal in the Investigation of Syncope and Epilepsy) study reported that implantable loop recorders can detect cardiac arrhythmias

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in patients misdiagnosed with epilepsy, thereby helping to avoid unnecessary antiseizure medications (ASMs) (4).

On the other hand, cardiac arrhythmias are relatively common in patients with epilepsy (PWE), occurring during both ictal and interictal periods (5,6). While the detection of arrhythmias during seizures may be limited by movement and muscle artifacts, interictal EEG recordings provide a more stable setting for identifying arrhythmias. Importantly, ictal or peri-ictal arrhythmias, particularly asystole or bradycardia, can be life-threatening and may require cardiological intervention in addition to ASMs (7,8). These arrhythmias may reflect complex brain-heart interactions related to autonomic dysfunction and have been associated with increased morbidity, including sudden unexpected death in epilepsy (5,9). In addition, several ASMs, particularly sodium channel blockers such as carbamazepine, lamotrigine, lacosamide, and phenytoin, have been associated with proarrhythmic effects, further emphasizing the importance of cardiac rhythm assessment in this population (5,6,10,11).

We hypothesized that incidental arrhythmias detected during outpatient EEG recordings, particularly in patients without a previously known cardiac diagnosis, may have clinical relevance and contribute to improved diagnostic accuracy and patient management. Therefore, this study aims to determine the frequency and types of arrhythmias incidentally detected during outpatient EEG recordings and to evaluate their clinical importance, diagnostic value, and contribution to patient management. This approach may facilitate earlier cardiology referral and improve clinical decision-making in patients evaluated for epilepsy or paroxysmal events.

Materials and Methods

Compliance with Ethical Standards

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki. Ethical approval was obtained from the Scientific Research Ethics Committee No. 2 of the Basaksehir Cam and Sakura City Hospital (approval no: 2025-56, date: 26.02.2025). Due to its retrospective design, the ethics committee waived the requirement for informed consent. All patient data were anonymized prior to analysis.

Study Design

This retrospective, descriptive, observational study was conducted between April 2023 and December 2024 at the outpatient adult EEG Laboratory of Basaksehir Cam and Sakura City Hospital. Routine EEG recordings with a minimum duration of 20 minutes and sleep-induced EEG recordings lasting 90 minutes, all evaluated by a clinical neurophysiologist (F.A.I.), were included. Portable EEG recordings and EEGs with excessive artifacts were excluded.

Electroencephalography were recorded using a 21-channel EEG system (Neurowerk, Sigma Medizin-Technik GmbH, Germany) with electrodes placed according to the international 10-20 system. A single-lead ECG recording (using two electrodes) was obtained simultaneously with the EEG. The recording parameters were set to a paper speed of 25 mm/s, a voltage sensitivity of 1 mV/cm, and a frequency range of 0.5-70 Hz.

To identify relevant cases, a keyword-based search was conducted of EEG reports using terms associated with arrhythmias, such as "arrhythmia," "extrasystole (ES)," "bradycardia," "tachycardia," "atrial fibrillation (AF)," "atrioventricular (AV) block," "R-R irregularity," and "QT prolongation." Electroencephalography type (routine or sleep), detected arrhythmia type, and EEG findings (normal or abnormal) were documented. Demographic and clinical data, including age, gender, indication for EEG referral, clinical diagnosis, history of epilepsy, cardiac and other comorbidities, and medications such as ASMs, antiarrhythmic agents, and other cardiac drugs, were obtained from medical records. Follow-up data, including neurology and cardiology visits, additional cardiac evaluations such as routine ECG, Holter monitoring, echocardiography, and other advanced cardiac tests, as well as neuroimaging findings [brain computed tomography (CT) or magnetic resonance imaging (MRI)], were also reviewed.

Furthermore, findings were compared between patients aged below 50 years and those aged 50 years or older. Particular attention was given to patients with no prior history of cardiology follow-up or known arrhythmia, who were first diagnosed with arrhythmia during an EEG and subsequently referred for cardiology evaluation.

All arrhythmias observed during EEG recordings were identified and reported by the interpreting physician, a neurologist and clinical neurophysiologist (F.A.I.). In routine clinical practice, neurologists and clinical neurophysiologists report arrhythmic findings detected on the simultaneously recorded single-lead ECG during EEG evaluation. The study workflow and patient selection process are summarized in Figure 1.

Statistical Analysis

We analyzed the data using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, USA). Continuous variables were assessed for normality. Normally distributed data were expressed as mean ± standard deviation and compared using the independent-samples t-test, while non-normally distributed variables were presented as median (range) and analyzed using the Mann-Whitney U test. Categorical variables were presented as numbers and percentages. Group comparisons for categorical variables were performed using the chi-square

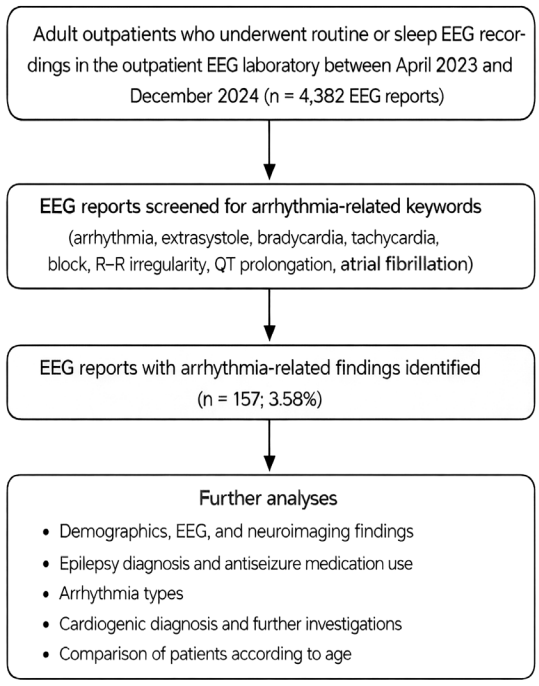

Figure 1. Flowchart shows the study design and EEG report screening process
EEG: Electroencephalograph

test or Fisher's exact test, as appropriate. Correlations between continuous variables were evaluated using Spearman's correlation analysis. A p-value <0.05 was considered statistically significant.

Results

Demographics, EEG, and Neuroimaging Findings

Among 4,382 reviewed EEG reports, 157 (3.58%) included keywords related to arrhythmia. Of these, 134 patients (85.4%) underwent routine EEG recordings, while 23 patients (14.6%) underwent sleep EEG recordings. The mean age of the patients was 57.78±19.61 years (range: 7-89 years). Seventy-one (45.2%) patients were female and 86 (54.8%) were male. Electroencephalography findings were reported as normal in 95 patients (60.5%) and abnormal in 62 patients (39.5%). Among those with abnormal EEG findings, focal or generalized slow-wave paroxysms were observed in 32 patients (51.6%), diffuse slowing in 17 patients (27.4%), epileptiform discharges in 12 patients (19.4%), and an ictal EEG pattern in one patient (1.6%). Neuroimaging (MRI or CT) was performed in 122 (77.7%) patients. Thirty patients (24.6%) had normal findings. Chronic ischemic changes or atrophy were reported in 71 patients (58.2%), while focal lesions (including stroke-related lesions, tumors, and other types) were detected in 21 patients (17.2%).

Epilepsy Diagnosis and Antiseizure Medication Use

An epilepsy diagnosis was confirmed in 53 patients (33.8%) based on medical records. Generalized seizures were the most commonly reported seizure type, occurring in 16 (30.2%) patients, while focal seizures were reported in only two (3.8%) patients. For 35 patients (66.0%), no detailed seizure type was available. The duration of epilepsy was less than one year in 14 (26.4%) patients, between one and five years in 14 (26.4%) patients, more than five years in 16 (30.2%) patients, and unknown in nine (17.0%) patients.

Fifty-seven patients (36.3%) were receiving at least one ASM: 46 (29.3%) were on monotherapy, nine (5.7%) on dual therapy (two ASMs), and two (1.3%) on polytherapy (three or more ASMs). The most frequently used ASMs were levetiracetam (42 patients, 26.8%), carbamazepine (15 patients, 9.6%), valproate (10 patients, 6.4%), lamotrigine (4 patients, 2.5%), and lacosamide (5 patients, 3.2%).

Arrhythmia Types

The most frequently reported arrhythmia types were ES in 55 patients (35.0%); AF in 33 patients (21.0%); bradycardia in 24 patients (15.3%); irregular R-R intervals in 12 patients (7.6%); tachycardia in 7 patients (4.5%); pacemaker rhythm in 4 patients (2.5%); and AV block in 1

patient (0.6%). Unspecified arrhythmias were reported in 21 patients (13.4%).

Patients with abnormal EEG findings had a higher prevalence of AF (30.6%) compared to those with normal EEG findings (21.0%). Conversely, ES was more frequent among patients with normal EEG results (44.3% vs. 21.0%). A significant association was found between EEG abnormalities and the presence of AF (p=0.017). Spearman's correlation analysis showed a significant positive correlation between age and the presence of AF (r=0.413, p<0.001), indicating that older patients are more likely to develop AF.

On the other hand, factors such as unknown spell, diagnosis of epilepsy, epilepsy duration, and ASM use were not significantly associated with the presence or type of arrhythmia (p=0.07, p=0.19, p=0.22, and p=0.59, respectively).

Cardiogenic Diagnosis and Further Investigations

Routine 12-lead ECG was performed in 66 patients (42.0% of the cohort); among these, 27 (17.2% of the cohort) were confirmed to have arrhythmia, while 39 (24.8% of the cohort) had normal ECG findings. Twenty-four-hour Holter monitoring was performed on 22 patients (14.0%); 21 of them (95.5%) showed abnormal results. Echocardiography was conducted in 45 patients (28.7%), revealing abnormalities in 18 cases (40.0%). In addition, 10 patients underwent further cardiac diagnostic procedures, including coronary angiography; all had abnormal findings.

A total of 84 patients had at least one known cardiac diagnosis. Previous arrhythmia diagnosis was present in seven patients (8.2%), hypertension in 31 patients (36.5%), coronary artery disease in 12 patients (14.1%), and valvular heart disease in 11 patients (12.9%). A combination of cardiac conditions was reported in 24 patients (18.2%). Thirty patients (19.2%) were receiving antiarrhythmic medication: beta-blockers (e.g., metoprolol, bisoprolol) in 18 patients (11.5%), amiodarone in 5 patients (3.2%), flecainide in 3 patients (1.9%), and other antiarrhythmics in 4 patients (2.5%). Seventy-five (48.1%) patients were receiving antiplatelet or anticoagulant therapy.

Notably, among patients with arrhythmias on EEG, 3.8% (n=6/157) who had no prior cardiac diagnosis were referred to cardiology after these arrhythmias were identified. These patients underwent further cardiac evaluation, and appropriate antiarrhythmic treatments were initiated. Detailed information about these cases is presented in Table 1.

Comparison of Patients According to Age

Age-related analyses revealed important differences in clinical and electrophysiological findings, which are summarized in Table 2. Although the rate of abnormal EEG findings was similar between the two groups, the distribution of arrhythmia types was significantly different (p<0.001). Atrial fibrillation occurred only in older patients, whereas sinus tachycardia and bradycardia were more common in younger patients. Cardiac comorbidities and the use of cardiac and antiarrhythmic medications were also significantly more common in the older group (p<0.001).

Discussion

The use of a one-channel ECG during routine and sleep EEG is recommended by international guidelines, including those issued by the IFCN and the ILAE. These guidelines primarily emphasize the role of the ECG in identifying extracerebral signals, such as pulse artifacts, which may interfere with accurate EEG interpretation (12). While this is technically useful, it limits the application of ECG to artifact recognition. However, even short single-lead ECG recordings may carry additional diagnostic value. In this study, several clinically significant arrhythmias, including AF and high-frequency ESs, were incidentally identified during EEG monitoring. Some of these arrhythmias were previously undiagnosed and required further cardiological evaluation and treatment. This suggests that routine ECG monitoring during EEG may serve not only as a technical aid but also as a simple, low-cost means of detecting potentially life-threatening cardiac abnormalities. Consistent with this concept, our findings demonstrate that even brief single-lead ECG recordings obtained during routine EEG can reveal clinically relevant arrhythmias, including previously unrecognized conditions requiring cardiological intervention.

Previous studies have reported arrhythmia detection rates on routine EEG ranging from 2% to 28.5% (12,13). In our cohort, the rate was 3.6%, which falls within this range but is at the lower end. Such variation can be explained by methodological differences, such as patient demographics, EEG duration, clinical setting, and expertise in ECG interpretation. For example, Kendirli et al. (14) reported an 18% detection rate in a population enriched for older patients, with longer EEG recordings and cardiologist involvement. Similarly, Onder et al. (15) found a 2% arrhythmia rate when ECGs were reviewed by neurologists; however, in a follow-up study from the same center, this rate nearly doubled when the ECG data were re-evaluated blindly by cardiologists. These findings suggest that systematic review by clinicians with expertise in cardiology can significantly improve the recognition of arrhythmias. Importantly, although only brief single-lead ECG recordings were used in our study, we identified clinically relevant arrhythmias, most commonly ESs. In several cases, these findings led to referral to cardiology and further interventions. These results demonstrate that routine ECG monitoring during EEG, when carefully interpreted, can

Table 1. Clinical characteristics and follow-up of patients without a prior cardiac diagnosis who were referred to cardiology after EEG-detected arrhythmias and subsequently underwent further cardiac evaluation and diagnosis

Patients	Age, gender	EEG type	Diagnosis of patients	EEG findings	ECG findings on EEG	12 lead routine ECG	Holter ECG (24 hours ECG monitoring)	Echocardiographic findings	Antiseizure medications	Other medications	Cardiac follow up
P1	40, Male	Routine	Epilepsy	Abnormal	ES	Normal	Abnormal (3155 VES)	Normal	LEV 500 mg/ day, 4 years	-	Beta blocker (bisoprolol 5 mg/day) started
P2	83, Male	Sleep	Seizure disorder, possible epilepsy	Normal	AF	AF	NA	Moderate calcific AS, grade 2 AR, mild MR	LEV 1000 mg/day, 2 years	-	Oral anticoagulation and beta-blocker (metoprolol 50 mg/day) started
P3	8, Female	Sleep	Epilepsy	Abnormal	Frequent ES	Anormal, (LBBB, inf. axis, VES: QRS 120 ms and compensatory pause)	Abnormal (frequent VES: 14% of all recording)	Normal	CBZ 600 mg/ day, 3 years (previously on VPA 1000 mg/day)	-	Beta-blocker (propranolol 45 mg/day) started
P4	53, Male	Sleep	Epilepsy	Normal	Frequent ES	Anormal (VES)	Abnormal (25.000 VES)	VES related cardiomyopathy	LEV 750 mg/ day (1 year)	-	Beta-blocker (bisoprolol 5 mg/day) started
P5	44, Male	Routine	Epilepsy, DM	Normal	Frequent ES (>1/ min)	Normal	Abnormal (4637 VES and 18 SVAE)	NA	LEV 1000 mg/day (3 years)	-	Beta-blocker (metoprolol 50 mg/day) started
P6	22, Male	Sleep	Possible epilepsy, PNES, ET, depression, OCD	Normal	ES	NA	Abnormal (311 SVEA)	Normal	VPA 1000 mg/day (2 years)	Aripiprazole 20 mg/day fluoxetine 60 mg/day quetiapine 400 mg/day	Beta-blocker (metoprolol 25 mg/day) started

AF: Atrial fibrillation, AR: Aortic regurgitation, AS: Aortic stenosis, CBZ: Carbamazepine, DM: Diabetes mellitus, ECG: Electrocardiography, EEG: Electroencephalography, ES: Extrasystole, ET: Essential tremor, F: Female, LBBB: Left bundle branch block, LEV: Levetiracetam, M: Male, MR: Mitral regurgitation, NA: Not available, OCD: Obsessive-compulsive disorder, PNES: Psychogenic non-epileptic seizure, SVEA: Supraventricular extrasystolic activity, VES: Ventricular extrasystole, VPA: Valproic acid

Table 2. Comparison of demographic, clinical, and electrophysiological findings between patients aged <50 and ≥50 years with EEG-detected arrhythmias

	Age <50 years n=41	Age ≥50 years n=116	p-value
Gender Female Male	 17 (41.5%) 24 (58.5%)	 54 (46.6%) 62 (53.4%)	0.57
Abnormal EEG	14 (34.1%)	48 (41%)	0.41
Arrhythmia type - Extrasystole (ES) - Atrial fibrillation (AF) - Sinus bradycardia - Irregular R-R intervals - Sinus tachycardia - Atrioventricular block - Unspecified arrhythmias	 19 (46.3%) 1 (2.4%) 5 (12.2%) 6 (14.6%) 5 (12.2%) 1 (2.4%) 4 (9.8%)	 36 (31%) 32 (27.6%) 19 (16.4%) 6 (5.2%) 2 (1.7%) 0 17 (14.7%)	<0.001
Cardiology visit	16 (39%)	59 (50.9%)	0.19
EEG type Routine EEG Sleep EEG	 27 (65.9%) 14 (31.1%)	 107 (92.2%) 9 (7.8%)	<0.001
Holter ECG Abnormality on Holter	7 (17.1%) 7 (100%)	15 (12.9%) 14 (93.3)	0.5 0.4
Echocardiography Abnormality on echocardiography	8 (19.5%) 2 (25%)	37 (31.9%) 16 (43.2%)	0.1 0.4
Further cardiac investigations Abnormal findings	1 (2.4%) 1 (100 %)	9 (7.8%) 9 (100 %)	0.4
Cardiac comorbidities	9 (33.3%)	75 (66.7)	<0.001
Other comorbidities	23 (82.1%)	88 (87.1%)	0.5
Diagnosis of epilepsy	18 (43.9%)	35 (30.2%)	0.1
Antiseizure medication use	19 (46.3%)	38 (32.8%)	0.1
Any cardiac medication use	9 (22.5%)	80 (69%)	<0.001
Antiarrhythmic medication use	5 (12.5)	25 (21.6)	<0.001
Neuroimaging abnormalities - Normal findings - Chronic ischemic lesions - Focal lesions	24 (58.5%) 18 (75%) 5 (20.8) 1 (4.2%)	98 (84.5%) 12 (12.2%) 66 (67.3%) 20 (20.4%)	0.001

Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate
ECG: Electrocardiography, EEG: Electroencephalography

offer useful diagnostic insights beyond its traditional role. In our cohort, despite shorter EEG durations and the absence of systematic cardiology review, arrhythmias with direct clinical consequences were still detected, underscoring the real-world relevance of EEG-coupled ECG evaluation.

Routine outpatient EEG is widely used not only in the evaluation of epilepsy but also in the differential diagnosis of various paroxysmal events, including those of neurological, psychiatric, or cardiogenic origin (16). Its low cost, accessibility, and non-invasive nature make it a practical tool in a broad range of clinical settings (17). In this context, the ECG channel embedded in EEG recordings can provide critical diagnostic clues beyond artifact recognition. Several studies have shown that cardiac arrhythmias, particularly those that mimic seizures, may be detected incidentally on EEG. Zaidi et al. (2) demonstrated that a significant proportion of patients initially diagnosed with epilepsy were later found to have cardiac syncope, and Tekin et al. (18) reported two cases of patients who had seizure-like episodes and asystole captured during their attacks on routine EEG monitoring, which led to life-saving cardiologic interventions. These findings underscore the importance of systematic ECG evaluation during EEG in patients with unexplained transient loss of consciousness.

In our study, ESs were the most frequently detected arrhythmia, followed by AF, which was observed predominantly in patients aged ≥50 years. This distribution is consistent with previous studies reporting an increased prevalence of AF with advancing age, particularly after the age of 60, with a marked rise observed in each subsequent decade. Additionally, the presence of cardiovascular comorbidities supports the notion that age may play

a significant role in both diagnostic and therapeutic strategies (19). Although ES is often considered a benign finding, its incidental detection during EEG should not be overlooked. As shown in Table 1, five patients with no known cardiac history were referred to cardiology after ES was observed on EEG. All underwent further evaluation, and pharmacological treatment was initiated for those with frequent ES. For example, in one patient (Patient 4), 24-hour Holter ECG monitoring revealed more than 25,000 ES episodes, leading to antiarrhythmic therapy. In another case (Patient 2), a new diagnosis of AF was made, and anticoagulant therapy was started after cardiology referral—a potentially life-saving intervention. Given the established link between AF and thromboembolic risk, these findings highlight the importance of routine ECG evaluation during EEG recordings.

Cardiovascular comorbidities, including various arrhythmias, are relatively common in PWE (5,20,21). Several mechanisms have been proposed to explain this co-occurrence. Some arrhythmias, such as ictal asystole, may develop during seizures because of brain-heart axis interactions and autonomic dysfunction (8,22). Additionally, interictal arrhythmias may arise due to shared genetic susceptibilities, such as ion channelopathies that affect both the cardiac and nervous systems. Certain ASMs, particularly sodium channel blockers, have also been linked to cardiac conduction abnormalities (21). Although statistical associations were not demonstrated, the frequent observation of ESs and AF among PWE in our cohort suggests that EEG-based ECG screening may still have practical clinical value in this population.

Epidemiological data indicate that the risk of arrhythmia is approximately 1.36-fold higher in PWE than in the general population, with an even greater risk reported among those on ASMs (23). In our cohort, approximately one-third of patients had a confirmed diagnosis of epilepsy, and 36% were receiving ASMs. Although no statistically significant association was found between epilepsy or ASM use and specific arrhythmia types—possibly owing to the limited sample size and a neurological rather than cardiological interpretation—ES and AF were frequently observed among PWE. Notably, in one case, AF was identified for the first time during an EEG recording that coincided with ictal activity, leading to a cardiology referral and the initiation of anticoagulation therapy. Although major ictal arrhythmias such as asystole or bradycardia were not observed, likely because routine EEG sessions are brief, our findings emphasize the diagnostic and clinical value of systematic ECG assessment in PWE. Even brief ECG segments embedded within EEG recordings may uncover clinically relevant cardiac abnormalities, contributing to improved patient management and safety.

In this study, most arrhythmias identified during EEG were not evident on brief, routine ECG recordings. However, extended cardiac monitoring subsequently confirmed these findings in nearly 90% of cases. This highlights the diagnostic value of prolonged EEG recordings with ECG channels, which may uncover rhythm disturbances that short-term ECG could miss. As demonstrated in Table 1, some patients without a prior cardiac diagnosis had clinically significant arrhythmias during EEG monitoring, resulting in cardiology referral and initiation of treatment. These observations underscore the potential role of EEG-detected arrhythmias in guiding diagnostic and therapeutic strategies and reducing morbidity. Our findings indicate that arrhythmias detected incidentally during EEG—particularly in patients without a known cardiac history—may represent an important opportunity for timely diagnosis and intervention.

Study Limitations

This study has some limitations. Since it is a retrospective, single-center study, there may be selection and information bias, and the generalizability of the findings may be limited. Arrhythmias were detected using a single-lead ECG integrated into the EEG system, a method that is less sensitive than a standard 12-lead ECG or Holter monitoring. In addition, the lack of multivariable analysis is another limitation, as independent predictors of arrhythmia could not be determined because of the study's descriptive design and the limited sample size for certain variables. Not all patients were evaluated by the cardiology service or underwent standardized cardiac testing, which might have led to underreporting of arrhythmias. Additionally, ECG findings were interpreted by a single neurologist, which may have limited the identification of subtle arrhythmic patterns. Finally, due to the lack of long-term follow-up, the prognostic significance of the detected arrhythmias could not be fully assessed.

Despite these limitations, this study has several important strengths. It includes a large real-world cohort of adult outpatients undergoing routine and sleep EEG recordings, thereby reflecting daily clinical practice. The screening of a large number of EEG reports enabled the systematic evaluation of incidental arrhythmias detected on EEG. All EEGs were acquired using standardized recording protocols and interpreted by a single experienced clinical neurophysiologist, ensuring consistency in EEG and ECG assessments. In addition, the study highlights the clinical relevance of incidental arrhythmias detected on EEG and demonstrates their potential impact on further cardiological evaluation and patient management, particularly in patients without a prior cardiac diagnosis.

Conclusion

While neurologists meticulously analyze EEG waveforms, equal attention should be given to the accompanying ECG recordings. In PWE or those undergoing differential diagnosis of paroxysmal events, identification of arrhythmias during EEG provides a simple, cost-effective, non-invasive means to improve diagnostic accuracy and clinical management. Furthermore, for individuals without a known cardiac history, even a 20-30-minute period of ECG monitoring during EEG recordings may help detect otherwise unrecognized cardiac abnormalities.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Scientific Research Ethics Committee No. 2 of the Basaksehir Cam and Sakura City Hospital (approval no: 2025-56, date: 26.02.2025).

Informed Consent: Due to its retrospective design, the requirement for informed consent was waived by the ethics committee. All patient data were anonymized prior to analysis.

Footnotes

Authorship Contributions

Surgical and Medical Practices: F.A.I., Concept: F.A.I., Design: F.A.I., D.K., R.O., Data Collection or Processing: F.A.I., D.K., R.O., Analysis or Interpretation: F.A.I., Literature Search: F.A.I., D.K., R.O., Writing: F.A.I.

Conflict of Interest: No conflicts of interest were declared by the authors.

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Case Report

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A Case Report and Current Literature Review of Pneumococcal Meningitis Complicated by Cortical Infarction Secondary to Infectious Cerebral Vasculitis in A Young Male

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Abstract

Bacterial meningitis rarely causes cerebral vasculitis and cerebral infarction. A 23-year-old male presenting with fever, headache, and neck stiffness was diagnosed with pneumococcal meningitis based on cerebrospinal fluid analysis and magnetic resonance imaging (MRI) of the brain. The patient's clinical course was complicated by cerebral vasculitis, as evidenced by a right parietal infarction on brain MRI, resulting in a prolonged intensive care unit stay. He was treated with intravenous antibiotics (ceftriaxone and vancomycin) and corticosteroids. Targeted antibiotic therapy and timely adjunctive initiation of corticosteroids to address inflammation are critical for improving long-term outcomes.

Keywords: *Streptococcus pneumoniae*, cerebral vasculitis, infarction, bacterial meningitis

Introduction

Bacterial meningitis is a critical infection involving the central nervous system, characterized by inflammation of the leptomeninges and the adjacent brain and spinal cord tissues. The most common symptoms include fever, headache, vomiting, neck stiffness, and photophobia. The estimated incidence ranges from 0.6 to 4 cases per 100,000 adults annually, with higher rates reported among elderly populations, particularly in low- and middle-income countries. In adults, the most common causative organisms are *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae* (1,2). Among immunocompromised patients, *Listeria monocytogenes* and Group B *Streptococcus* are also common pathogens. If left untreated, bacterial meningitis carries a mortality rate of up to 50%. Complications include seizures, hearing loss, cognitive dysfunction, and long-term neurological deficits. Cerebral vasculitis is a severe complication that can result in ischemic stroke and permanent neurological impairment and has been reported in up to 25% of cases of bacterial meningitis caused by *Streptococcus pneumoniae*. We report a case of a young patient with pneumococcal meningitis confirmed by cerebrospinal fluid (CSF) culture, complicated by cerebral vasculitis.

Case Report

Written informed consent was obtained prior to publication, and all identifying patient details were anonymized in the manuscript. A 23-year-old male with no significant past medical history presented to the emergency department (ED) with a severe occipital headache of two days' duration, accompanied by fever and vomiting for one day. The patient denied any history of diarrhea, dysuria, respiratory symptoms, joint pain, rash, or other

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constitutional symptoms. He reported a remote history of head trauma six years earlier that required suturing, with no subsequent history suggestive of CSF rhinorrhea.

On presentation, the patient was conscious, oriented, and febrile, with a blood pressure of 120/70 mmHg and a pulse rate of 104 beats per minute. Neurological examination revealed neck stiffness and a positive Kernig's sign, while the remainder of the systemic examination was unremarkable.

On the first day of hospitalization in the ED, the patient experienced a generalized tonic-clonic seizure followed by an altered level of consciousness. Intravenous (IV) antiepileptic therapy and supplemental oxygen via nasal cannula were initiated immediately. Baseline laboratory investigations demonstrated neutrophilic leukocytosis (white blood cell count: 17,140/mm³; neutrophils: 87.5%). Renal and liver function tests were within normal limits, as were blood glucose levels (123 mg/dL) and glycated (hemoglobin A1c: 5.6%). Chest radiography was unremarkable. Viral serology, including hepatitis B, human immunodeficiency virus, and hepatitis C, was negative.

Cerebrospinal fluid analysis revealed marked pleocytosis (white blood cell count: 1,067/mm³), predominantly polymorphonuclear leukocytes, elevated protein levels (836 mg/dL in a 1:5 dilution), and markedly reduced glucose levels (<2 mg/dL), findings consistent with bacterial meningitis. A non-contrast computed tomography scan of the brain showed no evidence of acute infarction or hemorrhage. Magnetic resonance imaging (MRI) of the brain demonstrated acute ischemic and inflammatory changes. Diffusion-weighted imaging (Figure 1A) revealed a focal area of hyperintensity in the left parietal cortex, consistent with an acute infarction (red arrow). The corresponding apparent diffusion coefficient map (Figure 1B) showed a concordant hypointense signal, confirming true restricted diffusion (red arrow). Axial T1-weighted post-contrast images (Figure 1C) demonstrated diffuse leptomeningeal enhancement (red arrow), a characteristic radiological feature of infectious meningitis.

Empirical treatment was initiated with IV vancomycin 1 g every 8 hours, ceftriaxone 2 g every 12 hours, dexamethasone 8 mg every 8 hours, and acyclovir 750 mg every 8 hours. Clindamycin 600 mg IV every 12 hours was also administered because aspiration was suspected. The patient was transferred to the intensive care unit for close monitoring. He required supplemental oxygen, which was gradually tapered as his condition improved. Because of persistent fever spikes, a tropical fever panel was ordered; results were negative for dengue, leptospirosis, and scrub typhus. Blood and urine cultures remained sterile; however, CSF culture grew *Streptococcus pneumoniae*. Acyclovir was discontinued, and antibiotic therapy was narrowed to ceftriaxone and vancomycin based on antimicrobial susceptibility testing.

Gradually, the patient's sensorium improved, and he was transferred to the general ward. Antibiotics were continued for 14 days, and dexamethasone was administered for 4 days. At the one-week follow-up, the patient reported residual neck pain and stiffness. Repeat CSF analysis demonstrated a decrease in white blood cell count (111/mm³) and protein level (59 mg/dL), indicating resolving meningitis. Repeat brain MRI showed decreased

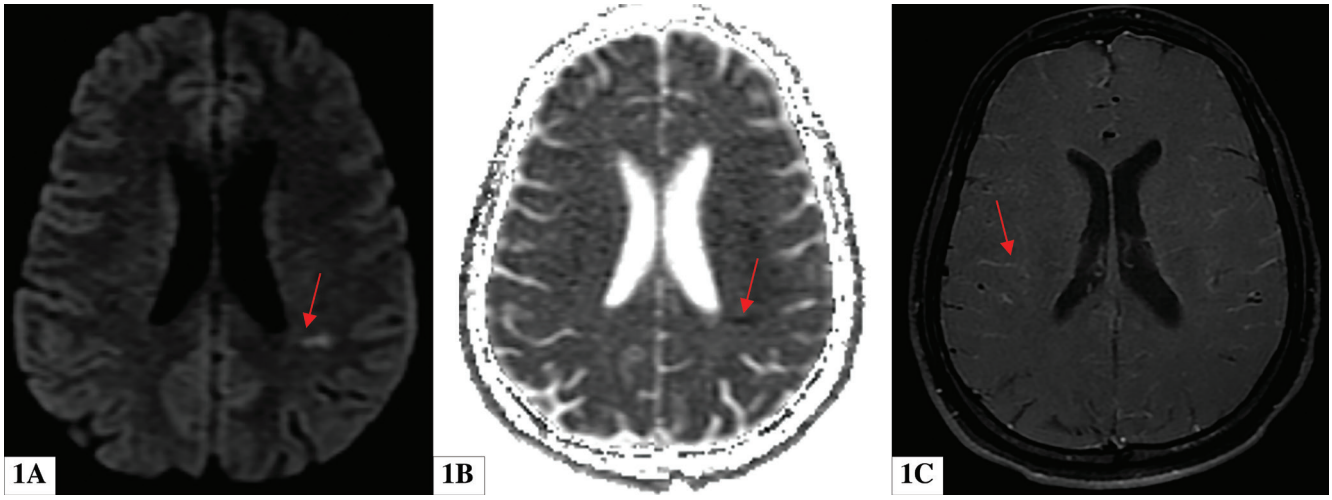

Figure 1. (1A) Brain MRI—axial diffusion-weighted imaging shows a hyperintense signal in the left parietal cortex, consistent with an acute infarct (red arrow). (1B) Brain MRI—corresponding apparent diffusion coefficient map shows a hypointense signal, confirming restricted diffusion (red arrow). (1C) Brain MRI—axial T1-weighted post-contrast image reveals diffuse leptomeningeal enhancement, typical of infectious meningitis (red arrow)
MRI: Magnetic resonance imaging

leptomeningeal enhancement compared with earlier imaging. The patient showed symptomatic improvement and was discharged on aspirin 75 mg once daily and a statin.

Discussion

The most common pathogens causing bacterial meningitis, a condition associated with high morbidity and mortality, include *Streptococcus pneumoniae* (36.5%), *Neisseria meningitidis* (28.8%), and *Streptococcus agalactiae* (15.4%). Cerebrovascular complications—including ischemic and hemorrhagic stroke, intracerebral hemorrhage, and cerebral venous sinus thrombosis—are well-recognized complications of bacterial meningitis and are often associated with poor outcomes. Ischemic stroke, particularly in pneumococcal meningitis, is thought to result from cerebral vasculitis and typically occurs early in the disease course. Up to 10% of bacterial meningitis cases develop ischemic stroke, while neurological complications occur in approximately 15% of cases. Vasculitic complications may present early, as in our case, or may manifest weeks to months later (3,4). Nomura et al. (5) reported progressive vascular involvement in both the anterior and posterior circulations by the second week of illness, as detected on magnetic resonance angiography. Similarly, Dargazanli et al. (4) described a patient who developed aphasia three months after discharge due to severe stenosis of the left carotid and middle cerebral arteries, highlighting delayed-onset vasculopathy.

Cerebrovascular disease in bacterial meningitis can present with variable patterns, affecting cortical regions, deep gray-matter structures such as the basal ganglia, or isolated vascular territories (6). Intracranial and subarachnoid hemorrhages have also been reported, although infrequently, and are typically associated with poor prognosis. The underlying mechanisms remain incompletely understood but likely involve a combination of inflammation-induced endothelial injury, vasospasm, and thrombosis. A review of published case reports (Table 1) highlights the heterogeneity in clinical presentation and imaging findings in pneumococcal meningitis complicated by cerebral vasculitis.

Management of bacterial meningitis complicated by cerebral vasculitis requires a multidisciplinary approach involving neurologists, infectious disease specialists, and intensivists. A high index of suspicion for vasculitis should be maintained in any patient with persistent fever or new neurological deficits despite appropriate antimicrobial therapy. Initial management includes empirical broad-spectrum antibiotics such as ceftriaxone, vancomycin, and ampicillin until culture results are available. Once the causative organism is identified, antibiotic therapy should be tailored accordingly. The blood-brain barrier (BBB) normally prevents pathogens from entering the central nervous system; however, during meningitis, inflammation disrupts the BBB, allowing bacterial invasion and subsequent complications.

Adjunctive corticosteroid therapy, particularly dexamethasone, has been shown to reduce inflammation, cerebral edema, and certain neurological complications in bacterial meningitis, especially in cases caused by *Streptococcus pneumoniae* (7-9). Although the duration and choice of corticosteroid therapy (e.g., dexamethasone versus methylprednisolone) vary across case reports, early administration of dexamethasone has been associated with improved outcomes. In our case, the patient received dexamethasone for four days during the acute phase, in accordance with current recommendations.

Conclusion

Pneumococcal meningitis may be complicated by cerebral vasculitis and infarction early in the disease course, as illustrated in this case. Early neuroimaging, CSF analysis, and timely initiation of appropriate antibiotics and corticosteroids are critical in reducing morbidity. Continued clinical vigilance is essential for early detection

Table 1. Shows a literature review of case reports of pneumococcal meningitis with neurological complications

Serial number	Author	Age/sex	The occurrence of neurological worsening since admission	Treatment given
1	Corchia et al. (3)	48/female	Day 1 of admission with confusion and MRA showing stenosis of the anterior and middle cerebral artery	Dexamethasone for 21 days
2	Dargazanli et al. (4) (2021)	34/male	Ninety days since discharge, presenting with acute aphasia	High-dose steroids, along with antibiotics and antiplatelets
3	Nomura et al. (5)	60/female	Altered mental status with imaging showing vasoconstriction in the anterior and posterior circulation	Intravenous methylprednisolone followed by oral steroids
4	Poil et al. (9) (2018)	48/male	Only persistent fever spikes since four days of admission, with imaging showing thalamic and basal ganglia lacunar infarction	Steroids restarted

MRA: Magnetic resonance angiography

of complications and prompt escalation of therapy when required.

The medical team managing bacterial meningitis should maintain a high index of suspicion for cerebral vasculitis in patients with pneumococcal meningitis who exhibit persistent fever spikes or any neurological deterioration despite appropriate antibiotic therapy. Early identification and timely initiation of corticosteroid therapy may reduce long-term neurological sequelae and improve hospitalization outcomes.

Ethics

Informed Consent: Written informed consent was obtained prior to publication, and all identifying patient details were anonymized in the manuscript.

Footnotes

Authorship Contributions

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

Conflict of Interest: No conflicts of interest were declared by the authors.

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Case Report

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Continuous Serratus Posterior Superior Intercostal Plane Block for Salvage Mastectomy: A Case Report and Current Literature

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Abstract

Serratus posterior superior intercostal plane block (SPSIPB) is a newly described truncal block. Here, we aim to share our experience with an SPSIPB catheter for pain management in a 71-year-old woman who underwent a salvage mastectomy and received a continuous infusion of 1 mg/mL bupivacaine solution at 5 mL/h for 48 hours. During follow-up, Numeric Rating Scale scores were ≤4, and Quality of Recovery-15 (QoR-15) scores improved at 48 h. Continuous SPSIPB is effective for postoperative pain management and for improving the QoR in patients undergoing breast surgery.

Keywords: Mastectomy, postoperative pain, catheterization, Quality of Recovery, serratus posterior superior intercostal plane block

Introduction

Effective pain management after breast cancer surgery is crucial, as poorly managed pain can significantly decrease a patient's quality of life (1). A new method for thoracic analgesia, the serratus posterior superior intercostal plane block (SPSIPB), targets the lateral cutaneous branches of the intercostal nerves and the dorsal rami. This is achieved by applying a local anesthetic to the area between the serratus posterior superior muscle and the intercostal muscles (2). We aim to share our experience using an SPSIPB catheter for pain management in a patient who underwent salvage mastectomy for end-stage breast cancer.

This case report follows the CAse REport guidelines. Written informed consent was obtained from the patient for publication of this report.

Case Report

A 71-year-old woman (weight 73 kg, height 163 cm) was admitted to the department of general surgery for surgical management of terminal breast cancer. Her medical history included two previous surgeries: one for cancer in her left breast 20 years earlier and another 4 years earlier to remove a mass from her right breast. After the second surgery, she discontinued her follow-up appointments.

At presentation, she had a foul-smelling, discharging mass in her right breast (Figure 1). Thoracic computed tomography revealed a malignant invasive tumor in the right breast with local necrosis and superimposed infection. The scan also demonstrated subcutaneous metastases, metastatic lymphadenopathy in the left axilla, and pulmonary and mediastinal metastases.

Her medical history also included hypertension and type 2 diabetes mellitus. Vital signs were within normal limits during the preoperative assessment. Cardiac evaluation revealed an ejection fraction of 55% with mild aortic and mitral regurgitation. Pulmonology consultation recommended avoiding fluid overload.

At hematology consultation, the patient had a hemoglobin level of 7.5 g/dL and was diagnosed with anemia of chronic disease. Administration of erythrocyte suspension during the perioperative period

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was recommended. Classified as an American Society of Anesthesiologists physical status classification III risk-group patient, she was scheduled for a salvage mastectomy under general anesthesia. Insertion of an SPSIPB catheter for pain management was also planned.

The patient was thoroughly informed about the block, and consent was obtained for its performance and for presentation of the case. The Numeric Rating Scale (NRS) and the Quality of Recovery-15 (QoR-15) scale were explained to the patient. Prior to surgery, routine monitoring was performed in the block room, where the preoperative QoR-15 measurement was obtained. The patient was premedicated with 1 mg midazolam.

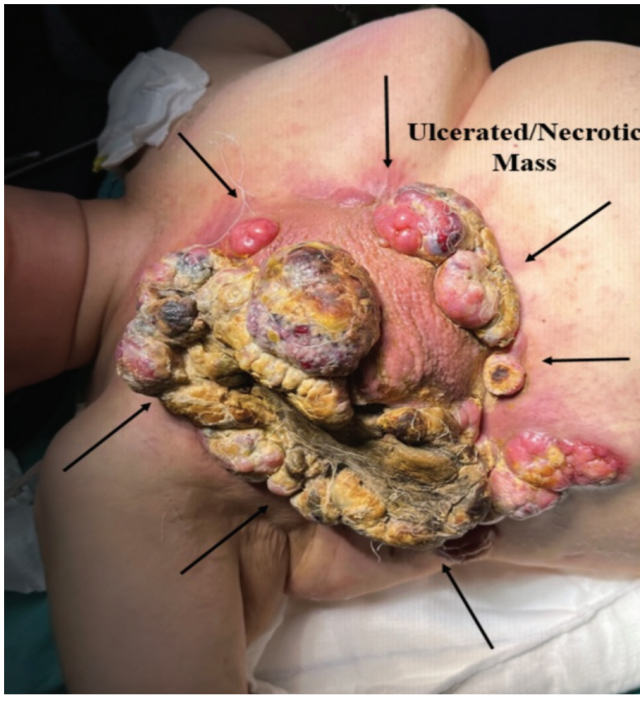

Figure 1. Preoperative appearance of the exophytic mass in the right breast. The arrows indicates the extensive necrotic and ulcerated tumor tissue

With the patient in the left lateral decubitus position, skin asepsis was ensured. A linear ultrasound probe (MyLab 30 Gold Cardiovascular, Esaote, Florence, Italy) was placed on the medial border of the right scapula at the level of the second and third ribs, ensuring appropriate field coverage (Figure 2A). An 18-G needle (Vygon Techniplex Tuohy 100-mm needle; Vygon, Paris, France) was advanced using an in-plane technique to the fascial plane between the third rib and the serratus posterior superior muscle after identification of the relevant anatomical landmarks (Figure 2B). After confirmation of correct placement with 5 mL of normal saline, the catheter was fixed at 6 cm, with 3.5 cm in-plane (Figure 2C). Subsequently, 20 mL of 0.25% bupivacaine was administered through the catheter.

The surgery lasted 125 min, and anesthesia duration was 145 min. A tumor mass weighing 1,270 g was excised, followed by breast reconstruction using a flap performed by the plastic surgery team. Postoperatively, the patient received 1 g acetaminophen and 70 mg tramadol [7 morphine milligram equivalents (MME)] before transfer to the recovery room. After 20 min, her resting NRS score was 0, and the dynamic NRS score decreased to 1. An infusion of 1 mg/mL bupivacaine was initiated at 5 mL/h via the catheter while the patient was in the recovery room. She was subsequently transferred to the postanesthesia care unit after achieving a modified Aldrete score of 9.

Postoperatively, the patient was prescribed 1 g paracetamol every 6 h. Tramadol at a dose of 0.5 mg/

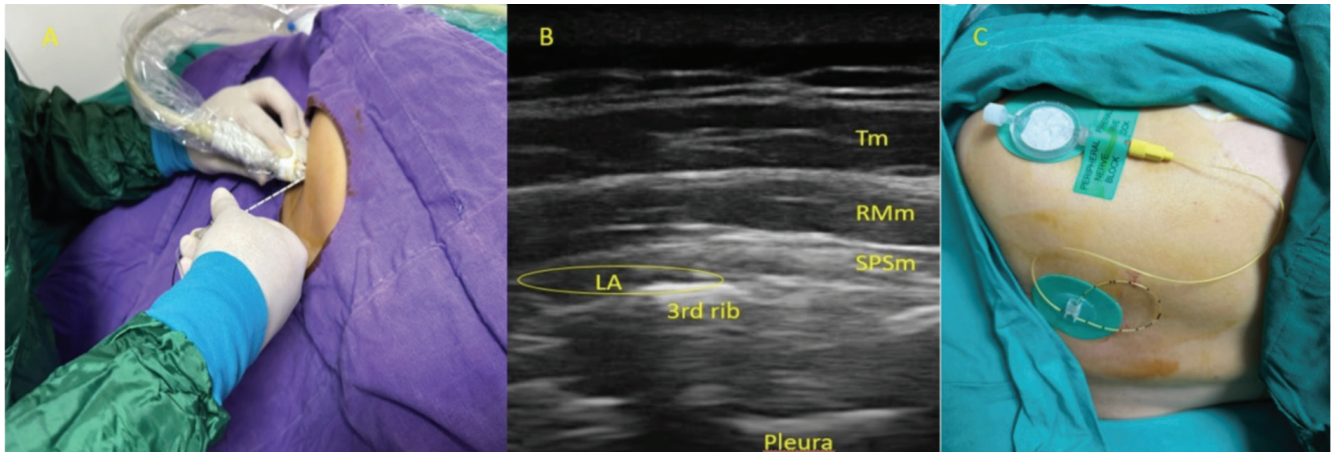

Figure 2. Placement of the SPSIPB catheter
(A) Patient position and probe placement, (B) ultrasound anatomy during the block, (C) the catheter fixed at the injection site

SPSIPB: Serratus posterior superior intercostal plane block, Tm: Trapezius muscle, RMm: Rhomboid major muscle, SPSm: Serratus posterior superior muscle, LA: Local anesthetic spread between the SPSm and the 3rd rib/intercostal muscle, Pleura: Pleural line

kg was administered if the dynamic NRS score was ≥4. Quality of Recovery-15 measurement were repeated at 24 and 48 h. The NRS scores at all other time points were ≤2, except at the 36th hour, when the dynamic NRS score reached 4 after administration of 30 mg tramadol (3 mg MME) (Table 1). The catheter was removed at 48 h. The patient's preoperative QoR-15 score was 112, which decreased slightly to 108 at 24 h and then increased to 129 at 48 h.

Discussion

The SPSIPB is a novel interfascial plane block targeting the thoracic intercostal nerves. In this case report, we demonstrated that a continuous SPSIPB catheter provided effective analgesia and reduced opioid consumption in a patient undergoing salvage mastectomy for end-stage breast cancer.

Thoracic paravertebral block (TPVB) is often considered the gold standard for analgesia in breast surgery; however, it carries risks such as pneumothorax, sympathectomy-related hypotension, and epidural spread. Compared with TPVB, SPSIPB is performed more superficially and laterally to the transverse process, potentially offering a superior safety profile while effectively targeting the lateral cutaneous branches of the intercostal nerves. Unlike the erector spinae plane block, which relies on diffusion of local anesthetic through the costotransverse foramen into the paravertebral space, SPSIPB delivers anesthetic directly into the intercostal plane (2,3). This direct application may provide more consistent lateral chest wall analgesia, which is crucial in extensive surgeries such as salvage mastectomy involving the axillary region.

Akin et al. (4) described the use of a continuous SPSIPB catheter for postoperative analgesia in a patient undergoing minimally invasive cardiac surgery. They reported excellent pain control and a high QoR score without opioid consumption. Although their report focused on cardiac surgery, our case extends the indication of continuous SPSIPB to major breast surgery, suggesting that this technique is a versatile and feasible option for prolonged analgesia in thoracic procedures involving the lateral chest wall.

Dada et al. (5) described rebound pain as increased pain sensitivity occurring 8-24 h after block application, most commonly 8-12 h after a single nerve block injection, which can adversely affect patient well-being and QoR (6). In our practice, non-steroidal anti-inflammatory drugs are avoided during the first 48 h after surgery because of potential negative effects on wound healing. Therefore, we prefer catheter-based postoperative analgesia to prevent rebound pain and minimize opioid use.

In this patient, extensive tissue excision and axillary dissection posed a high risk of severe postoperative pain. Continuous infusion through the SPSIPB catheter maintained NRS scores largely below 4/10. Although minor breakthrough pain occurred at the 36th hour, requiring a small rescue dose, QoR-15 scores improved significantly from 108 to 129, particularly in the pain and sleep domains. These findings suggest that continuous SPSIPB not only reduces pain intensity but also supports functional recovery.

This report includes only a single case, and future case series or controlled trials are required to further evaluate the effectiveness and safety of continuous SPSIPB catheters in this patient population.

Conclusion

The continuous SPSIPB catheter provided effective analgesia and minimized opioid consumption in this salvage mastectomy case. The technique supported high-quality recovery without severe pain episodes during the catheterization period.

Table 1. Postoperative clinical data

	20th min	1st h	2nd h	6th h	12th h	24th h	36th h	48th h
Resting NRS	0	0	0	0	0	1	2	0
Dynamic NRS	1	1	1	1	1	2	4	1
Ramsey Sedation Scale score	2	2	2	2	2	1	1	1
Additional analgesic	None	None	None	1 g acetaminophen	1 g acetaminophen	1 g acetaminophen	1 g acetaminophen +30 mg tramadol	1 g acetaminophen

NRS: Numeric Rating Scale

Ethics

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

Footnotes

Authorship Contributions

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

Conflict of interests: All authors declare no conflicts of interest.

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Letter to the Editor

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Spontaneous Intraparenchymal and Intraventricular Hemorrhage due to Arteriovenous Malformation in Pregnancy

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To the Editor,

Arteriovenous malformation (AVM) hemorrhage during pregnancy is a rare condition associated with high maternal and fetal morbidity and mortality. Whether pregnancy increases the risk of AVM rupture remains controversial. Hemodynamic changes during pregnancy are predicted to increase the risk of bleeding (1,2). This report presents maternal and fetal outcomes following a spontaneous intracranial hemorrhage secondary to AVM rupture during pregnancy.

A 32-year-old patient at 18 weeks' gestation, with a history of AVM surgery four years earlier, was admitted to the adult emergency department after awakening with a severe headache, vomiting, and a seizure. The patient had no prior history of seizures or substance use. This was her fourth pregnancy; she had previously undergone three cesarean sections. Upon arrival, persistent seizures lasting two hours necessitated intubation and transfer to the neurology service. The patient had not undergone prenatal screening tests for this pregnancy. On examination, a viable pregnancy consistent with 18 weeks' gestation was confirmed, with no obstetric pathology detected. Brain computed tomography revealed a large hemorrhagic area in the left parieto-occipital region extending into the ventricles (Figure 1).

Digital subtraction angiography identified a residual AVM, measuring approximately 21×15×12 mm, in the left high frontoparietal region, supplied by feeding arteries from the anterior cerebral artery and draining into the superior sagittal sinus via a cortical vein (Figure 2).

The patient underwent a left frontotemporoparietal decompressive craniotomy (Figure 3).

She was transferred to the neurosurgery ward on postoperative day 27 and was discharged on postoperative

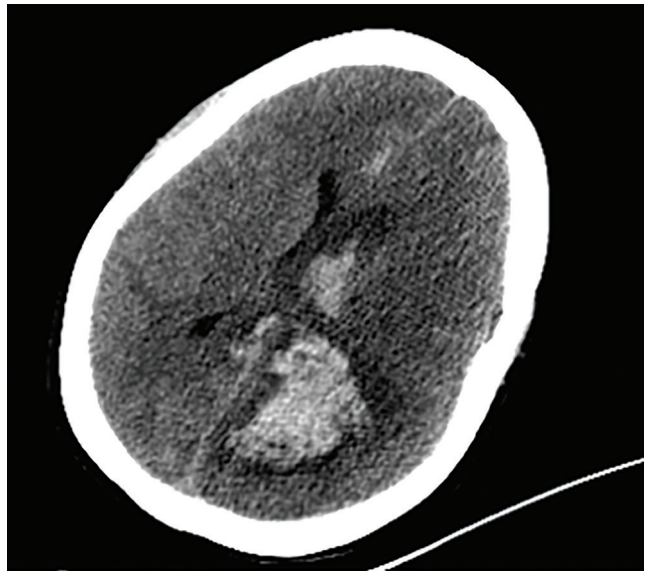

Figure 1. Preoperative cerebral CT scan showing a large hemorrhagic area in the left parieto-occipital region extending into the ventricles

CT: Computed tomography

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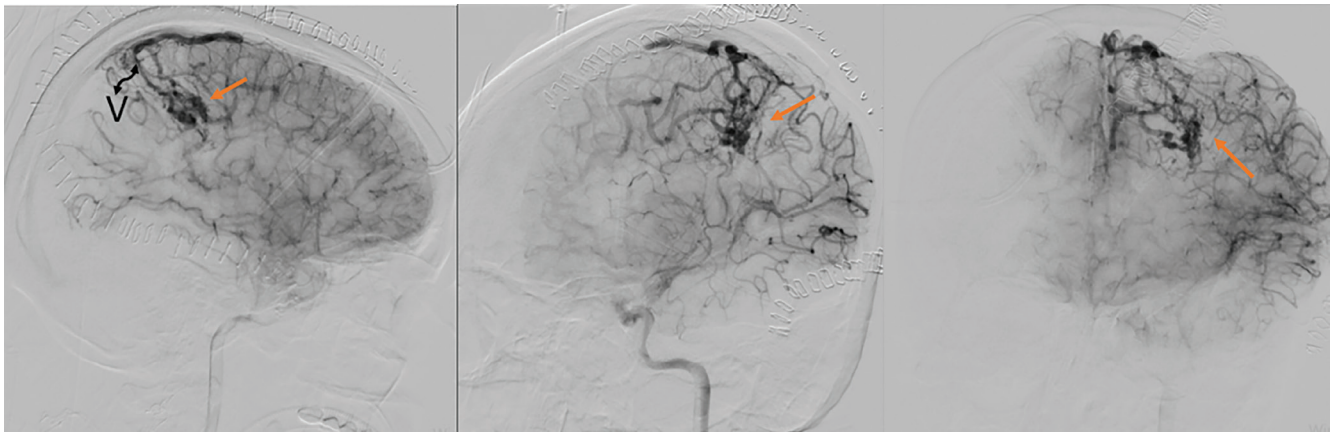

Figure 2. Digital cerebral angiography: arteriovenous malformation nidus (arrow) draining into the superior sagittal sinus via drainage veins

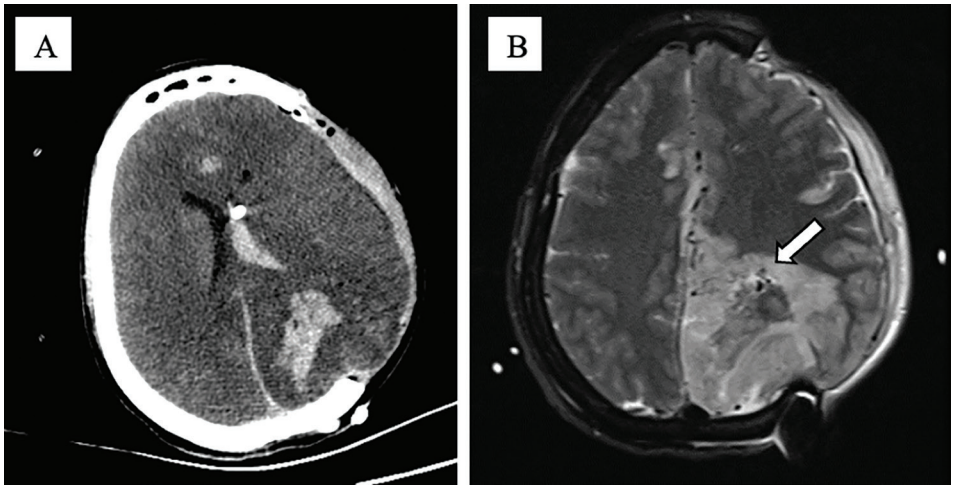

Figure 3. (A) Cerebral CT scan: postoperative left frontotemporoparietal decompressive craniotomy. (B) Postoperative MRI: hemorrhagic area in the left parieto-occipital region and arteriovenous malformation nidus (arrow)

CT: Computed tomography, MRI: Magnetic resonance imaging

day 29 with preserved consciousness, limited verbal responsiveness, and right-sided hemiplegia. During hospitalization, the quadruple screening test indicated a low risk. A second-trimester fetal anomaly scan revealed no abnormalities. At 35 weeks and 5 days of gestation, the patient presented to the obstetrics emergency department with labor pain. A cesarean section was performed, resulting in the delivery of a male infant weighing 2,200 g, with 1- and 5-minute Apgar scores of 7 and 8, respectively. The neonate was admitted for transient tachypnea and discharged on the second day without complications. The patient was discharged in stable condition on postoperative day five.

A recent study reported that pregnancy increases the risk of AVM rupture, with higher rupture rates observed during the second and third trimesters (3). A Finnish nationwide study by Pohjola et al. (4), analyzing data from more than 1.7 million births, demonstrated that approximately 43% of AVM ruptures occurred during the second trimester and nearly 24% during the third trimester. The authors also reported that, when appropriately managed, the majority of patients experienced relatively favorable outcomes. Another study reported a pooled AVM hemorrhage rate of 0.16 per pregnancy and emphasized the importance of individualized management strategies (1).

This case highlights several important clinical considerations: residual AVM following prior surgical intervention may rupture during pregnancy; aggressive neurosurgical management can be compatible with continuation of pregnancy; and close fetal surveillance throughout gestation enables timely identification of potential complications. Despite significant maternal morbidity, both the mother and the infant achieved favorable outcomes. This case further suggests that

pregnancy termination may not be mandatory, even following major neurosurgical procedures performed during the second trimester.

Footnotes

Authorship Contributions

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

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