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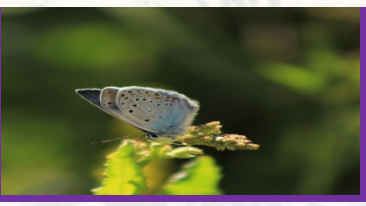

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IJCMBS

Original Article

Predictors of In-Hospital Mortality in Infective Endocarditis: A Retrospective Cohort Analysis

Enfektif Endokarditte Hastane İçi Ölüm Oranını Belirleyen Faktörler: Retrospektif Kohort Analizi

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Abstract

Background: Infective endocarditis (IE) remains a disease of high morbidity and mortality. The epidemiological profile has shifted, with fewer rheumatic cases but more healthcare-associated and prosthetic valve infections. Management remains complex, particularly regarding the role of antithrombotic therapies. We evaluated clinical features, microbiology, and predictors of in-hospital mortality among adult IE patients, focusing on anti-platelet therapy.

Materials and Methods We retrospectively reviewed 122 adult patients diagnosed with definite or possible IE at a tertiary University Hospital between 2000-2013 according to modified Duke criteria. Data on demographics, comorbidities, predisposing factors, clinical presentation, laboratory and echocardiographic findings, microbiology, antithrombotic use, surgical management, and outcomes were extracted. Univariable and multivariable analyses were performed to identify predictors of in-hospital mortality. **Results**: Results: The mean age was 52.5 ± 14.2 years; 63.1% were male. Rheumatic fever was present in 35.2%, prosthetic valves in 34.4%, and intracardiac devices in 7.4%. The most frequent pathogen was *Staphylococcus aureus* (25.5%), followed by *streptococc*i (16.3%). Culture-negative endocarditis accounted for 33.3% of cases. The overall in-hospital mortality was 26.2%. Non-survivors were significantly older (57.4 vs. 50.8 years) and had shorter duration of symptoms before admission (<15 days). Multivariable regression showed worsening echocardiographic findings (OR 5.44, p=0.026) and pre-existing antiplatelet therapy (aspirin OR 2.64, p=0.021; other antiplatelets OR 3.95, p=0.015) as the strongest independent predictors of death. **Conclusions:** This study highlights shifting epidemiology in Turkey with increasing age, prosthetic/device-associated cases, and a rising burden of *S. aureus.* Antiplatelet use was independently associated with increased mortality.

Keywords: Anti-platelet treatment, Infective Endocarditis, Mortality, Türkiye

ÖZ

Amaç: İnfektif endokardit (İE) halen yüksek morbidite ve mortaliteye sahip bir hastalıktır. Epidemiyolojik profil değişmiş, romatizmal hastalığa bağlı olgular azalırken sağlık hizmeti ile ilişkili ve protez kapak enfeksiyonları artmıştır. Yönetim hala karmaşık olup özellikle anti-trombotik tedavilerin rolü tartışmalıdır. Bu çalışmada erişkin İE hastalarında klinik özellikler, mikrobiyoloji ve hastane içi mortalite ile ilişkili prediktörler değerlendirildi, özellikle anti-trombosit tedaviye odaklanıldı.

Gereç ve Yöntem: Üçüncü basamak üniversite hastanesinde 2000–2013 yılları arasında modifiye Duke kriterlerine göre kesin veya olası İE tanısı alan 122 erişkin hasta kayıtları retrospektif olarak incelendi. Demografik veriler, eşlik eden hastalıklar, predispozan faktörler, klinik ve laboratuvar bulguları ve ekokardiyografi sonuçları, mikrobiyoloji, antitrombotik tedavi kullanımı, cerrahi tedavi ve sonlanım değerlendirildi. Hastane içi mortalitenin prediktörlerini belirlemek için tek değişkenli ve çok değişkenli analizler yapıldı.

Bulgular: Ortalama yaş 52,5 ± 14,2 yıl olup hastaların %63,1'i erkekti. Romatizmal ateş öyküsü %35,2, protez kapak varlığı %34,4, intrakardiyak cihaz varlığı %7,4 oranında saptandı. En sık izole edilen patojen *Staphylococcus aureus* (%25,5) idi; bunu *streptokoklar* (%16,3) izledi. Kültür negatif endokardit oranı %33,3 olarak bulundu. Genel hastane içi mortalite %26,2 idi. Kaybedilen hastalar daha yaşlıydı (57,4'e karşı 50,8 yıl) ve başvuru öncesi semptom süresi daha kısaydı (<15 gün). Çok değişkenli analizde ekokardiyografide kötüleşme (OR 5,44; p=0,026) ve önceden anti-trombosit tedavi kullanımı (aspirin OR 2,64; p=0,021; diğer anti-trombositler OR 3,95; p=0,015) bağımsız mortalite prediktörleri olarak saptandı.

Sonuç: Bu çalışma, Türkiye'de İE epidemiyolojisindeki değişimi; ileri yaşı, protez/cihaz ilişkili olguların artışını ve dolayısıyla *S. aureus* sıklığının yükselmesini gözler önüne sermektedir. Anti-trombosit tedavi kullanımı bağımsız olarak artmış mortalite ile ilişkili bulunmuştur.

Anahtar Kelimeler: Anti-trombosit tedavi, İnfektif Endokardit, Mortalite, Türkiye

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Highlights

- IE mortality remained high (26.2%), driven by adverse echocardiographic findings.
- *Staphylococcus aureus* was the leading pathogen in an older, prosthetic/device-heavy cohort.
- Pre-existing antiplatelet therapy independently predicted higher mortality.

Introduction

Infective endocarditis (IE) remains one of the most challenging cardiovascular infections due to its protean manifestations, diagnostic complexity, and persistently high mortality. A detailed analysis of global trends, largely informed by the Global Burden of Disease (GBD) study, reveals a significant and sustained increase in both the incidence and absolute number of cases and deaths over the past three decades. The global annual incidence of IE is estimated to be approximately 3-10 per 100,000 people, although study-specific ranges can be wider, from 1 to 15 cases per 100,000 per year, which is likely due to methodological differences (1,2). The epidemiology of IE has evolved considerably: while rheumatic heart disease-related IE has declined in many regions, healthcare-associated IE and prosthetic valve or intra-cardiac device infections have become increasingly prevalent (3). Consequently, the causative microbiology has shifted from oral streptococci toward Staphylococcus aureus, a pathogen linked with more aggressive disease and worse outcomes. Despite advances in diagnosis and treatment, the overall mortality rate remains persistently high, at approximately 25% (1,3).

A further clinical dilemma is the role of antithrombotic therapy during active IE. Thromboembolic events, especially ischemic stroke, are among the most feared complications, occurring in 20–40 % of patients (4). However, anticoagulation and antiplatelet use are controversial and carry a significant risk of hemorrhagic complications, particularly intracranial hemorrhage (ICH), which is strongly associated with poor prognosis (4-8). Observational studies and guideline committees agree that IE itself is not an indication for routine antithrombotic therapy; rather, management should be individualized based on comorbidities such as atrial fibrillation or mechanical prosthetic valves (9). This study aimed to analyze the clinical and epidemiologic features of adult IE patients at a tertiary referral center over a 14-year period, identify predictors of in-hospital mortality, and particularly assess the impact of antithrombotic exposure. Findings are contextualized within contemporary international literature and guideline recommendations.

Material and Methods

Study Population

The study was approved by the institutional Ethics Committee on June 4, 2014 (Approval No: GO 14/330-33). This retrospective cohort study included adult patients (≥18 years) admitted to our University Hospital between January 2000 and December 2013 with a diagnosis of definite or possible IE according to modified Duke criteria (10).

Diagnoses were determined according to the International Classification of Diseases-10 classification. Patients hospitalized within the study period with the codes I33 (acute and subacute endocarditis), I38 (endocarditis, valve unspecified), and I39 (endocarditis and heart valve disorders in diseases classified elsewhere) were identified. Of 171 patient files evaluated, 49 were excluded because infective endocarditis (IE) could not be confirmed or was unrelated (e.g., prophylaxis only, fever of unknown origin, fever due to other infections in patients with structural heart disease, or absence of echocardiography). Finally, 122 patients were included in the analysis. Patient charts and hospital databases were reviewed to collect demographic data, comorbidities, clinical presentation, laboratory parameters, echocardiographic findings, microbiology, and treatment modalities including antibiotic therapy, surgical interventions, and antithrombotic therapy. The endpoint (discharge, discharge with a sequel, transfer to another hospital, discharge by patient's own request, death) was recorded in detail, but analysed within two groups: survival or death. The primary endpoint of this study was to evaluate the rate of in-hospital mortality in patients with infective endocarditis. The secondary endpoints were designed to identify factors that may influence this primary outcome. These factors included the use of antithrombotic therapy, the distribution of causative microorganisms, the frequency of culture-negative cases, and the occurrence of major complications during hospitalization.

Statistical analysis

Statistical analyses were performed using PASW Statistics 18 (SPSS Inc., Chicago, IL). The distribution of numerical data was analyzed with the Kolmogorov-Smirnov test. Mean ± standard deviation (SD) was used for normally distributed data, while the median (range) values were specified for non-normally distributed data. The endpoint was grouped as survival or death. For categorical variables, Chi-square and Fisher's exact test were used. Categorical data were presented as number and/or percentage. Continuous variables were tested for normality using the Kolmogorov–Smirnov test. Normally distributed variables were compared using the Student's t-test, whereas non-normally distributed variables were analyzed using the Mann–Whitney U test. Categorical variables were compared using the chi-square test or Fisher's exact test where appropriate. Variables with a p value < 0.20 in univariate analyses were entered into the multivariate logistic regression model. A binary logistic regression analysis using a backward stepwise (likelihood ratio) method was then performed to identify independent predictors associated with mortality. Model calibration was assessed using the Hosmer–Lemeshow goodness-of-fit test. The results of the regression analysis are presented as odds ratios (ORs) with 95% confidence intervals (CIs). Statistical significance was defined as $p < 0.05$.

Ethical approval This study was conducted in accordance with the Declaration of Helsinki and institutional ethical guidelines. The study was approved by the Hacettepe University Non-Interventional Clinical Research Ethics Committee (Number: GO 14/330-33, Date: 04.06.2014). Since this study was retrospective, informed patient consent statement was not obtained.

Results

Out of 171 patient records identified, 49 were excluded due to non-infective endocarditis (IE) diagnoses (patients receiving IE prophylaxis only, fever of unknown origin with structural heart disease, or lacking echocardiography). Thus, 122 patient records were included for analysis. The mean age was 52.5 ± 14.2 years, and 63.1% were male. Approximately 86 (70.5%) had at least one chronic comorbidity, most commonly hypertension. **Table 1** summarizes demographic and clinical characteristics. Patients who died were significantly older (57.4 ± 12.8 versus 50.8 ± 14.3 years, $p = 0.023$) and more frequently hypertensive (59.4 % vs 36.7 %, $p = 0.026$) or diabetic (28.1 % vs 12.2 %, $p = 0.037$). History of rheumatic fever (35.2%), pre-existing valvular damage (51.6 %), prosthetic valves/devices (34.4 %), and prior infective endocarditis (10.7 %) were common but not significantly associated with mortality. Patients with hematological malignancies or solid organ tumors involving the bone marrow, those who received chemotherapy within the past 3 months, individuals who have used steroids for more than 30 days, those on immunosuppressive therapy due to solid organ transplantation, and recipients of active DMARDs (disease-modifying antirheumatic drugs) were classified as being under immunosuppression. Twenty-one (17,2%) patients were immunocompromised.

Fever was the most common presenting symptom, occurring in 82.8% of patients. Other common complaints were malaise (39.3 %), dyspnea (32 %), altered mental status (27 %), widespread body pain (24.6 %), nausea/vomiting (22.1 %) and chills (15.6 %). Dyspnea and altered mental status were significantly more common among non survivors ($p = 0.011$ and $p = 0.003$, respectively). Systolic murmur was detected in 63.9 % of patients; hepatosplenomegaly in 41 %; pneumonia in 30.3 %; cutaneous embolic lesions in 14.8 %; and acute cerebrovascular events in 17.2 %. Rash was present in 22 (18.0%) of all patients. Pneumonic infiltrates and skin rash were more frequent among those who died ($p = 0.005$ and $p = 0.024$). Presenting symptoms and physical findings are summarized in **Table 2**. Patients typically sought care a median of 14 days after symptom onset (Interquartile range 1 20). About 54.7 % sought medical care within two weeks, and 73.8 % within 30 days. Acute presentation (< 15 days) was associated with significantly higher mortality (77.4 % of deaths vs 46.5 % of survivors, $p = 0.003$). Presenting symptoms and physical findings are summarized in **Table 2**.

Table 1. Patient Characteristics and Outcomes

Variables	All Patients (n = 122)	Survived (n = 90) (73.8%)	Died (n = 32) (26.2%)	p
Age (years)*	52.5 ± 14.2	50.8 ± 14.3	57.4 ± 12.8	**0.023**
Gender				
Female	45 (36.8)	30 (33.3)	15 (46.9)	NS
Male	77 (63.1)	60 (66.7)	17 (53.1)	NS
Underlying Chronic Disease History	86 (70.5)	60 (66.7)	26 (81.3)	NS
Major Chronic Disease Categories**				
Hypertension	52 (42.6)	33 (36.7)	19 (59.4)	**0.026**
Diabetes mellitus	20 (16.4)	11 (12.2)	9 (28.1)	**0.037**
Coronary artery disease	24 (19.7)	15 (16.7)	9 (28.1)	NS
Heart failure	19 (15.6)	11 (12.2)	8 (25)	NS
Atrial fibrillation	19 (15.6)	13 (14.4)	6 (18.8)	NS
Cerebrovascular event	13 (10.7)	10 (11.1)	3 (9.4)	NS
Chronic obstructive pulmonary disease	9 (7.4)	5 (5.6)	4 (12.5)	NS
Chronic kidney disease	23 (18.9)	14 (15.6)	9 (28.1)	NS
-Hemodialysis dependent	*10 (8.2)*	*5 (5.5)*	*5 (15.6)*	NS
Rheumatological disease	12 (9.8)	9 (10)	3 (9.4)	NS
Malignancy	14 (11.5)	12 (13.3)	2 (6.3)	NS
Immunosuppression***	21 (17.2)	16 (17.8)	5 (15.6)	NS

Abbreviations: *Age is presented as mean ± standard deviation, ** Some patients had more than one chronic disease,
*** Immunosuppression was defined as cases with hematological malignancies or solid organ tumors with bone marrow involvement, chemotherapy use within the last 3 months, steroid use for more than 30 days, immunosuppressive therapy due to solid organ transplantation, and active DMARD (disease-modifying antirheumatic drugs) treatment. NS: Not statistically significant

Table 2. Distribution of Presenting Symptoms and Findings

Symptom	All Patients (n = 122)	Survived (n = 90)	Died (n = 32)	p
Fever	101 (82.8)	77 (85.6)	24 (75.0)	NS
Weakness/ Poor condition	48 (39.3)	34 (37.8)	14 (43.8)	NS
Dyspnea	39 (32.0)	23 (25.6)	16 (50.0)	**0.011**
Altered mental status	33 (27.0)	18 (20)	15 (46.9)	**0.003**
Widespread body pain	30 (24.6)	21 (23.3)	9 (28.1)	NS
Nausea/Vomiting	27 (22.1)	19 (21.1)	8 (25)	NS
Chills/Tremors	19 (15.6)	18 (20)	1 (3.1)	**0.024**
Chest pain	17 (13.9)	11 (12.2)	6 (18.8)	NS
Cough/Sputum	17 (13.9)	11 (12.2)	6 (18.8)	NS
Weight loss	16 (13.1)	14 (15.6)	2 (6.3)	NS
Palpitation	10 (8.2)	8 (8.9)	2 (6.3)	NS
Lateralized weakness/numbness	8 (6.6)	7 (7.8)	1 (3.1)	NS
Finding				
Cardiac Murmur	78 (63.9)	53 (58.9)	25 (78.1)	NS
Hepatomegaly/Splenomegaly	50 (41.0)	36 (40)	14 (43.8)	NS
Pneumonic infiltration	37 (30.3)	21 (23.3)	16 (50)	**0.005**
Rash	22 (18.0)	12 (13.3)	10 (31.3)	**0.024**
Acute cerebrovascular event	21 (17.2)	14 (15.6)	7 (21.9)	NS
Embolic skin finding	18 (14.8)	10 (11.1)	8 (25)	NS

Abbreviations: NS: Not statistically significant

At admission, 59 patients (48.3%) were taking antiplatelet agents, and 43 (35.2%) were taking anticoagulants, most commonly aspirin and warfarin. Digoxin (29.5 %), non-Digoxin antiarrhythmics (31,1%), ACE inhibitors/angiotensin receptor blockers (27 %), diuretics (14.8 %), and proton pump inhibitors (15.6 %) were also used. Aspirin (36.1 % overall) and other antiplatelet agents, clopidogrel, ticlopidine or dipyridamole (12.3 %) were significantly more common in non-survivors ($p = 0.019$ and $p = 0.011$). Warfarin use did not differ between groups. **Table 3** displays the data distribution on medications.

Table 3. Distribution of data on medication use

Medication/Drug Group	All Patients (%)	Survived (%)	Died (%)	p
Digoxin	36 (29.5)	25 (27.8)	11 (34.4)	NS
Acetylsalicylic acid	44 (36.1)	27 (30)	17 (53.1)	**0.019**
Clopidogrel/ Ticlopidine/ Dipyridamole	15 (12.3)	7 (7.8)	8 (25)	**0.011**
Warfarin	43 (35.2)	29 (32.2)	14 (43.8)	NS
Antiarrhythmics (non-digoxin)	38 (31.1)	28 (31.19)	10 (31.3)	NS
ACE inhibitor/ARB*	33 (27.0)	21 (23.3)	12 (37.5)	NS
Diuretics	18 (14.8)	10 (11.1)	8 (25)	NS
Penicillin G	5 (4.1)	3 (3.3)	2 (6.3)	NS
Insulin	11 (9.0)	7 (7.8)	4 (12.5)	NS
Chemotherapeutic agents	8 (6.6)	6 (6.7)	2 (6.3)	NS
DMARD**	10 (8.2)	7 (7.8)	3 (9.4)	NS
Steroid	13 (10.7)	9 (10)	4 (12.5)	NS
Proton pump inhibitor	19 (15.6)	12 (13.3)	7 (21.9)	NS

Abbreviations: *: Angiotensin-converting enzyme inhibitor / Angiotensin receptor blocker, **: Disease-modifying antirheumatic drugs NS: Not statistically significant

Laboratory and interventional technique results among groups are shown in **Table 4**.

Among predisposing conditions to IE, cardiac factors included rheumatic fever–related valve damage (68.3 % of those with valve disease), prosthetic valves/devices (34.4 %), and previous IE (10.7 %). Non-cardiac factors included surgery or invasive procedures within the previous six months (25.5 % of patients), central venous catheterization (14.8 %), immunosuppression (17.2 %), and recent hospitalization (38.5 %). None of these factors showed a significant association with survival. Due to the relatively small sample size, subgroup analyses stratified by valve type (native versus prosthetic) were not performed, which may limit the precision of statistical associations.

Anemia was prevalent (82.8 %), and nearly half of the patients had leukocytosis (median leukocyte count $9.8 \times 10^3/\mu L$; $p = 0.002$ for higher counts in non-survivors). Elevated neutrophil counts and high C-reactive protein and creatinine were more common among those who died, as expected. Median creatinine was 1.0 mg/dL but significantly higher in non-survivors ($p = 0.046$). Hypoalbuminemia (≤ 3.5 g/dL) was present in 61.5 % of patients. Echocardiography revealed a median ejection fraction of 62 %, with 34.9 % having < 60 %. Pulmonary artery pressure averaged 50 ± 19 mmHg and was higher in non-survivors ($p = 0.005$).

Since cases with no echocardiography results in their files were excluded, echocardiographic evaluation was performed on all patients. Both transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) were available for 89 patients (73%), while 26 patients (21.3%) had only TTE, and 7 patients (5.7%) had only TEE.

Echocardiography detected vegetations predominantly on native valves (63.2 % of cases) and prosthetic valves (30.3 %). Among prosthetic valve IE, 71 % involved mitral valve replacements (MVR), 19 % aortic valve replacements (AVR), and 5 % both valves. Native valve IE involved the mitral valve in 42 % of cases, the aortic valve in 38 %, both aortic and mitral valves in 6 %, the tricuspid valve in 5 %, and septal sites in 5 %. Device-related IE included pacemaker leads (4.1 %) and patent foramen ovale closure devices (1.6 %). Only 1 (1%) patient had both prosthetic and native valve endocarditis. In 4% of cases, the location was not specified. Vegetation site (native vs prosthetic or specific valve) was not associated with mortality.

Table 4. Distribution of Laboratory Findings

Test/Unit (NR)	Patient (n)	Mean ± SD* Median (Range)**	Survived	Died	p***
Hgb*/gr/dL (13.6 - 17.2)	122	11.1 ± 2.3	11.0 ± 2.3	11.2 ± 2.3	NS
MCV*/fL (80.7 - 95.5)	122	84.5 ± 7.4	84.7 ± 7.7	84.1 ± 6.7	NS
Leu **/x10³µL (4.3 - 10.3)	122	9.8 (39.8)	9.4 (39.8)	12.4 (31.2)	**0.002**
Hleu: **/x10³µL (4.3 - 10.3)	122	16.3 (142.1)	13.5 (142.1)	22.5 (82.5)	**<0.001**
Neu **/x10³µL (2.1 - 6.1)	122	7.9 (29)	8.3 (28.5)	9.9 (25.8)	**0.002**
NR */% (41 - 73)	122	77.1 ± 12.1	75.4 ± 12.5	81.8 ± 9.2	**0.003**
Thr*/x10³µL (156 - 373)	122	253.2 ± 149.5	253.4 ± 161.3	252.7 ± 112.1	NS
MPV*/fL (6.9 - 10.8)	122	8.2 ± 1.3	8.3 ± 1.3	8.1 ± 1.5	NS
ESR*/mm/sa (0 - 20)	113	55.8 ± 32.1	55.5 ± 32.5	51.6 ± 28.3	NS
CRP **/mg/dL (0 - 0.8)	102	9.1 (40.4)	8.5 (32.4)	10.2 (37.7)	**0.028**
Procal**/ng/mL (0 - 0.05)	38	1.67 (115.96)	0.8 (115.96)	5.9 (27.13)	NS
RF**/IU/mL (0 - 20)	24	22.3 (3850)	22 (3850)	20.7 (33.3)	NS
Cr **/mg/dL (0.67 - 1.17)	122	1.00 (13.2)	1.1 (13.2)	1.4 (7.6)	**0.046**
Albumin*/g/dL (3.5 - 5.2)	122	3.4 ± 0.7	3.4 ± 0.7	3.4 ± 0.7	NS
EF**/% (≥60)	106	62 (74)	60 (64)	74.5 (7)	NS
PAP*/mmHg (≤25)	66	50 ± 19	37.5 ± 14	52.5 ± 10.6	**0.005**

Abbreviations: MCV: Mean Corpuscular Volume, MPV: Mean Platelet Volume, *: Normally distributed values are expressed as mean ± standard deviation (SD).**: Non-normally distributed values are expressed as median (range),***The difference between the two groups was analyzed using the "T-test" for normally distributed values and the "Mann-Whitney U test" for non-normally distributed values. PAP: Pulmonary artery pressure, EF: Ejection fraction, RF: Rheumatoid factor, Procal: Procalcitonin, CRP: C-reactive protein, ESR: Hleu: Highest Leukocyte, Leu: Leukocyte, NR: Neutrophil ratio, Thr: Thrombocyte, Hgb: Hemoglobin, Neu: Neutrophil, Cr: Creatinine, NR: Normal Range

Among patients with prosthetic valve endocarditis, the mitral valve prosthesis was most commonly affected (71%). Aortic valve prosthesis was involved in 19% of cases, and combined aortic and mitral prostheses were seen in 5%. The type of prosthesis was not described in the medical reports for 5% of patients. **Figure 1** illustrates the distribution of valves and/or prosthetic devices involved. Follow-up echocardiograms were also evaluated and analyzed to reveal the relationship between deteriorating echocardiographic findings and adverse outcomes. The criteria for this deterioration were set as the occurrence of at least one of the following findings: An increase in the size of the vegetation, progression towards abscess formation, an increase in the degree of valve regurgitation, or development of a new chordae or valve rupture. Worsening echocardiographic findings were significantly associated with mortality in our study. Patients who showed deterioration on their control echocardiogram had a much higher death rate (60%) compared to those who did not (21.6%). This difference was found to be statistically significant (p=0.046). Blood cultures showed Staphylococcus aureus in 25.5% of cases, followed by other staphylococcal species (14.8%), streptococci (16.3%), enterococci (6.1%), gram-negative bacilli (4.0%), and fungi (0.8%). Culture-negative endocarditis accounted for 33.3% of patients, which is significantly higher than the recommended rate of less than 5%. The causative microorganism has not been linked to differences in mortality. Surgical treatment was performed in 29.5% of patients; the in-hospital mortality in the surgical group was 22%. The overall in-hospital mortality for the cohort was 26.2%. Bleeding events and disseminated intravascular coagulation were more frequent among non-survivors, which are among the well-known mortal outcomes of IE. Variables significantly linked to mortality (outcome: survival versus death) in univariate analyses were included in a multivariate logistic regression model with a backward stepwise (likelihood ratio) approach. These variables encompassed age; presence of hypertension; presence of diabetes mellitus; dyspnea at presentation; altered mental status at presentation; chills and rigors at admission; pneumonic infiltration; skin rash; acute presentation (symptom duration less than 14 days at admission); use of acetylsalicylic acid; use of clopidogrel/ticlopidine/dipyridamole; and worsening on follow-up echocardiography. Independent predictors of mortality were identified through the backward elimination process. Worsening on follow-up echocardiography and antiplatelet therapy (either acetylsalicylic acid or non-aspirin antiplatelet agents) showed the strongest independent association with mortality.

Additionally, variables that were significant at the time of hospital admission in categorical analyses—such as age, presence of diabetes mellitus, acetylsalicylic acid use, C-reactive protein level, serum creatinine level, and duration of symptoms—were entered into a separate logistic regression model using the backward stepwise (likelihood ratio) method. In this adjusted model, the presence of diabetes mellitus (odds ratio 4.7; p = 0.021; 95% CI) and C-reactive protein level (odds ratio 1.06; p = 0.041; 95% CI) remained independently associated with mortality. Model calibration was assessed using the Hosmer–Lemeshow goodness-of-fit test. Multivariable logistic regression identified worsening echocardiographic findings during follow-up (OR = 5.44, p=0.026) and pre-existing antiplatelet therapy (aspirin OR = 2.64, p=0.021; clopidogrel, ticlopidine, or dipyridamole OR = 3.95, p=0.015) as independent predictors of in-hospital mortality. Use of antiplatelet therapy was associated with increased mortality, independent of embolic events.

Table 5. Multivariable Logistic Regression Analysis Identifying Independent Predictors of Mortality

Variable	Wald χ^2	Odds Ratio (95% CI)	p value
Age	4.937	1.037 (1.004–1.070)	0.026
Admission date (≤2006 vs ≥2007)	5.148	2.619 (1.140–6.017)	0.023
Hypertension	4.834	2.524 (1.106–5.764)	0.028
Diabetes mellitus	4.136	2.810 (1.038–7.607)	0.042
Duration of symptoms (days)	4.927	1.030 (0.956–0.997)	0.026
Time to surgery (days)	2.661	1.047 (0.904–1.009)	0.103
Acetylsalicylic acid use	5.301	2.644 (1.156–6.051)	0.021
Clopidogrel, ticlopidine, or dipyridamole use	5.873	3.952 (1.301–12.010)	0.015
C-reactive protein level	5.963	1.058 (1.011–1.107)	0.015
Pulmonary artery pressure (mmHg)	6.399	1.041 (1.009–1.074)	0.011
Worsening on follow-up echocardiography	4.977	5.437 (1.228–24.071)	0.026
Newly developed heart failure	4.310	2.427 (0.178–0.952)	0.038

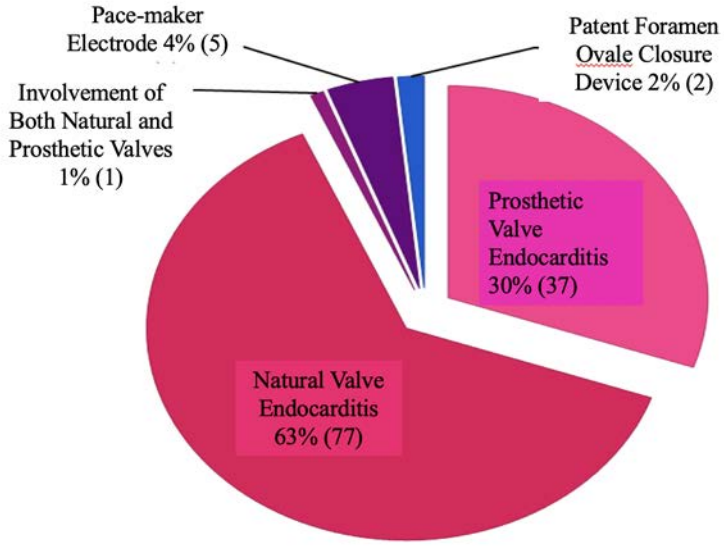

Figure 1. Distribution of data regarding the structure where vegetation was observed

Discussion

Our cohort's finding that antiplatelet therapy independently predicted in hospital mortality aligns with contemporary evidence discouraging routine antithrombotic use in active IE (4-9,12). Recent systematic reviews highlight that bleeding, including intracranial hemorrhage, complicates up to 5 % of cases and that no adequately powered trials demonstrate a protective effect of antiplatelet therapy (4,6,12). The 2023 ESC guidelines therefore

advise against routine antithrombotic therapy and emphasise individualised risk assessment (9). In our regression model, worsening echocardiographic findings and prior antiplatelet therapy were independently associated with in-hospital mortality. These findings highlight the prognostic importance of cardiac imaging during follow-up and the potential clinical implications of pre-existing antiplatelet use. We did not apply more complex multivariable or subgroup analyses because the number of mortality events in our cohort was limited, and additional modeling could lead to unstable statistical estimates. Therefore, we preferred a regression model appropriate for our sample size, which we believe provides reliable and interpretable results. Our observation of high mortality in patients with worsening echocardiographic findings and those on antiplatelet agents is consistent with these recommendations.
However, antiplatelet agents' impact on mortality should be interpreted with caution. Antiplatelet agents were not administered as part of IE treatment but were used before admission for underlying cardiovascular disease. Therefore, antiplatelet therapy likely reflects a higher baseline comorbidity burden rather than exerting a direct harmful effect. The association may thus represent an indirect relationship, where patients requiring antiplatelet therapy inherently have more severe systemic disease, contributing to worse outcomes.
The global burden of IE continues to climb; age-standardised incidence rose from 9.9 to 13.8 per 100 000 person years between 1990 and 2019 (1,10). Despite advances in diagnosis and therapy, in hospital mortality remains around 25 % worldwide (1,10). Demographically, the disease has shifted toward older patients with more comorbidities and greater exposure to prosthetic valves and implantable devices. Staphylococcus aureus has supplanted streptococci as the leading pathogen, and this shift to a more virulent organism contributes to the persistently high mortality (13). The Turkish epidemiological landscape mirrors these global changes yet shows unique features (14,15). Historically, Turkish cohorts described younger patients (mean age; 47 years) (14) and a dominance of rheumatic valve disease (14,15). Our cohort and recent national series show a transition to older patients with prosthetic valves and cardiac devices and a rise in healthcare-associated IE.
The 2025 multicentre study by Sarıcaoglu and colleagues (the Türkiye Endocarditis Group) provides the largest national dataset to date and further clarifies trends observed in our cohort and other Turkish series (16). This retrospective cohort included 1,044 patients with infective endocarditis diagnosed between 2013 and 2023 The median age of patients was 57 years (Interquartile range 44–68) and increased significantly over time. The prevalence of rheumatic and congenital heart disease declined, whereas the prevalence of intracardiac devices (prosthetic valves, cardiac implants) rose. They described a mortality rate of 22.5 %, and a predominance of staphylococci—particularly S. aureus—with decreasing degenerative and congenital heart disease as predisposing factors (16). These findings are partially consistent with our results and other recent worldwide data (17) since both studies identified independent risk factors for death. The Turkish study cited age ≥ 65, chronic kidney disease, nosocomial acquisition, Candida infection, prosthetic-valve IE, vegetations larger than 15 mm, and central nervous system emboli as risk factors. While our results support the significance of age and neurological deterioration, we did not find a significant association with vegetation size, the type of valve involved, or the causative agent.
Recent studies confirm the shift towards device-related and healthcare-associated infections and support our observation. Notably, Brucella species remain a notable cause of IE in Türkiye, but our data confirmed only 1 (1%) patient cultured positive for the regional pathogen.

Study limitations

Our study has some limitations. The retrospective design which is inherent in a review of past records. The analysis of data spanning a period from 2000 to 2013 also means that the findings may not fully reflect current trends in the epidemiology and management of infective endocarditis. The study period (2000–2013) represents a timeframe during which complete institutional records—mostly in physical form but fully accessible—enabled a reliable longitudinal analysis. Although more recent cases could provide additional insights, this period remains valuable for documenting the historical evolution of infective endocarditis in Türkiye. Additionally, the study's focus on a single institution may limit the generalizability of its findings to other centers with different patient populations and healthcare practices. The relatively small sample size of 122 patients, while robust for a single-center study, may affect the statistical power to detect associations between certain variables and clinical outcomes. Despite these limitations, the study provides valuable insights into the evolution of infective endocarditis in a major tertiary care center in Türkiye.

Conclusion

This study, conducted at a tertiary care center in Türkiye, reveals significant shifts in the epidemiology of IE that align with global trends. The patient population is aging, and while rheumatic fever remains a notable predisposing factor, the incidence of prosthetic valve and device-related infections is on the rise.

Logistic regression analysis indicated that the variables most strongly associated with mortality were worsening follow-up echocardiographic results and antiplatelet therapy. Specifically, use of acetylsalicylic acid and non-aspirin antiplatelets were independently associated with a higher risk of death. Therefore, managing these patients should include a careful reassessment of the need for anti-platelet therapy. Additionally, worsening findings on follow-up echocardiograms serve as an important alarm sign and warrant prompt attention. We also found that an acute duration of symptoms (less than 15 days) before admission was a significant predictor of death. Early identification of high-risk patients is critical. Timely and coordinated care is essential to improving patient outcomes and reducing the unacceptably high morbidity and mortality rates.

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Author Contributions: *Concept: SA, MDT. Literature Review: SA, MDT. Design: SA, MDT. Data acquisition: SA, MDT. Analysis and interpretation: SA, MDT. Writing manuscript: SA; MDT. Critical revision of manuscript: SA, MDT.*

Conflict of Interest: *The author(s) do not have any potential conflict of interest regarding the research, authorship and/or publication of this article.*

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Original Article

Brainstem Alteration in Migraine via 3D Volume Segmentation

Migrende Beyin Sapinin 3DHacim Segmentasyonu Aracliğiyla Değişimi

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Abstract

Background: Migraine is a multifaceted and complex disease that can be described as a mild headache or as a very severe headache lasting for days. It is a very common neurological disease in the society. Although migraine has a well-defined phenotype, some gaps in its pathophysiology can be partly filled by neuroimaging studies.

Materials and Methods: In this context, the present study aims to measure and compare the brainstem volumes of both patients diagnosed with migraine and healthy individuals by using 3D volume segmentation method. The study included 94 healthy participants (47 males and 47 females) with no illnesses or pathologies, and 98 participants (59 females and 39 males) with a migraine diagnosis who were between the ages of 18 and 50. Using ITK-SNAP software and 3D volume segmentation, brainstem volumes were assessed. To find differences, the brainstem volumes of the two groups were examined.

Results: The analyses showed that migraine patients and healthy people had significantly different brainstem volumes ($U = 2049.500$, $p < 0,01$). Compared to migraine patients, who had a median brainstem volume of 182.900 mm^3, healthy people had a median brainstem volume of 227.900 mm^3. Furthermore, healthy people had a broader range of brainstem volumes (117.800 mm^3 to 347.800 mm^3) than migraine patients (122.300 mm^3 to 259.300 mm^3). The group with migraines showed outliers. According to these findings, healthy people have bigger and more variable brainstem volumes than people who suffer from migraines.

Conclusions: The present study clearly showed the difference between brainstem volume of migraine patients and healthy individuals and also showed that this difference is statistically significant.

Keywords: Brainstem, Migraine, ITK- SNAP, Volume, Three-dimensional segmentation

ÖZ

Amaç: Migren, hafif baş ağrısından günlerce süren çok şiddetli baş ağrısına kadar çok yönlü ve karmaşık bir hastalıktır. Toplumda oldukça yaygın görülen bir nörolojik hastalıktır. Migrenin iyi tanımlanmış bir fenotipi olmasına rağmen, patofizyolojisindeki bazı boşluklar nörogörüntüleme çalışmalarıyla kısmen doldurulabilir. Bu bağlamda, mevcut çalışma, migren tanısı almış hastaların ve sağlıklı bireylerin beyin sapı hacimlerini 3B hacim segmentasyon yöntemi kullanarak ölçmeyi ve karşılaştırmayı amaçlamaktadır.

Gereç ve Yöntem: Bu çalışmada migren tanısı almış hastalar ile sağlıklı bireylerin beyin sapı hacimlerinin 3B hacim segmentasyon yöntemi kullanılarak ölçülmesi ve karşılaştırılması amaçlanmıştır. Çalışmaya herhangi bir hastalığı veya patolojisi olmayan 94 sağlıklı katılımcı (47 erkek ve 47 kadın) ve migren tanısı almış 18-50 yaşları arasındaki 98 katılımcı (59 kadın ve 39 erkek) dahil edilmiştir. ITK-SNAP yazılımı ve 3B hacim segmentasyonu kullanılarak beyin sapı hacimleri değerlendirilmiştir. Farklılıkları bulmak için iki grubun beyin sapı hacimleri incelenmiştir.

Bulgular: Analizler, migren hastalarının ve sağlıklı bireylerin beyin sapı hacimlerinin anlamlı derecede farklı olduğunu göstermiştir ($U = 2049.500$, $p < 0,01$). Ortanca beyin sapı hacmi 182.900 mm^3 olan migren hastalarıyla karşılaştırıldığında, sağlıklı bireylerin ortanca beyin sapı hacmi 227.900 mm^3'tür. Ayrıca, sağlıklı kişilerin beyin sapı hacimleri migren hastalarına (122.300 mm^3 ila 259.300 mm^3) göre daha geniş bir aralıktaydı (117.800 mm^3 ila 347.800 mm^3). Migren grubunda ise aykırı değerler gözlendi. Bu bulgulara göre, sağlıklı kişilerin beyin sapı hacimleri migren hastalarına göre daha büyük ve daha değişkendir.

Sonuç: Mevcut çalışma, migren hastalarının beyin sapı hacmi ile sağlıklı bireylerin beyin sapı hacmi arasındaki farkı açıkça ortaya koymuş ve bu farkın istatistiksel olarak anlamlı olduğunu göstermiştir.

Anahtar Kelimeler: Beyin sapı, Migren, ITK-SNAP, Hacim, Üç boyutlu segmentasyon

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Highlights

- This study shows that migraineurs have smaller brainstem volumes than healthy individuals.
- A novel method for volume calculation was utilized.
- Brainstem volume was calculated via segmentation, providing more accurate results.

Introduction

Migraine is a neurological disease that is thought to be caused as a result of the interaction of genetic and environmental factors, although the exact cause is unknown. A complex neurological condition, migraine is brought on by genetics, environmental circumstances, stress, hormone changes, dietary factors like caffeine and energy drinks, and changes in the pathways that the central nervous system uses to process pain. It is characterized by a throbbing headache usually felt on one side of the head, and may be accompanied by additional symptoms such as headache, nausea, vomiting, hypersensitivity to light or sound during attacks (1). Migraine can last for a few hours or a few days and can have a significant negative impact on the daily life of individuals (2).

This disease has a higher prevalence in women when compared with men and constitutes an important public health problem by affecting approximately one billion people worldwide. Studies for understanding the pathophysiology of migraine are carried out to develop accurate diagnosis and treatment methods and neuroimaging studies are also conducted in this context (3). According to previous studies, migraineurs may have volumetric alterations in both migraine-specific and pain-processing-related brain regions, including the brainstem. Reduced grey matter volume is frequently seen in these patients, especially in regions related to pain, cognition, and sensory integration. The entire brain volume, grey matter, brainstem, cerebellum, basal ganglia, thalamus, hippocampus, and amygdala are among the areas where volumetric losses have also been observed (4–6).

Since the brain stem is at the center of the pain pathways of migraine, it plays a critical role in understanding the pathophysiology of migraine. Structural changes in the brainstem have been observed in migraine patients and significant decreases in brainstem have been found especially in chronic migraine cases. Therefore, measuring the brainstem volume can make a significant contribution to better understanding the neurological effects and structural changes of migraine (7).

ITK-SNAP software, which has been used to measure brainstem volumes in the present study, is a software used for segmentation of three-dimensional medical images. In addition to providing semi-automatic and manual segmentation, it can simultaneously display images in three orthogonal planes. It is suitable for using many three-dimensional image formats, including DICOM and can make the segmentation of multiple images (8). In this study, we aimed to measure and compare the brainstem volumes of both patients diagnosed with migraine and healthy individuals by using ITK SNAP software.

Material and Methods

Study design

This retrospective study was conducted with the approval of the Bolu Abant Izzet Baysal University Non-Interventional Clinical Research Ethics Committee (2024/324). The study included MR images of 98 individuals (59 females and 39 males) diagnosed with migraine, as well as 94 individuals (47 males and 47 females) who did not have any diagnosis. These MR images were randomly selected from the Picture Archiving and Communication Systems (PACS) archive for analysis and evaluation.

Participants with a migraine diagnosis and MR images suitable for healthy brainstem volume measurement were included in the study. Individuals outside this age range, those without a migraine diagnosis, or those with brainstem images affected by surrounding pathological structures that hindered accurate measurement were excluded.

Inclusion criteria: Individuals aged 18–50 with a migraine diagnosis and suitable MR images for healthy brainstem volume measurement.

Exclusion criteria: Individuals under 18 or over 50, those without a migraine diagnosis, and those with MR images affected by surrounding pathological structures that prevented accurate measurement of brainstem

volume. Volumetric measurements of the brainstem were performed using ITK-SNAP software.

Segmentation and measurements

MR images obtained from the PACS archive in DICOM format were transferred to ITK-SNAP software. After the brainstem images transferred to ITK-SNAP were enclosed using the 'Segmentation Mode' available in the 'Toolbox'. For the enclosed brainstem image, the 'Lower / Upper Threshold' adjustment was made on the right panel. The area intended for volumetric measurement was left in white, while surrounding structures were left in blue to prevent them from being segmented. To perform volumetric measurement, a 'Bubble' was added to the center of the brainstem from the 'Add Bubble at Cursor' section. When the 'Forward' and 'Play' buttons were clicked, the 'Bubble' was spread across the brainstem surface, facilitating the segmentation of the appropriate structures. The brainstem images with volumetric measurements are shown in the sagittal plane **(Figure 1).** ITK SNAP also allows users to visualize the structures the volumes of which have been measured in three dimensions. **(Figure 2)** shows the three-dimensional modelling of the brainstem image of an individual with migraine whose volume measurement has been completed. The volume value of the completed brainstem measurement can be accessed from the 'Volume and Statistics' tab under the 'Segmentation' section in the top-left corner of the screen **(Figure 3)**. The ITK-SNAP software provides users with the volumetric value of the respective structures in mm^3 in a ready-to-use format.

Figure 1. Volumetric measurement of the brainstem of an individual with migraine by using ITK SNAP.

Statistical analysis

Conformity of the data to normal distribution was analysed with Shapiro-Wilk test. While descriptive statistics of the data which conformed to normal distribution were shown as minimum (min), maximum (max), mean (m) and standard deviation (sd), median and interquartile range (iqr) were used for variables which did not conform to normal distribution. The data used in the study were analysed with Paired Samples test conducted on brainstem volume measurements. Jamiovi Deskop software was used for analyses and Python 3.8.8 compiler and Jupyter Notebook 6.4.6 editor were used for drawing the figures.

Ethical approval

This study was conducted in accordance with the Declaration of Helsinki and institutional ethical guidelines. The study was approved by the Bolu Abant Izzet Baysal University Non-Interventional Clinical Research Ethics Committee (Number: 2024/324, Date: 03.12.2024). Since this study was retrospective, informed patient consent statement was not obtained.

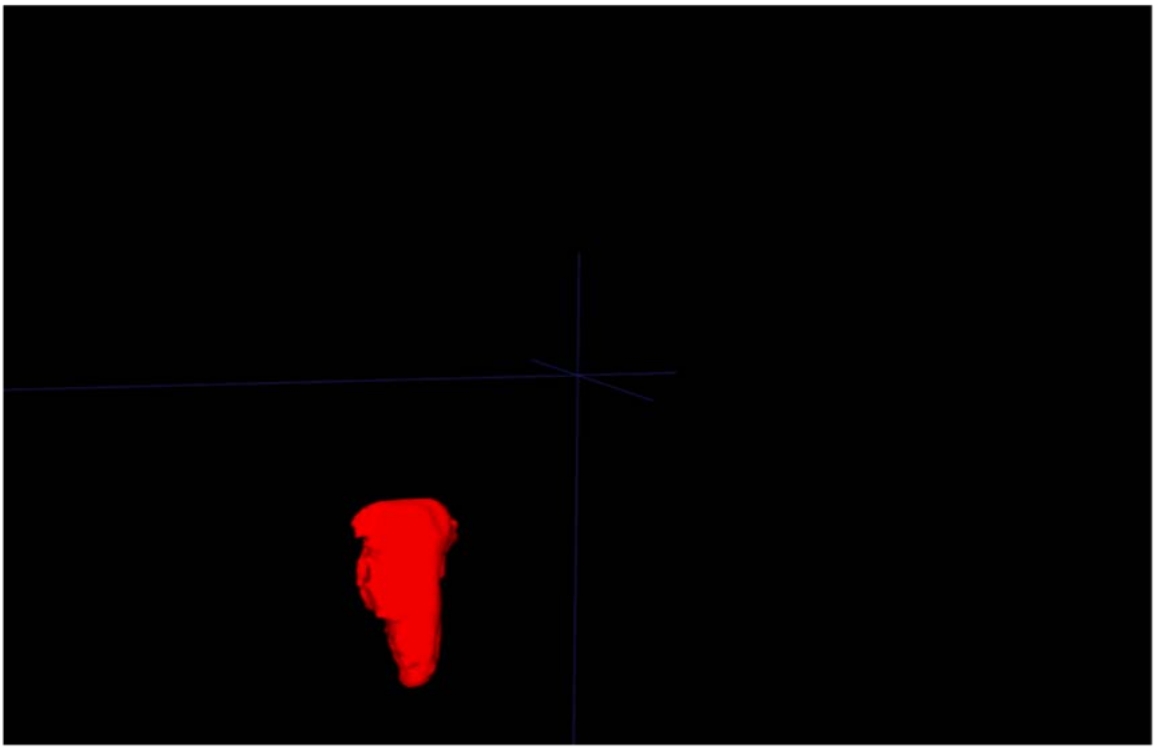

Figure 2. Three-dimensional imaging of the brainstem of an individual with migraine.

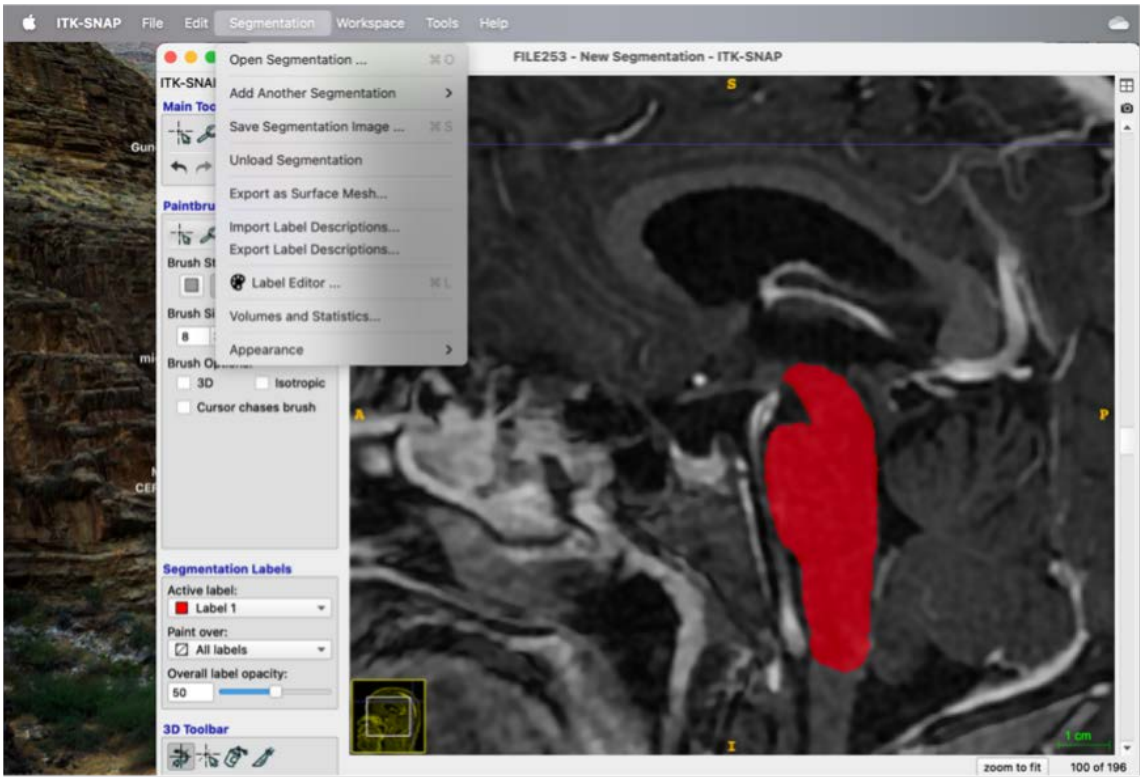

Figure 3. Section in ITK-SNAP where volume values of measured structures can be accessed.

Results

When the conformity of individuals to normal distribution was tested with Shapiro-Wilk Analysis, Shapiro-Wilk value was found as 0.905 and p value was found as 0.980 for healthy individuals. This result shows that the brainstem volume data of healthy individuals do not show a significant deviation from normal distribution ($p > 0.05$) and that the assumption of normal distribution is valid. Shapiro-Wilk value was found as 0.969 and p value was found as 0.021 for individuals with migraine. The brainstem volume data of individuals with migraine show a significant deviation from normal distribution and that the assumption of normal distribution is not valid ($p < 0.05$). These data show that the data obtained from healthy individuals are normally distributed, while there is a deviation from normal distribution in the data obtained from individuals with migraine. Analysis results are shown in **(Table 1)**.

Table 1. Comparison of Brainstem Volume Normality Between Healthy Individuals and Migraine Patients

	W	p
Healthy Group	0.995	0.980
Migraine Patients	0.969	0.021

Abbreviations: **W: Shapiro-Wilk test statistic, which measures the normality of data distribution. **p: Probability value indicating whether the data significantly deviate from a normal distribution (p > 0.05 suggests normality).*

Mann-Whitney U test was conducted to determine whether there was a significant difference between healthy individuals and individuals with migraine in terms of brainstem volume. As a result of the analysis, a statistically significant difference was found between healthy individuals and individuals with migraine in terms of brainstem volume ($U = 2049.500$, $p < 0.01$). U value was calculated as 2049.500 and the p-value indicating that this difference is significant was found to be less than 0.05. These data show that the volumetric differences between groups are not random. A p value less than 0.05 proves that there is a significant difference between groups. The U value obtained as a result of the test shows that the volumetric differences between the two groups are statistically significant. These results show that the brainstem volume differs between groups. Analysis results are shown in **(Table 2)**.

Table 2. Comparison of Brainstem Volumes Between Healthy Individuals and Migraine Patients

	U	p
Brainstem volume	2049.500	<0.01

Abbreviations: **U: Mann-Whitney U test statistic, which compares the distributions of two independent groups. **p: Probability value indicating whether there is a statistically significant difference between the groups (p <0.05 suggests a significant difference).*

Analysis results show statistically significant differences between healthy individuals and individuals with migraine in terms of brainstem volume. The median value of the brainstem volumes of healthy individuals (227.900) was found to be significantly higher than that of individuals with migraine (182.900). This shows that brainstem volumes of healthy individuals are larger than those of patients with migraine in general. It was found that the brainstem volumes of healthy individuals are larger than those of individuals with migraine and the distributions are larger, while the brainstem volumes of individuals with migraine are smaller and they show less variation. In addition to these results, it was found that minimum and maximum values showed a larger range in healthy individuals. While the minimum value of brainstem volume was 117.800 in healthy individuals, maximum value was measured as 347.800. In individuals with migraine, the minimum value of brainstem volume was found as 122.300, while the maximum value was found as 259.300. The brainstem volumes of individuals with migraine were found to be both lower and in a narrower range (137), while the volumes of healthy individuals were found to have a larger range (230). Analysis results are shown in **(Table 3)**.

Table 3. Descriptive Statistics of Brainstem Volumes Data

Variables	Median	Min.-Max.	Range
Healthy Group	227.900	117.800-347.800	230
Migraine Patients	182.900	122.300-259.300	137

Discussion

In the current study, difference between these two groups were statistically volumetric alterations of the brainstem were assessed using ITK-SNAP software in 98 individuals. The analysis revealed a significant difference in brainstem volume between migraine patients and healthy individuals. Specifically, the brainstem volume of healthy individuals was found to be significantly larger than that of migraine patients.

Migraine patients between the ages of 15 and 60 who were admitted to the neurology outpatient clinic of a tertiary hospital between January and July 2017 were included in a study examining the relationship between migraine and brainstem excitability. Migraine diagnosis was made according to International Headache Disorder Classification (IHS, 2013). Hearing threshold and brainstem excitability were measured in individuals with migraine and compared with the control group. As a result of the study, individuals with migraine were found to have both lower hearing threshold and increased sensitivity of brainstem auditory neurons (9).

In a study examining the cyclic neurophysiological characteristics of migraine attacks, neuronal excitability in the brainstem and primary somato-sensory region was compared between migraine stages for 30 consecutive days in two patients with episodic migraine. Electroencephalography (EEG) recordings of potentials associated with somatosensory and paired pulse paradigms were recorded for 30 days in both patients. Normalized current density in the brainstem and somatosensory region was recorded and analysed.

In both patients, increased excitability was found both in the brainstem and in the somatosensory region. As a result of the study, it was emphasized that migraine involves a system starting in the brainstem extending to the somatosensory region and that it is a cyclical excitatory disorder (10).

In a thesis published in 2012, brain volume changes in migraine patients were examined and compared with healthy individuals. The volumes of total intracranial and subcortical structures were measured with Freesurfer method on cranial MRs of all groups. As a result of the study, it was concluded that migraine may cause permanent central nervous system dysfunction and also atrophy in neocortical structures in individuals. It was also emphasized that atrophy level may be associated with the number of days or the frequency of attacks (11).

In another study, a case of chronic migraine-type chronic daily headache was presented in a patient with vascular malformation haemorrhage in midbrain and it was emphasized that the structural lesions in the brainstem could cause headache (12).

In a study conducted in 2019, magnetic resonance images of 28 childhood migraine (CHM) patients and 41 control patients with similar age and gender distribution were analysed. Migraine patients were also classified as migraine with aura (8 patients) and migraine without aura (20 patients) group. 'volBrain' program was used from T1 weighted images and subcortical grey matter volumes were measured and compared. As a result of the study, putamen volumes of CHM patients were found to be significantly increased when compared with the healthy control group. In addition, putamen volume increase was found to be higher in aura migraine group when compared with migraine without aura and control groups. It was pointed out that it may be easier to clarify the pathogenesis of migraine with the increase in imaging methods and the relationship between childhood migraine and subcortical grey matter structure volumes were also emphasized (13).

In a study which suggested that the changes in the anatomy and functioning of the brainstem may contribute to the onset and duration of headaches during migraine attacks, voxel-based morphometry of T1 weighted anatomic images (57 control, 24 migraine) and diffusion tensor images (22 control, 24 migraine) were used to evaluate the brainstem anatomy of individuals. A decrease was found in the grey matter volumes in spinal trigeminal core and dorsomedial pons of individuals with migraine. In addition, decreased grey matter was found in the regions of pain modulating systems such as midbrain periaqueductal grey matter and dorsolateral pons. The data found clearly showed that the structure of the brainstem can change during migraine attacks. It was concluded that migraine cycle can increase the probability of creating dynamic changes in the structure and functioning of the brainstem, which may trigger and change brainstem sensitivity. It was stated that it may be in a position to modify these changes that may occur in the functioning and structure of the brainstem and potentially prevent the triggering of migraine crisis (14).

In another study summarizing studies on grey matter changes in patients with migraine, the harmony between structural changes and functional changes which occur in the related brain sections during migraine attacks was

examined. Articles published between January 1985 and November 2015 were searched in 'PubMed' and 'Embase' and the references in the related primary articles were examined. Meta-analysis was conducted by using activation likelihood estimation (ALE). Eight clinical studies including a total of 390 subjects (191 patients and 199 controls) were analysed for structural changes. Five functional studies including 93 patients and 96 controls were also analysed. A decrease was shown in the grey matter volumes of migraine patients in bilateral inferior frontal gyrus, right precentral gyrus, left mid frontal gyrus and left cingulate gyrus.

On the contrary, an increase in activation was found in somatosensory, cingulate, limbic lobe and brainstem in patients with migraine. It was concluded as a result of the study that the changes in grey matter in migraine patients may show pain processing mechanism and related symptoms, while increased activation may suggest dysregulation of these areas or increased effort due to the use of compensatory strategies involving pain processing in migraine. It was emphasized that being informed about these structural and functional changes may also be useful for the follow-up and treatment of migraine (15).

In a study including 24 chronic migraine patients and 24 healthy controls, all of whom were women, MRI of the participants were processed with Freesurfer (automatic segmentation) method. As a result of the study, cerebellum and brainstem volumes of women with chronic migraine were found to be smaller when compared with the control group. Structural white matter anomalies were also found in the bilateral parieto-occipital regions of women with migraine. Although it is still unclear whether these structural brain changes are a cause or a consequence of migraine, it was emphasized in the study that there is a need for volumetric neuroimaging studies with larger groups especially on the chronification of migraine to shed light on this issue (16).

Study limitations

One of the major limitations of our research is the incapacity to evaluate the causal relationship between variations in brainstem volume and migraine. The study design's retrospective nature, which only permits the observation of associations rather than causal interactions, is the source of this shortcoming. To ascertain if anatomical alterations in the brainstem cause migraines or if migraines cause these alterations, a prospective study design in which individuals are monitored over time would be required. The very small sample size is another drawback that could limit how far the results can be applied. A bigger cohort would increase the study's statistical power and enable more reliable findings, even though our sample of 98 migraine patients and 94 healthy people offers insightful information. Furthermore, a sample that is more varied in terms of age, ethnicity, and migraine subtypes may offer a more comprehensive understanding of the potential variations in brainstem volumes among other groups. Additionally, even though ITK-SNAP software is an effective tool for 3D volumetric analysis, the quality of the results depends on the consistency and resolution of the imaging data because it relies on MRI scans. Measurement variability may be introduced by differences in MRI scanning hardware or techniques between institutions, which could compromise the validity of the results.

Finally, confounding variables that can affect brainstem volumes, such as medication use, comorbidities, or the intensity and duration of migraines, were not taken into consideration. To provide a more thorough knowledge of the connection between migraine and brainstem structure, future research should consider these parameters.

Conclusion

Analyses showed a significant difference between migraine patients and healthy individuals in terms of brainstem volume. According to independent samples t-test results, brainstem volumes of healthy individuals were found to be significantly higher than those of migraine patients. Confirmatory analyses with Mann-Whitney U test also showed that the difference was statistically significant. Lower brainstem volume in individuals with migraine indicate structural differences regarding the neurological basis of migraine. Considering the role of brainstem in pain regulation mechanisms in the literature, the results found emphasize the relationship between migraine pathophysiology and brainstem structure. The fact that healthy individuals have a wider range of volume suggests that the neurological structures of this group may show more variations.

In addition, the fact that individuals with migraine have both low and narrower range of brainstem volume shows the limiting effects of migraine to brainstem structure. This is completely different from the wider and more varied range of volume in healthy individuals. This difference can be considered as an important finding supporting the

potential pathological effects of migraine on the brainstem. This study provides an important basis to better elucidate the effects of migraine on the brainstem. However, there is a need for further research to determine whether these differences in the brainstem volume are a cause or a consequence of migraine. Future studies may contribute to answering this question by examining the effects of especially structural changes in the brainstem on migraine development.

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Ethical Approval: *The study was approved by the Bolu Abant Izzet Baysal University Non-Interventional Clinical Research Ethics Committee (Number: 2024/324, Date: 03.12.2024). Since this study was retrospective, informed patient consent statement was not collected.*
Author Contributions: *Concept: GTS, EZB, CA. Literature Review: GTS, EZB. Design: GTS, EZB, CA. Data acquisition: EZB, CA. Analysis and interpretation: EZB. Writing manuscript: GTS, EZB. Critical revision of manuscript: GTS. These authors contributed equally to this work.*
Conflict of Interest: *The author(s) do not have any potential conflict of interest regarding the research. authorship and/or publication of this article.*
Data Availability: *The data used to support the findings of this study are available from the corresponding author upon request.*
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Original Article

Scientific Accuracy and Reliability Analysis of YouTube Videos on Exosome Therapy: Content and Quality Assessment

Ekzozom Terapisine İlişkin Youtube Videolarinin Bilimsel Doğruluk Ve Güvenilirlik Analizi: İçerik Ve Kalite Değerlendirmesi

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Abstract

Background: This study aimed to assess the accuracy, reliability, and quality of YouTube videos on exosome therapy and their consistency with current scientific evidence and clinical guidelines.

Materials and Methods: This study utilized a descriptive cross-sectional design and systematically examined YouTube content related to "exosome therapy." A total of 100 videos were initially identified, of which 58 met the inclusion criteria. Each video was categorized by source, content type, and audience engagement indicators, while quality evaluation was independently performed by two reviewers using the DISCERN and JAMA benchmark tools. Statistical analyses were applied to assess group differences and correlations between variables, ensuring methodological rigor and reproducibility.

Results: Among 58 analyzed videos, most were uploaded by physicians (53.4%) or health organizations (39.7%) and mainly offered general educational content. Videos from physicians scored higher on DISCERN and JAMA criteria than those from patients ($p = 0.032$). A moderate positive correlation existed between video duration and quality ($\rho = 0.356$, $p = 0.007$), while popularity metrics such as views or likes showed no significant association with reliability.

Conclusions: The quality of YouTube content on exosome therapy varies considerably. Videos from physicians and health organizations are generally more accurate, yet gaps remain in transparency and disclosure. These results emphasize the need for collaboration among healthcare professionals, academics, and platform managers to provide reliable and transparent health information. Improved regulation, quality content creation, and user education may help reduce misinformation and support informed decision-making.

Keywords: Exosomes, Cell-Derived Microparticles, Regenerative Medicine, Social Media, Health Education

ÖZ

Amaç: Bu çalışmanın amacı, eksozom tedavisine ilişkin YouTube videolarının doğruluk, güvenilirlik ve bilimsel kalite düzeyini değerlendirmek ve mevcut literatür ile klinik kılavuzlarla uyumunu incelemektir.

Gereç ve Yöntem: Bu araştırma tanımlayıcı ve kesitsel bir tasarımda yürütülmüştür. "Exosome therapy" anahtar sözcüğü kullanılarak YouTube platformunda sistematik bir tarama yapılmış ve ilk 100 video değerlendirmeye alınmıştır. Uygulanan dâhil edilme ölçütlerini karşılayan 58 video analiz kapsamına girmiştir. Videolar; kaynağı, içerik türü ve izleyici etkileşimi göstergeleri açısından sınıflandırılmış, içerik kalitesi iki bağımsız değerlendirici tarafından DISCERN ve JAMA kriterleri kullanılarak incelenmiştir. Gruplar arası farklar ve değişkenler arasındaki ilişkiler uygun istatistiksel yöntemlerle analiz edilerek bulguların bilimsel geçerliliği ve güvenilirliği sağlanmıştır.

Bulgular: Analiz edilen 58 videonun çoğu hekimler (%53,4) ve sağlık kuruluşları (%39,7) tarafından yüklenmiş olup, içeriklerin büyük bölümü genel bilgilendirme niteliğindeydi. Hekimler tarafından hazırlanan videoların DISCERN ve JAMA puanları, hastalar tarafından yüklenen videolardan anlamlı derecede yüksek bulunmuştur ($p = 0,032$). Video süresi ile içerik kalitesi arasında orta düzeyde pozitif ilişki saptanırken ($\rho = 0,356$; $p = 0,007$), izlenme ve beğeni sayısı gibi popülerlik göstergeleriyle kalite arasında anlamlı bir ilişki görülmemiştir.

Sonuç: Eksozom tedavisine ilişkin YouTube içeriklerinin kalitesi değişkenlik göstermektedir. Hekimler ve sağlık kuruluşları tarafından hazırlanan videolar genellikle daha doğru bilgiler içerse de, açıklık ve şeffaflık açısından eksiklikler mevcuttur. Bu sonuçlar, doğru ve güvenilir sağlık bilgisinin halka ulaştırılabilmesi için sağlık profesyonelleri, akademik kurumlar ve dijital platform yöneticilerinin iş birliği yapması gerektiğini göstermektedir. İçerik denetimi ve kullanıcı eğitiminin güçlendirilmesi, çevrimiçi bilgi kalitesini artırarak bilinçli karar verme süreçlerine katkı sağlayabilir.

Anahtar Kelimeler: Eksozomlar, Hücre Kaynaklı Mikropartiküller, Rejeneratif Tıp, Sosyal Medya, Sağlık Eğitimi

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Highlights

- This study evaluated the accuracy, reliability, and quality of YouTube videos on exosome therapy.
- Videos uploaded by physicians showed significantly higher reliability and quality scores.
- Video popularity metrics such as views and likes were not associated with information reliability.

Introduction

Exosomes, nanoscale extracellular vesicles with a lipid bilayer, have garnered interest in the biomedical community because of their involvement in cellular communication. As research has expanded in recent years, there has also been an increasing interest in the possible role of exosomes in certain biologic processes (1). Their ability to carry a wide array of biomolecules, including proteins, lipids, and nucleic acids, has led to the consideration of their use as therapeutic tools in certain biologic and therapeutic processes, including the regeneration of tissues, immunomodulation, and the treatment of conditions of the nervous system (2). Their ability to suppress inflammation, participate in the process of tissue regeneration, and act as targeted delivery vehicles for drugs has all been demonstrated in preclinical studies DYSDYS (3–5).

Despite such potential, exosome therapies are still in the early stages of development as a treatment approach. The key areas, such as production methods, purification methods, and dosages, are not clearly established and, as such, adequate clinical practices are not established (6). It is imperative to note the importance of accurate, up-to-date, and evidence-based information for both health professionals and the public. With the current state of information technology, the internet and social media sites are now the key resources for health care information, as such, they provide fast and widespread access (7,8).

YouTube has become a popular platform for sharing information about emerging and complex medical issues such as exosome therapy, owing to reasons of wide reach, free accessibility, and availability of elaborate audiovisual displays (9). However, being a platform wherein information presented is neither reviewed and showed in advance, nor peer-checked, most of this content tends to be incomplete, misleading, and even non-evidence-based (8,10,11). Analysis of previous studies has indicated that most medical information highlighted through videos on the YouTube platform has neither subscribed to scientific medical literature, nor tends to conform to medical guidelines (12–14). There exists considerable diversity in this regard, and this tends to be even more worrisome in emerging medical fields, wherein establishing any standard clinical procedures has yet to be achieved (15,16).

Although numerous studies have evaluated the quality of YouTube content related to established diseases and well-standardized treatments, to our knowledge, no prior YouTube-based analysis has specifically focused on exosome therapy—an emerging and rapidly expanding therapeutic domain—within the context of evolving regulatory frameworks and international extracellular vesicle guidelines such as MISEV2018. Unlike established medical fields with clearly defined clinical pathways, exosome therapy remains in a transitional stage characterized by heterogeneous indications, limited high-quality clinical evidence, and growing commercial promotion. This unique combination creates a distinct vulnerability to misinformation and makes systematic evaluation of publicly available content methodologically and clinically relevant.

The current research aimed to systematically assess the scientific accuracy, reliability, and quality of videos uploaded on YouTube related to exosome therapy as well as their alignment with existing literature and guidelines.

Material and Methods

Study design

This research was conducted using a descriptive cross-sectional design to evaluate the reliability, scientific accuracy, and informational quality of YouTube videos related to exosome therapy.

Ethical approval

The analysis was limited to openly accessible online video content and did not involve direct interaction with individuals, identifiable personal data, or experimental procedures involving human or animal subjects. Therefore, formal approval from an institutional ethics committee was not required (17,18). Despite the absence of a requirement for ethical approval, the study adhered to established ethical principles applicable to research utilizing publicly available digital materials, ensuring responsible handling, objective evaluation, and appropriate reporting of online content.

Video Selection

The search for scientific data on the topic of exosome therapy was conducted on the YouTube website on January 15, 2025, using the search term "exosome therapy." The search terms were conducted in the usual search mode used by this platform, which is the "relevance" search, as detailed in previous research (7). The search is done in incognito mode and logged-off condition to remove the effect of personalization.

The first 100 videos listed in the search results. The selection of the first 100 videos was based on established methodology in digital health communication research, which indicates that users rarely proceed beyond the first few result pages. This approach enhances ecological validity by replicating real-world user behavior rather than constructing an artificially expanded dataset. Furthermore, performing the search in incognito mode minimized algorithmic personalization bias and improved methodological reproducibility (8,9).

Inclusion criteria were:

1.Primarily concentrating on exosome therapy definition, mechanisms, and use, or scientific evidence

2.English audio or subtitles.

3.Full-length accessibility without restrictions.

Exclusion criteria were:

•Content in other languages, but does not.

•Duplicate videos.

•Admittedly, commercial or promotional videos with no essential educational and scientific content.

•60-second or less video lengths were considered not suitable for inclusion, as these types of videos tend to contain a small amount of information and do not bring forward an unbiased coverage of signs, risks, and evidence. There was no limit on the length of the video, as it could provide more information (11).

•A total of 58 videos were left to analyze after applying this criterion (Figure 1).

Data Extraction

Inclusion criteria for the videos analyzed were the following:

•Title and URL

•Upload date and total days online

•Duration (minutes)

•No. of views, likes, dislikes (if available), and comments

•Scope or type of source: (a) Physician or healthcare professional, (b) Healthcare or related organization, or (c) independent creator/patient (14)

•Form of content: general information presentation, research presentation, patient testimony

Quality and Reliability Assessment

Two validated instruments were used:

1.DISCERN Instrument – This is a research tool that helps measure the quality of written or audiovisual health consumer information on treatment choices (19). It has 15 items covered in three areas: the reliability of the information, the quality of the treatment information provided, and the overall score. All the items are measured using a scale of 1-5. Total scores are interpreted using a scale that depicts excellent (63-75), good (51-62), fair (39-50), poor (27-38), or very poor (<27) scores (19,20).

2.JAMA Benchmark Criteria – It is a set of guidelines created to determine the authenticity of medical and health-related information found on the internet, including issues of authorship and currency (21). A total of 1 mark is awarded for each criterion, and a total of 4 is possible (21).

Two reviewers who are proficient in evidence-based medicine and medical education rated all video material. Any disagreements were resolved by consensus. The inter-rater reliability was calculated by Cohen's kappa coefficient.

Statistical analysis

All the procedures for the analysis of the data were conducted using the IBM SPSS Statistics version 25.0 software. The mean ± SD, median (minimum-maximum), or frequencies (%) were employed to summarize the descriptive data. For normality testing, the Shapiro-Wilk test was employed. To evaluate more than two groups, the Kruskal Wallis test was employed. To identify the variances between the groups, the Dunn Bonferroni test was employed.

To determine the association between the continuous variables, such as the length of the videos, number of views, and quality, Spearman's rank correlation coefficient test was employed. The results were considered significant if the p-value was <0.05.

Results

In total, 100 videos were found through the initial search. Starting with the application of inclusion and exclusion criteria, 42 videos were excluded because of being non-English with no subtitles, being duplicates, with a purely promotion focus, or being less than 60 seconds long. This resulted in 58 videos being selected to be included in the final examination **(Figure 1).**

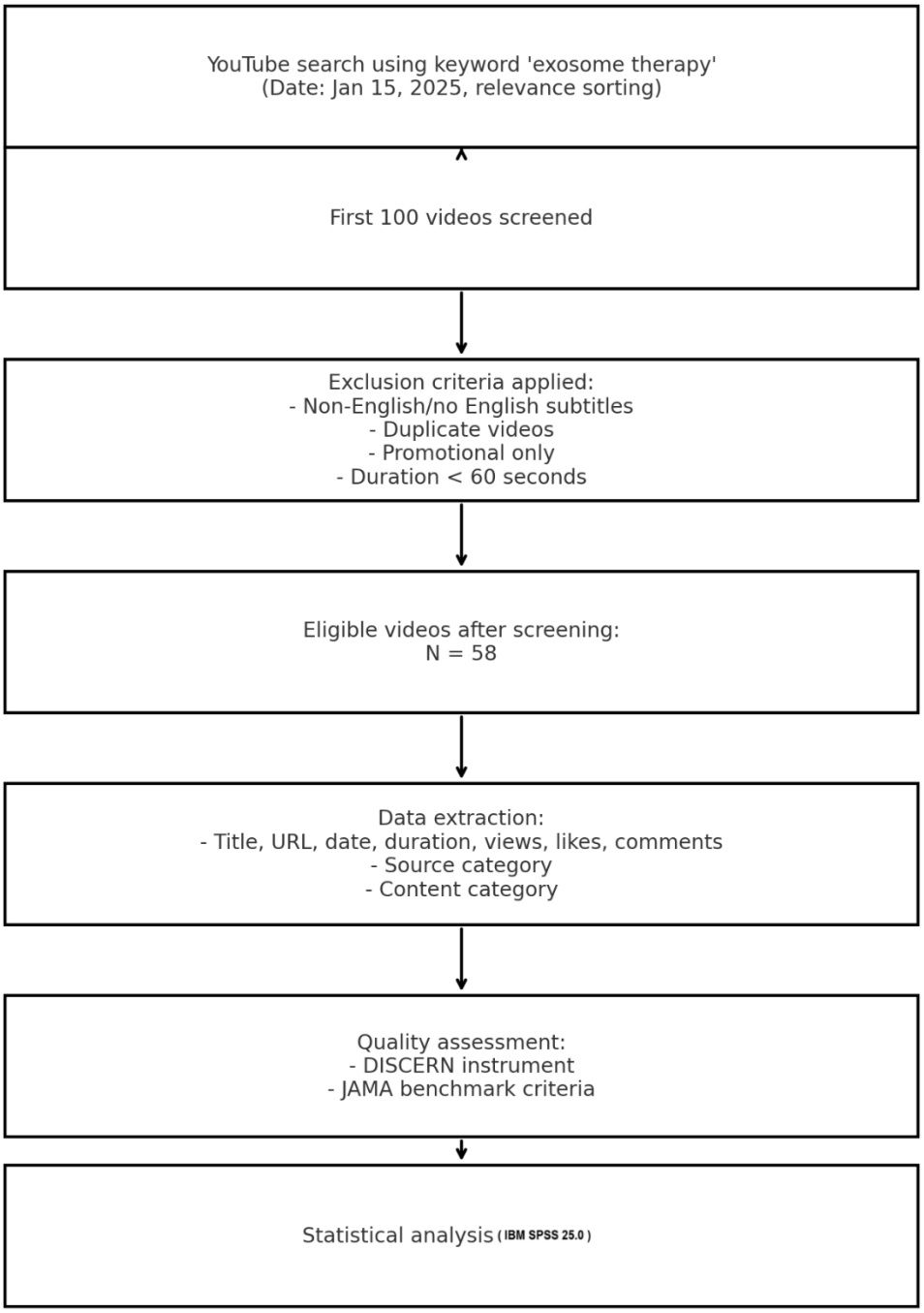

Figure 1. Flow diagram illustrating the identification, screening, eligibility assessment, and final inclusion of YouTube videos related to exosome therapy according to predefined inclusion and exclusion criteria.

Source and Content Characteristics

Of the analyzed videos, 53.4% (n = 31) were uploaded by physicians, 39.7% (n = 23) by health-related organizations, and 6.9% (n = 4) by patients or independent creators. In terms of content, the vast majority (87.9%, n = 51) provided general information on exosome therapy—covering definitions, indications, mechanisms, and potential benefits and risks. A smaller proportion featured patient experiences (6.9%, n = 4) or presented scientific/procedural demonstrations (5.2%, n = 3) **(Table 1) (Figure 2).**

Table 1. Source and content distribution of YouTube videos on exosome therapy (n = 58)

Variable	n	%
Source		
Physicians	31	53.4
Health-related orgs	23	39.7
Patients	4	6.9
Content type		
General information	51	87.9
Patient experiences	4	6.9
Procedural/scientific	3	5.2

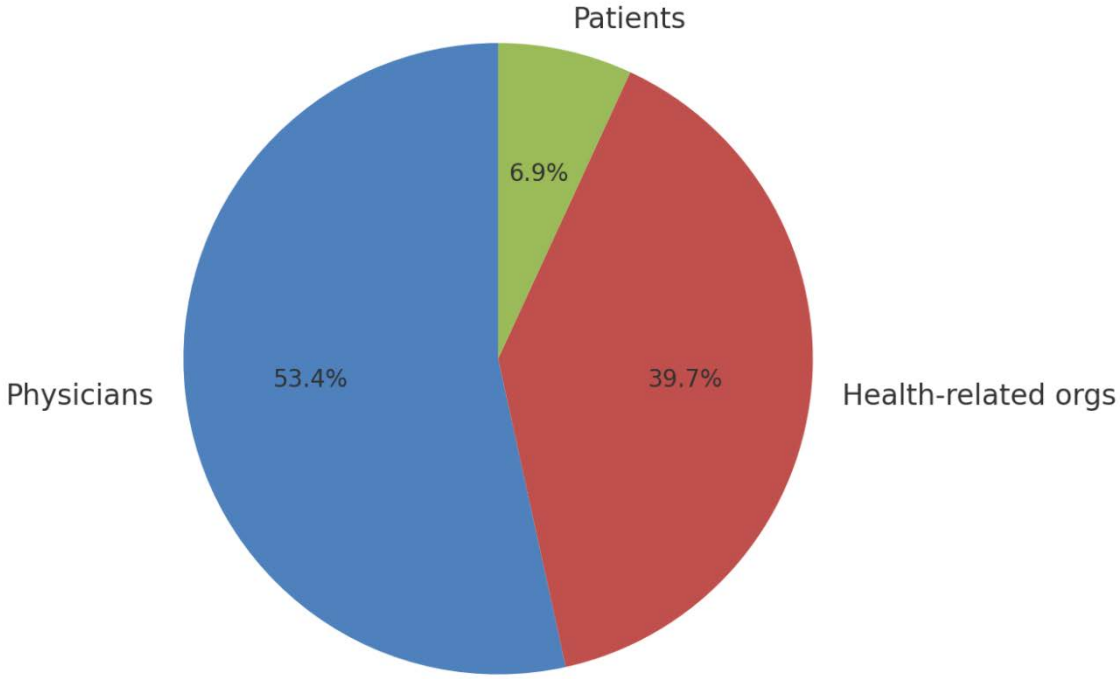

Figure 2. Distribution of YouTube videos on exosome therapy according to source category (physicians, health-related organizations, patients/independent creators), expressed as percentage of total included videos (n = 58).

Video Metrics

The average video length in seconds was 564 ± 744 seconds, with a range of 60 to 5,483 seconds. The average views were 34,215.8 ± 58,421.7, with a range of 120 to 251,043 views, whereas the median number of likes was 212, with an interquartile range of 46 to 689. The median number of comments posted per video was 18, with an interquartile range of 4 to 52. The video length and engagement values for videos from physicians were found to be higher compared to other sources but were not significant (p-value > 0.05).

Quality Assessment

On the other hand, based on the DISCERN classification, the results showed that 12.1% (n = 7) of the videos were described as poor, 44.8% (n = 26) were described as fair, 27.6% (n = 16) were described as good, and 15.5% (n = 9) were described as excellent. The total mean DISCERN score was 48.7 ± 10.9. Videos posted on the site by physicians were found to be associated with significantly higher DISCERN scores than the videos posted on the site by patients (p = 0.032) **(Table 2) (Figure 3).**

Table 2. Video characteristics and quality scores according to source category

Variable	Physicians (n=31)	Health-related orgs (n=23)	Patients (n=4)	p*
Duration (min)	11.3 ± 13.6	8.2 ± 9.4	4.9 ± 3.7	0.118
Views	41.027 ± 63,418	30.756 ± 51.992	9.123 ± 8,476	0.091
Likes	298 ± 611	184 ± 297	77 ± 52	0.127
Comments	21 ± 35	15 ± 26	8 ± 6	0.142
JAMA score	2.84 ± 0.66	2.57 ± 0.69	2.25 ± 0.50	0.054
DISCERN total	51.2 ± 9.7	46.3 ± 10.2	38.5 ± 8.3	0.032

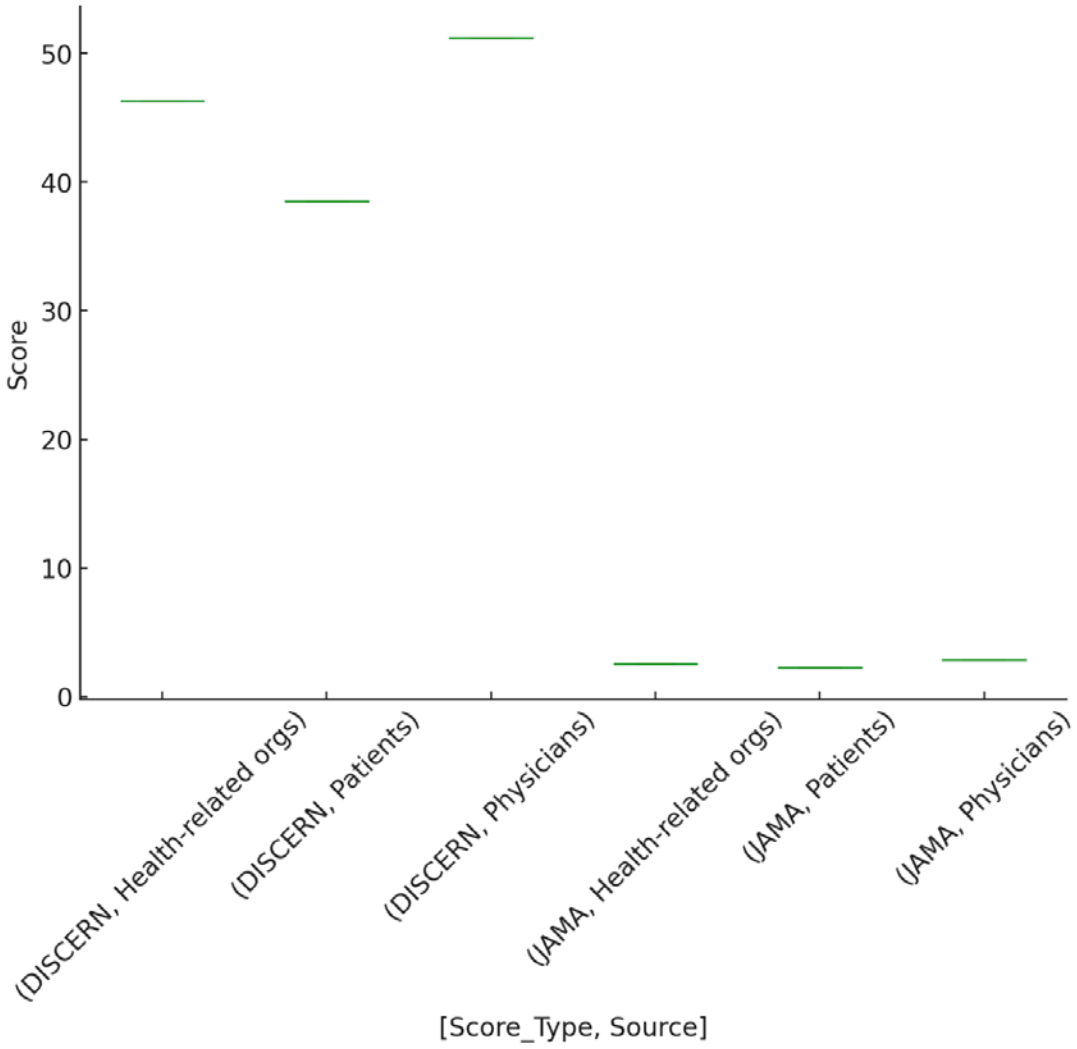

Figure 3. Comparison of DISCERN and JAMA quality scores across video source categories. Higher DISCERN scores indicate greater reliability and quality of treatment-related information, while JAMA scores reflect transparency criteria including authorship, attribution, disclosure, and currency.

Discussion

Beyond applying standardized evaluation tools, this study contributes methodologically by positioning exosome-related digital content within the broader context of regulatory uncertainty and translational research gaps. Evaluating online health information in such a rapidly evolving biomedical domain extends prior YouTube analyses that predominantly focus on well-established diseases with clearly defined clinical guidelines.

This systematic examination of the scientific accuracy, reliability, and quality of YouTube videos on exosome therapy

has shown a great variability according to the source and the nature of the video. Videos uploaded from the perspective of physicians have achieved a significantly higher level of DISCERN quality compared with those from the perspective of patients. This finding supports the notion that professional involvement in the communication of complex and evolving therapeutic fields is associated with higher informational quality, particularly in domains where standardized clinical pathways and regulatory oversight remain limited. (7,10).

Although most of the videos contained general information, a large number lacked important aspects of quality. The average JAMA quality score was 2.68, and the lowest-rated aspect of the videos was the "disclosure" component. This is not surprising, given the finding that online health-related videos tend to lack necessary disclosure statements regarding issues of interest and funding (8).). It should be noted that, given its newness and lack of structured protocols, this area of exosome therapy may lack sufficient disclosure on its videos to enable viewers to properly critique the videos and make determinations free of biases.

A positive correlation between video duration and score in the DISCERN scale has also been established, and this consistent with previous studies in various medical fields, which found that the more comprehensive videos were those related to benefits, risks, and uncertainties (7,8). Yet, quality cannot be absolutely guaranteed with lengthy videos, and some of which were in this study did not mention qualified references and knowledge gaps.

Notably, there were no statistically significant correlations between measures of popularity (views, likes, comments) and quality scores. This finding affirms earlier determinations that engagement metrics are inadequate predictors of scientific validity, since various studies have already found that content with greater views or likes tends to be non-compliant with medical guidelines and may provide inaccurate or incomplete medical data (8,10). Furthermore, this finding suggests that the recommendation mechanisms provided on the YouTube platform could be favoring content that rates more highly on entertainment value versus scientific integrity.

Given the cross-sectional and exploratory design of the study, the analytical approach was intentionally limited to non-parametric group comparisons and correlation analyses in order to avoid overfitting or causal inference beyond the scope of the available data. This methodological restraint strengthens the internal validity of the findings and ensures that interpretations remain aligned with the descriptive nature of digital content analysis.

While the finding regarding the superiority of videos produced by physicians in terms of quality score may not come as a shock, it is an important reinforcement of the value of professional production, particularly in new and evolving medical specialties, in which professional clinical advice and authority are currently absent. Of far greater import, however, is the lack of a positive and significant relationship between indicators and measures of popularity and quality scores, which speaks to the stark disconnect between the two. A reading of the data would suggest that the most used measures currently available, including view counts, likes, and comments, are not adequate indicators or measures of evidence-based information, and the proliferation of false information based upon visibility and not evidence is a serious issue.

Study limitations

The present study did not classify cosmetic applications of exosomes as a distinct content variable. Therefore, findings related to cosmetic or aesthetic use are limited to indirect observations and do not allow for detailed quantitative subgroup analysis. Future research should incorporate cosmetic and aesthetic categories as predefined coding variables to enable more comprehensive evaluation.

Another methodological limitation relates to the dynamic and continuously evolving nature of YouTube as a digital platform. Video availability, ranking algorithms, engagement metrics, and content characteristics may change over time due to user interaction patterns, algorithmic updates, or content removal. The present study was intentionally designed as a time-specific cross-sectional digital content analysis reflecting real-world user search behavior on January 15, 2025. Consequently, the findings should be interpreted as a structured snapshot of content available at that time rather than as a longitudinal representation of all exosome-related information on YouTube.

Although this design enhances ecological validity by replicating typical user exposure in relevance-based search mode, future studies employing longitudinal or repeated-sampling methodologies may provide deeper insight into temporal variability and evolving content quality trends.

Cosmetic and Aesthetic Dermatology Context: There exists considerable literature concerning the growing use of exosome-based products for skin rejuvenation, hair reconstruction, pigmentation, and wound healing in the cosmetic and aesthetic dermatology sectors (22). Nonetheless, the available, validating literature predominantly exhibits preclinical level, with a substantial scarcity of high-quality, large-scale clinical studies in this realm of research (23,24). Moreover, currently, there are no cosmetic exosome products considered accepted or approved by

the predominantly recognized global regulatory authorities, rendering the safety and efficacy of the products in question unverified (1,23,24).

With respect to the public health issue, the possible implication of the variations in the quality of information shown in the results of this study is related to the effect on patients seeking information on new treatments such as exosomes. These patients may be presented with information that sets up unrealistic expectations or treatment choices based on the information, which may be unreliable (16). Healthcare providers need to direct patients to credible sources or assist with the preparation of multimedia information.

In conclusion, the current research points to the existence of large disparities in the quality of exosome therapy YouTube resources. The aspect of a lack of transparency, the absence of regulatory control, and the possibility of misinformation concerning high-profile issues such as its cosmetic use makes it imperative to develop mechanisms for enhancing health information on the internet.

Conclusion

From our findings, the quality of information conveyed through YouTube videos on exosomes and their therapy appears to be very inconsistent. While videos produced by professionals, such as those produced by medical professionals and health bodies, were generally seen to have a better-quality score, issues of transparency remained. It was observed that declarations of conflict of interest and funding support were missing in most content forms.

Notably, there was no correlation found with popularity metrics and the quality of content, suggesting the effectiveness of engagement metrics like views, likes, and comments on a posting is not a good indicator of scientific validity. While longer postings were associated with more information, the posting itself was not a good indicator for the standard of evidence-based communication.

Noting that there has been a recent explosion in work related to exosomes, it has become even more important to enhance online health discourse in a positive way. Enhancing collaboration between healthcare professionals and online health community networks could be effective in managing miscommunication and improving informed decision-making among patients and healthcare professionals in relation to relatively new modalities like exosome therapy in healthcare practices.

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Ethical Approval: *Ethical approval was not required because the study analyzed publicly available online content without involving human participants or identifiable personal data..*

Author Contributions: *Concept: TGS Literature Review: Design:TGS, Data acquisition: TGS Analysis and interpretation: TGS Writing manuscript: TGS Critical revision of manuscript: TGS*

Conflict of Interest: *No funding was received for this study, and the authors declare that they have no conflicts of interest.*

Data Availability: *The data supporting the findings of this study were derived from publicly available YouTube videos. The dataset analyzed during the current study is available from the corresponding author upon reasonable request..*

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Original Article

Effectiveness of intratympanic steroid application in long-term tinnitus cases

Uzun süreli tinnitus olgularinda intratimpanik steroid uygulamasinin etkinliği

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Abstract

Background: To evaluate the effect of intratympanic steroid injection in patients with tinnitus refractory to long-term medical therapy.

Materials and Methods: This retrospective study included 98 patients (62 males, 36 females) with idiopathic subjective tinnitus aged 21–86 years. Patients received four intratympanic methylprednisolone injections administered at 3-day intervals. The Tinnitus Degree Index (TDI) and audiologic assessments were performed before treatment and 2 weeks after the fourth injection.

Results: The mean tinnitus duration was 4.79 ± 5.54 years. The mean TDI score decreased significantly after intratympanic steroid injection in both men and women ($p < 0.05$). Greater improvement (post-treatment minus pre-treatment TDI) was observed in patients with shorter tinnitus duration ($p < 0.05$). Pure-tone thresholds did not change significantly after treatment in either ear ($p > 0.05$).

Conclusions: Intratympanic methylprednisolone injection may reduce tinnitus severity, particularly in patients with relatively shorter tinnitus duration.

Keywords: Tinnitus, intratympanic injection, methylprednisolone, steroid

ÖZ

Amaç: Uzun süreli medikal tedaviye yanıt vermeyen tinnitus hastalarında intratimpanik steroid enjeksiyonunun etkisini değerlendirmek.

Gereç ve Yöntem: Bu retrospektif çalışmaya 21–86 yaş aralığında idiyopatik subjektif tinnituslu 98 hasta (62 erkek, 36 kadın) dahil edildi. Hastalara 3 gün arayla toplam dört intratimpanik metilprednizolon enjeksiyonu uygulandı. Tinnitus şiddeti Tinnitus Derece İndeksi (TDI) ile, odyolojik değerlendirmeler ise tedavi öncesi ve dördüncü enjeksiyondan 2 hafta sonra yapıldı.

Bulgular: Ortalama tinnitus süresi 4,79 ± 5,54 yıl idi. İntratimpanik steroid enjeksiyonu sonrası hem erkeklerde hem kadınlarda ortalama TDI skoru anlamlı düzeyde azaldı ($p < 0,05$). Tinnitus süresi ile TDI'daki değişim (tedavi sonrası − tedavi öncesi) arasındaki analizde, daha kısa tinnitus süresi olan hastalarda iyileşmenin daha belirgin olduğu görüldü ($p < 0,05$). Saf ses odyometrisinde tedavi sonrası her iki kulakta da işitme eşikleri açısından anlamlı bir değişiklik saptanmadı ($p > 0,05$).

Sonuç: İntratimpanik metilprednizolon enjeksiyonu, özellikle tinnitus süresi görece kısa olan hastalarda tinnitus şiddetini azaltmada etkili bir seçenek olabilir.

Anahtar Kelimeler: Tinnitus, intratimpanik enjeksiyon, metilprednizolon, steroid

Highlights

- Intratympanic methylprednisolone significantly reduces tinnitus severity in patients refractory to long-term medical therapy.
- Treatment efficacy is greater in patients with a shorter duration of tinnitus.
- No significant changes were observed in pure-tone audiometric thresholds after treatment.

Introduction

Tinnitus can be defined as the perception of sound in the absence of an external sound source (1). Subjective tinnitus is the most common form of tinnitus and is reported to affect approximately 10% of the general population and up to 33% of older adults (2,3). The cochlea is considered the most common site of origin of subjective tinnitus; however, disorders at other levels of the auditory pathway may also be responsible (2).

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Tinnitus may cause emotional and physical distress and is frequently accompanied by symptoms such as anxiety, depression, irritability, hearing impairment, hyperacusis, insomnia, and impaired concentration. In addition, severe depression may exacerbate tinnitus (4).
Multiple treatments and medications—including dietary modifications, patient education, vitamin supplements, anxiolytics, antidepressants, herbal medicines, and intratympanic steroid injection—have been used for the management of subjective tinnitus. (2,5,6) The safety of intratympanic steroid injection has been demonstrated in inner ear conditions such as sudden sensorineural hearing loss, Meniere's disease, and acoustic trauma (7). Steroids injected into the middle ear can penetrate the round window membrane and diffuse into inner ear fluids (1,8,9). Several previous studies have suggested potential benefit of intratympanic steroid injection in tinnitus (10,11). In the present study, we evaluated the effects of intratympanic steroid administration on tinnitus severity and hearing thresholds in patients with subjective tinnitus who did not respond to other treatments.

Material and Methods

Study Design and Participants

Between January 2020 and November 2023, 98 patients with idiopathic subjective tinnitus who presented to the Otolaryngology Department of a tertiary care university hospital were included. All patients reported unilateral, persistent tinnitus for at least 6 months and had previously received oral betahistine dihydrochloride without improvement in tinnitus symptoms. Tinnitus lasting longer than 6 months was defined as prolonged tinnitus. After assessment of tinnitus characteristics and duration and review of medical history, all patients underwent a comprehensive otolaryngologic examination. Otomicroscopy and pure-tone audiometry were performed to evaluate possible otologic conditions associated with tinnitus and to assess hearing thresholds. Patients with otitis media, otitis externa, otosclerosis, Ménière's disease, objective tinnitus, profound hearing loss, head trauma, ongoing systemic steroid therapy, acute tinnitus, or tinnitus duration of less than 6 months were excluded.

Intratympanic steroid injection protocol

After topical anesthesia with lidocaine spray via the external auditory canal, patients were placed supine with the head turned approximately 45° to the contralateral side. Using a 25-gauge needle, 0.5 mL of methylprednisolone solution was injected into the posteroinferior quadrant of the tympanic membrane. Patients remained in the same position for approximately 20 minutes. Injections were administered every 3 days for a total of four sessions.

Outcome measures

Tinnitus severity was assessed using a 12-item Tinnitus Degree Index (TDI) questionnaire administered before treatment and 2 weeks after the fourth injection. Each item was scored on a 5-point Likert scale (1 = never, 5 = always), yielding a total score range of 12–60. Severity was categorized as very mild (1–12), mild (13–24), moderate (25–36), severe (37–48), and catastrophic (49–60) **(Table 1)** (12). Hearing thresholds were assessed by pure-tone audiometry before and after treatment, and mean pure-tone thresholds were compared between time points. Procedure-related adverse events (e.g., otalgia and dizziness) were recorded from follow-up notes.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics (version 22.0; IBM Corp., Armonk, NY, USA). Normality of continuous variables was assessed using the Kolmogorov–Smirnov test. Continuous variables are presented as mean ± standard deviation (SD). Pre and post-treatment comparisons of continuous outcomes (TDI score and mean pure-tone thresholds) were performed using paired tests (paired t-test for normally distributed variables and Wilcoxon signed-rank test for non-normally distributed variables. The association between tinnitus duration and change in TDI (post-treatment minus pre-treatment) was assessed using Spearman's correlation coefficient. A p value of < 0.05 was considered statistically significant.

Ethical Approval

Patient records were reviewed retrospectively. The declaration of Helsinki recommendations was followed for the conduct of the study. Akdeniz University Faculty of Medicine Clinical Research Ethics Committee approval was obtained (KAEK-865, Date:15.11.2023)

Table 1. Tinnitus Degree Index (items and scoring).

Item	Question	Never (1)	Rarely (2)	Sometimes (3)	Often (4)	Always (5)
1	Does tinnitus make you feel uncomfortable or irritable?	1	2	3	4	5
2	Does tinnitus make you feel tired or stressed?	1	2	3	4	5
3	Does tinnitus make it difficult for you to relax?	1	2	3	4	5
4	Does tinnitus make you feel uncomfortable in silence?	1	2	3	4	5
5	Does tinnitus disturb your concentration?	1	2	3	4	5
6	Does tinnitus make it difficult to maintain satisfactory relationships with those around you?	1	2	3	4	5
7	Does tinnitus affect your performance at home, at work, or in other settings?	1	2	3	4	5
8	Does tinnitus affect your social life and leisure activities?	1	2	3	4	5
9	Does tinnitus affect your enjoyment of life in general?	1	2	3	4	5
10	Does tinnitus affect your ability to fall asleep?	1	2	3	4	5
11	How often do you find it difficult to ignore tinnitus?	1	2	3	4	5
12	How often are you bothered by tinnitus?	1	2	3	4	5

Results

A total of 98 patients were included in the study; 62 were male and 36 were female. The mean age was 53.7 ± 13.5 years. Tinnitus duration ranged from 6 months to 30 years, with a mean duration of 4.79 ± 5.54 years. Demographic characteristics are presented in **(Table 2).**

Table 2. Demographic characteristics of the patients

Variable	Female (n=36)	Male (n=62)	Total (n=98)
Age (years), range	36–86	21–85	21–86
Age (years), mean ± SD	57.06 ± 11.12	51.56 ± 14.37	53.70 ± 13.52
Smoking, n (Yes/No)	6/30	24/38	30/68
Tinnitus duration (years), range	0.5–30	0.5–30	0.5–30
Tinnitus duration (years), mean ± SD	5.20 ± 5.75	4.55 ± 5.47	4.79 ± 5.54

Before intratympanic steroid treatment, tinnitus severity was most frequently classified as moderate (36%) and severe (51%) **(Figure 1).**

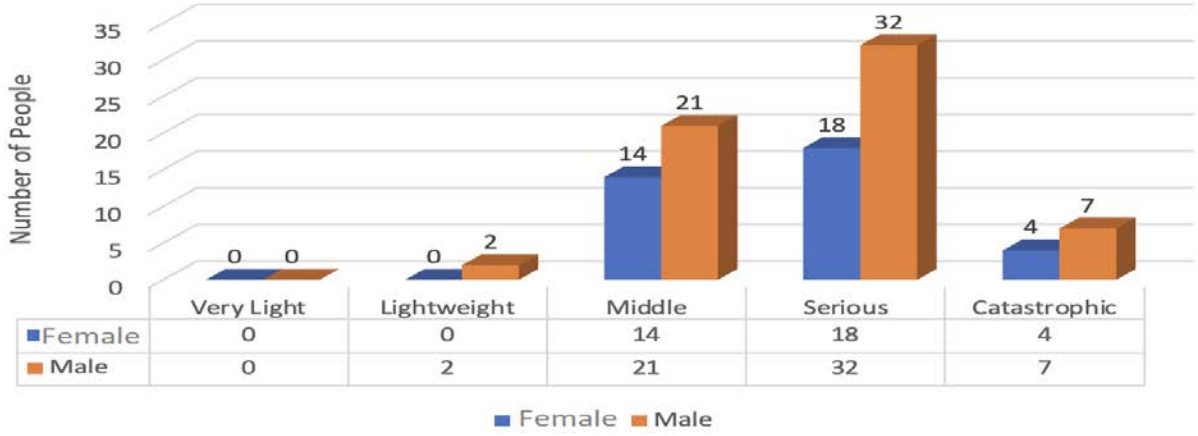

Figure 1. Distribution of tinnitus severity categories based on the Tinnitus Degree Index (TDI) before intratympanic steroid treatment.

After treatment, tinnitus severity was most frequently classified as mild (32%) and moderate (46%) **(Figure 2).**

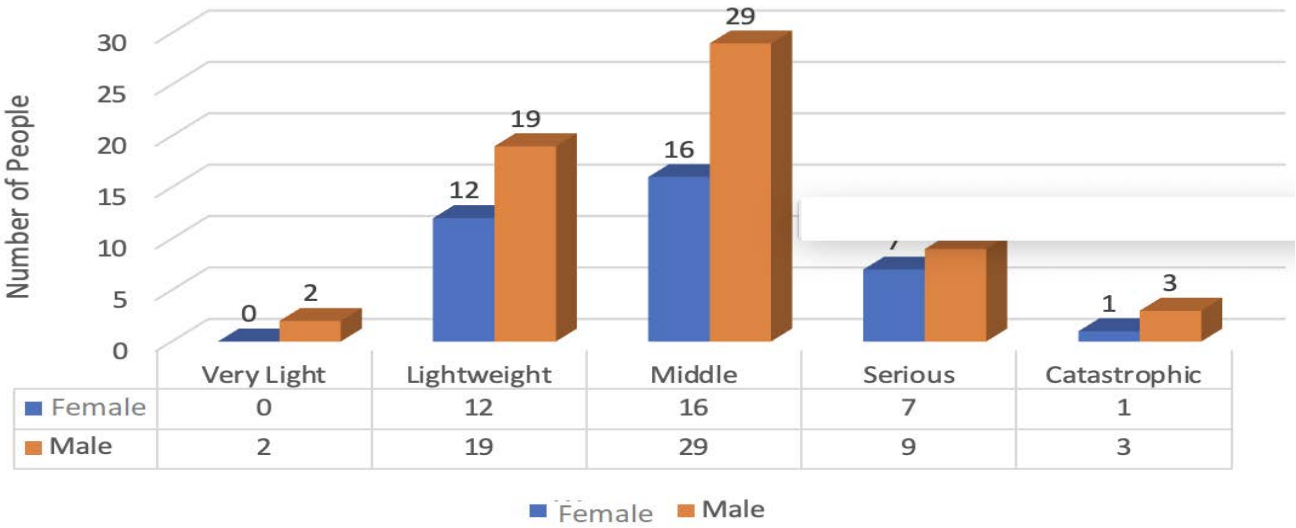

Figure 2. Distribution of tinnitus severity categories based on the Tinnitus Degree Index (TDI) after intratympanic steroid treatment.

Following intratympanic steroid injection, the mean Tinnitus Degree Index score decreased significantly ($p < 0.05$) in both men and women **(Figure 3).**

Figure 3. Comparison of mean TDI scores before and after intratympanic steroid treatment.

Mean pure-tone thresholds before and after intratympanic steroid treatment did not differ significantly for either the right or left ear ($p > 0.05$) **(Table 3).**

Table 3. Mean pure-tone thresholds before and after intratympanic steroid treatment

Ear	Time point	Range	Mean ± SD	p*
Right ear	Pre-treatment	10–65	27.55 ± 15.12	0.067
Right ear	Post-treatment	10–65	26.78 ± 14.38	
Left ear	Pre-treatment	10–70	27.60 ± 15.34	0.066
Left ear	Post-treatment	10–70	26.63 ± 15.28	

* p values represent pre- vs post-treatment comparisons within the same ear (paired analysis).

After intratympanic steroid injection, 11 of 98 patients reported mild otalgia and 9 reported transient dizziness. These complaints resolved spontaneously during follow-up.

Discussion

Tinnitus is a common otologic symptom that can significantly impair quality of life and may lead to social and psychological problems. The main management options include hearing aids with sound therapy/masking features, tinnitus retraining therapy, and various oral medications with limited or inconsistent efficacy. Although tinnitus retraining therapy is considered one of the treatment modalities with the most favorable outcomes, many patients continue to use oral medications. Importantly, none of these approaches is completely effective for all patients (13). Intratympanic therapy is a local treatment option used in inner ear disorders, in which various agents are delivered into the middle ear. It has been used for sudden sensorineural hearing loss, Ménière's disease, tinnitus associated with these disorders, and idiopathic tinnitus (5,10,14–16). The present study was conducted to evaluate the effect of intratympanic steroid treatment on tinnitus severity. Our findings suggest that intratympanic steroid treatment may reduce tinnitus severity, particularly in patients with shorter tinnitus duration.

Steroids injected intratympanically into the middle ear may penetrate the round window membrane and diffuse into inner ear fluids, exerting anti-inflammatory and electrolyte-modulating effects via steroid receptors (17). Although the exact mechanism remains unclear, proposed mechanisms include suppression of abnormal sensory cell excitability or hypersensitivity in the inner ear, reduction of immune-mediated/autoimmune inflammation, direct effects on the cochlear neuroepithelium, and increased cochlear blood flow (18). Nevertheless, the clinical effectiveness of intratympanic steroid injection for tinnitus has not been definitively established.

A major advantage of intratympanic steroid injections is the ability to achieve high local concentrations in the inner ear while minimizing systemic adverse effects. Seong reported no difference between intratympanic steroid and saline injections in tinnitus treatment within 6 months of symptom onset, suggesting that the indication for intratympanic steroid injection should be limited to selected cases (13). In contrast, Yener compared intratympanic dexamethasone with isotonic solution in tinnitus cases refractory to medical treatment and found a statistically significant therapeutic effect on tinnitus severity at the 1st and 6th months (19). Cesarani reported complete improvement in 34% of patients, significant improvement in 40%, and no change in 26% following intratympanic steroid treatment. The authors suggested that intratympanic steroid injections are more effective in acute tinnitus but less effective in chronic tinnitus (10). In our study, tinnitus severity was predominantly moderate (36%) and severe (51%) before treatment, whereas it was predominantly mild (32%) and moderate (46%) after intratympanic steroid treatment.

Sakata reported that intratympanic dexamethasone reduced symptoms in 77% of patients immediately and in 68% at 6 months, with no association between age and treatment efficacy (20). Shulman reported that intratympanic steroid treatment alleviated tinnitus perception in approximately 70% of patients with predominantly cochlear-type tinnitus in both the short and long term (21). The authors emphasized that factors potentially influencing efficacy include injection frequency and duration, tinnitus duration, and fibrosis or ossification of the round window membrane. It has also been suggested that tinnitus duration may be one of the most important determinants of response, with reduced efficacy in patients with longer tinnitus duration (22). Cesarani reported better outcomes when treatment was initiated within 3 months of the onset of subjective idiopathic tinnitus (10). Shim analyzed factors associated with cure rates and found that the time from symptom onset to treatment initiation was the only factor correlated with cure in acute subjective idiopathic tinnitus (23). Similarly, Sakata reported that treatment efficacy tended to decrease as the duration of tinnitus increased (11). In our study, the mean tinnitus duration was 57.48 months, and the reduction in TDI was statistically significant. Moreover, analysis of the relationship between the change in TDI and tinnitus duration suggested greater improvement among patients treated earlier after symptom onset. In the present study, only early outcomes were evaluated, and age was not included in the analysis. These findings suggest that early intratympanic steroid injection may be considered in patients who do not respond to conventional management.

Yener reported no difference in pure-tone hearing levels before and after intratympanic steroid treatment in tinnitus patients (19). Similarly, we found no significant change in pure-tone thresholds after treatment. Araújo reported minimal adverse effects, including mild dizziness and otalgia, which resolved spontaneously after intratympanic steroid injections (14). In our study, transient otalgia and dizziness were observed and resolved during follow-up. No serious complications were observed, suggesting that intratympanic steroid injections may be a safe option for selected tinnitus patients.

Overall, our findings indicate that intratympanic steroid therapy may be an effective alternative in patients with tinnitus who do not respond to conventional treatments, and that better outcomes may be associated with earlier treatment initiation. This study has several limitations. The retrospective design and the absence of a control group

limit causal inference. In addition, the effects of age were not evaluated and long-term outcomes were not assessed. Nevertheless, our findings may inform the design of future prospective, randomized, placebo-controlled, double-blind studies.

Limitations

Larger sample size and multicenter trials are required to validate the findings and improve the generalizability of the study.

Conclusion

In this study, intratympanic methylprednisolone was administered to patients with idiopathic subjective tinnitus who did not improve despite conventional management. Intratympanic steroid therapy was associated with a statistically significant reduction in tinnitus severity without significant changes in hearing thresholds. These results suggest that intratympanic steroid injection may be considered for selected patients, particularly when initiated earlier after symptom onset. Further prospective, randomized, placebo-controlled studies with standardized outcome measures and longer follow-up are warranted.

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IJCMBS

Original Article

Socio-demographic and clinical characteristics of migraine patients and the effect of treatment on their quality of life

Migrenli hastalarin sosyodemografik, klinik özellikleri ve tedavinin günlük yaşam kalitesine etkisi

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Abstract

Background: Migraine is a common neurological disorder that adversely affects quality of life and daily functioning. This study aimed to evaluate the demographic characteristics, clinical features, triggering factors, and treatment response of migraine patients.

Materials and Methods: A total of 152 patients (136 females, 16 males) aged 15–55 years, diagnosed with migraine at the Neurology Outpatient Clinic of Kocaeli University Faculty of Medicine, were prospectively evaluated. Diagnosis was based on International Headache Society (IHS) criteria. Patients with secondary headaches or incomplete data were excluded. Clinical and demographic data were analyzed according to age, sex, and migraine type (with or without aura).

Results: The mean age was 36.7 ± 10.0 years. Migraine was approximately three times more common in females (89.5%). A positive family history was present in 54.6% of patients. Headache was unilateral in 63.2% and throbbing in 96.1% of cases. Migraine with aura was identified in 40.1% of patients. The most frequent accompanying symptoms were photophobia (91.4%), phonophobia (92.8%), and nausea (90.8%). Stress was the most common trigger (72.4%). Following treatment, significant reductions were observed in attack severity, frequency, and migraine-related functional impairment ($p < 0.01$).

Conclusion: Migraine was most prevalent among individuals aged 20–40 years and more common in women. Family history, stress, and hormonal factors were prominent contributors. Both prophylactic and acute treatments effectively reduced symptom burden and improved functional outcomes.

Keywords: Migraine, Clinical and Demographic Characteristics, Symptoms, Triggering Factors, Treatment Effectiveness.

ÖZ

Amaç: Migren, yaşam kalitesini ve günlük işlevselliği olumsuz etkileyen yaygın bir nörolojik bozukluktur. Bu çalışma; migrenli hastaların demografik özelliklerini, klinik özelliklerini, tetikleyici faktörlerini ve tedavi yanıtlarını değerlendirmeyi amaçlamıştır.

Gereç ve Yöntem: Kocaeli Üniversitesi Tıp Fakültesi Nöroloji Polikliniği'ne başvuran, yaşları 15 ile 55 arasında değişen, %89,5'i kadın (n=136) ve %10,5'i erkek (n=16) olan toplam 152 migren tanılı hasta prospektif olarak değerlendirildi. Uluslararası Baş Ağrısı Derneği (IHS) sınıflamasına göre migren tanı kriterlerini karşılayan ve çalışmaya katılmayı kabul eden hastalar dahil edildi. İkincil baş ağrısı bozuklukları veya eksik klinik verileri olan hastalar çalışma dışı bırakıldı. Migren tanısı IHS kriterlerine göre konuldu. Bulgular yaş, cinsiyet ve migren tipine (auralı veya aurasız) göre istatistiksel olarak analiz edildi.

Bulgular: Hastaların yaş ortalaması 36,7 ± 10,0 yıl (dağılım: 15-55 yaş) idi. Migren, kadınlarda (%89,5) erkeklere (%10,5) göre yaklaşık üç kat daha fazlaydı. 83 hastada (%54,6) pozitif aile öyküsü mevcuttu. Baş ağrısı 96 hastada (%63,2) tek taraflı, 146 hastada (%96,1) ise zonklayıcıydı; 61 hastaya (%40,1) auralı migren tanısı konuldu. En sık eşlik eden semptomlar fotofobi (%91,4), fonofobi (%92,8) ve bulantı (%90,8) idi. Stres, 110 hastada (%72,4) en sık tetikleyici faktör olarak belirlendi. Tedavi sonrası atak şiddetinde, atak sıklığında ve migrene bağlı fonksiyonel bozuklukta anlamlı azalmalar gözlendi (atakla ilgili parametreler için $p < 0,01$).

Sonuç: Bu çalışmada migren, en sık 20 ile 40 yaş arasındaki hastalarda ve kadınlarda gözlenmiştir. Çalışma popülasyonunda pozitif aile öyküsü, stres ve hormonal faktörler sıklıkla tanımlanmıştır. Takip süresi boyunca hem profilaktik hem de akut tedavilerin migren semptomlarında ve fonksiyonel bozuklukta azalma sağladığı saptanmıştır. **Anahtar Kelimeler:** Migren, Klinik ve Demografik Özellikler, Semptomlar, Tetikleyici Faktörler, Tedavi Etkinliği

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Highlights

- Migraine is significantly more prevalent in females and is most frequently observed in patients between the ages of 20 and 40.
- Stress is the primary triggering factor, while photophobia and phonophobia are the most common symptoms accompanying migraine attacks.
- Both prophylactic and acute treatments significantly reduce attack frequency, severity, and migraine-related functional impairment.

Introduction

Migraine is a recurrent, idiopathic, episodic headache disorder characterized by attacks lasting between 4 and 72 hours. It is typically unilateral, pulsating in nature, aggravated by physical activity, and accompanied by nausea and/or vomiting as well as photophobia and phonophobia (1–3). The International Headache Society (IHS) classification distinguishes between migraine with aura and migraine without aura based on specific diagnostic criteria (4). Aura consists of fully reversible focal neurological symptoms, most commonly visual disturbances, that usually precede headache onset (1,3).

Migraine is one of the most prevalent neurological disorders worldwide. Population-based studies report a prevalence of approximately 15–17% in women and 6% in men in Western societies (5,6). The prevalence peaks during the third and fourth decades of life and declines thereafter (7,8). Gender differences are well established, with women demonstrating a 3–4-fold higher risk compared to men (7,8). Hormonal influences, particularly fluctuations in estrogen levels, are believed to contribute significantly to this disparity (9).

Although the exact pathophysiology of migraine remains incompletely understood (10), substantial evidence supports the involvement of the trigeminovascular system and cortical spreading depression (CSD) in migraine with aura (11). Activation of trigeminal afferents leads to the release of vasoactive neuropeptides and subsequent neurogenic inflammation, contributing to headache generation (3). CSD is considered the electrophysiological substrate of aura and may also activate central nociceptive pathways (11). Increasing evidence also suggests involvement of hypothalamic regulation and circadian mechanisms in attack initiation (12,13).

Migraine imposes a significant socioeconomic burden due to decreased productivity, absenteeism, and impaired daily functioning (14,15). Even between attacks, patients report reduced subjective well-being and quality of life (10,16). The Migraine Disability Assessment Scale (MIDAS) has been widely used to quantify migraine-related disability and functional loss (17,18).

Various internal and external factors may trigger migraine attacks. Commonly reported precipitating factors include stress, sleep disturbances, fasting, certain foods, environmental changes, and hormonal fluctuations (9,19). Menstrual cycle–related migraine and changes in migraine characteristics during menopause further support the modulatory role of sex hormones (9). Additionally, migraine demonstrates familial aggregation, with first-degree relatives having a two- to four-fold increased risk (7,20).

Effective management of migraine begins with accurate diagnosis and classification. Treatment strategies are generally divided into acute (abortive) and preventive approaches (1,3). Acute therapies aim to terminate attacks or reduce symptom severity and include non-steroidal anti-inflammatory drugs, triptans, antiemetics, and other agents (1,21). Preventive therapies are indicated in patients with frequent or disabling attacks and include beta-blockers, anticonvulsants, antidepressants, and other pharmacological agents (3,21). Beyond reduction of attack frequency and severity, an important therapeutic goal is improvement in functional capacity and quality of life.

Given the variability in sociodemographic characteristics, triggering factors, clinical presentation, and treatment response, regional data remain valuable for understanding migraine patterns in different populations. The present study aimed to evaluate the sociodemographic and clinical characteristics of migraine patients presenting to a tertiary neurology outpatient clinic and to assess the impact of acute and preventive treatments on attack parameters and quality of daily life.

Materials and Methods

Study Design and Participants

This prospective observational study was conducted on 152 consecutive patients diagnosed with migraine who were admitted to the Neurology Outpatient Clinic of Kocaeli University Faculty of Medicine. The study population consisted of 136 females (89.5%) and 16 males (10.5%), aged between 15 and 55 years. Migraine diagnosis was established according to the International Headache Society (IHS) diagnostic criteria. Inclusion criteria were a diagnosis of migraine according to IHS criteria and willingness to participate in the study.

Exclusion criteria included secondary headache disorders, presence of serious neurological or systemic diseases that could affect headache characteristics, and incomplete clinical data.

Ethical Approval

The study protocol was approved by the Institutional Ethics Committee of the Kocaeli University Faculty of Medicine (Approval number: KAEK 237-3, Dated 19.06.2022). The study was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants

Data Collection

A detailed medical history and neurological examination were performed for each patient. Clinical, demographic, and headache-related characteristics were recorded using a structured migraine assessment form developed by the department. The form included information on age, sex, educational status, age at onset of migraine, migraine type (with or without aura), headache characteristics (localization, duration, intensity, and frequency), accompanying symptoms, triggering factors, comorbid diseases, family history, and menstrual status in female patients. Imaging and laboratory findings, when available, were also documented. The menstrual cycle, which is closely related to migraine, was also evaluated as one week before menstruation, one day before menstruation, days 0-1, end of menstruation, and post-menstruation. Patients at post-menopausal state were identified, and categories were created for the worsening, improvement, and no change in migraine severity with menopause. Post-menopausal patients receiving hormone replacement therapy were noted as well (9).

The aura assessment, which is an important determinant in migraine classification, was conducted. Aura types were determined as visual, sensory, and both visual and sensory auras. Visual aura was categorized as zigzags, scotoma, hemianopsia, sparkling stars, lines, flashes, and undefined titles. Sensory aura was assessed under headings such as weakness, yawning, and numbness in the arms and legs. Aura durations were evaluated under four headings: <4 minutes, 4-15 minutes, 15-60 minutes, and >60 minutes. Subjects were asked to rate their own pain intensity; accordingly, pain was assessed as mild, moderate, or severe (3,4).

The nature of the pain was determined by asking patients about three categories: throbbing, pressing, and piercing. Pain frequency was assessed by asking whether it occurred daily, more than once a week, between 1 and 4 days a month, once every 3 months, or very rarely. Findings that may accompany headache were determined to be photophobia, phonophobia, nausea, and vomiting. In terms of the onset of pain, if it started mildly and gradually increased, it was classified as "insidious"; if it started intensely and continued at that intensity, it was classified as "sudden". The time to peak intensity of pain was categorized as 1 hour, 2 hours, and more than 3 hours in the study. The time of onset of pain during the day was evaluated under four headings: morning, noon, evening, and night sleep, while the time of resolution of pain was assessed under three headings: within 12 hours, 12-24 hours, and longer than 24 hours. Pain localization, which is important in migraine clinics, was classified as unilateral, bilateral, both unilateral and bilateral, and localized in the back of the head (occipital) (1). Neurological examinations were performed and full blood count, biochemistry, lipid and cholesterol profiles, thyroid function tests, EEG and cranial brain tomography examinations were obtained for each patient. Treatment was planned based on the frequency of attacks, their severity, and the intensity of accompanying symptoms, with prophylactic and acute treatments administered. Propranolol (40-120 mg twice daily for six months) was administered as prophylactic treatment, while naproxen sodium (550 mg) and zolmitriptan (2.5-5 mg) were used for attack treatment, depending on the severity of the pain. Metoclopramide was administered as an antiemetic depending on the presence and intensity of accompanying symptoms, and responses to treatment were evaluated in terms of a reduction in attack frequency, pain intensity, and pain duration. The response time to acute treatment was assessed by evaluating the symptom relief to be within 2 hours or within 4 hours (4). Symptoms accompanying migraine headache were assessed before and after treatment; if the severity was severe before medication, it was scored as 3 points; if moderate, 2 points; if mild, 1 point; and if there were no accompanying symptoms, 0 points. Cases were followed up monthly for 6 months via outpatient clinic or telephone visits.

The deterioration in the patient's quality of daily life caused by migraine headache was assessed by evaluating the severity of the pain and the functional impairment during the pain; severe pain was scored as 3 points, moderate pain 2 points, mild pain 1 point, and no pain 0 points. Classification was performed both before the treatment and at follow-up visits after treatment. Patients' daily quality of life was assessed before and after treatment using the Migraine In Assessment Scale (MIDAS) (15). The MIDAS questionnaire is a short, seven-item (five of which are scored) questionnaire developed to enhance doctor-patient communication and help identify headache patients with a clear need for treatment. Patients were followed up monthly for six months, either through outpatient clinic visits or telephone interviews. Treatment response was evaluated based on changes in attack frequency, severity, duration, accompanying symptoms, and functional impairment.

Treatment Protocol

Treatment strategies were determined according to attack frequency and severity. Propranolol (40–120 mg/day) was used for prophylactic treatment. Acute attack treatment consisted of naproxen sodium (550 mg) for mild to moderate attacks and zolmitriptan (2.5–5 mg) for severe attacks. Metoclopramide was administered as an antiemetic when necessary.

Statistical Analysis

Statistical analyses were performed using SPSS version 11.5 (SPSS Inc, Chicago, IL, USA). Data distribution was assessed using the Kolmogorov–Smirnov test. Normally distributed variables were expressed as mean ± standard deviation, and non-normally distributed variables as median and interquartile range. Categorical variables were presented as frequencies and percentages. Comparisons between groups were performed using the Student's t-test for continuous variables and the Chi-square test for categorical variables. A p value < 0.05 was considered statistically significant.

Results

The study population comprised 152 patients, with a marked female predominance of 89.5% (n=136) compared to 10.5% (n=16) males. The mean age of the participants was 36.7 ± 10.0 years, with the largest concentration in the 36–45 age group (35.5%, n=54), followed by the 26–35 age group (25.7%, n=39). Regarding educational background, 42.1% (n=64) of the total cases were primary school graduates. In a subgroup analysis, it was observed that 42.6% (n=26) of patients in the migraine with aura group and 41.8% (n=38) in the migraine without aura group held a primary school degree. Statistical evaluations showed that there was no significant difference between migraine with and without aura groups in terms of age distribution, gender, or educational levels (p > 0.05) **(Table 1).**

Table 1. Age and Gender Distribution According to Migraine Aura Status

Demographic Characteristics	Subgroup	Aura Migraine (%)	Migraine Without Aura (%)	Total,(%)
Age Groups	15-25	9(14.8)	14(15.4)	23 (15.1)
	26-35	17(29.7)	22(24.2)	39(25.7)
	36-45	25(41.0)	29(31.9)	54(35.5)
	>45	10(16.4)	26(28.6)	36(23.7)
Gender	Male	9(14.8)	7(7.7)	16(10.5)
	Female	52(85.2)	84(92.3)	136(89.5)

Migraine with aura was diagnosed in 40% (n=61) of the patients. Within this group, visual aura findings were highly prevalent: scotoma was reported in 37.7% (n=23) of cases, while sparkling stars and flashes were each reported in 34.4% (n=21). The duration of these aura episodes was between 4 and 15 minutes for 65.6% (n=40) of the patients.

The clinical hallmark of the headache was its unilateral (one-sided) localization in 63.2% (n=96) of cases and its throbbing nature in 96.1% (n=146). Accompanying symptoms were nearly universal, with photophobia detected in 91.4% (n=139), phonophobia in 92.8% (n=141), and nausea in 90.8% (n=138). The presence of nausea showed a statistically significant difference between age groups (p < 0.01), peaking at 96.3% in the 36–45 age group. The frequencies of photophobia, phonophobia, and pain characteristics (throbbing/unilateral) did not show a significant difference based on gender, age, or migraine subtype (p > 0.05).

The evaluation of factors facilitating migraine attacks identified stress as the primary trigger, affecting 72.4% (n=110) of the total population. Other notable triggers included exercise (24.5%, n=37), hunger (21.1%, n=32), and insomnia (19.7%, n=30). Stress showed a statistically significant correlation with age (p < 0.05), reaching its highest impact in patients over the age of 45 (88.9%, n=32). For the remaining triggers such as exercise and hunger, no statistically significant differences were observed across the different age classifications (p > 0.05) **(Table 2).**

Table 2. Symptoms and Triggers According to Gender and Aura Status

Category	Feature	Group 1	Percentage (%)	Group 2	Percentage (%)	p
Aura Status	Presence of Vomiting	Migraine with Aura	68.9 (n=42)	Migraine Without Aura	49.5(n=45)	p<0.05
Gender	Pain Duration: <12 hours	Female	22.1 (n=30)	Male	62.5 (n=10)	p<0.01

	Duration of pain: 12-24 hours	Female	33.8(n=46)	Male	12.5 (n=2)	
	Pain Duration: >24 hours	Female	44.1 (n=60)	Male	25.0 (n=4)	
Gender	Alcohol Consumption	Male	12.5 (n=2)	Female	0.0 (n=0)	p<0.01
Trigger	Cold	Male	31.3 (n=5)	Female	9.6 (n=13)	p<0.01

Among the female participants, 46.7% (n=71) identified a direct relationship between their headaches and their menstrual cycle. However, when examining the onset of headache at different phases of the cycle, no statistically significant difference was found between age groups ($p > 0.05$). In contrast, the menopausal transition had a statistically significant impact on headache characteristics ($p < 0.001$). Among 22 menopausal women, 31.8% (n=7) reported improvement, 27.2% (n=6) reported worsening, and 40.9% (n=9) reported no change in symptoms. The distribution of migraine types (with or without aura) did not differ significantly according to menopause state ($p > 0.05$) **(Table 3).**

Table 3. Distribution of Symptoms, Triggering Factors, Comorbidity, Family History, and Menopause Period by Age Group

Category	Characteristic	15-25 years old (n=23)	26–35 years (n=39)	36–45 years (n=54)	> 45 years old (n=36)	Total/ Overall (n=152)	p
Symptoms	Presence of Nausea	22 (95.7%)	30(76.9%)	52 (96.3%)	34 (94.4%)	138(90.8%)	p<0.01
	Morning Pain Onset	14 (60.9%)	19 (48.7%)	40 (74.1%)	19(52.8%)	92 (60.5%)	p<0.01
Trigger	Stress	15 (65.2%)	29 (74.4%)	34 (63.0%)	32 (88.9%)	110(72.4%)	p<0.05
Comorbidity	Hypertension	0 0.0%)	0 (0.0%)	0 (0.0%)	8 (22.7%)	12 (7.9%)	p<0.01
	Thyroid Diseases	0(0.0%)	7 (17.9%)	0 (0.0%)	7 (19.4%)	17 (11.2%)	p<0.05
	Epilepsy	2 (8.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.3%)	p<0.01
History	Family History Presence	18(78.3%)	14 (35.9%)	32 (59.3%)	19 (52.8%)	83 (54.6%)	p<0.01
Menopause	No change	—	—	—	8 (22.2%)	—	p<0.001

The analysis of migraine onset revealed that 49.7% (n=75) of patients experienced their first symptoms between the ages of 15 and 25, while 35.8% (n=54) started between 26 and 35 years. There was a statistically significant difference in the age of onset relative to current age group distribution ($p < 0.01$), yet no significant variation was found based on gender or the presence of aura ($p > 0.05$). A positive family history was reported by 54.6% (n=83) of cases. This genetic factor was significantly more prevalent in the 15–25 age group, reaching 78.3% (n=18) ($p < 0.01$) **(Table 4)**.

Table 4. Distribution of Migraine Onset Age and Family History Source

Feature	Group / Details	Percentage (%)
Age of Onset of Pain	15–25 years	49.7
	26-35 years	35.8
	36-45	11.9
	Over 46 years old	2.6
Family History Source	Maternal (General)	29.6
	(Subgroup: 26-35 years old)	12.8
	From the sibling's side (General)	17.1
	(Subgroup: 36-45 years old)	27.8

The impact of treatment on daily quality of life was notable, as demonstrated by changes in MIDAS categories. Before intervention, 37.5% (n=57) of patients experienced severe functional impairment; following treatment, this proportion decreased to 4.6% (n=7). Improvements in MIDAS categories were observed across genders, age groups, and migraine types.

Prophylactic therapy (Propranolol) was associated with a reduction in attack frequency in 74.0% (n=112) of patients.

Acute treatment (Naproxen/Zolmitriptan) reduced attack severity in 56.8% (n=86) and shortened pain duration in 58.3% (n=89) of cases. Following acute therapy, 68.4% (n=104) of patients achieved a completely pain-free state, and 47.4% (n=72) reported complete resolution of associated symptoms such as nausea and vomiting ($p < 0.001$) **(Table 5).**

Table 5. Treatment Outcomes and MIDAS Improvements (n = 152)

Category	Outcome	Total (n=152)	p
Prophylactic Therapy	Reduction in attack frequency	112 (74.0%)	$p < 0.01$
Acute Therapy	Reduction in attack severity	86 (56.8%)	$p < 0.01$
Acute Therapy	Shortening of pain duration	89 (58.3%)	$p < 0.01$
Acute Therapy	Completely pain-free after treatment	104 (68.4%)	$p < 0.001$
Acute Therapy	Resolution of associated symptoms	72 (47.4%)	$p < 0.001$
MIDAS	Severe functional impairment (Pre-treatment)	57 (37.5%)	—
MIDAS	Severe functional impairment (Post-treatment)	7 (4.6%)	—

Note: Some patients received both prophylactic and acute therapies; therefore, percentages may overlap.

Discussion

In the present study, migraine was most frequently observed between 26 and 45 years of age, with a marked female predominance. This age distribution overlaps with epidemiological data indicating peak prevalence during the third and fourth decades of life (7,22). While this consistency strengthens the external validity of our findings, it is noteworthy that our cohort represents a tertiary referral population, which may partially explain the concentration in economically active age groups. The pronounced female predominance observed in our study parallels prior reports demonstrating a 3–4-fold higher prevalence among women (7,8). Beyond hormonal influences (9), emerging evidence suggests sex-specific differences in trigeminovascular activation and central pain modulation pathways (23), which may further explain the observed disparity.

Educational status did not significantly differ between migraine subtypes in our cohort. Although some regional studies have suggested associations between lower educational levels and migraine burden (24), larger population-based analyses have yielded inconsistent findings (25). The absence of association in our study suggests that socioeconomic indicators may influence healthcare-seeking behavior or disability perception rather than migraine subtype itself.

Migraine with aura was identified in 40% of patients. Although slightly higher than the 18–36% range reported in population-based studies (26), this difference may reflect referral bias inherent to tertiary clinics. Importantly, we did not observe demographic differences between aura and non-aura subtypes, consistent with prior reports (27,28). This finding reinforces the concept that aura represents a neurophysiological phenomenon within the migraine spectrum rather than a demographically distinct clinical entity.

Visual aura was the dominant aura subtype in our study. Previous research consistently identifies visual symptoms as the most prevalent aura manifestation (11,12,29,30). However, the relatively high detection rate in our cohort may reflect structured clinical evaluation rather than true epidemiological variation. Given that aura symptoms are transient and frequently underreported (30), detailed interviewing appears critical for accurate classification.

The majority of aura episodes lasted between 4 and 15 minutes. While IHS criteria define aura duration as 5–60 minutes (1), clinical series often report clustering within shorter intervals (11,31,32). Our findings support the notion that aura duration is typically brief and self-limited, reinforcing its underlying cortical spreading depression mechanism (11).

Headache characteristics in our cohort were highly consistent with established migraine descriptors: throbbing quality (96.1%) and unilateral localization (63.2%) (3,24,33). The predominance of gradual onset further supports classical trigeminovascular activation models (33). The high prevalence of these canonical features suggests diagnostic homogeneity within our sample.

Photophobia, phonophobia, and nausea were reported at high rates, aligning with previous literature (4,34). Nausea was significantly less frequent in the 26–35 age group compared to other age groups ($p < 0.01$), and vomiting was more frequent in aura patients. These findings may indicate greater brainstem and autonomic involvement in aura-associated attacks, consistent with cortical spreading depression propagation toward subcortical autonomic centers (11). This mechanistic interpretation warrants further neurophysiological investigation.

A significant gender difference in pain duration was observed, with women experiencing longer attacks. Prior data similarly suggest prolonged migraine duration in females (35). While estrogen withdrawal remains a widely cited explanation (9), sex-specific differences in central sensitization and inflammatory mediator response may also contribute (24). Our findings add clinical support to the biologically mediated sex-difference hypothesis.

Morning predominance of headache onset was observed in our study. Previous chronobiological research implicates circadian rhythm influences and early-morning cortisol fluctuations in migraine initiation (12,13). Our findings are

compatible with this framework, suggesting a potential interaction between hypothalamic regulation and trigeminovascular activation.

Stress emerged as the most prominent triggering factor (72.4%), consistent with existing evidence identifying psychosocial stress as a major migraine precipitant (19). While causality cannot be established in this design, the statistically significant distribution across age groups highlights the importance of stress-modulation strategies in migraine management.

Hormonal modulation was further supported by the relationship between migraine attacks and menstrual cycle, as well as significant alterations during menopause. Previous literature confirms the modulatory role of estrogen fluctuations in migraine pathogenesis (9). Our findings reinforce the clinical relevance of hormonal status assessment in female migraine patients.

Family history was present in 54.6% of patients and was significantly associated with younger age groups. Familial aggregation is well documented, with first-degree relatives demonstrating a two- to four-fold increased risk (7,20). The higher prevalence of positive family history in younger patients may suggest stronger genetic penetrance in early-onset cases, although genetic subtyping was beyond the scope of this study.

Comorbid conditions including hypertension, thyroid disease, and epilepsy were observed in our cohort. Migraine comorbidity patterns have been extensively described (36), and shared pathophysiological pathways—particularly involving ion channel dysfunction and vascular regulation—may explain these associations. Recognition of comorbidity burden remains essential for optimized treatment planning.

Our findings demonstrated a substantial improvement in quality of life following treatment, as reflected by the marked reduction in severe MIDAS categories. Preventive therapy was associated with a decrease in attack frequency, whereas acute treatment appeared particularly effective in reducing attack severity and shortening pain duration (1,3,21). Additionally, a considerable proportion of patients achieved complete pain relief and resolution of accompanying symptoms after acute therapy. These findings support the complementary roles of preventive and acute treatments in migraine management and are consistent with previous literature emphasizing their differential therapeutic benefits (17,18).

Overall, our findings are consistent with established migraine epidemiology and clinical characteristics, while contributing region-specific data derived from a university hospital–based patient cohort. The structured evaluation of aura features and the comprehensive assessment of treatment response represent notable strengths of the study. Preventive and acute therapies demonstrated complementary roles in migraine management, underscoring the importance of individualized treatment strategies. Future research incorporating longer follow-up periods, neurobiological biomarkers, and controlled comparative treatment designs is warranted to further refine migraine subtype differentiation and optimize personalized management approaches.

Study Limitations

This study has several limitations. First, it was conducted at a single tertiary care university hospital involving patients presenting to the neurology outpatient clinic. Consequently, as patients seeking care at a specialized university clinic typically present with more severe symptoms, the findings may not be fully generalizable to the general migraine population. Second, a portion of the data—specifically regarding triggering factors and historical attack characteristics—relied on self-reporting and patient recall. The structure of the questionnaire may have introduced response bias; while it focused patients' attention on their symptoms, it may have also inadvertently influenced them to report symptoms they perceived were expected. Third, the follow-up period was limited to six months; longer follow-up studies are required to evaluate the long-term efficacy and sustainability of the treatment. Finally, the study did not include a placebo control group, and treatment regimens were determined based on the patients' clinical needs (attack frequency and severity) rather than randomization, which limits the ability to perform a direct randomized comparison between the treatment groups.

Conclusion

This prospective study aimed to evaluate the sociodemographic and clinical characteristics of migraine patients and the effects of acute/preventive treatments administered. Migraine was observed most frequently between the ages of 20 and 40 and was more common in women. Positive family history, stress, and hormonal factors were observed to have a significant relationship with migraine occurrence. Both prophylactic and acute treatments were associated with reductions in migraine-related symptoms and functional impairment.

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IJCMBS

Review Article

The No-reflow Phenomenon in Acute Coronary Syndromes: A Comprehensive Review

Akut Koroner Sendromlarda No-reflow Fenomeni: Kapsamlı Bir İnceleme

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Abstract

Invasive interventions have long been widely used in acute coronary syndromes. Effective reperfusion of the ischemic myocardium should be the primary strategy in patients with acute coronary syndrome. Successful reperfusion is strongly associated with improved clinical outcomes. Conversely, inadequate reperfusion is associated with increased mortality and cardiovascular events in the subsequent period. In some patients, mechanical opening of the coronary arteries is insufficient. Restoring epicardial blood flow does not always ensure microvascular circulation and tissue perfusion. In this microcirculation disorder, called the "no-reflow" phenomenon, there is no mechanical occlusion in the coronary artery, but there is significant myocardial perfusion impairment. Given the recent advances in diagnostic tools and pharmacological treatments, this review aims to provide a comprehensive update on the no-reflow phenomenon to help guide clinical management.

Keywords: Acute coronary syndrome, No-reflow

ÖZ

Akut koroner sendromlarda (AKS) invaziv girişimler uzun süredir yaygın olarak uygulanmaktadır. Akut koroner sendromlu hastalarda iskemik miyokardın etkili bir şekilde reperfüze edilmesi ana stratejiyi oluşturmalıdır. Başarılı reperfüzyon, klinik sonuçların iyileşmesiyle güçlü biçimde ilişkilidir. Buna karşın, yetersiz reperfüzyon, takip eden dönemde mortalite ve kardiyovasküler olaylarda artışla ilişkilidir. Bazı hastalarda koroner arterlerin mekanik olarak açılması yeterli olmamaktadır. Epikardiyal kan akımının sağlanması her zaman mikrovasküler dolaşım ve doku perfüzyonunu sağlamamaktadır. "No-reflow" fenomeni adı verilen bu mikrosirkülasyon bozukluğunda koroner arterde mekanik bir tıkanma yokken miyokardda önemli perfüzyon bozukluğu mevcuttur. Tanısal araçlardaki ve farmakolojik tedavilerdeki son gelişmeler göz önüne alındığında, bu derleme, klinik yönetime/uygulamaya rehberlik etmek amacıyla no-reflow fenomeni üzerine kapsamlı bir güncelleme sunmayı amaçlamaktadır.

Anahtar Kelimeler: Akut koroner sendrom, No-reflow

Highlights

- Successful mechanical opening of the coronary artery does not always ensure tissue perfusion**.**
- The no-reflow phenomenon is associated with higher mortality and adverse clinical outcomes.
- Prevention strategies such as direct stenting are often more effective than treating established no-reflow.

Introduction

Percutaneous coronary interventions (PCIs) continue to be the primary treatment modality for acute coronary syndromes, aiming to achieve effective reperfusion. he primary goal is to achieve revascularization and reperfusion of the coronary arteries. After percutaneous coronary intervention, the abrupt cessation of coronary blood flow (TIMI 0–1) in the absence of angiographic evidence of dissection, thrombus, spasm, or significant residual stenosis is defined as "no-reflow." No-reflow can occur in both acute coronary syndromes and stable coronary artery disease and is caused by structural and functional changes in the coronary microcirculation. No-reflow is also associated with an increased incidence of rehospitalization, negative ventricular remodelling, malignant arrhythmias, and heart failure. It is an independent predictor of myocardial infarction and heart-related mortality (1). Risk factors include age over 65 years, hypertension, smoking, dyslipidaemia, diabetes, renal insufficiency, atrial fibrillation, high thrombus burden, delayed primary interventions, and the use of high-pressure or oversized stents (2). Many methods have been developed to assess reperfusion effectiveness, and these have undergone some changes in recent years, reflecting both evolving treatment strategies and technological advances.

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With percutaneous coronary intervention becoming the standard of care, angiographic evaluation has become the primary standard for determining reperfusion success. Cardiac magnetic resonance imaging, on the other hand, has demonstrated higher sensitivity and better prognostic classification than angiography for detecting no-reflow and reperfusion injury. Despite this, coronary angiography remains the most common and accessible method for assessing no-reflow in practice.

Material and Methods

This review was conducted by searching the PubMed, Scopus, and Google Scholar databases for studies published between 1974 and 2024. The search focused on keywords such as 'no-reflow phenomenon', 'microvascular obstruction', 'acute coronary syndromes', 'percutaneous coronary intervention', and 'myocardial reperfusion'. Priority was given to clinical trials, meta-analyses, and the most recent clinical practice guidelines. Only studies published in the English language were included to ensure that the information presented is up-to-date and clinically accurate.

Ethical approve

Ethical committee approval is not required for this study.

Pathophysiology

The “no-reflow” phenomenon is characterized by complex functional and structural alterations within the coronary microcirculation. While it was initially demonstrated in the myocardium by Kloner et al. (3), contemporary research highlights that the process is multifactorial rather than a single event (2). During percutaneous intervention, the disruption of an atherosclerotic plaque may lead to distal embolization. This increase in vascular resistance, combined with the release of proinflammatory and vasoconstrictive mediators, contributes to further microinfarctions (4). The primary mechanisms include distal atherothrombotic embolization, ischemic damage, reperfusion injury, and individual susceptibility to microvascular injury (5). Prolonged ischemia results in myocyte and endothelial cell death, which impairs nitric oxide production and increases vascular endothelial growth factor (VEGF) levels, leading to interstitial edema (5). Furthermore, the sudden restoration of blood flow triggers reperfusion injury through neutrophil influx and the production of free oxygen radicals (6). These processes collectively result in the characteristic endothelial edema and intraluminal obstruction observed in no-reflow areas **(Table 1).**

Table 1. Pathophysiological Components of No-Reflow

Mechanism	Key Factors	Microvascular Impact
Distal Embolization	Plaque debris, microthrombi	Increased resistance and microinfarctions
Ischemic Damage	ATP depletion, NO impairment	Endothelial swelling and interstitial edema
Reperfusion Injury	Neutrophils, free oxygen radicals	Post-ischemic inflammation and capillary plugging
Structural Changes	Fibrin clumps, endothelial protrusions	Physical obstruction of the microluminal space

Prognosis and frequency

No-reflow leads to reduced five-year survival in patients with acute coronary syndromes (with a mortality rate of 18.2% in those with no-reflow compared to 9.5% in patients with normal coronary flow). The increase in mortality associated with no-reflow was observed to be independent of other variables such as infarct size, multivessel disease, or Killip class (7). Larger infarct size was also noted in the no-reflow group (15% of the left ventricle in the no-reflow group compared with 8% in normal-flow patients). Furthermore, no-reflow has been associated with an increased incidence of systolic heart failure and malignant arrhythmias (ventricular tachycardia, ventricular fibrillation, and high-degree atrioventricular [AV] block).

The no-reflow rate varies depending on the patient subgroups included in the studies. The incidence of no-reflow during percutaneous coronary interventions has been reported to range from 2% to 5% (8-9). No-reflow is more frequently observed in coronary lesions with high thrombus burden and in degenerated saphenous vein grafts. The rate was higher (1.2-9.0%) when coronary rotational atherectomy was used and was generally reversible (10-11).

Diagnosis

Several different classifications are used to assess coronary blood flow:

TIMI flow classification is a standard angiographic measure used to assess the degree of reperfusion in coronary arteries. It plays a critical role in determining the success of reperfusion after percutaneous coronary intervention, particularly in acute coronary syndromes. According to this classification, TIMI 0 flow represents complete

obstruction, with no antegrade blood flow distal to the lesion.

1. TIMI 1 flow represents a situation where blood flow partially bypasses the occlusive lesion but cannot adequately fill the distal coronary bed, and perfusion is severely inadequate.

TIMI 2 flow represents a situation where the distal coronary bed is filled, but the flow rate is significantly slower than normal.

TIMI 3 flow indicates that complete reperfusion, equivalent to a normal flow rate, has been achieved.

TIMI 0–1 flow is considered no-reflow.

2. Coronary Myocardial Perfusion Classification (Myocardial Blush Grade, MPG) complements the TIMI flow classification and directly reflects the degree of myocardial capillary perfusion.

MPG 0 indicates no myocardial blush in the distribution area of the treated artery and significant microvascular obstruction.

MPG 1 indicates minimal, but very weak, insufficient staining.

MPG 2 indicates myocardial staining is present but less intense than usual.

MPG 3 indicates complete microvascular reperfusion with normal intensity and rapid myocardial staining.

MPG 0–1 is associated with no reflow.

3. TIMI Myocardial Perfusion Grade (TMP) is an angiographic assessment method developed to measure true perfusion at the myocardial level, unlike the TIMI flow classification, which assesses epicardial vascular patency. This classification is based on the rate of contrast medium filling and disappearance in the myocardial tissue.

TMP 0 indicates that contrast is completely absent from the myocardial tissue and indicates the presence of severe microvascular obstruction.

TMP 1 indicates that contrast reaches the myocardium but distributes very slowly and is limited, resulting in a significant perfusion defect.

TMP 2 indicates that contrast distributes to some extent in the myocardium but clears more slowly than normal and represents partial suboptimal reperfusion.

TMP 3 indicates that contrast rapidly fills and disappears normally in the myocardial tissue, indicating complete and effective microvascular reperfusion.

TMP 0–1 is associated with no-reflow.

In addition to angiographic assessment, functional measurements such as Coronary Flow Reserve (CFR) and the Index of Microcirculatory Resistance (IMR) provide crucial diagnostic data; specifically, an IMR value >40 is highly predictive of significant microcirculatory dysfunction (12). Other modalities, including myocardial contrast echocardiography and positron emission tomography, may also be utilized. However, gadolinium-enhanced cardiovascular magnetic resonance imaging (CMR) remains the gold standard, as it allows for the precise visualization of microvascular obstruction (MVO) and intramyocardial haemorrhage (12). Table 2 provides a comparative overview of the standard angiographic perfusion grades used in clinical practice. **(Table 2).**

Table 2. Comparison of Angiographic Diagnostic Classifications (TIMI, MBG, and TMP)

Parameter	Definition	Grading (0-3)	Clinical Significance
TIMI Flow Grade	Rate of epicardial coronary blood flow.	0: No perfusion; 1: Penetration without albumin; 2: Partial perfusion (sluggish); 3: Complete perfusion.	Primary tool for epicardial patency; may overlook microvascular obstruction (MVO).
Myocardial Blush Grade (MBG)	Intensity of myocardial contrast opacification (density-based).	0: No blush; 1: Minimal blush; 2: Moderate blush; 3: Normal myocardial blush.	Visual assessment of myocardial tissue-level perfusion and microvascular integrity.
TIMI Myocardial Perfusion (TMP)	Rate of contrast clearance from the myocardium (time-based).	0: No entry; 1: Entry but no clearance; 2: Delayed clearance; 3: Normal entry and clearance.	Superior to MBG in predicting long-term survival and recovery of left ventricular function.

Prevention

In patients with acute coronary syndromes or those at high risk for no-reflow, direct stenting may be considered—provided the plaque is soft and non-calcified—whereas high-pressure post-dilatation should generally be avoided. Furthermore, when using rotational atherectomy, shorter burr runs (<20 seconds) and lower speeds (140,000 to 150,000 rpm) are advisable, while decelerations of more than 5,000 rpm should be avoided. For SVG PCI, the use of distal embolic protection devices and pretreatment with intracoronary vasodilators should be considered.

In 2024, Luke P. Dawson et al. developed and externally validated the NORPACS risk score to predict the development of angiographic no-reflow in patients undergoing PCI for acute coronary syndrome. They created a simple and practical scoring system consisting of six variables strongly associated with no-reflow. The results indicate that the score can be used in clinical practice to identify high-risk patients at an early stage, thereby allowing the implementation of preventive strategies. (13). The specific weight of each parameter and the clinical risk threshold are detailed in **(Table 3).**

Table 3. The NORPACS Scoring System and Risk Stratification

Variable	Definition / Criteria	Points
Cardiogenic Shock	Presence of cardiogenic shock at presentation	4
Symptom Duration	STEMI symptom duration **>195 minutes**	3
Lesion Location	Specific coronary segment involved	3
Stent Specifications	Anticipated stent length **≥20 mm**	2
Vessel Anatomy	Vessel diameter **<2.5 mm**	2
Baseline Flow	Pre-procedural TIMI flow grade **<3**	2
Total Score Assessment	**Score ≥8 indicates a no-reflow risk exceeding 20%**	**Max: 16**

Beside the NORPACS score, recent studies have used artificial intelligence to evaluate various hematological markers. These studies suggest that parameters such as the mean platelet volume-to-lymphocyte ratio (MPVLR) may provide additional help in predicting the risk of no-reflow phenomenon (14).

Treatment

If no-reflow occurs following percutaneous coronary intervention, alternative causes—including coronary dissection, systemic hypotension, distal thrombus migration, and vasospasm—must first be excluded through angiographic imaging. Once vascular patency is confirmed, vasodilators should be administered directly into the distal vessel, preferably via a microcatheter. Throughout this process, maintaining a therapeutic activated clotting time (ACT) is essential, and hemodynamic support devices (e.g., Impella, intra-aortic balloon pump) should be utilized if clinically indicated. In cases involving a high thrombus burden, thrombectomy should be performed. The pharmacological agents utilized, including their specific administration routes and dosages, are summarized in **(Table 4)**. (2, 15, 16).

For intracoronary administration of drugs, a microcatheter or over-the-wire balloon should be used in the distal coronary artery. This minimizes systemic side effects and ensures drug access to microcirculation. A double-lumen microcatheter or thrombectomy catheter enables distal drug delivery without compromising wire position. If no-reflow persists and the patient is hemodynamically stable, drugs can be administered as multiple boluses. If flow improvement is not achieved with the first bolus, different vasodilators should be used. Calcium channel blockers (CCBs) (verapamil, diltiazem, nicardipine) cause smooth muscle relaxation and coronary vasodilation through channel binding in vascular smooth muscle, cardiac myocytes, and nodal cells. (CCBs) have been shown to have limited benefits in no-reflow therapy in a limited number of studies (17,18). Adenosine causes vasodilation in the coronary microcirculation and relaxes smooth muscle by binding to A2 receptors, and its effect lasts quite briefly. It also has anti-inflammatory properties and inhibits platelet aggregation, supporting ischemic preconditioning by limiting reperfusion injury. Side effects include bradycardia, hypotension, dyspnoea, bronchospasm, and flushing (19). The REOPEN-AMI (Comparison of Intracoronary Nitroprusside and Adenosine in Acute Myocardial Infarction) trial demonstrated a significant improvement in coronary circulation and peak troponin compared with placebo or sodium nitroprusside, leading to a reduction in major cardiovascular events (20). In addition to traditional antiplatelet therapy, ticagrelor loading plays a key role in preventing microvascular injury. Beyond potent P2Y12 inhibition, ticagrelor improves microcirculatory flow by increasing local adenosine levels. This mechanism provides an additional protective effect against the no-reflow phenomenon during primary percutaneous interventions (2, 12). Sodium nitroprusside is a potent vasodilator that inhibits platelet aggregation in the coronary circulation. It is metabolized to its active form, nitric oxide, and its duration of action is longer than that of vasodilators. (21).

Table 4. Pharmacological Agents and Clinical Considerations in No-Reflow Management

Drug/Group	Route	Dose	Side Effects	Contraindications
Adenosine	IC/IV	• 50–200 μg bolus (IC) • 70 μg/kg/min (IV)	Bradycardia, transient AV block, hypotension	High-grade AV block, severe asthma
Verapamil	IC	• 100–250 μg bolus	Hypotension, heart block, negative inotropy	Severe heart failure, advanced AV block
Diltiazem	IC	• 400 μg bolus	Hypotension, bradycardia	Heart failure with low EF
Nicardipine	IC	• 50–200 μg bolus	Hypotension, tachycardia	Severe aortic stenosis
Nitroprusside	IC	• 50–200 μg bolus	Profound hypotension, headache	Severe hypotension, hypovolemia
Epinephrine	IC	• 50–200 μg bolus	VT/VF risk, tachycardia, hypertension	Severe tachyarrhythmias
GP IIb/IIIa inhibitors	IV			
Abciximab	IV	• Bolus: 0.25 μg /kg • Infusion: 0.125 μg /kg/min	Bleeding, thrombocytopenia	Active bleeding, recent surgery
Eptifibatide	IV	• Bolus: 180 μg /kg • Supplement: 25 μg /kg IV bolus • Infusion: 2 μg /kg/min	Bleeding, hypotension	Severe renal failure (if not adjusted)
Tirofiban	IV	• Bolus: 25 μg /kg • Infusion: 0.15 μg /kg/min	Bleeding	Hypersensitivity, active bleeding

Epinephrine has been effectively used in the treatment of no-reflow syndromes resistant to other treatments or in cases where these cannot be used. The recently published COAR study compared intracoronary epinephrine and adenosine in the treatment of no-reflow in normotensive patients with acute coronary syndromes and found epinephrine to be more effective than adenosine in correcting no-reflow, with a higher rate of TIMI III coronary flow (90.1% vs. 78%, p=0.019) (22). However, despite its efficacy, the use of intracoronary epinephrine carries a significant risk of inducing malignant arrhythmias, specifically ventricular tachycardia and ventricular fibrillation. Therefore, continuous electrocardiographic and hemodynamic monitoring is essential during its administration. (12, 22,23) Glycoprotein IIB/IIIA inhibitors are potent antiplatelet agents that block platelet aggregation. While some studies suggest limited routine benefit, according to the 2023 ESC guidelines, GP IIb/IIIa inhibitors should be considered as a 'bail-out' therapy if there is evidence of no-reflow or thrombotic complications (recommendation class IIa, level of evidence C) (12). Recent evidence indicates that their intracoronary administration may be particularly useful in managing microvascular obstruction in high-risk patients (12, 24). The role of intracoronary fibrinolytic agents in the treatment of no-reflow is still debated. Although some initial positive data documented benefits for myocardial reperfusion, subsequent studies have not confirmed these findings (25).

Study limitations

There are some limitations to this review. First, since it is a narrative review rather than a systematic meta-analysis, we did not perform a statistical analysis of the data. Second, we only included studies published in English, which means we might have missed relevant findings in other languages. Finally, because the review covers a long period (1974–2024), the definitions of no-reflow have changed over time, making it difficult to compare older studies with modern ones directly.

Conclusion

The no-reflow phenomenon is a complex condition that increases mortality and morbidity after percutaneous coronary intervention in patients with acute coronary syndrome. Necessary precautions should be taken when performing interventions on lesions at high risk of no-reflow, and patients' treatment should be managed using a combination of pharmacological and non-pharmacological methods.

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