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ORIGINAL ARTICLE

Mu Opioid Agonistic Effect on Neuropeptide Gene Expression Levels Involved in Hypothalamic Feeding Regulation

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Abstract

Background: The regulation of food intake in the hypothalamus is one of most complicated through the integration of various neuroendocrine mechanisms. In this region, orexigenic and anorexigenic peptides play a role by responding to different stimuli. Additionally, central opioidergic systems are involved in the regulation of feeding behavior. Several neuropeptides expressed in the hypothalamus also contribute to the regulation of food intake. The aim of this study was to investigate the effects of mu opioidergic agonist/antagonist molecules on both orexigenic and anorexigenic peptides gene expression levels in the hypothalamus.

Methods: In our study, 48 male Wistar Albino rats were divided into 4 groups as control, morphine, naloxone and morphine+naloxone. The control group received subcutaneous SF solution for 5 days; morphine group received morphine at a dose of 10 mg/kg/day for 5 days; naloxone group SF was administered for 5 days and naloxone at a dose of 3 mg/kg 1.5 hours after the last injection: morphine+naloxone group received naloxone 1.5 hours after 5 days of morphine injection. Hypothalamus tissues were isolated from brains at the end of experimental period. Anorexigenic and orexigenic peptide expression levels were analysed by RT-PCR method. Differences between groups were statistically analyzed using one-way factorial ANOVA and Tukey post-hoc test.

Results: Morphine administration results in a decrease in the expression levels of OX2R and LepR genes, but did not change ORXA, OX1R, AgRP, NPY, POMC gene expression. Naloxone administration increased AgRP and NPY expression while decreasing OX2R, LepR and APLNR gene expression levels.

Conclusions: Our findings suggest that morphine may affect the gene expression of molecules related to regulation of nutrition and metabolism in the hypothalamus. Further studies are needed to clarify the possible mechanistic effects of mu opiodergic activity on the central control of feeding in morphine dependence manner.

Key words: AgRP, apelin, hypothalamus, neuropeptides, NPY, morphine dependence, POMC, rat

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INTRODUCTION

Opioid peptides are primarily used in pain management (1). The hypothalamus and several other brain regions contain opioid receptors (2). Three major types of opioid receptors have been identified in the central nervous system such as mu, delta and kappa (3). Morphine is a mu opioid receptor (MOR) agonist widely used for preventing pain sensation in myocardial infaction and cancer issues (4). It is pointed that consecutive administration of morphine may cause dependence and tolerance development (5). Naloxone is often used for threating morphine addiction as an opioid receptor antagonist. Even a single dose of naloxone exposure is sufficient to show withdrawal symptoms. Because of this feature, it is frequently used in experimental morphine studies to detect withdrawal symptoms and addiction (6).

Central opioid systems are also involved in the regulation of feeding behaviour (7). Injection of morphine and various morphine derivatives into various hypothalamic regions increases food intake (8). It has been reported that morphine can increase food intake when injected systemically or into brain regions such as nucleus accumbens (NAc), amygdala, ventral tegmental area (VTA), hypothalamus (4, 9).

The hypothalamus controls food intake and energy balance. It has over 40 regions and nuclei related to many neuroendocrinological regulation processes (10). Morphine dose-dependently increased food intake when injected into the paraventricular nucleus (PVN) and perifornical hypothalamus, whereas injection of naloxone into the PVN decreased food intake (11). In addition, pretreatment with naloxone was found to prevent morphine-induced feeding behaviour (12). Injections of morphine and other selective μ-opioid agonists to lateral septum area have also been reported to trigger feeding (13). Hypothalamic neuropeptides and their receptors play essential roles in the regulation of feeding behavior (14). Agouti-related protein (AgRP) (15), neuropeptide Y (NPY) (16), pro-opiomelanocortin (POMC) (17), orexin A (ORXA), orexin receptor type 1 (OX1R), orexin receptor type 2 (OX2R) (18), leptin receptor (LepR) (19), apelin and apelin receptors (APLNR) (20) plays roles by inducing or inhibiting food intake in hypothalamic region. The regulation of the motivational aspect of feeding by opioid systems in the mesolimbic region is important in food intake (21). Recent studies have focused on neuropeptides found specifically in the arcuate nucleus, PVN and lateral hypothalamus. It is thought that direct or indirect effects of these neuropeptides may be effective in the relationship between opiate and food intake (14). It is important to understand the relationship of these neuropeptides in the hypothalamus with morphine dependence and changes in feeding behaviour. Therefore, the aim of this study was to examine the possible changes in hypothalamic neuropeptides and receptor expression levels in morphine dependence manner. In addition, comparative analyses of changes in these neuropeptide expressions will provide a holistic perspective in understanding of neuroendocrinological regulation of feeding in hypothalamus under opioidergic influence.

MATERIALS AND METHODS

Test Animals

Forty-eight 10-week-old male Wistar Albino rats weighing 300-350 g were used in this study. The animals were placed in groups of four in standard plastic cages (temperature 22 ± 2°C) with food and water on a 12-hour light/dark cycle. They were fed standard rat chow and tap water. The animals were randomly divided into four groups as control group (C), morphine addiction group (M), naloxone group (N) and morphine addiction+naloxone group (M+N). In order to create a dependency model, morphine (10 mg/kg) was administered intraperitoneally to the morphine groups every morning between 09:00 and 10:00 for 5 days. Groups C and N were administered saline for 5 days. Naloxone (3 mg/kg) was injected into naloxone groups 1.5 hours after the last injection, and saline was injected into other groups. All experimental procedures in this study were approved by Necmettin Erbakan University Experimental Medicine Application and Research Centre Animal Experiments Local Ethics Committee (Ethics Number: 041-2023). The experimental studies were carried out in this centre. Animal rights are protected under the 'Guide for the Care and Use of Laboratory Animals'.

Experimental protocol

Total RNA isolation

Brain tissues of rats from all groups were rapidly removed. Hypothalamus brain regions were isolated. They

were immediately frozen in liquid nitrogen and stored at -80°C for gene expression analysis. The TRIzol method was used to isolate total RNA. Spectrophotometric analysis and agarose gel electrophoresis were used to determine the density and quality of the total RNA samples. To eliminate possible cDNA contamination, DNAse-I (Thermo Scientific; EN0521) digestion was performed according to the manufacturer's directions. Bio-Rad iScriptTM cDNA Synthesis Kit (#170- 8891, USA) was used to synthesise cDNA from total RNA samples.

Primer design and Quantitative real time-PCR analysis Primers for AgRP, NPY, POMC, ORXA, OX1R, OX2R, LepR, apelin and ALPNR and the reference genes (PGK1, RPL13A and GAPDH) were generated using the IDT PrimerQuest (https://eu.idtdna.com/site) program. Quantitative expression analysis of target and reference genes was performed using a real time PCR device (Bio-Rad CFX Connect Real Time PCR System). Briefly, polymerase chain reaction was performed by 10 μl of 2X SyberGreen master mix, 5 pMol each primer and 2 μl cDNA in 20 μl dH2O total volume. The temperature profile of the reaction was set as +95 ˚C 10 min denaturation than 40 cycles of 95˚C 30 sec, 60˚C 30 sec and 72˚C 30 sec.

Statistical analysis

For the OX1R parameter, 95% confidence level (α=0.05) and 91% statistical power were targeted, effect size was accepted as 0.64 and total standard deviation was accepted as 0.3. Based on these data, the minimum group size was calculated as n=12 (22). For gene expression analysis, Ct values of all genes were normalized to the Ct values of PGK1, RPL13A and GAPDH reference genes and ΔCt values were calculated. Gene expression differences groups were expressed as mean ± SEM values and analyzed by one-way factorial ANOVA with Tukey post-hoc test. *p<0.05 is considered significant.

RESULTS

AgRP gene expression levels were significantly higher in the M+N group compared to the M group (p<0.05, Figure 1A). NPY gene expression levels were significantly higher in the N and M+N groups compared to the K group (p<0.001, Figure 1B). NPY gene expression was also significantly higher in the N group compared to the M group (p<0.01). However, there was no significant difference in POMK gene expression levels between the groups (Figure 1C).

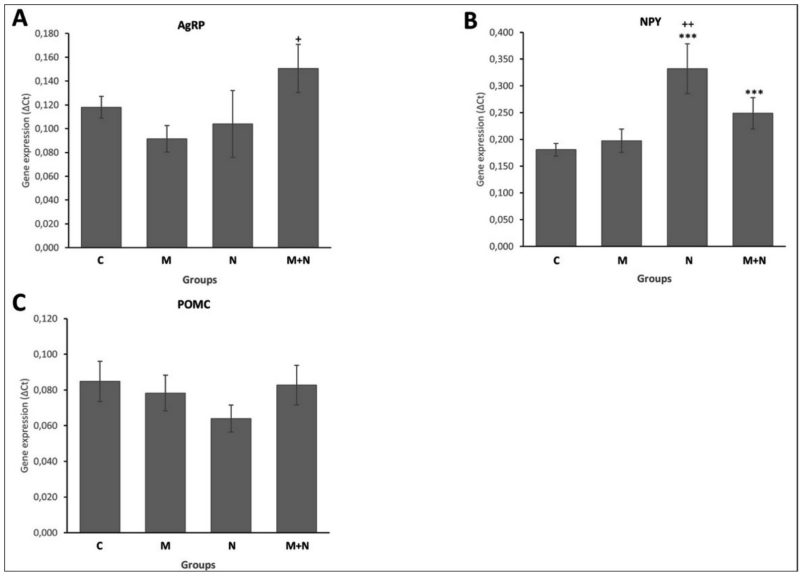

Figure 1: Changes in hypothalamic expression of AgRP, NPY and POMC

Bar graphs showing gene expression levels of AgRP (A), NPY (B) and POMC (C). All data +p<0.05 is considered significant according to the morphine group. were expressed as mean ± SEM values and analysed by one-way factorial ANOVA with Tukey post-hoc test. ***p<0.001 is considered significant according to the control group; ++p<0.01, +p<0.05 is considered significant according to the morphine group.

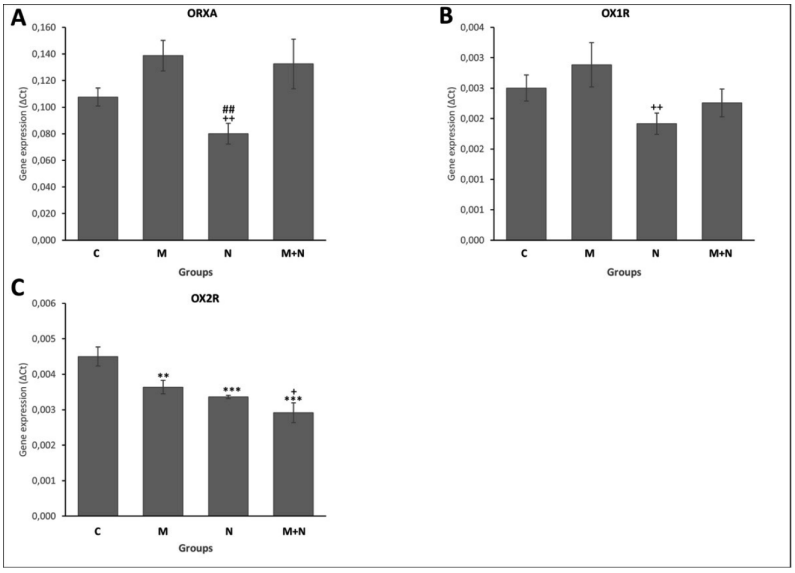

Figure 2: Changes in hypothalamic expression of ORXA, OX1R and OX2R.

Bar graphs showing gene expression levels of ORXA (A), OX1R (B) and OX2R (C). All data were expressed as mean ± SEM values and analyzed by one-way factorial ANOVA with Tukey post-hoc test. ***p<0.001, **p<0.01 is considered significant according to the control group; ++p<0.01, +p<0.05 is considered significant according to the morphine group; ##p<0.01 is considered significant according to the M+N group.

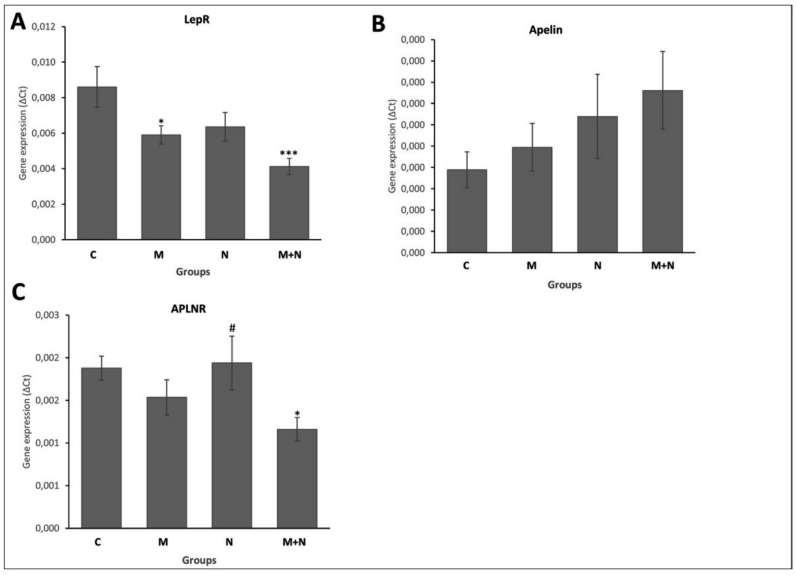

Figure 3: Changes in hypothalamic expression of LepR, Apelin and APLNR.

Bar graphs showing gene expression levels of LepR (A); apelin (B) and APLNR (C). All data were expressed as mean ± SEM values and analyzed by one-way factorial ANOVA with Tukey post-hoc test. *** p<0.001, *p<0.05 is considered significant according to the control group; #p<0.05 is considered significant according to the M+N group.

ORXA gene expression was significantly decreased in the N group (Figure 4.18.) compared to the M ($p<0.01$) and M+N group ($p<0.01$) (Figure 2A). OX1R gene expression was significantly decreased in the N group compared to the M group ($p<0.01$) (Figure 2B). OX2R gene expression levels were significantly decreased in the M ($p<0.01$), N ($p<0.001$) and M+N ($p<0.001$) groups compared to the control group. Also, OX2R gene expression was significantly decreased in the M+N group compared to the M group ($p<0.05$) (Figure 2C).

LepR expression was significantly decreased in the M ($p<0.05$) and the M+N ($p<0.001$) group compared to control (Figure 3A). There was no significant difference in apelin gene expression level between the groups (Figure 3B). APLNR gene expression was decreased in the M+N group compared to the control ($p<0.05$), whereas it was significantly increased in the N group compared to the M+N group ($p<0.05$) (Figure 3C).

DISCUSSION

In our study, we examined the possible changes in the levels of some hypothalamic neuropeptides that are involved in feeding as a result of morphine dependence. In the morphine group the level of OX2R and LepR were lower than in the control group. In the withdrawal group, NPY expression were higher than in the control group, while OX2R, LepR and APLNR levels were lower. In the naloxone-only group, NPY level were increased, whereas OX2R level were decreased in comparison to the control group. Since these hypothalamic neuropeptides are involved in many food intake signals, we may consider that opioids play a larger role in appetite regulation than previously recognized (23). A wide range of hypothalamic neuropeptide levels were analysed in our study. Many mechanisms arising from peripheral organs such as adipose tissue, gastrointestinal tract and skeletal muscles and many factors in central nervous system regulate food intake. The hypothalamus is the main regulatory centre of these mechanisms. Many studies have questioned the effects of opioids on food intake and hyperphagia (24, 25). The fact that biochemical measurements investigated in human and animal models show opioidergic signalling disorders in obese individuals increases the importance of this issue (26, 27).

Orexigenic AgRP-NPY and anorexigenic POMC hypothalamic neurons have been reported to be critical regulators of feeding and foraging behaviour (28). AgRP and NPY co-expressed at highest levels in the arcuate nucleus (29, 30). In our study, we found that hypothalamic AgRP expression was higher in the withdrawal group than in the morphine group. Opioids have been reported to inhibit AgRP-expressing neurons directly and indirectly via the MOR. This suggests that it is mediated by activating opioid receptors in non-AGRP neurons (23). In our study, NPY expression was decreased in the control and morphine groups compared to the naloxone group. This may suggest that NPY neurons have little effect on the hyperphagia effect of opioid addiction. Our results and recent studies contradict the view that the ability of NPY to potently stimulate food intake depends in part on the functioning of mu- and kappa-opioid receptors (31). Regional variation may account for this discrepancy. An autoregulatory feedback mechanism in POMC expression mediated by beta-endorphin acting through mu-opioid receptors in POMC neurons was also revealed (32). In our study there was no difference between POMC expressions. Given the specific regions of the hypothalamus, it seems likely that there are differences between groups. Orexin has been reported to reduce the electrical activity of POMC cells mainly by regulating synaptic inputs (33). Orexinergic neurons are found mainly in the lateral hypothalamus. They increase food intake by projecting to many regions (18). Orexinergic neurons located in the hypothalamus evoke their effects via two metabotropic receptors: OX1R and OX2R (34). In and around ARCPOMC cells there is strong immunoreactivity for orexin receptors (35). ORXA is a potent agonist of OX1R and OX2R (36). μ-, δ- and κ-opioid receptors are thought to modulate orexin neurons in the hypothalamus (14). In our study, the increasing trend in ORXA expression in morphine groups may support this viewpoint. In addition, according to our results, we can say that this effect of orexin on opiate exposure is mediated by OX2R rather than OX1R.

Leptin and apelin are adipokines that regulate food intake and are expressed in the hypothalamus. They exert their effects by binding to their receptors (LepR and APLNR, respectively) (37, 38). Leptin is responsible for satiety signalling. Leptin increases the firing rate of the POMC neurons and suppresses the frequency of the action potentials of the AgRP and NPY neurons (39). In our study, LepR expression was decreased in morphine groups. This may indicate the importance of hypothalamic LepRs in the hyperphagic effect of morphine. In

our previous study, we found that opioid exposure did not change APLNR expression in the hippocampus (40). In the present study, we did not find any difference in hypothalamic APLNR in morphine group, consistent with our previous study. However, APLNR was increased in the naloxone group. Moreover, this increase was suppressed by morphine in withdrawal group. This may indicate that hypothalamic apelin receptors are more likely to be activated by apelinergic signals from different regions during opiate exposure. Furthermore, this suppression increases the importance of the apelinergic system in opiate addiction, given their hyperphagic effects.

Opiates may inhibit or activate hypothalamic neuropeptides and receptors involved in regulation of feeding. Further studies with region- and neuron-specific transgenic animal models are necessary for a better understanding of these effects.

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Abbreviations list

APLNR: apelin receptors
LepR: leptin receptor
MOR: mu opioid receptor
Nac: nucleus accumbens
ORXA: orexin A
OX1R: orexin receptor type 1
OX2R: orexin receptor type 2
POMC: pro-opiomelanocortin
PVN: paraventricular nucleus
VTA: ventral tegmental area

Ethics approval and consent to participate

This project has been approved by Necmettin Erbakan University Experiments Animals Local Ethics Committee (Project Number: 2023-041 Date: 15.09.2023)

Consent for publication

There is no data on any individual in our study.

Availability of data and materials

The data that support the finding of this study are available from corresponding author upon reasonable request.

Competing interests

The authors declare no competing interest.

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Authors' contributions

Conceptualization and methodology: F.B.K.C., Z.E.T. and S.K. Data curation and project administration: F.B.K.C., Z.E.T., A.S., K.Z.C.S., and S.K. Investigation and data analysis: Z.E.T., A.S., K.Z.C.S., C.E.G. and E.K. Manuscript writing—original draft: F.B.K.C., C.E.G., E.K., Y.A.C., and S.K. Manuscript editing and manuscript review: F.B.K.C., E.K., Y.A.C. and S.K.

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ORIGINAL ARTICLE

Trait Anxiety, Depression, and Insomnia Among Benign Paroxysmal Positional Vertigo Cases: A Multidisciplinary Cross-Sectional Study

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Abstract

Background: Benign paroxysmal positional vertigo is the most common peripheral vestibular disease and is often associated with psychiatric conditions, including anxiety, depression, and insomnia. Studies evaluating trait anxiety in benign paroxysmal positional vertigo cases are limited. Our study aimed to assess trait anxiety, depression, and insomnia levels among those cases to investigate and emphasize the clinical value of evaluating psychiatric comorbidities.

Methods: Individuals who applied to an otorhinolaryngology outpatient clinic and were diagnosed with benign paroxysmal positional vertigo were consecutively invited to participate. An extensive psychiatric assessment, Beck Anxiety Inventory, Beck Depression Inventory, Insomnia Severity Index, and Penn State Worry Questionnaire, was applied.

Results: Of 35 benign paroxysmal positional vertigo patients (21 females, 14 males, mean age: 51), almost half were diagnosed with anxiety disorders, and one-third were diagnosed with depressive disorders. 34.3% (n = 12) of the sample had mild anxiety, whereas 28.6% (n = 10) had moderate and 31.4% (n = 11) had severe anxiety. 25.7% (n = 9) of the cases reported mild depressive symptoms, while 22.9% (n = 8) had moderate, and 11.4% (n = 4) had severe depression scores. 77.1% (n = 27) of the patients had mild to severe insomnia severity. All 35 participants in the study showed higher trait anxiety levels than the cut-off values of the scale.

Conclusions: Evaluating benign paroxysmal positional vertigo cases for psychiatric conditions could contribute to the practical and integrated treatment of the disease, reduce its triggering causes, and increase the quality of life of the patients.

Keywords: Benign paroxysmal positional vertigo, anxiety, depression, nervousness, insomnia

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INTRODUCTION

Diagnosed in almost one in four patients with vertigo, benign paroxysmal positional vertigo (BPPV) is the most common peripheral vestibular disease (1). BPPV is characterized by an abrupt onset, recurrent episodes of dizziness and nystagmus triggered by the positions of the head, resulting in decreased functionality and quality of life (2,3). Apart from dizziness, the most common symptoms of BPPV include fatigue, impaired balance, and intolerance of motion (4).

As the most accepted mechanism, calcium carbonate crystal particles known as otoliths in the inner ear's semicircular canals cause abnormal endolymph stimulation, thus precipitating BPPV symptoms (5). BPPV is diagnosed by examining the patient's medical history with provocation tests such as the Dix-Hallpike maneuver. Spontaneous remissions are frequent; however, recurrence rates are reported as high as 56% (6).

The association of various mental health conditions with BPPV is a clinically significant topic that is often unaddressed. Sudden episodes of vertigo caused by this condition may trigger anxiety and worry among patients, along with depressive mood or insomnia (7). Particularly, vestibular vertigo may lead to increased levels of anxiety through the activation of common neural pathways (8).

Studies evaluating the relationship between BPPV and psychiatric disorders demonstrate high rates of comorbidity that appear to be bidirectional. Few studies have related BPPV and varying levels of anxiety symptoms (9,10). Kozak et al. (2018) reported a 39.1% prevalence rate for mood or anxiety disorders in BPPV cases (11). Meanwhile, poor sleep quality and dizziness symptoms were associated in patients with BPPV (12). In a recent systematic review and meta-analysis, Yeo et al. (2024) found a 3-fold increased risk of anxiety among patients with BPPV and recommended further studies to confirm these associations (13). On the other hand, individuals with anxiety disorders were at two times higher risk of developing BPPV (14). Numerous studies endorsed the impaired neuroendocrine response and neural inflammation in cases of anxiety and depression, which are suspected to be crucial elements in the disease mechanism of BPPV (14).

Current treatment algorithms for BPPV primarily involve vestibular rehabilitation to reposition particles with specific maneuvers or surgical interventions. However, in clinical work, there is limited attention to detecting and treating highly comorbid psychiatric conditions (13). Raising awareness about the importance of psychiatric evaluation in patients with BPPV is needed to reduce the disease's triggering causes and symptoms, thus increasing the quality of life. Our study aimed to assess anxiety, depression, and insomnia among patients with BPPV, with a specific focus on trait anxiety. First, we hypothesized that the anxiety and depression scores of patients would be higher than the cut-off values. Second, we thought that the insomnia severity scores of the BPPV cases would be higher. Finally, we expected to see high trait anxiety levels in BPPV patients.

MATERIALS AND METHODS

Participants and procedure

Individuals aged 18 years and over who applied to the otorhinolaryngology outpatient clinic of a public hospital with dizziness between January and December 2022 and were diagnosed with BPPV after a clinical examination and received maneuver treatment within the last year were consecutively invited to participate in the study. Written informed consent was obtained from all the voluntary participants. Details about patients' age, gender, the presence of type 2 diabetes mellitus, the presence of hypertension, the presence of thyroid disorders, and other otorhinolaryngologic diseases such as chronic rhinosinusitis were recorded. Participants were asked if they had made any sudden movements in the previous two weeks. Then, as part of the initial screening, participants were assessed about whether they had stress, insomnia, or depressive symptoms such as depressed mood or loss of interest and whether they experienced anxiety. A psychiatric examination was recommended for each patient, regardless of psychological symptoms, to evaluate the effects of triggering factors such as stress and insomnia. Thirty-five out of 69 patients (50.7%) diagnosed with BPPV within one year agreed to receive a psychiatric interview. A comprehensive psychiatric assessment was performed for each participant, as detailed below, and if necessary, appropriate treatment

was recommended by the psychiatrist. Patients with a severe mental disorder diagnosis that might affect their capacity to provide informed consent and complete the self-report questionnaires (i.e., psychotic disorders, acute manic episodes, major neurocognitive disorders, or substance use disorders) were excluded from the study. After 15 days, participants were invited to attend the otorhinolaryngology and psychiatry outpatient clinics for control appointments.

Psychiatric clinical assessment

Along with an extensive psychiatric evaluation based on DSM-5 descriptive criteria, Beck Anxiety Inventory (BAI), Beck Depression Inventory (BDI), Insomnia Severity Index (ISI), and Penn State Worry Questionnaire (PSWQ) were applied to the participants (15). BAI and BDI are 21-item, 4-Likert-type scales developed by Beck et al. (1961; 1988) (16,17). ISI consists of 7 items in the 5-Likert type and aims to evaluate insomnia severity (18). PSWQ is a 16-item 5-Likert-type scale developed to assess the trait of anxiety in adults (19). All the assessment tools were validated for the Turkish population (20,21,22,23). Previously identified cut-off values for all the scales were applied during the psychiatric evaluation: For BAI (8-15 mild, 16-25 moderate, and 26-63 severe), for BDI (10-16 mild, 17-29 moderate, and 30-63 severe), for ISI (8-14 mild, 15-21 moderate, and 22-28 severe) and PSWQ (16-39 mild, 40-59 moderate, and 60-80 severe).

Statistical analysis

Numerical data with normal distribution were presented with mean and standard deviation (SD) values. Kolmogorov-Smirnov test was used to test normality. Normally distributed numerical data were analyzed using the Student t-test and Pearson correlation. Numerical data that failed the normality tests were assessed with the Mann-Whitney-U test and Spearman correlation. Categorical data were analyzed using Chi-square and one-way analysis of variance tests. Statistical analysis was performed using SPSS version 25.0. A p-value of $< .05$ was considered significant.

Ethical considerations

Ethical approval for the study was obtained from the local ethics committee of Süleyman Demirel University for clinical research on 06.01.2022 with decision number 1/13. The Declaration of Helsinki principles were followed throughout the study (24). Each patient provided written informed consent to participate in this study. The study's patient recruitment process was conducted between January and December 2022.

RESULTS

The mean age of 35 patients who were diagnosed with BPPV and who agreed to attend the psychiatric interview was 51.77 (±12.73). Twenty-one (60%) of the patients were female, and 14 (40%) were male. BPPV was left-sided in 57.2% (n = 20) and right-sided in 42.8% (n = 15) of the patients. Two patients (5.7%) had lateral canal BPPV, and 33 (94.3%) had posterior canal BPPV. Fifteen (42.8%) patients had at least one chronic disease, such as type 2 diabetes mellitus, arterial hypertension, or hypothyroidism. Four patients (11.4%) were diagnosed with an anxiety disorder and used psychiatric medication. After the psychiatric assessment in the study process, a total of 16 (45.7%) patients, including four previously diagnosed, were diagnosed with anxiety disorders according to DSM-5 (15). Among those, four patients (25%) were diagnosed with both anxiety disorder and depressive disorder. Of new diagnoses, seven patients (58.3%) were diagnosed with generalized anxiety disorder, while five (41.7%) were diagnosed with unspecified anxiety disorder. A total of 11 patients (31.4%) were diagnosed with depression, and two (5.7%) were diagnosed with insomnia disorder. Of 31 patients who did not previously use psychiatric medication, 21 (67.7%) were recommended a psychopharmacological treatment (Table 1).

Among 34 patients who did not agree to attend the psychiatric evaluation, 13 (38.2%) were using medication with a diagnosis of anxiety disorders, and one (2.9%) was using medicines with a diagnosis of insomnia disorder.

Table 1. Sociodemographic and Clinical Characteristics	
Age (mean ± SD)	51.77 ± 12.73
Female Gender (%, n)	60 (21)
Left-sided BPPV (%, n)	57.2 (20)
Posterior Canal BPPV (%, n)	94.3 (33)
Chronic Disease (%, n)	42.8 (15)
Anxiety Disorders (%, n)	45.7 (16)
Depressive Disorders (%, n)	31.4 (11)
Insomnia Disorder (%, n)	5.7 (2)
SD: Standard Deviation, BPPV: Benign Paroxysmal Positional Vertigo	

The mean BAI score was 21.11 (±12.09), indicating a moderate level of anxiety. 94.2% (n = 33) of the sample showed mild to severe levels of anxiety accordingly (Figure 1). In detail, 34.3% (n = 12) of the patients had mild anxiety, 28.6% (n = 10) moderate, and 31.4% (n = 11) severe anxiety, while 5.7% (n = 2) had none/low levels. A mild level of depression was seen among the sample, with a mean BDI score of 15.02 (±9.44). Likewise, 60% of the sample had mild to severe depressive symptoms. Results demonstrated that 25.7% (n = 9) of the patients had mild depressive symptomatology, while 22.9% (n = 8) had moderate, 11.4% (n = 4) had severe, and 40% (n = 14) had none/low levels.

Table 2. Scale Score Distributions								
	None/Low		Mild		Moderate		Severe	
	n	%	n	%	n	%	n	%
BAI	2	5.7	12	34.3	10	26.6	11	31.4
BDI	14	40	9	25.7	8	22.9	4	11.4
ISI	8	22.9	13	37.1	11	31.4	3	8.6
PSWQ	-	-	10	28.6	18	51.4	7	20
BAI: Beck Anxiety Inventory, BDI: Beck Depression Inventory, ISI: Insomnia Severity Index, PSWQ: Penn State Worry Questionnaire								

Insomnia severity scores showed that 37.1% (n = 13) of the patients had mild insomnia, 31.4% (n = 11) had moderate, 8.6% (n = 3) had severe insomnia, while 22.9% (n = 8) had none/low levels. The mean ISI score was 12.08 (±6.69), pointing to a mild degree of insomnia. Only one-fifth (23%) of the sample reported the absence of insomnia. According to PSWQ scores, 28.6% (n = 10) of the patients had mild, 51.4% (n = 18) had moderate, and 20% (n = 7) had severe trait anxiety. A mean score of 48.51 (±14.58) indicated moderate levels of trait anxiety throughout the sample. All 35 of the patients showed some degree of trait anxiety, varying from mild to severe. Details regarding scale scores are summarized in Table 2.

Table 3. BAI, BDI, ISI and PSWQ Correlations

		BAI	BDI	ISI	PSWQ
BAI	r	1	0.719**	0.271	0.645**
	p		**< 0.001**	0.115	**< 0.001**
BDI	r	0.719**	1	0.425*	0.438*
	p	**< 0.001**		**0.011**	**0.008**
ISI	r	0.271	0.425*	1	0.338*
	p	0.115	**0.011**		**0.047**
PSWQ	r	0.645**	0.438**	0.338*	1
	p	**<0.001**	**0.008**	**0.047**	
	N	35	35	35	35

There was no significant difference between the anxiety, depression, insomnia, and trait anxiety scores when those with and without chronic disease diagnosis were compared. No significant difference was found between male and female patients in terms of any of the scale scores. There was also no significant difference in the scores on the scales between those who had used psychiatric medication before evaluation and those who had not. As expected, BAI, BDI, ISI, and PSWQ were positively correlated (Table 3).

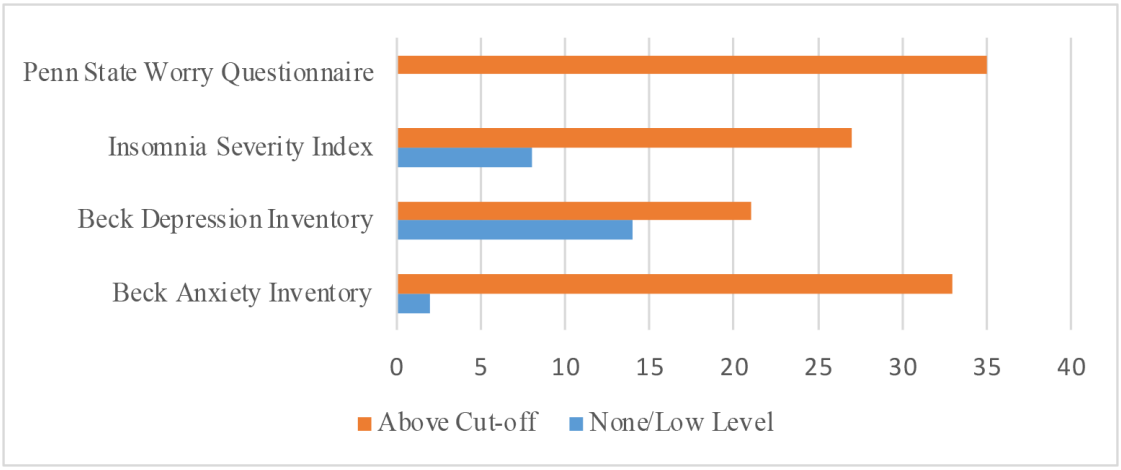

Figure 1: Scale Scores of the BPPV Sample

DISCUSSION

Our study aimed to evaluate the anxiety, depression, insomnia, and trait anxiety levels of patients diagnosed with BPPV. The results showed that anxiety, especially trait anxiety levels, were high in a large majority of the cases. Similarly, mildly increased scores were observed in depression and insomnia scales.

Almost all the patients with BPPV (94.2%) demonstrated mild to severe levels of anxiety. Moreover, a significant proportion of those (45.7%) were diagnosed with an anxiety disorder. Adjusted worldwide estimates suggest the prevalence of anxiety disorders in the general population from 5.3 to 10.4% (25). This finding is in line with the results of the meta-analysis of Yeo et al. (2024), which comprised 2902 BPPV cases from 23 studies, reporting a 3-fold increased risk of anxiety disorders (13). Even though our sample size is limited to be generalized, an anxiety disorder diagnosis in almost one in every two patients with BPPV points to clinical attention of this comorbidity.

Trait anxiety is described as anxiety that is part of an individual's personality or way of perceiving the world. Our study showed that all the patients with BPPV had some degree of trait anxiety, either mild, moderate, or severe. While BAI measures a prolonged state of anxiety, which is defined as anxiety that occurs in response to stressful situations, trait anxiety assessed with PSWQ refers to an ongoing situation of worry that might affect vertiginous symptoms in the long term. Trait anxiety appears to be involved with both hypotheses attempting to explain the association between vestibular diseases and psychiatric conditions. According to the otogenic hypothesis, vertigo may lead to various symptoms of secondary psychological distress because of its unpredictable nature, leading to persistent worry and decreased quality of life in patients with BPPV (26,27). Likewise, psychogenic theory suggests the manifestation of secondary dizziness due to pre-existing psychological distress, often related to hyperventilation and other somatic signs of anxiety and worry (28). Our results on heightened trait anxiety levels support both and could be considered a possible means to the bidirectional connection between BPPV and anxiety disorders. This finding requires further investigation.

We obtained signals of the relative importance of anxiety and trait anxiety among BPPV patients. The high risk of developing BPPV in patients with anxiety disorders was previously reported, and sudden changes in head movements were suggested to trigger fear and worry (10). The link between vestibular dysfunction and emotional processing mechanisms might be discussed in light of several explanations. Psychological distress could stimulate vestibular dysfunction by disrupting compensation mechanisms or changing somatosensory input throughout the body (29). Neuroanatomical regions and neurotransmitters that take part in emotional responses and vestibular systems are similar.

An integrated network of numerous neural components is involved in the co-existence of vertigo and anxiety, including the vestibulo-parabrachial nucleus network and afferent interoceptive information processing (30).

Almost two-thirds of our study sample demonstrated elevated levels of depressive symptoms, while one-third were clinically diagnosed with a depressive disorder. This finding supports the increased depression rates among BPPV patients (11). A recent Mendelian randomization study reported a significant association between neuroticism and mood swings as possible risk factors for BPPV (31). Psychological stress might trigger a systemic response resulting in sustained chronic inflammation that ultimately affects the functioning of balance receptors in the inner ear and promotes BPPV (32). Considering that a stable visual perception is essential for individuals with BPPV, impaired visual balance control caused by the enhancement of neural network activity due to mood swings and depression might contribute to the pathophysiology of BPPV (33). A further exploration and more profound understanding of these mechanisms would help develop more effective treatment strategies and preventive interventions for BPPV.

Poor sleep quality is a risk factor for psychiatric disorders such as anxiety and depression (34,35). Insomnia alone can increase the risk of BPPV, but it can also cause BPPV by giving rise to anxiety and depression (36). We found that more than three-quarters of patients with BPPV had insomnia to some extent. A retrospective cohort study reported that insomnia increased the risk of BPPV in male patients (37). We found no statistical difference between females and males concerning anxiety, depression, insomnia, or trait anxiety in our BPPV sample, pointing to an overall increase in insomnia regardless of gender. Considering insomnia was identified as a possible trigger for vertigo attacks, it is of clinical value to evaluate BPPV patients for sleep disorders and carry out appropriate treatments.

Cohen et al. (2004) reported that comorbid chronic diseases were more common in patients with BPPV (38). In this study, we found no difference between BPPV patients with metabolic diseases and those without in terms of the scale scores. However, a longer follow-up should be considered since the chronic processes in comorbid metabolic diseases would be more detectable.

Our study has certain limitations, such as the relatively small sample size, a cross-sectional design that does not permit causality, the lack of a control group, and the conduction of the study during the COVID-19 pandemic. Rather small sample size limits the generalizability of our findings. It was less than intended because the number of BPPV patients who applied to the outpatient clinic within one year was less than expected. This might be related to the coincidence of our study with the COVID-19 pandemic, in which worldwide physical restrictions were implemented. Patients invited to participate in the study might have been unwilling because of the expected increased time spent at the hospital. The cross-sectional assessment of psychiatric symptoms in BPPV patients did not allow us to draw associations regarding causality. Another limitation was the psychiatric assessment rates, which were in connection with the voluntariness of BPPV patients. Relying on the voluntary participation of patients might have caused voluntary response bias. Patients who did not agree to a psychiatric examination may not have benefited from psychiatric treatment before for various reasons or could not tolerate the medication. In addition, patients' observed reluctance to join a psychiatric interview could be linked with fear of confronting a psychiatric diagnosis, thus with stigmatization. The initial screening of stress might have caused a selection bias, resulting in the participation of patients with higher levels of anxiety. The lack of evaluation regarding marital status, education level, and employment status, which might contribute to anxiety disorders and depression as risk factors, constitutes another limitation. Since the cut-off values of the scales were specific and broadly accepted, a control group was not included. Moreover, we assumed that the comparison would not be homogeneous, as there may have been multifactorial causes of anxiety, depression, and insomnia in those without a BPPV diagnosis that were not evaluated. Özdilek et al. (2009) reported that anxiety scale scores were higher in BPPV patients when compared to those in the control group (10). Since a psychiatrist conducted the objective evaluation, self-report scales were preferred to observe patient ratings and insights.

A strength of our study might be the evaluation of trait anxiety in patients with BPPV, which was studied scarcely in similar studies. Due to the two-way relationship between anxiety and vertigo, it is not easy to

distinguish which one triggers the other in most clinical cases where they co-occur. However, elevated levels of trait anxiety might pave the way for vertigo and BPPV. It may appear as a symptom often not considered to apply for psychiatric consultation, but that strengthens this vicious circle and affects physical health.

Identifying individuals prone to trait anxiety through routine psychological symptom screening and directing them to further psychiatric clinical evaluation may be beneficial in terms of the recommended multidisciplinary approach in the management of BPPV cases. In the clinical care of vertigo and BPPV, it is important to keep in mind the high rates of comorbid psychiatric disorders. In this way, a comprehensive evaluation and treatment may be possible, not only regarding the BPPV symptoms but also the etiology, triggers, and high recurrence rates. Focusing on the psychological factors that play an active role in BPPV and integrating them into the treatment process may provide a key clinical benefit in alleviating the chronic burden of the disease. Therefore, a careful assessment of patients with BPPV regarding psychiatric conditions, especially anxiety disorders, is of great value to a better-integrated approach to treatment, care, and prevention of further episodes of the disease and an increased quality of life.

Evaluating BPPV patients for anxiety, particularly trait anxiety, as well as depression and insomnia, could help increase patients' awareness of the close relationship between psychiatric conditions and BPPV. Offering a psychiatric assessment as part of integrated care might have benefits for the psychological causes and triggers of the disease and in preventing possible recurrences.

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Abbreviations list

COVID-19: Coronavirus Disease 2019

BAI: Beck Anxiety Inventory

BDI: Beck Depression Inventory

BPPV: Benign Paroxysmal Positional Vertigo

DSM-5: Diagnostic and Statistical Manual of Mental Disorders 5th Edition

ISI: Insomnia Severity Index

PSWQ: Penn State Worry Questionnaire

SPSS: Statistical Package for the Social Sciences.

Ethics approval and consent to participate

This study was approved by the Local Ethics Committee of Süleyman Demirel University for clinical research on 06.01.2022 with decision number 1/13.

Consent for publication

Informed consent was obtained from all individual adult participants included in this study.

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Competing interests

The authors have no commercial associations or sources of support that might pose a conflict of interest.

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Authors' contributions

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ORIGINAL ARTICLE

Global Trends in Prenatal Mosaicism Research: Insights from a Bibliometric Analysis (1980–2023)

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Abstract

Background: The coexistence of at least two cell lines with different genetic structures (chromosomal or single gene mutation) originating from the same zygote in an organism is defined as mosaicism. This study aimed to present a medical perspective by examining scientific articles published on diagnosis of prenatal mosaicism from a perinatal and genetic perspective with statistical methods.

Methods: The source of our study is the Web of Science (WoS) database. The articles indexed between 1980-2023 were included in our research in the database, and the studies of 2024 were not included since the effect factors are not clear yet. While searching the database, the words "Prenatal Mosaicism" were used as keywords

Results: We reached a total of 2124 publications by analyzing the WoS database using the term "prenatal mosaicism". When the citations of the documents written about prenatal mosaicism are evaluated, we found that the highest citation was made in 2022. Co-citation analysis has shown that there are 9932 authors investigating the issue of prenatal mosaicism. Collaboration and citation collaboration was observed between Mackay Memorial Hospital, National Taiwan University and National Yang Ming University. Prenatal screening and Aneuploidy were found the strongest relationship with prenatal mosaicism.

Conclusions: It is observed that the publications related prenatal mosaicism are associated with prenatal diagnosis and screening and this diagnosis has the highest publication, citation and impact power.

Key words: Prenatal Diagnosis, Mosaicism, Genetics, Bibliometry

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INTRODUCTION

Prenatal diagnostic methods describe tests developed with the aim of detecting chromosomal structural and numerical anomalies and ensuring healthy offspring. These tests have methodological, reproducibility, consistency, sensitivity and specificity differences among themselves. The differences in methods and the accuracy of their application methods affect genetic counseling and perinatal management. The reliability of the ideal diagnostic test should be high. The selection of the test should be determined by considering the fetal week, the competence of the center performing the test and the family's preference.

Fetuses requiring prenatal diagnosis are determined by family history, obstetric history, genetic history, various biochemical and sonographic tests. Chorionic villus sampling, amniocentesis, fetal skin biopsies and cordocentesis are used for diagnosis. None of these tests can diagnose all fetal anomalies, which test to be selected should be determined specifically for the pregnancy. Patients should be informed in a way that they understand the limitations of genetic tests, that possible genetic results cannot be recognized in some cases, and that genetic disorders can cause very different clinical and phenotypic results. The diagnosis of mosaicism, which is a prenatal genetic diagnosis, explaining it to the family and predicting its clinical results may involve various difficulties.

Basically, chromosomal anomalies can be examined in two groups as structural and numerical. The most frequently observed chromosomal numerical anomalies are aneuploidies that contain extra or missing chromosomes. Sometimes, extra chromosome sets that are multiples of 23 chromosomes can be encountered (triploidy, tetraploidy, etc.). In an organism, the coexistence of at least two cell lines with different genetic structures (chromosomal or single gene mutation) originating from the same zygote is defined as mosaicism. Abnormalities in the number of chromosomes can be mosaic, which means that the abnormal number of chromosomes is not present in all cell lines. Mosaicism occurs with at least one mitotic error. A mosaic individual can be formed when a genetic anomaly occurs with a new mutation in the mitotic divisions of a zygote with a normal genetic structure and these cells continue to divide, or mosaicism can occur with a second mutation during the mitotic divisions of an anomalous gamete that was formed with a meiotic error (1).

In CVS (Chorion villus sampling) and amniocentesis, which are frequently used in prenatal diagnosis, classical karyotyping methods are routinely applied, and the ability of these methods to recognize aneuploidies is quite strong. Sometimes, if there is no mosaicism in the specific fetal cell line obtained by prenatal testing, mosaicism in the fetus may not be detected by karyotype analysis. Chromosomal mosaicism rates detected by amniocentesis, CVS and cordocentesis may be quite different from each other due to the different areas from which the cell material is obtained. While mosaicism is less common in amniocentesis samples (0.25-0.50%), it is more common in chorionic villus sampling (1-3.2%) (2-5). When preimplantation genetic tests (PGT) performed within the indication in assisted reproductive treatments are also evaluated as diagnostic tests, the incidence of chromosomal aneuploidies increases. In series where PGT results are screened retrospectively, chromosomal mosaicism is encountered at quite high and variable rates (29.1-50%). (6,7).

As can be seen, the incidence of chromosomal mosaicism varies according to many clinical and laboratory factors such as the type of test, the cell series taken, and the age of the pregnant woman. Factors that make mosaicism diagnosis difficult also reduce the chance of predicting prenatal results. Categorization is possible according to the reasons for false positive or negative results in prenatal diagnoses of mosaic individuals and the diagnostic laboratory methods. It can be thought that the diagnosis of mosaicism will increase with the development of the frequency and reliability of the prenatal tests used, and academic progress will be made in this direction.

The number of perinatal and genetic studies on mosaicism in prenatal diagnosis is increasing day by day. Studies can be grouped according to the verification of diagnoses, the variety and reliability of the methods used to establish the diagnosis. The aim of this study is to conduct a holistic bibliometric analysis of academic articles examining prenatal mosaicism and to present a comprehensive data with existing publications.

MATERIALS AND METHODS

The source of our study is the Web of Science (WoS) database and includes the Korean journal database, core collection index, Russian Science Citation Index and Sci ELO (Scientific Electronic Library Online) citation index.

The articles indexed between 1980-2023 were included in our research in the database, and the studies of 2024 were not included since the impact factors are not clear yet. While searching the database, the words "Prenatal Mosaicism" and "Prenatal Mosaicism Diagnosis" were used as keywords. Datawrapper free open web-based application was used to visualize global research productivity. VOS-viewer 2019 program was used to determine the scientific relevance of the data.

RESULTS

General Features and Global Productivity

We reached a total of 2124 publications by analyzing the WoS database using the term "Prenatal Mosaicism" and "Prenatal Mosaicism Diagnosis". In our study, we excluded 71 studies of 2024 from evaluation, since the citations were not yet completed. We have listed the date of the remaining 2124 articles published from the past by 2023, and we saw that the first article was published in 1982. This study presented prenatal cytogenetic analyses in a cross-sectional manner retrospectively in a single center and determined the true mosaicism rates (8). The articles were written in 21 different languages, the most widely used was English, which accounts for about 97.9 % of all articles. Most of the documents (78.1 %) were research articles, followed by reviews and meeting abstracts (Table 1). We analyzed the distribution of the documents written about prenatal mosaicism in the branches of science, we saw that there were studies in 40 different fields in total, we found that the branch of science that carried out the most studies was genetics heredity. The field of genetics and heredity was followed by obstetrics and gynecology, reproductive biology, pediatrics, biochemistry molecular biology and medicine general internal respectively (Table 2). The number of documents written about prenatal mosaicism was increasing every year. Since 1999, a large number of documents have been published every year, and the most productive year was 2022 (Figure 1). 123 articles were published in 2022, although the majority of these publications were research articles. The most cited research article of these years was the "Genome-Wide Fetal Aneuploidy Detection by Maternal Plasma DNA Sequencing" published in the Obstetrics and Gynecology (9).

2124 articles have been published on prenatal mosaicism in the field of genetics and heredity. 701 of these articles were published by the Prenatal Diagnosis, Tawanese Journal of Obstetrics Gynecology and American Journal of Medical Genetics. The most cited year for the articles on prenatal mosaicism published in the Prenatal Diagnosis at 2022. Among the publications on prenatal mosaicism in this journal, the most cited article was " Cytogenetıc Results From The Unıted-States Collaboratıve Study on CVS." (10)

We evaluated the countries in which articles written about prenatal mosaicism were prepared, and found the most productive countries as the United States of America (USA), China and Taiwan. About 26.5 % of all publi-

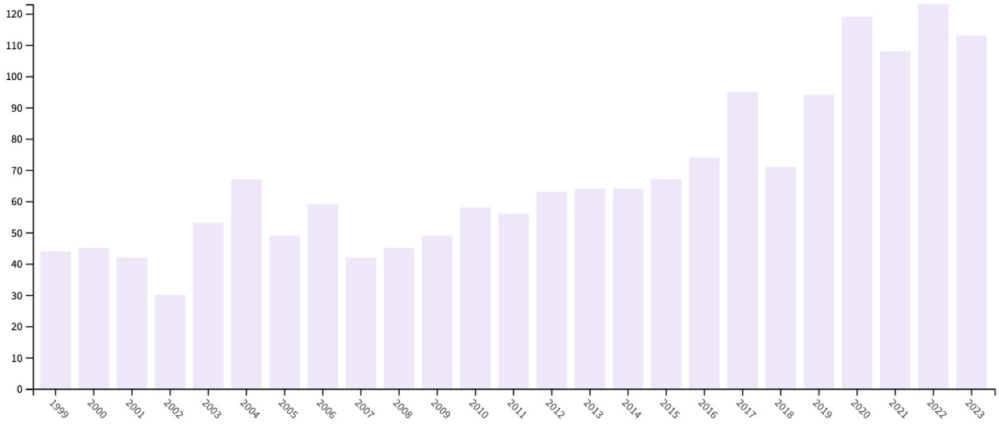

Figure 1: Graph of publications about Prenatal Mosaicism by years.

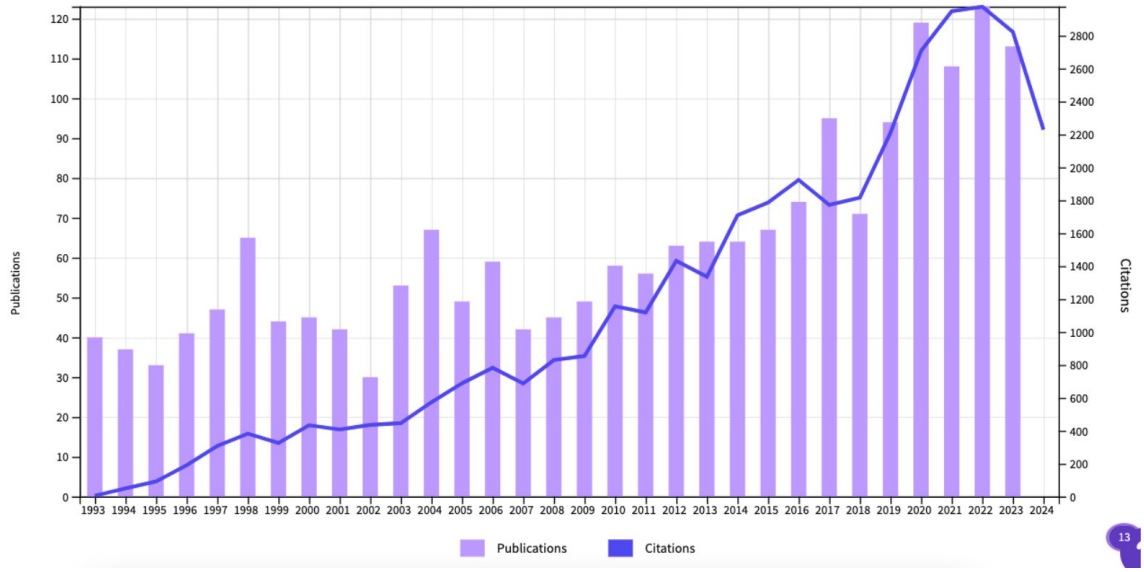

Figure 2: Graph of citations about Prenatal Mosaicism by years.

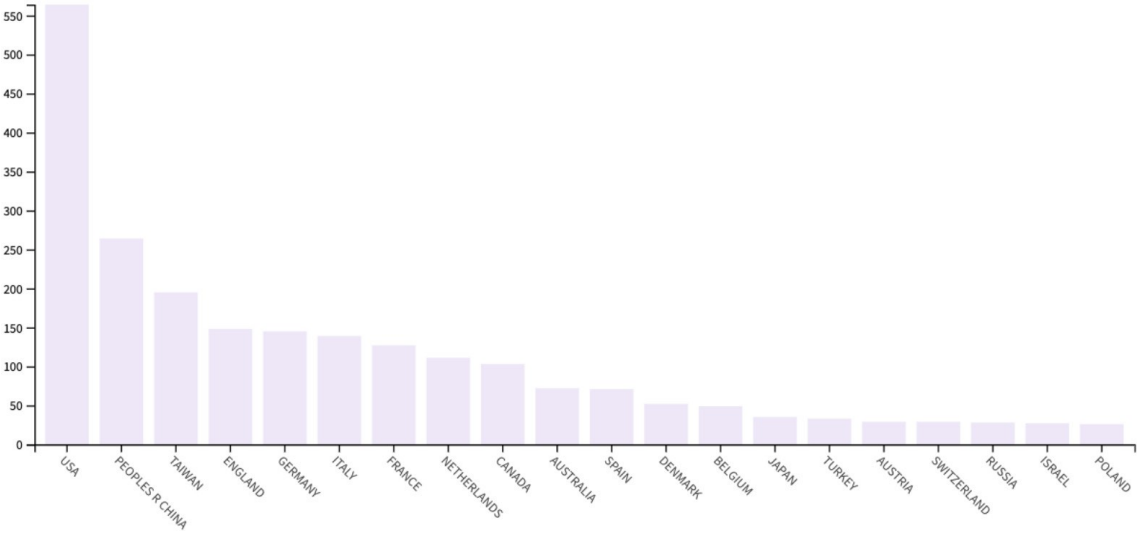

Figure 3: The top ten publishing country bar charts on Prenatal Mosaicism.

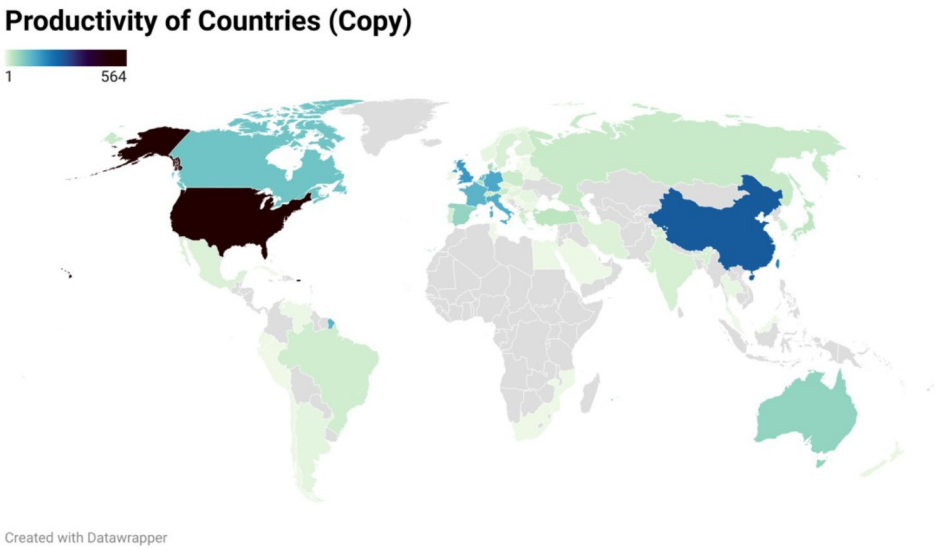

Figure 4: Prenatal Mosaicism publication density according to the countries

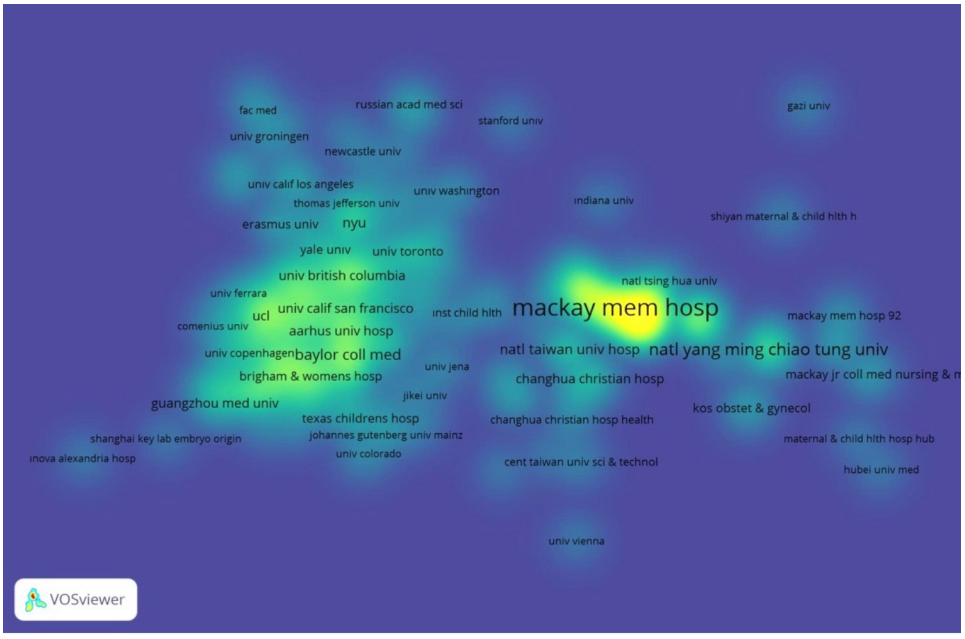

Figure 5: Intensity map of the cooperation analysis of the institutes

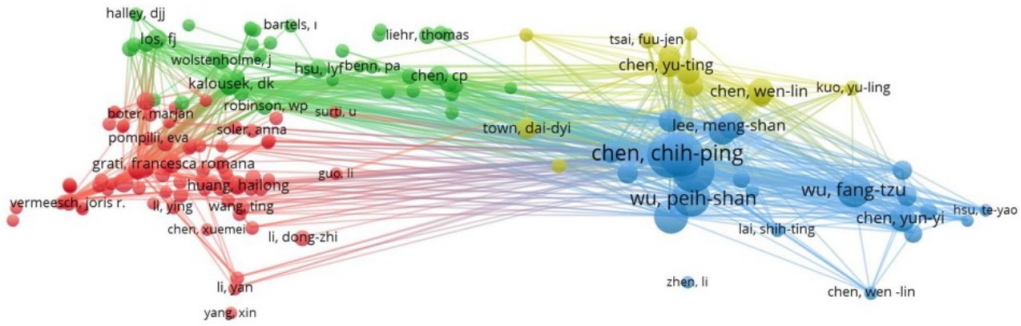

Figure 6: Network visualization map of co-citation analysis of active authors

cations were produced in the USA (Figure 3). We found that the productivity of African countries and Central Asian Countries countries are very low on prenatal mosaicism. The most productive countries were in North America and Europe (Figure 4).

Productivity of Authors and Institutions

We compared authors' productivity, institutions, and H-Index. Chen CP, Ming Chi University Technology, Taiwan was found most productive researcher. The 10 most productive authors and countries are presented in Table 3. We also compared the productivity of universities and organizations in the WoS database. The most productive organisation was the Mackay Memorial Hospital host 165 (7.7%) publications in the field of prenatal mosaicism. (Figure 5).

Authorship and Institutions Co-citation

Co-citation analysis has shown that there are 9932 authors investigating the issue of prenatal mosaicisim. Organizations that published at least 5 documents about prenatal mosaicisim and received 5 citations were classified, 176 out of a total of 2749 organizations were found to meet these requirements. Among these 176 organizations, the most active was determined as Mackay Memorial Hospital, Taiwan. Collaboration and citation collaboration were observed between Mackay Memorial Hospital, National Taiwan University and National Yang Ming University. Organizations belonging to the European Union countries and USA were cooperating among themselves around the USA. (Figure 5).

Authors' collaborations were evaluated, a total of 9932 authors with at least 10 publications on perinatal mosaicism were separated. After this filtering, 44 active authors were identified, and their cooperation was evaluated among themselves. Collaboration clustering around 5 active authors was detected. Of these five writers Chen Chih Ping, Wang Wayseen and Grata Fancesca Romana were the most active and collaborative (Figure 6).

Articles written about prenatal mosaicism were reviewed and the most cited, average number of citations per year, authors and publishers were examined. The document by Bianchi DW M. Genome-Wide Fetal Aneuploidy Detection by Maternal Plasma DNA Sequencing was the first in terms of total number of citations and average number of citations per year (10). The 10 most cited articles are presented in Table 5. The citation relations between the articles were indicative of the tendencies of the publishers and the authors. When the citations of the articles were examined on a yearly basis, it was observed that the most cited articles were written between 2018-2020 (Figure 7).

Productivity of Journals

Journals containing publications on prenatal mosaicism were examined in terms of the number of publications and citations they received. Fifteen journals with the largest number of articles are presented in Table 6 with their publication numbers and impact factors. 864 journals publishing on prenatal mosaicism were examined, the 90 most active journals with at least 10 articles were found. It was observed that the Prenatal Diagnosis printed 19.8 % of the articles published on prenatal mosaicism. The 2023

impact factor of this journal is 2.7, and its effectiveness on genetics and heredity seems to be high (Figure 8).

International Collaboration

When the researches published by countries on prenatal diagnosis were examined, the most active country was determined as the USA. Collaborations of countries on research were also examined. The intersection point of all researcher countries was the USA. China, Taiwan, France and England were the countries that cooperated most with the USA (Figure 9). A collaborative connection was formed around China. In this cluster Australia, Belgium and South Korea were also included. (Figure 9).

Table 1. Publication types of prenatal mosaicism literature between 1982-2023

Research Areas	Number of Publication	% of 2124
Article	1877	78.1
Review	202	8.4
Proceedings Paper	43	1.7
Letter	119	4.9
Editorial Material	47	3.4
Meeting Abstracts	73	3.1
Note	71	0.8
Book Chapter	22	0.5
Early Access	3	0.2
Corrections	5	0.1

Table 2. The top ten research areas of documents in prenatal mosaicism according to Web of Science database between 1982-2023

Research Areas	Number of Publication	% of 2124
Genetics Heredity	1194	56.5
Obstetrics and Gynecology	960	45.1
Reproductive Biology	96	4.5
Pediatrics	92	4.3
Biochemistry Molecular Biology	89	4.1
Medicine General Internal	88	4.1
Medicine Research Experimental	75	3.5
Cell Biology	50	2.1
Radiology Nuclear Medicine	46	1.9
Acoustics	41	1.6

Table 3. The first ten authors by record count in prenatal mosaicism literature between 1982-2023

Authors	Institution	Record Count	% of 2124	H-index
Chen CP	Ming Chi Univ Technol, Dept Mat Engn, New Taipei City 24301, Taiwan	164	7.7	16
Chern SR	MacKay Mem Hosp, Dept Med Res, Taipei, Taiwan	132	6.2	15
Wang W	MacKay Mem Hosp, Dept Med Res, Taipei, Taiwan	119	5.6	17
Wu PS	Gene Biodesign Co Ltd, Taipei, Taiwan	88	4.1	10
Chen SW	MacKay Mem Hosp, Dept Med Res, Taipei, Taiwan	78	3.6	10
Wu FT	MacKay Mem Hosp, Dept Med Res, Taipei, Taiwan	69	3.2	8
Lee CC	MacKay Mem Hosp, Dept Med Res, Taipei, Taiwan	58	2.7	13
Chen YY	MacKay Mem Hosp, Dept Med Res, Taipei, Taiwan	47	2.2	8
Pan CW	MacKay Mem Hosp, Dept Med Res, Taipei, Taiwan	45	2.1	9
Chen WL	MacKay Mem Hosp, Dept Med Res, Taipei, Taiwan	44	2.0	11

Mem: Memorial, Hosp: Hospital, Dept: Department, Med: Medicine, Res: Research

Table 4. The top ten funding organisations by number of prenatal mosaicism literature

Institutions	Number of Publication	% of 2124
Mackay Memorial Hospıtal Taipeı Taiwan	119	5.6
Ministry Of Science and Technology Taiwan	86	4.0
Unıted States Department of Health Human Services	81	3.8
National Institutes of Health USA	76	3.5
National Natural Science Foundation Of China	47	2.2
Spanish Government	30	1.4
Eunice Kennedy Shriver National Institute of Child Health and Human Development	29	1.3
National Key Research Devalopment Program of China	25	1.1
National Science and Technology Council Taıwan	24	1.1
The National Institute of General Medical Sciences	11	0.5

USA: United States of America

Trend Topics

While reviewing the articles on prenatal mosaicism, we also identified new trends and topics in this regard. Frequently used keywords in the articles on prenatal mosaicism, the frequency of these words and their interrelationships would provide insight into new research topics. The words genetic counselling, prenatal diagnosis and genetic counselling identified the subjects with the strongest association with prenatal diagnosis. Aneuploidiy, trisomy, non-invasive prenatal testing, placenta, QF-PCR, were found to be the types of clinical and laboratory conditions that had the strongest relationship with prenatal mosaicism. The most frequently repeated clinical analyzes in the articles on prenatal mosaicism were observed as prenatal screening and non-invasive prenatal testing (Figure 10).

Table 5. The top ten most cited manuscripts about prenatal mosaicism

No	Article	Author	Journal Name/ Published	TC	ACY
1	Genome-Wide Fetal Aneuploidy Detection by Maternal Plasma DNA Sequencing	Bianchi DW, Platt LD, Goldberg JD, Abuhamad AZ, Sehnert AJ et al.	Obstet Gynecol, 2012	493	37.9
2	Somatic Mutation, Genomic Variation, and Neurological Disease	Poduri A, Evrony GD, Cai X, Walsh CA.	Science, 2013	410	34.1
3	Fanconi Anemia and Its Diagnosis	Auerbach AD	Mutation Research, 2009	408	25.5
4	Neurofibromatosis Type 2 (NF2): A Clinical and Molecular Review	Evans DG	Orphanet Journal of Rare Diseases, 2009	337	21.6
5	Mechanisms of mosaicism, chimerism and uniparental disomy identified by single nucleotide polymorphism array analysis	Conlin LK, Thiel BD, Bonnemann CG, Medne L, Ernst LM, et al.	Human Molecular Genetics,2010	329	21.9
6	Prenatal testing in ICSI pregnancies: incidence of chromosomal anomalies in 1586 karyotypes and relation to sperm parameters	Bonduelle M, Van Assche E, Joris H, Keymolen K, Devroey P et al.	Human Reproduction, 2002	312	13.5
7	Chromosomal mosaicism confined to the placenta in human conceptions	Kalousek DK, Dill FJ.	Science,1988	307	7.5
8	Cytogenetic results from the U.S. Collaborative Study on CVS	Ledbetter DH, Zachary JM, Simpson JL, Golbus MS, Pergament E et al.	Prenatal Diagnosis, 1992	285	8.6
9	Non-invasive prenatal testing for trisomies 21, 18 and 13: clinical experience from 146,958 pregnancies	Zhang H, Gao Y, Jiang F, Fu M, Yuan Y, et al.	Ultrasound in Obstetrics & Gynecology, 2015	261	26.1
10	Non-invasive prenatal testing for aneuploidy: current status and future prospects.	Benn P, Cuckle H, Pergament E	Ultrasound in Obstetrics & Gynecology, 2015	230	10.55

TC: Total Citation; ACY: Average Citations per Year

Table 6. The first fifteen journal by number of publications and citations on prenatal mosaicism

Journal Name	No	% of 2124	JIF
Prenatal Diagnosis	421	19.8	2.7
Taiwanese Journal of Obstetrics Gynecology	163	7.6	1.9
American Journal of Medical Genetics, Part A	117	5.5	1.7
American Journal of Medical Genetics	87	4.1	3.6
Molecular Cytogenetics	52	2.4	3.5
Journal of Medical Genetics	43	2.0	3.5
Clinical Genetics	41	1.9	2.9
American Journal of Human Genetics	35	1.6	10.5
European Journal of Human Genetics	33	1.5	5.3
Frontıers In Genetıcs	32	1.5	1.1
Fetal Diagnosıs and Therapy	31	1.4	1.6
Ultrasound in Obstetrics Gynecology	29	1.3	6.1
European Journal of Medical Genetics	27	1.2	1.6
Genetics in Medicine	23	1.1	8.8
Cytogenetic and Genome Research	22	1.0	1.7
No: Number of publications; JIF: Journal Impact Factor			

DISCUSSION

Mosaicism in Amniocentesis

Amniotic fluid cells originate from various fetal anatomic organs, such as the reproductive system, respiratory apparatus, and epithelial system. Samples may also contain fragments of maternal tissue, maternal blood, and placental or membrane cells. In routine karyotyping, mosaicisms can sometimes be limited to a single cell or culture and are often disregarded as cell culture or chromosome preparation artifacts ("pseudomonasity") (11).

Mosaicism can be detected at different stages of cytogenetic evaluation in amniocentesis. Most often this is considered as an artifact in cell culture (12). Another remarkable frequency of mosaic cells detected in amniocentesis is the detection of two or more colonies. These cells can be observed in culture or in a single sample. However, this should not be observed in different cultures of the same amniocentesis (13). The more important situation in which mosaic cells are detected is the presence of two or more cells with the same chromosome abnormality distributed in two or more independent cultures. It is likely that these cases represent true mosaicism present in fetal tissues (1).

Mosaicism in Chorionic Villus Sampling

In the early stages of fertilization, tissue and organ differentiation begins and during this time, the development of extra-embryonic tissues occurs (14). It is thought that errors occurring during mitosis of extra-embryonic cells may also be related to mosaicism and that this probability is higher than embryonic cell lines (15). Chorionic villi consist of two layers. There is a mesenchymal area inside and a trophoblastic layer outside. It is thought that the mesenchymal layer is more closely related to embryo development (16).

Cells obtained by CVS may be taken from placental or fetal cell lines. The obtained material can be examined cytogenetically by direct cell preparation or by cell culture

and multiplication. When placental mosaicism and fetal mosaicism cannot be distinguished, confirmation by amniocentesis or cordocentesis may be necessary. Cases where confirmation cannot be made are called limited placental mosaicism. Approximately 87% of mosaicism detected by CVS is limited to the placenta, while the rest is true fetal mosaicism (17). The karyotype obtained by amniocentesis analyzes the genetic structure of a heterogeneous group of cells derived from embryonic ectoderm and amniotic ectoderm and mesoderm and should be interpreted accordingly. Therefore, the possibility of missing a hidden mosaic line even with high cell rates in amniocentesis should not be ignored.

Mosaicism present in both cytotrophoblast and mesenchyme is mainly of meiotic origin and the absence of any normal cells in a layer also increases the probability of meiotic origin of the abnormality (18,19). Fluorescence in situ hybridization (FISH) can be used as a laboratory method with higher reliability in amniocentesis evaluation when the diagnosis cannot be confirmed by CVS cytogenetics. In cases where amniocentesis results are controversial and fetal blood sample is evaluated by cordocentesis, FISH is useful in genetic counseling due to its advantage of providing rapid results. FISH studies using probes specific to the relevant chromosome offer the advantage of direct and rapid evaluation of large numbers of uncultured cells and at the same time elimination of artefacts caused by cell culture.

Laboratory Techniques in Diagnosis of Mosaicism

For the diagnosis of chromosomal mosaicism in prenatal diagnosis, FISH, Quantitative Fluorescence Polymer Chain Reaction (QF-PCR) and various chromosomal microarray tests (Array Comparative Genomic Hybridization-aCGH, Single Nucleotide Polymorphism-SNP array) can be used. Each test may have advantages and disadvantages over the other. FISH analysis using a subset of specific probes for the most common chromosomal aneuploidies (13, 18, 21, X and Y) can be used to evaluate the presence of these conditions in homogeneous or mosaic form in prenatal samples.

FISH eliminates the contamination and time disadvantages of cell culture and provides rapid evaluation. It can also provide high reliability results without the need for the metaphase cell counting step required to detect low mosaic levels (20). In addition to its diagnostic success, the FISH technique also has several limitations. The first of these is the inadequacy of hybridization. This may be related to the inadequacy of the obtained material or the preparation of the probe. The second limitation is the contamination of maternal tissue and blood during the acquisition of the material. Another limitation is that the results are obtained only with the relevant probe and narrow-spectrum data are obtained. Therefore, in order to use the correct probe, the clinician should be aware of the prenatal conditions that he strongly suspects (21).

QF-PCR is a DNA-based test for the detection of common aneuploidies by amplification of repeat sequences at specific polymorphic loci. It is a highly reliable test for the diagnosis of aneuploidy and a powerful test for the detection of mosaicism and maternal contamination (22). During QF-PCR, an allelic pattern consisting of two identical repeat sites within the same chromosomal region is diagnostic of two copies of the target region, whereas three peaks or two peaks in a 2:1 ratio within the same chromosomal region are indicative of trisomy for the target region. The detection of maternal cell contamination, triploidy and mosaicism at a rate as low as 15% is an important advantage of these techniques. During this test, maternal contamination can be detected by comparing maternal and fetal alleles (23, 24).

Multiplex Ligation-Based Probe Amplification (MLPA) tests, which are PCR-based and less labor intensive than FISH and less expensive, can detect trisomies and mosaicism. In MLPA, the free ends of the probes are complementary to the primers in the target regions. MLPA is designed to determine the relative abundance of up to 40 to 45 nucleic acid targets. The use of MLPA for prenatal diagnosis includes the detection of aneuploidies, common microdeletion syndromes, and subtelomeric copy number alterations, the identification of marker chromosomes, and the detection of familial copy number alterations in single genes (25). The success of MLPA in the diagnosis of mosaicism may vary depending on the prenatal situation. MLPA has the ability to use multiple probes for each chromosome. When the fetal sex is male, the possibility of maternal contamination can be determined by X chromosome detection. However, the ability to detect triplolypsies in female fetuses is limited. The recommended approach to examine the possibility of maternal contamination in amniotic fluid samples is to determine fetal hemoglobin (Hb) levels in samples with macroscopic red cell contamination, and these are tested

only in samples with fetal Hb levels of 85% or greater by MLPA (26).

Another test that can be used in prenatal diagnosis is microarray tests. In the microarray method, the strength of the signals from the probes is automatically determined to provide information about the copy number of that region of the genome. Microarray analysis can detect aneuploidies of all 23 chromosomes as well as submicroscopic copy number abnormalities (such as microdeletions and microduplications) throughout the genome (27). Genomic alterations can be detected reproducibly at appropriate weeks of pregnancy with high resolution. It can also detect chromosomal abnormalities that routine prenatal chromosomal assessment methods cannot detect and copy number abnormalities of undetermined clinical significance (28,29). It may be difficult to detect mosaicism below a certain level (~10-20%) with microarray analysis. This limitation is not specific to Chromosomal Microarray Analysis and is in fact a general difficulty for all genetic tests. When microarray analysis is performed with cell culture materials for prenatal diagnosis, the probability of detecting mosaicism in microarray analysis may be higher in samples obtained without direct culture, since the probability of proliferation of healthy cell lines is high (30). However, when microarray analysis is performed on fresh CVS, feto-placental mosaicism, which is present in approximately 1-2% of all samples, may pose analytical difficulties since the differentiation in cytotrophoblastic and mesenchymal tissue is lost separately when DNA is extracted. Detection of mosaicism with limited copy number changes in cytotrophoblasts on microarray may pose diagnostic difficulties (31).

Mosaicism in Non-Invasive Prenatal Test (NIPT) using Cell Free DNA (cfDNA)

NIPT is based on the detection of cfDNA fragments in the maternal peripheral blood. cfDNA fragments are released during a series of cellular processes including apoptosis, necrosis and microparticle secretion from all organs. These fragments may originate from maternal cells or from the destruction of cytotrophoblasts. cfDNA can be detected in maternal peripheral blood from the fifth week of gestation and decreases to undetectable levels a few hours after birth (32, 33). Current NIPT procedures cannot be performed without modern molecular technologies (e.g. next-generation sequencing). This method can be used to screen for Trisomies 13, 18 and 21 as well as sex chromosome aneuploidy and single-gene disorders. Measurement of the fetal cfDNA fraction in maternal blood is necessary for the accuracy and quality of the test. It is important to ensure that placental cfDNA is sufficiently measurable in maternal plasma to produce a meaningful result. Early gestational weeks, increasing parity, maternal age, vitamin B12 deficiency, active autoimmune diseases and maternal obesity are identified as some of the factors that reduce the detectable fetal fraction (34, 35).

In most cases where NIPT is performed or the test is performed, trophoblastic DNA is identical to DNA in fetal tissues. Although highly sensitive and specific, an important limitation is pregnancies with placental confinement mosaicism (36). In addition, biological causes such as maternal malignancy, fetoplacental mosaicism, or non-identical vanishing twins may also cause incorrect estimation of fetal status (37). Karyotype studies evaluating the reliability of the test have shown that NIPT may give false-positive results in 1/1100 of fetuses with postnatal normal genomes and false-negative results in 1/61. The above reasons may play a role in misleading results. It should be kept in mind that especially in cases where the karyotype of the placenta is misleading, there may be different karyotypic anomalies in different regions of the placenta itself (38, 39).

The most recent development in prenatal genetic evaluation is observed as the definition of NIPT and microarray analysis methods. The current trend in prenatal testing is characterized by a major shift from invasive sampling to the use of noninvasive or less invasive peripheral blood testing. Today, NIPT is observed to be the most likely candidate to replace invasive testing. Nevertheless, the technique continues to require validation with invasive testing, especially in cases where the diagnosis can be variable, such as mosaicism, due to the disadvantage of cell dominance from the placental area. Even in cases where invasive testing is used, the diagnosis of chromosomal mosaicism in the preimplantation period and prenatal stage in in vitro fertilization is full of uncertainties and many factors must be taken into account to establish the correct diagnosis.

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Abbreviations list

CVS: Chorionic Villus Sampling
PGT: Preimplantation Genetic Testing
MLPA: Multiplex Ligation-Based Probe Amplification
FISH: Fluorescence In Situ Hybridization

Ethics approval and consent to participate

The data presented in the study were obtained from publicly available search databases and did not require ethics committee approval.

Consent for publication

The research does not contain personal data and does not require consent.

Availability of data and materials

Data for the research can be obtained from the web of science database.

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Authors' contributions

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ORIGINAL ARTICLE

Preoperative Predictability of Bowel Resection in Incarcerated Inguinal Hernias

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Abstract

Background: Incarcerated inguinal hernias are among the most frequently performed surgeries in emergency settings. In cases of strangulation, bowel and omentum resection may be necessary, which alters the nature of the surgery. This study aimed to investigate whether bowel resection in incarcerated inguinal hernias can be predicted using preoperative laboratory tests

Methods: This single-center, retrospective study reviewed patients who underwent surgery for incarcerated inguinal hernias at Ankara Bilkent City Hospital between 2019 and 2023. The patients' demographic characteristics, laboratory parameters, and operative notes were examined. Patients who underwent bowel resection were classified as Group 1, while those who did not undergo bowel resection were classified as Group 2. Differences in laboratory parameters between Group 1 and Group 2 were analyzed.

Results: Out of 154 patients included in the study, 32 (20.8%) were in Group 1, and 122 (79.2%) were in Group 2. There was no statistically significant difference in preoperative evaluations of WBC, NLR, LUC, LUC%, lactate, and RDW values for predicting strangulation and bowel resection (p=0.278; p=0.053; p=0.163; p=0.073; p=0.494; p=0.973). However, LDH levels were significantly higher in the group requiring bowel resection (p=0.033).

Conclusion: LDH levels can predict bowel resection in patients with incarcerated inguinal hernias preoperatively. Normal levels of other parameters do not rule out strangulation. This should be particularly noted in patients undergoing manual reduction.

Key words: Inguinal Hernia, Strangulation, LDH, Bowel Resection

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INTRODUCTION

Incarcerated inguinal hernias account for 9% of all inguinal hernias (1). An incarcerated inguinal hernia is a condition requiring emergency surgery, and the incarceration it causes can lead to obstruction and perforation, which may become life-threatening (2). Although elective inguinal hernia surgeries are performed with very low mortality rates (0.07%) (3), the mortality rate in emergency surgeries can rise up to 5% (3). The most significant factor contributing to this is the resection of incarcerated abdominal organs (2,3).

In incarcerated inguinal hernias, the reduction or absence of blood supply to the organ within the hernia sac is termed "strangulation," which may necessitate organ resection (4). The diagnosis of strangulation can be determined through physical examination, laboratory tests, and the presence of sonographic findings (5). During surgery, the decision for organ resection is based on the reversibility of ischemic conditions affecting the bowel or omentum. Laboratory tests used to predict the need for organ resection include white blood cell count (WBC), lactate, C-reactive protein (CRP), lymphocyte/CRP ratio, platelet/CRP ratio, neutrophil/lymphocyte ratio (NLR), and lactate dehydrogenase (LDH) (6–9). LDH is present in many cells throughout the body and is an enzyme essential for energy production. It is one of the parameters used to indicate tissue damage (10). Since tissue damage occurs in incarcerated hernias, LDH is utilized as a marker for tissue ischemia (10).

This study aimed to evaluate the predictability of organ resection in incarcerated inguinal hernias using preoperative laboratory tests. Specifically, it assessed whether the number and percentage of large unstained cell (LUC), a newly used inflammatory marker(11), are beneficial for this purpose, and investigated the success rates of other parameters in our series.

MATERIALS AND METHODS

Method

From April 2019 to December 2023, patients diagnosed with incarcerated hernia who underwent emergency surgery at the General Surgery Clinic of Ankara Bilkent City Hospital were retrospectively reviewed. Totally 179 patients rewieved but 25 patients were excluded due to the inaccessibility of electronic data or insufficient information in their medical records. The study included 154 patients who were admitted to the clinic and underwent surgical intervention for incarcerated hernia, all of whom were over 18 years old. Data was collected from the patients' medical records, including demographic and clinical characteristics, operation notes (presence of organ resection), and laboratory parameters (WBC, Neutrophil count, Lymphocyte count, NLR, LDH, LUC, LUC%, Red Cell Distribution Width - RDW, Lactate). Based on the surgical notes (intraoperative exploration), patients were categorized into two groups: Group 1, consisting of those with strangulation and organ resection, and Group 2, consisting of those with incarceration but with a viable intestine showing signs of normal/edematous/warm application and no organ resection.

Patients with malignancies, rheumatological diseases, pregnant women, those under 18 years of age, and those with inaccessible electronic records were excluded from the study. Additionally, those with any organ other than the bowel (omentum, ovary, etc.) in the incarcerated hernia sac were not included in the study.

The medical research and ethics committee of Ankara Bilkent City Hospital Hospital approved the study (reference number: TABED 2-24-554).

Statistics

Statistical analyses were performed using IBM Statistical Package for the Social Sciences version 26 (IBM SPSS Corp.; Armonk, NY, USA). Numerical data were presented as percentages (%). The normality of data distribution was assessed using the Kolmogorov-Smirnov test. Continuous variables showing normal distribution were described using mean ± standard deviation, while data not following a normal distribution were expressed as median (range). For continuous variables with normal distribution, the Student's T test was used; for those without normal distribution, the Mann-Whitney U test was employed. To compare categorical variables, Pearson's chi-square test or Fisher's exact test was applied. The area under the curve (AUC) analysis was conducted for LDH values. A p-value of <0.05 was considered statistically significant.

RESULTS

The study included 154 patients, with a mean age of 68 ± 15 years. Among these, 30 (19.5%) were female and 124 (80.5%) were male. According to the surgical notes, strangulation was observed in 32 (20.8%) patients, who underwent organ resection, while no strangulation was detected in 122 (79.2%) patients, who did not undergo organ resection.

In Group 1 the mean age was 72 ± 13 years, with 11 (34.4%) females and 21 (65.6%) males. In Group 2, the mean age was 67 ± 16 years, with 19 (15.6%) females and 103 (84.4%) males. Laboratory values for both groups are shown in Table 1. No statistically significant differences were found in the preoperative evaluation of WBC, NLR, LUC, LUC%, lactate, and RDW in relation to strangulation or organ resection ($p = 0.278$; $p = 0.053$; $p = 0.163$; $p = 0.073$; $p = 0.494$; $p = 0.973$). However, the LDH value was found to be significantly higher in the group undergoing organ resection ($p = 0.033$) (Table 1).

In the receiver operating characteristic (ROC) analysis for LDH to identify patients requiring organ resection, the area under the curve (AUC) was found to be 0.626 (95% confidence interval: 0.517-0.735, $p < 0.024$) [Figure 1] [Table 2]. The test's sensitivity was 84.38%, and specificity was 33.61%, with a positive predictive value of 25.0% and a negative predictive value of 89.13%.

DISCUSSION

Incarcerated hernia surgeries are performed almost as frequently as appendectomies (12). Inguinal hernia surgeries account for 75% of these emergency hernia operations (13). As expected, the mortality rates of patients operated under emergency conditions are high (3), and organ resection plays a significant role in this. Therefore, predicting organ resection in incarcerated inguinal hernias in advance is important both for selecting patients suitable for the reduction procedure and for perioperative management. In our series, a significant relationship was found between only elevated preoperative LDH levels and organ resection.

In patients presenting with incarcerated inguinal hernia where bowel ischemia is not suspected, manual reduction is one of the recommended treatment options (14). However, differentiating between pain due to bowel ischemia and hernia-related pain is not always possible. Additionally, there are several laboratory parameters thought to predict ischemia in inguinal hernias, but there is no consensus, and numerous studies have been

Table 1. Comparison of Demographic and Laboratory Characteristics Between Groups

Characteristics	Group 1 N (%) *	Group 2 N (%) *	p-value
Age	72±13	67±16	0.088§
Gender			0.017£
- Female	11 (34.4)	19 (15.6)	
- Male	21 (65.6)	103 (84.4)	
WBC (x10⁹/L)	11.91 (32.6-4.35)	9.83 (31.53-4.24)	0.278§
RDW (%)	14.5 (61.1-12.5)	14.0 (60.6-1.6)	0.973§
NLR	6.95 (129.2-1.33)	5.3 (60.9-0.1)	0.053§
LUC (x10⁹/L)	0.1 (0.26-0.0)	0.12 (0.9-0.0)	0.163§
LUC %	1.0 (2.6-0.2)	1.2 (25.9-0.3)	0.073§
Lactate	1.69 (5.96-0.85)	1.65 (4.83-0.55)	0.494§
LDH (U/L)	252 (409-170)	230 (753-146)	0.033§

* Minimum and maximum values are shown for continuous variables. § Mann Whitney U test; £ Chi-Square Test

(WBC: White Blood Cell, RDW: Red Cell Distribution Width, NLR: Neutrophil Lymphocyte Ratio, LUC: Large Unstained Cells, LDH: Lactate Dehydrogenase)

Table 2. Diagnostic Performance of Risk Factor (LDH)					
Risk Factor	**AUC (%95 CI)**	**Cut-off Value**	**p-value**	**Sensitivity**	**Specificity**
LDH	0.626 (0.517-0.735)	204	<0.024	84.38	33.61
(LDH: Lactate Dehydrogenase, AUC: Area Under Curve, CI: Confidence Interval)					

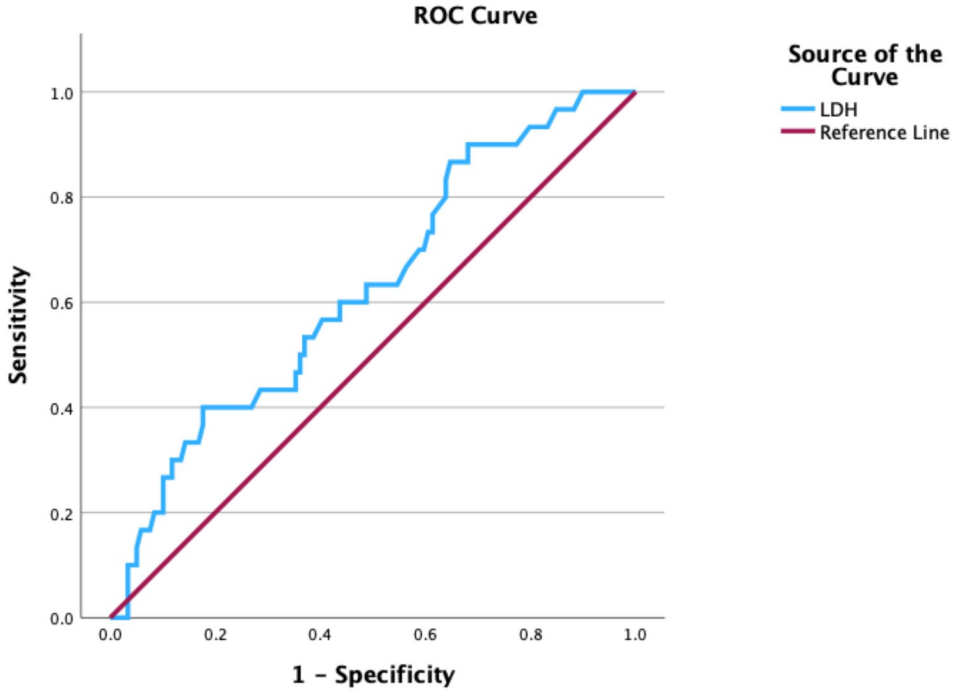

Figure 1: ROC Analysis for Small Bowel Resection

published on the subject (10). As in our study, LDH has previously been reported to predict bowel resection by Xie et al. (15). However, in this study, WBC and NLR, which were not significant in our study, were shown to predict organ resection. In another study, Kadıoğlu et al. (16) reported a relationship between ischemia-modified albumin and organ resection. In a further study by Peksöz et al. (17), WBC, NLR, C-reactive protein (CRP), and the lymphocyte-CRP ratio (LCR) were found to be associated with organ resection. Overall, as seen in the aforementioned studies, there is a relationship between elevated inflammatory markers and organ resection. This can be attributed to the progression of ischemia, leading to bacterial translocation and the onset of an infectious process. The insignificance of these parameters in our study could be related to the clinical approach of avoiding manual reduction in incarcerated hernias and performing surgery as soon as possible from the time of diagnosis.

Another laboratory parameter frequently used to detect bowel ischemia and indicative of impaired tissue oxygenation is lactate. Lactate is the final product of anaerobic glycolysis, and its elevation indicates inadequate oxygen utilization in the tissue (18). It is commonly used in daily practice for conditions such as myocardial infarction, shock, and critically ill patients in intensive care

units (10). Additionally, lactate has been reported to predict mortality in septic patients (19). Given this, it would not be incorrect to consider lactate as an inflammatory marker. Indeed, in a study by Şahin et al. (10), which examined 67 patients with incarcerated hernias, elevated lactate, along with WBC and NLR, was observed in cases requiring small bowel resection. Therefore, these parameters not only indicate intestinal ischemia but, as mentioned above, may also reflect bacterial translocation. In connection with this, Xie et al. (15) demonstrated that inflammatory parameters and lactate did not rise in patients with strangulated omentum who underwent omentum resection, likely due to the absence of bacterial translocation caused by omental infarction.

In patients presenting with incarcerated inguinal hernia, the rate of bowel resection is 14% within the first 12 hours, rising to 50% after 12 hours (16). Considering the complications caused by bacterial translocation in addition to bowel ischemia in strangulated cases, early intervention is crucial. Particularly in patients who undergo manual reduction, low levels of lactate, WBC, and CRP should not be assumed to rule out strangulation. In this patient group, routine assessment of LDH in addition to these parameters could be beneficial.

LUC has recently been used as an inflammatory parameter. A high LUC rate indicates bone marrow activation(11). In our study, the LUC value was expected to be high in strangulated patients because the inflammatory process was greater in non-strangulated patients, but it was not found to be statistically significant. This suggests that LUC may be a marker of inflammation and does not indicate the severity of infection.

The most significant limitation of this study is its retrospective nature, as data were obtained from the electronic information system, which may result in incomplete or insufficient information. Another limitation is that, in our study, the prediction of small bowel resection was based on laboratory parameters, while radiological imaging is frequently used to assess ischemia in these patients.

In conclusion, LDH levels predict bowel resection in incarcerated inguinal hernias. Due to NPV of LDH; low LDH value is ruled out from strangulation. In particular, the absence of high lactate, WBC, and CRP values in jailed individuals who undergo manual reduction should not be interpreted as a lack of bowel ischemia.

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Abbreviations list

WBC: White blood cell count
NLR: Neutrophil-lymphocyte ratio
LUC: Large unstained cells
LUC%: Percentage of large unstained cells
RDW: Red cell distribution width
LDH: Lactate dehydrogenase
CRP: C-reactive protein
AUC: Area under the curve
CI: Confidence interval
NPV: Negative Predictive Value

Ethics approval and consent to participate

This study was approved by Ankara Bilkent City Hospital Hospital approved the study (Date: 02.10.2024 Number: TABED 2-24-554).

Consent for publication

Our study is based on content analysis of the document. It does not contain any personal data.

Availability of data and materials

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Competing interests

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ORIGINAL ARTICLE

Reflections of Simulation-based Education on the National Core Curriculum of Turkey: A Content Analysis

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Abstract

Background: Simulation-based education prepares medical students to interact with real patients by resembling real environments. There are a variety of methods in simulation-based education from low-fidelity to high-fidelity, and from basic task trainers to complicated mixed methods. Although it is not specified whether a topic in the national core curriculum is related to simulation-based education or not, the national core curriculum draws a general approach for selecting appropriate learning activities in undergraduate medical education. This study aims to reveal adequate simulation methods for the topics in the national core curriculum and to present a tool for simulation method selection criteria.

Method: A content analysis was conducted in a qualitative design. The literature review was conducted to deeply understand the principles of simulation-based education and was used as a guide to evaluate the topics in the national core curriculum. The content analysis of the National Core Curriculum-2020 was conducted to structure a tool for the simulation method selection criteria in undergraduate medical education.

Results: Several simulation methods can be used according to the utilization of medical schools. A total of 20 number main skills were identified as suitable for simulation-based education and methods were matched with these skills with at least three alternatives.

Conclusion: The tool we conducted covers basic to complicated simulation methods that every medical school can adopt according to its facilities. We recommend our tool as a guide in selecting adequate resources while developing simulation-based education in undergraduate medical education.

Keywords: simulation-based education, medical education, medical school

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INTRODUCTION

Simulation-based education prepares medical students to interact with real patients by resembling real environments (1). Simulation-based education has the highest impact when it is structured as a part of the main curriculum. So, it is recommended not to plan simulation-based training as an individual activity but to plan it as an integrated activity (1). To succeed in structuring an integrated curriculum, the principles of the simulation, as well as the materials and methods related to it, should be well understood by curriculum developers.

There are a variety of methods in simulation-based education from low-fidelity to high-fidelity, and from basic task trainers to wearable mixed methods. There are extended reality which are augmented reality (AR) and metaverse/virtual reality (VR) and traditional simulationmethods which are high/low-fidelity simulators (2).

Traditional simulation is defined as simulating a patient-doctor encounter with the help of mannequins and simulated participants (SPs) in the real-like world. There are low-fidelity task trainers, medium and high-fidelity mannequins, and high-fidelity simulated participants (3). Moulage, which is defined as a make-up to make the scenario more realistic, contributes to improving the reality of the simulation. Moulage can be a small scar to a deep wound according to the scenario. It can be applied to either an SP or a mannequin (4). In addition to moulage, facilitators which are defined as the individuals who are the components of the simulation with determined tasks, contribute to creating a real-like environment (5).

High-fidelity mannequins are well-known for their contribution to learning by providing experience and improving self-confidence (6, 7). They can be used for clinical decision-making training and clinical skills training (8, 9). High-fidelity simulators are successful in simulating doctor-patient encounter with their vital responses and changeable findings according to the scenario (10). One of the main limitations of high-fidelity mannequins is they are quite expensive and after repeated applications, they eventually need part replacement (11).

Simulated participant methodology is recommended when the simulation targets competencies related to patient interaction. So, the simulated participant methodology is mostly used for communication skills training. In addition, the SP methodology is one of the most enriching methods with real human existence and its modifiability (12). Because they are real humans, SP methodology may require the highest attention from educators. The engagement of the SPs' should be supported to improve the quality of the simulation (13).

Low-fidelity is mostly used in technical skills training. Recent literature showed that using low-fidelity simulation is sufficient enough to gain technical skills rather than theoretical training + low-fidelity simulation (14). Also, low-fidelity simulators found that they improve the quality of classic training by improving active learning (15). A study showed that simulation conducted with low-fidelity simulators would cause a lower level of stress compared to high-fidelity simulators (16). Yet, in a meta-analysis, high-fidelity simulations were found more effective in learning compared to low-fidelity simulations (17). Still, low-fidelity simulators are accepted as they're sufficient for technical skills training (18, 19). Medium-fidelity mannequins provide reality feeling less than high-fidelity mannequins and more than low-fidelity mannequins. They are low cost mannequins compared to high-fidelity ones (3). Disadvantages of the traditional simulation can be stated as they require more staff, a specific area, and a specific time to apply (11).

Task trainers, which are low-fidelity simulators, are recommended for technical skills training because of their repeatability and cost-effectiveness (3, 20). New technologies provide opportunities for using task trainers more effectively and especially 3D prints play a major role in building replacement parts (21, 22). Not only they are cost-effective but also, they are more accessible too. So, task trainers can be seen as the first step of simulation-based education.

Virtual reality is described as the creation of a whole environment that is needed for simulation training and studying in this created world (metaverse) by tools like headsets or gloves. Different from VR, AR adds some digital data into the real environment (23). One of the main advantages of VR is that almost anything can be added to it. For example, VR can simulate like you're in an emergency room or a disaster area (24). It can allow you to operate a patient (25) in addition to communication, and even you can use a microscope in a VR setting (26). Another advantage of VR is that it is more cost-effective compared to traditional simulators because of its accessibility and feasibility (11). Although VR has some limitations, especially in performing technical skills, it can still be adopted by surgical trainees as a preparatory tool (25).

Hybrid method is defined as using together two different traditional simulation methods in the same session (27). Wearable simulators are highly improved versions of the hybrid method and they're more cost-effective than high-fidelity simulators (28, 29). Wearable simulators provide the closest real patient interaction by their use with simulated participants (28). Mixed method is defined as using together at least two different simulation methods and one of them should be VR or AR (23).

Recent literature mainly focuses on the impact of VR training in medical education (25, 30-32). In a comparison of VR to traditional simulation with high-fidelity mannequins, students stated that VR is a good opportunity to prepare for high-fidelity simulation in technical skills, however, the sickness and dizziness caused by VR limits the use of VR (32). Although they stated sickness because of VR, the participants expressed VR as more enjoyable and fun compared with high-fidelity simulation (31, 32). Among the mixed methods, the integration of VR with 3D hand animation was the most notable method that resembles real environments (33). Another VR+ 3D model was used for percutaneous renal access and it prevents participants from real radiation that traditional simulation (34). Considering most of the study targeted triage, VR or AR presented as alternative methods to traditional simulation in disaster management (24). The common agreement on VR use is improving and assessing the clinical decision-making skills of the participants (32, 35, 36). It should be noted that VR is relatively a new method and to evaluate its effectiveness, the participants need to be well prepared for the method and need to have sufficient experience to prevent the results from the bias of being a new method.

Augmented reality is not as popular as VR in medical education, and it is usually used as an alternative to VR. There are limited studies on AR and one of them suggested that AR would work more useful if seniors use it because of its decompensated environment (37). The disadvantage of AR is that it adds things to the real environment. So, it is not cost-effective because it still needs traditional environments (23).

The effectiveness of simulation-based education depends on how well it is conducted and used (1). The curriculum developers should have a clear understanding of aims and learning outcomes to select appropriate learning activities. The national core curriculum (NCC)-2020 in Turkey is recommended for use as a guide while developing undergraduate medical education (38). The National Core Curriculum-2020 contributes to an understanding of aims and learning outcomes in Turkey. It is known that technology-enhanced methods are superior to traditional teaching however, the use of simulation is limited for medical students compared with nursing students and residents (36). So, this field continues to improve for undergraduate medical education. This study aims to reveal adequate simulation methods for the topics in the National Core Curriculum-2020 and to present a tool for the selection of the appropriate simulation method.

Research questions:

1- What are the reflections of the simulation-based education in the National Core Curriculum-2020 in Turkey?

2- How can the National Core Curriculum-2020 enlighten the program developers for structuring a simulation-based education?

MATERIALS AND METHODS

Constructivism, which is defined as the worldview we give the meaning of the world, was adopted to conduct the study. The use of constructivism in the research methodology allows researchers to express their understanding of the data in accordance with their background (39). So, it is important to know the background of the researchers to clearly understand the study. In our study, one researcher was a medical educator with the lens of a theoretical background for simulation-based education and the second researcher was an experienced physician and also a senior resident in the Department of Emergency Medicine with the lens of a practical background of simulation-based education. These different perspectives of the researchers contributed to the richness of the results.

The literature review was conducted to deeply understand the principles of simulation-based education and was used as a guide to investigate the topics in the national core curriculum. The content analysis of the NCC-2020 was conducted to structure a tool for the simulation method selection criteria in undergraduate medical education. The Standards for Reporting Qualitative Research (SRQR) checklist was followed to ensure the quality of the study.

The National Core Curriculum is the main document for medical schools to ensure the quality of undergraduate medical education. The National Core Curriculum was first developed in 2000 to conduct a framework for the medical schools in Turkey. Its first revision was completed in 2014 after the commission of the deans of medical schools had been structured. The current version of the NCC was finalized in 2020 and it is agreed that all medical schools should structure their undergraduate medical curriculum according to the NCC (38). The National Core Curriculum Working Group is still working on the upcoming version of the NCC. So, the version of 2020 is still a valid and valuable instrument to follow. There are mainly three sections in the NCC-2020: 1- the competencies and sub-competencies, 2- the content of the competencies, and 3- the behavioral and social sciences and humanities. This study focuses on section two -which involves the symptoms/findings/situations, the core diseases/problems, and the basic medical practices- and section three in accordance with competencies and sub-competencies in section one (38).

The simulation methods were categorized according to their usage patterns rather than their fidelity level. Cost-effectiveness was the second criterion while considering a method for a topic. Finally, the methods that threaten the safety of the participants were considered as a last alternative. Familiarity with the method was not considered as a criterion because different faculty members could have different experiences with simulation methods. So, there is a need for training trainer programs repeatedly to ensure that all faculty members have the same level of knowledge and skills for the selected method.

Two researchers independently analysed the National Core Curriculum (NCC)-2020 and evaluated the topics relevant to simulation-based education. After investigating the NCC-2020 independently, they met repeatedly to get to a consensus about the topics they considered adequate for simulation-based education. Then they matched the simulation methods for each topic in the NCC-2020 independently. Finally, they met repeatedly to get to a consensus on the order of the alternatives for each topic. Three expert opinions were taken for the appropriateness of the simulation method for each topic presented in the tool. Table 1 shows the details of the tool.

The ethical approval was not applicable to this study based on the content analysis methodology.

RESULTS

There are technical and non-technical competencies which can be provided by simulation-based education. Several methods can be used according to the utilization of medical schools. A total of 20 number main skills were identified as suitable for simulation-based education and methods were matched with these skills with at least three alternatives. Table 1 shows the alternatives for selecting the adequate method.

Clinical decision-making was determined in the first and second sections of the NCC-2020. To diagnose a symptom/finding/situation adequately, clinical decision-making skills should be used. There were 141 symptoms/findings/situations and 342 core diseases/problems in NCC-2020. Each of them can be structured by simulation-based education in addition to theoretical education. Clinical decision-making skills are considered to be structured in the same simulation methods. So, there is only one clinical decision-making line in Table 1 which represents all of the clinical decision-making situations.

Related Competency in National Core Curriculum	Main skill	Recommended Simulation Method 1	Recommended Simulation Method 2	Recommended Simulation Method 3	Level of medical students
Medical expert Competency 1	Clinical reasoning	Wearable simulator + simulated participant	High-fidelity mannequin	Virtual reality	Year 3,4,5,6
	Clinical skills -History taking	Simulated participant with or without wearable simulator	High-fidelity mannequins	Virtual reality	Year 1,2,3,4
	Clinical skills -Physical examination	Simulated participant with or without wearable simulator	High-fidelity mannequins	Task trainers with or without virtual reality	Year 3,4,5,6
	Clinical skills -Recording and reporting	Medium/Low fidelity mannequin and facilitator	Simulated participant with/without facilitator	Virtual reality	Year 3,4,5,6
	Clinical skills -Applications about laboratory	Simulated participant with/without facilitator	Medium/Low fidelity mannequin and facilitator	Virtual reality	Year 3,4,5,6
	Clinical skills -Invasive applications	Medium/Low fidelity mannequin and facilitator	Wearable simulator + simulated participant	High-fidelity mannequins	Year 3,4,5,6
	Clinical skills -Noninvasive applications	Simulated participant with or without wearable simulator	High fidelity mannequin and facilitator	Virtual reality	Year 3,4,5,6
	Clinical skills -Preventative medicine	Simulated participant	High fidelity simulator with voice response	Virtual reality	Year 3,4,5,6
	Clinical skills -Healthiness	Simulated participant	Medium/Low fidelity mannequin and facilitator	Virtual reality	Year 3,4,5,6
	Clinical skills -Scanning	Simulated participant	Medium/Low fidelity mannequin and facilitator	Virtual reality	Year 3,4,5,6
Ethics and professionalism Competency 2	Apply good medical practices	Simulated participant	High fidelity mannequin with voice response	Virtual reality	Year 4,5,6
	Fulfils her/his duties within legal rights and liabilities	Medium/Low fidelity mannequin and facilitator	Simulated participant with/without facilitator	Virtual reality	Year 4,5,6
Health advocate Competency 3	Manages the process (healthcare service, training, and supervising the individuals and community) for improving health.	Medium/Low fidelity mannequin and facilitator	Simulated participant with/without facilitator	Virtual reality	Year 4,5,6

Leader-Manager Competency 4	Shows adequate leadership	Simulated participant and facilitators	Medium / Low fidelity mannequin and facilitators	Virtual reality	Year 4,5,6
Team member Competency 5	Shows interprofessional competency	Medium / Low fidelity mannequin and facilitators	Simulated participant and facilitators	Virtual reality	Year 4,5,6
Communicator Competency 6	Effectively communicate with patients and their relatives	Simulated participant	High fidelity simulator with voice response	Virtual reality	Year 1,2,3,4,5,6
	Effectively communicates patients with special needs and different sociocultural backgrounds	Simulated participant with or without wearable simulator	High fidelity simulator with voice response	Virtual reality	Year 1,2,3,4,5,6
	Involves patient in decision making process	Simulated participant	High fidelity simulator with voice response	Virtual reality	Year 1,2,3,4,5,6
Scholar Competency 7	Embraces evidence-based approach	Medium / Low fidelity mannequin and facilitator	Simulated participant and facilitator	Virtual reality	Year 3,4,5,6
Lifelong learner Competency 8	Manage her / his own learning process	Facilitator(s)	Simulated participant and facilitator	Virtual reality	Year 1,2,3,4,5,6

ere were 157 basic practical skills (BPS) in NCC-2020. They were categorized into nine subheadings. The invasive and non-invasive applications subheading was divided into two to ensure the clarity of the selected simulation methods. The "scientific research principles and practices" subheading couldn't match with any simulation method and was excluded from the study. In conclusion, there were nine main categories for the BPS section. In order to match BPS with adequate simulation methods, each of these nine subheadings was considered as one type of main skill. Table 1 shows the details of these nine main skills related to the BPS.

The behavioral and social sciences and humanities section (section three) was evaluated according to their relation with competencies in section one. For example, the "Communication problems" subheading was considered a component of the competency of "Communicator". There were 10 main skills associated with simulation methods in this category. Table 1 shows the details of these 10 main skills related to section three.

DISCUSSION

The selection criteria for simulation methods is based on the context of each medical school (40). High-fidelity mannequins, which are the dominant component of traditional methods, are more complicated and capable than their first versions. Thus, they provide a great opportunity to gain experiences in clinical-like environments for medical students (4, 32). In our study, high-fi-

delity mannequins can be seen as a great alternative, especially the skills which do not require human interaction like communication.

Extended reality (VR and AR) is seen as a major alternative to traditional methods (11). While using VR, the limitation of training on psychomotor skills is tended to underestimated and it is mostly recommended to use traditional methods (before or after VR) to compensate for this limitation (25). On the other hand, high-fidelity simulators and SPs in traditional methods are safer for participants than VR and AR considering the dizziness etc. they cause (32). Due to these limitations, extended reality was considered the last alternative in our study.

The simulated participant method is a great alternative, especially for the skills that need human interaction (12). Wearable simulators + SPs method is more reasonable than traditional mannequins when considering the level of resembling real patient interaction (29). In our study, we highly recommended the simulated participant method for non-technical skills independent that non-technical skills were combined with technical skills or not.

Task trainers as a low-fidelity traditional method, maintain its importance and stand at the core of the simulation-based education for technical clinical skills training (14, 15). In our study, we recommended low-fidelity simulators as a common alternative, especially for technical skills.

The tool we conducted covers basic to complicated simulation methods which every medical school can adopt according to their facilities. We recommend our tool as a guide in selecting adequate resources while developing simulation-based education in undergraduate medical education.

One of the limitations of the study is that our study focuses on undergraduate medical education and the National Core Curriculum-2020. Thus, the tool is not structured for postgraduate medical education. Still, there are common skills in undergraduate and postgraduate medical education which can be structured in the same way. Another limitation is that this study only analyzed the core curriculum that is unique to Turkey. Although the general trends in medical education in Turkey are based on the World Federation for Medical Education (WFME), the documents of WFME were not analyzed in our study.

A source regarding which simulation method is selected for which skill by medical faculties could not be found in the literature review. Further research about the simulation centers' preferences for selection simulation methods in their programs should be conducted to understand the feasibility of each method.

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Abbreviations list

AR: Augmented Reality
VR: Virtual Reality
SP: Simulated Participant
NCC: National Core Curriculum
SRQR: Standards for Reporting Qualitative Research
BPS: Basic Practical Skills
WFME: World Federation for Medical Education

Ethics approval and consent to participate

The ethical approval was not applicable to this study

based on the content analysis methodology.

Consent for publication

Our study is based on content analysis of the document. It does not contain any personal data.

Availability of data and materials

Data from the study were not stored digitally or physically.

Competing interests

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Authors' contributions

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ORIGINAL ARTICLE

Retrospective Analysis of Out-of-Hospital Births in Ankara Emergency Medical Services

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Abstract

Background: In Emergency Medical Services (EMS), out-of-hospital (OOH) births are rare but not exceptional. Our study aims to evaluate the data of patients who gave birth in OOH in the Ankara province and to analyze the prehospital obstetric organization.

Methods: We evaluated the records (such as age, nationality, district, type of hospital to which they were transported, and transportation time) in the Emergency Medicine Automation System (ASOS) database of 403 pregnancies who gave birth outside the hospital in Ankara between 2021 and 2023 and were transported to a hospital by ambulance.

Results: Between 2021 and 2023, Ankara EMS intervened in a total of 403 OOH birth cases. While 214 (53.1%) of the patients were citizens of the Republic of Türkiye, 189 (46.9%) were foreign nationals. Foreign nationals who gave birth at OOH were mostly of Middle Eastern and Asian origin. The mean age of the mothers in our study was 26.9 ± 5.7 years. We found a significant difference in the incidence of OOH births in peripheral regions between years. While there were 13 (14.6%) cases in 2021, there were 62 (36.3%) cases in 2022 and 52 (36.4%) cases in 2023.

Conclusions: A well-designed EMS obstetric care organization can provide patients with more accessible and better service. An increase in the number of foreign nationals within the demographic structure could potentially lead to a rise in the number of out-of-hospital births.

Key words: Out-of-hospital births, pre-hospital, obstetrics

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INTRODUCTION

In Emergency Medical Services (EMS), out-of-hospital (OOH) births are rare but not exceptional (1). In Türkiye, pregnant women generally prefer to give birth in hospitals, but due to the unpredictable nature of birth, births outside the hospital can occur. EMS workers consider it a clinical event of importance due to the high mortality and morbidity rates associated with OOH births for both mother and baby (2, 3). The annual incidence of OOH births varies between 0.08% and 1.99% across countries (2). In a study evaluating OOH births on a national basis in the United States of America (USA), the incidence was 0.02 (4). Türkiye has limited data on OOH births, and there is no regular publication of national data. Our study aims to evaluate the data of patients who gave birth in out-of-hospital (OOH) settings in the Ankara province and to analyze the prehospital obstetric organizations.

MATERIALS AND METHODS

Study Design and Participants

Ankara EMS conducted the study. We evaluated the records (such as age, nationality, district, type of hospital to which they were transported, and transportation time) in the Emergency Medicine Automation System (ASOS) database of 403 pregnancies who gave birth outside the hospital in Ankara between 2021 and 2023 and were transported to a hospital by ambulance. We excluded cases with missing data from the study. Our study was approved by the Ankara Etlik City Hospital Ethics Committee (with approval number AEŞH-BADEK-2024-1073 and dated 30/10/2024).

Statistical Analysis

IBM Corp. released IBM SPSS for Windows version 27.0 in 2020, which we used to analyze all the data. IBM SPSS Statistics for Windows, Version 27.0. Armonk, NY: IBM Corp). We used the Chi-Square (2) test to compare qualitative data while evaluating the study data, in addition to descriptive statistical methods such as frequency, percentage, mean, standard deviation, median, min-max, and IQR. The data's normality was checked with the Kolmogorov-Smirnov test, skewness-kurtosis, and graphical methods like the histogram, Q-Q plot, stem and leaf plot, and boxplot. We used a one-way ANOVA test in the study to compare quantitative data compatible with normal distribution between groups. We used the Kruskal-Wallis test to compare data not compatible with normal distribution between groups. The statistical significance level was considered a $p < 0.05$.

RESULTS

Table 1 displays the statistical data from our study. Between 2021 and 2023, Ankara EMS intervened in a total of 403 OOH birth cass. While 214 (53.1%) of the patients were citizens of the Republic of Türkiye, 189 (46.9%) were freign nationals. Foreign nationals who gave birth at OOH were mostly of Middle Eastern and Asian oriin. The mean age of the mothers in our study was 26.9 ± 5.7 years, while the median age was 26 years (mi 16–max 42). We evaluated OOH births by year, intervening in 89 cases in 2021, 171 in 2022, and 143 in 2023. The data indicates a significant trend in out-of-hospital (OOH) births over the years, with a notable increase in 2022. The demographic diversity among foreign nationals, primarily from Middle Eastern and Asian regions, highlights the multicultural aspect of maternal health services in the area. The mean age of mothers suggests a relatively young population, which may have implications for healthcare policy and resource allocation in maternal and child health programs. Further analysis could provide insights into the factors influencing the choice of OOH births among different nationalities.

While the least number of cases was in 2021 (n = 89), the most were in 2022 (n = 171). The community characteristics revealed that the majority of applications (n=276, 68.5%) originated from urban areas. Considering the hospitals to which the patients were transported, most cases (n=149, 37%) were transported to state hospitals. Transporters transported 141 (35%) patients to training and research hospitals, 103 (25.6%) patients to city hospitals, 6 (1.5%) patients to university hospitals, and 4 (1%) patients to private hospitals. The mean arrival time at the scene was 386.6 ± 493.4 seconds. Table 2 displays comparisons of cases by year. We found a significant difference in the incidence of OOH births in peripheral regions between years. While there were 13 (14.6%) cases in 2021, there were 62 (36.3%) cases in 2022 and 52 (36.4%) cases in 2023. We also found a significant difference in the ar-

Table 1. Characteristics of Cases			
		n **Mean ± SD**	%
Age (Years) [a]		26.9 ± 5.7	
Patient's Nationality [b]	Turkish	214	53.1
	Foreign national	189	46.9
Year[b]	2021	89	22.1
	2022	171	42.4
	2023	143	35.5
District where the case occurred	City center	276	68.5
	Periphery of the city	127	31.5
Transported to...[b]	General State Hospitals	149	37.0
	Training and Research Hospitals	141	35.0
	City Hospitals	103	25.6
	University Hospitals	6	1.5
	Private Hospitals	4	1.0
Arrival at scene time (in seconds) [a] (Arrival at scene time- Ambulance Assignment time)		386.6 ± 493.4*	
a: Mean ± SD / Median (Min-Max), b: n / %, *: Second			

rival time at the scene: in 2021, it was 343.0 (252.5–482.5) seconds, in 2022, it was 272.0 (198.0–382.0) seconds, and in 2023, it was 271.0 (190.0–381.0) seconds.

DISCUSSION

People may choose to give birth at home because they do not want medical intervention or because of their beliefs. Apart from these two reasons, the majority of out-of-hospital (OOH) births occur due to various factors such as inadequate care during pregnancy, lack of preparation for childbirth, limited transportation options, living in a remote area from a health facility, and premature birth (5). There are also studies reporting that residing more than 35 kilometers away from a health facility is among the risk factors for OOH birth (6). In our study, 68.5% of the cases were in the central district, while 31.5% were in the peripheral districts. We found a significant difference in OOH births in the peripheral districts between the years. Distance to the hospital and transportation time are important factors for OOH births. A study evaluating OOH births in the USA reported a mean age of 28 years.(4) In another study conducted in Brazil (7), the mean age was

Table 2. Comparisons of Cases by Year						
		2021 (n=89) [1]	**2022 (n=171) [2]**	**2023 (n=143) [3]**	**P**	**Difference**
Age (Years)		27.5 ± 5.1	26.8 ± 5.9	26.7 ± 5.9	0.582 [a]	--
Patient's Nationality	Turkish	49 (55.1%)	88 (%51.5)	77 (53.8%)	0.838 [b]	--
	Foreign national	40 (44.9%)	83 (3 - 19)	66 (46.2%)		--
District where the case occurred	City center	76 (85.4%)	109 (63.7%)	91 (63.6%)	**0.001** [b]	Between 1 and 2-3
	Periphery of the city	13 (14.6%)	62 (36.3%)	52 (36.4%)		Between 1 and 2-3
Transported to...	City Hospitals	20 (22,5%)	32 (18.7%)	51 (35,7%)	**<0,001** [b]	Between 2 and 3
	Training and Research Hospitals	47 (52.8%)	60 (35.1%)	34 (23,8%)		Between 1 and 2-3
	Public Hospitals	19 (21.3%)	76 (44.4%)	54 (37.8%)		Between 1 and 2-3
	University Hospitals	1 (1.1%)	1 (0.6%)	4 (2.8%)		--
	Private Hospitals	2 (2.2%)	2 (1.2%)	0 (0.0%)		--
Arrival at scene time (in seconds) (Arrival at scene time- Ambulance Assignment time)		343.0 (252.5 – 482.5)	272.0 (198.0 – 382.0)	271.0 (190.0 – 381.0)	**0.001** [c]	Between 1 and 2-3
a: One-Way Anova Test (Mean ± SD), b: Chi-Square Test (n (%)),c: Kruskal-Wallis Test (Median (IQR))						

25.43±6.73, and in Sweden (8), the mean age was 29. The mean age of the mothers in our study was found to be 26.9 ± 5.7 years, which is consistent with the literature. Among the OOH birth cases, 214 (53.1%) were citizens of the Republic of Türkiye, while 189 (46.9%) were foreign nationals. We identify immigrants and refugees as a risk group for OOH 9. We predict that the increase in the foreign population in Türkiye will increase the number of OOH births. We also found a significant difference in the arrival time at the scene for OOH cases. [In 2021=343.0 (252.5–482.5) seconds, in 2022=272.0 (198.0–382.0) seconds, and in 2023=271.0 (190.0–381.0) seconds] This positive decrease in arrivals at the scene may be due to the increase in the number of ambulance teams at Ankara EMS in the relevant years. While Ankara EMS provided service with 168 active EMS teams in 2021, this number increased cumulatively to 171 in 2022 and 177 in 2023. EMS teams are usually the first to arrive on the scene. They provide emergency care to the patients and transport them to the hospital as soon as possible. This is why EMS teams play a crucial role in pre-hospital emergency obstetric organizations. However, EMS personnel describe birth cases as one of the most stressful and challenging operational situations they find themselves in (10). We believe that establishing a telemedicine system for effective communication between EMS personnel and gynecology specialists can alleviate these concerns. EMS agencies should have continuing education programs, appropriate equipment, and obstetric emergency care protocols to improve the care of obstetric women in labor (11). Of the 1926 healthcare professionals working in Ankara EMS, 1485 (77.1%) received pre-hospital birth emergencies and obstetrics

training. The rate of paramedics receiving this training is 86%. To increase these rates, training organizations continue. In addition, every ambulance team has birth kits containing materials such as clamps, thermal blankets, sponges, etc. In conclusion, a well-designed EMS obstetric care organization can provide patients with more accessible and better service. An increase in the number of foreign nationals within the demographic structure may lead to a rise in the number of out-of-hospital births. An increase in EMS teams can expedite the provision of emergency medical care to OOH births. We require additional research to supplement our limited data-driven study.

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Abbreviations list

EMS: Emergency Medical Services (EMS)
OOH: out-of-hospital
ASOS: Emergency Medicine Automation System

Ethics approval and consent to participate

This study was approved by the Ankara Etlik City Hospital Ethics Committee (with approval number AEŞH-BADEK-2024-1073 and dated 30/10/2024).

Consent for publication

Our study is retrospective. It does not contain any personal data.

Availability of data and materials

Data from the study were not stored digitally or physically.

Competing interests

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ORIGINAL ARTICLE

Are Youtube Videos a Useful Source of Information on Avoidant/Restrictive Food Intake Disorder?

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Abstract

Background: Social media platforms are widely used to share health information via videos. Avoidant/restrictive food intake disorder (ARFID) is a new eating disorder term that is one of the most searched topics online. This study aims to determine the quality and content of videos about ARFID on YouTube.

Methods: On May 6, 2024, the term "Avoidant/restrictive food intake disorder and/or ARFID" was searched on YouTube. The videos' quality was assessed using three scoring systems: DISCERN, Global Quality Score (GQS), and the Journal of the American Medical Association (JAMA). DISCERN scores defined the top 25% of videos as the most reliable and top-quality (Q1).

Results: Videos (N = 295) were assessed, and 192 videos met our inclusion criteria. The most common video topic was the symptoms and diagnoses of ARFID (64.6%). Videos associated with ARFID were fair to poor quality according to DISCERN (90.6%) and GQS (79.7%). 80.2% of the videos targeted patients, and they had lower quality scores than those targeting healthcare providers. 68.42% of videos for healthcare providers were high-quality (Q1), while only 14.29% of videos targeting patients were Q1. The GQS and JAMA scores showed a negative correlation with the viewer interaction scores of the videos.

Conclusions: Our findings underline the low quality of YouTube videos about ARFID. It is concerning to find that viewer interaction with the videos increases as video quality decreases. The present study highlights the risk of spreading poor-quality information via YouTube videos to the public, particularly patients.

Key words: avoidant/restrictive food intake disorder (ARFID), eating disorders, information seeking behavior, internet, health literacy

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INTRODUCTION

Avoidant/Restrictive Food Intake Disorder (ARFID) is an eating disorder that is characterized by avoidant/restrictive eating behaviors that lead to a failure to meet appropriate nutrient and/or energy needs, with consequent physical or psychosocial consequences (1). ARFID diagnosis emerged first in the DSM-5, which extends the DSM-IV diagnosis of feeding disorder in infancy or early childhood to any age and is also distinct from other eating disorders due to not being driven by concerns about shape or weight (2).

ARFID is a heterogeneous disorder due to three different presentations: selective/picky eating, lack of interest in eating, and fear of the aversive consequences of eating, such as vomiting or choking (1, 3). Although the DSM-5 provides detailed criteria and presentations for ARFID, its development and clinical features can vary significantly among individuals, resulting in diverse symptomatic profiles. These different ARFID profiles lead to uncertainties in clinical practice, treatment modalities, and clinicians' diagnostic difficulties (4). Moreover, professionals' knowledge and awareness of ARFID may impact the diagnosis and treatment approach (5). For example, a lack of experience differentiating ARFID from "normative picky eating" can lead to overdiagnosis (6). Clinicians who have not previously cared for pediatric ARFID report less confidence in clinical management than those who have cared for ARFID (5). This low experience and confidence in the clinical management of ARFID by healthcare professionals may lead clinicians to search for other information sources, such as the Internet, to gain more knowledge about ARFID approaches and therapies or patient experience. Besides healthcare providers, patients often use the Internet to access medical issues and information or share their own experiences about the illness. Notably, individuals with eating disorders (EDs) often prefer to deal with their difficulties on their own and look for support and information on the Internet (7).

The Internet has become a common platform for accessing medical information, with YouTube emerging as one of the most widely used websites in the world. This platform hosts a wealth of health-related content and videos that can be freely shared by individuals, including patients and healthcare professionals (8, 9). Although YouTube is an effective platform for sharing useful medical information, the lack of a peer-review process can lead to the dissemination of misleading information. Indeed, the potential benefits of the videos and websites depend on their content and quality. Research on the quality and reliability of YouTube videos with various medical topics is increasing (10-15). In this regard, few studies evaluating social media content on eating disorders such as anorexia nervosa (AN), binge eating disorder (BED), and bulimia nervosa (BN) have shown heterogeneity in the quality of information (16-18). However, there is no research on the quality and content of YouTube videos related to ARFID. Accordingly, this study aims to (a) evaluate the characteristics (e.g., like ratio, daily viewing rate, popularity index, viewer interaction, target audience, upload source of videos, contents of videos) and quality of the YouTube videos about ARFID, and compare characteristics and quality of the videos between the target audience (healthcare providers and patients), (b) determine the associations of characteristics and quality levels of the videos.

MATERIALS AND METHODS

On May 6th, 2024, a search was conducted on the YouTube website (http://www.youtube.com) using the keyword "Avoidant/restrictive food intake disorder and/or ARFID". All videos in English, uploaded at any time, were eligible for analysis. Individual accounts were not used in the video search to avoid bias. The search resulted in 295 videos. Irrelevant videos (n=74), duplicates (n=7), short videos including playlists (n=14), and videos with a non-English language (n=8) were excluded (Supplemental Figure S1). The videos were independently evaluated in duplicate by two authors of the article (EA and BB), who are child and adolescent psychiatrists.

Data was collected for each video, including the URL, upload source, upload date, video length, number of views, likes, dislikes, and comments (see all URL addresses of YouTube videos in Supplementary material). The daily viewing rate (number of views divided by the number of days since upload) and viewer interaction [(number of likes-number of dislikes)/total number of viewsX100)] were calculated. The like ratio is defined as the like/ (like + dislike) percentage. Additionally, we calculated the video popularity index of the video (like ratio X viewing rate/100) (19). We also recorded the video sources (universities or professional societies, commercial organizations, websites providing health-related information,

general educational websites, patient personal websites, and others) and target audience (healthcare providers, patients). We determined healthcare providers as the target audience if the video stated that it was intended for healthcare professionals in the video content or description or if medical terminology was frequently used with detailed explanations. Videos that focused on patients' awareness, knowledge, and behavioral approach regarding ARFID and directly appealed to individuals with ARFID identified their target audience as patients. Each video was evaluated for content information related to ARFID, including symptoms and diagnosis based on DSM-5, treatment, outcomes, comparison to other eating disorders, the patient's experience, therapist treatment session, patient education, and professional education.

We used three different scoring systems to evaluate the quality of medical videos. The first system we used was the DISCERN scoring system, which consists of 15 questions, each scored from 1 to 5 (20). This system classifies items as excellent (63–75 points), good (51–62 points), fair (39–50 points), poor (27–38 points) and very poor (15–26 points). This system is widely used for evaluating the reliability and quality of medical videos (8, 21). We also determined the quartile (Q) of the videos according to the DISCERN scores. The top 25% of videos were classified as the most reliable and top-quality videos (Q1), while the rest were classified as others (Q2-4). The second scoring system we used was the global quality score (GQS) system. This system was defined by Bernard et al. in 2007 and is used to assess the instructive aspects of a video (22). The overall quality of the video is evaluated between 1 and 5 points using this system, and it is commonly used to assess the quality of medical videos (9, 23, 24). The third scoring system we used was the Journal of the American Medical Association (JAMA) scoring system. This system was published by Silberg et al. in 1997 and consisted of four criteria, with one point awarded for each criterion, resulting in a total possible score of four points (25). The JAMA scoring system is frequently used to evaluate the reliability and quality of medical videos, and we used it to ensure consistency in our evaluations (21, 24). Assessment questions and criteria for all score systems (DISCERN, GAS, and JAMA) are presented in the Supplementary material.

Our study complied with the ethical principles of the Declaration of Helsinki. Since YouTube videos are publicly available and free of charge, no ethical approval was required.

Statistical analysis

The normality of variables was assessed using the Shapiro-Wilk test. Median (interquartile range-IQR) was used for continuous variables, and the Mann-Whitney U-test was used to compare continuous variables due to skewed distribution. Categorical variables were expressed as percentages, and Pearson's chi-squared and Fisher's exact analysis were used to compare categorical variables. Spearman's correlation coefficient was calculated to investigate the association among the continuous variables. Inter-rater reliability was assessed for the three scoring systems (JAMA, GQS, and DISCERN) using intra-class correlation estimates and their 95% confidence interval (intraclass correlation > 0.80 for all scoring systems). Intrarater reliability for categorical variables (e.g., target audience) was assessed using Cohen's kappa (k) coefficient. Kappa values were interpreted according to criteria defined by Landis and Koch (k coefficient > 0.90; almost perfect agreement) (26). Statistical significance was determined with p-values less than .05. The Statistical Package for Social Science (SPSS version 20.0, IBM Corp., Armonk, New York, USA) software was used for all analyses.

RESULTS

Of the 295 videos that were evaluated, 192 videos met our inclusion criteria. Thirty videos (15.6%) were closed for comments, while four videos (2.1%) were turned off to dislike and like by video sources on YouTube. The target audience of videos were 19.8% (n=38) healthcare providers and 80.2% (n=154) patients. The median duration of the videos was 425 (IQR=790) seconds and significantly higher for videos that targeted healthcare providers ($p < 0.001$). The number of views was higher for videos that targeted patients ($p = 0.005$). The median number of comments in the sample was 3 (IQR=26), and significantly higher for videos that targeted patients (Mdn=7) than the healthcare providers (Mdn=3), $U = 2919$, $p < 0.001$. The median number of likes of the videos was 27 (IQR=138), and significantly higher for videos that targeted patients (Mdn=36) than the healthcare providers (Mdn=6), $U = 3871$, $p < 0.001$. Additionally, the videos targeted patients had more dislikes for their videos than the healthcare providers group, $U = 3392$, $p=0.008$. However, the like ratio and daily viewing rate of the videos were similar in the groups ($p=0.063$, $p=0.101$, respectively). Consid-

Table 1. The characteristics of the videos and comparisons by target audience groups

	Total, *n*= 192	Healthcare providers, *n*= 38 (19.8%)	Patients, *n*= 154, (80.2%)	*Test statistics*	*p*-value
Duration in seconds; median (IQR)[a]	425 (790)	3175 (3785)	343 (573)	1302	**<0.001**
Views; median (IQR)[a]	1391.50 (6838)	398 (2371)	2114 (7326)	3786	**0.005**
Number of days since upload	787.50 (1277.25)	403.50 (1131)	889 (1363.75)	3628.50	**0.022**
Like ratio[a]	100 (2.21)	100 (0)	100 (2.56)	1576.50	0.063
Daily viewing rate; median (IQR)[a]	2.19 (11.53)	1.22 (5.84)	2.52 (11.62)	2423	0.101
Viewer interaction; median (IQR)[a]	1.88 (2.74)	1.37 (2.01)	1.98 (2.74)	3366.50	**0.014**
Popularity index; median (IQR)[a]	2.83 (11.14)	1.55 (6.08)	3.07 (11.36)	1660	0.123
Video sources; *n* (%)					
Commercial organization[s]	42 (21.9)	8 (21.1)	34 (22.1)	0.019	0.891
University or society	15 (7.8)	12 (31.6)	3 (1.9)	-	**<0.001**
Health-related websites	74 (38.5)	16 (42.1)	58 (37.7)	0.335	0.562
General educational websites	10 (5.2)	1 (2.6)	9 (5.8)	-	0.690
Patient personal websites	41 (21.4)	0	41 (26.6)	12.86	**<0.001**
News channel[s]	10 (5.2)	1 (2.6)	9 (5.8)	-	0.690

Note: IQR: Interquartile range; a: Mann Whitney U; b: Pearson Chi-Square; c: Fisher's Exact Test; Like ratio: like/ (like + dislike) percentage; video popularity index: (like ratio X viewing rate/100); the daily viewing rate (number of views divided by the number of days since upload); viewer interaction [(number of likes-number of dislikes)/total number of viewsX100)]

ering the video sources, we found that they consisted of health-related websites (n=74, 38.5%), commercial organizations (n=42, 21.9%), patient personal websites (n=41, 21.4%), the university or society (n=15, 7.8%), general educational websites (n=10, 5.2%), news channel (n=10, 5.2%). The characteristics of the videos and comparisons between two target audience groups (healthcare providers vs. patients) are summarized in Table 1.

YouTube video contents are summarized in Table 2. Symptoms and diagnosis of ARFID were mentioned in 64.6% of the videos, and its rate was higher in videos that targeted healthcare providers. Treatment and outcomes of ARFID were mentioned in 38.5% and 42.7% of the total videos, respectively. Videos targeting healthcare providers had more content about ARFID treatment (78.9%) and outcomes (73.7%) (both p values <0.001). Comparison to other eating disorders (e.g., anorexia nervosa, bulimia nervosa, binge eating disorder) and differences from picky eating were mentioned more frequently in videos targeting healthcare providers than those targeting patients (p<0.001, p=0.002, respectively). However, videos targeting patients presented the patients' experiences more than those targeting healthcare providers (28.6% vs. 13.2%), p=0.050). Regarding the video presenters, psychologists (26%) were the most frequent, followed by patients (22.4%) and therapists (11.5%). However, the percentage of psychiatrists (5.2%), dietitians (4.7%), and medical doctors (3.6%) as presenters in YouTube videos was low. The presenters of 16.7% of videos consisted of other health providers (nurses, social workers, family coaches, life coaches, documentary producers, and announcers), and 9.9% were unknown presenters.

Table 2. YouTube video content according to the target audience					
	Total, *n*= 192	**Healthcare providers, *n*= 38 (19.8%)**	***Patients, n= 154 (80.2%)***	***χ2***	***p*-value**
ARFID symptoms and diagnosis; *n* (%)[a]	124 (64.6%)	34 (89.5%)	90 (58.4%)	12.83	**<0.001**
ARFID treatment; *n* (%)[a]	74 (38.5%)	30 (78.9%)	44 (28.6%)	32.65	**<0.001**
Outcomes of ARFID; *n* (%)[a]	82 (42.7%)	28 (73.7%)	54 (35.1%)	18.57	**<0.001**
Comparison to other EDs; *n* (%)[a]	64 (33.3%)	24 (63.2%)	40 (26.0%)	18.96	**<0.001**
Experience of the patient; *n* (%)[a]	49 (25.5%)	5 (13.2%)	44 (28.6%)	3.81	**0.050**
Therapist session; *n* (%)[b]	7 (3.6%)	0 (0%)	7 (4.5%)	-	0.348
Case example; *n* (%)[b]	14 (7.3%)	11 (28.9%)	3 (1.9%)	-	**<0.001**
Exposure therapy; *n* (%)[b]	14 (7.3%)	0 (0%)	14 (9.1%)	-	0.076
Differences from picky eating; *n* (%)[a]	41 (21.4%)	15 (39.5%)	26 (16.9%)	9.26	**0.002**
Note: EDs: Eating Disorders, a: Pearson Chi-Square, b: Fisher's Exact Test					

Table 3. Quality evaluation of YouTube videos based on the target audience.					
	Total, *n*= 192	**Healthcare providers, *n*= 38 (19.8%)**	**Patients, n= 154 (80.2%)**	**U statistics**	**p-value**
DISCERN; median (IQR)	30 (12)	47 (17.25)	28 (8)	810.50	<0.001
Very poor; *n* (%)	56 (29.2%)	3 (7.9%)	53 (34.4%)		
Poor; *n* (%)	91 (47.3%)	9 (23.7%)	82 (53.2%)		
Fair; *n* (%)	27 (14.1%)	10 (26.3%)	17 (11.0%)		
Good; *n* (%)	17 (8.9%)	15 (39.5%)	2 (1.3%)		
Excellent; *n* (%)	1 (0.5%)	1 (2.6%)	0 (0%)		
GQS; median (IQR)	2 (1)	4 (2)	2 (1)	1288.50	<0.001
Poor; *n* (%)	8 (4.2%)	3 (7.9%)	5 (3.2%)		
Generally poor; *n* (%)	93 (48.4%)	5 (13.2%)	88 (57.1%)		
Moderate; *n* (%)	52 (27.1%)	5 (13.2%)	47 (30.5%)		
Good; *n* (%)	23 (12%)	12 (31.6%)	11 (7.1%)		
Excellent; *n* (%)	16 (8.3%)	13 (34.2%)	3 (1.9%)		
JAMA; median (IQR)	2 (0)	2 (1)	2 (0)	1843	<0.001
Note: IQR: Interquartile range, JAMA: Journal of the American Medical Association, GQS: global quality score.					

Table 4. Association between quality scores and the features of the videos

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.
1. Duration of videos	1	-.002	.083	.029	.027	.065	-.078	.574***	.641***	.116
2. Comments		1	.824***	-.597***	.659***	.667***	.255**	-.076	-.049	-.125
3. Views			1	-.647***	.700***	.778***	.030	.050	.109	.023
4. Like ratio				1	-.347***	-.436***	.234**	.030	.051	.026
5. Popularity index					1	.961***	-.028	.068	.096	.031
6. Daily viewing rate						1	.151*	.109	.127	.031
7.Viewer interaction							1	-.133	-.167*	-.310***
8. DISCERN								1	.737***	.357***
9. GQS									1	.238***
10. JAMA										1

Note: Like ratio: like/ (like + dislike) percentage, video popularity index: (like ratio X viewing rate/100); the daily viewing rate (number of views divided by the number of days since upload); viewer interaction [(number of likes-number of dislikes)/total number of viewsX100)], GQS: global quality score, JAMA: Journal of the American Medical Association, *p<.05, **p<.01, ***p<.001.

The DISCERN, GQS, and JAMA scores of the videos were significantly higher for the videos targeting healthcare providers than those targeting patients (all p values < 0.001; see Table 3). While the DISCERN had a strong correlation with GQS (r=0.737, p < 0.001), the DISCERN and GQS scores had a weak correlation with the JAMA score (r=0.357, p < 0.001; r=0.238, p < 0.001). The GQS and JAMA scores negatively correlated with the viewer interaction scores (r=-0.167, p =0.022; r=-0.310, p < 0.001, respectively), while they had no associations with other features of the videos (comments, views, like ratio, popularity index, daily viewing rate).

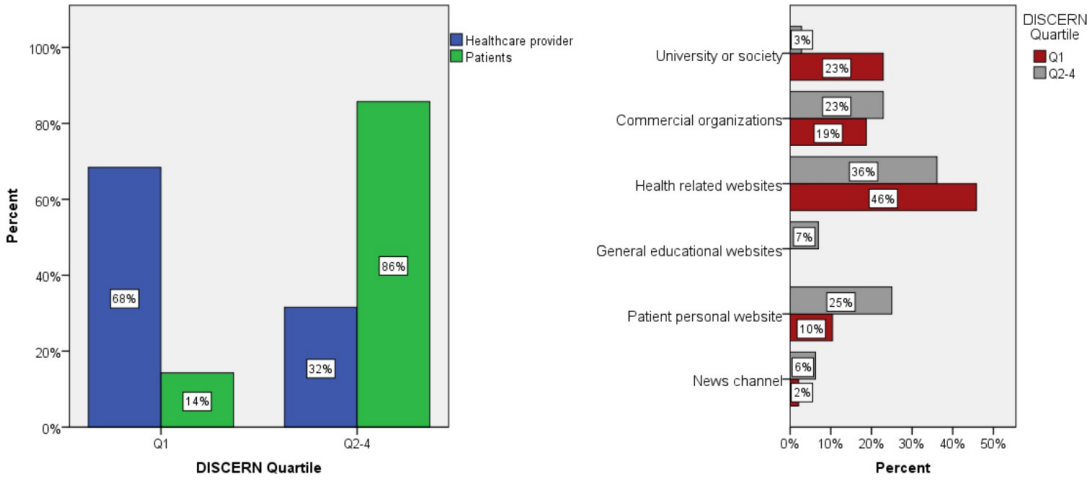

Figure 1: Distribution of target audience according to DISCERN quartile of the videos (Left panel); distribution of DISCERN quartile according to video upload sources (Right panel)

The DISCERN and GQS scores had positively moderate correlations with the duration of the videos (r=0.574, p =0.022; r=0.641, p < 0.001, respectively). The association between quality scores and the features of the videos are summarised in Table 4. According to the DISCERN score, 22.92% of the videos in Q1 were obtained from the university or society, while the other video sources were as follows in order of frequency: health-related websites (45.83%), commercial organizations (18.75%), patient personal websites (10.42%) and news channel (2.08%). While 68.42% of the videos prepared for the healthcare providers were among the Q1, only 14.29% of the videos targeted the patients were among the Q1. The distribution of the DISCERN quartile according to the target audience and video sources is illustrated in Figure 1.

DISCUSSION

Social media platforms are widely used for sharing health information with the public. One prominent form of social media is YouTube, a popular platform offering people free and unlimited access. However, the quality of the information in shared videos is critical for help-seeking patients due to the lack of a peer-review process. Our results showed that most YouTube videos associated with ARFID had fair to poor quality according to both DISCERN (90.6%) and GQS (79.7%). The primary upload sources of moderate-poor quality (Q2-4) videos were health-related websites (36%) and patient personal websites (25%). We found that all personal patient website videos targeted patients as the audience. Our findings suggest that these low-quality videos can risk spreading misinformation to the public, particularly patients.

In our study, most YouTube videos about ARFID (80.2%) targeted patients, and the quality of those videos was lower than those that targeted healthcare providers. While more than half of the videos prepared for the healthcare providers were among the high-quality (Q1), only 14.29% of the videos targeted the patients belonged to this top quality. This was expected because a significant proportion of videos were from the websites of ARFID patients. Moreover, videos targeting patients had fewer sources from universities or society compared to those targeting healthcare providers. Similar to our findings, the quality of the videos targeting patients was poor in videos related to various medical topics (8, 21). Even though the quality of these videos was low, their viewer interaction was higher than videos that targeted healthcare providers. With high viewer interaction and poor quality, these patient-targeted videos indicate the risk of spreading false and inaccurate information about ARFID. While the popularity of videos does not directly indicate the quality of the content, prior evidence has demonstrated that online crowding can lead healthcare consumers to make unsafe healthcare decisions (27, 28). Individuals who are not confident in their answers to health questions are 28.5% more likely to be influenced to change their views when provided with online social feedback from other people (27). Also, it was concerning to find that as video quality decreases, viewer interaction with the videos increases, suggesting that viewers cannot realize high-quality videos on social media. Our findings align with studies that have shown that patients can be receptive to false information on YouTube videos based on the discrepancy between the quality of videos and interaction parameters (8). Healthcare providers should be aware of the deceptive nature of social media videos and the potential for patients to be exposed to misinformation about ARFID. They should direct patients to accurate online resources during face-to-face meetings.

Regarding the content of the videos, 58.4% of YouTube videos that targeted patients focused on ARFID symptoms and diagnosis. The heterogeneous presentations of ARFID may have contributed to a larger number of videos about its symptoms and diagnosis. It is a new diagnosis introduced in the DSM-5 eating disorder category as an umbrella term to encompass a range of feeding problems previously described in ICD-10 and DSM-IV (29, 30). Diagnostic challenges may arise due to the ambiguous definition of ARFID, as current criteria do not clearly define weight and nutritional symptoms or psychosocial impairment (6). These diagnostic challenges may have increased the sharing of videos by health-related websites or commercial organizations to inform patients about ARFID. Regarding the video presenters, psychologists (26%) were the most frequent, followed by patients (22.4%) and therapists (11.5%). However, medical doctors, including pediatricians and psychiatrists, were less common as presenters. The first point of contact for ARFID patients is usually the family doctor or general pediatrician since it is typically identified in children and young people who experience significant eating difficulties, usually between 2 and 6 years of age (31). The low rate of video sharing by medical doctors

about ARFID may be related to low awareness of the diagnosis of ARFID.

Moreover, videos targeting healthcare providers contained more information about ARFID symptoms, diagnosis, treatment, outcomes, comparison to other eating disorders, and differences from picky eating compared to videos targeting patients. Our findings suggest a tendency to share these differential diagnostic issues of ARFID among healthcare providers. The classification of diagnoses is mainly targeted at clinicians, and an element of clinical judgment is required when making a diagnosis (4). Some confusion exists amongst clinicians as to whether the experience of psychosocial impairment alone is sufficient to diagnose ARFID or whether people must also meet other criteria related to unmet energy or food needs (5). Uncertainties in diagnostic issues of ARFID may contribute to greater information sharing via YouTube videos to healthcare providers.

Contrary to the findings above, YouTube videos can be used as an advantage for patients seeking information about patient experience. Our results showed that 25.5% of the videos presented patients' experiences, and most of those targeted the patients as the audience. Recent studies have confirmed low help-seeking rates for eating problems among individuals with EDs (32, 33). There are several barriers to seeking help for EDs, including concern for others, self-sufficiency, fear of losing control, denial and failure to perceive the severity of the illness, and stigma and shame. (32). In the context of barriers to help-seeking, social media posts can raise awareness about the disease among patients, serving as the first step in seeking help. Social media platforms provide a relevant avenue for young women with eating disorders to communicate and exchange ideas related to the disease and health (34). Additionally, evidence suggests that help-seeking behavior is strongly associated with one's mental health literacy (35). Social media, such as videos, can help overcome traditional barriers (e.g., reading and/or writing skills) to health literacy by making information more accessible and engaging (28). However, using social media safely requires new e-health literacy skills. Our findings underlined that videos with shorter duration or higher viewer interaction index seem to be associated with lower quality. Healthcare providers should know how to access high-quality information on social media to guide people with eating disorders on e-health literacy in the digital platform.

This study had some limitations. YouTube is a dynamic social media platform whose content is continuously updated. Our study design was cross-sectional, so it only provides information for a specific point in time. We only assessed the videos published on YouTube, so the findings may not apply to other social media platforms. However, we analyzed all YouTube videos related to ARFID rather than a specific number of videos based on keywords. Also, we did not assess the reliability and validity of the scoring systems. However, we utilized three different scoring systems widely used to evaluate medical videos and found strong correlations between them in our study. Additionally, two child and adolescent psychiatrists independently assessed the quality of the videos using three objective scoring systems.

Considering the high rate of video sharing targeting patients, the quality and content of these videos are critical for individuals with EDs. In addition to receiving information about ARFID diagnosis and its results, sharing patient experiences is particularly prevalent in videos targeting patients. Also, it was concerning to find that as video quality decreases, viewer interaction with the videos increases, suggesting that viewers watch the video on social media regardless of their quality. Additionally, the videos targeting healthcare providers include more content on the differential diagnosis of ARFID, which may reflect uncertainties regarding diagnostic issues of ARFID and low confidence among professionals. Creating high-quality educational videos that bring healthcare professionals and patients together in the future would be beneficial for providing accurate information about ARFID.

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Abbreviations list

AN: Anorexia nervosa
ARFID: Avoidant/restrictive food intake disorder
BED: Binge eating disorder
BN: Bulimia nervosa
GQS: Global Quality Score
DSM: Diagnostic and Statistical Manual of Mental Disorders
EDs: Eating disorders
JAMA: Journal of the American Medical Association

Ethics approval and consent to participate

Our study complied with the ethical principles of the Declaration of Helsinki. Since YouTube videos are publicly available and free of charge, no ethical approval was required.

Consent for publication

There is no data regarding any individual in this research.

Availability of data and materials

Data available on request from the authors.

Competing interests

The author(s) declare no competing interests.

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Authors' contributions

Idea/Concept: EA. Design: EA, BB. Control/Supervision EA. Data Collection And/Or Processing: EA, BB. Analysis And/Or Interpretation: EA. Literature Review: EA, BB. Writing The Article: EA, Critical Review: BB.

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CASE REPORT

A Rare Cause of Tension Pneumothorax: Echinococcus Granulosus

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Abstract

Hydatid cysts, caused by the Echinococcus parasite, are predominantly found in the liver and the lungs. While pulmonary hydatid cysts can lead to various complications, such as rupture into the bronchus, tension pneumothorax is extremely rare. Diagnosis typically involves a combination of clinical evaluation, radiologic imaging, and serologic testing. In this case presented, an adult patient with tension pneumothorax was diagnosed with a hydatid cyst through these methods. Surgical intervention was necessary excise the cyst, followed by medical treatment to manage any remaining issues. This case highlights the unusual occurrence of tension pneumothorax as a complication of pulmonary hydatid cysts and emphasizes the importance of prompt diagnosis and treatment.

Key words: Hydatid cyst of the lung, rare complication, tension pneumothorax

INTRODUCTION

Hydatid disease is a zoonotic infection caused by the Echinococcus genus, with Echinococcus (E.) granulosus and E. multilocularis being the most prevalent species in humans. The less are E. vogeli and E. Oligarthropoli (1). This disease is particularly endemic in developing countries and can affect multiple organs, with the liver (50-54%) and lungs (35-40%) being the most frequently involved sites. Other organs that can be affected include the kidneys, spleen, brain, skeleton, and heart (2).

The most common complication of pulmonary hydatid cysts is rupture into the bronchus, which can lead to significant respiratory issues. Tension pneumothorax, while a serious condition, remains a very rare complication associated with hydatid cysts. This highlights the importance of early diagnosis and intervention to manage potential complications effectively.

CASE REPORT

The 42-year-old woman's presentation is concerning for a significant respiratory issue. With her history of persistent cough, dyspnea, and right Frank pain, along with vital signs indicating hypotension (70/40 mmHg) and tachycardia (110/min), she is likely in respiratory distress (respiratory rate: 22/min, oxygen saturation: 88). The decreased breath sounds on the right side further support this. Posterior-Anterior chest X-ray (PA CXR) findings of a total pneumothorax on the right, along with accompanying effusion in the right lung lower zone, suggest a significant pleural process. (Figure 1)

After tube thoracostomy, it's encouraging that the patient's vital signs improved significantly, indicating successful decompression of the pneumothorax and drainage of fluid. Although the control PA CXR shows "expansive" findings (Figure 2), massive air leak from

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the tube thoracostomy continued, and a Thorax Computed Tomography (CT) was ordered.

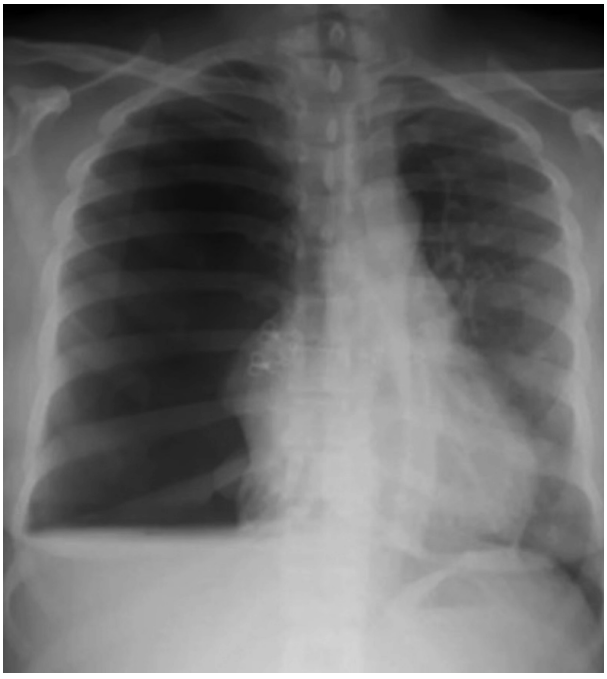

Figure 1. Posterior-Anterior chest X-ray (PA CXR) findings of a total pneumothorax on the right, along with accompanying effusion in the right lung lower zone, suggest a significant pleural process

The thorax CT findings indicating a hydatid cyst cavity that has perforated into the pleural space in the middle lobe of the right lung (Figure 3), an enucleated hydatid cyst membrane located in the posterior costophrenic sinus (Figure 4), pneumothorax on the right, metastatic diffuse milimetric level cystic lesions in bilateral lungs (Figure 5) and a 17 cm type-1 hydatid cyst in the 7th-8th segment of the liver (Figure 4). The patient underwent surgery to address the complications of a perforated hydatid cyst.

Rigid bronchoscopy was performed to aspirate any residual material from the bronchial tree.

The enucleated cyst membrane was removed, and the thoracic cavity was thoroughly washed with povidone-iodine via thoracotomy. The bronchial openings were sutured and the perforated hydatid cyst cavity was quilted, and partial decortication of the parietal pleura was performed. The patient was then placed in supine position, and the liver hydatid cyst was aspirated lapa-

Figure 2. After tube thoracostomy, it's encouraging that the patient's vital signs improved significantly, indicating successful decompression of the pneumothorax and drainage of fluid. Although the control PA CXR shows "expansive" findings

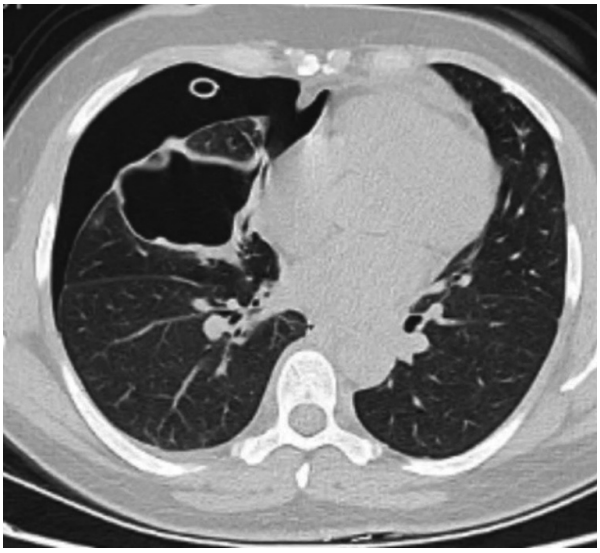

Figure 3. The thorax CT findings indicating a hydatid cyst cavity that has perforated into the pleural space in the middle lobe of the right lung

Figure 4. An enucleated hydatid cyst membrane located in the posterior costophrenic sinus and a 17 cm type-1 hydatid cyst in the 7th-8th segment of the liver

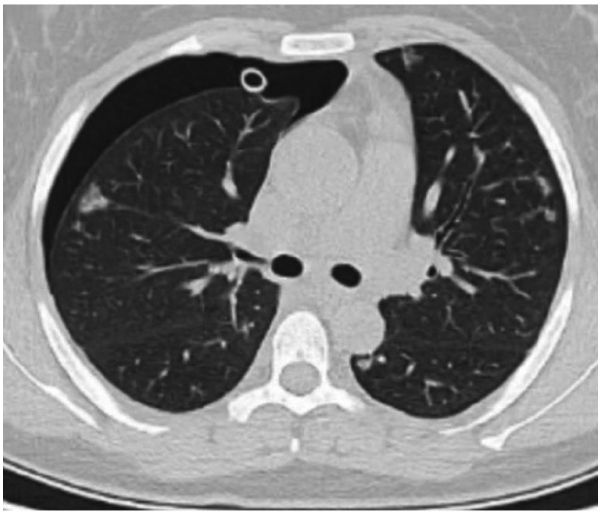

Figure 5. Metastatic diffuse milimetric level cystic lesions in bilateral lungs

roscopically, followed by saline washing by the general surgeon.

Postoperative pathology confirmed the presence of a hydatid cyst membrane. Starting on the 2nd postoperative day, the patient was prescribed albendazole (andazol) at a dosage of 400 mg twice daily, with biochemistry parameters remaining within normal limits. The patient was discharged on the 5th postoperative day and would continue follow-up for 3 months while on albendazole, with regular monitoring of biochemistry parameters to ensure ongoing safety and effectiveness of the treatment.

DISCUSSION

Pulmonary hydatid cysts are often asymptomatic and typically only become symptomatic when they grow large enough to compress lung tissue or when complications arise. The clinical presentation can vary significantly based on whether the cyst perforates the pleura or the bronchus.

Complications such as perforation into the pleural cavity can lead to hydropneumothorax, while perforation into the bronchus may result in symptoms like asphyxia, bronchospasm, and even anaphylaxis. Pleural complications occur with an incidence ranging from 0.5% to 18.2% (3), Aribas et al. reported that these complication rates are even higher (32.5%) (4). Sayir et al found that ,involving 412 patients, the rate of complicated hydatid cysts was 42.71%. Among these complicated cases, 56.8% had ruptured into the bronchial tree, while 43.2% had perforated into the pleural cavity. The incidence of tension pneumothorax among patients with hydatid cysts that ruptured into the pleura was reported to be 1.52% (5). Cernay et al. reported an incidence of tension pneumothorax of 1.3% in their study of 336 patients with ruptured hydatid cysts (6). If the cyst ruptures into the pleural cavity, it may cause pneumothorax, tension pneumothorax, pleural effusion or empyema (7). In our case, the cyst ruptured and opened into the pleura and caused tension pneumothorax, which is a very rare complication. It is a very rare case because It was accompanied by a giant type-1 hydatid cyst in the liver, and there were also bilateral metastatic diffuse cystic formations of several millimeters in size.

Common symptoms in patients with tension pneumothorax include air hunger, tachycardia, agitation, and severe chest pain. Radiologically, mediastinal compression and shifting are observed, making this a life-threatening condition. Tube thoracostomy is a critical intervention that can significantly improve the patient's overall condition and is often life-saving (5). In our patient, the symptoms associated with tension pneumothorax improved significantly following the tube thoracostomy performed under emergency conditions.

Hydatid cyst rupture can occur spontaneously, as a result of trauma, or iatrogenically. Severe coughing can also trigger rupture. If the cyst is located peripherally, it is more likely to open into the pleural space (4, 5). In our case, the perforated hydatid cyst cavity was located peripherally. Severe cough was the first symptom and there was no history of trauma.

The treatment for hydatid cysts located in the lung is primarily surgical. When hydatid cysts rupture into the pleural space, they can lead to complications such as pleural thickening, secondary echinococcosis, and the formation of adhesions. Kuzucu et al. reported that decortication was performed in 24.4% of patients (7). In our case, partial decortication was performed in the areas of contamination in the parietal pleura.

Medical treatment for hydatid cysts in the lungs is recommended in cases of multiple cysts, when surgery poses significant risks, and both before and after surgical or percutaneous interventions. Albendazole is preferred due to its antihelminthic efficacy being ten times greater than that of other medications (8). The recommended dosage of albendazole is 10-15 mg/kg/day, administered in two divided doses for three weeks, followed by a one-week break between treatment sessions, with a total duration of at least three months. Studies have shown that a three-month course of albendazole significantly reduces the viability of protoscoleces and cysts (9). A three-month course of albendazole has been shown to significantly reduce the viability of protoscoleces and cysts (10). In our patient, we administered albendazole treatment for three weeks in two divided doses each month during the postoperative period, monitoring biochemistry parameters closely. After a one-week break, we completed the treatment over a total duration of three months.

It is important to remember that tension pneumothorax can very rarely occur as a result of a ruptured hydatid cyst, particularly in endemic areas or in patients with a history of exposure to hydatid cysts. This condition requires urgent intervention and surgical management.

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Abbreviations list

E: Echinococcus
PA CXR: posterior-anterior chest x-ray
CT: computed tomography

Ethics approval and consent to participate

Ethical committee approval is not required because of this article is a case report. Informed consent was obtained from patient.

Consent for publication

Informed consent was obtained from patient.

Availability of data and materials

The data of the study are not stored digitally or physically.

Competing interests

There is no potential conflict of interest to declare.

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Authors' contributions

Idea/Concept: MGB. Control/Supervısıon MGB. Data Collection And/Or Processing: MGB. Literature Review: MGB. Writing The Article: MGB. Critical Review: MGB. References And Fundings: MGB.

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CASE REPORT

Sudden Cardiac Arrest Associated with Widespread Coronary Vasospasm After Oral Amoxicillin/Clavulanic Acid Intake: A Rare Case of Kounis Syndrome

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Abstract

Kounis syndrome is known as a type of acute coronary syndrome that occurs secondary to hypersensitivity reactions and constitutes a life-threatening medical emergency. Although multiple etiologies of KS have been elucidated, pharmacological agents are the most prevalent. Antimicrobial agents and nonsteroidal anti-inflammatory drugs (NSAIDs) are the most frequently utilized medications. KS is not rare, and its frequency has been reported to increase since it was first described in 1950. However, it is often underdiagnosed owing to its wide range of clinical manifestations. Diagnostic evaluation should encompass laboratory, electrocardiographic, echocardiographic, and angiographic evidence in addition to clinical symptoms and signs. In this case study, we presented a 56 year old patient without any chronic disease who presented with sudden cardiac arrest after taking oral amoxicillin/clavulanic acid.

Key words: Oral antibiotic use, cardiac arrest, coronary vasospasm, Kounis syndrome

INTRODUCTION

Kounis syndrome (KS) is defined as a hypersensitivity reaction triggered by an allergic event leading to acute coronary syndrome (ACS). Also known as "allergic myocardial infarction", this condition can lead to coronary artery vasospasm and subsequent myocardial ischemia via allergic mediators (1).This phenomenon may occur as a result of various pharmaceutical agents, including nonsteroidal anti-inflammatory drugs (NSAIDs) and analgesics, antibiotics, anti-neoplastics, proton pump inhibitors, contrast agents, corticosteroids, anti-hypertensive drugs, and other medications, particularly those frequently used in routine clinical practice. Environmental exposure, insect bites, food and stents can also be causative agents of KS (2).

KS was first described in 1950 as a reaction to penicillin and has been increasingly described in the literature. Desai et al reported a 1.1% incidence of Kounis syndrome-associated ACS among patients admitting to hospitals in the USA with hypersensitivity, allergic, or anaphylactic reactions (3). Three different subtypes of KS have been described:

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Type 1: This variant arises from coronary blockage and spasm, representing the most prevalent mechanism at approximately 72.6% of all cases. It is predominantly seen in younger individuals who lack cardiovascular risk factors. Endothelial dysfunction and microvascular angina serve as the underlying causes of this condition, which is characterized by electrocardiographic evidence of ischemia induced by coronary spasm. Elevated or normal cardiac enzyme levels may serve as a potential indicator of progression towards acute myocardial infarction.

Type 2: Manifests in individuals with atherosclerotic conditions, where a sudden surge of inflammatory agents can trigger either isolated coronary artery spasms or plaque rupture or erosion, resulting in acute myocardial infarction. This form represents approximately 22.3% of all KS instances.

Type 3: Seen in patients with prior coronary stent implantation. These patients may experience an allergic response leading to in-stent thrombosis, which is characterized by an eosinophil-rich thrombus. This can result in ischemia owing to platelet activation, adhesion, and aggregation induced by inflammatory mediators. This type constitutes approximately 5.1% of all cases of Kounis syndrome. (4).

CASE REPORT

A 56-year-old male patient with no past medical history was administered oral 1000 mg amoxicillin/clavulanic acid for a dental abscess. It has been confirmed that the patient did not receive any other medical treatment other than this treatment. The patient developed sudden severe chest pain after receiving the first dose of medication. Within 10 minutes of the onset of the pain, the patient lost consciousness and fainted. The emergency health services team called to the house, determined that the patient was in cardiac arrest and started cardiopulmonary resuscitation. The patient's first intervention was successful. After intubation and hemodynamic stabilization, the electrocardiogram (ECG) of the patient revealed sinus tachycardia with the heart rate of 130beats/minute and ST elevation in leads DII, DIII, and aVF and 3 mm ST depression in leads V2-6 (ECG 1). The patient underwent immediate coronary angiography with the diagnose of ST segment elevation myocardial infarction

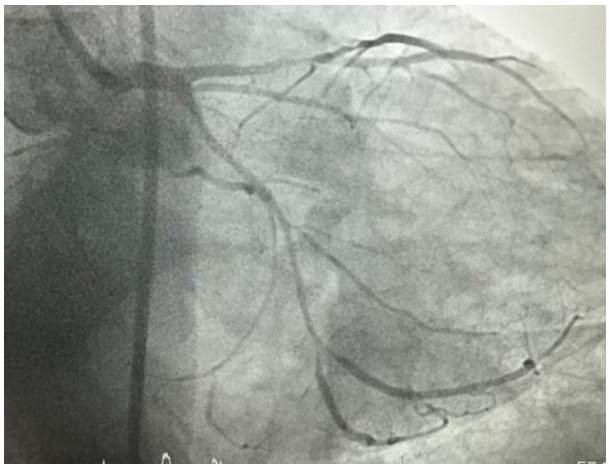

Figure 1. The first image of the patient's left coronary system in the presence of spasm on coronary angiography

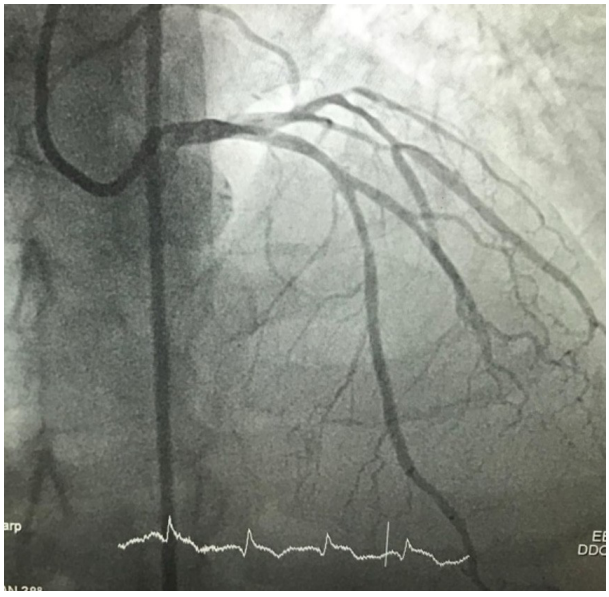

Figure 2. The second image of the patient's left coronary system in the presence of spasm in coronary angiography.

(STEMI). On coronary angiography, the left main coronary artery (LMCA) was normal. In the left anterior descending coronary artery (LAD) there was a long segment obstruction that was critically restricting the coronary blood flow (Figure 1) In circumflex artery (Cx), long segment obstruction throughout the main artery was observed (Figure 2).

The right coronary artery (RCA) was non-dominant, and we detected a critical osteal lesion (Figure 3).

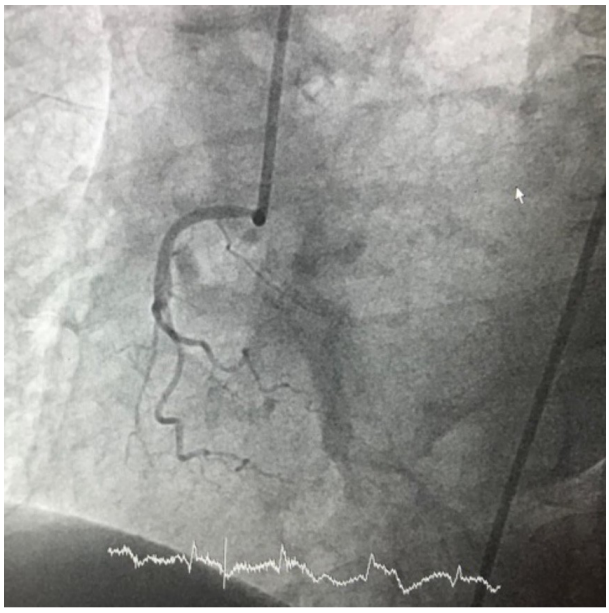

Figure 3. The patient's right coronary system in the presence of spasm on coronary angiography.

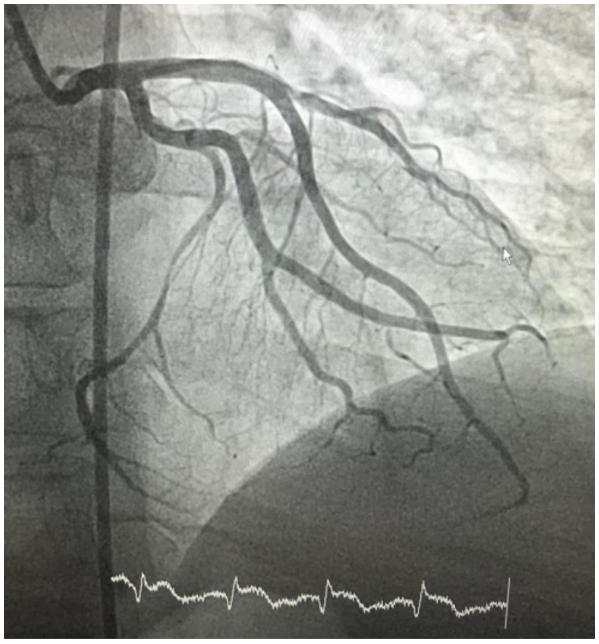

Figure 4. The first image of the patient's left coronary system on coronary angiography when the coronary spasm begins to resolve.

Ventricular tachycardia developed simultaneously while intracoronary nitrate was applied through the left guiding catheter. During the coronary angiography procedure, 300mg intravenous amiodarone were administered to the patient, who was hemodynamically stable.

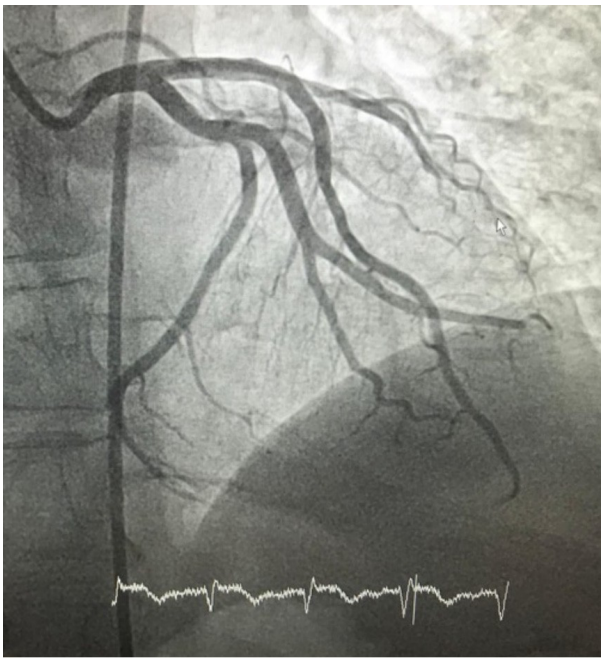

Figure 5. The last image of the patient's left coronary system on coronary angiography after the coronary spasm had completely resolved.

Normal sinus rhythm was achieved without the need for electrical cardioversion (ECG 2). In the images taken after intracoronary 200 μg nitrate, the LAD (Figure 4) and then the CX coronary spasms were completely resolved. In the final images of the coronary angiography, a myocardial bridge was seen in a short segment of the LAD mid-region, causing 40% stenosis (Figure 5).

The transthoracic echocardiography of the patient, who was taken to the coronary intensive care unit after hemodynamic stabilization, revealed a left ventricular ejection fraction (LVEF) of 55%, no significant wall motion abnormality, and mild mitral and tricuspid valve regurgitation. Laboratory parameters at the time of admission to the emergency department are presented in the table (Table 1). The patient was followed up under coronary intensive care unit for a day and then transferred to the anesthesiology and reanimation department. The patient, who was evaluated as hypoxic brain after neurological examinations and whose spontaneous breathing did not return despite all efforts and could not be extubated, died due to resistant pneumonia after 34 days of intensive care follow-up.

DISCUSSION

In this case report we present a 56-year-old patient without any chronic disease who presented with sudden cardiac arrest after taking oral amoxicillin/clavulanic acid. As it was seen in our case, Kounis syndrome is prevalent in 40–70-year-old male individuals and is mostly accompanied by chest pain (5)

Kounis syndrome (KS) is a clinical condition that precipitates acute coronary syndrome (ACS) due to hypersensitivity reactions. Within 60 minutes of exposure to the etiological agent, symptom onset occurs in 80% of cases. A recent investigation revealed that the predominant cardiac manifestations were chest discomfort (60%) and reduced blood pressure (75%). The study also documented dermatological, respiratory, and gastrointestinal involvement in 70%, 30%, and 20% of individuals, respectively. The study also found that electrocardiographic changes, such as ST-segment elevation or depression, were present in 85% of cases. Elevated cardiac biomarkers, particularly troponin levels, were detected in 70% of the patients, indicating myocardial damage. These findings underscore the importance of prompt recognition and management of Kounis syndrome to prevent potentially fatal complications (6).

The primary mechanism of KS pathogenesis involves the activation and degranulation of mast cells through various processes, leading to an increase and release of inflammatory mediators in both cardiac tissue and systemic circulation. This activation can result in coronary vasoconstriction, trigger platelet activation, cause plaque rupture, or initiate the coagulation cascade. Acute myocardial injury or sudden coronary or stent thrombosis may develop from coronary artery spasm (7). In the current case we present, there was no known ischemic coronary artery disease in the patients past medical history. Immediate coronary angiography did not show any atherosclerotic lesion or thrombus formation other than the noncritical muscular bridge in the mid-LAD region, but widespread severe coronary spasm was detected.

In a case report presented by Ralapanawa et al. a 74-year-old male patient with a history of diabetes and hyperlipidemia was admitted to the emergency room with anginal chest pain after taking oral amoxicillin. The patient, whose laboratory tests were stable, was discharged after relief of the chest pain from the emergency department (8). However, in our case, although there was no risk factor, unfortunately the patient had a sudden cardiac arrest at home and died despite all interventions due to prolonged hypoxia. This shows us that the severity of coronary vasospasm may vary and that the clinical condition of the patient before the first medical contact is very important for survival.

In the management of anaphylaxis, epinephrine remains the gold standard treatment. Timely administration is crucial, as it enhances patient survival. Nevertheless, caution is warranted in cases of acute coronary syndrome, where epinephrine may potentially aggravate ischemia, extend the QT interval, and trigger coronary vasospasm and cardiac arrhythmias. Because adrenaline can increase the production of thromboxane B2 synthesized by platelets and have a triggering effect on platelet aggregation (9,10). Although the use of adrenaline in the treatment of Kounis syndrome seems controversial. In the current case, adrenaline was compulsorily administered during the intervention of sudden cardiac arrest. However, its effect could not be evaluated due to ongoing hemodynamic instability.

In the management of acute coronary syndrome, acetylsalicylic acid (ASA) is commonly employed. Nevertheless, this medication carries the risk of inducing allergic reactions, which may manifest as anaphylactoid symptoms. Furthermore, ASA has the potential to aggravate pre-existing anaphylaxis in affected individuals. Its benefit in KS is unclear because, while it may provide benefits, it may also potentially worsen anaphylaxis. In the treatment of KS, calcium channel antagonists are regarded as the optimal anti-ischemic therapy, owing to their efficacy in counteracting the vasospastic pathophysiological mechanism commonly associated with this condition (11).

Kounis syndrome (KS) is an acute coronary syndrome triggered by hypersensitivity reactions. This case study demonstrates the importance of considering KS in patients with cardiac symptoms after allergen exposure, particularly antibiotics. The patient's cardiac arrest following amoxicillin/clavulanic acid administration and angiographic evidence of coronary vasospasm are consistent with KS. Prompt diagnosis and tailored treatment are crucial for improved outcomes. Management involves balancing allergic and cardiac manifestations. The case underscores the need for increased awareness among healthcare providers. Future research should focus on standardized diagnostic criteria, treatment protocols, long-term prognosis, and preventive strategies for KS patients.

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Abbreviations List

ACS: Acute coronary syndrome
Cx: Circumflex artery
ECG: Electrocardiogram
KS: Kounis syndrome
LAD: Left anterior descending coronary artery
LMCA: Left main coronary artery
LVEF: Left ventricular ejection fraction
RCA: Right coronary artery
STEMI: ST elevation myocardial infarction

Ethics approval and consent to participate

Ethical committee approval is not required because of the article is a case report. Informed consent was obtained from patient.

Consent for Publication

Although the personal information of the patient presented in the case was kept confidential, consent to share data was obtained from the patient and her relatives. This case study was conducted in accordance with the principles of the Declaration of Helsinki.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declaration of Conflicting Interests

The author declares that he has no conflicts of interest.

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