E-ISSN: 2791-8823

CSMJ

THE JOURNAL OF BAŞAKŞEHİR ÇAM AND SAKURA CITY HOSPITAL

Figure 1. Transverse section demonstrating preoperative and postoperative views

CAM & SAKURA MEDICAL JOURNAL

April
2025 Volume: 5 Issue: 1

www.csmedj.org

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Volume: 5 • Issue: 1 • April 2025

Editorial Board

CAM & SAKURA MEDICAL JOURNAL

CSMJ

Volume: 5 • Issue: 1 • April 2025

Editorial Board

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Publisher Contact
Address: Molla Gürani Mah. Kaçamak Sk. No: 21/1
34093 İstanbul, Turkey
Phone: +90 (530) 177 30 97
E-mail: info@galenos.com.tr/yayin@galenos.com.tr
Web: www.galenos.com.tr
Publisher Certificate Number: 14521

Printing at: Son Sürat Daktilo Dijital Baskı Merkezi Sanayi ve Ticaret Ltd. Şti.
Gayrettepe Mahallesi, Yıldızposta Caddesi, Evren Sitesi A Blok No: 32
D: 1 - D: 3 34349 Beşiktaş, İstanbul, Türkiye
Phone: +90 (212) 288 45 75 **E-mail:** info@sonsuratdaktilo.com
Printing Date: July 2025

E-ISSN: 2791-8823
International scientific journal published quarterly.

CSMJ

Volume: 5 • Issue: 1 • April 2025

Editorial Board

CSMJ

Volume: 5 • Issue: 1 • April 2025

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Volume: 5 • Issue: 1 • April 2025

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Cam and Sakura Medical Journal is indexed in **DOAJ, J-Gate, Türk Medline, EBSCO** and **Gale**.

The journal is published electronically.

Owner: Başakşehir Cam and Sakura City Hospital

Responsible Manager: Merih Çetinkaya

CSMJ

Volume: 5 · Issue: 1 · April 2025

Contents

DOI: 10.4274/csmedj.galenos.2025.2025-7-1

REVIEW

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Cam and Sakura Med J 2025;5(1):1-8

CSMJ

Enhancing Pediatric Congenital Heart Disease Outcomes: The Role of Machine Learning Models and AI-Driven Methodologies

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ABSTRACT

Congenital heart disease (CHD) presents a complex etiology involving multifaceted genetic and environmental interactions. The global prevalence of CHD approximates 8 per 1,000 live births, with elevated rates observed during prenatal periods, attributed to spontaneous pregnancy loss and elective terminations. Timely and precise diagnosis remains fundamental for optimal clinical outcomes, necessitating collaborative efforts among genetic counselors, obstetric practitioners, and pediatric cardiovascular specialists. While conventional diagnostic approaches such as electrocardiography and echocardiography continue to serve as cornerstone tools, sophisticated imaging techniques including cardiac computed tomography and magnetic resonance imaging are increasingly incorporated into clinical practice. Nevertheless, diagnostic challenges persist due to limited clinical recognition, inadequate healthcare infrastructure, and scarcity of specialized practitioners, potentially compromising diagnostic timeliness. Within this framework, artificial intelligence (AI)—specifically machine learning and deep learning technologies—has emerged as a transformative approach in pediatric cardiovascular medicine. AI systems demonstrate capability in identifying complex patterns within extensive datasets, thereby enhancing diagnostic precision, facilitating risk assessment, and enabling personalized therapeutic interventions. Contemporary AI implementations have demonstrated potential in optimizing cardiac imaging interpretation, supporting clinical decision-making processes, and forecasting patient outcomes. Despite promising developments, AI integration within pediatric CHD management remains constrained. Single-institutional studies and the relative rarity of CHD limit data accessibility, emphasizing the necessity for multi-center collaborative research initiatives. Additionally, AI-based systems can enhance postoperative surveillance, simulate therapeutic approaches, and identify complications through wearable monitoring technologies. Such innovations prove particularly valuable in resource-constrained environments where pediatric cardiovascular expertise remains limited. This comprehensive review examines the current state, existing challenges, and future prospects of AI implementation in pediatric cardiovascular medicine. Leveraging AI's comprehensive potential may revolutionize care delivery pathways, enhance prognostic outcomes, and optimize health management for children with CHD.

Keywords: Artificial intelligence, congenital heart disease, machine learning, pediatric cardiology

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Received: 07.07.2025 **Accepted:** 09.07.2025 **Publication Date:** 22.07.2025

Cite this article as: Karimov E, Zaim Gökbay İ. Enhancing pediatric congenital heart disease outcomes: the role of machine learning models and AI-driven methodologies. Cam and Sakura Med J. 2025;5(1):1-8

Introduction

Congenital heart diseases (CHD) demonstrate multifactorial etiology, arising from sophisticated interactions between genetic predisposition and environmental influences. Literature examining neonatal populations reports CHD incidence at approximately 8 cases per 1,000 live births (1,2). Research evidence suggests elevated CHD incidence during prenatal periods, correlating with increased rates of spontaneous pregnancy loss and fetal demise, alongside elective pregnancy terminations following prenatal diagnosis (3). Within this clinical context, genetic specialists, gynecological and obstetric practitioners, and particularly pediatric cardiovascular specialists must possess a comprehensive understanding of CHD risk factors and employ timely diagnostic methodologies for effective clinical management (4).

Primary diagnostic approaches in pediatric cardiovascular medicine following comprehensive clinical evaluation encompass electrocardiographic (ECG) and echocardiographic (ECHO) assessments (5). However, cardiac computed tomography (CT) and cardiac magnetic resonance imaging (MRI) are progressively utilized as diagnostic tools in subsequent clinical phases (6). Regarding CHD, particularly for prenatal or postnatal monitoring, diagnoses are generally established through ECHO evaluation when clinical suspicion emerges. Nevertheless, timely diagnostic achievement depends upon clinical awareness, available hospital infrastructure, and accessibility of experienced specialists (7). Navigating these diagnostic processes can prove time-intensive for both patients and healthcare providers. Furthermore, the broad spectrum of conditions and limitations in clinical decision support systems for preoperative and postoperative care contributes to increased clinician burden.

Through technological advancement, artificial intelligence (AI) tools, particularly machine learning (ML) and deep learning, have gained increasing prominence in medical practice, reflecting their adoption across various scientific disciplines. ML utilizes statistical modeling to identify patterns within historical data, enabling computational systems to predict future scenarios under comparable conditions.

The expanding implementation of AI has been enhanced by workforce growth and accumulated expertise within this domain. However, the application of by numerous physicians and healthcare professionals appears limited to conversational AI systems. Nevertheless, with appropriate data integration and system training, AI demonstrates substantial potential, particularly in areas such as CHD, characterized by significant disease variability and numerous diagnostic and therapeutic approaches.

Contemporary literature regarding AI applications primarily emphasizes developing diagnostic algorithms and postoperative monitoring in CHD. The primary challenge involves limited availability of large datasets, necessary for creating AI algorithms in single-center studies, particularly for rare conditions like CHD. Consequently, there is an urgent need for multicenter studies or extended data collection periods to accumulate sufficient information in this field.

AI is increasingly utilized in clinical applications, including diagnosis, monitoring, and treatment of CHDs, contributing to notable advances in pediatric cardiovascular medicine. The capacity to enhance diagnostic accuracy of imaging modalities such as cardiac MRI, echocardiography, cardiac CT angiography, and electrocardiography through AI algorithms enables more reliable and earlier detection of CHDs in both prenatal and postnatal stages.

Recently developed AI-based models are being implemented across various subspecialties within pediatric cardiology, including screening protocols, physical examination findings evaluation, diagnostic process support, medical image analysis, prognosis prediction, risk assessment, and personalized patient-specific medical approaches. ML techniques can also predict complication risk and progression, offering opportunities for preventive interventions (8).

However, AI technology integration into comprehensive care for children with CHD remains limited in the current literature, thereby hindering the full realization of its potential in this area. In complex diseases like CHD, the diversity of treatment options, especially postoperative approaches, can be simulated to create patient-specific treatment plans, potentially reducing mortality and morbidity. Furthermore, utilizing monitoring or wearable devices during postoperative periods can facilitate arrhythmia detection and the development of early warning systems for healthcare personnel. Additionally, AI can assist by providing relevant educational materials for early diagnosis and triage in rural areas where specialist healthcare personnel are scarce.

This survey aims to explore challenges and opportunities associated with integrating AI technologies into pediatric cardiology. Addressing these points will help improve healthcare quality and patient outcomes in pediatric cardiology.

Types of Machine Learning Models

ML, a computer science subdiscipline, simulates human cognitive processes through algorithms designed to learn

from data inputs. As a fundamental component of big data analytics, ML finds application in diverse fields including pattern recognition, computer vision, and biomedical research. ML enables computational systems to derive insights from data, thereby providing predictive and decision-making capabilities without dependence on explicit programming protocols (9). This involves training algorithms on comprehensive datasets to identify significant patterns and iteratively improve performance metrics. Within medical applications, ML algorithms emerge as essential tools, capable of processing complex datasets to enhance diagnostic process precision, personalize therapeutic strategies, and predict patient prognoses (10,11).

ML is generally structured around three fundamental paradigms: supervised, unsupervised, and reinforcement learning models. Supervised learning involves training algorithms on datasets where each input is paired with a corresponding, predefined output label. This approach enables models to infer patterns between input features and expected outcomes, allowing for predictions on new, unobserved instances. It is widely applied in predictive tasks, particularly classification and regression problems. While classification models categorize data into distinct groups, regression models are used to predict values along a continuous spectrum.

Common classification techniques comprise logistic regression, decision trees, random forests, support vector machines (SVM), K-nearest neighbors (K-NN), naïve Bayes, and artificial neural networks. In the context of regression, frequently utilized models include linear and polynomial regression, ridge, and lasso regression, elastic net, support vector regression, and neural networks (12,13).

Unsupervised learning, by contrast, operates on data lacking explicit labels, with the goal of uncovering intrinsic structures or relationships within the dataset. Key methodologies in this category include clustering, dimensionality reduction, and mining for association rules. Clustering methods—such as K-means and hierarchical clustering—organize similar data points based on feature resemblance. Meanwhile, dimensionality reduction techniques like Principal Component Analysis minimize the feature set while preserving essential information content (14).

Reinforcement learning, the third paradigm, centers on training an agent to take a series of actions within an environment to optimize long-term cumulative rewards (15).

Figure 1 presents various types of ML models, and the subsequent section elucidates commonly used predictive models.

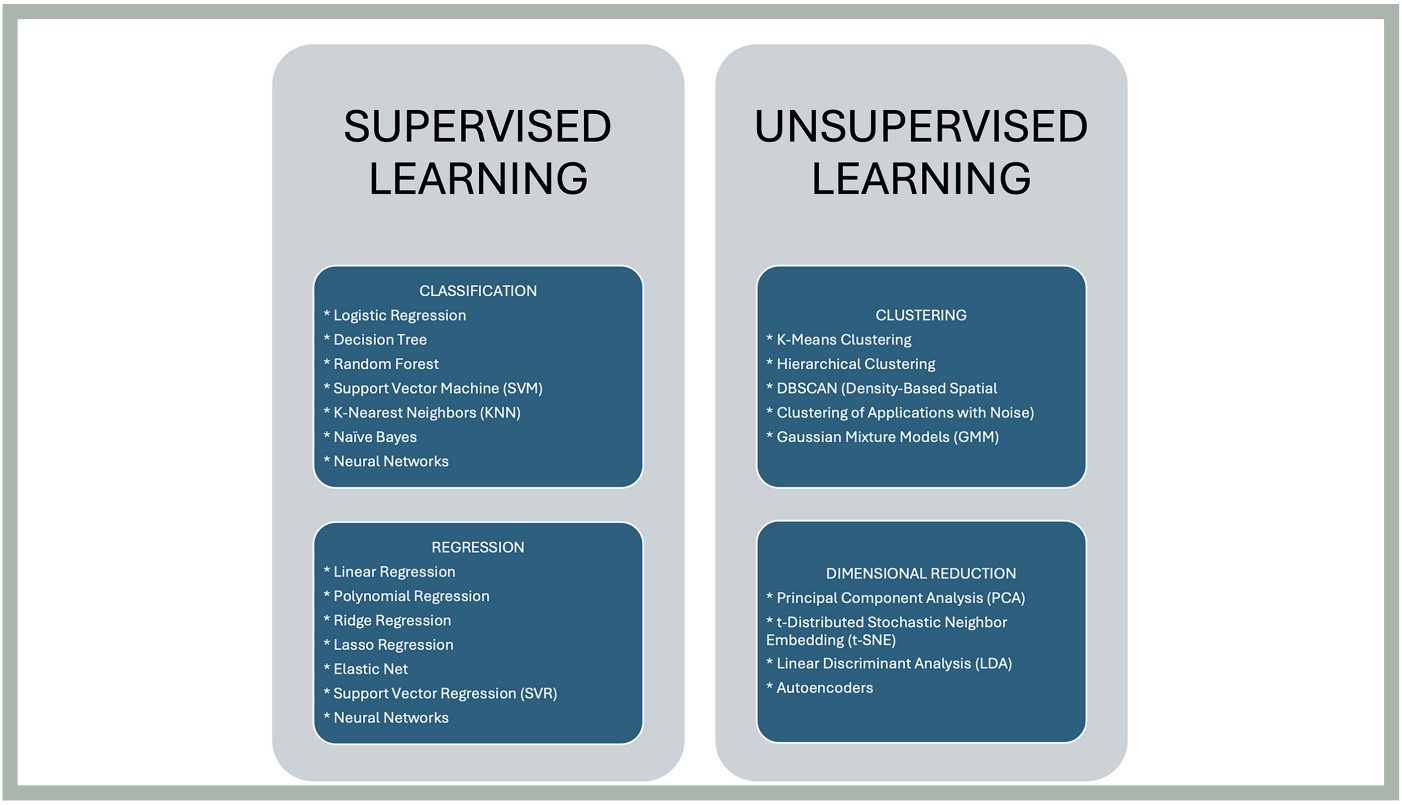

Figure 1. Types of machine learning

Data Classification and Predictive Models

Outcome prediction, risk assessment, and customization of treatment and follow-up for CHD patients now involve various ML models and AI tools, each with distinct advantages and limitations. A predictive model constitutes a mathematical equation designed to forecast outcomes based on one or more input variables. This tool employs data and algorithms to predict outcomes. Given a defined set of measured attribute values for an object x, the objective is to predict the unknown value of another attribute y. The attribute y is designated as the "output" or "response" variable, while the set $x = \{x_n,\cdots, x_1\}$ constitutes the "input" or "predictor" variables. The essence of predictive, also known as machine, learning is to construct a prediction function f(x) that approximates y with minimal error.

Data classification is a supervised learning method, that assigns new observations to one of several predefined categories, based on quantitative attribute Emser et al. (16). Data classification can be approached through two methods: one focuses on creating binary distinctions between two classes, assigning labels of 0 or 1 to data items, while the other aims to model P(y|x), providing both class labels and class membership probabilities. SVM exemplify the former approach, whereas logistic regression, decision trees, artificial neural networks, and K-NN represent the latter, differing in their data approximation methods.

SVM utilize statistical learning theory to estimate model performance on new data by considering the characteristics of the data and the performance on the training dataset performance. They create boundaries between datasets by solving complex optimization problems. Different kernel functions allow varying levels of model flexibility. Because they are founded on statistical principles, these machines have been studied extensively. They have demonstrated performance comparable to or better than other ML algorithms in medical studies. A disadvantage of SVM is that classification results only show simple divisions, without indicating class membership probabilities (17).

Logistic regression does not require a direct linear relationship between the independent and dependent variables themselves, but instead assumes linearity between the log-odds of the outcome and the predictor variables (18). This model is fundamentally based on the concept of odds in the context of binary outcomes. When focusing on a specific event, its odds are defined as the probability of occurrence relative to the probability of non-occurrence. These odds are often used to represent the likelihood of an event. The logistic regression framework applies the natural logarithm of the odds—referred to as the logit—as a linear function of the predictor variables.

In the case of a single predictor variable, denoted as XXX, the model can be written as:

ln^{f0}(odds)=β0+β1X\ln(\text{odds}) = \beta_0 + \ beta_1Xln(odds)=β0+β1X

where ln^{f0}\lnIn denotes the natural logarithm, β0\beta_0β0 is the intercept, and β1\beta_1β1 represents the coefficient for XXX. The coefficient β1\beta_1β1 indicates the change in the log-odds of the outcome for each one-unit increase in XXX. Since the difference between logarithms corresponds to the logarithm of a ratio, exponentiating β1\beta_1β1 provides the odds ratio, reflecting how the odds change with a one-unit increase in the predictor variable (19).

Decision trees represent a ML technique that creates models without requiring specific data requirements or assumptions (20). Before examining decision trees, it is essential to establish a foundation of terminologies. The root node serves as the starting point, initiating dataset division based on features or conditions. Decision nodes arise from subsequent root node splitting, representing intermediate decisions within the tree structure. Conversely, leaf nodes signify terminal points where further division is infeasible, denoting final classifications or outcomes. A sub-tree, analogous to a subgraph, constitutes a specific section of the overall decision tree. Pruning involves selective node removal to mitigate overfitting and enhance model simplicity. Branches or sub-trees represent distinct pathways of decisions and outcomes within the tree.

In hierarchical models such as decision trees, parent nodes represent decision criteria or conditions, while child nodes denote possible outcomes or subsequent decisions based on those criteria. These structures are used to derive solutions by analyzing previously resolved instances. The process typically begins by dividing the dataset into two subsets: one for training, where the tree is constructed, and one for testing, where the accuracy of the resulting decisions is validated. Each instance in the dataset is described by a set of attributes, one of which is selected to guide the decision-making process. All input attributes are assigned value categories—discrete attributes with limited unique values, form their own categories, while continuous or highly varied numeric attributes are grouped into defined intervals.

Within the tree, attributes are represented as internal or decision nodes, each branching into paths corresponding to different value categories. The terminal nodes, or leaves, of the tree indicate decision outcomes, effectively mapping the predicted class for the decision attribute. To classify a new, unseen instance, traversal begins at the root node and

proceeds along branches that match the instance's attribute values, until a leaf node is reached, signifying the final decision (21).

While binary classification (e.g., positive vs. negative) is common, decision trees can also be extended to multi-class scenarios to accommodate more complex decision categories. Early theoretical foundations for decision trees were introduced by Clopper and Pearson (22) in 1934 through binary decision frameworks. However, practical applications in ML gained momentum later. In 1984, Leo Breiman proposed the Classification and Regression Tree algorithm, which popularized concepts like binary splits and the Gini impurity metric—both now standard in decision tree construction (23). Subsequently, Quinlan (24,25,26) introduced the ID3 algorithm in 1986, followed by the improved C4.5 model in 1993. These innovations paved the way for the integration of decision trees into ensemble learning approaches such as random forests and boosting techniques, cementing their role as foundational tools in modern ML.

The K-NN algorithm is another simple yet effective classification technique. It assigns a class to a new data point based on the majority class among its k closest neighbors in the feature space. Unlike some models, K-NN lacks a generalization phase, which may hinder interpretability. However, it offers transparency by presenting specific training instances that influenced a decision. This case-based reasoning is often viewed favorably in medical contexts, as it reflects clinical decision-making based on prior similar experiences (27).

Naïve and semi-naïve Bayes methods are simpler and faster than other classifiers (28). Although often outperformed by models like logistic regression or random forests, certain models remain popular for tasks such as text classification and spam filtering, especially where computational resources are limited (29). Naïve and semi-naïve Bayes methods utilize conditional probability tables. The decisions made by Bayesian classifiers, can be seen as aggregating information gains. The formula used to calculate the information needed to determine if something belongs to class C explains decisions by combining information gains that either support or oppose the class. This method works for semi-naïve Bayes as well, but it uses combined attribute/value pairs instead of simple values. This information gain can be arranged in a table to show the evidence for or against a decision (30).

The Application of Machine Learning Methods in Congenital Heart Disease

ML models, and AI-driven methods are transforming healthcare with innovative approaches to enhance diagnosis, treatment, and management of illnesses, particularly concerning pediatric cardiac conditions. This section explores how AI can contribute to addressing these complex cardiac issues. Furthermore, it examines how AI can improve diagnostic accuracy and personalize treatments, ultimately leading to enhanced outcomes for young patients.

Between 2011 and 2017, Qu et al. (31) conducted research at a prominent cardiac center in China, comprehensively examining unborn infants for potential cardiac defects via ultrasonography. Suspicious cases underwent confirmation through echocardiograms conducted by at least two pediatric cardiology specialists. The study scrutinized a total of 1,127 potential predictors of cardiac anomalies, employing an Explainable Boosting Machine to forecast defects and evaluating performance using Receiver Operating Characteristic curves. Predictors were prioritized based on their predictive contribution, and corresponding thresholds were established. The study encompassed 5,390 mother-child pairs, with the predictive model achieving a 76% accuracy rate. Predominantly, the top 35 predictors comprised laboratory test results, with only a single predictor originating from questionnaire data. The model exhibited an overall accuracy of 0.65, with sensitivity and specificity values of 0.74 and 0.65, respectively. Maternal uric acid levels, glucose levels, and blood clotting efficiency emerged as the most reliable and influential predictors of cardiac defects. Threshold analysis indicated that elevated uric acid levels, shortened activated partial thromboplastin time, and elevated glucose levels were the most salient predictors, correlating with 1.17-1.54 times, increased risk of cardiac defects. Based on these findings, the authors developed an online tool designed to facilitate screening and prevention of cardiac defects.

Owens et al. (32) used data from the Statewide Planning and Research Cooperative System spanning January 1, 2000, to December 31, 2014, to investigate maternal delivery hospitalizations and associated neonatal admissions among women diagnosed with cardiomyopathy, adult congenital heart disease (ACHD), pulmonary hypertension (PH), and valvular heart disease. The study employed the International Classification of Diseases, Ninth Revision, Clinical Modification, to identify cases and capture maternal major adverse cardiac events (MACE), neonatal clinical complications, and obstetric outcomes. Outcomes were analyzed using multivariate logistic regression.

Among the 2,284,044 delivery admissions reviewed, 3,871 involved women with cardiac conditions: 676 with cardiomyopathy, 1,528 with valvular heart disease, 1,367 with ACHD, and 300 with PH. Major cardiac events were reported in

16.1% of those with heart disease, with the highest incidence among patients with cardiomyopathy and PH. Neonatal complications were also more frequent among offspring of affected mothers, particularly in the cardiomyopathy and PH subgroups. Women with heart disease showed a significantly elevated risk of neonatal adverse outcomes, and this risk was most pronounced in the cardiomyopathy and PH cohorts. Independent predictors for neonatal complications included preeclampsia, MACE, preexisting diabetes mellitus, and other obstetric issues.

In another study, Xu et al. (33) retrospectively examined pediatric patients diagnosed with infective endocarditis between January 2010 and December 2021 at a single institution. Data collected included demographics, clinical symptoms, microbiological findings, ECHO data, pre-existing cardiac conditions, and outcomes. The study included 90 children, with 60% having a history of heart disease. *Staphylococcus aureus* emerged as the most commonly isolated pathogen, observed more frequently in patients without structural heart disease compared to those with underlying heart conditions.

ECHO analysis identified vegetations in 88 patients: 41 on the left side of the heart, 45 on the right, and 2 cases with bilateral involvement. Right-sided vegetations were more often seen in patients with heart disease, while left-sided vegetations predominated in those without. Embolic events were documented in 25 cases, with a higher incidence in the non-heart disease group. Spontaneous resolution of vegetations occurred in nine patients, and four patients died during hospitalization. Logistic regression indicated that the absence of structural heart disease and the presence of moderate to severe valvular dysfunction were independent risk factors for embolic complications.

Babič et al. (34) examined cardiovascular disease, encompassing a diverse array of conditions that impair heart and vascular function, including coronary artery disease, arrhythmias, and congenital or acquired structural abnormalities. The term is frequently associated with vascular obstructions or stenoses that may precipitate acute events such as heart attacks, angina, or cerebrovascular incidents. In their study, three datasets were analyzed: the Heart Disease Database, the South African Heart Disease Dataset, and the Z-Alizadeh Sani Dataset. The team applied various ML models, specifically Decision Trees, naïve Bayes, SVM, and Neural Networks, for predictive analytics, supplemented by descriptive methods based on rule-based association and decision logic.

Model performance was evaluated using data from multiple sources. For the Cleveland, Hungary, Switzerland, and Long Beach VA datasets, classification accuracies were reported as 88.09% for Decision Trees, 86.76% for naïve Bayes, 88.53% for SVM, and 89.93% for Neural Networks. Model accuracy rates on the South African dataset were slightly lower: Decision Trees achieved 73.87%, naïve Bayes 71.17%, SVM 73.70%, and Neural Networks 68.48%. With respect to the Z-Alizadeh Sani dataset, the results indicated accuracies of 85.38% for Decision Trees, 83.33% for naïve Bayes, 86.67% for SVM, and 86.32% for Neural Networks. Based on these findings, the researchers concluded that the implemented models yielded robust and consistent outcomes, often matching or surpassing those found in comparable studies.

In a separate investigation, Pachiyannan et al. (35) introduced a novel ML-based framework designed to reduce neonatal mortality in cases of CHD. The model processes infant medical records to pinpoint critical mortality risk factors, thereby supporting timely clinical intervention and individualized care strategies for neonates at elevated risk. By integrating maternal health history and prenatal indicators, the diagnostic tool facilitates accurate evaluation of newborns affected by CHD. The Cardiac Deep Learning Model yielded encouraging performance metrics, demonstrating a sensitivity of 91.74%, specificity of 92.65%, a positive predictive value of 90.85%, negative predictive value of 55.62%, and a miss rate of 91.03%. These findings imply that the model may serve as a valuable clinical resource, equipping healthcare providers with decision support capabilities to mitigate CHD-related neonatal mortality and enhance treatment outcomes.

Lee et al. (36) carried out a retrospective analysis involving ECG data from 1,035 pediatric patients aged under five at Chang Gung Memorial Hospital in Taoyuan, Taiwan. Based on ECG interpretations, patients were grouped into five diagnostic categories: normal cardiac anatomy, non-significant right heart disease, significant right heart disease, non-significant left heart disease, and significant left heart disease. ECG signals underwent preprocessing via continuous wavelet transformation and were then divided into two-second segments to augment the dataset. Following this, transfer learning was implemented using three pre-trained deep learning architectures: ResNet-18, InceptionResNet-V2, and NasNetMobile. These models were assessed using standard classification metrics, including accuracy, sensitivity, specificity, F1 score, and the area under the receiver operating characteristic curve (AUC-ROC).

Among the evaluated models, ResNet-18 achieved the best overall results for identifying clinically significant CHD, reaching an accuracy of 73.9%, F1 score of 75.8%, and AUC of 81.0%. While InceptionResNet-V2 demonstrated strong

performance in detecting left-sided heart abnormalities, it required significantly more computational resources.

Notably, the AI models outperformed pediatric cardiologists' interpretations of conventional ECGs. The authors highlighted the potential of AI-enhanced ECG analysis as a valuable adjunct tool in CHD screening for young children, with ResNet-18 emerging as a particularly effective model.

Niyogi et al. (37) examined the transformative role of AI in the diagnosis, treatment, and lifelong management of CHD. The study addressed recent progress in prenatal detection, postnatal intervention, and chronic monitoring, while also recognizing limitations such as the lack of standardized datasets and ethical complexities. Notable advancements include the use of AI in fetal echocardiography and genetic screening, facilitating more precise prenatal risk assessment. Additionally, the integration of AI into imaging diagnostics has improved classification and severity evaluation of CHD subtypes. The authors also emphasized the role of AI-driven clinical decision support systems, which contribute to personalized care plans and better prognostic evaluations. Remote AI monitoring tools were also noted for their potential to detect complications early, supporting long-term patient management.

Chen et al. (38) introduced a deep learning–based diagnostic system, Congenital Heart Disease diagnosis via Electrocardiogram (CHDdECG), designed for the detection of congenital heart defects using pediatric ECGs. This approach combines automated feature extraction via wavelet transformation with selected expert-identified features. Trained on a dataset of 65,869 cases, CHDdECG achieved a ROC-AUC of 0.915 and a specificity of 0.881 on a real-world test set of 12,000 cases. On two external validation datasets (7,137 and 8,121 cases), the model yielded ROC-AUC scores of 0.917 and 0.907, and specificities of 0.937 and 0.907, respectively. The system outperformed cardiologists in CHD detection, with automatically extracted features contributing more significantly to model performance than manually selected ones. These findings highlight the promise of ECG-based deep learning for pediatric CHD screening, offering insights beyond conventional diagnostic approaches.

Conclusion

The studies reviewed underscore the significant potential of AI to revolutionize cardiovascular medicine by enhancing diagnostic precision, enabling personalized treatment approaches, and ultimately improving patient outcomes. AI algorithms have demonstrated their capability to analyze intricate datasets derived from electrocardiograms and advanced imaging modalities. This facilitates early and accurate detection of critical cardiovascular conditions, such as coronary heart disease and congenital heart defects, often surpassing the performance of conventional diagnostic techniques.

Moreover, decision support systems powered by AI offer considerable potential in personalizing treatment plans and enhancing the precision of outcome predictions. The integration of AI into remote patient monitoring facilitates the early identification of clinical complications, allowing for prompt intervention and better long-term disease management. Collectively, these technological advancements are poised to substantially influence healthcare delivery by providing clinicians with sophisticated tools to reduce cardiovascular-related mortality, improve patient outcomes, and support the timely and customized care of individuals at elevated risk.

Future research should focus on standardizing datasets, addressing ethical considerations, and validating AI models across diverse populations to fully realize the transformative potential of AI in cardiovascular care.

Authorship Contributions

İ.Z.G.: Supervision, Study planning, Methodology Planning, and Main manuscript editing.

E.K.: Main manuscript writing, Revision, Screening, Data extraction.

All authors have read and agreed to the published version of the manuscript.

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

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

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DOI: 10.4274/csmedj.galenos.2025.2025-2-1

ORIGINAL ARTICLE

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Cam and Sakura Med J 2025;5(1):9-16

CSMJ

Evaluation of Cognitive Functioning and Laterality in Women with Polycystic Ovary Syndrome

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What is known on this subject?

There are very few studies on cognitive functions in polycystic ovary syndrome (PCOS). Although there are various studies on spatial perception and manual skills, the test for spatial perception, line splitting task, used in our study was not utilized in previous studies. Again, studies on hand preference are severely limited.

What this study adds?

This is the first study to address the effect of hormones on lateralization through motor functions and attention in PCOS. The findings of this study primarily reveal an alteration in spatial attention, independent of hormones, in PCOS. However, it revealed that dehydroepiandrosterone also had a significant effect, although mild.

ABSTRACT

Objective: To investigate potential differences in laterality and cognitive performance between women with polycystic ovary syndrome (PCOS) and healthy individuals.

Material and Methods: Thirty women with PCOS and thirty-four healthy controls were recruited. Beck depression inventory, state and trait anxiety inventory (STAI), hand preference questionnaire, line splitting task (LBT), finger tapping, Rey auditory verbal learning test (RAVLT), and Stroop Test were administered to the patient and control groups. In addition, blood levels of androgens were measured.

Results: Although the depression score in the PCOS group was higher than the control group ($p=0.048$), there was no significant difference in the STAI scores ($p>0.05$). Stroop scores were found to be significantly lower in the PCOS group ($p=0.007$, $p=0.043$, $p=0.017$). The evaluation of Stroop interference scores and RAVLT scores revealed significant differences in RAVLT 1, RAVLT 2, and RAVLT 8 recognition sub-scores between groups ($p=0.003$, $p=0.002$, $p=0.038$, $p=0.010$ respectively). The absolute rate of right-handedness was statistically lower in the PCOS group ($p=0.04$). Only LBT values of absolute right-handed subjects (Hand Preference Questionnaire Score: 13) were involved to compare spatial distribution of attention between the groups. It seems that the bisection judgement bias of the PCOS group shifted slightly to the right ($p=0.025$). A significant interaction was found between LBT scores and dehydroepiandrosterone levels ($p<0.05$).

Conclusion: Several cognitive domains and laterality seem to be affected in PCOS.

Keywords: Brain laterality, cognitive functioning, polycystic ovary syndrome

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Received: 27.02.2025 **Accepted:** 21.04.2025 **Publication Date:** 22.07.2025

Cite this article as: Sağsöz N, Koçak OM, Bender RA. Evaluation of cognitive functioning and laterality in women with polycystic ovary syndrome. Cam and Sakura Med J. 2025;5(1):9-16

The findings of this study were presented as a poster at the 25th European Congress of Obstetrics and Gynaecology, held jointly with the 15th Congress of the Turkish Society of Obstetrics and Gynecology, between May 17-21, 2017.

CAM & SAKURA MEDICAL JOURNAL

Introduction

Polycystic ovary syndrome (PCOS) is a complex hormonal condition marked by elevated androgen levels, irregular or absent ovulation, and the presence of multiple cysts on the ovaries (1). Endocrinologic and androgenic disturbance might lead to psychological and mood disorders (1).

Cognitive differences between the sexes have always been of interest and may be due to gender differences (2,3). However, the effects of sex differences both in functional cerebral asymmetry and cognitive functioning have not been resolved yet (3). It has also been demonstrated that exposure to prenatal testosterone may have an effect on cognitive functions (2,4,5). However, there are many results regarding the effects of hyperandrogenism on cognitive functions in adulthood. It is generally accepted that women have higher scores on verbal and fine motor tasks than men. Men have higher scores on mathematical abilities and spatial tasks than women, as indicated by research (3). However, data are limited and unclear. Moreover, a factor such as depression affects cognitive functions. Depression may be common in patients with PCOS (6).

In this study, we aimed to assess whether the laterality and cognitive performance of patients with PCOS are different from those of the healthy control group.

Material and Methods

This study enrolled 30 women diagnosed with PCOS and 34 healthy controls from the outpatient clinic of a university hospital. The diagnosis of PCOS was established according to the Rotterdam criteria (2003). Cases of congenital adrenal hyperplasia, androgen-producing neoplasms, and Cushing's syndrome were excluded (7). It was preferred that the patients be at least high school graduates.

The exclusion criteria include systemic diseases, including renal, cardiovascular, and liver diseases, and endocrinopathies such as thyroid disease and diabetes mellitus. Moreover, patients using oral contraceptives and other hormonal drugs within the last 6 months were also excluded.

Modified-Ferriman-Gallwey score (FGS) was used to evaluate clinical hirsutism (8). The study protocol was approved by the Kırıkkale University Institutional Review Board (approval no: 2009/183; approval date: 29.06.2009), and written informed consent was obtained from all participants prior to enrollment.

Laboratory Measurements

A basal hormonal profile was obtained between 2 and 5 days of a spontaneous or progesterone-induced menstrual cycle, if necessary. A Venous blood sample was taken between 08:00-09:00 A.M. after an overnight fasting period of 8-10 hours, after that all samples were stored at -20 °C until analysis.

Serum follicle-stimulating hormone, luteinizing hormone, and estradiol levels were measured using a chemiluminescent enzyme immunometric assay on an Immulite analyzer, with a commercial kit provided by Diagnostic Products Corporation. Serum dehydroepiandrosterone sulfate (DHEAS) and total testosterone levels were assessed using chemiluminescence immunoassays (Elecsys 1010/2010 kit, Roche Diagnostics GmbH, Mannheim, Germany). Free testosterone and androstenedione levels were measured by enzyme immunoassay (EIA) (Diagnostics Systems Laboratories Inc., Webster, TX, USA). Sex hormone-binding globulin (SHBG) levels were also determined using EIA (BioSource Inc.). 17-hydroxyprogesterone levels were measured by enzyme-linked immunosorbent assay on a spectrophotometer (BioTek Instruments Inc., USA) using EIA kits from DSL (Diagnostic Systems Laboratories Inc., USA). The Free Androgen Index (FAI) was calculated using the following formula:

FAI: T (nmol/L) x100/ SHBG (nmol/L)

Evaluation of Cognitive Functions and Severity of Depression and Anxiety

In this study, the following tests were applied to all participants.

1. Beck depression inventory (BDI): Depression was scored using the Beck depression scale (9).

2. State and trait anxiety inventory (STAI): STAI 1 and STAI 2 were used to identify chronic anxiety lasting more than 1 year (10).

3. Hand preference questionnaire (HPQ): The hand preference scale was developed by Chapman and Chapman (11). The Turkish validity and reliability study was conducted by Nalçaci et al. (12). This questionnaire was developed to assess which hand is predominantly used in the performance of different actions carried out in daily life. It is a 13-question survey. The right hand was scored as 1, the left hand as 3, and a "both of them" response scored 2, thus hand preference was scored as a continuous value between 13 and 39 points. Therefore, as the score increases, there is a shift from right to left (12).

4. Finger tapping test: Motor speed was evaluated with the finger tapping test. The finger tappingtest test is a fast and reliable test used in the evaluation of fine motor movement. This test, all participants were instructed to press a button as quickly as possible using the index finger of the right hand,

followed by the left hand, for 20 seconds each. The procedure was repeated twice (right, left) (13).

5. Line bisection task (LBT): Spatial distribution of attention was evaluated using LBT. LBT is a simple and reliable test for assessing the spatial distribution of attention (14). In LBT, participants were requested to draw the midpoint of 10 different lines of different lengths, ranging from 9 cm to 18 cm, each extending by 1 cm. The deviation of the line from the midpoint was calculated and included in the analysis. Here, after a reliable test, right hand dominant individuals generally have a very slight right neglect, known as pseudo-neglect. The right hemisphere is responsible for managing attention.

6. Rey auditory verbal learning test (RAVLT): RAVLT is a neuropsychological test designed to assess verbal memory, also providing rich data on multiple memory processes. When applying this test, two lists of 15 words each were used (list A and list B). In the first 5 repetitions, the words in list A were read in the same order with gaps of approximately 1 second, and when the reading was finished, the person was asked to remember the words read (Rey 1-5) (total count of words remembered in the first trial indicates immediate verbal memory). Trials 1 and 5 show the learning performance. In the sixth application, list B was read and the patient was instructed to memorize the words in this list (Rey 6). List B in the sixth application is the interference list, which is expected to have a disruptive effect on remembering the words in list A. After this interference trial, the participant is immediately asked to recall the words from list A, which she heard five times previously (Rey 7). After 20 minutes, the participant is asked to recall the words in list A again (Rey 8). This application provides information about the "delayed recall" task. Then they were asked to identify the original words from list A within a set of 50 words, including 15 target words from list A, 15 distractor words from list B, and 20 entirely new words. The last application is the recognition application (15).

7. Stroop Test: Stroop Test includes 3 cards. Word (W), color (C), and colored word (WC). In the first condition, the person reads the words directly. In the second, she says the names of the colors in the list. In the third, she reads the word list printed with a different ink color than the written word, during which the Stroop effect is observed. The Stroop effect is characterized by a slower response time when the individual is obliged to say the color of the ink instead of reading the word itself, compared to plain reading (16,17). The following formula was used to calculate the Stroop interference scores of the participants.

Stroop interference = WC- [(WxC)/(W+C)]

Statistical Analysis

All statistical analyses were conducted using SPSS software, version 21.0 (SPSS Inc., Chicago, IL, USA). Data are presented as mean ± standard deviation. The Kolmogorov-Smirnov test was applied to assess data normality, confirming a normal distribution ($p>0.05$). Given the homogeneity of variances, parametric tests were employed. Group comparisons for STAI and BDI scores, as well as for mean hand preference scores, were performed using the Student's t-test. Nominal variables were analyzed using the chi-square test. An ANCOVA test was applied to examine the effect of PCOS and related hormones on cognitive test performance. For all implementations of RAVLT, individual groups were compared by Student's t-test. All analyses were performed two-tailed and $p<0.05$ was considered statistically significant.

Results

Table 1 presents the demographic and clinical profiles of the study groups. No statistically significant differences were observed in mean age or educational attainment between groups ($p=0.066$ and $p=0.188$, respectively). As anticipated, the PCOS group exhibited significantly higher body mass index and FGS values compared to controls ($p=0.006$ and $p<0.001$, respectively).

The blood parameters and hormone values of the groups are also presented in Table 1. Among these parameters, free testosterone and FAI showed statistically higher levels; however, 17-OH progesterone showed a borderline statistically significant elevation ($p=0.002$, $p=0.006$, and $p=0.050$, respectively). As expected, SHBG levels were found to be statistically lower in the PCOS group ($p<0.05$).

Cognitive test results are shown in Table 2. In the PCOS group, the depression scale indicated borderline significance. There was no difference between the groups in terms of STAI (anxiety) ($p>0.05$).

HPQ: No significant difference was observed when the participants were compared according to the groups in terms of the hand preference scores ($p=0.540$). To understand the effect of hormones on hand preference, the ANCOVA test was performed using DHEAS and free testosterone as covariates, group as a constant factor, and hand preference as an independent variable. Accordingly, although no effect of free testosterone on hand preference was observed, DHEA had a significant effect [$F(1.60)=0.364$, $p=0.433$; $F(1.60)=3.923$, $p=0.05$, respectively]. The Absolute right-handedness rate was statistically lower in the PCOS group ($p=0.04$).

Table 1. General characteristics and blood parameters of all participants

	PCOS (n=30) Mean ± SD	Control (n=34) Mean ± SD	p
Age (years)	22.7±2.24	24.2±3.81	0.066
Education			0.188
High school	8	7	
College student	16	13	
University graduate	6	14	
BMI (kg/m^2)	22.9±3.64	20.7±2.45	0.006
FGS	8.87±3.49	5.71±2.29	<0.001
Hb (gr/dL)	12.92±1.16	13.08±1.33	0.626
FSH (mIU/mL)	5.38±1.52	6.024±2.30	0.198
LH (mIU/mL)	9.14±3.74	9.76±10.38	0.851
LH/FSH	1.82±1.02	1.98±4.41	0.847
E_2 (pg/mL)	64.88±65.40	77.59±73.31	0.470
T testosterone (ng/mL)	0.560±0.29	0.456±0.26	0.131
F testosterone (pg/mL)	2.71±2.12	1.33±0.68	0.002
17-OH progesteron (ng/mL)	1.57±1.20	1.089±0.56	0.050
Androstenedione (ng/mL)	3.58±1.69	2.91±1.96	0.147
DHEAS (µU/dL)	290.39±167.13	226.48±67.96	0.058
SHBG (nmol/L)	34.21±20.65	46.29±25.94	0.045
FAI	2.59±2.2	1.24±0.8	0.06
Insulin (µU/mL)	11.80±6.47	9.82±4.48	0.166
T cholesterol (mg/dL)	167.33±37.75	158.94±33.38	0.349
LDL (mg/dL)	90.67±31.53	83.21±28.85	0.327
HDL (mg/dL)	56.13±9.16	60.16±12.12	0.143

PCOS: Polycystic ovary syndrome, BMI: Body mass index, FGS: Ferriman-Gallwey score, Hb: Hemoglobin, FSH: Follicle-stimulating hormone, LH: Luteinizing hormone, DHEAS: Dehydroepiandrosterone sulfate, SHBG: Sex hormone-binding globulin, FAI: Free androgen index, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, SD: Standard deviation

Table 2. Cognitive tests results

Cognitive tests	PCOS (n=30) Mean ± SD	Control (n=34) Mean ± SD	p
BDI	10.07±6.878	6.74±6.307	0.048
STAI-1	56.67±13.904	58.68±11.502	0.529
STAI-2	54.50±9.504	56.41±8.968	0.411
HPQ	15.50±4.67	14.76±4.86	0.540
Absolute right hand	36%	64%	0.04
Right hand 1 (tapping)	78.33±8.8	84.35±7.9	0.006
Right hand 2	79.27±9.8	84.03±7.3	0.03
Left hand 1	67.40±78.7	70.44±77.8	0.145
Left hand 2	67.63±9.9	69.68±6.7	0.148
LBT_{mean} (mm)	-0.04±0.20	0.039±0.19	0.108
LBT_{mean} (mm)* 13 cut-off	-0.096±0.21 (n=14)	0.042±0.15 (n=25)	0.025
Rey 1	7.07±1.660	8.44±1.926	0.003

Table 2. Continued

Cognitive tests	PCOS (n=30) Mean ± SD	Control (n=34) Mean ± SD	p
Rey 2	9.97±2.428	11.56±1.521	0.002
Rey 3	11.50±41.697	12.24±1.653	0.084
Rey 4	12.97±1.691	12.79±1.452	0.662
Rey 5	12.53±2.161	13.35±1.368	0.081
Rey 6	6.57±1.775	7.12±1.855	0.231
Rey 7	12.30±1.860	12.79±2.086	0.324
Rey 8	11.73±2.57	12.94±1.984	0.038
Rey recognition	13.67±1.863	14.65±0.646	0.010
Stroop 1	99.5±13.33	108.79±13.07	0.007
Stroop 2	71.10±12.25	77.53±12.63	0.043
Stroop 3	43.90±8.39	49.24±8.95	0.017
Stroop interference	2.96±6.04	4.26±7.22	0.44

**Data obtained from individuals with a Handedness Questionnaire Score of 13, indicating absolute right-handedness. PCOS: Polycystic ovary syndrome, BDI: Beck depression inventory, STAI: State and trait anxiety inventory, HPQ: Hand preference questionnaire, LBT: Line splitting task, SD: Standard deviation*

Finger tapping test: Repeated measures ANCOVA was also applied for the finger tapping test and it revealed a significant main group effect [F(1.61)=4.606, p=0.036]. Accordingly, the control group performed more finger taps than the PCOS group. At the same time, the hand preference effect was also detected [F(1.61)=72.796, p<0.001]. Finally, as expected, an interaction between right hand and hand preference was determined [F(1.61)=15.381, p<0.001].

LBT: In the LBT, there was no significant difference between the groups in terms of the mean distance from the center. However, due to the possibility that hand preference has an effect on the spatial distribution of attention in PCOS, absolute right-handed (Hand Preference Questionnaire Score: 13) individuals were included in the comparison between the groups to eliminate this effect, and the Student's t-test was used. In this analysis, 14 patients remained in the patient group and 25 in the control group. Accordingly, a significant difference was found between the groups in terms of distance from the center (p=0.025). In the ANCOVA test, free testosterone and DHEAS were treated as covariates, the LBT as the dependent variable, and the group as the independent variable. According to this, a significant main group effect and a significant DHEA effect were detected [F(1.60)=6.303, p=0.015], [F(1.60)=6.814, p=0.011, respectively].

RAVLT: Since each subgroup test of RAVLT differs, each subgroup test was compared between groups separately with a Student's t-test. In these comparisons, there was a significant difference was observed between the groups in Rey 1, Rey 2, Rey 8, and Rey recognition practices, with p values of (p=0.003, p=0.002, p=0.038, and p=0.010, respectively). In all these applications, the performance of the control group was better (Figure 1).

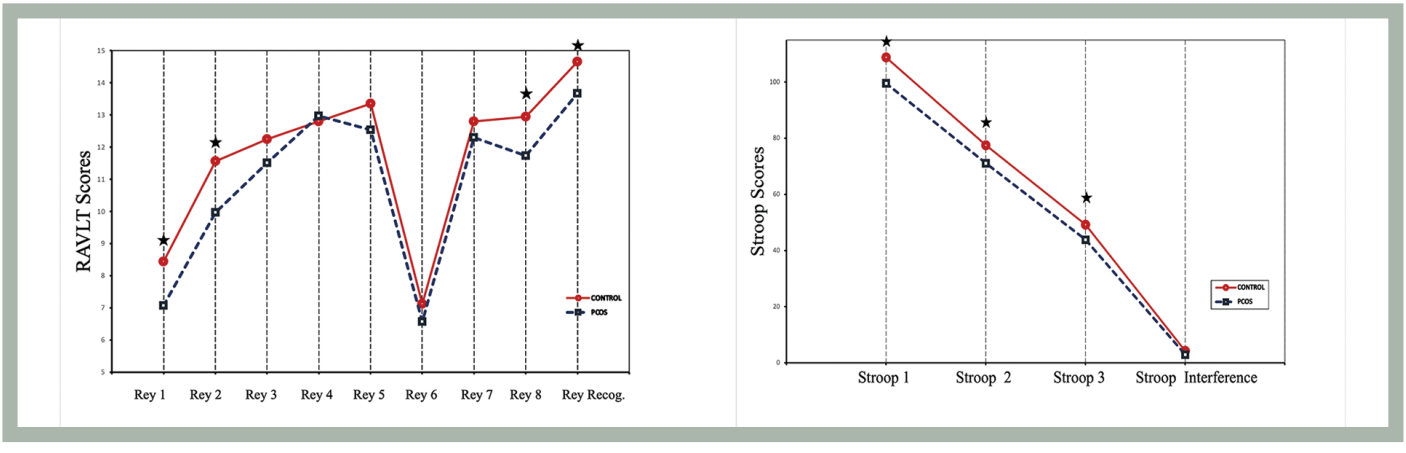

Figure 1. Demonstration of RAVLT and Stroop values in patients and control groups
★: p<0.05, RAVLT: Rey auditory verbal learning test, PCOS: Polycystic ovary syndrome

Stroop Test: In order to compare the groups in terms of Stroop Test performances, the number of words read for each of the 3 tests (word, color, color-word card) was analyzed using the Student's t-test separately (Table 2). As a result of the comparison of the groups, it was observed that the PCOS group performed significantly worse in all the 3 cards (p=0.007, p=0.043, p=0.017 respectively) (Figure 1). However, when the Stroop interference score was calculated, it was revealed that the groups did not differ in their capacity to resist the interference of the dominant response (p=0.44).

Discussion

Women with PCOS have elevated serum levels of testosterone, androstenedione, and DHEAS (1,18). In this study, patients with PCOS displayed higher plasma levels of androgens than controls, as expected.

While a borderline level of depression was observed in the PCOS group, in this study, no change was observed in anxiety tests. Moreover, no relationship was observed between depression and other cognitive functions and lateralization in this study. Although Barnard et al. (2) stated that depression impairs cognitive functions, Sukhapure et al. (19) showed that depression and anxiety do not impair cognitive functions, similar to our study. We think that depression is mild and does not affect cognitive disorders; occurs through different mechanisms. Soyupek et al. (18) found that the presence of depression in particular negatively affected hand function. There was no change in hand strength and dexterity in patients with PCOS in their study. In their study, hand dexterity was evaluated with the grooved pegboard test (18). In our study, the HPQ was used. There was no difference in the hand questionnaire scores between the two groups, but the absolute right-handedness rate was lower in the polycystic patient group. The rate of individuals who performed all tasks using their right hand was lower among patients with PCOS compared to controls. No statistically significant effects of androgens on handedness were observed, and only DHEA-S was found to be borderline effective (p=0.05). When we evaluated fine motor speed performance in PCOS, PCOS patients exhibited significantly slower finger tapping performance in the right hand than the control group. The low scores observed on the left hand in the PCOS group did not reach statistical significance.

There are limited studies in the literature on cognitive functioning and cerebral asymmetry in PCOS (2,4,20). Sex-related differences in cognitive functioning are thought to be influenced by variations in androgen and estrogen levels (2). In a study by Barnard et al. (2), individuals with PCOS were assessed using mental rotation, spatial rotation, and word recognition tasks, alongside the evaluation of the impact of anti-androgen treatment. While performance in spatial and mental rotation tasks did not significantly differ, participants exhibited reduced speed and accuracy in word recognition. Anti-androgen therapy showed only limited improvement in certain cognitive functions. The findings suggested that PCOS does not lead to a masculinized cognitive profile (2). Sukhapure et al. (19) showed that cognitive functions change with testosterone. Similarly, we have seen in our study that DHEA may be important in some cognitive functions (19). Franik et al. (21) also found that free testosterone was associated with verbal psychomotor speed. Androstenedione level showed a negative correlation with executive functions. 17-OH-P levels had a positive effect on phonological verbal fluency scores (21). Another study reported reduced performance among individuals with PCOS in cognitive domains typically favoring females, including verbal fluency, verbal memory, and fine motor skills. In contrast, no significant differences were identified in cognitive tasks generally associated with male advantage, such as mental rotation, spatial visualization, spatial perception, and perceptual speed (4). The same authors later showed in a prospective randomized study that anti-androgen and estrogen treatment improved verbal tests. However, most cognitive tests could not be corrected with this pharmacological treatment. It was also stated that these tests could not be easily corrected with hormonal treatment (22). Contrary to all these studies, Barry et al. (20) found that patients with PCOS had an advantage over other women in visuospatial cognition, and this was positively correlated with testosterone. Although we found in our study that many cognitive functions were affected and decreased in patients with PCOS, only spatial distribution of attention (LBT) may be related to DHEA in the PCOS group with absolute right-handedness. Rees et al. (23) evaluated cognitive function and white matter microstructure with diffusion tensor magnetic resonance imaging. Cognitive performance decreased in the PCOS group. It was also stated that the white matter microstructure may be affected by insulin androgens, and this relationship in PCOS may differ from that in the control group (23).

In our study, the LBT test, in which we evaluated spatial perception in PCOS patients, was not statistically different from controls. The LBT test was statistically significantly shifted more to the left only in the absolute right-handed group, indicating that the pseudo-neglect state of the right brain is

more common in the absolute right-handed group. Moreover, the spatial distribution of attention (LBT) may be related to DHEA in the PCOS group with absolute right handedness. When we looked at the literature, we could not find any study on the LBT in the PCOS.

The effects of DHEA on the human brain have not yet been clarified. DHEA is found in higher concentrations in the human brain than in the plasma and is actually a neurosteroid, synthesized *de novo* in the brain. It modulates the effects of various receptors in the brain, such as the γ-aminobutyric acid type A receptor, the N-methyl-D-aspartate receptor, and the sigma subtype 1 receptor (24). Davis et al. (25) also found that cognitive functions increased in women with high DHEA sulfate levels in their study. In our study, the effect of DHEAS was observed, especially in the absolute right-handed group.

In this study, PCOS patients performed significantly worse on the RAVLT test than controls in the first and second repetitions. According to these test results, immediate verbal memory is impaired in patients with PCOS. However, the learning curve associated with repetitions did not show statistically significant differences. It has also been observed that recognition in long "delayed recall" tasks is impaired in patients with PCOS. The worse performance of Rey recall scores compared to controls also indicates a difference in priming. Although language, which is a cognitive domain that strongly displays laterality, is affected by PCOS, it is difficult to say that lateralization is different in PCOS patients. This indicates that PCOS patients may have problems with attention, but they are not different from controls in terms of verbal memory. Similarly, the literature indicates that verbal learning studies using different tests show that verbal learning may be impaired in PCOS patients (4,22). Again, in a literature evaluation where both the RAVLT and the Stroop Test were performed, it was observed, similar to our study, that both tests were negatively affected in patients with PCOS (26).

The Stroop Test is a neurocognitive test that measures frontal lobe functions such as information processing speed, selective attention skills, and the ability to inhibit cognitive interference. Interestingly, in this study, PCOS patients read fewer words on all 3 cards, but there was no significant difference between the groups in terms of the Stroop interference score. That is, although their reading speed is slow, their ability to resist interference, which is an executive function, does not differ from the control group.

Study Limitations

A primary limitation of this study is the small sample size within the patient cohort.

Conclusion

This is the first study to address the effect of hormones on lateralization through motor and attention in PCOS. The findings of this study primarily reveal a change in spatial attention in PCOS independent of hormones. However, it also revealed that DHEA also had a significant effect, albeit mildly.

Tests assessing cognitive functions vary greatly among patients with PCOS. However, studying subgroups in patients with PCOS may provide more accurate information. In our study, patients with absolute right hands had different results than other patients.

In the present study, interpreting findings as a whole showed us that there would be a general slowness in PCOS that has been suggested by slower finger tapping performance in the absolutely right-handed group and slower reading in the Stroop Test.

Immediate verbal memory and word recall were also significantly lower in patients with PCOS. There is no robust evidence to claim that PCOS is a clinical condition where laterality is affected according to the LBTs.

There are not enough data to show that androgens affect cognitive functions in PCOS. Further studies are needed regarding the effectiveness of DHEA in this regard.

Ethics

Ethics Committee Approval: The study protocol was approved by the Kırıkkale University Institutional Review Board (approval no: 2009/183; approval date: 29.06.2009).

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

Footnotes

Authorship Contributions

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

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

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

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DOI: 10.4274/csmedj.galenos.2025.2025-3-2

ORIGINAL ARTICLE

17

Cam and Sakura Med J 2025;5(1):17-24

CSMJ

The Effect of Vitamin D Level on the Clinical Course of the Disease in Patients with Lower Respiratory Tract Infection

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What is known on this subject?

Vitamin D contributes to immune function and has been implicated in respiratory infection outcomes. Deficiency may elevate the risk of severe disease manifestations, including increased hospitalization, intensive care needs, and prolonged recovery in children.

What this study adds?

This study identifies a statistically significant link between low vitamin D levels and severe lower respiratory tract infection in infants. It demonstrates that deficient vitamin D status correlates with greater clinical support requirements and suggests that maintaining adequate levels may mitigate disease burden.

ABSTRACT

Objective: Vitamin D deficiency is a significant public healthcare issue worldwide. New research suggests that there is a link between vitamin D deficiency and the progression of various infectious diseases, particularly viral infections. The aim of this study is to evaluate the impact of vitamin D deficiency on the clinical course of lower respiratory tract infections (LRTIs) in hospitalised infants.

Material and Methods: This retrospective study included 178 pediatric patients (113 males, 65 females) aged 1-24 months, hospitalized with LRTI between October 15, 2017, and May 15, 2019. Patients were categorized into vitamin D deficient (<12 ng/mL, n=22), insufficient (12-20 ng/mL, n=31), and sufficient (>20 ng/mL, n=125) groups. Demographic, socio-economic, nutritional, and clinical characteristics were compared. The severity of LRTI was assessed using the Modified Wang Respiratory Scoring System. The association between indicators of disease severity [Wang score, intensive care unit (ICU) admission, oxygen therapy, length of hospitalization, and respiratory support] and vitamin D levels was analyzed.

Results: The mean 25(OH)D level was 26.53±12.14 ng/mL. A total of 29.78% (n=53) of patients had vitamin D levels below 20 ng/mL. Vitamin D levels were significantly higher in infants who received regular vitamin D supplementation during the first six months and in those who were fed with formula (p<0.001). Patients with severe LRTI had noticeably lower vitamin D levels than those with mild-to-moderate cases (median: 21.20 ng/mL vs. 27.20 ng/mL, p=0.021). Vitamin D deficiency was found to be an independent risk factor for severe LRTI [odds ratio (OR): 4.32, 95% confidence interval (CI): 1.63-11.47], ICU admission (OR: 4.74, 95% CI: 1.73-12.94), and the need for oxygen support (OR: 2.74, 95% CI: 1.30-5.96).

Conclusion: Vitamin D deficiency appears associated with more severe clinical courses in infants with LRTI. Optimizing vitamin D status could reduce morbidity. Larger prospective studies are warranted.

Keywords: Vitamin D deficiency, pediatric respiratory infection, disease severity, respiratory support, Wang score

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Received: 13.03.2025 **Accepted:** 30.04.2025 **Publication Date:** 22.07.2025

Cite this article as: Kangel D, Kıral A. The effect of vitamin D level on the clinical course of the disease in patients with lower respiratory tract infection. Cam and Sakura Med J. 2025;5(1):17-24

This article is based on the thesis titled "Investigation of the effect of vitamin D level on the clinical course of the disease in patients diagnosed with lower respiratory tract infections between 1 month and 24 months," written by Demet Kangel and submitted on 2019 (thesis no: 623556).

CAM & SAKURA MEDICAL JOURNAL

Introduction

Lower respiratory tract infections (LRTIs) represent a major cause of child morbidity and mortality, particularly in low-resource settings. The World Health Organization reports that LRTIs contribute to approximately 19% of deaths among children under five (1). Viral pathogens, particularly respiratory syncytial virus, are the leading cause of infection (2).

Recent studies have shown that vitamin D plays an essential role in the innate immune system by helping to fend off infection regardless of whether the body has encountered the pathogen before (3). Innate immunity involves the synthesis of peptides with antimicrobial properties, such as β-defensins and cathelicidins (e.g., hCAP-18/LL-37), that target viruses, bacteria and fungi. hCAP-18, the sole human cathelicidin, increases the killing of microorganisms in phagocytic vacuoles, attracts neutrophils and monocytes, and is regulated by a vitamin D-dependent pathway (4). Pathogenic antigens stimulate Toll-like receptors on macrophages, leading to increased expression of the vitamin D receptor and the 1α-hydroxylase enzyme, which converts 25(OH)D into its active form, 1,25-(OH)2D (5). This active metabolite then binds to the promoter of the cathelicidin gene, enhancing hCAP-18 production–a process observed in myeloid cells, bronchial epithelial cells, and keratinocytes (4,5,6). Additionally, Weber et al. (4) demonstrated that 25(OH)D can stimulate the production of intracellular hCAP-18 through autocrine activation of 1α-hydroxylase.

Evidence has shown that vitamin D can enhance the lung barrier function of epithelial cells, stimulate the synthesis of antimicrobial proteins and surfactants, promote the autophagy of cells infected with pathogens, and reduce the production of pro-inflammatory cytokines (7,8,9). Numerous observational studies and these laboratory studies have reported an independent association between low circulating 25(OH)D concentrations and an elevated risk for LRTIs caused by different microorganisms (10,11). This study aimed to investigate the association between vitamin D levels and the severity and prognosis of LRTIs in paediatric patients who were hospitalised.

Material and Methods

Study Design and Patient Selection

This retrospective study was conducted at İstanbul Medeniyet University, Göztepe Training and Research Hospital. The medical records of 178 infants aged 1-24 months, hospitalized with LRTI between October 2017 and May 2019, were collected. The study included patients between 1 month and 24 months of age who were hospitalized with a diagnosis of LRTI. Patients had no known chronic disease or malnutrition, and vitamin D levels were tested within 15 days before the diagnosis or within one month afterward. Patients with a history of birth below 32 weeks, immunosuppression, malnutrition, a diagnosis of bronchopulmonary dysplasia, chronic congenital respiratory disease, known or newly diagnosed hemodynamically significant structural cardiac disease, neuromuscular disease, multiple recurrent wheezing episodes, and vitamin D-25(OH) levels above the intoxication limit (>100 ng/mL) were excluded. The study design is summarized in Figure 1.

Definition

A diagnosis of pneumonia was made based on a temperature of over 38 °C, the detection of infiltrates on chest radiography, and the presence of tachypnoea and respiratory distress (12). The diagnosis of bronchiolitis was made with wheezing and/or rales on auscultation, signs of increased respiratory effort such as tachypnea, retraction, and absence of infiltration on chest radiography (13). Patients with more than one recurrent wheezing episode were excluded from the study.

Levels of serum 25(OH) vitamin D below 12 ng/mL were classified as “vitamin D deficiency,” between 12 and 19.9 ng/mL as “vitamin D insufficiency,” and levels of serum 25(OH) vitamin D 20 ng/mL and above as “vitamin D sufficiency” (14).

Data Collection

Vitamin 25 (OH) D levels, Ca, P, ALP values, treatments received during hospitalization, length of hospitalization, need for pediatric intensive care unit (PICU), and length of ICU admission were recorded. If available, the polymerase chain reaction test results for nasopharyngeal swab samples were recorded. The Modified Wang Scoring System was used to determine the severity of the disease (15).

Demographic characteristics of all patients were recorded. Patient age, gender, weight, height, season of birth, birth week, birth weight, type of birth, family history of atopy and asthma, smoking exposure at home, current vitamin D use (use of vitamin D-containing preparations in the last 1 month), use of vitamin D prophylaxis (regular use of ≥400 U vitamin D for ≥6 months), diet for the first 6 months, age at transition to supplementary food, maternal educational status, home heating type, number of siblings, number of people living at home and number of bedrooms in the house were recorded. The ratio of the number of people living in the house to the number of rooms was used to define household crowding (16,17).

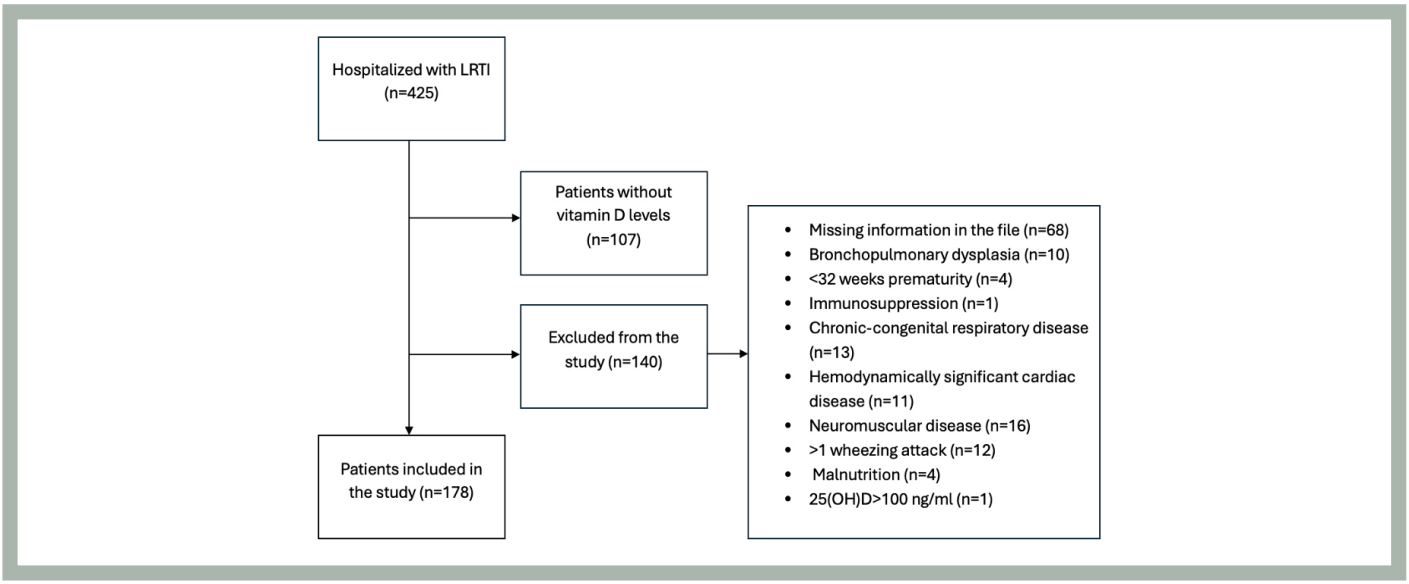

Figure 1. Design of the study
LRTI: Lower respiratory tract infection

Prior to study commencement, permission was received from the Ethics Committee of University of Health Sciences Turkey, İstanbul University Göztepe Training and Research Hospital (decision no: 2019/0255, date: 22.05.2019).

Serum 25 (OH) Vitamin D Level Measurement Technique

A 2 cc blood sample taken in a serum separator tube was measured with the Abbott Architect i2000 device using the Architect 25 (OH) vitamin D5P02 kit and chemiluminescence microparticle immunoassay method.

Statistical Analysis

Statistical analyses were performed using SPSS (Statistical Package for the Social Sciences) version 17.0. The conformity of the variables to normal distribution was examined by histograms and the Kolmogorov-Smirnov test. Mean, standard deviation, median, and minimum-maximum values were used to present descriptive analyses. Nominal variables were compared with Pearson chi-square and Fisher's exact tests in univariate analyses. Logistic regression analysis was used for multivariate analysis. Mann-Whitney U test, was used for non-normally distributed (non-parametric) variables between two groups, and Kruskal-Wallis test, was used for comparing variables across more than two groups. Spearman's correlation test was used to analyze the relationships between the measured data variables. P values below 0.05 were considered statistically significant.

Outcome

The main aim of the study was to assess the relationship between serum vitamin D levels and the severity and prognosis of the disease.

Results

A total of 178 patients were included in our study: 113 boys (63.48%) and 65 girls (36.52%), aged between 1 and 24 months. The mean age of the patients was 7.53±6.36 months. Of these patients, 94 (53%) were hospitalised with pneumonia and 84 (47%) with bronchiolitis. During follow-up, 117 patients (66%) were managed with medical treatment, 49 patients (27%) required non-invasive mechanical ventilation (IMV), and 12 patients (7%) required IMV. Twenty-four patients (13%) required follow-up in the paediatric ICU. The mean length of stay in hospital was 6.86±4.2 days. For the 24 patients requiring PICU, it was 7.5±5.9 days. The mean 25(OH)D level was 26.53±12.14 ng/mL. None of the patients with vitamin D deficiency exhibited signs or symptoms of rickets and/or tetany.

In our study, when socio-demographic characteristics were examined according to vitamin D sufficiency status, no relationship was found between vitamin D deficiency and age, gender, mode of delivery, gestational week, birth weight, season of delivery, season of hospitalization, exposure to smoking, maternal educational status, heating type, and household crowding. 25 (OH) vitamin D levels were significantly higher ($p<0.001$) in those who were exclusively breastfed during the first 6 months compared to those who were not exclusively breastfed and both breastfed and formula-fed (Table 1).

When the relationship between vitamin D levels and patient characteristics was analyzed, the rate of vitamin D deficiency was higher in patients requiring PICU (25.00%) compared to those not requiring PICU (10.39%) ($p=0.047$).

Accordingly, the mean vitamin D level in patients requiring PICU (20.44±9.60 ng/mL) was lower than in patients not requiring PICU, (27.48±12.24 ng/mL) (p=0.01). When all patients were compared by treatment received, the rate of vitamin D deficiency was higher in patients receiving IMV (41.67%) compared to those receiving non-IMV (10.20%)

Table 1. Identify demographic characteristics, nutritional status, and vitamin D use factors that may impact vitamin D deficiency

		Deficiency (<12 ng/mL)		Insufficiency (12-20 ng/mL)		Sufficency (≥20 ng/mL)		p
		n	%	n	%	n	%	
Age (months)	<4	8	(11.11)	14	(19.44)	50	(69.44)	0.799
	≥4	14	(13.21)	17	(16.04)	75	(70.75)	
Gender	Male	13	(11.50)	14	(12.39)	86	(76.11)	0.056
	Female	9	(13.85)	17	(26.15)	39	(60.00)	
Type of birth	NSVD	9	(11.84)	10	(13.16)	57	(75.00)	0.378
	C/S	13	(12.87)	21	(20.79)	67	(66.34)	
Gestational age (week)	32-37	4	(12.90)	4	(12.90)	23	(74.19)	0.766
	>37	18	(12.24)	27	(18.37)	102	(69.39)	
Birth weight (gram)	<2500	2	(16.67)	2	(16.67)	8	(66.67)	0.105
	2500-3999	15	(9.93)	26	(17.22)	110	(72.85)	
	≥4000	5	(33.33)	3	(20.00)	7	(46.67)	
Season of birth	Winter	3	(6.25)	11	(22.92)	34	(70.83)	0.614
	Spring	3	(9.09)	5	(15.15)	25	(75.76)	
	Summer	7	(15.91)	7	(15.91)	30	(68.18)	
	Autumn	9	(16.98)	8	(15.09)	36	(67.92)	
Season of hospitalization	Winter	14	(11.76)	21	(17.65)	84	(70.59)	0.846
	Spring	3	(13.64)	3	(13.64)	16	(72.73)	
	Summer	1	(20.00)	2	(40.00)	2	(40.00)	
	Autumn	4	(12.50)	5	(15.63)	23	(71.88)	
Smoking exposure	No	18	(13.64)	21	(15.91)	93	(70.45)	0.511
	Yes	4	(8.70)	10	(21.74)	32	(69.57)	
Mother's educational status	Did not attend school	0	(0.00)	1	(14.29)	6	(85.71)	0.653
	Primary school	8	(14.29)	8	(14.29)	40	(71.43)	
	Secondary school	10	(16.95)	13	(22.03)	36	(61.02)	
	High school	2	(5.88)	6	(17.65)	26	(76.47)	
	College	2	(9.09)	3	(13.64)	17	(77.27)	
Way of heating	Natural gas	21	(13.91)	22	(14.57)	108	(71.52)	0.244
	Charcoal	1	(3.70)	9	(33.33)	17	(62.96)	
Person to bedroom ratio	≤1	9	(17.65)	7	(13.73)	35	(68.63)	0.235
	1-2	12	(13.19)	15	(16.48)	64	(70.33)	
	≥2	1	(2.78)	9	(25.00)	26	(72.22)	
Current use of vitamin D	No	20	(34.48)	19	(32.76)	19	(32.76)	**<0.001**
	Yes	2	(1.67)	12	(10.00)	106	(88.33)	
Vitamin D use in the first 6 months	No	14	(41.18)	13	(38.24)	7	(20.59)	**<0.001**
	Yes	8	(5.56)	18	(12.50)	118	(81.94)	
Nutrition for the first 6 months	Breast milk	18	(16.82)	27	(25.23)	62	(57.94)	**<0.001**
	Breast milk and formula	3	(4.92)	4	(6.56)	54	(88.52)	
	Baby formula	1	(10.00)	0	(0.00)	9	(90.00)	

NSVD: Normal spontaneous vaginal delivery, C/S: Cesarean section

and medical treatment (10.26%) (p=0.024). Patients were classified into two groups, mild-moderate and severe, based on the Wang score. When the mean vitamin D levels were analyzed, the mean 25 (OH) vitamin D level of the severe group (21.54±10.15 ng/mL) was found to be lower than that of the mild-moderate group (27.42±12.27 ng/mL) (p=0.021) (Table 2).

When the factors affecting intensive care needs, the Wang score and the need for oxygen support, were analysed using multivariable analysis, vitamin D deficiency was found to increase the need for intensive care by 4.74 times, [95% confidence interval (CI): 1.73-12.94], a severe Wang score by 4.32 times, (95% CI: 1.63-11.47) and the need for oxygen support by 2.48 times, (95% CI: 1.09-5.61) (Tables 3, 4 and 5).

Discussion

This study investigated how vitamin D deficiency influences the clinical progression of LRTIs in infants aged 1-24 months. The findings indicate that reduced serum 25(OH)D levels are significantly linked to a more severe disease trajectory, reflected in parameters such as the need for pediatric intensive care, oxygen supplementation, and longer hospitalization durations.

The inverse correlation observed between vitamin D levels and clinical severity, as measured by the Modified Wang Score, underscores this relationship. Children with severe LRTIs exhibited considerably lower serum vitamin D levels than those with mild to moderate disease (p=0.021). Notably, infants with vitamin D deficiency, showed a markedly higher

Table 2. **The disease characteristics and vitamin D levels**

		Deficiency (<12 ng/mL)		Insufficiency (12-20 ng/mL)		Sufficency (≥20 ng/mL)		p	Vitamin D (ng/mL)		p
		n	%	n	%	n	%		Mean	± SD	
Diagnosis	Pneumonia	13	(13.83)	19	(20.21)	62	(65.96)	0.415	25.45	11.78	0.380
	Bronchiolitis	9	(10.71)	12	(14.29)	63	(75.00)		27.74	12.48	
	Medical therapy	12	(10.26)	19	(16.24)	86	(73.50)		27.11	12.16	
Treatment	NIMV	5	(10.20)	11	(22.45)	33	(67.35)	**0.024**	26.54	11.92	0.345
	IMV	5	(41.67)	1	(8.33)	6	(50.00)		20.78	12.24	
Need for PICU	Yes	16	(10.39)	25	(16.23)	113	(73.38)	**0.047**	27.48	12.24	**0.010**
	No	6	(25.00)	6	(25.00)	12	(50.00)		20.44	9.60	
O_2 support needs	Yes	11	(10.19)	16	(14.81)	81	(75.00)	0.222	27.61	12.29	0.115
	No	11	(15.71)	15	(21.43)	44	(62.86)		24.86	11.79	
Wang score	Mild + moderate	16	(10.60)	24	(15.89)	111	(73.51)	0.069	27.42	12.27	**0.021**
	Severe	6	(22.22)	7	(25.93)	14	(51.85)		21.54	10.15	
Length of stay (day)	6	10	(9.17)	16	(14.68)	83	(76.15)	0.085	27.82	12.03	0.062
	>6	12	(17.39)	15	(21.74)	42	(60.87)		24.48	12.10	

IMV: Invasive mechanical ventilation, NIMV: Non-invasive machanical ventilation, PICU: Pediatric intensive care unit, SD: Standard deviation

Table 3. **Results of multivariate analysis of factors identified in univariate analysis as predictors of need for intensive care**

	β	SE	Wald	p	OR	95% confidence interval	
						Min	Max
Age (month)	-0.080	0.047	2.817	0.093	0.923	0.841	1.013
Male	1.361	0.605	5.054	**0.025**	3.900	1.191	12.775
Birth weight (>4000 gr)			9.651	**0.008**			
<2500 gr	3.298	1.276	6.679	**0.010**	27.046	2.218	329.745
2500-3999 gr	1.378	1.115	1.528	0.216	3.968	0.446	35.311
Vitamin D insuffiency (<20 ng/mL)	1.556	0.512	9.224	**0.002**	**4.742**	1.737	12.947

β: Beta coefficient, SE: Standard error, OR: Odd ratio, Min: Minimum, Max: Maximum

Table 4. **Results of multivariate analysis of factors identified in univariate analysis as predictors of Wang score**

	β	SE	Wald	p	OR	95% confidence interval	
						Min	Max
Age (month)	-0.049	0.041	1.401	0.237	0.952	0.878	1.033
Male	1.504	0.605	6.176	0.013	4.500	1.374	14.738
Family history	0.518	0.481	1.160	0.281	1.679	0.654	4.310
Birth weight (>4000 gr)			8.786	0.012			
<2500 gr	3.381	1.289	6.885	0.009	29.411	2.353	367.672
2500-3999 gr	1.649	1.121	2.167	0.141	5.204	0.579	46.787
Vitamin D insuffiency (<20 ng/mL)	1.465	0.497	8.668	0.003	4.326	1.632	11.470

β: Beta coefficient, SE: Standard error, OR: Odd ratio, Min: Minimum, Max: Maximum

Table 5. **Results of multivariate analysis of factors identified in univariate analysis as predictors of oxygen requirement**

	β	SE	Wald	p	OR	95% confidence interval	
						Min	Max
Age (month)	-0.069	0.030	5.194	**0.023**	0.934	0.880	0.990
Male	1.046	0.393	7.064	**0.008**	2.845	1.316	6.151
Family history	1.158	0.384	9.076	**0.003**	3.183	1.499	6.761
Birth weight (>4000 gr)			3.667	0.160			
<2500 gr	1.662	0.951	3.051	0.081	5.270	0.816	34.016
2500-3999 gr	1.235	0.698	3.132	0.077	3.437	0.876	13.492
Nutrition in the first 6 months - breastfed			3.500	0.174			
Breastfed & formula	-0.808	0.730	1.226	0.268	0.446	0.107	1.864
Formula	-1.301	0.754	2.976	0.085	0.272	0.062	1.194
Vitamin D insuffiency (<20 ng/mL)	0.909	0.417	4.756	**0.029**	**2.482**	1.096	5.619

β: Beta coefficient, SE: Standard error, OR: Odd ratio, Min: Minimum, Max: Maximum

probability of requiring intensive care (OR: 4.74, 95% CI: 1.73-12.94) and respiratory support (OR: 2.74, 95% CI: 1.30-5.96). These observations reinforce the role of vitamin D as an immunomodulatory agent in pediatric respiratory pathology and align with prior literature findings (17,18,19).

Vitamin D is known to activate innate immune responses by upregulating antimicrobial peptides such as cathelicidins and β-defensins (3,4). It further supports immune function by preserving epithelial barrier integrity and modulating inflammation. In our cohort, these immunological mechanisms may underlie the increased disease severity observed in vitamin D-deficient patients. Previous research has similarly demonstrated associations between lower vitamin D concentrations and increased incidence and severity of pneumonia, bronchiolitis, and other LRTIs (6,7,8), which our study corroborates.

Several published studies report heightened susceptibility to viral and bacterial respiratory pathogens among individuals with deficient vitamin D status. For instance, Ginde et al. (6) established a connection between reduced vitamin D levels and increased respiratory infection vulnerability. McNally et al. (17) identified higher deficiency rates in infants with severe bronchiolitis. Likewise, Ganmaa et al. (10) observed that vitamin D supplementation may alleviate infection severity. Our findings support the concept that that deficiency is not only linked to clinical severity but also that sufficient levels may have a protective, preventive role.

Given these outcomes, maintaining adequate vitamin D levels during infancy and early childhood emerges as a crucial strategy to mitigate LRTI-related morbidity. This is particularly pertinent for high-risk groups, including premature infants and those with recurrent infections or chronic conditions.

Regular monitoring and timely supplementation in these populations should be encouraged (11,17). On a broader scale, implementing universal vitamin D prophylaxis in early life may carry public health benefits (10).

Study Limitations

This study is not without limitations. Its retrospective nature limits the capacity to establish causality definitively. Furthermore, potentially confounding variables such as nutritional patterns, sunlight exposure, and genetic predispositions could not be comprehensively assessed. Additionally, as data were derived from a single center, results may not be generalizable to other regions. Larger, multicentric prospective studies are necessary to elucidate these associations more clearly and strengthen the evidence base regarding vitamin D's role in LRTI outcomes.

Conclusion

This study demonstrates a meaningful association between vitamin D deficiency and increased severity of LRTIs among hospitalized infants. Our results indicate that insufficient vitamin D levels correlate with greater need for intensive care, elevated respiratory support demands, and a more severe disease presentation. These outcomes underscore the immunoregulatory function of vitamin D and support the view that its deficiency represents a potentially modifiable contributor to the progression of LRTIs.

Maintaining sufficient vitamin D levels, especially within vulnerable pediatric populations, may serve as an effective preventive measure to reduce the morbidity burden related to LRTIs. Nevertheless, due to the retrospective nature of this research and its inherent limitations, future large-scale and prospective studies are essential to confirm these associations and further evaluate the therapeutic utility of vitamin D supplementation in clinical settings.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of University of Health Sciences Turkey, İstanbul University Göztepe Training and Research Hospital (decision no: 2019/0255, date: 22.05.2019).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

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

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

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

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DOI: 10.4274/csmedj.galenos.2025.2025-5-4

ORIGINAL ARTICLE

25

Cam and Sakura Med J 2025;5(1):25-30

CSMJ

Benign Acute Childhood Myositis: Evaluation of Clinical and Laboratory Features

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What is known on this subject?

Benign acute childhood myositis (BACM) is a self-limited, post-viral condition, most often seen after influenza or other viral upper respiratory tract infections. It presents acutely with bilateral calf pain, difficulty walking, or inability to walk, often leading to concern about more serious conditions (e.g., Guillain-Barré syndrome). Neurological examination is typically normal, and immobility is pain-related, not due to weakness or neurological deficits. Elevated creatine kinase is a hallmark laboratory finding.

What this study adds?

The study retrospectively analyzed 14 pediatric BACM cases in a 3-month period at Ordu University, Turkey. This can be considered a high number for a three-month period. This study retrospectively analyzed 14 pediatric cases of BACM within a 3-month period at a university hospital in Turkey. This represents a notably high case count for such a short timeframe. In previous comprehensive studies conducted in Turkey, an average of 7 to 12 BACM cases over a 3-month period has been reported in major tertiary care centers. The relatively high number of cases in our study can be attributed to the fact that the data collection period coincided with the peak season of viral respiratory infections in our region. Seasonal clustering of viral infections is a well-known trigger for BACM, and these findings emphasize the importance of increased clinical awareness during such periods. 85.7% were male, which is a higher male predominance than typically reported. Neutrophil-to-lymphocyte ratio (NLR) values were low/normal, consistent with viral etiology. We did not encounter any other studies in the literature specifically investigating NLR values in BACM cases.

ABSTRACT

Objective: Benign acute childhood myositis (BACM) is a self-limiting condition often following viral upper respiratory infections, manifesting with leg pain, difficulty walking, and muscle tenderness. Although the symptoms are distressing, BACM typically resolves without specific treatment, and the prognosis is generally good. This study evaluates the clinical presentation and laboratory findings of 14 pediatric BACM cases to better understand their features and facilitate differentiation from serious neurological conditions like Guillain-Barré syndrome.

CAM & SAKURA MEDICAL JOURNAL

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Received: 18.05.2025 **Accepted:** 29.05.2025 **Epub:** 19.06.2025 **Publication Date:** 22.07.2025

Cite this article as: Altınok Eİ, Yurdakul Ertürk E, Kasar T, Yapar Gümüş C, Altınok V. Benign acute childhood myositis: evaluation of clinical and laboratory features. Cam and Sakura Med J. 2025;5(1):25-30

ABSTRACT

Material and Methods: This retrospective study included 14 pediatric patients diagnosed with BACM at Ordu University between February and May 2023. Patients were selected based on their presentation with leg pain and/or difficulty walking after a viral upper respiratory infection. Demographic data, clinical symptoms, laboratory results, and the course of the disease were analyzed.

Results: The mean age of the 14 patients was 8.92±3.04 years, and 85.7% were male. Neurological examinations were normal in all cases. Symptoms included leg pain (57%), fever (35%), sore throat (28.5%), and cough (35.7%). The mean creatine kinase (CK) level was 3816±1909 IU/L, and it decreased over 4.5±3.9 days. Leukopenia was observed in 35.7% of patients. Most patients showed improvement within 48 hours, and recovery took an average of 2.46±3.4 days.

Conclusion: BACM is commonly seen in children following viral upper respiratory infections, with the most frequent symptoms being leg pain, muscle tenderness, and difficulty walking. In our study, 85.7% of the patients were male, which aligns with prior reports indicating a higher prevalence in boys. Elevated CK levels were a hallmark of the condition, with levels returning to normal within days. The absence of neurological abnormalities in all patients and the presence of typical viral symptoms support the diagnosis of BACM. The neutrophil-to-lymphocyte ratio was consistent with a viral etiology, further supporting the viral origin of the condition.

Keywords: Benign acute childhood myositis, neutrophil-to-lymphocyte ratio, school-aged children, leg pain

Introduction

Benign acute childhood myositis (BACM) is a condition that typically follows a 1-5 day prodromal period after a viral upper respiratory tract infection, presenting with leg pain, inability to walk, or difficulty walking. Symptoms can vary greatly in severity, including fatigue, muscle pain, sensory sensitivity, and difficulty walking (1). Due to the acute onset and the distressing symptoms of immobility, this condition can raise anxiety in both parents and healthcare providers, sometimes leading to excessive testing and investigation. A normal neurological examination and the fact that immobility is often secondary to pain are characteristic features of the disease (1,2).

BACM is most commonly associated with influenza virus infection and appears after symptoms of a respiratory tract infection. Prevalence and incidence data on BACM are limited. The typical laboratory finding is elevated serum creatine kinase (CK) levels, which peak within the first 2-5 days and then gradually decrease (2). Most symptoms and laboratory findings improve within one week without specific treatment, although supportive therapy may be required. The most significant complications from a clinical perspective are rhabdomyolysis and subsequent kidney failure. Ensuring proper hydration is critical to avoid the risk of myoglobinuria (3).

Familiarity with the clinical and laboratory findings of BACM is essential for distinguishing it from serious conditions such as Guillain-Barré syndrome (GBS) and transverse myelitis, which require more extensive investigation and treatment. For this reason, we present the clinical and laboratory features of 14 cases of BACM diagnosed in the last three months.

Material and Methods

Fourteen cases of BACM which presented to the pediatric outpatient clinics and emergency department of Ordu University with leg pain and/or sudden onset of difficulty walking between February 20 and May 20, 2023 were included in the study. The patients' demographic data, reasons for hospital visit, laboratory findings, and course of clinical and laboratory features were retrospectively analyzed. Ethical approval was obtained from the Ordu University Clinical Research Ethics Committee with the decision number 2023/162, date: 09.06.2023.

Statistical Analysis

The data were summarized as mean and standard deviation or median and interquartile range, depending on the distribution of the variables. The normality of the data distribution was assessed using the Shapiro-Wilk test. Depending on the data distribution, either parametric or non-parametric significance tests were used for statistical analyses. A p value of <0.05 was considered statistically significant. All analyses were performed using IBM SPSS Statistics version 26.0.

Results

The mean age of the 14 pediatric patients evaluated in our study was 8.92±3.04 years, and 85.7% (n=12) were male. Neurological examinations were normal in all cases. A total of 57.1% (n=8) of the patients were hospitalized due to severe symptoms or markedly elevated CK levels. All patients received intravenous hydration.

At that time, respiratory polymerase chain reaction (PCR) testing for viral etiology was not available in our hospital; therefore, we presumed a viral origin in most patients based on their clinical symptoms. Three of our patients had undergone respiratory PCR testing at an external center, and all were found to be positive for influenza virus. In one patient, *Streptococcus* A was identified through a throat culture. The specific causative agent in the remaining cases was unknown.

At admission, 2 patients (N/A %) did not report neither leg pain nor difficulty walking. In 4 patients (28.5%), both complaints were present, while 8 patients (57%) reported only leg pain. Additionally, at admission or within the week prior, the following accompanying symptoms were noted: fever in 5 patients (35%), nasal discharge in 6 (42%), sore throat in 4 (29%), cough in 5 (36%), abdominal pain in 2 (14%), vomiting in 3 (21%), and diarrhea in 3 (21%) (Table 1).

The mean leukocyte count at admission was 5608±3357/mm^3. Leukopenia was observed in 5 patients (35.7%), while leukocytosis was present in 1 patient (7.1%). The mean neutrophil-to-lymphocyte ratio (NLR) was 1.69±2.75, with a median value of 0.81. No cases of thrombocytopenia were recorded.

The mean serum CK level was 3816±1909 IU/L. CK levels began to show a significant decline within an average of 4.5±3.9 days (range: 2-12 days) from the onset of symptoms. The mean aspartate aminotransferase (AST) level was 166±135 IU/L, and the mean alanine aminotransferase (ALT) level was 40±22 IU/L. Serum creatinine levels were within normal limits in all patients.

Although findings began to improve in most patients within 48 hours, the mean time to complete recovery was 2.46±3.4 days (range: 1-13 days). Demographic characteristics, presenting complaints, clinical courses, and key laboratory parameters of the patients are presented in Table 2.

Discussion

BACM is a clinical condition that commonly occurs after viral upper respiratory tract infections and is characterized by pain in the lower extremities, difficulty walking, or an inability to walk. It usually resolves spontaneously. This disease is more frequent in school-aged boys, and due to the sudden onset of symptoms, can be confused with serious neurological conditions (1,2,3). Therefore, it is important for clinicians to be able to recognize BACM to avoid unnecessary advanced testing and invasive procedures.

In the present study, 14 cases of BACM were identified over a 3-month period, which is a notably high number when compared to the incidence rates reported in the literature. According to a study by Al Qahtani et al. (4), conducted in Saudi Arabia, the incidence of BACM was estimated at 3.17 per 100,000 children over a five-year period. Similarly, Costa Azevedo et al. (5) retrospectively reviewed five years of data on pediatric patients presenting with elevated creatine phosphokinase levels and found that 100 out of 174 cases were consistent with BACM, with a median age of 6 years, and 77% were male. The relatively high number of cases in our cohort within a short timeframe may reflect a regional outbreak, increased awareness and diagnosis of the condition,

Table 1. Prodromal symptoms of BACM cases

Patient no	Fever	Runny nose	Sore throat	Cough	Abdominal pain	Vomiting	Diarrhea
1	-	+	+	-	-	-	-
2	-	-	-	-	-	+	+
3	-	-	-	+	-	-	+
4	-	-	-	-	+	+	-
5	+	-	-	-	-	-	-
6	+	-	-	-	-	+	-
7	+	+	-	+	-	-	-
8	-	+	+	+	-	-	-
9	+	-	-	-	-	-	-
10	-	-	-	-	-	-	-
11	+	+	+	-	-	-	-
12	-	+	+	+	-	-	-
13	-	+	-	+	-	-	-
14	-	-	-	-	+	-	+

BACM: Benign acute childhood myositis

Table 2. Demographic, clinical, and laboratory data of BACM cases

Total number of patients (n)	14
Sex (n, %)	
Male	12, 85.7%
Female	2, 14.3%
Age (mean, median, range)	8.93, 8 (6-17)
Follow-up type (n, %)	
Inpatient	6, 42.9%
Outpatient	8, 57.1%
Presenting symptoms	
Inability to walk (%)	26.6%
Leg pain (%)	85.7%
Laboratory values (mean, median, range)	
Leukocyte count	5608, 4975 (2600-15660)
Neutrophil/lymphocyte ratio	1.69, 0.81 (0.45-11.1)
Platelet count	198.214, 214.500 (109.000-296.000)
Creatinine	0.47, 0.47 (0.24-0.8)
Aspartate aminotransferase	166, 121 (62-531)
Alanine aminotransferase	40, 35 (15-93)
Creatine kinase	3816, 3603 (935, 7122)
Creatine kinase normalization time (mean, median, range)	4.5, 3 (2-12) day
Symptom resolution time (mean, median, range)	2.4, 2 (1-13) day

BACM: Benign acute childhood myositis

or a clustering of cases due to seasonal viral trends. These findings underscore the importance of clinician awareness, especially during peak viral seasons.

In our study, 85.7% of the patients were male, which is significantly higher than the approximately 2:1 male-to-female ratio reported in the literature, with our findings showing a 6:1 ratio. This is consistent with a study by Müjgan Sonmez et al. (6) in Turkey which reported that BACM occurs five times more often in males. Most cases in our study were of school age, which supports previous reports that BACM is more common in this age group.

A review of the literature indicates that the most common symptoms of BACM are calf pain, generalized muscle pain, and difficulty walking (3,7). In our study, 85.7% of the patients presented with muscle pain and tenderness. A study conducted with 38 children diagnosed with BACM showed a similar rate of 81% (7). The diagnosis of BACM can be made even in the absence of the classical symptoms of leg pain and difficulty walking. Particularly in cases following viral infections with a marked elevation of serum CK levels, BACM should be considered even if typical musculoskeletal symptoms such as muscle pain or gait disturbance are absent.

The literature indicates that the clinical spectrum of BACM is broad, and some cases may present without muscle pain or difficulty walking (8,9). Several studies emphasize that BACM diagnosis should also be considered in children with elevated CK levels during or after viral infections, even when typical musculoskeletal complaints are not evident. Therefore, diagnosing BACM in two patients in your study who presented with viral symptoms but without leg pain or gait difficulty, yet had biochemical evidence of muscle involvement, is consistent with the broader clinical spectrum described in the literature. This approach highlights the need to recognize atypical or subclinical forms of BACM.

Prodromal symptoms indicative of upper respiratory tract infections were frequently observed in our cohort, which is consistent with previous reports in the literature (1,6,7). Because of the unavailability of respiratory PCR testing at our institution during the study period, the etiology in most cases was presumed to be viral based on clinical presentation. However, in three patients who underwent respiratory PCR testing at external centers, influenza virus was identified. Additionally, *Streptococcus* A was isolated from a throat culture in one patient. The specific causative agent remained unidentified in the remaining cases.

Sudden difficulty walking or inability to walk should raise concerns about GBS, one of the most important neurological emergencies for differential diagnosis (8). Muscle pain is a common feature of both diseases. While areflexia or hyporeflexia can rarely be observed in viral myositis, GBS

typically presents with preserved reflexes, which can be misleading for diagnosis. An elevated serum CK level is an important laboratory finding that helps differentiate viral myositis from GBS. In our study, all patients had normal neurological examinations, while some reported cases from Turkey showed hypoactive deep tendon reflexes in BACM patients (10).

In our study, all patients had elevated CK levels, with a mean of 3816 IU/L, and the levels tended to normalize within an average of 4.5 days. These findings are consistent with those reported in the literature. However, in two patients, it took up to 12 days for CK levels to return to normal, while others showed earlier improvement. None of the patients developed serious complications such as rhabdomyolysis or kidney failure, indicating that the disease typically follows a benign course.

Elevations in other muscle enzymes such as AST and ALT were also observed in our study. This reflects systemic biochemical changes secondary to muscle inflammation. A similar study by Danış et al. (11) reported an average AST level of 128 IU/L, while our study found an average of 166 IU/L.

We also analyzed parameters reflecting both inflammation and viral infection response, such as leukocyte count and the NLR. Leukopenia was present in 35.7% of the patients, and leukocytosis was seen in one patient. These findings can be interpreted as supportive of a viral etiology.

The average NLR in our study was found to be 1.69. NLR is a simple, cost-effective, and easily accessible biomarker used to diagnose and assess the severity of inflammation and infection. In viral infections, lymphocytosis is generally seen, whereas bacterial infections typically show neutrophilia, resulting in low NLR values (12,13,14). The NLR value observed in our study supports a viral etiology and is consistent with the fact that BACM often follows influenza and other viral upper respiratory infections. Although there is limited research specifically on NLR in BACM a low or normal NLR is a typical finding in cases of myositis associated with viral infections. Thus, NLR can be considered a supportive parameter in distinguishing BACM from bacterial infections in addition to clinical evaluation.

Conditions such as trauma, osteomyelitis, rheumatoid arthritis, deep vein thrombosis, dermatomyositis, polymyositis, and intracranial pathologies should be kept in mind for differential diagnosis. Therefore, it is important to gather information about the patient's history, including family history of neuromuscular diseases, recent history of strenuous exercise, trauma, medication use, metabolic disorders, and thyroid diseases. While most cases in the pediatric population are benign, close monitoring of patients is crucial.

Study Limitations

This study has several limitations. First, the retrospective nature of the study may have led to incomplete data or recall bias, particularly concerning prodromal symptoms and symptom onset. Second, although similar cases have been reported in the literature, and the total number of patients in this study may not be very large, the clustering of 14 BACM cases within a brief, three-month period is noteworthy. This temporal concentration likely reflects a seasonal surge in viral respiratory infections, which are known triggers for BACM. Therefore, despite the relatively modest sample size, the study provides valuable insights into the management and follow-up of BACM during peak viral seasons. Third, viral serology or PCR testing was not routinely performed in all cases, which restricts our ability to definitively identify the viral etiology in each patient. Lastly, long-term follow-up data were not available, which prevents conclusions about possible late sequelae or recurrence.

Conclusion

BACM is a self-limiting condition most commonly affecting school-aged boys following viral upper respiratory infections. It typically presents with sudden lower extremity pain and difficulty walking and can mimic more serious neuromuscular or neurological disorders. Awareness of BACM and its clinical and laboratory features, including elevated CK levels and low NLR, can help clinicians avoid unnecessary diagnostic procedures and hospitalization. Although the disease follows a benign course in most cases, careful evaluation and close monitoring are essential to exclude other serious conditions and to ensure patient safety.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Ordu University Clinical Research Ethics Committee with the decision number 2023/162, date: 09.06.2023.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: T.K., Concept: E.İ.A., V.A., Design: E.Y.E., Data Collection or Processing: E.Y.E., T.K., V.A., Analysis or Interpretation: T.K., C.Y.G., Literature Search: E.Y.E., T.K., Writing: E.İ.A., T.K.

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

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

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DOI: 10.4274/csmedj.galenos.2025.2025-3-1

ORIGINAL ARTICLE

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Cam and Sakura Med J 2025;5(1):31-36

CSMJ

Successful Control of a Colistin and Carbapenem Resistant *Klebsiella pneumoniae* Outbreak in an Intensive Care Unit

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What is known on this subject?

There is an ongoing silent endemic of healthcare associated infections leading to patient morbidity and mortality. Outbreaks mainly due to Gram-negative bacterial infections in health-care settings have a major role in the spread of antimicrobial resistant strains.

What this study adds?

In this report, an outbreak of OXA-48 producing *K. pneumoniae* with colistin resistance could be controlled with strict infection control precautions. Infusion pump devices may be infection sources. Environmental screening and isolation of colonized patients have a crucial role in the control of multi-resistant Gram-negative bacterial epidemics.

ABSTRACT

Objective: Multi-drug-resistant bacteria burden is rising in both developing and high-income countries. We describe here a cluster of colistin and carbapenem-resistant *K. pneumoniae*, (CCRKP) in an educational and training hospital in Turkey, mainly associated with intensive care unit (ICU) stays.

Material and Methods: After CCRKP growth was detected in the microbiological samples of 21 patients who had a history of ICU hospitalization and were admitted to the hospital currently, the situation was classified as an epidemic. Rectal and environmental surveillance cultures were obtained. Carbapenemase production was tested by carbapenem inactivation method, and carbapenemase genes, including blaOXA-48, blaNDM-1, blaKPC, blaVIM, blaIMP and blaGES, were investigated by multiplex polymerase chain reaction (PCR). *mcr1/2* genes associated with plasmid-mediated colistin resistance were investigated by PCR. CCRKP isolated from rectal and environmental screenings were evaluated further for epidemiologic relationships with clinical isolates. Pulsed-field gel electrophoresis was done using Xba-I enzyme for digestion.

Results: CCRKP rectal colonization prevalence was 57% (8/14) on the screening day. Five of these eight patients were colonized only, and none of these asymptomatic carriers developed infection. CCRKP was detected on an infusion pump, which was used for some of the previous patients and was suspected to be a cross contamination source. The outbreak isolate was found to be of genotype A; OXA-48 positive,

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Received: 18.03.2025 **Accepted:** 16.06.2025 **Publication Date:** 22.07.2025

Cite this article as: Öncül A, Hamidi AA, Yıldız Sevgi D, et al. Successful control of a colistin and carbapenem resistant *Klebsiella pneumoniae* outbreak in an intensive care unit. Cam and Sakura Med J. 2025;5(1):31-36

ABSTRACT

NDM negative by PCR. *mCR* gene 1/2 was negative. One of the infected patients and one of the colonized patients isolates were different, and the remaining 22 isolates were indistinguishable. After strict infection control interventions, eight cases were detected in a five month period. Rectal swabbing was stopped after no new cases had been observed for two months. CCRKP hasn't been detected in clinical specimens for one year since then.

Conclusion: Environmental screening and isolation of colonized patients have a crucial role in controlling outbreaks of multidrug-resistant Gram-negative bacteria.

Keywords: Carbapenem-resistant *Enterobacteriaceae*, infection control, *Klebsiella pneumoniae*, outbreak

Introduction

Healthcare-associated infections (HAI) are major causes of mortality and morbidity, especially in intensive care units (ICU) of hospitals worldwide. HAIs due to carbapenem resistant bacteria are rising in both developing and high-income countries as a consequence of international traveling (1,2). Crude mortality rates of as much as 70% have been linked to infections caused by carbapenem-resistant *Enterobacteriaceae* (CRE) (3). Colistin is usually one of the last treatment options for such infections despite its toxicity (4). Colistin resistance is still relatively uncommon, but published outbreaks or ongoing spread of this multidrug-resistant (MDR) bacterium and the capability of plasmid-mediated resistance transmission are raising concern for worldwide spread in the future (5,6,7,8).

According to the World Health Organization the Central Asian and European Surveillance of Antimicrobial Resistance Network 2023 annual report, Turkey has a carbapenem resistance of 49.1% for invasive Klebsiella strains. The high prevalence of carbapenem-resistant *K. pneumoniae*, as well as the relatively high number of *Acinetobacter* spp. and their high levels of resistance, are a cause for concern and likely reflect the dissemination of resistant clones within healthcare institutions.

To prevent the CRE to become endemic in a hospital, early detection of outbreaks through laboratory based and active surveillance, good communication between infection control team and clinicians, maintaining infection control preventions and continuous education should be provided.

We present here a cluster of colistin and carbapenem-resistant *K. pneumoniae* (CCRKP) in an educational and research hospital in Turkey, mainly related to the ICU stay. The epidemiologic and molecular outbreak investigations, and preventive infection control measures that followed are detailed in the study.

Material and Methods

Setting

This outbreak investigation took place in a 720-bed educational and research hospital in İstanbul that has a sixteen-bed anesthesiology and critical care ICU. The ICU is a mixed unit that serves level-3 care to critically ill patients with acute emergencies and postoperative patients. The hospital receives referrals from neighboring state hospitals. The ICU is open-plan with twelve patient areas, featuring fixed separators and 2-meter distances between beds. There are four additional single bed isolation rooms with a corridor opening to the common area, of which two also have negative pressure ventilation. The nursing ratio is one nurse to two patients, but it could be one to three during night shifts. The ICU has full-time physician coverage. An infection control nurse and infectious diseases specialist routinely make visits to the unit on weekdays. Infectious diseases residents provide twenty-four-hour, 7-day consultation. Microbiological cultures are taken from potential sites of infection in clinically indicated patients, but there is no active microbiological surveillance for MDR bacterial colonization.

Patients

A case was defined as any patient newly found to have at least one clinical isolate of *K. pneumoniae* from November 12th, 2015 to April 12th, 2016 that was resistant to any carbapenem (ertapenem, imipenem, or meropenem) and colistin (CCRKP). CCRKP was detected in clinical samples of twenty-one patients within a five-month period. These patients were either in the ICU or had a history of staying in the ICU during their hospitalization. All antimicrobial susceptibility reports of *K. pneumoniae* isolated from patients in the ICU were reviewed retrospectively to identify CCRKP. Rectal screening was performed on all patients in the ICU to determine asymptomatic fecal carriers.

Identification and Susceptibility Testing

Identification was done by MALDI-TOF MS (Bruker, Daltonics) and susceptibility tests were carried out using BD-Phoenix automated system and minimal inhibitory concentrations were determined following EUCAST guidelines. *In vitro* susceptibility of the isolates to ampicillin/sulbactam, piperacillin/tazobactam, ceftriaxone, ceftazidime, cefepime, imipenem, ertapenem, meropenem, amikacin, gentamicin, netilmicin, aztreonam, ciprofloxacin, levofloxacin, and trimethoprim/sulfamethoxazole was evaluated. Carbapenemase production was tested by the carbapenem inactivation method.

Detection of Resistance Genes

Carbapenemase genes, including blaOXA-48, blaNDM-1, blaKPC, blaVIM, blaIMP and blaGES, were investigated by multiplex polymerase chain reaction (PCR) (9). The *mcr-1/2* genes associated with plasmid-mediated colistin resistance were examined also with PCR (10).

Microbiological Screening

Rectal screening samples were inoculated immediately in trypticase soy broth (5 mL) with a 10 µg ertapenem disk (Oxoid, Basingstoke, Hampshire, England), and processed as previously described. Cotton swabs humidified with isotonic serum were used for environmental screening. The surfaces and medical equipment frequently touched by hand were selected for screening. Eighteen CCRKP isolates of fifteen patients' clinical samples, five rectal colonizing isolates, and the isolate detected on the infusion pump were evaluated by arbitrarily-primed-PCR and pulsed-field gel electrophoresis (PFGE) for epidemiologic relatedness. PFGE was performed using the Xba-I enzyme for digestion (11).

Ethical Approvement

The study was approved by the University of Health Sciences Turkey, Şişli Hamidiye Etfal Training and Research Hospital Ethics Committee on 29th November 2016, decision number: 720.

Statistical Analysis

The epidemiological and laboratory characteristics of the patients were recorded using standard descriptive statistics. The Statistical Package for the Social Sciences (version 18, SPSS Inc., Chicago, IL, USA) was used to analyse the data. Descriptive statistics for numerical parametric variables were calculated as the mean ± standard deviation (SD), and for categorical variables as percentages.

Results

Patients

CCRKP was detected in the microbiological samples of 21 patients between 12.11.2015 and 12.04.2016. With the exception of amikacin, the isolate demonstrated resistance to all antibiotics that were tested. All these patients were hospitalized in an adult ICU, or the cultures were taken on wards, although they had a history of ICU admission in this period; thus, the situation was evaluated as an ICU outbreak. When the microbiology records were reevaluated, one ICU patient with CCRKP was also detected 10 months before the outbreak started. There were no CCRKP cases in 2014 (Figure 1).

Screening Results

Three of the 14 patients who were hospitalized on the screening day were already infected. Rectal colonization was detected in 8 patients, including these 3 patients. CCRKP rectal colonization prevalence was 57% (8/14). The mean length of ICU stay was 33±22 days (mean ± SD) for colonized patients. Only five patients were colonized, and none of these asymptomatic carriers developed an infection.

During environmental surveillance, CCRKP was detected on an infusion pump, which was used for some of the previous patients. All the other environmental samples taken from high touch equipment, bed environments, and sinks were negative for CRE.

Molecular Assay Results

One of the infected patients and one of the colonized patients' isolates were different, and the remaining 22 isolates were indistinguishable by both methods (Figure 2). The outbreak isolate was identified as genotype A and was found to be OXA-48 positive but NDM negative by PCR. *mCR* gene 1/2 was negative. The isolate of the unrelated colonized patient was genotype F and OXA-48 positive. The isolate of the unrelated infected patient was of genotype E and positive for OXA-48. This patient was transferred to our hospital from another medical center.

Infection Control Precautions

Preventive measures were implemented by the hospital infection control committee based on microbiological findings. Terminal cleaning of the unit was performed under the supervision of nurses. The staff was reeducated about resistant microorganisms, transmission routes, and the importance of hand hygiene. Contact isolation precautions

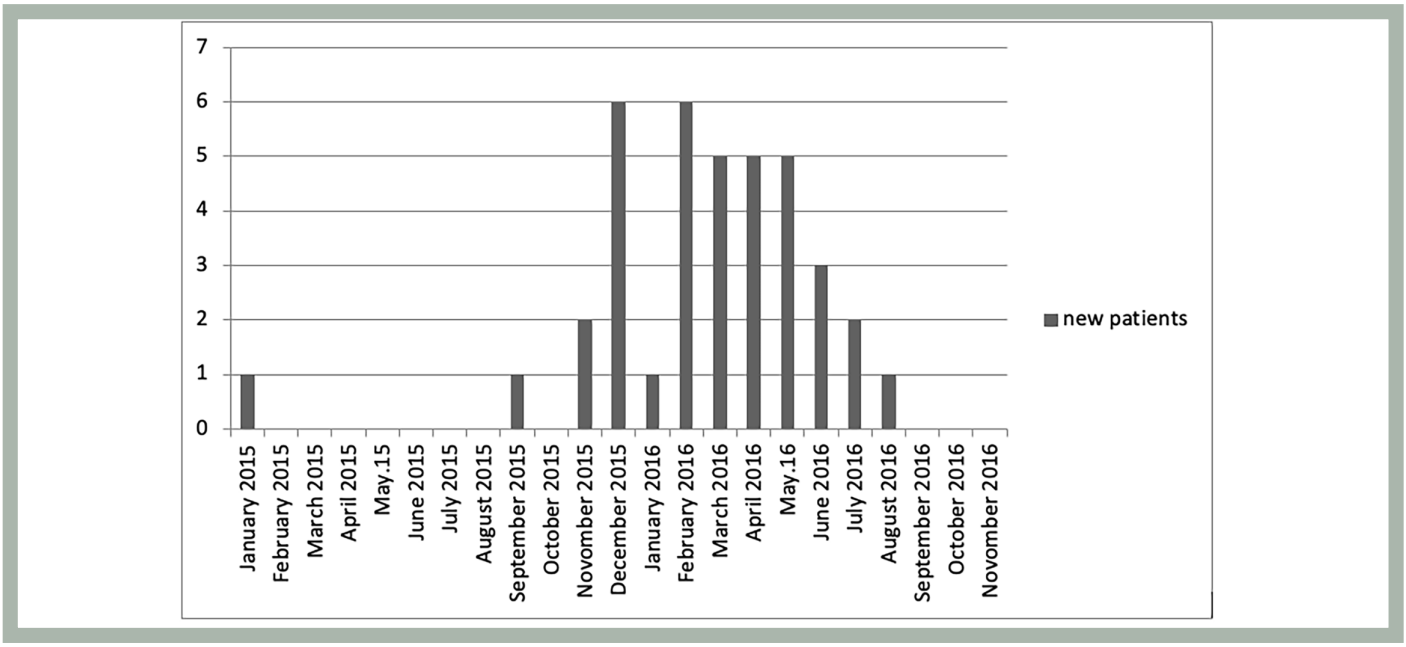

Figure 1. Colistin and carbapenem resistant *Klebsiella pneumonia* outbreak timeline

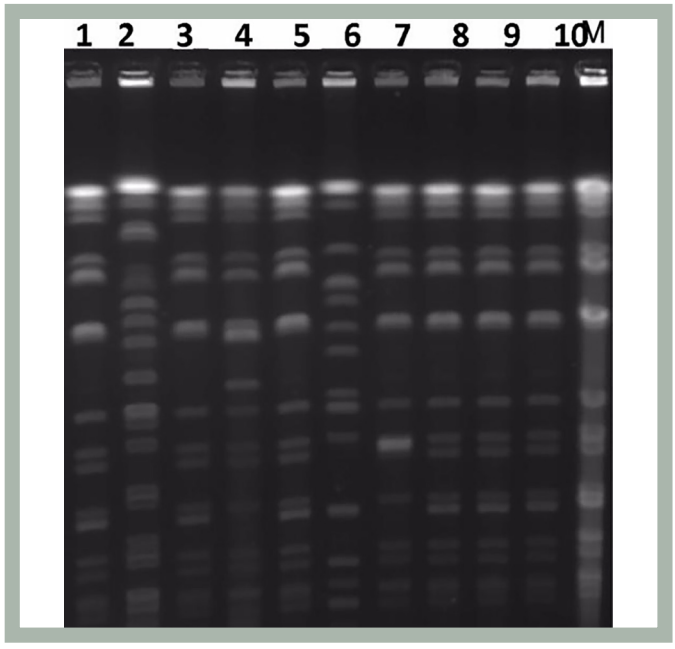

Figure 2. Epidemiologic relatedness of isolates by PFGE
2, 6: Epidemiologically different isolates, 1,3-5,7-9: Epidemiologically indistinguishable cluster isolates, PFGE: Pulsed-field gel electrophoresis

were taken for all the infected and colonized patients. Patients colonized/infected with CCRKP were transferred to single rooms when possible. The ICU had four isolated rooms, so the remaining patients and nurses giving care were cohorted. Sharing of medical equipment was restricted. All the medical staff and hospital directors were informed at a mortality-morbidity meeting, during which cases of CRE-related mortality were presented. surgical clinics, especially, were informed about the ongoing outbreak since they could postpone their elective cases that would need prolonged postoperative ICU stay. The importance of hand hygiene was emphasised throughout the hospital, particularly in the ICU. The manual buttons at the entrance of isolation rooms were relocated to knee level to decrease hand contact. The manual hand washing spouts were replaced with non-touch ones. The infusion pump detected as contaminated by the outbreak strain was cleaned, disinfected twice with bleach, and then microbiologically sampled. After microbiological confirmation of sterility, it was put back into use in the ICU.

Follow-up

In 14 patients, the 30-day mortality rate (6/14) was found to be 43%, whose bacterial isolate was available for molecular study and were shown to have been infected with the OXA-48 producing outbreak strain. No mortality occurred in five patients who received amikacin combined with meropenem or tigecycline. Bacteremia was present in these patients. There were two patients who received a combination of colistin and meropenem; both were bacteremic and died. One patient with rectovesical fistula and one patient managed with a cystofix device had positive urine cultures; antibiotics were not administered to these patients and no mortality occurred. In 2016, CCRKP growth was detected in the clinical samples of 30 patients and in the rectal swabs of 5 patients. After

interventions, eight cases were detected in a five-month period. The number of cases gradually decreased, and no new cases were observed for two months; then rectal swabbing was stopped. No CCRKP has been detected in clinical specimens since then for one year.

Discussion

The presence of MDR-Gram-negative bacteria (GNB) has been linked to severe HAIs over the past ten years, with their prevalence showing a consistent upward trend (12). Plasmid-acquired carbapenemases in *Enterobacteriaceae* are now being identified all over the world in an increasing trend (13).

The types of carbapenemases vary among countries, but some factors like international travel, transportation of food products, and migrations are responsible for introducing these resistant microorganisms to countries far beyond their origin (14).

Asymptomatic CRE colonization of the gastrointestinal tract may occur before infection, constituting an unidentified reservoir within hospitals (15,16). In our routine, CRE surveillance was not performed before the outbreak. Within the first two months of the cluster, the infection control team educated the unit about CRE, and contact isolation precautions were taken for the infected cases. Hand hygiene compliance was observed continuously. As these preventive measures were not sufficient, 'Facility Guidance for Control of Carbapenem Resistant *Enterobacteriaceae* (CRE) November 2015 Update' recommendations were implemented (17). By rectal screening, we detected that more than half of the patients were colonized, and by further evaluation, we found that all isolates but one were related. None of these colonized patients became infected, so without screening, contact precautions would not be taken for these patients and there would be an ongoing spread in the unit. Landelle et al. (18) have published a protracted outbreak of MDR *Acinetobacter baumannii* caused by intercontinental transfer of colonized patients and could be terminated by cohorting all colonized or infected patients in a separate isolation unit with dedicated healthcare personnel. It is well known that *Klebsiella pneumoniae* can spread via healthcare workers' hands from colonized patients or environmental reservoirs to other patients in both endemic and epidemic situations (15). We did not screen healthcare personnel's hands, as it is not recommended by guidelines, but we reinforced their hand hygiene practice and cohorted the colonized/infected patients' nurses (15).

Contaminated sinks have been shown to be a reservoir for *Klebsiella oxytoca* outbreaks (19). In a study from China, whole-genome sequencing and analysis revealed that one sink was the source of ST 16 high risk clone *Klebsiella pneumoniae*, acquisition in two patients (20). In environmental screening, we did not isolate any CRE in the sinks, monitors, bed rails, and isolation room buttons. It was determined that some of the automatic hand washing units were replaced by manual units during previous renovations. In terms of outbreak control, all the manual hand washing taps were replaced with automatic faucets. During the outbreak period, isolation room doors were operated using manually operated buttons. Although the buttons didn't carry CRE on screening, this could cause intermittent breaks in hand hygiene and contact isolation, so the buttons were moved to knee level.

Environmental cleaning has an important role in outbreak control. Recent reports suggest that GNB may exhibit greater survivability than Gram-positive organisms. It has been shown that survival for more than a year under certain conditions can be achieved by *Escherichia coli*, *Klebsiella* spp. and *Pseudomonas* spp. (21). The household personnel were reeducated, and cleaning and disinfection with chlorine tablet solutions (500 ppm) was performed twice a day.

Medical equipment that is used for patients can be contaminated, and after inadequate cleaning or disinfection, can become a source of outbreaks. Yan et al. (22) found that 31.34% (21/67) of bed units occupied by CRKP patients had positive results for one or more surrounding surfaces. Additionally, 7.99% (49/613) of environmental samples and 3.57% (4/112) of ICU staff samples tested positive for CRKP (22). In our outbreak investigation, only an infusion pump that was used previously for some of the infected patients was found to be contaminated with the outbreak isolate, and thought to be the probable cause of cross-contamination.

Conclusion

"This outbreak demonstrates the critical need for active surveillance, environmental screening, and strict infection control measures in limiting the spread of OXA-48, producing *K. pneumoniae*." A contaminated infusion pump was suspected to be the contamination source. Environmental screening and isolation of colonized patients has a crucial role in the control of multi-resistant Gram-negative bacterial epidemics.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, Şişli Hamidiye Etfal Training and Research Hospital Ethics Committee on 29th November 2016, decision number: 720.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: İ.O.B., Z.K.Ç., B.O., Concept: A.A.H., N.U., Design: A.Ö., M.E.B., Data Collection or Processing: İ.O.B., Z.K.Ç., B.O., Analysis or Interpretation: A.A.H., N.U., B.O., Literature Search: A.Ö., D.Y.S., Writing: A.Ö., D.Y.S., M.E.B., E.A.

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

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

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DOI: 10.4274/csmedj.galenos.2025.2024-9-2
CASE REPORT
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Cam and Sakura Med J 2025;5(1):37-40
CSMJ

Intra-abdominal Abscess Drainage from Douglas Pouch to Vagina after Liposuction

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What is known on this subject?

The increasing demands of women have led to the development of different methods in the field of gynecology.

What this case report adds?

This report aims to raise awareness about a rare, hence, severe complication of female cosmetic surgery.

ABSTRACT

Female genital cosmetic surgery covers procedures performed to correct or change the genital anatomy without a specific organic condition or disease. The increasing demands in the last decade led to the improvement of methods in cosmetic gynecology. This report aims to raise awareness about a rare hence severe complication of female cosmetic surgery. The case of an abdominal abscess caused by ileal perforation that occurred during abdominal liposuction for aesthetic surgery, and drained from the Douglas pouch to the vagina is presented. Intestinal perforation may rarely occur after abdominal liposuction in patients who have previously had an abdominal operation or have abdominal diastasis, as in our patient. In the advancing field of female genital cosmetic surgery, the application of liposuction for monsplasty or autologous fat grafting to the labia majora can present significant morbidity and mortality complications. Documenting these complications in the literature will disseminate knowledge. Awareness of risk factors and complications in the planning and application of operations can greatly support cosmetic gynecologists in improving patient safety.

Keywords: Cosmetic gynecology, intra-abdominal abscess, liposuction, monsplasty

Introduction

Female genital cosmetic surgery covers procedures performed to correct or change the genital anatomy without a specific organic problem or disease. Achieving the aesthetic goals that women desire regarding their genitalia positively affects their reproductive, sexual, and emotional health. A woman who is content with her own body is happy, self-confident, and productive. The increasing demands of women in the last decade have led to the development of different methods in the field of gynecology.

Liposuction of the mons pubis for aesthetic and functional purposes, or abdominal liposuction for autologous fat grafting to the labia majora, is a new area of operation in cosmetic gynecology. As they are reconstructive surgeries that are not performed for medical indications, it is believed that there is still insufficient scientific

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Received: 11.09.2024 **Accepted:** 31.01.2025 **Epub:** 04.06.2025 **Publication Date:** 22.07.2025

Cite this article as: Polat G, Sağlam ZA. Intra-abdominal abscess drainage from douglas pouch to vagina after liposuction. Cam and Sakura Med J. 2025;5(1):37-40

This case report was presented at University of Health Sciences Turkey, Çam and Sakura City Hospital Obstetrics and Gynaecology Days, March 2024, İstanbul.

evidence regarding the indications, risks, safety, efficacy, and applications of monsplasty and labioplasty.

We present the case of an abdominal abscess caused by ileal perforation that occurred during abdominal liposuction for aesthetic surgery, and drained from Douglas pouch to the vagina. This case aims to raise awareness about a rare complication that may occur in female cosmetic surgery.

Case Report

A 38-year-old patient, who is gravida 2, para 2, with a prior section, and who underwent liposuction and abdominoplasty 5 days prior at a different hospital, had a computed tomography (CT) scan due to complaints of gradually increasing abdominal pain, fever, and no gas or stool discharge. She was referred to our hospital with the preliminary diagnosis of an ileum perforation. When the patient presented to the surgery department, she was diagnosed with acute abdomen due to her symptoms: abdominal pain, tenderness, and positive rebound and defense during her abdominal examination. Her vital signs were within normal limits: blood pressure was 120/80 mmHg, heart rate was 78 beats per minute, respiratory rate was 18 breaths per minute, and body temperature was 36.9 °C. Her laboratory results were as follows: leukocyte count: 23,550/µL, hemoglobin: 8.8 g/dL, C-reactive protein: 173 mg/L, international normalized ratio: 1.29, serum creatinine: 0.4 mg/dL, and procalcitonin: 1.78 ng/mL.

The patient underwent exploratory laparotomy at our clinic. During the laparotomy, widespread necrosis and intestinal contents were observed in the area extending to the pelvis. The punctate perforation areas were observed when the small intestine was dissected and closed with primary repair. The abdomen was irrigated with physiological saline. A drain was placed in the pelvis, and antibiotic treatment was initiated after consulting with the infectious diseases department. Body fluid culture grew *Enterococcus faecalis* and Candida albicans. The patient had a fever on the 3rd postoperative day and underwent a gynecological consultation due to vaginal discharge. During the gynecological examination, a culture was taken from the discharge. Speculum examination revealed pus emerging from the posterior fornix. During manual vaginal examination, a 2 cm laceration area was felt in the posterior fornix. The vagina was irrigated with physiological saline. Repeated CT scan showed localized effusion in the abdomen and thickening in the peritoneum. Collections of small locules in the mesentery were also observed. Results from the abdominal drainage catheter were obtained. The posterior fornix laceration closed spontaneously on the 16th postoperative day, and the patient was discharged with full recovery on the 22nd postoperative day (Figures 1, 2).

Discussion

Cosmetic liposuction, which is performed to change the contour or shape of the body, has been advancing rapidly and becoming widespread over the last 50 years (1). It is the most frequently performed procedure by plastic surgeons in Germany and Brazil and the second most common surgery in the world (2,3). Complications encountered after cosmetic liposuction are generally mild. Since it is considered a minimally invasive, safe, and minor surgery, the possibility of serious morbidity or mortality is not taken into account.

In female cosmetic genital surgery, abdominal liposuction is applied to the labia major and vagina for fat filling, or to the pubic region for monsplasty. Complications such as pain, bleeding, infection, scar formation, skin collapse, seroma, adhesions, change in sensation, dyspareunia, change in sexual pleasure, abnormal hair growth, and the need for re-operation may occur as a result of these procedures. Rarely, serious complications such as intestinal perforation, necrotizing fasciitis, and embolism may occur after abdominal liposuction, as in our case (4,5). The frequency of these complications may increase with the increase in liposuction volume. It has been published that during the liposuction procedure performed in a center providing outpatient treatment, aspiration ranges from 0.5 to 8 liters, with an average of 2.6 liters (4). In our practice, a much lesser amount of 20-100 cc of liposuction is applied. The reported incidence of bowel and internal organ perforation during liposuction, as in our case, is <0.1 percent (4). When these cases were evaluated, it was seen that the patients had previous abdominal surgery or had abdominal diastasis. To prevent these complications, patients' medical history must be adequately documented, and physical examination must be performed carefully for abdominal diastasis before the operation. It should not be forgotten that liposuction is a surgical procedure and should be performed under especially aseptic conditions. Using inadequate depth during the suction technique may cause destruction of the subcutaneous vascular system and skin necrosis. All liposuction patients should be re-examined within 24 hours after the procedure (6).

Genital cosmetic procedures are profitable and there is growing patient interest and demand. Patients expect cosmetic changes in their genitalia with easily applicable, safe and minimally complicated procedures. Before the operation, the patient's expectations and the physical medical consequences should be discussed, and patients should be

informed. Educating the patients is necessary to assist them in making conscious decisions. Consequences that exceed patient expectations may affect their physical and psychological well-being.

We have insufficient data regarding the early or late complications and risks of liposuction application for monsplasty or labia major autologous fat grafting. In cosmetic surgical procedures, data analysis and evaluation of results are inadequate due to very limited or incomplete patient records (7). Survey results regarding patient satisfaction or improvement in sexual function without a comparison group should be interpreted with caution. Currently, there is no standardized training program or specific training area in the field of female cosmetic genital surgery. These operations are conducted by inexperienced individuals who are trained through courses organized by experienced professionals in this

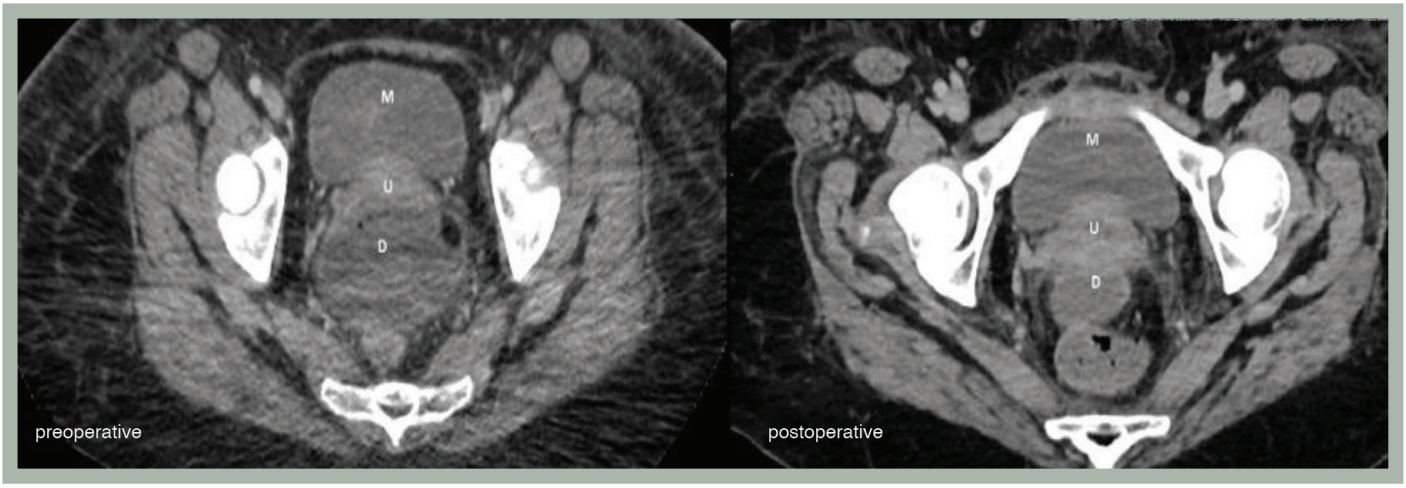

Figure 1. Transverse section demonstrating preoperative and postoperative views

Figure 2. Sagittal section demonstrating preoperative and postoperative views

field. The lack of restrictive legal rules and adequate education services are important shortcomings. In its committee opinion updated in 2020, the American College of Obstetricians and Gynecologists recommended that patients be informed about the lack of sufficient data on the indications, risks, safety, and effectiveness of female genital cosmetic operations (8). The long-term effects of aging, menopause, and natural anatomical and physiological changes due to pregnancy on those who undergo cosmetic surgery are topics that will be discussed.

Considering this rapidly developing field, performing liposuction for monsplasty or autologous fat grafting to labia majora may cause severe fatal complications. Documenting these complications in the literature will enhance and share knowledge. Awareness of risk factors and complications in the planning and application of operations can greatly support cosmetic gynecologists in improving patient safety.

Ethics

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

Footnotes

Authorship Contributions

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

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

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

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