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Contents

EDITORIAL

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Laboratory Medicine in the Era of Climate Change: From Awareness to Responsibility

İklim Değişikliği Çağında Laboratuvar Tıbbı: Farkındalıktan Sorumluluğa

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Climate change describes long-term changes in global temperatures and weather patterns. Although natural factors such as solar variability and volcanic activity can influence the climate, the rapid warming observed since the 19th century is largely the result of human activities. The burning of fossil fuels for energy, transport, and industry has increased atmospheric concentrations of greenhouse gases such as carbon dioxide and methane, which trap heat and raise global temperatures. Deforestation, agriculture, and oil and gas production further contribute to these emissions (1).

There is now broad scientific consensus that human activity has been the dominant driver of global warming over the past two centuries. The Earth's average surface temperature is approximately 1.4 °C higher than in the pre-industrial era, and the most recent decade has been the warmest on record. Importantly, climate change is not only about temperature increase. Because the climate system is interconnected, warming influences water cycles, ecosystems, and extreme weather patterns, leading to droughts, water scarcity, wildfires, sea-level rise, floods, melting ice, stronger storms, and biodiversity loss.

The scientific foundation for understanding this process was strengthened by the early atmospheric carbon dioxide measurements of Charles David Keeling, which clearly demonstrated a continuous rise in greenhouse gas concentrations. Based on such evidence, global climate governance developed under the umbrella of the United Nations through key agreements, including the 1992 United Nations Framework Convention on Climate Change, the 1997 Kyoto Protocol, and the 2015 Paris Agreement. These frameworks, supported by the Intergovernmental Panel on Climate Change Assessment Reports, provide the legal and scientific basis for international mitigation and adaptation efforts (2–4).

In addition to climate-specific agreements, the United Nations incorporated climate action into the broader 2030 Agenda for Sustainable Development. Among the 17 Sustainable Development Goals, Goal 13 directly addresses climate change, while other goals—such as clean energy, sustainable cities, responsible consumption and production, and protection of terrestrial and marine ecosystems—reinforce an integrated approach linking environmental protection, economic development, and social equity (5,6).

Sustainability itself, as defined in the 1987 Brundtland Report, refers to development that meets present needs without compromising the ability of future generations to meet their own. In practical terms, it requires a careful balance between environmental protection, social fairness, and economic viability. Growth and well-being cannot be considered sustainable if natural systems are degraded or inequalities are deepened (7).

Against this global background, it is important to recognize that the healthcare sector is not environmentally neutral. Healthcare activities are estimated to account for approximately 4–5% of global greenhouse gas emissions. Energy-intensive hospital operations, procurement of medical technologies and pharmaceuticals, transportation, and complex supply chains all contribute to this footprint. Hospitals operate continuously and depend heavily on heating, cooling, ventilation, sterilization, and diagnostic systems. Reducing the carbon footprint of healthcare therefore requires systematic improvements in energy efficiency, sustainable procurement, waste reduction, and the integration of lower-carbon technologies in both clinical and laboratory settings (8).

Research and clinical laboratories are central to patient care and scientific progress, yet their environmental impact

is often underestimated. Continuous operation, strict ventilation requirements, refrigeration systems, automation platforms, and the widespread use of single-use materials result in high electricity and water consumption, as well as substantial plastic and chemical waste. When procurement, diagnostics, pharmaceuticals, and supply chain emissions are included, the overall footprint of laboratory services becomes significant (9).

Recognizing this, professional organizations in laboratory medicine have begun to address sustainability more explicitly. In Europe, the European Federation of Clinical Chemistry and Laboratory Medicine promotes the transition toward greener laboratory practices in alignment with the European Green Deal, while maintaining quality and patient safety (10). At the global level, the International Federation of Clinical Chemistry and Laboratory Medicine works to identify high-quality scientific evidence, develop practical recommendations for laboratories in both developed and developing countries, support education, and advance human biomonitoring related to environmental exposures (11). These initiatives underline that laboratory medicine has a responsibility not only to ensure analytical excellence but also to consider its environmental consequences.

A first step toward sustainability in laboratories is understanding and measuring their carbon footprint. This includes evaluating emissions associated with electricity consumption, heating and cooling systems, equipment use, purchased goods, and waste streams. In most laboratories, energy demand is the largest contributor, particularly due to ventilation systems, refrigeration units, and continuous instrument operation. Water consumption in cooling and washing processes also represents a substantial resource burden (7).

From a chemical perspective, safer-by-design approaches aim to reduce hazardous substances at the planning stage of experiments and diagnostic procedures. In today's complex chemical environment, humans are exposed to numerous synthetic compounds throughout life—an exposure pattern often described by the concept of the exposome, which links environmental chemicals to measurable biological effects. Appropriate segregation, handling, and treatment of hazardous and liquid chemical waste are therefore essential to protect both environmental and occupational health (7).

Sustainability also involves reducing material use, limiting dependence on single-use plastics, and applying lifecycle thinking to laboratory operations. Procurement decisions that prioritize durability, energy efficiency, and lower environmental impact contribute meaningfully to long-term improvements. Industry partners and suppliers likewise play a role by improving production standards and transparency. Ultimately, meaningful change requires institutional leadership, a culture that values environmental responsibility, and structured education that equips laboratory professionals with the knowledge and skills needed to implement sustainable practices. Emissions related to professional travel for conferences and collaborations should also be acknowledged as part of the overall environmental footprint of scientific work (9).

Even small and practical changes in daily laboratory routines can create meaningful environmental benefits when applied consistently. Simple actions such as reducing unnecessary energy use, optimizing test requests, minimizing single-use materials, or improving waste segregation may appear minor individually, yet collectively they can lead to substantial impact. Education and the development of green skills are therefore essential to embedding sustainability into routine laboratory practice. We have only one planet, and there is no alternative environment to replace it. Protecting natural resources and reducing our ecological footprint are responsibilities we carry not only for ourselves but also for future generations. Caring for our planet today is the most meaningful legacy we can leave—ensuring a healthier world for those who come after us.

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REVIEW

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Genetic Landscape and Diagnostic Challenges of MODY: A Comprehensive Review of Etiology, Subtypes, and Future Perspectives

MODY'nin Genetik Yapısı ve Tanısal Zorlukları: Etiyoloji, Alt Tipler ve Gelecek Perspektiflerine Kapsamlı Bir Bakış

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ABSTRACT

Maturity-onset diabetes of the young (MODY) is a monogenic, autosomal-dominant form of diabetes. Because of the phenotypic overlap with other types of diabetes, MODY remains difficult for clinicians to diagnose; many cases are misdiagnosed as type 1 or type 2 diabetes, and more than three-quarters of cases remain undetected. Significant progress has been made in elucidating the intricate molecular pathways and diverse etiologies of MODY, facilitated by next-generation sequencing techniques. In this review, we provide a comprehensive overview of the pathogenesis, subtypes, associated genes, and mutations of MODY, as well as current genetic testing methods, treatment strategies, and future perspectives.

Keywords: MODY, next-generation sequencing (NGS), *GCK, HNF4A, PDX1*

ÖZ

Genç yaşta başlayan olgunluk tipi diyabet (MODY), monogenik, otozomal dominant kalıtsal bir diyabet türüdür. MODY tanısı, birçok vakanın tip 1 veya tip 2 diyabet olarak yanlış teşhis edilmesi ve diğer diyabet türleriyle fenotipik örtüşme nedeniyle vakaların dörtte üçünden fazlasının teşhis edilememesi nedeniyle klinisyenler için hala bir zorluk olmaya devam etmektedir. Yeni nesil dizileme yöntemleri, MODY'nin karmaşık moleküler mekanizmalarının ve heterojen etiyolojisinin anlaşılmasında büyük ilerlemeler sağlamıştır. Bu derlemede, MODY'nin patogenezi, alt tipleri, ilişkili genleri ve mutasyonlarının yanı sıra mevcut genetik test yöntemleri, tedavi stratejileri ve geleceğe yönelik perspektifler hakkında kapsamlı bir genel bakış sunuyoruz.

Anahtar Kelimeler: MODY, yeni nesil dizileme (NGS), *GCK, HNF4A, PDX1*

Introduction

Maturity-onset diabetes of the young (MODY) is a monogenic, autosomal dominant (AD) form of diabetes caused by pancreatic beta-cell dysfunction and is not insulin dependent (1). Genetic mutations cause loss of exocrine pancreatic function and deterioration of β-cells (2). In this AD hereditary disease, 63% of carriers develop diabetes before age 25, and 96% before age 55. This shows that the disease primarily occurs before age 25 (3). MODY can be misclassified as type 1 diabetes because it typically presents at or before age 25. Similarly, it can be misclassified as type

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2 diabetes because it coexists with overweight or obesity. However, MODY is a different type of diabetes (4). While type 1 diabetes is an autoimmune disease, MODY is not an autoimmune disease. While type 2 diabetes is characterized by insulin resistance, MODY is characterized by a defect in insulin production (5). While type 1 and type 2 diabetes are polygenic, MODY is a monogenic form of diabetes caused by a variation in a single gene (4). MODY is much rarer than type 1 and type 2 diabetes. Approximately 1–5% of patients with diabetes have MODY (6). Due to its rarity and confusion with other types of diabetes, many misdiagnoses occur (7). Since it is an AD hereditary disease, clinicians' ability to make the correct molecular diagnosis, the development of new techniques, advances in genetic testing, and easier access to genetic tests are all essential for accurate diagnosis (8). In addition, MODY can be diagnosed with up to 100% sensitivity using direct sequencing (9). In most cases, molecular genetic tests should be performed before starting specific treatments (10). Next-generation sequencing (NGS), including whole-exome sequencing (WES) and whole-genome sequencing (WGS), has made great strides in elucidating the complex molecular mechanisms and heterogeneous etiology of MODY (11). Fourteen subtypes of MODY have been identified, and they differ in several respects. Some features (such as glycemic phenotype) can even vary within the same pedigree (12). Therefore, a family history of diabetes, particularly the presence of family members with diabetes aged 25 years or younger, is an important criterion for diagnosing MODY. Responses to treatment and clinical course vary among MODY subtypes. H*epatocyte nuclear factor 1-alpha (HNF1A)*-MODY (MODY3), *GCK*-MODY (MODY2), *hepatocyte nuclear factor 4-alpha (HNF4A)* -MODY (MODY1), *hepatocyte nuclear factor 1-beta (HNF1B)*-MODY (MODY5), and *ABCC8*-MODY (MODY12) are the most prevalent of these. *NEUROD1*-MODY (MODY6), *IPF1/PDX1*-MODY (MODY4), and *INS*-MODY (MODY10) are less common subtypes. Since then, several alleged variants of MODY, including APPL1 (MODY14), PAX4 (MODY9), KLF11 (MODY7), and BLK (MODY11), have been disqualified as genuine MODY (13). Therefore, MODY subtypes should be genetically characterized and distinguished. Each subtype is defined by the gene that harbors the causative mutation, and variant–phenotype relationships exist among these genes (14). Making these distinctions is essential for the clinical picture and for the correct treatment.

Genetic Basis of MODY

As understanding of the underlying causes of MODY has improved, many subtypes have been identified. The most common subtypes are caused by mutations in the genes *HNF1A*, *GCK*, *HNF4A*, and hepatocyte nuclear *HNF1B* (15). *HNF* genes play an important role in liver development and function. However, these genes' pancreatic activities are affected in MODY. The *GCK* gene plays a role in glucose-stimulated insulin secretion in the pancreas, while also contributing to glucose uptake and the conversion of glucose to glycogen in the liver. Compared with *GCK*-MODY, *HNF1A*-MODY presents with more characteristic phenotypes (such as polyuria, polydipsia, and weight loss) (16). The *HNF1B* gene encodes a member of the homeodomain-containing nuclear transcription factor superfamily, which regulates the organogenesis of the pancreas, liver, genitourinary system, kidney, intestine, and lungs. Therefore, it is characterized by a wide spectrum. Management of *HNF1B*-MODY includes intensive insulin therapy during the early period, whereas *HNF1A*-MODY can be managed with a low-carbohydrate diet. The genes commonly mutated in MODY generally affect the insulin-producing β-cells of the pancreas. In particular, the *HNF4A* and *HNF1A* genes play a vital role in β-cell production. The *HNF4A* and *HNF1A* genes encode transcription factors that regulate genes involved in insulin secretion. Because these genes play a role in the regulation of insulin secretion, a mutation leads to loss of function and deterioration of β-cells (16). Specific inherited gene variants cause MODY to manifest differently. Understanding the effects of genetic variants is critical to clinical interpretation. For example, individuals with *HNF1A* and *HNF4A* gene variants show increased sensitivity to sulfonylureas, a class of insulin-stimulating drugs. More accurate results can be obtained with treatments that take this effect into account (17). Since the correct diagnosis, prognosis, and management of MODY are of critical importance, genotype-phenotype relationships should be investigated. Further studies are needed to investigate the pathogenetic effects of non-genetic regulators (18).

Diagnostic Approach to MODY

MODY is suspected based on three main features: (1) a strong family history of diabetes of any type, with affected relatives presenting between the second and fifth decades; (2) onset of diabetes usually before the age of 25; (3) clinical features inconsistent with type 1 diabetes (insulin independence or a low insulin requirement, absence of antibodies to pancreatic antigens, and preserved β-cell function with persistently detectable C-peptide despite hyperglycemia) or with type 2 diabetes (absence of insulin resistance, obesity, and acanthosis nigricans) (19). Some extra-pancreatic features that can be used to suspect MODY subtypes include macrosomia and neonatal hypoglycemia in *HNF4A*-MODY, renal cysts in *HNF1B*-MODY, and stable, non-progressive, mild hyperglycemia in *GCK*-MODY. This is because MODY comprises 14 subtypes, each characterized

by distinct gene variants, patterns of hyperglycemia, and other features (20).

Because of phenotypic overlap with other types of diabetes, MODY remains difficult for clinicians to diagnose; many cases are misdiagnosed as type 1 or type 2 diabetes, and more than 80% go undetected. As misdiagnosis can lead to inadequate treatment, the focus must be on correct diagnosis to ensure a stronger link to clinically important treatment benefits, such as a more precise prognosis of complication risk, appropriate genetic counseling for family members—especially children—and, most importantly, it directs the choice of the most appropriate treatment. The etiology of the disease determines the appropriate course of treatment, but only molecular genetic testing can verify this. Molecular genetic testing in patients is essential to establish the diagnosis of MODY, define the subtype, anticipate the clinical course, and guide treatment options. Significant has been made in deciphering the complex molecular pathways and heterogeneous etiology of monogenic diabetes (including MODY), with the advent of current technologies such as NGS that include targeted gene panels, WES, and WGS. Accurate diagnosis of MODY leads to treatment adjustments across its three subtypes. For most *GCK*-MODY patients, pharmacological treatment is typically unnecessary, though a low glycemic index diet may be advised. In contrast, patients with *HNF1A*-MODY and *HNF4A*-MODY can achieve optimal glycemic control using sulfonylureas instead of insulin. Consequently, diagnosing MODY can significantly alter care pathways, reduce or even eliminate treatment burdens for individuals, and decrease costs for both patients and society. Despite this, only a handful of studies have explored the cost-effectiveness of MODY screening. Findings suggest that genetic testing for a carefully selected population of young patients with diabetes aged 25–40 years holds promise as a cost-effective intervention in high-income countries (21). Testing is increasing globally, with most developed countries offering at least one academic, health-service, or commercial laboratory for testing. While some regions face resource limitations, it's essential to identify target populations for molecular genetic testing to enhance detection rates. Various algorithms are available to assist in molecular diagnosis by using clinical and laboratory parameters to identify candidates. One example is the MODY probability calculator developed by Exeter University, which proved useful and showed good discriminatory ability with an optimal probability cut-off of 36% in a Portuguese cohort (22).

MODY is a heterogeneous group of monogenic forms of diabetes. Although it was initially defined as a clinical syndrome of early-onset diabetes, subtypes caused by specific gene mutations have emerged as distinct pathological entities. Furthermore, strict adherence to classical criteria for screening for MODY mutations results in poor sensitivity, which hampers effective screening strategies. Some researchers have explored various clinical biomarkers to improve the accuracy of candidate selection for molecular diagnosis. Although molecular diagnosis has become more accessible, there is a pressing need for improved clinical screening strategies for monogenic diabetes. These enhancements would improve identification of candidates for molecular diagnosis and optimize cost-effectiveness. Direct sequencing and NGS techniques can detect mutations in the MODY gene with approximately 100% sensitivity. When clinical characteristics point to specific gene mutations, such as mild fasting hyperglycemia (for *GCK* gene mutations), diabetes linked to renal cysts (for *HNF1B* mutations), or pancreatic cysts and exocrine pancreatic dysfunction (for CEL mutations), phenotype-based targeted gene testing may be performed in addition to NGS. To identify affected family members and provide genetic counseling, a precise diagnosis of MODY is necessary. Genetic testing for the same mutation should be offered to diabetic relatives in all forms of MODY, as they may also benefit from treatment (23).

Technologies in Genetic Diagnosis

When considering testing, casting a wider net may be desirable, as additional subtypes and phenotypic connections among them are being reported. Genetic testing remains the definitive method for confirming monogenic forms of diabetes. Traditionally, Sanger sequencing has been considered the gold standard for molecular genetic testing of human disorders. This method involves determining the nucleotide sequence of specific genes and comparing it to reference sequences. However, Sanger sequencing has limitations. For instance, it cannot detect large genetic rearrangements such as the complete deletion of the *HNF1B* gene, a common cause of renal cysts and diabetes (RCAD). Additionally, it does not reliably identify certain variants of mitochondrial DNA associated with mitochondrial diabetes. The emergence of NGS technologies is transforming MODY diagnostics by enabling massively parallel DNA sequencing. Targeted NGS (tNGS) is particularly noteworthy, as it facilitates the simultaneous analysis of multiple gene sequences (24). This tNGS approach not only increases the diagnostic yield simply by testing more genes but also identifies patients with rare syndromic forms of diabetes whose diagnosis was not suspected.

When a MODY patient does not exhibit sufficiently clear clinical features, in-depth genomic screening, such as WES or WGS, can be the most effective genetic testing

option. In exome sequencing, selecting specific genes for testing is unnecessary, allowing detection of MODY-related genes that targeted gene sequencing may miss. This advantage makes exome sequencing particularly valuable in cases where targeted approaches are ineffective due to ambiguous clinical presentations. Similarly, WGS offers even broader coverage than exome sequencing, as it analyzes the entire genome, including non-coding regions that might harbor relevant variants. WGS can identify mutations not only in known MODY genes but also in regulatory elements and intronic regions, potentially unveiling novel pathogenic variants. In cases where exome and targeted gene sequencing are insufficient, WGS serves as a powerful diagnostic tool that provides a comprehensive genetic overview and clarifies ambiguous cases (25). Single-nucleotide variants (SNVs) and small insertion, deletion, and duplication variants are detected by sequencing, while partial and complete gene deletions, which represent a small percentage of all mutations in MODY genes, are detected by copy-number variant (CNV) analysis. CNVs are large-scale deletions or duplications of DNA, ranging in size from approximately 50 to 1,000,000 base pairs. Historically, CNVs were difficult to detect using Sanger sequencing or early tNGS panels because of limitations in identifying DNA dosage changes and the small size of CNVs, often requiring adjunct methods such as microarray-based genomic hybridization or multiplex ligation-dependent probe amplification (MLPA), which increased costs and labor. However, new bioinformatics techniques like tNGS now leverage raw NGS data to predict CNV presence more efficiently (26). MODY subtypes, types of genetic tests, and corresponding genotype–phenotype information are illustrated in Figure 1.

Chromosomal microarray analysis (CMA) is also a genomic technique that allows for high-resolution detection of CNVs, including whole-gene deletions or duplications, and has become an important adjunct to sequence-based testing in suspected cases of MODY. In patients with a clinical phenotype consistent with MODY but whose sequencing panel (targeting SNVs and small indels) is negative, CMA can identify structural rearrangements in genes such as *HNF1B* (MODY5) or other genes where exon- or gene-level deletions are known to occur. For example, a heterozygous deletion on chromosome 17q12—which includes *HNF1B*—was detected by microarray analysis in a patient with early-onset diabetes and renal and urinary anomalies after NGS panels failed to detect a mutation (27). Clinical laboratory guidelines for MODY genetic testing recommend that when panel sequencing is negative but clinical suspicion remains high—particularly for genes known to exhibit gene-dosage alterations such as *HNF1A*, *HNF4A*, *GCK*, and *HNF1B*—deletion/duplication analysis (via MLPA or CMA) should be considered (28). In this way, microarray analysis improves diagnostic yield, ensures that structural variants are not overlooked, and contributes to more accurate subtype assignment and tailored management for MODY patients. MODY 1 results from missense mutations in the *HNF4A* gene, while MODY 2 is caused by point mutations in the *GCK* gene. MODY 3 arises from variants in the *HNF1A* gene, including missense, nonsense, and splicing mutations, as well as in-frame amino acid deletions, insertions, duplications, and whole-gene deletions. MODY 5, on the other hand, is associated with *HNF1B* whole-gene deletions or other structural variants and linked to RCAD syndrome.

Challenges in Genetic Diagnosis

In the era of NGS, clinicians frequently encounter variants of unknown significance (VUS) in genetic testing. VUS may be reclassified over time as genetic knowledge grows. We have limited data on the optimal approach to VUS in MODY (29). With a proper diagnosis and treatment of MODY, switching from injections to oral hypoglycemic medications or to lifestyle changes alone can greatly enhance a patient's quality of life. Insulin treatment may be less necessary if the diagnosis is made early. Clinical prediction models may make it easier to identify which individuals will benefit from molecular genetic testing. To categorize the variants that cause MODY, reporting novel variants and their associated symptoms is crucial. Routine genetic testing in suspected cases will expand existing understanding (30). Using four cohorts from diverse settings, It has been demonstrated that pathogenic variants in the three MODY-associated genes are relatively common in the population. In clinically selected individuals, pathogenic variants in *HNF1A* and *HNF4A* are associated with the highest risk of diabetes; however, in clinically unselected individuals, their risk is significantly reduced. It was demonstrated that the features of the environment in which the variants were discovered, rather than the types of variants, were responsible for this decreased risk. Unexpectedly, the penetrance of pathogenic *GCK* variants was comparable across cohorts despite differences in their environments.

Studies show that pathogenic variants in common MODY genes are not ultra-rare and often display reduced penetrance when found incidentally. Genetic counseling should consider the setting, family history, and health status. An exception is *GCK*-MODY, which shows near-complete penetrance across contexts, supporting its inclusion in the ACMG secondary gene list to prevent unnecessary treatment (31). Experiences with genetic testing in other conditions demonstrate the importance of understanding personal experiences with chronic illness and lay beliefs

about inheritance. Health professionals should explore how individuals with MODY perceive their health and diabetes, as family beliefs shape the meaning of genetic information. Without addressing these views, families may dismiss the results. Using simple language or visuals can improve understanding. Clarifying motivations for predictive testing helps manage expectations and concerns during genetic counseling (32).

Clinical Implications of Genetic Diagnosis

First, diabetes diagnosed before six months of age is frequently caused by mutations in genes encoding components of the ATP-sensitive potassium channel: the sulfonylurea receptor 1 subunits or the inward-rectifier potassium channel (Kir6.2). Treatment with high-dose sulfonylureas, compared with insulin, can improve glycemic control. Second, individuals who have modest, stable fasting hyperglycemia, especially in young people, may have a glucokinase mutation and may do not need special care. Thirdly, low-dose sulfonylureas can be used to treat people with familial young-onset diabetes who do not meet the diagnostic criteria for type 1 or type 2 diabetes, because these individuals may harbour mutations in the transcription factors HNF-1A or HNF-4A. Finally, patients with extrapancreatic features, such as renal disease or deafness, usually require early insulin therapy (33). Accurate genetic diagnoses are crucial because they frequently result in improved diabetes management and allow predictive genetic testing of their asymptomatic relatives. Reducing the risk of diabetes-related complications later in life requires early diagnosis and adequate treatment (34).

During the first decade of life, patients with MODY1 exhibit relatively normal glucose tolerance. Testing and subsequent diagnosis are typically predicated on unintentional hyperglycemia detected during concurrent illness or family screening. Due to hormonal changes that result in insulin resistance and disruption of glucose regulation, glucose intolerance typically manifests during adolescence or in early adulthood. Patients should be managed with a low-carbohydrate diet at diagnosis and during the early stages of the disease, when their blood glucose and glycated hemoglobin levels are still within the "non-diabetic" range. Sulfonylureas

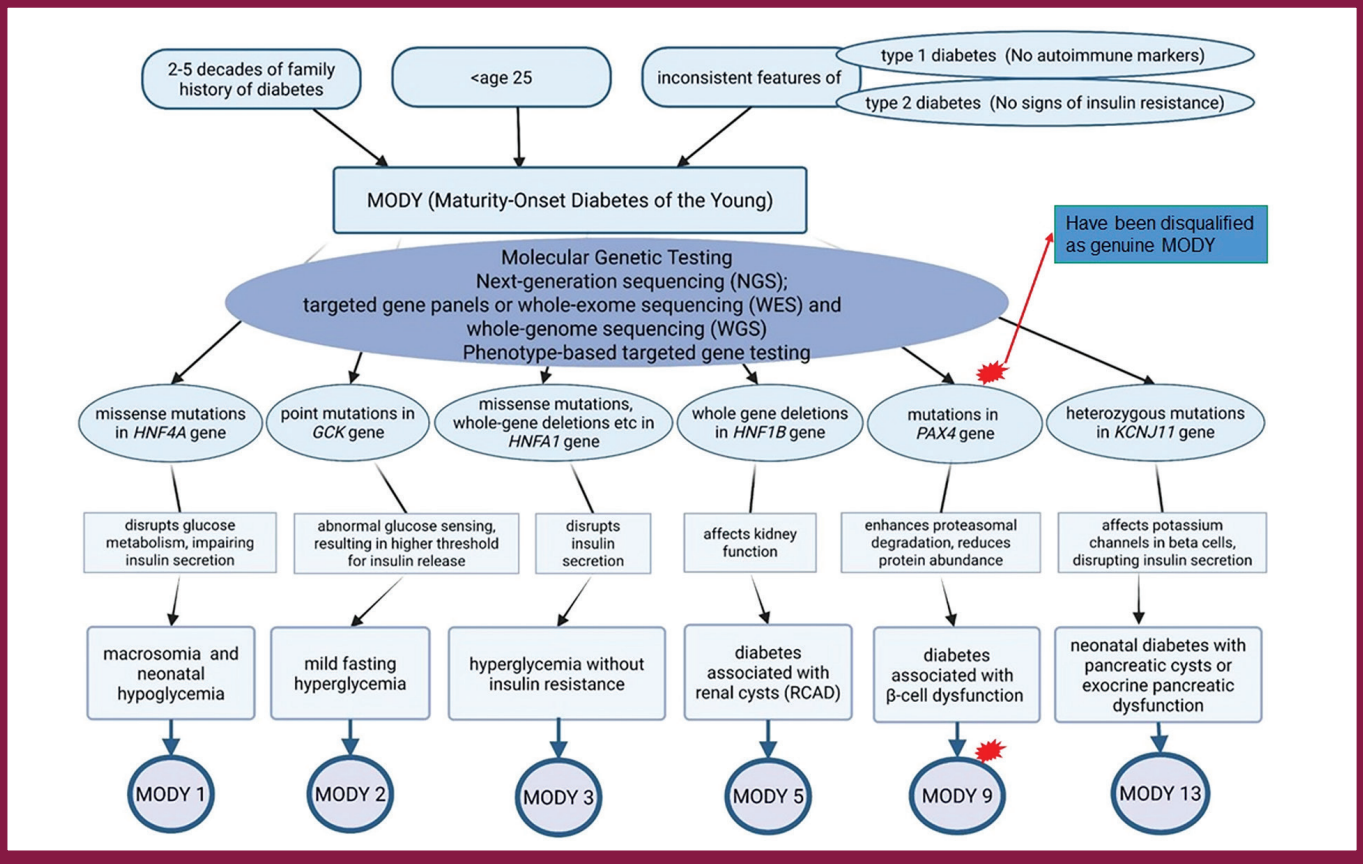

Figure 1. Overview of MODY subtypes, genetic tests, and genotype–phenotype data.
MODY, maturity-onset diabetes of the young; RCAD, renal cysts and diabetes.

are recommended instead of insulin when diet appears to be failing, because they provide better glycemic control. Regarding sulphonylurea derivatives, their safety and long-term efficacy, associated improvements in quality of life, and improved patient compliance are well established. Heterozygous variants in the *PDX1* gene, encodes the transcription factor *PDX1* essential for the formation and function of the pancreas and its β-cells, result in *PDX1*–MODY, a rare, mild form of monogenic diabetes. Diabetes appears to result from dominant-negative suppression of transcription caused by mutations in the insulin gene. Individuals with *PDX1*-MODY develop early-onset type 2 diabetes and have no extra-pancreatic manifestations. *PDX1* indirectly disrupts the incretin pathway and is crucial for glucose-stimulated insulin release, especially in postprandial hyperglycemia. Orally administered antihyperglycemic medications have been proposed as a treatment. Case reports have documented the efficacy of DPP-4 inhibitors in combination with metformin. Due to a degree of hepatic insulin resistance, patients with *HNF1B*-MODY respond poorly to sulfonylureas, and early insulin therapy may be necessary.

Future Directions in MODY Diagnosis

Considerable progress in technologies and informatics for generating and evaluating large biologicaldatasets has promoted a paradigm shift in how biomedical problems are addressed. Investigation of human health and disease at the omics level provides new opportunities. Omics data should be analyzed and integrated as a whole to achieve optimal results. Different levels of data, such as genomics, transcriptomics, proteomics, and metabolomics, can be evaluated jointly. The complexity of the human genome and its regulation at multiple levels requires consideration of data across those levels. A multi-omics approach enables characterization of patients' molecular and cellular profiles. In this way, the underlying causes of pathologies and cell-level errors that have not yet had an impact can be analyzed. A multi-omics approach can also be used to classify variants of MODY. NGS techniques, such as WES and WGS, together with CNV analysis, can be used to specify the MODY variant in question. Translation of variant gene sequences into protein sequences allows researchers to gather focused information on specific variant genes and proteins and facilitates their studies by integrating genomics and proteomics. The integration of omics data with this new method holds great potential, as it paves the way for precision medicine.

Development of targeted therapies requires confirmation of suspected MODY variants with genetic testing. Targeted therapies provide a basis for further pre-symptomatic screening of genetically related individuals of the patient. Early molecular genetic diagnosis enables necessary modifications to therapy. Diagnosing monogenic diabetes may be challenging because symptoms are similar. Genetic testing enables a genetic diagnosis and identifies the definitive cause of the symptoms. Targeted therapies are needed for the appropriate management of MODY.

Although NGS has made diagnosis easier by reducing the cost of genetic testing, our knowledge of DNA and pathogenic genes is far from sufficient. The vast amount of data produced by NGS must be analyzed using computational tools to enable effective research and to reduce time and costs. Nevertheless, artifical intelligence and machine learning may be effective tools for evaluating DNA sequencing data, as well as overall patient data and broader factors that may influence the disease. Ten algorithms used in precision medicine employ machine learning (35). Support Vector Machine (classifies and analyzes symptoms to improve diagnostic accuracy), Deep Learning (used in medical image analysis such as computed tomography scan, magnetic resonance imaging, colonoscopy, mammograpy etc), Logistic Regression (evaluates the potential risks and patient survival rates), Discriminant analysis (classifies patients for operation process, symptom-relief satisfaction data), Decision Tree (used in real-time healthcare monitoring, detection of aberrant data and helps in therapeutic decision), Random Forest (widely used in healthcare system for predicting metabolic pathways of individuals, mortality rates, healthcare cost and diagnosis), Lineer Regression (computational analyses and predictions), Naive Bayes, KNN (preserving patient information, pattern classification), HMM (drug side effect extraction from online forums, examining patient data), and Genetic Algorithm (36).

Conclusion

Genetic testing is essential for accurately diagnosing MODY, a monogenic form of diabetes. It enables precise identification of the causative gene mutation, guides personalized treatment decisions, and differentiates MODY from type 1 or type 2 diabetes, reducing misdiagnosis and ensuring appropriate management and family screening.

Footnotes

Authorship Contributions

Concept: Ş.S.Ş., E.E.D., A.C.K., E.İ., M.E., G.H., Design: M.E., G.H., Data Collection or Processing: Ş.S.Ş., E.E.D., A.C.K., E.İ., Analysis or Interpretation: Ş.S.Ş., E.E.D., A.C.K., E.İ., M.E., G.H., Literature Search: Ş.S.Ş., E.E.D., A.C.K., E.İ., M.E., G.H., Writing: Ş.S.Ş., E.E.D., A.C.K., E.İ., M.E., G.H.

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Comparison of Online and Hybrid Education Models for First Aid and Emergency Care Students

İlk ve Acil Yardım Öğrencilerinde Online ve Hibrit Eğitim Modellerinin Karşılaştırılması

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ABSTRACT

Background: The Coronavirus Disease 2019 pandemic disrupted education and training processes, necessitating a transition to remote learning that significantly altered teaching methods for both students and instructors. To highlight the challenges arising from this rapid shift in applied health sciences, the present study aimed to compare the perceptions of professional competence among First and Emergency Aid students who received online versus hybrid education during the pandemic.

Materials and Methods: This descriptive cross-sectional study was conducted among second-year students at two universities: one providing fully online education (n = 59) and the other offering hybrid instruction (n = 61).

Results: No statistically significant difference was observed between the groups in understanding theoretical courses (p = 0.088); however, students who received face-to-face instruction within the hybrid model demonstrated significantly better comprehension of practical courses (p < 0.001).

Conclusion: In conclusion, while online education is adequate for acquiring theoretical knowledge, it is insufficient for developing clinical and technical skills. Accordingly, these findings suggest that practical courses in health education programs, such as First and Emergency Aid, should be conducted face-to-face whenever possible; when in-person attendance is required, appropriate safety measures should be implemented.

Keywords: Pandemic, professional competence, online education, hybrid education, first and emergency aid, paramedic

ÖZ

Amaç: Koronavirüs Hastalığı 2019 pandemi döneminde eğitim ve öğretimin kesintiye uğraması ve uzaktan yapılması öğrenci ve öğreticiler için eğitim yöntemlerinde değişime sebep oldu. Bu hızlı değişimin, uygulamalı eğitim bilimlerinde oluşturduğu zorluklara dikkat çekmek için pandemi döneminde online ve hibrit eğitim gören İlk ve Acil Yardım programı öğrencilerinin mesleki yeterlilik algılarının karşılaştırılması amaçlandı.

Gereç ve Yöntemler: Tanımlayıcı ve kesitsel olan çalışma online eğitim yapan bir üniversite (n = 59) ile, hibrit eğitim yapan bir üniversitenin (n = 61) İlk ve Acil Yardım programı 2. sınıf öğrencileri ile gerçekleştirildi.

Bulgular: Teorik derslerin anlaşılması açısından her iki grup arasında fark bulunmaz iken (p > 0,088), uygulamalı derslerin anlaşılmasında yüz yüze eğitim alan grup lehine fark tespit edildi (p < 0,001).

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ÖZ

Sonuç: Sonuç olarak; online eğitimin bilgi edinmede yeterli, ancak klinik ve teknik beceri edinmede yetersiz olduğu bulunmuştur. Zorunlu koşullarda İlk ve Acil yardım gibi sağlık eğitimi verilen programlarda uygulamalı derslerin gerekli önlemler alınarak yüz yüze verilmesi önerilmelidir.

Anahtar Kelimeler: Pandemi, mesleki yeterlilik, çevrim içi eğitim, hibrit eğitim, ilk ve acil yardım, paramedik

Introduction

The Coronavirus Disease 2019 (COVID-19) pandemic has led to profound economic, social, and cultural changes worldwide, particularly in the field of health (1). Education became the second-most affected sector after healthcare. Face-to-face instruction was suspended globally, forcing millions of learners and educators to adopt alternative methods to maintain the continuity of education (2).

With the measures implemented to control the rapidly spreading pandemic, the online education model emerged as the most practical solution for ensuring educational continuity and achieving learning objectives (3). However, this process was also accompanied by various limitations and challenges (4). Previous studies have reported that online education offers advantages such as low cost, flexibility in time and location for both students and instructors, ease of communication, and opportunities to review recorded materials (5,6). Conversely, adverse effects such as sleep disturbances, decreased motivation, impaired social interaction, excessive phone and internet use, anxiety, and stress-related depression have been identified (7–9).

Face-to-face interaction remains crucial for effective communication (10). Clinical practice holds indisputable importance for professional development, especially in health-related disciplines. Such practices enable students to integrate theoretical knowledge with patient care, develop problem-solving abilities, and gain professional autonomy and teamwork skills (11,12).

The First and Emergency Aid (Paramedic) program, an associate degree in health sciences, combines theoretical and clinical training. The effectiveness of this program largely depends on adequate clinical experience. Although online education is an efficient method of knowledge acquisition, it poses challenges for applied health sciences (13). The transition away from face-to-face education during the pandemic created uncertainty in paramedic training, which relies heavily on interaction and hands-on experience, leading to professional concerns among students. Previous research has shown that online education is less effective for clinical training, where practical and technical skills must be developed (13,14). Moreover, studies conducted with paramedic graduates before the pandemic revealed higher perceived professional competence among graduates who participated in hands-on training (15,16).

Despite several studies investigating the effects of the pandemic on practice-based education among various health professional groups, limited research has focused on paramedic students who are the first healthcare providers to interact with patients in pre-hospital settings (4,17–19). Therefore, this study aimed to examine the effects of hybrid and online educational methods on paramedic students and to evaluate their perceptions of professional competence.

Materials and Methods

Based on an appraisal of the aforementioned findings, albeit with controversies, we hypothesized that:

$H0_1$: There is no significant difference between the views of students who received the hybrid and online education models.

$H1_1$: The views of paramedic students who received training during the pandemic regarding the hybrid education model are more positive than their views regarding the online education model.

$H0_2$: The hybrid education model does not contribute more to students academic success compared to online education.

$H1_2$: The hybrid education model contributes more to students' success than online education.

$H0_3$: The hybrid education model does not affect students' perceptions of professional competence in practical courses.

$H1_3$: The hybrid educational model positively affects students' perceptions of professional competence in practical courses.

Type of study: The study is a two-center, descriptive cross-sectional study.

Population and Sample of the Study

The study population consisted of paramedic students enrolled in the Vocational School of Health Services at two universities: one located in a metropolitan area offering hybrid education (School A), and the other located in a smaller city providing fully online education (School B). While students at School A completed their theoretical courses online and practical courses face-to-face, those at School B took all courses online. Before the Council of Higher Education (YÖK) decision mandating online education at the beginning of the pandemic (2020), both universities had completed one semester of face-to-face instruction. Subsequently, School A continued with two

semesters of hybrid education, whereas School B maintained two additional semesters of online education. Data were collected in March 2021 after the students had completed their second academic year.

The required sample size was calculated using G*Power software, assuming an effect size of 0.5, statistical power of 80%, and a margin of error of 5%, resulting in a minimum sample size of n = 98. A total of 61 of 65 students from School A and 59 of 62 students from School B voluntarily participated in the study. No sampling procedure was applied; all students who provided informed consent were included.

Data Collection and Analysis

Data Collection Tools: The questionnaire used for data collection was developed by the researchers based on a comprehensive literature review. It consisted of two sections. The first section included questions about the students' sociodemographic characteristics, grade points averages (GPAs), and opinions regarding the teaching method they received. The second section assessed students' perceptions of professional competence using a 5-point Likert scale (1 = strongly disagree, 5 = strongly agree). These items measured the students' confidence in performing basic and advanced emergency procedures (e.g., intravenous injection, nasogastric tube insertion, and cardiopulmonary resuscitation [CPR]. The responses reflected students' self-reported competence rather than their actual performance; therefore, no multiple-choice or knowledge-based test questions were included, and objective performance measurement was not conducted.

Ethical approval was obtained from the Gümüşhane University Scientific Research and Publication Ethics Committee (approval number: 2021/3, dated: 14.04.2021), and administrative permission was obtained from the institutions where the study would be conducted. Students who voluntarily participated in the study were informed about the data collection forms. An online link was sent to the students who had provided written consent, and they were asked to complete the questionnaire. The study was conducted in accordance with the Declaration of Helsinki.

Statistical Analysis

Data were analyzed using the IBM SPSS Statistics 25.0 software package. Descriptive statistics (frequency, percentage, median, and interquartile range) were used to summarize the data. The Shapiro–Wilk test and histogram plots were applied to examine the normality of distribution. Since the data did not show a normal distribution (Shapiro–Wilk $p < 0.05$), non-parametric tests were used.

The Mann–Whitney U test was applied to compare the median scores between the online and hybrid education groups for continuous variables such as perceived competence levels in theoretical and practical courses. This test was preferred because it does not assume normal distribution and is appropriate for comparing two independent groups when ordinal data are used, such as Likert-type scales. The level of statistical significance was set at $p < 0.05$. All analyses were two-tailed. The results were presented with corresponding z and r values to indicate effect size and direction.

Results

Of the 120 students who participated in the study, 51.7% were female and 48.3% were male. The proportion of female students was higher in College B (66.1%) than in the other group. The proportions of students with a GPA of 3.01 or higher at the end of the training process were 32.2% in the online group and 62.3% in the hybrid group. While 42.5% of all participants wanted education to continue online, 44.1% of students who received only online education wanted it to continue in a hybrid format, and 63.9% of students who received hybrid education wanted it to continue only online. Among all participants, 68.3% attended online courses at home, and 71.7% used their smartphones for online education (Table 1).

The reasons students wanted to take their courses online were as follows: 38.3% preferred online education because it allowed them to study at their convenience, and 12.5% preferred it because they were employed. Problems encountered while attending online courses included technical connection issues (62.7%), inability to ask questions about unclear topics (54.2%), and lack of socialization (37.3%). Among hybrid students, 39.3% reported technical problems, 21.3% reported difficulty in asking questions about unclear topics, and 34.4% reported a lack of social interaction (Table 2).

In Tables 3 and 4, data on the comprehension of theoretical and practical courses are presented according to the educational method received by the students. There was no statistically significant difference between the online and hybrid education groups in terms of understanding theoretical courses ($p = 0.088$). The median score of online students was 3.00, and the median of hybrid students was 3.25.

A statistically significant difference in the comprehensibility of practical courses was found between the two groups ($p < 0.001$). The median for online students was 2.50, and for hybrid students, 3.50. Both groups stated that practical courses should be conducted face-to-face (Table 4).

Table 1. Demographics characteristics of students.

		Online education		Hybrid education		Mean of all participants	
		n	%	n	%	n	%
Gender	Female Male	39 20	66.1 33.9	23 38	37.7 62.3	62 58	51.7 48.3
Student GPA	2.00 and less 2.01–2.50 2.51–3.00 3.01–3.50 3.51 and more	3 10 27 19 0	5.1 16.9 45.8 32.2 0	1 8 14 24 14	1.6 13.1 23.0 39.3 23.0	4 18 41 43 14	3.3 15.0 34.2 35.8 11.7
How would you like the training to proceed?	Online Hybrid Face to face	12 26 21	20.3 44.1 35.6	39 10 12	63.9 16.4 19.7	51 36 33	42.5 30.0 27.5
Which tool is used to participate in distance learning?	Own computer Own smartphone Someone else's computer Someone else's device Other	15 42 1 1 0	25.4 71.2 1.7 1.7 0	9 44 5 0 3	14.8 72.1 8.2 0 4.9	24 86 6 1 3	20.0 71.7 5.0 0.8 2.5
Where do you participate in online training	My own home House of relatives Neighbor house	56 2 1	94.9 3.4 1.7	26 3 32	42.6 4.9 52.5	82 5 33	68.3 4.2 27.5
	Total	**59**	**100.0**	**61**	**100.0**	**120**	**100.0**

GPA, grade point average.

Table 2. Students' views on online and hybrid education.

		Online education		Hybrid education		Mean of all participants	
		n	%	n	%	n	%
Reasons for wanting online courses	I take lessons when I am available School lessons are boring I can't concentrate at school I am working	29 1 1 9	49.2 1.7 1.7 15.3	17 1 5 6	27.9 1.6 8.2 9.8	46 2 6 15	38.3 1.6 5 12.5
Drawbacks of following lectures online	Always have access to the internet Technical issues Individualization Staying away from social environments Not being able to ask questions	26 37 16 22 32	44.1 62.7 27.1 37.3 54.2	16 24 13 21 13	26.2 39.3 21.3 34.4 21.3	42 61 29 43 45	35 50.83 24.16 35.83 37.5

Multiple responses were allowed. Percentages are based on the number of students within each group.

The training method applied to the students and their skills related to health practices are presented in Table 5. A significant difference was found, favoring students who received hybrid education, in perceived competence for advanced health practices related to their profession ($p < 0.001$). Students in the hybrid education group reported greater confidence in performing practical procedures, such as intravenous and intramuscular injections; endotracheal intubation; nasogastric and urinary CPR resuscitation; and defibrillation. The median for students who received online education was 2.14, and the median for students who received hybrid education was 4.00 (Table 5).

Discussion

This study demonstrates the negative impact of fully online education on students' professional competence by comparing the perceptions of competence in practical courses among paramedic students who received hybrid and fully online education. In professions involving applied scientific disciplines, in-person instruction is essential. During the pandemic, the educational activities of paramedic students were adversely affected: clinical and laboratory practices could not be conducted, and students graduated and entered the profession through the online education system (20).

Table 3. Students' opinions on theoretical courses.

What is the method of education you received at school?	Online			Hybrid education			Total			
	Mean	n	SD	Mean	n	SD	Mean	n	SD	
I have no problems understanding the theoretical courses.	3	59	1.31306	2.9836	61	1.13272	2.9917	120	1.21956	
The time allocated for theoretical courses is sufficient for understanding the subject matter.	3.339	59	1.13882	3.0656	61	1.24992	3.2	120	1.19944	
The course materials used to teach the theoretical courses are adequate.	2.6441	59	1.30994	3.2623	61	1.09395	2.9583	120	1.23938	
I consider myself proficient in theoretical courses.	2.8814	59	1.31418	3.5574	61	0.90415	3.225	120	1.17009	
	Online education			Hybrid education						
	Mean rank	Sum of ranks	Median	Mean rank	Sum of ranks	Median	u	p	z	r
	55.03	3246.50	3.00	65.80	4013.50	3.25	1476.50	0.088	-1.705	-0.160

Mann–Whitney U test applied; z, standardized test value, p, probability value, r, effect size, $p < 0.05$ indicates significance. SD, standard deviation.

Table 4. Students' opinions on applied courses.

What is the method of education you received at school?	Online			Hybrid education			Total			
	n	SD	Mean	n	SD	Mean	n	SD	Mean	
I have no difficulty understanding the practical components of applied courses.	2.3559	59	1.551	3.4918	61	1.05866	2.9333	120	1.43623	
The course materials used to facilitate understanding of the practical training are adequate.	2.1017	59	1.15512	3.4754	61	0.9765	2.8	120	1.26757	
I can readily ask the lecturer about topics I do not understand during the lecture.	3.339	59	1.1687	3.7049	61	1.08542	3.525	120	1.13732	
I think that providing practice-based courses exclusively through distance education is insufficient.	4.0339	59	1.46177	2.918	61	1.6155	3.4667	120	1.63436	
	Online education			Hybrid education						
	Sum of ranks	Median	Sum of ranks	Median	Sum of ranks	Median	u	p	z	r
	41.31	2437.50	2.50	79.06	4822.50	3.50	667.50	0.001	-5.962	-0.540

Mann–Whitney U test applied; z, standardized test value, p, probability value, r, effect size, $p < 0.05$ indicates significance. SD, standard deviation.

A significant majority of students educated during the COVID-19 pandemic were digital natives born in the 2000s who actively use technology. The internet, computers, and mobile devices are integral to every aspect of their lives. The transition to remote education during the pandemic represented a novel experience for these young people, who were already accustomed to the digital world (21). In our study, the majority of students who received hybrid education expressed a preference for online learning, while half of those who received exclusively online education were satisfied with it. Different rates have been reported in the literature: 54.6% of medical students (2), 60% of health students (13), and 53.9% of nursing students (22) reported that they did not find online education effective. However, medical and nursing students stated that online education was comparable to traditional teaching because it met the course objectives, conveyed content accurately, and ensured appropriate use of time (23). In contrast, first aid and emergency care students exhibited negative attitudes toward online education (24). The reasons why hybrid-

Table 5. Students' self-perceived professional competence in clinical skills according to education method.

According to the method of education you received at school;	Online education			Hybrid education			Total		
	Mean	n	SD	Mean	n	SD	Mean	n	SD
I feel competent in intravenous route opening practice.	2.9661	59	1.33863	4.3607	61	0.7535	3.675	120	1.28444
I feel competent in administering intramuscular injections.	2.5593	59	1.29016	4.2131	61	1.03465	3.4	120	1.4284
I feel competent in tracheal intubation practice.	1.8814	59	1.05184	3.5738	61	1.20359	2.7417	120	1.41121
I feel competent in nasogastric catheter application.	1.7458	59	0.99296	3.5246	61	1.20563	2.65	120	1.41807
I feel competent in urinary catheterization.	2.0169	59	1.25247	3.3443	61	1.20948	2.6917	120	1.39504
I feel competent in cardiopulmonary resuscitation.	2.2881	59	1.20417	4.1311	61	1.00789	3.225	120	1.44049
I feel competent in using defibrillators.	2.0169	59	1.22463	3.7049	61	1.05427	2.875	120	1.41755

	Online education			Hybrid education						
	Mean rank	Sum of ranks	Median	Mean rank	Sum of ranks	Median	u	p	z	r
	36.42	2148.50	2.14	83.80	5111.50	4.00	378.50	0.000	-7.470	-0.680

Mann–Whitney U test applied; z, standardized test value, p, probability value, r, effect size, $p < 0.05$ indicates significance. SD, standard deviation.

education students preferred online learning included avoidance of in-person attendance for laboratory practices, transportation issues related to living in a metropolitan area, and risk of exposure to COVID-19 during hospital-based clinical practices.

Most students indicated that the main reason they preferred to continue their studies online was the ability to attend classes from any location at their convenience. Saving time, easy access to lessons, and the opportunity to rewatch lectures, aspects of flexibility provided by online education, were also cited as key preferences. Nursing students, in particular, value online education for its temporal and spatial flexibility, the ability to stay with family while attending classes, and reduced transportation costs (25,26). Medical students prefer online education because it enables them to review recorded lectures and removes temporal and spatial constraints (2,27,28). In line with the literature (29), our study found that a large proportion of students attended classes from their homes using their phones. Online education may continue to be preferred beyond the pandemic because of its flexibility in time management. However, students frequently reported issues such as lack of socialization, technical problems before or during classes, and inability to ask questions about topics they did not understand. These issues, including the inability to ask questions during lessons, not having a conducive home learning environment, spending excessive time in front of a computer, and difficulty focusing, have been highlighted in many studies (22,27,28,30). Medical students also mentioned the inability to examine cadavers during anatomy classes.

First aid and emergency care students reported that online education did not offer good learning opportunities, that acquired information was not retained, and that they experienced difficulties in learning (20). Although our students expressed positive views of online education, they also shared negative perceptions of their own motivation. Our results indicate that theoretical courses can be effectively delivered online or face-to-face and that the education provided was sufficient, even though distance education had not previously been implemented. No significant difference was observed between groups in their understanding of theoretical content delivered online; however, online education was preferred because of its advantages. Synchronous classes that offer an educational atmosphere closer to face-to-face education have been shown to increase the acceptability of online learning among students. Similarly, nursing students (31) and operating theatre students (32) stated that distance learning methods are sufficient for the theoretical components of courses but inadequate for practical training. Some studies report no difference between face-to-face and online instruction regarding learning outcomes, while other studies suggest that online education is more effective and efficient for

medical students (27). Therefore, theoretical courses can be effectively supported by online education.

Within the health professions, the First and Emergency Aid (Paramedic) program plays a critical role in enabling accurate diagnosis and timely intervention in prehospital care. In Türkiye, the Regulation on the Working Procedures and Principles of Ambulance and Emergency Care Technicians and Emergency Medical Technicians, published in 2009 under Decision No. 27181, emphasizes the critical importance of competencies in defibrillation and endotracheal intubation. A lack of proficiency in these skills may result in patient death. Error-free application of skills can only be acquired through high-quality, effective training in first aid and emergency care (20,33,34). In our study, students who received hybrid education reported significantly higher levels of perceived professional competence in practical courses (including IV/IM administration, intubation, nasogastric and urinary catheterization, CPR, and defibrillation) than students who received online education. Participation in face-to-face clinical practice appears to increase students' confidence and sense of readiness in performing professional skills. When students' academic achievement was evaluated based on GPA, 85.3% of those who received hybrid education had an average GPA of 2.5 or higher, which is consistent with our findings. Our study compared students enrolled in two associate-degree programs in different cities, both offering the same curriculum before and after the COVID-19 pandemic. Although the educational content remained consistent, the aim was to evaluate the impact of differing delivery models—one fully online and the other hybrid. Institutional characteristics, environmental factors, and potential variations in student demographics were not taken into account. This methodological limitation should be considered when interpreting the findings.

Paramedic students who received education during the pandemic reported feeling anxious about the risk of harming patients (20). Similarly, 75% of medical students who trained during the pandemic reported that they could not treat patients without in-service training and that they felt professionally inadequate (13). The education students receive at university is a crucial period during which they acquire the professional knowledge and skills necessary to obtain employment after graduation. Graduating with professional qualifications and competencies enhances self-confidence and reduces anxiety about finding employment. Face-to-face clinical practices, whether bedside or simulation-based, conducted under the supervision of instructors, provide effective training and confidence for quick and accurate interventions in real-life scenarios.

Study Limitations

The primary limitation of this study is that the vocational schools compared are situated in cities with differing socio-cultural and environmental characteristics**.** One of the universities, located in a metropolitan area, implemented a hybrid education model, while the other, situated in a smaller city, adopted a fully online approach. Although this study provided an opportunity to compare two educational delivery models, institutional structures, available resources, and student profiles may differ across universities. Our study compared students enrolled in two associate degree programs located in different cities, both offering the same curriculum before and after the COVID-19 pandemic. Although the educational content remained consistent, the aim was to evaluate the impact of differing delivery models—one fully online and the other hybrid. Institutional characteristics, environmental factors, and potential variations in student demographics were not taken into account. Therefore, the findings may have been influenced not only by the educational model but also by environmental and institutional factors.

Additionally, the data were based solely on students' self-reports. Only their perceptions of professional competence were assessed; objective measures such as knowledge levels or actual performance were not included. Since the study was conducted during the pandemic, psychological and environmental conditions specific to that period may have affected students' perceptions.

Conclusion

Face-to-face clinical training is essential for health sciences students to feel professionally competent and to reinforce their theoretical knowledge. Our study revealed that the negative aspects of online education during the pandemic stemmed mainly from systemic problems, and students perceived these aspects more positively when adequate planning and preparation were in place. Although distance education appears sufficient for delivering theoretical knowledge, it remains inadequate for fostering perceived professional competence in clinical and technical skills. Face-to-face clinical practice enhances students' perceived professional competence and self-efficacy in applied skills. Hybrid education, which combines online theoretical instruction with in-person clinical practice, improves students' perceptions of professional competence and supports their preparedness for professional roles. Therefore, in health education programs such as First Aid and Emergency Aid, a hybrid education model that includes face-to-face practical training should be prioritized over fully online education.

In light of these findings, future research should investigate how hybrid education models can be further optimized to balance theoretical knowledge acquisition with clinical skill development. It is also recommended that future studies include larger and more diverse samples from various universities and employ research designs that integrate subjective perceptions of competence with objective assessments of knowledge and performance.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Gümüşhane University Scientific Research and Publication Ethics Committee (approval number: 2021/3, dated: 14.04.2021), and administrative permission was obtained from the institutions where the study would be conducted.

Informed Consent: No sampling procedure was applied; all students who provided informed consent were included.

Footnotes

Authorship Contributions

Concept: Ş.N.K., B.Y.K., B.N.B.D., Design: N.D.B., B.Y.K., B.N.B.D., Data Collection or Processing: B.Y.K., B.N.B.D., Analysis or Interpretation: N.D.B., Literature Search: B.Y.K., Writing: Ş.N.K., B.Y.K.

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Re-Establishing Scientific Bridges with Our Cultural Heartland: The Case of the Damascus School of Medicine

Gönül Coğrafyamızla Yeniden Bilim Köprüleri Kurmak Bağlamında: Şam Mekteb-i Tıbbiyesi

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ABSTRACT

Background: This study examines in detail the Damascus School of Medicine (Şam Mekteb-i Tıbbiyesi), established by the Ottoman Empire during difficult times to provide modern medical education, with respect to its academic and administrative staff, curriculum, and the functioning of its educational programs from its establishment to its closure. The aim of the study is to elucidate the relationship between the medical schools that the Empire established in the capital and the Damascus School of Medicine.

Materials and Methods: The primary sources for this study are archival documents that contain significant information on the establishment, operation, and closure of the Damascus School of Medicine, as well as the book "Şam Türk Tıbbiye Mektebi" (The Turkish School of Medicine in Damascus) by Ali Rıza Atasoy, who served as an administrator of the school for a period of time. These sources have been analyzed within the context of the research question.

Results: The Damascus School of Medicine was structured as a direct extension of the schools in İstanbul. The curriculum was implemented identically, the language of instruction was Turkish, and diplomas were issued in İstanbul. The teaching and administrative staff were also drawn from the medical schools in İstanbul. This structure enabled the school to train qualified healthcare personnel within a short period.

Conclusion: The Damascus School of Medicine stands as the most concrete provincial representation of centralized medical education in the Ottoman Empire. Its strong structural ties to İstanbul made it a significant conduit for modern medical education outside Anatolia. However, with the loss of Ottoman sovereignty over Syria, this institution was relegated to the background of historical memory.

Keywords: The Damascus School of Medicine, medical education, Ottoman Empire, Abdulhamid II

ÖZ

Amaç: Bu çalışmada Osmanlı İmparatorluğu'nun zor zamanlarında modern tıp eğitimi vermek üzerek kurmuş olduğu Şam Mekteb-i Tıbbiye'si, kuruluşundan kapanışına kadar geçen zaman diliminde akademik ve idari kadrosu, müfredatı, eğitim programlarının işleyişi gibi konular bakımdan detaylı bir şekilde ele alınmıştır. İncelemeler sonucunda İmparatorluğun payitahtta kurduğu tıbbiyelerle Şam Mekteb-i Tıbbiyesi arasındaki ilişkiyi ortaya koymak amaçlanmıştır.

Gereç ve Yöntemler: Çalışmada Şam Mekteb-i Tıbbiyesi'nin kuruluşu, işleyişi ve kapanışına dair önemli pek çok bilgiyi içeren arşiv vesikaları ve okulun bir dönem idareciliğini de yapmış olan Ali Rıza Atasoy'un "Şam Türk Tıbbiye Mektebi" adlı eseri birincil kaynaklar olarak ele alınmış, araştırma sorusu bağlamında analiz edilmiştir.

Bulgular: Şam Mekteb-i Tıbbiyesi, İstanbul'daki mekteplerin doğrudan bir uzantısı gibi yapılandırılmıştır. Müfredat birebir uygulanmış, öğretim dili Türkçe olmuş, diplomalar İstanbul'dan gönderilmiştir. Eğitim ve yönetim kadroları da İstanbul'daki tıbbiyelerden sağlanmıştır. Bu yapı, mektebin kısa sürede nitelikli sağlık personeli yetiştirmesine imkân sağlamıştır.

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ÖZ

Sonuç: Şam Mekteb-i Tıbbiyesi, Osmanlı'da merkezî tıp eğitiminin taşradaki en somut temsilidir. İstanbul'la kurduğu güçlü yapısal bağlar, onu modern tıp eğitiminin Anadolu dışındaki önemli bir taşıyıcısı hâline getirmiştir. Ancak Suriye'nin Osmanlı hâkimiyetinden çıkmasıyla bu kurum tarihsel hafızada geri plana itilmiştir.

Anahtar Kelimeler: Şam Mekteb-i Tıbbiyesi, tıp eğitimi, Osmanlı İmparatorluğu, II. Abdülhamit

Introduction

During a period of political, military, and economic turbulence in the Ottoman Empire, educational modernization gained momentum due to the efforts of Sultan Abdulhamid II. The intense demand for trained physicians from both the army and the populace caused these efforts to focus on medical schools as well. The renewal of medical education institutions, which began in the first quarter of the 19th century, led to the establishment of three modern medical schools by the beginning of the 20th century: two in the capital city and one in Damascus.

Tıbhane-i Amire was the first Western-style military medical school, established to meet the need for military physicians, and it began its educational activities on March 14, 1827, in the Tulumbacıbaşı Mansion in Şehzadebaşı. In 1836, the school was relocated to the Otlukçu Barracks at Sarayburnu. With the Tanzimat reforms, it was moved to Galatasaray, renamed Mekteb-i Tıbbiye-i Adliye-i Şahane in 1839, and its language of instruction was changed to French. After the building was completely destroyed in a fire in Beyoğlu in 1848, education continued at the Humbarahane-i Âmire. After being located here for a long period, the school was moved first to the Gergeroğlu Mansion because of the 1865 cholera epidemic, and then, after the epidemic ended, to the Demirkapı Barracks in Sirkeci (1). Just as the school's Tıbhane-i Amire —the first western-style medical school—constantly changed its location, the duration and content of its education also varied over the years. With the 1839 transition to French-language education, the duration of study gradually increased to 10 years, resulting in substantially fewer graduates and a failure to meet the demand for physicians. The primary factor identified as causing the very low number of graduates, despite all the support, was instruction in a foreign language (2). To solve this problem, a new school was established to train civilian physicians solely to meet the growing health needs of the public; it provided medical education in Turkish. Thus, the second medical school, named Mekteb-i Tıbbiye-i Mülkiye (non-military medical school), began its educational activities on March 3, 1867, in the Menemenli Mustafa Pasha Mansion. The benefits of Turkish-language education were quickly recognized, and in 1870 the language of instruction at the military medical school was changed from French to Turkish (1).

Many problems arose because buildings allocated for medical education were not originally constructed as medical schools. In the 1890s, numerous complaints regarding the poor physical conditions of the medical school reached the palace. Consequently, by decree of Sultan Abdulhamid II, the construction of a new building for the military medical school began in Haydarpaşa in 1895 (3). The foundations of the new medical school building were laid with prayers on February 11 (16 Sha'ban), the Sultan's birthday; education began on November 6, 1903, when the Mekteb-i Tıbbiye-i Şahane relocated to the new building. By 1909, the military and civilian medical schools were merged into the Haydarpaşa Building and continued to operate as Darülfünun-i Osmani Faculty of Medicine until 1933 (3).

From the outset, there was a desire to extend these significant educational developments in the capital to other major centers across the Ottoman Empire, and efforts were made toward that end. Abdulhamid II, who took a particular interest in this matter, planned to establish educational centers in various regions such as Halep, Bursa, Izmir, and Diyarbakır to expand modern medical education (4,5). The Damascus School of Medicine, established on August 31, 1903, emerged from these efforts and became the first and only medical school founded outside the capital (6). The opening of this medical school during such a period of financial, military, and political constraints was influenced not only by Abdulhamid II's emphasis on education but also by the missionary and propaganda activities of increasingly prevalent foreign schools in Damascus (7). The medical school, which began its education in the Ziver Pasha Mansion in 1903, was only able to move to its permanent building, constructed in the garden of the Damascus Hamidiye Gureba Hospital, on March 21, 1914. Education was provided in this building, which was constructed entirely by the Ottoman Empire, for only two years. With the outbreak of World War I and the spread of the conflict to the province of Syria, the medical school was relocated to Beirut in 1916. Following the occupation of Beirut on October 4, 1918, the medical school was closed, and its instructors were arrested (4). During the brief period it provided education, the Damascus School of Medicine graduated 240 doctors and 289 pharmacists (8).

This study aims to examine the Damascus School of Medicine, established by the Ottoman Empire to provide modern medical education during its difficult period, from its founding to its closure, through analysis of archival documents and primary sources from the period regarding its academic and administrative staff, curriculum, and the operation of its educational programs. It also aims to elucidate the relationship between the medical schools founded in the imperial capital and the Damascus School of Medicine.

Materials and Methods

In this study, the period from the establishment of the Damascus School of Medicine to its closure, as well as its academic and administrative staff, curriculum, and the functioning of its educational programs, were examined in detail, while the school's relationship with other medical schools in the capital was analyzed at each of these stages. For this purpose, archival documents, which contained records of nearly all relevant processes, and the work "Şam Türk Tıbbiye Mektebi" (The Turkish School of Medicine in Damascus) by Ali Rıza Atasoy, who also served as an administrator of the school for a period, were treated as primary sources. All relevant documents and secondary sources were analyzed within the context of the study's question.

Results

The Establishment of the Damascus School of Medicine

Requests for the establishment of a medical school in Damascus were conveyed to the imperial capital on various occasions by regional administrators, beginning in the early 1890s. In 1892, a series of reports was sent to the central government, first by the Director of Education for Syria and then by the Health Inspectorate of Syria (9,10) (Figure 1). These reports mentioned the growing influence of foreign medical schools in the regions of Syria and Lebanon and the necessity for the Ottoman State to open a medical school to counter them. One of the foreign schools was the American Medical and Pharmacy School of Beirut, established in 1865 as a college complex with preparatory, higher-education, and medical sections, while the other was the St. Joseph Faculty of Medicine, established in Beirut by the French in 1883 (7).

The second report, which provided a comprehensive account of the foreign medical schools, noted that these institutions engaged not only in educational activities but also in certain missionary practices, and recommended that measures be taken to address this situation. The estimated budget required for the construction and operation of the proposed medical school was also detailed, item by item, in the same report (10). In 1895, the Inspector of Agriculture for Syria and Beirut drafted another report on the same issue, but the central government responded negatively, citing insufficient funds (10).

Finally, a 1900 report by Mirliva Hayreddin Pasha stated that physicians graduating from the Mekteb-i Tıbbiye-i Şahane and the Mekteb-i Tıbbiye-i Mülkiye could not meet the public's need for doctors, noted that foreign schools exploited this need as an opportunity for missionary activities, and recommended the establishment of a new medical school (10,11). The response to this report was also that, although it was acknowledged that many benefits would result from establishing the requested school, it was not possible due to economic constraints (10).

Despite the Sultan's wish, the public's clear need, and the officials' persistent demands, financial inadequacies

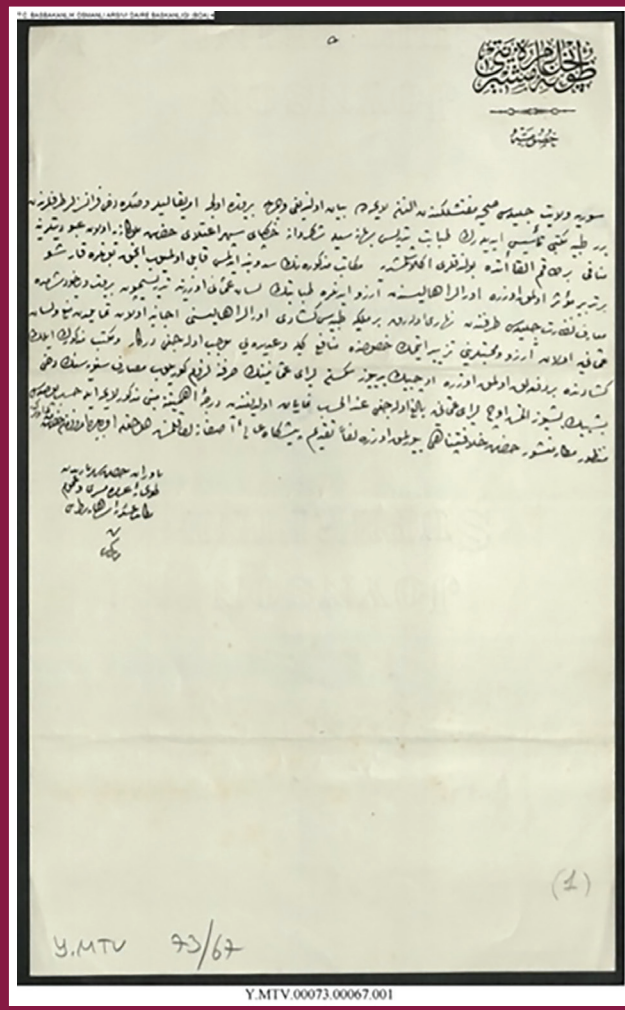

Figure 1. Proposal sent from the Syrian province health inspectorate.

repeatedly prevented the school's construction. However, persistent reports ensured that the urgency and importance of the need for the medical school were understood in the capital, and action was taken to establish the medical school in Damascus despite wartime conditions. The budget required for the establishment of the medical school and its affiliated clinical hospital was determined based on the expenses of the Mekteb-i Tıbbiye-i Mülkiye in İstanbul. For a period, calculations were performed to determine where and how the budget could be met, and new tax items were introduced (4). Finally, on April 16, 1903, an imperial decree establishing a medical school in Damascus was issued, stipulating that the school be built in the garden of the Damascus Hamidiye Gureba Hospital (12) (Figure 2). Because it was desirable to start education as soon as possible, the Ziver Pasha Mansion on Salihiye Avenue in Damascus was deemed a suitable temporary location until the new building was completed. With the Sultan's permission, the school opened on August 31, 1903, and officially began education on October 5, 1903 (10) (Figure 3).

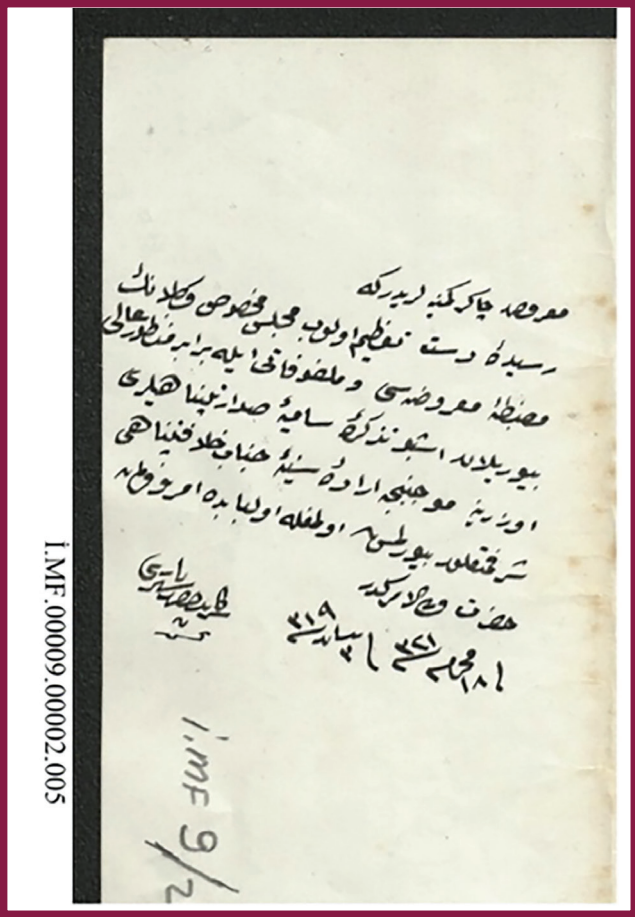

Figure 2. The decree regarding the opening of the school.

In addition to medical education, pharmacy education was initiated as a single class at the school. A three-year curriculum in pharmacy was established, and the school produced its first graduates in 1906 (13). The graduation ceremony was conducted in the same manner as for pharmacists graduating from the Mekteb-i Tıbbiye-i Şahane, and the students' diplomas were prepared and sent from İstanbul (14) (Figure 4). By 1909, ten students who had completed their six-year education were the school's first medical graduates (10). The diplomas of these students were similarly prepared by the Darülfünun-i Osmani Faculty of Medicine, which was established by the merger of the civilian and military medical schools in İstanbul. By 1914, the school had moved from the Ziver Pasha Mansion into its permanent building, which was constructed in the garden of the Damascus Hamidiye Gureba Hospital. Due to the outbreak of World War I, the medical school was able to continue its educational activities at this location for only two years (4). It continued its educational activities in Beirut for another two years, from 1916 to 1918.

Figure 3. Groundbreaking ceremony for the Damascus Medical School.

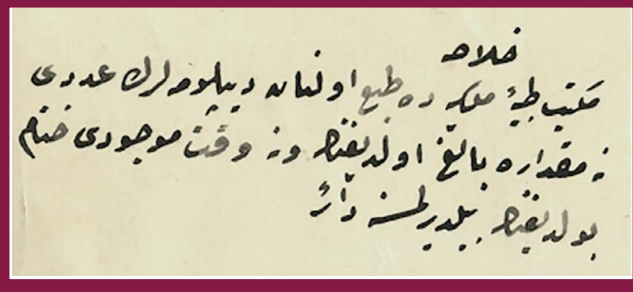

Figure 4. Document stating that the diplomas of graduates of the pharmacy class of the Damascus Medical School were printed at the Mektebi Tıbbiye-i Mülkiye.

The School's Administrators

Founding Director

Feyzi (Hasan) Pasha

After the imperial decree establishing the Damascus School of Medicine was issued, Feyzi (Hasan) Pasha, who was in Damascus at the time as the head of the Syrian Health Commission to combat a cholera outbreak, was appointed both to lead the school's establishment and to serve as its director for a period (1,8,10,15) (Figure 5). Feyzi Pasha was a well-trained physician who graduated with first-class honors from the Mekteb-i Tıbbiye-i Şahane in 1871, after which he went to Paris to complete his specialization in internal medicine alongside prominent physicians of the era. He then returned to his alma mater to assume the role of professor of internal medicine. He served as the founding director of the Damascus School of Medicine (1).

First Director Doctor Memduh

Four months after the school's opening, Feyzi Pasha returned to İstanbul, and Mr. Memduh—who had been an assistant in obstetrics and gynecology (fenn-i kıbale) at the Mekteb-i Tıbbiye-i Mülkiye in İstanbul—was sent to serve as director (8,16). A committee responsible for the school's administrative affairs also arrived with Doctor Memduh (8). This committee included Mr. Ali, secretary; Mr. Zeki, surgeon; Mr. Ethem, pharmacist; Mr. Mehmet Emin, librarian; Mr. İbrahim Fikri, museum officer; Mr. Vasil el-Mueyyed, accounting officer; Mr. Necati, head prefect; Mr. Rıza, prefect; an imam; and service personnel (10).

The school, which operated in Damascus until 1916 and then in Beirut for two years, had a total of seven directors during this period. The individuals and their appointment years are, respectively: Feyzi Pasha (1903), Doctor Memduh (1903–1907), Doctor İsmail Hakkı of Milas (1905), Doctor Şerif (1909), Doctor Arifi Pasha (1912), Doctor Hasan Reşat (1913), and Doctor Ethem Akif (1915) (17–22). With the exception of Feyzi Pasha, all the others had graduated from the Mekteb-i Tıbbiye-i Mülkiye and were appointed to the Damascus School of Medicine while serving in various other posts (8).

The School's Instructors

First Instructors

After preparations to establish the school and its instructional building were completed, the process of identifying and appointing instructors for first-year courses began. For this purpose, a competition was held on July 20, 1903, among physicians who had graduated from the medical schools in İstanbul (4). Mr. İsmail Hakkı and Mr. Mustafa Hakkı won the competition and were appointed as the school's first instructors (8). Mr. İsmail Hakkı, an assistant instructor of natural philosophy, physics, and geology at the Civilian School of Medicine in İstanbul, was assigned to teach the same courses at the Civilian School of Medicine in Damascus. Similarly, Mr. Mustafa Hakkı, who served as an assistant instructor for organic, inorganic, and analytical chemistry courses in İstanbul, was assigned to Damascus as the instructor for these subjects (8,23). The instructors, whose appointment decrees were issued on September 8, 1903, set out for Damascus on September 29, 1903 (4).

Academic Staff

As a result of appointments made in late 1903 and early 1904, the academic staff for the school's first-year class was completed (4). Accordingly, Mr. Ligor was appointed assistant chemistry instructor to Mr. İsmail Hakkı and Mr. Mustafa Hakkı (24,25); first, Mr. Mustafa and then Mr. Bedri were appointed French[1] instructors; Mr. Mehmet Latif was appointed religious studies[2] instructor; and Mr. Abdülvehhap was appointed Turkish instructor (4,8,26–28).

The newly established school's material deficiencies and physical needs were met over time, and the academic staff was expanded to accommodate the addition of new classes. All the school's instructors were graduates of the medical schools in İstanbul and were appointed to Damascus from various duties in those schools or Anatolia (8,10). Archival records from the period indicate that the instructors to be sent were examined, and those who passed the examination were appointed (28,29).

Set of Regulations

The Damascus School of Medicine was, like other medical schools, administratively attached to the Ministry of Education and academically to the Council of Instructors of İstanbul Medical School. Immediately after its establishment,

1 BOA, MF.MKT., 827/48, 20 Zİ.1322 (26 January 1904). According to this document, Mr. Mustafa was first appointed as the French instructor for the school, but upon his resignation, Mr. Bedri was appointed on the same date. Likely due to his short tenure, Ali Rıza Atasoy directly mentions Mr. Bedri as the first French instructor. See also: Atasoy AR. Şam Türk Tıbbiye Mektebi. İstanbul: Milli Mecmua Basımevi; 1945. p. 10.

2 BOA, MF.MKT., 821/34, 19 Ş 1322 (27 December 1904). The document concerning the instructor's appointment could not be found; however, it is understood from this record that he was dismissed due to his insufficient Turkish. Atasoy mentions Mr. Abdülaziz of Damascus as the religious studies instructor, but no supporting document could be found. See also: Atasoy AR. Şam Türk Tıbbiye Mektebi. İstanbul: Milli Mecmua Basımevi; 1945. p. 10; İhsanoğlu E. Suriye'de Modern Osmanlı Sağlık Müesseseleri, Hastahaneler ve Şam Tıp Fakültesi. Ankara: Türk Tarih Kurumu; 1999. p. 41; Tuna A. Şam Mekteb-i Tıbbiyesi [Master's thesis]. İstanbul: İstanbul University, Department of History, Institute of Social Sciences; 2018. p. 41.

Figure 5. Doctor Ferik Feyzi Pasha.

the Ministry of Education prepared and submitted a set of regulations to define both the administrative and educational activities of the school. The regulations were not immediately approved by state officials and remained pending for some time, during which problems arose. Finally, in 1906, it was decided that the Regulations of the Medical Schools in İstanbul would be implemented at the Damascus School of Medicine, thereby aligning it with the regulations as the medical schools in İstanbul (4).

For a short period, the school was attached to the Ministry of Education for financial affairs and to the Ministry of Military Schools for instructor appointments and the preparation of diplomas. In 1908, it was reaffiliated with the Ministry of Education, along with the Mekteb-i Tıbbiye-i Mülkiye in İstanbul (30). A year later, when the civilian and military medical schools in İstanbul were merged in the Haydarpaşa building and became a branch of the Ottoman University under the name "Faculty of Medicine," the Damascus School of Medicine similarly became a branch of the Darülfünun. A document dated May 18, 1915, records the school's name as "Darülfünun-ı Osmanî Tıb Fakültesi Şam Tabip Eczacı Şubeleri" (Ottoman University Faculty of Medicine, Damascus Branches for Physicians and Pharmacists) (31) (Figure 6). The "*Tıp Fakültesi ve Şuâbatı Nizamnamesi*" (Regulations for the Faculty of Medicine and its Branches), created for the Darülfünûn-ı Osmani Faculty of Medicine on March 5, 1916, also became applicable to the Damascus School of Medicine (10).

Curriculum

Three months after the imperial decree establishing the Damascus School of Medicine, which was founded to provide medical and pharmacy education, was issued, the Ministry of Education prepared a curriculum consistent with

Figure 6. Directorate of the Damascus Medical and Pharmacist Branches of the Darülfünûn-ı Osmânî Medical Faculty.

the civilian medical school in İstanbul (32). Furthermore, the first set of regulations presented to the Bâbıâli included the statement: "The school is divided into six classes, and all courses taught in the medical schools in İstanbul will be taught here." (4). According to this program, medical education was designed to last six years, and pharmacy education was designed to last three years. Unlike at other medical schools, Turkish language classes were added to the curriculum and continued annually through the fifth year. This harmony between the schools continued after the transition to the Darülfünûn-ı Osmani Faculty of Medicine in 1909. Indeed, the courses in French, biographical historiography (tabaqat), and scribal arts (kitabet), which had been removed from the curriculum of the Faculty of Medicine in 1909, were also removed from the Damascus School of Medicine in the same year (33).

Student Admission Requirements

For students enrolling in the school's medical department, the requirements were to have graduated from a preparatory school or to demonstrate equivalent knowledge by passing an examination. Requirements for students enrolling in the pharmacy department included graduating from middle school and having worked in a pharmacy for three years (34). It was stated that the relevant diplomas must include documentation of completion of a Turkish language course (4). Additionally, requirements for both medical and pharmacy students included possessing a certificate of good character attested by three prominent individuals from their neighborhood and endorsed by the neighborhood headman and being no older than sixteen years of age (4,34). It was announced that students could register from the beginning of September to the end of October (34). Students enrolled in the Damascus School of Medicine had the same rights as students at the İstanbul medical schools and were exempt from military service (4).

Procurement Services and Foreign Students

To enable the school to offer a complete, high-quality education as soon as possible, efforts were made to supply necessary educational and other supplies expeditiously (35–38). To complete the procurement at the lowest possible cost, authorities ordered that materials arriving for the school be exempt from customs duties and that the relevant equipment be delivered promptly to the school, without being held up at customs (39–41). After the needs were met, and especially once educational procedures were established quickly, the school's student population grew rapidly and became more diverse (4). Notably, four years after the school opened, archival documents from the period indicate that some foreign students enrolled in schools in Beirut applied to transfer their enrollment to the Damascus School of Medicine (42). Similarly, foreign nationals who wished to enroll in the medical schools in both Damascus and İstanbul were permitted to register if they met the necessary conditions (43–45). An examination of the school's entire student body showed that the vast majority were Muslim Arabs, with smaller numbers of Christian Arabs, Jewish Arabs, and Turks (8).

Student Exchange

Occasionally, students transferred between the Damascus School of Medicine and the medical schools in İstanbul. An example of this is Mr. Salih Ahmet of Damascus, a pharmacy student who wished to transfer his registration from the Darülfünun-ı Osmani Faculty of Medicine in İstanbul to the Damascus School of Medicine (41). In some cases, requests from students expelled from the Civilian School of Medicine for absenteeism or disciplinary violations to transfer to the Damascus School of Medicine to complete their education were accepted (46–49).

Examinations

While classes at the school continued uninterrupted throughout the year, a final examination was held for each course at the end of the academic term. In the examinations, students' performance was classified into four categories: aliyyü'l a'lâ (excellent), a'lâ (very good), karibü'l-a'lâ (good), and sıfır (fail). A student who failed one course was required to take a supplementary examination; a student who failed the supplementary examination or received failing grades in two courses was required to repeat the year. Successful students were entitled to advance to the next class (10,50) (Figure 7). The examinations were conducted orally by a delegation sent from İstanbul, which also certified the diplomas of the foreign schools in Beirut (51). The school's entrance examinations, like the final examinations for medical and pharmacy students, were also conducted by this delegation (52).

Diplomas and Award Ceremonies

The first graduates of the Damascus School of Medicine were pharmacy students who completed the three-year program and passed the general examination (53). As with all subsequent graduations, the regulations of the Mekteb-i Tıbbiye-i Mülkiye in İstanbul were applied exactly to these students' diplomas and graduations (13,54). After the delegation from İstanbul conducted the general examinations, an award ceremony was first held in the presence of the instructors, students, and the public (55). Afterward, the diplomas prepared in İstanbul, sent to Damascus, and lacking the signatures of the local instructors or administrators were presented to the graduating students (8,14). Finally, the students who completed their pharmacy education with the first- and second-highest honors were awarded the gold medal in education (56). Aside from graduation, the request to implement award ceremonies at the Damascus School of Medicine for the top three medical and pharmacy students in the final examinations of the Mekteb-i Tıbbiye-i Mülkiye was accepted, and a special budget was allocated for this purpose (10). At the end of its approximately fifteen years' educational service, 529 students had graduated from the school, including 240 physicians and 289 pharmacists (8).

The Mobilization Years, the School's Relocation to Beirut, and Its Closure

The Damascus School of Medicine was also affected by the First World War, which began on July 28, 1914, and encompassed all Ottoman territories. At the onset of the war, educational activities were suspended temporarily, during which the school's administration was transferred from the Ministry of Education to the Ministry of Foreign Affairs. During the suspension of education, the instructors and students of the Damascus School of Medicine, like those of the medical school in İstanbul, were conscripted and assigned to various fronts (4,57,58). At this time, the possibility of moving the school to Beirut, which had been raised previously, was discussed again; the school director stated that, if such a plan existed, official procedures would need to be initiated. Thereupon, it was decided to relocate the school and some other institutions from Damascus to Beirut (4,10). Thus, the Damascus School of Medicine was relocated to the French Medical School building in Beirut and renamed Beirut Medical School (59).

Some time after relocating to Beirut, the school continued its operations to meet the army's needs for trained physicians during the war. To address the shortage of academic staff, the school's instructors who were serving in the army were discharged from military service. While the war continued at full intensity, with the occupation first

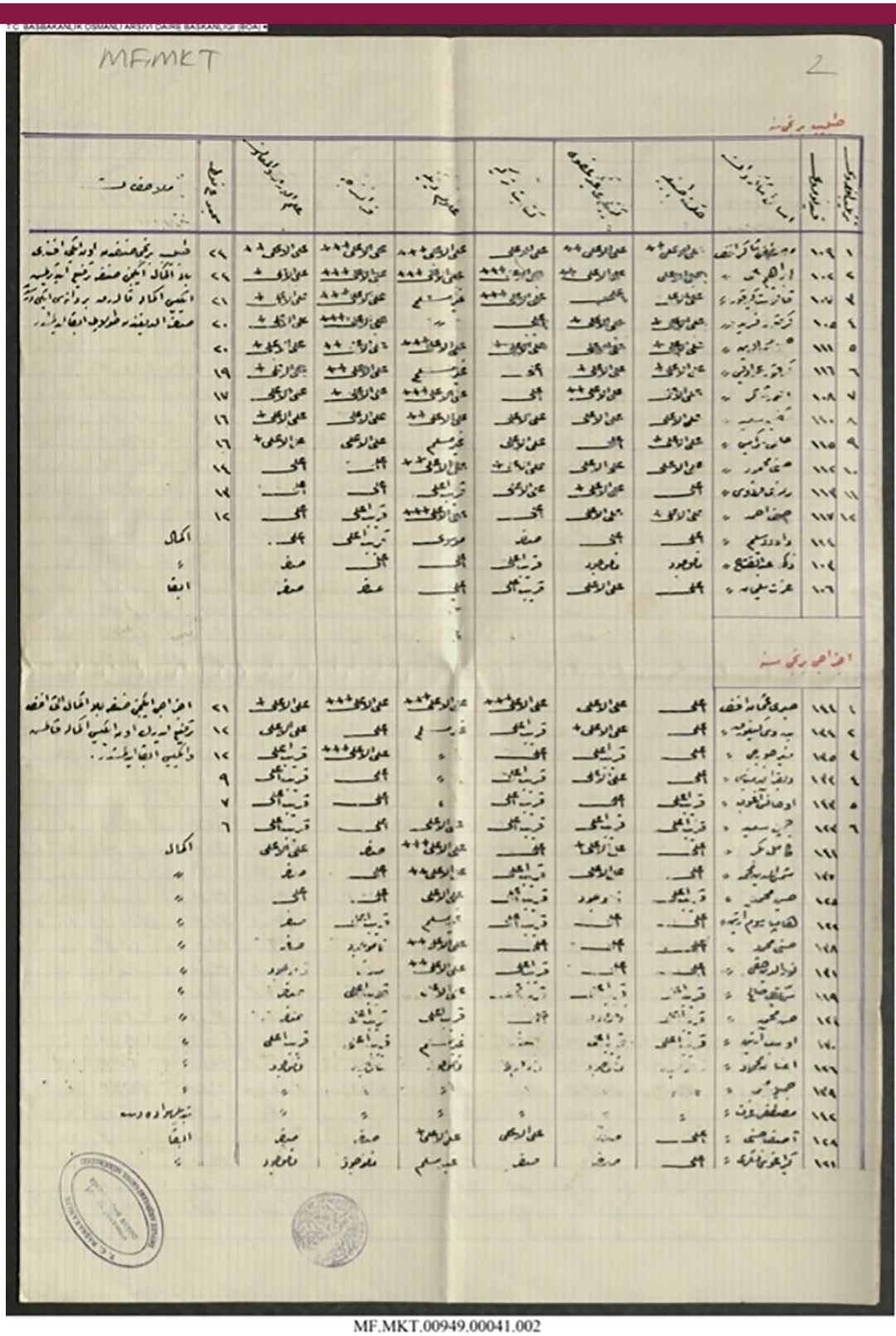

Figure 7. The students' grade sheets.

of Palestine and then of Damascus, the school's instructors requested that the governorate of Damascus relocate the school to Antep. The governorate did not initially take this request seriously, but when its justification was later understood, the relocation could not be carried out because the roads were held by enemy forces. The school, which had existed in Beirut for about three years, was permanently closed when the city was occupied on October 4, 1918 (4).

Discussion

The Ottoman Empire owes its ability to persist for centuries not only to its numerous other characteristics but also, in part, to its robust institutions. Educational institutions are at the forefront of these. By the last century, when the Empire was beset by various wars and troubles, the prescription for salvation was again accepted as the reorganization of educational institutions in accordance with modern scientific understanding. Sultan Abdulhamid II continued to develop and expand these renewal efforts initiated by his predecessors. To this end, he first laid the foundations for the new medical school building in Haydarpaşa in 1895 to solve the long-unresolved spatial problem of the Mekteb-i Tıbbiye-i Şahane. This structure, which began its educational activities on November 6, 1903, incorporated the civilian medical school six years later (in 1909) and thereafter served under the name Darülfünun-ı Osmani Faculty of Medicine.

Within the same time frame, successive letters from the Empire's province of Syria to the capital reported both the public's serious need for physicians and the presence of foreign schools conducting missionary activities that exploited this need, and called for the establishment of a medical school in the region as soon as possible. Despite these reports and the Sultan's ambition to spread modern medical institutions throughout the Empire, financial constraints temporarily delayed construction of the school. However, over time the urgency and importance of the need became apparent, and, with great sacrifices by the public and the palace, the Damascus School of Medicine, which provided medical education in Turkish, was established in Damascus.

The Damascus School of Medicine, the Empire's third medical school, operated in a manner that was, in many administrative and academic aspects, harmonious with and at times even subordinate to the medical schools in İstanbul. All of the school's administrative and academic personnel were appointed from the capital. Instructors were selected based on the results of a central examination administered to graduates of medical schools in İstanbul. Likewise, the curriculum of the İstanbul medical schools was implemented unchanged in Damascus, and any change made to the curriculum in İstanbul was applied to the Damascus school shortly thereafter. The school's general examinations were conducted by a team of instructors sent from İstanbul, and the diplomas were designed, printed, and sent from there. A ceremony similar to that held for the top graduates of the İstanbul medical schools was also organized for the graduates of the Damascus School of Medicine. The school's expenses; the school operated in Damascus for thirteen years and in Beirut for two years between 1903 and 1918, ranging from educational materials to all other expenditures, were covered by the central government.

The relationship between Damascus and İstanbul, through the Damascus School of Medicine, was not merely a one-sided provision of services from İstanbul. During the First World War, the school's instructors and students were mobilized and served on the front lines in defense of the homeland. Furthermore, during the short fifteen years it was active, it graduated 240 doctors and 289 pharmacists who assumed duties in various regions of the empire to meet the public's healthcare needs. The school served as a virtual administrative, scholarly, and human bridge between Damascus and İstanbul.

Conclusion

It has been 122 years since 1903, the year in which the Mekteb-i Tıbbiye-i Şahane began its educational activities in the Haydarpaşa building and a Turkish Medical School was founded in Damascus. At that time, Syria ceased to be part of the homeland; the Damascus School of Medicine was closed; and the medical school building in Haydarpaşa, despite having endured various hardships, continued to be used as an educational institution, albeit for different purposes. On April 15, 2015, the Mekteb-i Tıbbiye-i Şahane building in Haydarpaşa was allocated to the University of Health Sciences, thereby restoring its historical identity; our university has embraced the intellectual legacy of Sultan Abdulhamid II, undertaking the mission of disseminating modern medical education throughout our cultural heartland. As long as the adherents of an ideal maintain their existence and intellectual continuity, everything is bound to return to its origin sooner or later. In this vein, our country, as in the past, began restoring education and health services to the region by opening the University of Health Sciences Çobanbey Faculty of Medicine on February 5, 2021, under very difficult conditions while the Syrian civil war raged. At present, as Syria gradually regains its freedom, it is time for the Damascus School of Medicine building, which still stands, to be restored. The reopening of the Damascus School of Medicine as a medical school, housed in its own historic building and enabled through an educational affiliation with

the University of Health Sciences—which has been based in the historic Mekteb-i Tıbbiye-i Şahane building in Haydarpaşa since its inception—holds significant meaning for our past, present, and future. Through this, not only will the revival of this important scientific heritage be achieved, but the meaningful scientific support provided by today's medical students will also contribute to the region's rapid recovery.

Ethics

Ethics Committee Approval: This study does not require ethics committee approval as it does not involve any procedures on human or animal subjects.

Informed Consent: Not required.

Footnotes

Authorship Contributions

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

Conflict of Interest: No conflict of interest was declared by the author(s).

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The Role of Pulmonary Function Tests in Preoperative Pulmonary Risk Assessment in Patients with Known and Suspected Pulmonary Disease

Bilinen ve Şüpheli Akciğer Hastalığı Olan Hastalarda Preoperatif Pulmoner Risk Değerlendirmesinde Solunum Fonksiyon Testlerinin Rolü

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ABSTRACT

Background: This study aims to evaluate the diagnostic accuracy of preoperative oxygen saturation (SpO_2) measurements and advanced pulmonary function tests (PFTs) in predicting postoperative pulmonary complications (PPCs) in patients with known or newly diagnosed pulmonary disease who are undergoing elective surgery. The objective is to determine the predictive value of these tests for PPC risk assessment, thereby improving surgical risk stratification and facilitating the development of targeted preventive strategies for high-risk patients.

Materials and Methods: This study analyzed data from patients with known pulmonary disease (n = 92) and newly diagnosed pulmonary disease (n = 108) who underwent elective surgery at University of Health Sciences Türkiye, Şişli Hamidiye Etfal Training and Research Hospital between 2022 and 2023. Patients were assessed preoperatively using the CANET scoring system to evaluate the risk of PPCs. Preoperative SpO_2 and PFT measurements, including Forced Expiratory Volume in One Second (FEV_1) and Forced Vital Capacity (FVC), were compared between groups by logistic regression analysis to predict PPCs ($p < 0.05$).

Results: Logistic regression analysis demonstrated that low SpO_2 values (odds ratio [OR] = 0.66, 95% confidence interval [CI] [0.50–0.88], p = 0.004) were significant risk factors for the development of PPCs in Group 1 (known pulmonary disease), while low FEV_1 values (OR = 0.98, 95% CI [0.96–1.00], p = 0.030) were significant risk factors in Group 2 (newly diagnosed pulmonary disease).

Conclusion: This study highlights the importance of evaluating preoperative SpO_2 and PFTs jointly in risk assessment using the CANET scoring system, especially in patients with pulmonary disease. Particularly in patients with newly diagnosed pulmonary disease, consideration of PFT results is critical for predicting and preventing PPCs. Integrating PFTs into surgical risk assessment protocols can improve patient outcomes.

Keywords: Spirometry, complications, postoperative, pulmonary, risk factors

ÖZ

Amaç: Bu çalışmanın amacı, elektif cerrahi geçirecek olan bilinen veya yeni tanı konmuş akciğer hastalığı olan hastalarda postoperatif pulmoner komplikasyonları (PPK) tahmin etmedeki preoperatif oksijen satürasyonu (SpO_2) ölçümlerinin ve solunum fonksiyon testlerinin (SFT) tanısal doğruluğunu değerlendirmektir. Böylece, bu testlerin PPK risk değerlendirmesi için öngörü değerini belirlemek, böylece cerrahi risk sınıflandırmasını iyileştirmek ve yüksek riskli hastalar için hedeflenen önleyici stratejilerin geliştirilmesini kolaylaştırmaktır.

Gereç ve Yöntemler: Bu çalışmada, 2022–2023 yılları arasında Sağlık Bilimleri Üniversitesi, Şişli Hamidiye Etfal Eğitim ve Araştırma Hastanesi'nde elektif cerrahi geçirecek olan bilinen (n = 92) ve yeni tanı almış (n = 108) akciğer hastalığı olan hastaların verileri analiz edildi. Hastalar, PPK riskini değerlendirmek için preoperatif CANET skorlama sistemi kullanılarak değerlendirildi. PPK' leri tahmin etmek için zorlu ekspiratuar volüm (FEV_1) ve zorlu vital kapasite (FVC) dahil olmak üzere ameliyat öncesi SpO_2 ve PFT ölçümleri lojistik regresyon analizi kullanılarak gruplar arasında karşılaştırıldı ($p < 0,05$).

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öz

Bulgular: Yapılan lojistik regresyon analizi, düşük SpO_2 değerlerinin (olasılık oranı [OR] = 0,66, %95 güven aralığı [GA] [0,50–0,88], p = 0,004) Grup 1'de (bilinen akciğer hastalığı) PPK gelişimi için önemli bir risk faktörü olduğunu, düşük FEV_1 değerlerinin (OR = 0,98 (0,96–1,00), %95 CI, p = 0,030) Grup 2'de (yeni teşhis konulmuş akciğer hastalığı) önemli bir risk faktörü olduğunu gösterdi.

Sonuç: Bu çalışma, özellikle akciğer hastalığı olan hastalarda CANET puanlama sistemini kullanarak preoperatif risk değerlendirmesinde preoperatif SpO_2 ve SFT sonuçları ile birlikte değerlendirmenin önemini vurgulamaktadır. Özellikle yeni teşhis konmuş akciğer hastalığı olan hastalarda, SFT sonuçlarını dikkate almak PPK'leri tahmin etmede ve önlemede kritik bir rol oynar. SFT' leri cerrahi risk değerlendirme protokollerine entegre etmek hasta sonuçlarını iyileştirebilir.

Anahtar Kelimeler: Spirometri, komplikasyonlar, postoperatif, pulmoner, risk faktörleri

Introduction

Pulmonary diseases, such as chronic obstructive pulmonary disease (COPD), asthma, bronchiectasis, lung cancer, and pleural effusion, pose significant risks during surgical procedures. The frequent underdiagnosis of these conditions increases the risk of postoperative complications. Given that a substantial proportion of COPD patients (78%) remain undiagnosed, the development of advanced screening methods is crucial. Accurate preoperative diagnosis of pulmonary diseases is vital but challenging, even with guidelines such as GOLD. There is a need for more effective strategies to identify and manage these conditions before surgery to reduce surgical risks and postoperative pulmonary complications (PPCs) (1).

Reducing surgical risks involves thorough preoperative assessment, focusing on modifiable risk factors. Anesthetic evaluation is crucial for managing anesthesia-related complications. Consultation with a pulmonologist for pulmonary disorders is vital. This combined approach of risk assessment, anesthesia evaluation, and pulmonologist input significantly improves patient safety and reduces morbidity and mortality during surgery (2).

Evaluating pulmonary function is crucial for predicting potential complications and mortality in surgical patients. A decline in lung function during the perioperative period significantly elevates these risks. Although pulmonary function tests (PFTs), such as spirometry, are commonly employed for preoperative risk assessment, the scientific community debates their efficacy in predicting PPCs. PPCs frequently arise from substantial lung function impairment due to surgery-related factors. Therefore, identifying these factors is essential for accurate risk stratification and PPC prevention. Further investigation is needed to elucidate the predictive role of PFTs for PPCs(3).

PPCs pose a significant threat to surgical patients, often leading to conditions such as pneumonia, atelectasis, respiratory failure, infections, COPD exacerbations, pulmonary thromboembolism, and the need for mechanical ventilation. Identifying potential risk factors for PPCs is crucial for implementing preventive measures and improving patient outcomes. Previous research has explored these risk factors in specific surgical populations, including those undergoing upper-abdominal surgery, esophagectomy, total knee arthroplasty, and coronary artery bypass surgery. By recognizing and addressing these risk factors preoperatively, clinicians can substantially decrease the incidence of PPCs and enhance patient outcomes (4,5).

The CANET scoring system is a valuable tool for assessing the risk of PPCs such as pneumonia, atelectasis, and acute respiratory failure. It assigns points based on parameters such as age, preoperative oxygen saturation (SpO_2), history of respiratory infection, anemia, the type and duration of surgery. A higher score indicates a higher risk of PPCs. This study aims to evaluate the reliability and utility of the CANET scoring system (which includes SpO_2 measurements) and of preoperative PFT results for predicting PPCs in patients undergoing surgical consultation. Furthermore, it emphasizes the importance of preoperative pulmonary assessment in surgical patients newly diagnosed with respiratory diseases. The study utilized the CANET scoring system to determine preoperative pulmonary risk in patients with newly or previously diagnosed respiratory diseases (6).

Materials and Methods

Study Population

This study included 200 patients, aged 18 years or older, who requested preoperative pulmonary evaluation at the Department of Chest Diseases Clinics of University of Health Sciences Türkiye, Şişli Hamidiye Etfal Training and Research Hospital Hospital between January 1, 2022, and January 1, 2023, prior to undergoing elective surgery. The study population consisted of patients who underwent preoperative pulmonary assessment. Exclusion criteria included patients under 18 years of age, patients with psychiatric illness, and other patients deemed unsuitable for evaluation.

Data Collection

All necessary data were collected retrospectively from the hospital's electronic database. The primary data

collected included patients' demographic characteristics, comorbidities, preoperative SpO_2 values, PFT results, and CANET scores calculated to assess surgical risk. The PPC, defined as the primary endpoint, included the following clinically significant conditions occurring within one month after elective surgery: asthma exacerbation, COPD exacerbation, pneumonia, atelectasis, and respiratory failure. Furthermore, the patients' need for intensive care unit (ICU) admission was recorded as a secondary outcome variable. All patients were scored using the CANET scoring system to assess the risk of postoperative PPC. During data collection, consideration was given to preoperative SpO_2 values measured using a standard pulse oximeter while the patient was resting in room air, and to the results of the PFT performed using a standardized spirometry device in accordance with the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines. Primarily, the percent predicted values (% predicted) of Forced Expiratory Volume in One Second (FEV_1), Forced Vital Capacity (FVC), and FEV_1/FVC were recorded during PFTs.

Study Design and Grouping

This observational study uses a retrospective design to investigate the effectiveness of preoperative assessments in predicting PPCs. Patients were categorized into two main groups based on their pulmonary disease status: Group 1 (Known Pulmonary Disease), which consisted of patients with a pre-existing diagnosis of a chronic pulmonary condition such as COPD, asthma, bronchiectasis, or restrictive disorders; and Group 2 (Newly Diagnosed Pulmonary Disease), which included patients in whom a pulmonary disease was diagnosed or first suspected during the preoperative evaluation, based on chest X-ray and spirometry results.

Data Analysis

Data from patient files recorded in the hospital system were used to assess the development of PPC, and a standardized follow-up protocol was applied to all patients. All patients were scored using the CANET Scoring System to assess the risk of postoperative PPCs. During data collection, preoperative SpO_2 values (measured using a standard pulse oximeter while the patient rested in room air) and the results of PFTs (performed using a standardized spirometry device in accordance with ATS/ERS guidelines) were taken into consideration. Logistic regression analyses were performed to compare the effectiveness of SpO_2 and PFTs in predicting PPCs. Receiver operating characteristic (ROC) curves were used to evaluate the ability of SpO_2 and FEV_1 to predict PPCs, and cutoff values were determined to optimize sensitivity and specificity for clinical use. To ensure a clear and clinically meaningful assessment of the degree of pulmonary impairment, FEV_1 values (expressed as a percentage of predicted) were classified into three distinct categories. These categories are defined as Normal (≥80%), Mild Impairment (60–79%), and Moderate/Severe Impairment (<60%). During data analysis, the predictive ability of SpO_2, FVC, and FEV_1 for PPC was assessed using ROC curves. Subsequently, backward (Wald) multivariable logistic regression analysis was performed, including variables with a p-value <0.20 and clinical covariates (age, sex, and smoking history), to identify independent risk factors.

Statistical Analysis

Analyses were performed using SPSS Statistics for macOS, version 30.0 (IBM Corp., Armonk, NY, USA). Patient characteristics were presented as n (%) for categorical variables and mean ± standard deviation for continuous variables, and were compared among diagnostic groups using the chi-square test or independent-samples t-test, as appropriate. ROC curves were plotted to evaluate the discriminative ability of preoperative SpO_2, FVC, and FEV_1 to predict PPC for all patients and within each diagnostic group. Logistic regression analyses were then performed to determine the factors independently associated with PPC. Initially, each variable was evaluated using univariate logistic regression analysis. Variables with a p-value <0.20 in univariate analysis, as well as clinically relevant covariates (age, sex, and smoking history), were included in the multivariate model. Multivariate logistic regression was performed using the backward (Wald) method. The results were presented as odds ratios (OR) with 95% confidence intervals (CI). The threshold for statistical significance was set at $p < 0.05$.

Results

The mean ages were 62 ± 15 years (Group 1, n = 92) and 60 ± 15 years (Group 2, n = 108). No significant differences were found with respect to age, gender, age groups, or smoking status ($p > 0.05$). SpO_2 levels differed significantly between Group 1 (96.5 ± 1.8%) and Group 2 (97 ± 1.5%) ($p = 0.038$). Although Group 2 had slightly more PPCs, no significant differences were observed in ICU follow-up ($p = 0.682$) or in PPC development ($p > 0.05$) (Table 1). PFT results showed a significant difference in FVC, but not in the FEV_1/FVC ratio ($p > 0.05$). FEV_1 values differed significantly ($p < 0.05$). CANET scores showed no significant intergroup differences ($p = 0.401$; Table 2).

ROC analysis showed that SpO_2, FVC, and FEV_1 had low discriminative power for PPCs (area under the curve [AUC] 0.60–0.70). Overall AUCs were as follows: SpO_2, 60% (cut-off 96%); FVC, 60.2% (cut-off 82%); and FEV_1, 62.7% (cut-off 79%).

Group-specific analysis revealed a significant prediction of SpO_2 in Group 1 and a significant prediction of FEV_1 in Group 2. SpO_2, FVC, and FEV_1 significantly affected the development of PPCs across all patients ($p < 0.05$); higher values predicted lower PPC incidence. Group-specific analysis showed SpO_2 significance in Group 1 and FEV_1 significance in Group 2 ($p < 0.05$) Logistic regression analysis demonstrated that low SpO_2 values (OR = 0.66, 95% CI [0.50–0.88], p = 0.004) were significant risk factors for the development of PPCs in Group 1 (known pulmonary disease), whereas low FEV_1 values (OR = 0.98, 95% CI [0.96–1.00], p = 0.030) were significant risk factors in Group 2 (Table 3).

The distribution of risk factors for the development of PPCs in patients is presented in Table 4. When all patients were evaluated together, univariate analysis showed that female sex was associated with a significantly lower risk of PPC compared with males. Smoking status was identified as a strong risk factor: the risk of complications increased 4.5-fold among current smokers and approximately 3.7-fold among former smokers. Furthermore, low SpO_2, FVC, and FEV_1 were significantly associated with the development of complications.

Discussion

This study compared two patient groups. Group 1 included patients with a prior diagnosis of lung disease (e.g., asthma, COPD, bronchiectasis), whereas Group 2 included patients whose lung disease was newly diagnosed during preoperative pulmonary risk assessment. The study aimed to determine the risk of PPCs in both groups using spirometric measurements (PFTs: FEV_1, FVC, FEV_1/FVC) and the Canet scoring system criteria (SpO_2) as part of preoperative pulmonary risk assessment. Although the difference was not statistically significant, the proportion of PPC cases in the newly diagnosed pulmonary disease group (47.2%) was slightly higher than that in the previously diagnosed group (33.7%). This numerical difference may be clinically significant. These patients had neither been previously diagnosed with respiratory diseases nor received any follow-up or treatment for them. Preoperative emergency interventions, such as bronchodilator therapy and respiratory physiotherapy, were initiated to stabilize the patients. As previously reported, this study confirms the

Table 1. Baseline characteristics and clinical findings of patients stratified by study groups.

Characteristics	Group-I (n = 92)	Group-II (n = 108)	p-value
	n (%) or mean ± SD	n (%) or mean ± SD	
Age (year)	62 ± 15	60 ± 15	0.466
<50	17 (18.5)	28 (25.9)	0.449
51–80	68 (73.9)	72 (66.7)	
>80	7 (7.6)	8 (7.4)	
Sex			0.646
Male	43 (46.7)	54 (50)	
Female	49 (53.3)	54 (50)	
Smoking history			0.085
Smoker	19 (20.7)	30 (27.8)	
Non-smoker	30 (32.6)	44 (40.7)	
Ex-smoker	43 (46.7)	34 (31.5)	
Comorbidity disease	90 (97.8)	99 (91.7)	0.111
Cancer	20 (22.2)	19 (19.2)	
Hypertension	11 (12.2)	13 (13.1)	
Heart diseases	4 (4.4)	10 (10.1)	
Gastrointestinal system diseases	32 (35.6)	27 (27.3)	
Diabetes mellitus	2 (2.2)	2 (2)	
Other	21 (23.3)	28 (28.3)	
PPC	31 (33.7)	51 (47.2)	0.053
ICU follow-up	12 (13)	11 (10.2)	0.682
Preoperative oxygen saturation SPO_2 (%)	96.5 ± 1.8	97 ± 1.5	0.038

ICU, intensive care unit; PPC, postoperative pulmonary complications; SD, standard deviation; SPO_2, preoperative oxygen saturation.

Table 2. Comparison of preoperative pft results and canet risk score distribution between the study groups.

PFT	Group-I (n = 92)	Group-II (n = 108)	p-value
	n (%) or mean ± SD	n (%) or mean ± SD	
FVC	80.8 ± 23.1	71.7 ± 21.7	0.006
Normal (%)	58 (66.7)	56 (56.6)	0.158
Abnormal (%)	29 (33.3)	43 (43.4)	
FEV_1	78 ± 23.9	70.5 ± 23.3	0.032
Normal (%)	49 (56.3)	32 (32.3)	0.004
Mild (%)	21 (24.1)	37 (37.4)	
Moderate/Severe (%)	17 (19.5)	30 (30.3)	
FEV_1/FVC	78.7 ± 12.6	80.6 ± 11.8	0.288
Normal (%)	71 (81.6)	82 (82.8)	0.828
Abnormal (%)	16 (18.4)	17 (17.2)	
CANET risk score			0.401
Low (below 26 points)	19 (20.7)	28 (25.9)	
Medium (26-44 points)	35 (38)	45 (41.7)	
High (45 points and above)	38 (41.3)	35 (32.4)	

FEV_1, Forced Expiratory Volume; FVC, Forced Vital Capacity; PFT, pulmonary function test; SD, standard deviation.

Table 3. The effect of PFTs on the development of PPCs.

Group	Risk factor	AUC (95% CI)	Cut-off	p-value	Sensitivity (%)	Specificity (%)
All patients	SpO_2	0.600 (0.515–0.684)	≤96	0.022	39.0	80.5
	FVC	0.602 (0.520–0.684)	≤82	0.019	73.0	49.1
	FEV_1	0.627 (0.546–0.708)	≤79	0.003	71.6	53.6
Group-I	SpO_2	0.643 (0.517–0.769)	≤96	0.032	51.6	73.8
	FVC	0.622 (0.500–0.744)	≤79	0.068	67.9	61.0
	FEV_1	0.578 (0.452–0.705)	≤81	0.239	64.3	55.9
Group-II	SpO_2	0.599 (0.487–0.712)	≤96	0.089	31.4	87.7
	FVC	0.563 (0.450–0.677)	≤82	0.280	76.1	41.5
	FEV_1	0.649 (0.540–0.758)	≤72	0.011	65.2	64.2

Used test: Receiver operating characteristic curve analysis. AUC, area under the curve; CI, confidence interval; FEV_1, Forced Expiratory Volume; FVC, Forced Vital Capacity; PFT, pulmonary function test; SPO_2, preoperative oxygen saturation.

importance of identifying pulmonary complaints during the preoperative period (7).

Age and gender were similar between groups, but smoking habits differed. Group 1 had a higher overall number of smokers, whereas Group 2 had more current smokers. This aligns with research showing that preoperative smoking cessation improves long-term success, thereby emphasizing its importance in evaluations (8). Studies (9,10) have consistently shown an increased incidence of serious complications in current smokers, including PPCs, surgical site infections, prolonged ICU stays, wound complications, neurological complications, and septic shock within 30 days after surgery. Consistent with Bluman et al. (11) findings, smoking increases the risk of PPCs, underscoring the need for smoking cessation before and after surgery. Group 1, which had prior lung disease, had higher rates of cancer and gastrointestinal issues, likely reflecting referral patterns from thoracic and general surgery clinics.

In our study, the age variable was not significant on its own, it but was retained in the multivariate model due to its potential relationship with respiratory function. In the multivariate analysis, smoking status and indicators of low respiratory reserve remained independent risk factors. The risk of complications increased fourfold among current smokers and threefold among former smokers. Female sex continued to show a protective effect; low SpO_2 and low FVC were also determined to be independent risk factors.

In this study, univariate analysis in Group I revealed

Table 4. Distribution of risk factors affecting the development of PPCs.

Group	Variables	Univariate		Multivariate*	
		OR (95% CI)	p-value	OR (95% CI)	p-value
All patients	Age	0.99 (0.97–1.02)	0.635		
	Sex (Female vs. Male)	0.42 (0.24–0.75)	0.004		
	Smoke (Smoker vs. Non-smoker)	4.45 (2.02–9.80)	<0.001	4.02 (1.75–9.20)	0.001
	Smoke (Ex-smoker vs. Non-smoker)	3.72 (1.83–7.58)	<0.001	3.07 (1.44–6.53)	0.004
	SpO_2	0.76 (0.63–0.92)	0.004	0.78 (0.62–0.97)	0.029
	FVC	0.98 (0.97–1.00)	0.018	0.98 (0.97–1.00)	0.022
	FEV_1	0.98 (0.97–1.00)	0.018		
Group-I	Age	1.02 (0.99–1.06)	0.194		
	Sex (Female vs. Male)	0.61 (0.26–1.46)	0.269		
	Smoke (Smoker vs. Non-smoker)	1.52 (0.42–5.48)	0.525		
	Smoke (Ex-smoker vs. Non-smoker)	2.37 (0.84–6.70)	0.105		
	SpO_2	0.66 (0.50–0.88)	0.004	0.72 (0.53–0.96)	0.024
	FVC	0.98 (0.96–1.00)	0.082		
	FEV_1	0.99 (0.97–1.01)	0.386		
Group-II	Age	0.98 (0.95–1.01)	0.113		
	Sex (Female vs. Male)	0.32 (0.15–0.70)	0.004		
	Smoke (Smoker vs. Non-smoker)	9.07 (3.11–26.47)	<0.001	7.80 (2.55–23.92)	<0.001
	Smoke (Ex-smoker vs. Non-smoker)	6.28 (2.29–17.21)	<0.001	6.46 (2.19–19.12)	<0.001
	SpO_2	0.81 (0.62–1.06)	0.128		
	FVC	0.99 (0.97–1.01)	0.244		
	FEV_1	0.98 (0.96–1.00)	0.030	0.98 (0.96–1.00)	0.036

*Backward Wald. Used test: Univariate logistic regression analysis and multivariate logistic regression analysis, multivariate logistic regression was performed using the Backward (Wald) method.
CI, confidence interval; FEV_1, Forced Expiratory Volume; FVC, Forced Vital Capacity; OR, odds ratio; PPC, postoperative pulmonary complications; SPO_2, preoperative oxygen saturation.

that only low SpO_2 was statistically significant; no other variables were significant. After multivariate analysis, low SpO_2 was the only variable that remained independently associated with complications. In Group II, univariate analysis showed that smoking history, female sex, and low FEV_1 were significant. In the multivariate model, the risk of complications increased approximately eightfold in current smokers and approximately sixfold in former smokers. Female sex continued to demonstrate a protective effect, and low FEV_1 remained an independent risk factor in the model.

This study used the Canet scoring system for 30-day PPC risk assessment, categorizing patients into low, intermediate, or high risk. The Canet system, validated in Turkey and based on factors such as age and SpO_2, effectively stratified PPC risk in this population (12). Group 2 patients with undiagnosed lung disease were identified preoperatively by history, physical examination, chest X-ray, and PFTs. This led to timely intervention and improved outcomes. Thorough preoperative evaluation, even in low-risk patients, is crucial for early detection and prevention of PPCs. Preoperative SpO_2 was lower in Group 1 (known lung disease, 92%) than in Group 2 (newly diagnosed, 96%), indicating potential hypoxemia in Group 1. Lower SpO_2 may increase the risk of postoperative complications. While SpO_2 is useful, it is limited; PFTs and imaging are required for a comprehensive respiratory assessment. Group 2 had a higher PPC rate, although this difference was not statistically significant. This may be due to lack of preoperative diagnosis and treatment, while Group 1's ongoing treatment might have mitigated risk.

Studies link impaired lung function (low FVC and low FEV_1/FVC) to a higher risk of PPCs, highlighting the importance of preoperative assessment. PFTs, including FEV_1, FVC, and FEV_1/FVC, are crucial for identifying respiratory dysfunction and predicting PPCs, thereby allowing for preoperative interventions to optimize lung health (13,14). This study analyzed PPC risk in patients with severe COPD ($FEV_1 \leq 1.2$ L, FEV_1/FVC <75%) who underwent non-cardiothoracic surgery.

Thirty-seven percent experienced PPCs, with ninety-seven percent of those patients receiving anesthesia lasting more than two hours. Two-year mortality was 47%. PFTs were poor predictors of PPC; ASA score was a better predictor. Prolonged anesthesia (>2 hours) may increase the risk of bronchospasm and the length of ICU stay. General anesthesia and prolonged operative time are risk factors. Preoperative assessment is more predictive than PFTs (15).

This study examined whether spirometry and arterial blood gas data could predict serious PPCs after elective abdominal surgery in 480 at-risk patients. Low preoperative FEV_1 (<61% predicted) and low PaO2 (<9.33 kPa) significantly increased PC risk, with FEV_1 being the strongest predictor. Age, ischemic heart disease, and surgery for malignant tumors were also independent risk factors. The authors conclude that preoperative respiratory function evaluation is useful for identifying increased PC risk in selected patients undergoing abdominal surgery (16).

Low FEV_1 and FVC values found in our study patients significantly increase the risk of PPCs. Low preoperative SpO_2 levels also increase the risk of complications. Logistic regression confirms an association between FEV_1, FVC, and PPCs, showing that PPC risk decreases with each unit increase in FEV_1 and FVC. Diagnostic sensitivity and specificity for FEV_1 and FVC cutoff values are approximately 59% each, indicating a need for more precise diagnostic parameters. The study demonstrates that low lung function (FEV_1 and FVC) and low SpO_2 are major risk factors for PPCs, though current cut-off values may not be perfect predictors. This systematic review summarizes the existing scientific literature on the ability of PFTs to predict PPCs in non-thoracic surgery. It suggests that spirometry and other PFTs enhance preoperative risk assessment. Spirometry should be considered for individuals planning upper abdominal surgery, especially those with key indicators for COPD (17).

Study limitations

This study, while providing valuable insights, is constrained by its retrospective design and single-center nature. The retrospective approach raises concerns regarding potential selection bias and the presence of missing data, which could affect the accuracy of the findings.

Conclusion

In this study, the Canet risk scoring method and PFT measurements were used to predict PPCs. This scoring system has been validated and is used in Turkey, and has been shown to be effective in predicting PPCs and mortality risk. Although pulmonary disease is commonly diagnosed, it remains underdiagnosed preoperatively among patients undergoing major surgery. Both previously known and newly diagnosed pulmonary diseases can increase the risk of postoperative complications. Static PFTs can help identify at-risk patients and improve surgical outcomes. Therefore, we recommend routine performance of PFTs before surgery, especially in patients without known lung disease.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the University of Health Sciences Türkiye, Şişli Hamidiye Etfal Training and Research Hospital Ethics Committee (approval number: 2451, dated: 26.09.2023), and administrative permission was obtained from the institutions where the study would be conducted.

Informed Consent: Retrospective study.

Footnotes

Conflict of Interest: No conflict of interest was declared by the author(s).

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The Relationship Between Varicocele and Lower Extremity Chronic Venous Insufficiency: A Population-Based Case-Control Study

Varikosel ile Alt Ekstremite Kronik Venöz Yetmezliği Arasındaki İlişki: Nüfusa Dayalı Olgu-Kontrol Çalışması

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ABSTRACT

Background: This study explores the potential relationship between varicocele and varicose veins, focusing on their shared pathophysiological mechanisms and clinical implications, and includes an additional subgroup analysis across age groups. Varicocele is a major cause of male infertility, affecting 15–20% of men in the general population and up to 30–40% of infertile men. Varicose veins, caused by venous valve dysfunction, are more prevalent in older individuals. Despite their structural and functional similarities, the possible link between these two venous disorders has not been adequately investigated.

Materials and Methods: A retrospective, population-based case-control study was conducted in a province in Türkiye using the Ministry of Health Public Hospitals Research Database. A total of 1,279 patients with varicose veins and 5,091 age- and sex-matched controls (1:4 ratio) were included. Diagnoses were identified using ICD-10-CM codes, and diagnostic validity was ensured by requiring at least two separate clinical entries for the same diagnosis. Conditional logistic regression was used to evaluate the association between varicose veins and varicocele, adjusting for confounders including age, diabetes, cardiovascular disease, chronic obstructive pulmonary disease, liver disease, and kidney disease. The lack of Doppler ultrasonographic confirmation and absence of varicocele grading data were acknowledged as limitations of the retrospective design.

Results: The prevalence of varicocele was 1.3% in cases and 0.3% in controls ($p < 0.001$). Logistic regression analysis revealed an odds ratio of 2.41 (95% confidence interval: 1.80–4.92) for the association between varicocele and a history of varicose veins, and the association was more pronounced among younger patients.

Conclusion: This study demonstrates a significant association between varicocele and varicose veins, particularly in individuals under 50 years of age. These findings suggest shared pathophysiological mechanisms and warrant further investigation into the underlying venous dysfunction that links these conditions.

Keywords: Varicocele, venous insufficiency, age

ÖZ

Amaç: Bu çalışma, varikosel ve varis arasındaki olası ilişkiyi, bu iki durumun ortak patofizyolojik mekanizmaları ve klinik sonuçları açısından incelemekte; ayrıca yaş gruplarına göre ek bir alt analiz içermektedir. Varikosel, erkek infertilitesinin başlıca nedenlerinden biridir ve genel popülasyonda %15–20, infertil erkeklerde ise %30–40 oranında görülür. Venöz kapak fonksiyon bozukluğuna bağlı olarak gelişen varisler ise özellikle ileri yaşlarda daha sık görülmektedir. Yapısal ve fonksiyonel benzerliklerine rağmen, bu iki venöz hastalık arasındaki olası bağlantı yeterince araştırılmamıştır.

Gereç ve Yöntemler: Bu retrospektif, popülasyon temelli olgu-kontrol çalışması, Türkiye'de bir ilde yürütülmüş olup Sağlık Bakanlığı Kamu Hastaneleri Araştırma Veritabanı kullanılmıştır. Varis tanısı olan 1.279 hasta ve yaş ile cinsiyet açısından 1:4 oranında eşleştirilmiş 5.091 kontrol dahil edilmiştir. Tanılar ICD-10-CM kodları kullanılarak belirlenmiş ve aynı tanı kodunun en az iki ayrı klinik kayıtta bulunması tanısal geçerliliği sağlamıştır. Varis ve varikosel arasındaki ilişki, yaş, diyabet, kalp hastalığı, kronik obstrüktif

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öz

akciğer hastalığı, karaciğer ve böbrek hastalıkları gibi karıştırıcı faktörler için düzeltme yapılarak koşullu lojistik regresyon ile analiz edilmiştir. Doppler ultrasonografik doğrulamanın bulunmaması ve varikosel derecelendirmesinin değerlendirilememesi, retrospektif tasarımın sınırlamaları olarak belirtilmiştir.

Bulgular: Varikosel prevalansı olgularda %1,3, kontrollerde ise %0,3 olarak saptanmıştır (p < 0,001). Lojistik regresyon analizi, varis öyküsü ile varikosel arasında anlamlı bir ilişki olduğunu göstermiştir (olasılık oranı = 2,41; %95 güven aralığı: 1,80–4,92). Bu ilişki özellikle genç hastalarda daha belirgindir.

Sonuç: Bu çalışma, varikosel ile varis arasında anlamlı bir ilişki olduğunu ve bu ilişkinin özellikle 50 yaş altı bireylerde daha belirgin olduğunu göstermektedir. Bulgular, iki durum arasında ortak venöz disfonksiyon mekanizmaları olabileceğini düşündürmekte ve bu konuda ileri araştırmalara ihtiyaç olduğunu ortaya koymaktadır.

Anahtar Kelimeler: Varikosel, venöz yetmezlik, yaş

Introduction

Recent studies support the relationship between varicocele and systemic venous insufficiency (1–5). Varicocele, known to be one of the leading causes of male infertility, is an abnormal dilation and tortuosity of the pampiniform plexus vessels in the spermatic cord. It is seen in 15–20% of the population. This rate increases to 30–40% among infertile men (6). The significant impact of varicocele on male infertility is supported by evidence that varicocele is present in 70–80% of men with secondary infertility (7).

Varicose veins are extensions of the superficial subcutaneous veins of the lower extremities, characterized by tortuosity and dilation, and accompanied by valvular insufficiency. Varicose veins most commonly occur in the superficial veins of the lower extremities, but also affect the veins of the spermatic cord (varicocele), the esophagus, the anorectum (hemorrhoids), and other veins (8). Varicose veins are among the most common vascular diseases in humans, affecting approximately 10–20% of the world's population. The probability of encountering varicose veins in women is 2 to 4 times higher than in men (8,9) This frequency increases with age. For example, among people living in Switzerland, the probability of having varicose veins at age 20 is 20%, whereas it reaches 80% around age 60 (9). In this context, a retrospective, population-based case-control study conducted in a province in Türkiye aimed to investigate the relationship between varicocele and varicose veins and to understand the potential impact of this link on male infertility. Furthermore, one of the main aims of this study was to assess the differences in prevalence between age groups and to provide insight into whether varicocele can be considered a systemic venous disorder.

We hypothesized that varicocele may represent a localized manifestation of systemic venous insufficiency and aimed to investigate whether the presence of varicose veins is associated with a higher prevalence of varicocele across age groups.

Materials and Methods

In this study, patient data were obtained from the Ministry of Health Public Hospitals Research Database. Patients' ages were calculated from dates of birth recorded in the database. The diagnoses of varicocele, varicose veins, and other diseases were determined using the International Statistical Classification of Diseases and Related Health Problems, 10th edition (ICD-10-CM codes), as recorded in patient files (10). The codes used included I86.2 for varicocele, I87.2 for varicose veins, and the relevant ICD codes for male infertility, diabetes, chronic obstructive pulmonary disease (COPD), heart disease, liver disease, and kidney disease. Only records with complete data were included. Ethical approval for this study was obtained from the Mersin University Rectorate Clinical Research Ethics Committee (approval number: 2023/546, dated: 06.09.2023).

Statistical Analysis

Comprehensive data on the characteristics of patients with varicocele and varicose veins were analyzed in a retrospective, province-wide, population-based study covering 2015–2022. Data were obtained from the public hospitals' research database affiliated with the Ministry of Health in Türkiye. A total of 1,279 cases with varicose veins and 5,091 randomly selected controls were included in this study. Conditional logistic regression analyses were performed to examine the association between varicose veins and varicocele. Conditional logistic regression was performed to analyze the experimental data. All statistical analyses were conducted using SPSS software version 13.0 for Windows (SPSS, Chicago, IL, USA). Statistical significance was set at $p < 0.05$. In this study, cases and controls were matched on age (±2 years) and index year. Each case was matched to four controls. Matching IDs (MATCH_IDs) were created during this process and used in the conditional logistic regression analysis. These details are now explicitly stated.

Results

The demographic characteristics of the patients (Table 1), the prevalence of varicocele (Table 2), and the distribution by age group of patients with varicose veins and of the control group with varicocele (Table 3) are presented. No significant difference was observed between the patients with varicose veins and the control group regarding age distribution (Table 1). Furthermore, the prevalence of diabetes and atherosclerotic heart disease was significantly higher in patients with varicose veins than in the control group; by contrast, no significant differences were observed for COPD and chronic kidney disease (Table 1).

The prevalence of varicocele was 1.3% in cases and 0.3% in controls ($p < 0.001$). Conditional logistic regression, adjusted for age, diabetes, heart disease, COPD, liver disease, kidney disease, and edema, indicated that the odds ratio (OR) for a prior diagnosis of varicose veins in cases compared with controls was 2.41 (95% confidence interval [CI]: 1.80–4.92) (Table 2). Furthermore, the ORs for patients aged <50 years, 51–65 years, and >65 years were 3.72 (95% CI = 1.90–7.33), 2.56 (95% CI = 0.28–7.10), and 0.92 (95% CI = 0.16–5.24), respectively (Table 3). Additionally, the prevalence of male infertility was 14.7% in patients with both varicocele and varicose veins, compared to 13.5% in those with varicocele alone; however, this difference was not statistically significant.

Table 1. Demographic characteristics.

Variables	Varicose vein patients (n = 1279) (%)	Control group (n = 5091) (%)	p-value
Age			0.986
⩽50	312 (25.09)	1356 (26.61)	
51–65	357 (27.91)	1432 (28.12)	
>65	610 (47.69)	2303 (45.23)	
Diabetes	120 (9.38)	299 (5.87)	<0.001
Heart disease	195 (15.24)	512 (10.05)	<0.001
COPD	87 (6.80)	263 (5.16)	0.0620
Kidney and liver disease	75 (5.86)	304 (5.97)	0.716
Varicocele	15 (1.17)	16 (0.31)	<0.001

COPD, chronic obstructive pulmonary disease; OR, odds ratio.

Table 2. Varicocele prevalence.

Presence of varicocele	Total (n = 6370) (%)	Varicose vein patients (n = 1279) (%)	Control group (n = 5091) (%)
Yes	31 (0.5)	15 (1.17)	16 (0.31)
OR (95% CI)	–	2.16 (1.42–3.63)*	0.4
Adjusted OR (95% CI)	–	2.41 (1.80–4.92)*	0.4

*p < 0.001. Adjustments were made for diabetes, heart disease, COPD, liver disease, and kidney disease. OR was calculated using conditional logistic regression based on age and index year. COPD, chronic obstructive pulmonary disease; OR, odds ratio; CI, confidence interval.

Table 3. Varicocele rates among varicose vein patients and controls by age group.

Presence of varicocele	⩽50 years		51–65 years		⩾65 years	
	Varicose vein patients (n, %)	Control (n, %)	Varicose vein patients (n, %)	Control (n, %)	Varicose vein patients (n, %)	Control (n, %)
Yes	10 (3.3)	10 (0.5)	10 (1.3)	2 (0.3)	1 (0.2)	4 (0.2)
OR (95% CI)	1.00	2.33 (0.98–5.30)*	1.00	0.70 (0.21–3.10)	1.00	3.42 (1.83–5.50)
Adjusted OR (95% CI)	3.72 (1.90–7.33)	1.00	2.56 (0.28–7.10)*	1.00	0.92 (0.16–5.24)	1.00

*p < 0.01; OR was calculated using conditional logistic regression based on age and index year. CI, confidence interval; OR, odds ratio.

Discussion

Our findings support the hypothesis that varicocele may not be merely a localized phenomenon but rather a component of systemic venous insufficiency, consistent with prior histopathological and biochemical evidence suggesting shared alterations in vessel wall integrity. Although this study did not include direct histopathological or molecular analyses, our findings are consistent with prior reports suggesting shared venous wall changes, endothelial dysfunction, and altered metallothionein expression in both varicocele and varicose veins. These similarities support the hypothesis of a common systemic venous pathology.

This study, one of the few to examine the relationship between varicocele and varicose veins, suggests that these two conditions may be linked through common pathophysiological processes and clinical outcomes. Our findings support the possibility that varicose veins are associated with varicocele, and this association appears to be more pronounced in certain age groups. In particular, the higher association observed in individuals under 50 years of age supports the hypothesis that hormonal and vascular changes in this age group may strengthen this association. Furthermore, the prevalence of male infertility was 15.1% in patients with both varicocele and varicose veins and 14.5% in those with varicocele only; however, this difference was not statistically significant.

The pathophysiology of varicocele is typically associated with valvular insufficiency in the testicular veins. This can lead to infertility through mechanisms such as venous stasis, increased testicular temperature, and oxidative stress, all of which adversely affect sperm parameters (11). Similarly, the underlying mechanism of varicose veins is valvular insufficiency in the peripheral veins resulting in reflux, weakening, and dilatation of the vessel walls (8). In both cases, it has been suggested that these venous system disorders may result from a genetic predisposition or a systemic weakness in vessel wall structure (12).

The results of our study support this systemic approach. Lee et al. (13) observed increased expression of hypoxia-inducible factor 1-alpha and metallothionein in both varicocele and varicose veins, and this increase was associated with decreased apoptosis in the vessel walls. This suggests that both conditions may lead to similar biochemical changes in vessel walls. However, the study by Yazici et al. (14) suggested that varicocele may be a localised condition rather than a systemic venous disorder. These conflicting findings continue to fuel debate over whether varicocele is a purely localised condition or a systemic disease.

Furthermore, understanding how the relationship between varicocele and varicose veins varies with factors such as age, lifestyle, and comorbidities is an important area of research. In the literature, the incidence of varicose veins is reported to be higher in older individuals, whereas the incidence of varicocele is higher in younger individuals (15).

However, the higher likelihood of asymptomatic varicocele among older adults and their lower propensity to seek medical attention may mask the true prevalence of varicocele in this age group. Evidence suggests that a more comprehensive evaluation of varicocele in this age group is warranted. In addition, studies have reported a higher incidence of varicose veins in elderly patients (16). Canales et al. (17) reported that the prevalence of varicocele was higher in older men than in younger control subjects. However, another study by Lai et al. (18) demonstrated that newly diagnosed varicocele cases were more common in patients aged 19–39 years than in older age groups. Infertility issues may be more prevalent in this age group, leading to a higher likelihood of seeking medical assistance. Older men may be less concerned about infertility and may have a higher incidence of asymptomatic varicoceles (19).

In our study, a lower prevalence of varicocele was observed in elderly patients, which may be be attributable to the majority of cases being asymptomatic or to a lower rate of medical consultation for varicocele in the province studied in Türkiye. Yazici et al. (14) suggested that patient age could introduce bias when evaluating the relationship between varicocele and varicose veins. In this study, we found that the association between varicocele and varicose veins was stronger in patients under the age of 50. However, further studies are needed to confirm these findings. In addition, the effect of varicocele on infertility remains a matter of debate. Abdel-Meguid (20) reported that varicocelectomy improves semen quality. However, a systematic review by Evers and Collins (21) suggested that varicocelectomy is not an effective treatment for male infertility. In our study, we found that male infertility was not more common in patients with both varicocele and varicose veins than in those with varicocele only. This finding suggests that the effects of both conditions on infertility may be related to shared pathophysiological processes rather than to independent mechanisms.

The strengths of our study include the use of a population-based design and a large sample size. Furthermore, diagnoses were based on ICD codes, and detailed analyses were conducted across different age groups. However, methodological limitations should also be considered. For example, varicocele laterality (unilateral versus bilateral) was not assessed in detail. Furthermore, data on important variables such as body mass index, smoking status, and socioeconomic factors were not available. These factors may affect our results.

Study Limitations

The distinction between superficial and deep venous insufficiency could not be made because the ICD-10-CM codes used in the national database do not specify the anatomical level of venous reflux. Because varicocele grading was not available, all varicocele cases (Grades I–III) were analyzed collectively. This may have reduced the ability to detect dose-response effects.

Varicocele grading could not be evaluated in this study. Because the database only included ICD-10 codes, clinical stage information was not available. This methodological limitation should be addressed in prospective clinical studies.

The manual entry of ICD codes by clinicians is a potential limitation that could lead to diagnostic errors. Therefore, the results should be interpreted with caution. Furthermore, because the database does not include a clinical grading of varicocele, this information could not be used in the analyses.

Conclusion

In conclusion, our findings support the relationship between varicocele and varicose veins. However, more prospective, multicentre, and detailed studies are needed to clarify this relationship. In particular, considering these two conditions in the context of systemic venous insufficiency may inform novel diagnostic and therapeutic approaches.

Clinically, recognizing varicocele as a potential indicator of systemic venous insufficiency could guide broader cardiovascular assessment and promote early identification of patients at risk for venous disease progression.

Ethics

Ethics Committee Approval: Ethical approval for this study was obtained from the Mersin University Rectorate Clinical Research Ethics Committee (approval number: 2023/546, dated: 06.09.2023).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: A.B., Design: A.B., Data Collection or Processing: A.B., E.E.T., Analysis or Interpretation: E.E.T., Literature Search: A.B., Writing: E.E.T.

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Retrospective Evaluation of Hemoglobin Variants Detected During HbA1c Testing via Capillary Electrophoresis Hemoglobin Variants Detected During HbA1c Testing

Kapiler Elektroforez Yoluyla HbA1c Testi Sırasında Saptanan Hemoglobin Varyantlarının Retrospektif Değerlendirilmesi

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ABSTRACT

Background: This study aimed to determine the prevalence of hemoglobin (Hb) variants detected during hemoglobin A1c (HbA1c) analysis using capillary electrophoresis and to evaluate the clinical significance of these incidental findings in the population.

Materials and Methods: A retrospective analysis was performed on 64,381 patients who underwent HbA1c testing in our laboratory between 01.09.2024 and 30.04.2025. HbA1c levels were measured by capillary electrophoresis (Capillarys 3; Sebia, France), and chromatograms were manually reviewed for Hb variants. Statistical analyses were performed using XLSTAT® software.

Results: Hb variants were detected in 172 cases (0.25%). The most common variants were HbD (41.9%), HbF (33.7%), and HbS (14.5%). A statistically significant difference among variant groups was observed only for mean corpuscular Hb concentration (p = 0.0033).

Conclusion: Detection of hemoglobin variants during HbA1c analysis using capillary electrophoresis may contribute to the identification of clinically silent hemoglobinopathies in the population. Therefore, employing highly sensitive methods is crucial for accurate clinical interpretation.

Keywords: Hemoglobinopathies, hemoglobin variants, glycosylated hemoglobin A, HbA1c, capillary electrophoresis, mass screening

ÖZ

Amaç: Bu çalışmada, kapiller elektroforez yöntemi ile hemoglobin A1c (HbA1c) analizleri sırasında hemoglobin (Hb) varyantlarının sıklığını belirlemek ve toplumda rastlantısal olarak saptanan varyantların klinik önemini değerlendirmek amaçlanmıştır.

Gereç ve Yöntemler: 01.09.2024–30.04.2025 tarihleri arasında laboratuvarımızda HbA1c testi yapılan 64.381 hastanın verileri retrospektif olarak incelenmiştir. HbA1c ölçümleri kapiller elektroforez yöntemi (Sebia Capillarys 3, Fransa) ile gerçekleştirilmiş, elde edilen kromatogramlar varyantların varlığı açısından manuel olarak değerlendirilmiştir. İstatistiksel analizler XLSTAT® yazılımı kullanılarak yapılmıştır.

Bulgular: Toplam 172 (%0,25) olguda Hb varyantı tespit edilmiştir. En sık görülen varyantlar HbD (%41,9), HbF (%33,7) ve HbS (%14,5) olarak belirlenmiştir. Varyant tipleri arasında hematolojik parametreler açısından yalnızca ortalama eritrosit Hb konsantrasyonu (MCHC) için istatistiksel olarak anlamlı fark bulunmuştur (p = 0,0033).

Sonuç: HbA1c analizleri sırasında kapiller elektroforez yöntemi ile Hb varyantlarının saptanması, toplumda sessiz seyreden hemoglobinopatilerin belirlenmesine katkı sağlayabilir. Bu nedenle, yüksek duyarlılığa sahip yöntemlerin kullanılması klinik açıdan önemlidir.

Anahtar Kelimeler: Hemoglobinopatiler, hemoglobin varyantları, glikozile hemoglobin A, HbA1c, kapiller elektroforez, toplum taraması

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Introduction

Hemoglobin A1c (HbA1c) is a widely used biochemical parameter in the diagnosis and management of diabetes. However, the presence of certain hemoglobin (Hb) variants can interfere with HbA1c measurement methods, thereby reducing measurement accuracy. Hb variants are often present in the population without causing clinical symptoms, leading to missed diagnoses in some individuals. This makes the clinical recognition of these variants more difficult.

In clinical laboratories, HbA1c levels can be measured using various methodologies, including enzymatic assays, immunoturbidimetric methods, boronate affinity chromatography, capillary electrophoresis, and ion-exchange high-performance liquid chromatography (ion-exchange HPLC). Among these methods, ion-exchange HPLC and capillary electrophoresis are the most commonly employed. These methods are based on differences in affinity, electrical charge, or immunoreactivity of glycated Hb molecules. Anion- and cation-exchange HPLC and capillary electrophoresis can detect Hb variants such as HbF, HbS, HbC, HbD, and HbE (1,2). The literature includes various studies regarding the frequency of Hb variant detection during HbA1c analysis. For example, a study by Roy et al. (3), conducted in the North Bengal region of India, detected Hb variants in 27.4% of 449 individuals undergoing HbA1c testing, with HbE being the most common variant.

Capillary electrophoresis-based systems offer a significant advantage in HbA1c analysis because they can directly detect chromatographic anomalies associated with Hb variants (e.g., HbF, HbS, HbC, HbD, HbE). A study by Kulkarni and Shivashanker (4) emphasized that clinically silent variants could be incidentally detected during HbA1c measurement using capillary electrophoresis. These findings highlight the importance of this method in detecting asymptomatic hemoglobinopathies in the population.

On the other hand, Strickland et al. (5) reported that some HbA1c analyzers failed to detect rare Hb variants, which can affect measurement results. Mäenpää et al. (6) tested the Hb Tacoma variant across seven HbA1c methods; significant interference was reported in only one. Kangastupa et al. (7) investigated the prevalence of Hb variants in the Finnish population using capillary electrophoresis and emphasized its diagnostic value.

In light of this information, we aimed to determine retrospectively the frequency of Hb variants in patients whose HbA1c was analyzed by capillary electrophoresis in our laboratory. This study is the first large-scale report in Türkiye on the detection rate of Hb variants during HbA1c analysis by capillary electrophoresis.

Materials and Methods

Patients whose HbA1c tests were performed using the capillary electrophoresis method between 1 September 2024 and 30 April 2025 were retrospectively evaluated. Individuals with Hb variants identified on the test chromatograms were included in the study. Patients with repeat testing in whom variants had been previously detected, patients with missing chromatogram data, and patients with rejected test results were excluded from the study.

In our laboratory, HbA1c was measured using the Sebia Capillarys 3 capillary electrophoresis system (Sebia, France).

The chromatograms obtained during the HbA1c test were manually reviewed using the device's software (Sebia PHORESIS), and abnormal peaks related to Hb variants (e.g., peaks outside the HbA1c window or variant alerts) were recorded. These samples were then confirmed using the Sebia Capillarys 3 capillary-electrophoresis method for Hb variant analysis.

Hematological parameters were measured using an automated hematology analyzer (Sysmex XN, Sysmex, Japan). The data obtained for the following parameters were included in the analysis: Hb, hematocrit (Hct), mean corpuscular volume (MCV), mean corpuscular Hb (MCH), and mean corpuscular Hb concentration (MCHC).

This study was approved by the Institutional Ethics Committee of Ankara Training and Research Hospital (decision number: E-25-586/2025, dated: 11.09.2025) and conducted in accordance with the principles of the Declaration of Helsinki.

Statistical Analysis

Data obtained in the study were analyzed using Microsoft Excel (v365, Microsoft Corporation, USA) and XLSTAT® software (v2023.3.1.1416, Lumivero, USA). Descriptive statistics for continuous variables were presented as mean, standard deviation (SD), minimum, and maximum values. Categorical variables were presented as counts and percentages. Hematological parameters (Hb, Hct, MCV, MCH, MCHC) across Hb variant groups were compared using one-way analysis of variance to assess whether statistically significant differences existed among variant types. A p-value of <0.05 was considered statistically significant.

Results

In this study, Hb variants were detected in 172 individuals, identified among 64,381 HbA1c tests performed using the capillary electrophoresis method. Of these, 108 (62.8%) were female and 64 (37.2%) were male.

The mean age of all participants was 47.4 years (range: 8–91 years). The dataset included 12 patients under the age of 18. The age and gender distribution of the detected variants is presented in Table 1. The overall frequency of variant detection was calculated to be 0.25%, and ten variant types were observed.

Among the detected variants, HbD was the most frequent, observed in 72 individuals (41.96%), followed by HbF in 47 individuals (27.3%) and HbS in 25 individuals (14.5%). Rarer variants included O-Arab? (7 cases, 4.1%), HbE (3 cases, 1.7%), HbC, suspected HbJ, BALTIMORE, and Alpha Thalassemia (individual cases, each 0.6%), and an undefined variant labeled Z12 (5 cases, 3%).

In this study, mean values of hematological parameters (Hb, Hct, MCV, MCH, and MCHC) and their statistical differences were evaluated across Hb variants. The mean values (± SD) are presented in Table 2. The analysis revealed a statistically significant difference only in the MCHC parameter among the variant groups ($p = 0.0033$). No statistically significant differences were observed among the groups for Hb, Hct, MCV, and MCH ($p > 0.05$).

A total of 38 individuals with HbA1c levels ⩾6.5 were classified as diabetic. The largest subgroup among diabetic individuals comprised males with the HbD variant (n = 10), followed by males with the HbS variant (n = 4), and subgroups with the HbF variant. Among females, one notable case involved an individual with a suspected BALTIMORE variant who had an HbA1c level above 6.5. The distribution of diabetic individuals by gender and variant type is presented graphically in Figure 1.

Discussion

In this large-scale retrospective study involving 64,381 HbA1c measurements, we identified Hb variants in 172 individuals by capillary electrophoresis. Accordingly, the prevalence of Hb variants was determined to be 0.25% in the overall test population. To our knowledge, this is the

Table 1. Mean age, age range, and gender distribution by hemoglobin variant type.

Variant type	Male	Female	Total
HbD	54.9 (16–91) (n = 28)	49.0 (17–76) (n = 44)	51.3 (16–91) (n = 72)
HbF	44.8 (11–82) (n = 18)	46.7 (12–86) (n = 40)	46.1 (11–86) (n = 58)
HbC	–	20.0 (20–20) (n = 1)	20.0 (20–20) (n = 1)
HbS	43.6 (20–73) (n = 10)	40.2 (8–79) (n = 17)	41.4 (8–79) (n = 27)
HbE	–	51.0 (48–56) (n = 3)	51.0 (48–56) (n = 3)
O-Arab?	45.8 (14–68) (n = 6)	37.0 (37–37) (n = 1)	44.6 (14–68) (n = 7)
Alpha thalassemia?	–	43.0 (43–43) (n = 1)	43.0 (43–43) (n = 1)
HbJ?	42.0 (42–42) (n = 1)	–	42.0 (42–42) (n = 1)
BALTIMORE?	–	54.0 (54–54) (n = 1)	54.0 (54–54) (n = 1)
Z12 (unknown)	45.0 (45–45) (n = 1)	–	45.0 (45–45) (n = 1)
Total	49.1 (11–91) (n = 64)	46.4 (8–86) (n =1 08)	47.4 (8–91) (n = 172)

Hb, hemoglobin.

Table 2. Hematological parameters (Hb, Hct, MCV, MCH, MCHC) by hemoglobin variant type.

Variant type	Hb (g/dL)	Hct (%)	MCV (fL)	MCH (pg)	MCHC (g/dL)
HbD	14.0 ± 1.7	41.8 ± 4.9	82.8 ± 5.5	27.8 ± 2.4	33.5 ± 1.2
HbF	13.1 ± 1.8	40.0 ± 5.0	80.2 ± 11.9	26.3 ± 4.6	32.7 ± 1.3
HbC	13.5	39.8	87.1	29.5	33.9
HbE	14.2 ± 1.0	43.0 ± 2.1	84.0 ± 4.2	27.8 ± 2.2	33.0 ± 0.8
HbS	13.6 ± 1.7	41.1 ± 5.3	81.6 ± 6.4	27.1 ± 2.3	33.2 ± 1.0
O-Arab?	13.8 ± 1.4	40.1 ± 4.2	78.9 ± 3.3	27.1 ± 2.0	34.3 ± 1.6
Alpha thalassemia?	13.0	39.5	86.1	28.3	32.9
HbJ?	13.6	41.4	86.0	28.3	32.9
BALTIMORE?	14.1	43.6	87.0	28.2	32.3
Z12 (unknown)	16.5	46.3	85.9	30.6	35.6

Hb, hemoglobin; Hct, hematocrit; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume.

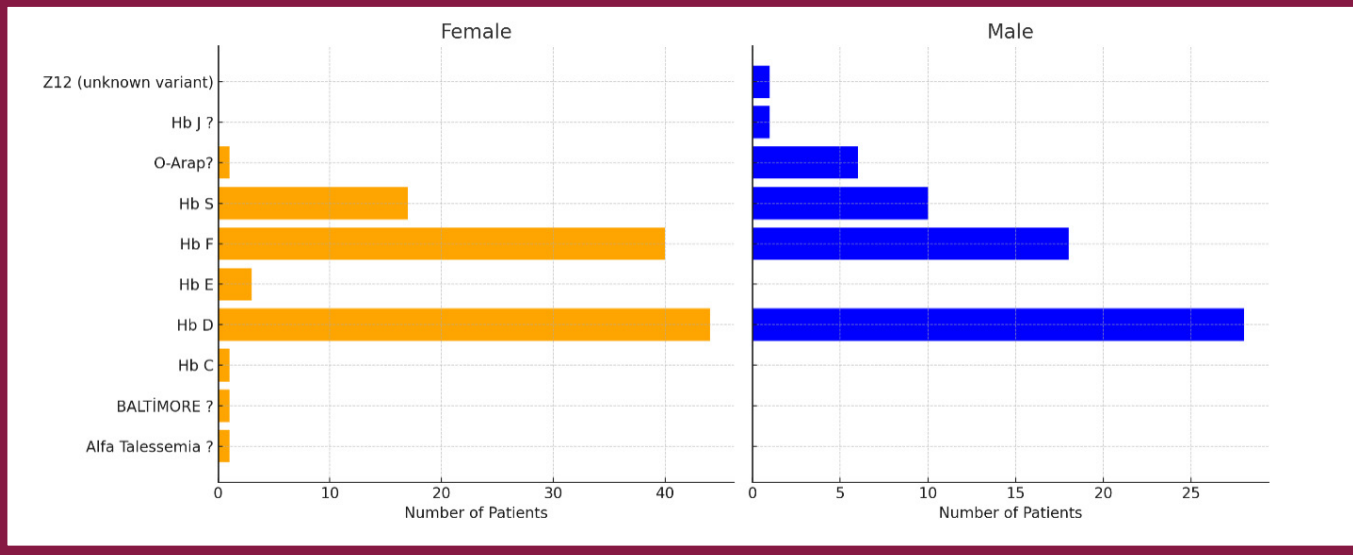

Figure 1. Distribution of variants by gender.

first large-scale study from Türkiye to report the rate of Hb variant detection via capillary electrophoresis-based HbA1c analysis.

In the literature, the rates of Hb variants detected during HbA1c measurement vary greatly depending on the scope of the study, sample size, and target population. For example, a study from North Bengal, North India reported a prevalence of 27.4% among 449 individuals (3). In contrast, the variant-carrier rate was reported as 3.77% in a multiethnic patient group (sample of 13,913 individuals) in the USA (8). In a series of 319,290 tests performed on the Sciex HPLC platform, the variant detection rate was 0.03% (9). A French study using ion-exchange HPLC found Hb variants in 0.71% of 51,382 individuals (10). Likewise, a study conducted in South India reported Hb variants in 0.83% of 10,200 HbA1c samples analyzed by ion-exchange HPLC (11). In Southern China, HbA1c measurements in over 311,000 individuals revealed a variant frequency of 0.35% (12). In a study involving 9,792 Tunisian diabetic patients, the frequency of variant detection using capillary electrophoresis during HbA1c analysis was 2.33% (13). As can be seen from these comparisons, international studies have reported rates ranging from 0.03% to 27%. Our 0.25% detection rate is relatively low compared with some studies, which is likely attributable to the large, unselected patient population.

Differences in rates can be attributed to several factors. First, there is the sample-size effect: Small cohorts (e.g., 100–500 participants) can sometimes yield higher rates because of local variant prevalence, while large population-based studies have reported lower rates (0.3–0.8%) (3). Second, the demographic and ethnic composition of the population is a determining factor. For example, HbE carriage is common in India and Southeast Asia, while HbS is much more common in African American populations. In the multiethnic US population, HbS and HbC have been reported at frequencies of approximately 3% (8). Third, the type of analytical method and the instrument used make a difference. Capillary electrophoresis systems can separate many variants more effectively by using longer separation times and higher resolving power, thereby providing greater sensitivity for variant detection. On the other hand, in conventional ion-exchange HPLC instruments, some variants may be concealed within HbA or HbA1c peaks and therefore remain undetected, leading to falsely high or falsely low HbA1c results. Immunoassay-based methods are generally not affected by most variants (unless the mutation is epitope-dependent) because they use antibodies that recognize the N-terminus of the Hb β-chain. For example, immunoturbidimetric results in carriers of HbS or HbC often closely reflect actual values. Boronate affinity methods (e.g., Afinion) have been reported to be ineffective against common variants because they do not distinguish structural differences (14,15). In summary, while low rates may be observed in a series studied by HPLC within the same population, laboratories using capillary electrophoresis may report relatively higher rates. The routine protocols of the laboratories where these studies are conducted also play a role: some clinical laboratories may ignore an abnormal peak, while others' software may alert clinicians to a variant and prompt diagnostic investigation. For example, higher detection rates have been observed in studies conducted at academic center laboratories (16). All these factors (sample,

ethnic composition, method, and instrument) explain the differences in variant detection rates.

It is well-documented that certain Hb variants can affect the accuracy of HbA1c measurements, potentially leading to falsely elevated or decreased results. For example, in individuals with HbS or HbC traits, HPLC-based methods may underestimate true HbA1c levels due to co-elution of the variant with the HbA peak. Although capillary electrophoresis systems are generally capable of detecting and differentiating most common variants, rare hemoglobinopathies may still interfere with measurement windows (14,15). Consequently, in patients with identified Hb variants, HbA1c values should be interpreted with caution and, if necessary, be confirmed using an alternative method such as immunoassay or boronate affinity chromatography.

When variant types reported in previous studies were examined, the most frequently detected variant in the French study was HbS, particularly among individuals of African descent (10). In Southern China, the most common variants were HbE, Hb New York, HbJ-Bangkok, and Hb Q-Thailand. A total of 117 variants were identified, 18 of which were novel mutations (12). In the study conducted in South India, HbD, HbE, and HbS were the most frequently observed variants (11). In a study by Roy et al. (3) in Northern Bengal, India, Hb variants were detected in 27.4% of individuals undergoing HbA1c testing; HbE was the most frequent variant, followed by HbD. In our study, the most frequently detected variants were HbD, elevated HbF, and HbS. Regional differences within and between countries may influence these frequencies. For instance, in Türkiye's southern regions, such as Çukurova, the carrier rate of HbS may reach 8–10%, whereas it is significantly lower in the eastern regions (17). These differences can be attributed to patterns of migration and ethnic composition in both countries.

Epidemiological studies indicate that the prevalence of Hb variants varies significantly across ethnic and geographic populations. In Africa, HbS is the most common variant. Studies in Sub-Saharan Africa report carrier rates of hemoglobinopathies ranging from 10% to 40%; for instance, a study conducted in Benin reported carrier rates of 21.7% for HbS and 10.2% for HbC (18). In the Middle East and Mediterranean region, HbS and HbD are frequently observed. HbD-Punjab is prevalent in Iran and Pakistan (19). In East and Southeast Asia (e.g., China and Thailand), HbE is the most common variant. Increased HbF levels may also be observed due to HbConstant Spring and certain α/β-thalassemias. Hemoglobinopathies were historically rare in industrialized Northern and Central European countries, but have become much more common due to immigration from endemic regions (20). In the United States, sickle cell trait is present in approximately 7–9% of African Americans (21). Other structural variants, such as HbC and HbE, are particularly prevalent in populations from West Africa and Southeast Asia, respectively, and are increasingly encountered in immigrant communities in Europe and North America (20). In a large-scale study conducted in the U.S., the most frequently observed variants were HbS (2.85%), HbC (0.61%), and HbE (0.13%) (8). These findings demonstrate that the distribution of Hb variants is influenced by regional and ethnic factors and that the results of our study should also be interpreted in this context.

In our study, the most frequently detected variants were HbD (41.86%), HbF (33.72%), and HbS (15.70%). This distribution appears to be consistent with the hemoglobinopathy patterns observed in certain regions of Türkiye. Accordingly, the high detection rate of HbD may reflect the known prevalence of HbD-Punjab in some Turkish regions.

Study Limitations

This study has several limitations. Due to its retrospective design, variables such as patient history, ethnic background, and clinical findings could not be assessed. Additionally, the study is based on data from a single center, and therefore, the results may not be generalizable to the entire population. In addition, no advanced genetic testing was performed in cases where Hb variants were detected; the identification of variants was based solely on capillary electrophoresis. This may limit the definitive classification of the variants. Nevertheless, the large sample size suggests that asymptomatic hemoglobinopathies can be incidentally detected during routine HbA1c testing. However, integration of such findings into population-based screening programs would require confirmatory testing and comprehensive epidemiological studies.

These findings demonstrate that Hb variants, which may be clinically silent in the general population, can be incidentally detected during routine HbA1c testing, especially when using high-resolution methods such as capillary electrophoresis. Given its high sensitivity in chromatographic separations (22), capillary electrophoresis not only ensures accurate glycemic assessment but also serves as a valuable tool for identifying asymptomatic hemoglobinopathies. Since HbA1c testing is already widely used for diabetes screening and follow-up, the incidental detection of such variants may offer insights into their prevalence and support targeted screening strategies. Therefore, laboratory professionals should remain aware of the detection capabilities and limitations of their analytical systems, apply confirmatory testing when necessary, and interpret HbA1c values cautiously in patients with suspected or known Hb variants.

Conclusion

Capillary electrophoresis is a sensitive screening tool for the detection of silent hemoglobinopathies in the general population. The use of highly discriminative methods such as capillary electrophoresis during HbA1c measurements can facilitate the early and incidental identification of Hb variants, thereby playing a clinically significant role in the recognition of otherwise undiagnosed hemoglobinopathies. This study underscores the importance of carefully interpreting HbA1c results in light of possible Hb variants during clinical decision-making. The incidental detection of Hb variants during routine HbA1c testing may offer an opportunity for early diagnosis of hemoglobinopathies and genetic counseling.

Additionally, the Hb variant distribution observed in this large dataset provides insights into variant frequencies in the patient population undergoing testing and may inform future screening and diagnostic strategies. In this context, expanding hemoglobinopathy screening, particularly in regions with high migration rates, and performing HbA1c analyses using methods capable of detecting variants are strongly recommended.

Ethics

Ethics Committee Approval: This study was approved by the Institutional Ethics Committee of Ankara Training and Research Hospital (decision number: E-25-586/2025, dated: 11.09.2025) and conducted in accordance with the principles of the Declaration of Helsinki.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: E.F.Y., M.A., Design: E.F.Y., M.A., Data Collection or Processing: E.F.Y., H.A.T., M.E.Y., Analysis or Interpretation: E.F.Y., M.A., M.E.Y., M.Ş., Literature Search: E.F.Y., M.A., M.F.A., Writing: E.F.Y., M.A., H.A.T., M.F.A.

Conflict of Interest: No conflict of interest was declared by the author(s).

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Comparison of AI-Based Triage Systems in High-Energy Thoracic Trauma: A Pilot Study Using ChatGPT and Gemini

Yüksek Enerjili Toraks Travmalarında Kılavuz Temelli Klinik Karar Verme Sürecinde ChatGPT-4 ve Gemini 1.5'in Karşılaştırmalı Performansı: 30 Sentetik Olguda Simülasyon Çalışması

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ABSTRACT

Background: High-energy thoracic trauma is a leading cause of morbidity and mortality in polytrauma patients. Timely diagnosis and management are crucial for patient outcomes. Artificial intelligence (AI) systems such as ChatGPT and Gemini have demonstrated potential in providing clinical decision support. This study presents a dataset of 30 synthetic thoracic trauma cases and explores the feasibility of using AI tools to assist in triage and early management decisions.

Materials and Methods: Thirty synthetic cases, reflecting real-world patterns of high-energy thoracic trauma, were developed based on established trauma mechanisms, clinical findings, and evidence-based physiological parameters. Each case includes vital signs, injury mechanism, physical findings, and a structured clinical question regarding immediate management. These cases were formatted for AI analysis. Responses from ChatGPT and Gemini will be analyzed for clinical appropriateness, adherence to trauma guidelines (e.g., Advanced Trauma Life Support), and concordance with experts.

Results: Initial simulations (5-case pilot) demonstrated greater adherence to trauma protocols with ChatGPT, particularly in managing tension pneumothorax, tamponade, and flail chest. Gemini responses were more conservative and occasionally delayed critical interventions. A full-scale analysis of all 30 cases is underway, using a scoring system based on accuracy, guideline conformity, and intervention prioritization. Preliminary findings suggest AI tools can assist in high-stakes clinical decision-making, particularly in environments with limited specialist access. ChatGPT's ability to provide structured, guideline-based responses is promising. However, human oversight remains essential. Large-scale validation with real patient data is necessary before clinical deployment.

Conclusion: AI-based models show potential in enhancing early decision-making in high-energy thoracic trauma. While encouraging, these tools require careful integration into clinical workflows and further validation in real-time settings.

Keywords: Thoracic trauma, artificial intelligence, triage, ChatGPT, Gemini, emergency surgery, clinical decision support

ÖZ

Amaç: Yüksek enerjili toraks travması, çoklu travmalı hastalarda önlenebilir ölümlerin önde gelen nedenlerinden biridir. Bu çalışmada, iki gelişmiş büyük dil modelinin (large language model) — ChatGPT-4 (OpenAI) ve Gemini 1.5 (Google DeepMind) — yüksek enerjili toraks travmalarında kılavuzlara uygun klinik karar önerileri üretme yeterliliği değerlendirildi.

Gereç ve Yöntemler: Çeşitli yaralanma mekanizmaları, fizyolojik parametreler ve klinik bulguları içeren 30 sentetik klinik senaryo geliştirildi. Her olgu, klinik özetler ve yönetim sorularını içeren standart istemlerle ChatGPT-4 ve Gemini 1.5 tarafından bağımsız

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ÖZ

olarak değerlendirildi. Yanıtlar, model kimliği gizlenen iki uzman travma cerrahı tarafından, İleri Travma Yaşam Desteği ve Doğu Travma Cerrahisi Derneği kılavuzlarına uyuma göre ikili uyum puanlama sistemiyle değerlendirildi. İstatistiksel analizlerde McNemar testi, Cohen'in Kappa katsayısı, ki-kare analizi ve alıcı işletim karakteristiği (AİK) eğrisi kullanıldı.

Bulgular: ChatGPT-4 %83,3 (25/30), Gemini 1.5 ise %60,0 (18/30) oranında kılavuz uyumu sağladı. McNemar testi ChatGPT-4 lehine bir eğilim gösterse de istatistiksel olarak anlamlı değildi ($p = 0,0654$). Modeller arası uyum zayıftı ($\kappa = 0,15$), genel fark anlamlı bulunmadı ($\chi^2 = 2,95$; $p = 0,0856$). Gemini'nin ChatGPT-4'e göre AİK eğrisi altında kalan alanı (AUC) 0,62 idi.

Sonuç: ChatGPT-4, özellikle anatomik ve radyolojik değerlendirme alanlarında Gemini 1.5'e göre daha yüksek kılavuz uyumu göstermiştir. Ancak, sınırlı model uyumu ve istatistiksel anlamlılığın olmaması, klinik uygulamadan önce hekim denetimi ve ileri doğrulama gerekliliğini vurgulamaktadır. Bulgular, yapay zekâ destekli travma karar destek sistemlerinin potansiyelini göstermekle birlikte, akut bakımda hekim yargısının önemini koruduğunu ortaya koymaktadır.

Anahtar Kelimeler: Torasik travma, yapay zeka, triyaj, ChatGPT, Gemini, acil cerrahi, klinik karar destek sistemi

Introduction

High-energy thoracic trauma represents a critical challenge in emergency medicine, accounting for 20–25% of trauma-related mortality and contributing to an additional 50% of deaths among patients with polytrauma (1). The Golden Hour concept emphasizes that survival outcomes fundamentally depend on rapid recognition, accurate assessment, and timely implementation of evidence-based interventions within the first 60 minutes after injury. Contemporary trauma care relies heavily on standardized protocols, particularly the Advanced Trauma Life Support (ATLS) guidelines developed by the American College of Surgeons Committee on Trauma (2), which provide systematic approaches to primary and secondary survey methodology, diagnostic prioritization, and therapeutic decision-making.

The complexity of thoracic trauma management stems from the anatomical diversity of potential injuries, ranging from simple pneumothorax to life-threatening conditions such as massive hemothorax, cardiac tamponade, and tracheobronchial disruption (3). Each injury pattern requires specific diagnostic approaches and therapeutic interventions, and management decisions often depend on integrating the clinical presentation, physiologic parameters, imaging findings, and mechanisms of injury (4). The time-sensitive nature of these decisions, combined with the high stakes of potential adverse outcomes, creates an environment where clinical decision support tools could provide substantial value.

Artificial intelligence (AI) and machine learning technologies have demonstrated increasing sophistication in medical applications, with large language models (LLMs) showing particular promise in knowledge-based medical tasks. Recent studies (5-7) have evaluated AI performance in medical licensing examinations, diagnostic reasoning, and clinical documentation, with several models achieving performance levels comparable to or exceeding those of human physicians in controlled testing environments (8). However, the translation of these capabilities to acute care scenarios, particularly in trauma medicine where rapid decision-making under uncertainty is paramount, remains largely unexplored (9).

The potential applications of AI in trauma care extend beyond simple knowledge retrieval to include pattern recognition, risk stratification, and decision support in resource-limited environments. Emergency departments and trauma centers increasingly face challenges related to physician workload, diagnostic accuracy under time pressure, and standardization of care across different experience levels. AI-assisted decision support could address these challenges by providing consistent, guideline-based recommendations (10) and maintaining the speed necessary for acute care environments, although notable limitations in accuracy have been documented.

This study aims to evaluate the performance of two leading LLMs, ChatGPT-4 and Gemini 1.5, in providing guideline-concordant recommendations for the management of high-energy thoracic trauma. Through a systematic evaluation of 30 synthetic clinical scenarios designed to reflect authentic trauma presentations, we assess the capacity of these AI systems to support clinical decision-making in acute care settings while identifying specific areas of strengths and limitations that inform future development and implementation strategies.

Materials and Methods

This study employed a retrospective simulation framework involving 30 synthetically generated high-energy thoracic trauma scenarios. Case construction was guided by existing literature on trauma epidemiology, injury biomechanics, and acute clinical management protocols.

Cases were reviewed by two board-certified trauma surgeons to ensure plausibility, clinical relevance, and alignment with real-world trauma profiles.

Two state-of-the-art LLMs were evaluated: ChatGPT-4 (OpenAI) and Gemini 1.5 (Google DeepMind). Each model was independently queried using the 30 cases in a structured prompt format. Each model was queried in a new and isolated session to avoid memory-related carryover effects and minimize prompt-context drift. Prompts included anonymized clinical summaries detailing the mechanism of injury, vital signs, physical findings, and a primary clinical question (e.g., airway management, need for imaging, and need for thoracostomy).

Model outputs were assessed for:

- Clinical appropriateness: Whether the recommendation aligned with accepted trauma protocols.
- Guideline concordance: Based on ATLS, Eastern Association for the Surgery of Trauma (EAST), and trauma surgical best practices.
- Intervention prioritization: Accuracy and urgency of life-saving measures.

Responses were scored dichotomously (1 = guideline-concordant; 0 = discordant or delayed) by an independent panel of trauma specialists blinded to model identity. Statistical analysis included descriptive statistics, McNemar's test, Cohen's Kappa coefficient, chi-square tests, and receiver operating characteristic (ROC) curve analysis to evaluate diagnostic performance and model agreement.

The study was conducted without human subject data and was therefore exempt from institutional review board (IRB) approval.

Inclusion Criteria

A total of 30 synthetic cases were included in this study (Table 1). These cases were designed to emulate real-world presentations of high-energy thoracic trauma, based on established injury patterns observed in clinical practice. Inclusion criteria for case construction were as follows:

- Mechanism of injury consistent with high-energy blunt or penetrating thoracic trauma (e.g., motor vehicle collisions, falls from height, crush injuries).
- Presence of physiologic instability (e.g., hypotension, tachypnea, hypoxia) or pathognomonic thoracic injury signs (e.g., subcutaneous emphysema, flail chest, distended neck veins).
- Availability of clearly defined clinical findings, vital signs, and a specific diagnostic or management question related to acute trauma care.
- Relevance to guideline-based decision-making processes, particularly those addressed by the ATLS and EAST recommendations.

Each synthetic case was developed to provide sufficient detail for AI models to interpret the scenario and to propose a prioritized clinical action plan.

Statistical Analysis

Responses from the two AI models were dichotomously scored (1 = guideline-concordant; 0 = discordant or delayed) by an independent panel of trauma specialists blinded to model identity. Descriptive statistics were used to summarize categorical variables as frequencies and percentages.

A paired comparison of binary outcomes was conducted using the McNemar test to detect significant differences in guideline-concordant responses between the two models. Agreement between ChatGPT and Gemini was assessed using Cohen's Kappa coefficient. A chi-square test was performed to examine associations between model performance and case-specific variables. This test was used solely to evaluate differences in paired proportions and was not intended to represent clinical agreement or imply clinical equivalence between the models.

A paired t-test was not applied because the model outputs were binary (0/1), and this test requires continuous, normally distributed data. ROC curves were generated to evaluate the diagnostic performance of each model in predicting expert-aligned responses. In this study, ROC analysis was used as an exploratory model-to-model comparison tool rather than a clinical diagnostic metric, with ChatGPT's outputs serving as the benchmark. The area under the curve (AUC) was calculated to quantify discriminatory power. All analyses were performed using SPSS version 27 (IBM Corp.) and GraphPad Prism version 9.0, with statistical significance set at a p-value < 0.05.

Results

In the context of AI-assisted decision-making in trauma care, concordant response scores refer to the degree of alignment between an AI model's clinical recommendations and established trauma management guidelines, such as ATLS or EAST.

The purpose of concordance scoring is to assess the reliability and clinical appropriateness of AI-generated responses, particularly in high-stakes scenarios such as high-energy thoracic trauma. Each response is evaluated by expert reviewers or automated protocols for its consistency with evidence-based clinical standards.

Concordant response scores provide a quantifiable framework to determine the clinical utility of AI models. In our study, models, such as ChatGPT-4 and Gemini 1.5, were evaluated on 30 synthetic thoracic trauma cases. The scoring system allowed a standardized comparison based on adherence to trauma guidelines, revealing significant differences in model performance (Table 2).

Table 1. Synthetic thoracic trauma cases dataset.

Case ID	Age	Gender	Mechanism of injury	Clinical findings	Vital signs	Primary question
1	72	Male	Assault with blunt object	Subcutaneous emphysema and decreased breath sound on the right	BP: 101/74 mmHg, HR: 122 bpm, RR: 28 bpm, SpO_2: 92%	What should be the immediate clinical approach and need for intervention?
2	54	Female	Assault with blunt object	Massive hemothorax requiring immediate decompression	BP: 80/63 mmHg, HR: 99 bpm, RR: 31 bpm, SpO_2: 86%	What should be the immediate clinical approach and need for intervention?
3	58	Male	High-speed motor vehicle collision	Multiple left rib fractures with minimal hemothorax	BP: 74/77 mmHg, HR: 132 bpm, RR: 19 bpm, SpO_2: 96%	What should be the immediate clinical approach and need for intervention?
4	40	Female	Pedestrian struck by car	Flail chest with bilateral pulmonary contusion	BP: 116/48 mmHg, HR: 97 bpm, RR: 35 bpm, SpO_2: 98%	What should be the immediate clinical approach and need for intervention?
5	63	Male	Assault with blunt object	Multiple left rib fractures with minimal hemothorax	BP: 95/70 mmHg, HR: 140 bpm, RR: 25 bpm, SpO_2: 90%	What should be the immediate clinical approach and need for intervention?
6	64	Female	Pedestrian struck by car	Flail chest with bilateral pulmonary contusion	BP: 91/68 mmHg, HR: 99 bpm, RR: 27 bpm, SpO_2: 97%	What should be the immediate clinical approach and need for intervention?
7	57	Male	High-speed motor vehicle collision	Subcutaneous emphysema and decreased breath sound on the right	BP: 120/66 mmHg, HR: 95 bpm, RR: 20 bpm, SpO_2: 94%	What should be the immediate clinical approach and need for intervention?
8	61	Female	Pedestrian struck by car	Cardiac tamponade signs with hypotension and tachycardia	BP: 80/73 mmHg, HR: 103 bpm, RR: 23 bpm, SpO_2: 95%	What should be the immediate clinical approach and need for intervention?
9	20	Male	Fall from height	Pulmonary contusion with right-sided small pneumothorax	BP: 91/80 mmHg, HR: 123 bpm, RR: 29 bpm, SpO_2: 95%	What should be the immediate clinical approach and need for intervention?
10	34	Female	Pedestrian struck by car	Massive hemothorax requiring immediate decompression	BP: 111/69 mmHg, HR: 123 bpm, RR: 20 bpm, SpO_2: 89%	What should be the immediate clinical approach and need for intervention?
11	50	Female	High-speed motor vehicle collision	Cardiac tamponade signs with hypotension and tachycardia	BP: 107/59 mmHg, HR: 121 bpm, RR: 33 bpm, SpO_2: 88%	What should be the immediate clinical approach and need for intervention?
12	53	Female	Industrial accident	Jugular venous distention and muffled heart sounds	BP: 100/40 mmHg, HR: 119 bpm, RR: 27 bpm, SpO_2: 90%	What should be the immediate clinical approach and need for intervention?
13	75	Male	High-speed motor vehicle collision	Pulmonary contusion with right-sided small pneumothorax	BP: 108/52 mmHg, HR: 97 bpm, RR: 22 bpm, SpO_2: 95%	What should be the immediate clinical approach and need for intervention?
14	69	Female	Fall from height	Cardiac tamponade signs with hypotension and tachycardia	BP: 83/41 mmHg, HR: 91 bpm, RR: 21 bpm, SpO_2: 96%	What should be the immediate clinical approach and need for intervention?
15	52	Female	Pedestrian struck by car	Flail chest with bilateral pulmonary contusion	BP: 86/76 mmHg, HR: 119 bpm, RR: 36 bpm, SpO_2: 89%	What should be the immediate clinical approach and need for intervention?
16	40	Female	Fall from height	Pulmonary contusion with right-sided small pneumothorax	BP: 97/60 mmHg, HR: 106 bpm, RR: 22 bpm, SpO_2: 90%	What should be the immediate clinical approach and need for intervention?
17	31	Male	Motorcycle crash	Tracheobronchial injury suspected with severe air leak	BP: 106/78 mmHg, HR: 134 bpm, RR: 19 bpm, SpO_2: 87%	What should be the immediate clinical approach and need for intervention?

Table 1. Continued.

Case ID	Age	Gender	Mechanism of injury	Clinical findings	Vital signs	Primary question
18	66	Male	High-speed motor vehicle collision	Open chest wound with paradoxical movement	BP: 102/58 mmHg, HR: 114 bpm, RR: 34 bpm, SpO_2: 85%	What should be the immediate clinical approach and need for intervention?
19	60	Female	Motorcycle crash	Massive hemothorax requiring immediate decompression	BP: 89/48 mmHg, HR: 101 bpm, RR: 29 bpm, SpO_2: 96%	What should be the immediate clinical approach and need for intervention?
20	19	Male	High-speed motor vehicle collision	Sternal fracture with anterior chest wall deformity	BP: 118/69 mmHg, HR: 134 bpm, RR: 28 bpm, SpO_2: 96%	What should be the immediate clinical approach and need for intervention?
21	23	Male	Assault with blunt object	Flail chest with bilateral pulmonary contusion	BP: 103/44 mmHg, HR: 101 bpm, RR: 34 bpm, SpO_2: 87%	What should be the immediate clinical approach and need for intervention?
22	34	Male	Assault with blunt object	Multiple left rib fractures with minimal hemothorax	BP: 74/44 mmHg, HR: 122 bpm, RR: 27 bpm, SpO_2: 94%	What should be the immediate clinical approach and need for intervention?
23	30	Male	Motorcycle crash	Massive hemothorax requiring immediate decompression	BP: 98/75 mmHg, HR: 101 bpm, RR: 27 bpm, SpO_2: 92%	What should be the immediate clinical approach and need for intervention?
24	32	Female	Industrial accident	Open chest wound with paradoxical movement	BP: 84/80 mmHg, HR: 100 bpm, RR: 30 bpm, SpO_2: 90%	What should be the immediate clinical approach and need for intervention?
25	44	Female	High-speed motor vehicle collision	Open chest wound with paradoxical movement	BP: 117/80 mmHg, HR: 102 bpm, RR: 32 bpm, SpO_2: 98%	What should be the immediate clinical approach and need for intervention?
26	40	Female	Assault with blunt object	Pulmonary contusion with right-sided small pneumothorax	BP: 70/59 mmHg, HR: 98 bpm, RR: 29 bpm, SpO_2: 92%	What should be the immediate clinical approach and need for intervention?
27	21	Male	Fall from height	Tracheobronchial injury suspected with severe air leak	BP: 96/46 mmHg, HR: 117 bpm, RR: 31 bpm, SpO_2: 88%	What should be the immediate clinical approach and need for intervention?
28	41	Female	High-speed motor vehicle collision	Cardiac tamponade signs with hypotension and tachycardia	BP: 94/75 mmHg, HR: 97 bpm, RR: 36 bpm, SpO_2: 90%	What should be the immediate clinical approach and need for intervention?
29	59	Male	Industrial accident	Pulmonary contusion with right-sided small pneumothorax	BP: 90/42 mmHg, HR: 140 bpm, RR: 27 bpm, SpO_2: 95%	What should be the immediate clinical approach and need for intervention?
30	56	Male	Industrial accident	Massive hemothorax requiring immediate decompression	BP: 76/40 mmHg, HR: 128 bpm, RR: 34 bpm, SpO_2: 95%	What should be the immediate clinical approach and need for intervention?

BP, blood pressure; HR, heart rate; RR, respiratory rate.

The implementation of such scoring systems is essential for validating AI tools in critical care environments. While high concordance implies safe and actionable recommendations, discordant outputs underscore the need for clinician oversight and further training of these models.

ChatGPT-4 achieved concordant responses in 25 out of 30 cases (83.3%). Gemini 1.5 achieved concordant responses in 18 out of 30 cases (60.0%; Figure 1).

ChatGPT-4 demonstrated a significantly higher concordance with trauma management guidelines,achieving an accuracy of 83.3%, compared to Gemini 1.5's 60.0%. This discrepancy suggests that ChatGPT-4 may offer more reliable clinical decision support in acute trauma scenarios, aligning more consistently with established protocols such as ATLS. These findings underscore the potential of LLMs to augment emergency triage and intervention planning, provided they are appropriately validated and supervised.

Contingency table:

- Both correct: 16
- ChatGPT only correct: 9
- Gemini only correct: 2
- Both incorrect: 3 McNemar test statistic = 2.00, p-value = 0.0654
- Interpretation: A statistically significant result ($p < 0.05$) indicates a difference in accuracy between the two models.

The McNemar test was applied to evaluate whether the difference in accuracy between ChatGPT and Gemini was statistically significant. The test focuses specifically on discordant pairs—instances where one model was correct and the other was not (Table 3). The analysis yielded a test statistic of 2.00 (p = 0.0654).

• Interpretation: While ChatGPT outperformed Gemini in more cases (9 vs. 2), the difference did not reach statistical significance at the conventional threshold (p < 0.05). This suggests a trend toward superior performance by ChatGPT, but the evidence is insufficient to conclusively reject the null hypothesis. Larger datasets or stratified subgroup analyses may be required for more robust inference.

Table 2. Characteristics of concordant response scoring.

Feature	Description
Definition	Binary assessment of whether the AI output adheres to recognized clinical guidelines.
Scoring method	1 = guideline-concordant, 0 = discordant or inappropriate.
Assessment criteria	Timeliness, accuracy, clinical appropriateness, and intervention prioritization.
Review process	Scored by trauma care experts or automated algorithms using decision matrices.
Use case	Evaluating AI reliability in trauma triage and acute management contexts.

AI, artificial intelligence.

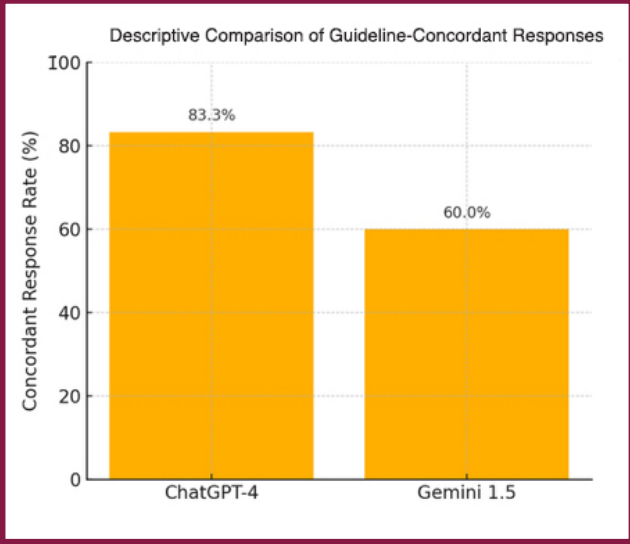

Figure 1. Comparison of guideline-concordant response rates between ChatGPT-4 and Gemini 1.5 across 30 synthetic high-energy thoracic trauma cases.

Cohen's kappa score was 0.15, indicating the level of agreement between the two models' responses (Table 4).

Cohen's Kappa coefficient is a statistical measure used to assess the level of agreement between two raters or models beyond chance. This analysis quantifies how often ChatGPT and Gemini provided the same classification (i.e., guideline-concordant or discordant responses) across 30 trauma cases.

The resulting Cohen's Kappa score of 0.15 indicates only slight agreement between the two AI models. According to the commonly accepted benchmarks (Landis and Koch, 1977), this suggests that the models often diverged in their decisions. Low inter-model agreement may reflect differences in algorithmic reasoning, training data, or interpretation of clinical priorities.

• Implications: While both models aim to mimic clinical reasoning, the modest level of agreement highlights variability in AI-generated recommendations. This variability underscores the necessity for human oversight and systematic validation of AI models before integration into clinical workflows.

Chi-square statistic = 2.95, p-value = 0.0856

• Interpretation: This test assesses whether the overall success rates of the two models differ significantly.

The chi-square test was conducted to determine whether the proportion of guideline-concordant responses differs significantly between ChatGPT-4 and Gemini 1.5 (Table 5). The resulting chi-square statistic was 2.95 (p = 0.0856).

• Interpretation: Although ChatGPT-4 showed a numerically higher rate of concordant responses (83.3%) compared to Gemini 1.5 (60.0%), the observed difference

Table 3. Contingency table of concordant responses between models.

Comparison	Number of cases
Both models correct	16
ChatGPT only correct	9
Gemini only correct	2
Both models incorrect	3

Table 4. Agreement assessment between ChatGPT and Gemini.

Metric	Value
Cohen's Kappa score	0.15
Interpretation	Slight agreement

Table 5. Frequency distribution of guideline-concordant and discordant responses.

Model	Concordant	Discordant
ChatGPT-4	25	5
Gemini 1.5	18	12

did not reach statistical significance at the conventional alpha level ($p < 0.05$). This indicates that while ChatGPT-4 appears more consistent with clinical guidelines, the sample size may be insufficient to definitively establish superiority using this method alone.

- Clinical implication: Chi-square analysis supports preliminary findings but also underscores the importance of larger sample sizes and complementary statistical methods for robust comparative assessments.

The ROC analysis comparing Gemini's concordance with ChatGPT's reference standard yielded an AUC of 0.62.

The ROC curve compares the classification performance of Gemini 1.5, using ChatGPT-4's decisions as the reference standard (Figure 2). The area under the ROC curve (AUC) was calculated to be 0.62.

- Interpretation: The AUC reflects the model's ability to distinguish between concordant and discordant classifications. An AUC value of 0.5 indicates no discriminative ability, while a value close to 1.0 indicates excellent performance. The observed AUC of 0.62 suggests a moderate ability of Gemini 1.5 to emulate ChatGPT-4's decision-making pattern, but it indicates limitations in reliability and clinical precision.
- Clinical relevance: Although ROC analysis is typically used in binary classification contexts with a definitive ground truth, its application here illustrates the divergence in decision patterns between AI models. This supports the broader argument that AI model selection and validation must be context-specific, particularly in safety-critical domains such as trauma care.

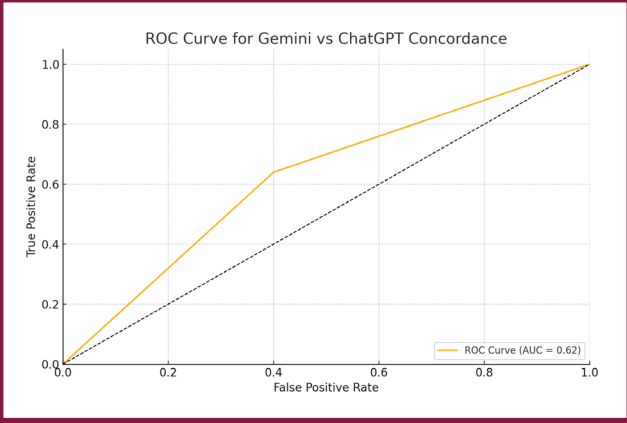

Figure 2. ROC curve showing Gemini 1.5 discriminative performance using ChatGPT-4 as reference.
ROC, receiver operating characteristic.

Discussion

Previous comparative studies evaluating large language models in acute clinical scenarios have reported variability in temporal accuracy and guideline adherence. showing that ChatGPT provided more guideline-consistent and timely interventions in emergency neurosurgical contexts than Gemini. The authors emphasized the significance of timeliness and context awareness in AI-generated clinical recommendations—both of which are critical in trauma scenarios. These findings align with our observations, particularly in high-stakes situations such as the management of tension pneumothorax or cardiac tamponade, where delays can result in catastrophic outcomes.

The findings of this study underscore the potential of AI models in enhancing clinical decision-making in high-stakes environments such as thoracic trauma care. ChatGPT-4 demonstrated superior guideline adherence compared to Gemini 1.5, particularly in cases requiring immediate and protocol-driven interventions. This observation aligns with previous literature, in which ChatGPT has shown relatively high performance in structured clinical assessments (11,12).

Despite promising results, the slight agreement between ChatGPT-4 and Gemini (Cohen's kappa = 0.15) suggests significant variability in how each model interprets and applies clinical guidelines. This phenomenon has been documented in other comparative studies, such as those evaluating AI model performance on neurosurgical board examinations and radiologic decision-making tasks (13,14). The inconsistency between models highlights the influence of underlying architectures, training corpora, and inference mechanisms on the clinical applicability of AI-generated responses.

Concordant response scoring in this context provided a standardized, objective measure of AI performance. This methodology has gained traction in recent AI benchmarking efforts within the healthcare domain (15,16). Our findings contribute to this growing body of literature by applying such metrics in a trauma-specific setting—an area that demands rapid, accurate, and guideline-concordant decisions (Table 6).

While ChatGPT-4 achieved a higher rate of correct responses, the lack of statistical significance in McNemar's test ($p = 0.0654$) and the chi-square test ($p = 0.0856$) underscores the need for cautious interpretation. Larger datasets or prospective validation in real-world clinical encounters may be required to confirm the superiority. Additionally, ROC curve analysis yielded an AUC of 0.62 for Gemini 1.5, indicating limited but detectable discriminative ability when benchmarked against ChatGPT-4. Importantly, the statistical agreement identified by McNemar's test does

not imply clinical equivalence between the models and, therefore, has limited interpretive value in evaluating their real-world performance. Similarly, the ROC results should be interpreted as an exploratory comparison of relative discriminative behavior between models rather than as a measure of clinical diagnostic accuracy.

The modest AUC and observed discordance raise important considerations regarding the use of AI in critical care. As Haemmerli et al. (17) and Aghamaliyev et al. (18) have noted, AI tools must be evaluated not only for accuracy but also for the potential consequences of delayed or inappropriate recommendations. In trauma care—where decisions often have immediate life-or-death consequences—this requirement is paramount.

Table 6. Case-by-case concordance scores.

Case ID	ChatGPT score (guideline-concordant)	Gemini score (guideline-concordant)
1	1	0
2	1	0
3	1	1
4	1	0
5	1	1
6	1	1
7	0	0
8	1	0
9	1	0
10	1	1
11	1	0
12	1	1
13	1	1
14	1	1
15	1	1
16	1	1
17	1	1
18	1	1
19	0	0
20	1	1
21	0	1
22	1	1
23	1	1
24	1	0
25	0	0
26	1	0
27	1	1
28	1	0
29	0	1
30	1	1

Moreover, the pattern of conservative responses observed in Gemini mirrors findings from previous assessments in ophthalmology and otolaryngology, where the model often opted for watchful waiting or further diagnostic evaluation rather than decisive action (19,20). While such caution may be appropriate in certain contexts, it can be detrimental in acute trauma scenarios.

In contrast, ChatGPT-4's more assertive clinical posture reflects its alignment with structured, guideline-based responses, making it potentially more suitable for integration into triage decision-support tools. Nonetheless, the necessity of clinical oversight cannot be overstated, as even small inaccuracies in high-acuity settings can have cascading effects.

In summary, our findings support the hypothesis that ChatGPT-4 is more consistent with established trauma protocols than Gemini 1.5. However, both models exhibited limitations, particularly in inter-model reliability. These results reinforce the need for hybrid models of care in which AI augments, but does not replace, human clinical judgment.

Future Directions

To further validate and refine the role of AI in trauma care, several avenues of research should be pursued. First, prospective studies using real patient data—preferably in multicenter emergency or trauma settings—are essential to evaluate AI performance under real-world constraints, including time pressure, incomplete data, and diagnostic ambiguity.

Second, future work should aim to develop more nuanced and multidimensional evaluation metrics, incorporating partial correctness, clinical rationale quality, and decision-making efficiency alongside strict guideline adherence. The use of expert panels and Delphi methods may aid in establishing more robust scoring frameworks.

Additionally, future studies will incorporate repeated querying on different days, randomization of case order, and session resets such as clearing cache/cookies to evaluate reproducibility and quantify model-level variability. These methodological refinements will help assess intra-model variability and enhance the robustness of comparative LLM analyses.

Third, expanding the sample size and diversity of trauma mechanisms (e.g., penetrating injuries, blast trauma, pediatric cases) will enhance the generalizability and clinical utility of AI models. Stratified analysis by injury type or severity could yield insights into model-specific strengths and weaknesses.

Fourth, integration of multimodal data—including radiological images, ultrasound findings, and vital sign trends—into model prompts may significantly enhance

diagnostic accuracy and triage appropriateness. Future models capable of processing such heterogeneous inputs should be evaluated.

Lastly, the incorporation of AI into clinical workflows must be accompanied by rigorous usability studies, clinician-AI interaction analyses, and ethical evaluations. Ensuring transparency, interpretability, and accountability in AI-driven recommendations is paramount, especially in high-stakes domains like trauma surgery.

Study Limitations

Despite its structured methodology and expert-reviewed design, this study possesses several limitations. First, the use of synthetic trauma cases, while beneficial for standardization and reproducibility, may not fully replicate the complexity and variability observed in real-world clinical encounters. As such, generalizability to live patient care settings is limited and necessitates cautious interpretation of findings.

Second, the binary concordant scoring system, although practical for assessing guideline adherence, lacks granularity in capturing partial correctness or contextual appropriateness. This may oversimplify the spectrum of clinical acceptability, especially in nuanced cases where multiple valid management strategies may coexist.

Third, the relatively small sample size (n = 30) restricts the statistical power of comparative analyses. While trends favoring ChatGPT-4 were observed, several tests did not reach conventional thresholds of statistical significance, thereby limiting the strength of inferential claims.

Additionally, because each case was tested only once per model, the study does not capture intra-model variability across repeated sessions. This limitation has been added to acknowledge that LLM outputs may vary depending on prompt order, timing, or session resets. Future studies incorporating repeated testing will be necessary to quantify reproducibility.

Furthermore, expert assessment of AI responses, though blinded and based on consensus guidelines, is inherently subjective. Inter-rater variability was not formally quantified, which may affect the consistency of scoring across cases.

Finally, the models were evaluated in a retrospective, asynchronous simulation framework, without real-time interaction, iterative questioning, or multimodal inputs (e.g., imaging, labs), which are crucial elements in actual trauma evaluation. Therefore, performance under dynamic clinical conditions remains untested.

Conclusion

This study demonstrates that LLMs, particularly ChatGPT-4, possess promising capabilities in supporting early decision-making in high-energy thoracic trauma scenarios. ChatGPT-4 outperformed Gemini 1.5 in terms of guideline adherence, intervention prioritization, and overall clinical appropriateness. Although the statistical analyses did not yield definitive significance across all measures, the trend consistently favored ChatGPT-4.

These findings highlight the potential role of AI in supplementing clinical workflows where rapid, evidence-based decisions are critical. In the high-stakes environment of trauma care—where time-sensitive decisions directly influence morbidity and mortality—AI-based support tools may offer tangible improvements in triage, diagnosis, and immediate management, particularly in settings with limited access to experienced trauma surgeons.

Nevertheless, the variability in model performance and low inter-model agreement reinforce the importance of human oversight and rigorous validation. AI models remain prone to hallucinations, contextual misinterpretations, and overly cautious or delayed recommendations, all of which could carry significant clinical risks in acute settings.

Until such systems achieve consistent reliability, AI should be viewed as an adjunct rather than a replacement for expert clinical judgment. Moreover, their utility must be continuously re-evaluated through prospective validation studies, including real patient scenarios, multi-center collaborations, and integration with real-time decision-support systems.

Future research should focus on expanding the sample size, incorporating diverse trauma etiologies, and testing AI models across heterogeneous healthcare environments. The ultimate goal should be the development of interoperable, context-sensitive AI tools that support equitable and high-quality emergency care without compromising patient safety.

Ethics

Ethics Committee Approval: Not required.
Informed Consent: Not required.

Footnotes

Authorship Contributions

Surgical and Medical Practices: N.Ç.Y., Concept: N.Ç.Y., Design: N.Ç.Y., Data Collection or Processing: N.Ç.Y., M.S.A., O.K., Analysis or Interpretation: N.Ç.Y., O.K., Literature Search: N.Ç.Y., O.K., Writing: N.Ç.Y., M.Ö.

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CASE REPORT

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Bell's Palsy Following Lumbar Disc Herniation Surgery: Presentation of A Rare Case Lumbar Disc Herniation and Bell's Palsy

Lomber Disk Hernisi Ameliyatı Sonrası Bell Paralizisi: Nadir Bir Olgu Sunumu

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ABSTRACT

Bell's palsy (BP) is an acute, idiopathic, unilateral facial nerve paralysis. Although rare, facial nerve palsy has been reported following prone positioning during surgery. We present a case of BP detected 18 hours after lumbar disc surgery, emphasizing diagnostic and therapeutic considerations.

Keywords: Bell's palsy, spinal surgery, prone position

ÖZ

Bell paralizisi (BP), yüz kaslarının tek taraflı felciyle seyreden, ani başlangıçlı ve çoğunlukla nedeni bilinmeyen bir durumdur. Prone pozisyonda cerrahi uygulanan hastalarda nadiren de olsa fasiyal sinir felci bildirilmektedir. Bu olgu sunumunda, lomber disk cerrahisi sonrası postoperatif 18. saatte BP gelişen bir olgu üzerinden tanı, tedavi ve olası nedenler tartışılmıştır.

Anahtar Kelimeler: Bell paralizisi, spinal cerrahi, pron pozisyon

Introduction

Bell's palsy (BP) is an acute-onset unilateral lower motor neuron facial paralysis that is idiopathic in the majority of cases (1–4). Possible causes include infections (e.g., viral, such as herpes simplex; bacterial, such as Lyme disease), cerebrovascular events, tumors, trauma, and Guillain-Barré syndrome. The most common mechanism is inflammation and edema that compress the facial nerve within the fallopian canal (3).

Symptoms vary depending on the extent and location of the lesion. Diagnosis is usually clinical; imaging is reserved for atypical cases or when alternative etiologies are suspected (1–4). Steroids and antiviral agents are commonly used treatments; early administration of corticosteroids has been shown to improve outcomes (5–10).

This report aims to highlight an uncommon case of BP developing after lumbar disc surgery performed in the prone position.

Case Report

Written informed consent was obtained. A 74-year-old male (80 kg) with a history of coronary artery disease and hypertension was scheduled to undergo surgery for lumbar disc herniation because of foot drop. His medications included acetylsalicylic acid, candesartan, and doxazosin. Preoperative examinations were unremarkable.

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Following standard monitoring and induction of anesthesia, the patient was intubated with a 7.5-mm spiral endotracheal tube. Maintenance included 2% sevoflurane in 50:50 O_2-air and a remifentanil infusion at 0.05 mcg/kg/min. The patient was placed in the prone position with appropriate padding of the head, face, and chest to avoid compression.

Vital signs remained stable throughout the 90-minute procedure. Intraoperative fluid administration totaled 2500 mL, with 600 mL of blood loss and 350 mL of urine output. The patient was extubated uneventfully and transferred to the ward.

At postoperative hour 18, the patient reported right-sided facial numbness. Clinical examination revealed an inability to raise the right eyebrow, drooping of the mouth and forehead on the same side, ptosis, and flattening of the nasolabial fold (Figure 1).

Otolaryngologic evaluation and magnetic resonance imaging revealed no abnormalities. A diagnosis of peripheral facial nerve palsy was considered, likely secondary to prone positioning. Prednisolone (1 mg/kg/day, tapered over 2 weeks) and vitamin B12 (for 1 month) were initiated. To prevent corneal injury, artificial tears, ointment, and eye patches were recommended. The patient was discharged on postoperative day 8, and near-complete recovery was observed at the 5-month follow-up.

Figure 1. Facial asymmetry. Right eyebrow and eyelid drooping and nasolabial sulcus effacement.

Discussion

BP is typically diagnosed clinically, with imaging used only when other pathologies are suspected. Although 80–90% of patients recover fully, residual deficits such as impaired eye closure, an asymmetric smile, or synkinesis may occur (1–4,11,12). Although viral, autoimmune, and ischemic theories have been suggested for its etiology, most cases show spontaneous and complete recovery within the first three months (13). The extent of initial paralysis is a major prognostic factor (1–5).

Corticosteroids are considered first-line treatment, especially when initiated within 72 hours (14). According to the American Academy of Neurology, the recommended dosing includes 1 mg/kg/day for 6 days, followed by a taper to complete a total of 10 days (9,10). Antiviral therapy alone is less effective, but may be beneficial when used in combination with other therapies (6–10).

The prevalence of BP has been reported to increase with age, in diabetic patients, and in the third trimester of pregnancy (11). BP is characterized by involvement of the facial nerve; however in some patients it may be accompanied by additional neurological symptoms, such as facial tingling, neck pain or headache, balance disturbances, weakness of the ipsilateral extremities, and memory problems (15).

Although BP developing after anesthesia is rare, it remains clinically important. BP often represents an idiopathic condition (16). BP resulting from the prone position is thought to be of traumatic origin. Inflammation and edema resulting from compression of the facial nerve, which runs along the fallopian canal in the temporal bone, are the most common causes of BP (3). Lower cranial nerve palsy has been reported in a patient ventilated in the prone position, caused by compression of cranial nerves IX–XII in the mandibular retrocondylar–peripharyngeal space secondary to edema and inflammation (17).

Many cases of facial paralysis reported in the anesthesiology literature have been associated with head malpositioning or excessive jaw maneuvers used to maintain airway patency (18). Tension can occur in the stylomandibular, sphenomandibular, and capsular ligaments during jaw-forward maneuvers, leading to erosion and subluxation of the temporomandibular joint. Anesthesiologists often must apply significant pressure to the jaw, where the facial nerve courses superficially, when positioning face masks for preoxygenation and for mask oxygenation after extubation. Current ventilation masks are designed with anatomically appropriate shapes and sizes, and when used carefully, even with a tight fit, they are highly unlikely to cause nerve paralysis or skin necrosis (19).

However, prolonged application exceeding several hours can often cause circulatory compromise in areas with bony prominences (20,21).

Prone positioning presents challenges in maintaining physiological head alignment. Though rare, facial nerve palsy due to prone positioning has been documented (2,11,17). Improper head positioning, mandibular pressure, or excessive airway maneuvers may be contributing factors (2,17–19). Our case did not involve difficult intubation or mask ventilation; the patient was easily ventilated by a single provider and intubated in a single session. Furthermore, care was taken to ensure that the head remained in the appropriate position while prone. Therefore, the most likely cause of BP in our case was thought to be impaired axonal conduction of the facial nerve due to compression from edema or inflammation within the fallopian canal of the temporal bone.

Conclusion

BP remains a predominantly clinical diagnosis with variable etiology and prognosis. Clinicians should be aware of facial nerve palsy as a potential complication of prone positioning. Early diagnosis and prompt corticosteroid treatment can enhance recovery. Further multicenter studies are needed to establish preventive protocols and management strategies in surgical settings.

Ethics

Informed Consent: Written informed consent was obtained.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.K., A.S.T., H.K., A.A.Y., Concept: G.K., A.K., A.S.T., Design: G.K., A.K., Data Collection or Processing: A.K., A.S.T., H.K., A.A.Y., Literature Search: G.K., A.K., Writing: G.K., A.K.

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