



Ankara Üniversitesi Tıp Fakültesi mecmuası

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Challenges in Intensive Care Airway Management: A Comprehensive Review

Yoğun Bakım Havayolu Yönetimindeki Zorluklar: Kapsamlı Bir Derleme

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Abstract

This review delves into the complexities of difficult airway management in intensive care units (ICUs). We categorise difficult airway management into five classes according to the American Society of Anesthesiologists guidelines. The review highlights the higher incidence of difficult airway cases in ICUs compared to operating rooms, attributed to various factors such as the critical status of ICU patients, fluid therapy complications, and the emergency nature of many intubations. We discuss the effectiveness of traditional anatomical indices in predicting difficult airways, noting their limited predictive value. We also propose a difficult airway algorithm for ICU settings, which adapts to three potential scenarios: anticipated, unanticipated, and critical "Can't Intubate Can't Ventilate" situations. This algorithm is complemented by the Vortex Approach, a cognitive tool designed to streamline decision-making in difficult airway scenarios. We conclude with best practice recommendations adapted from the National Audit Project 4, emphasising the need for specialised training, equipment readiness, and a collaborative team approach in ICU airway management.

Keywords: Airway management, intensive care, intubation

Öz

Bu derleme, yoğun bakım ünitelerinde (YBÜ) zor havayolu yönetiminin zorluklarını ele almaktadır. Amerikan Anestezi Uzmanları Derneği kılavuzlarına göre zor havayolu yönetimini beş sınıfa ayırıyoruz. Derleme, zor havayolu olgularının YBÜ'lerde operasyon odalarına kıyasla daha yüksek oluşunu vurgulamakta; bu durumun nedenleri arasında yoğun bakım hastalarının kritik durumu, sıvı terapisi komplikasyonları ve birçok entübasyonun acil niteliği bulunmaktadır. Geleneksel anatomik indekslerin zor havayollarını tahmin etmedeki etkinliğini tartışıp, bunların sınırlı tahmin değerlerine dikkat çekmeyi amaçlıyoruz. Ayrıca, YBÜ için üç potansiyel senaryoya uyum sağlayan bir zor havayolu algoritması öneriyoruz; öngörülen, beklenmeyen ve kritik "Entübe Edememe-Havalandıramama" durumları. Bu algoritma, zor havayolu senaryolarında karar almayı kolaylaştırmak için tasarlanmış bilişsel bir araç olan Vortex Yaklaşımı ile tamamlanmaktadır. YBÜ havayolu yönetiminde uzmanlaşmış eğitim, ekipman hazırlığı ve işbirlikçi ekip yaklaşımı ihtiyacını vurgulayan Ulusal Denetim Projesi 4'ten uyarlanan en iyi uygulama önerileriyle sonuca varıyoruz.

Anahtar Kelimeler: Havayolu yönetimi, yoğun bakım, entübasyon

Introduction

The approach to the airway in the intensive care unit (ICU) is a complex procedure, placing this subgroup of patients in a high-risk category for difficult airway (DA) management (1).

In a Closed Claims analysis (2,3) by the American Society of Anesthesiologists (ASA) Closed Claims Project—a database that records all anesthetic events leading to legal complaints – it was found that for events related to the airway, occurrences outside the operating room environment, such as in the emergency room

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or ICU, resulted in a fatal outcome in approximately 87% of cases, with permanent brain injury in the remaining cases. These findings were recently supported by a multicenter observational project in the United Kingdom (1).

Definitions and Prevalence

The difficulty in airway management can be classified into 5 distinct categories, according to ASA recommendations (4):

a) Difficult mask ventilation or supraglottic device use [e.g., laryngeal mask airway (LMA), laryngeal tube, or intubating LMA (ILMA®)]: when adequate ventilation by an Anesthesiologist is not possible due to inadequate mask sealing, excessive leakage, or excessive resistance to gas flow.

b) Difficulty in supraglottic device placement: with the need for multiple placement attempts in the presence or absence of tracheal pathology.

c) Difficult direct laryngoscopy (DL): when no portion of the vocal cords can be visualised after multiple attempts of conventional laryngoscopy.

d) Difficult tracheal intubation: when tracheal intubation requires multiple attempts in the presence or absence of tracheal pathology.

e) Failed intubation: when the placement of the endotracheal tube (ETT) fails after multiple attempts.

According to the literature, the incidence of DA is higher in the ICU compared to the operating room, ranging between 10 to 22% of all intubations (5-8).

Why do patients in ICUs experience DA?

Various factors can explain this:

- Patients in ICUs are at the limit of their functional reserves, particularly in terms of cardiorespiratory function, often experiencing multi-organ failure and a significant need for vasopressors, making them more susceptible to hypoxia or sedatives and with a poorer response to fluids (9);

- These patients often have a positive fluid balance due to the need for abundant prior fluid therapy. This can lead to airway oedema or interstitial pulmonary oedema (10).

- Patients need to be more adequately positioned for airway management, and often access to the head is limited by the presence of monitoring/infusion pumps or extracorporeal therapies, making DL difficult (11).

- In ICUs, Orotracheal Intubation can potentially occur as an emergent procedure, either due to the reasons mentioned above or due to ventilatory weaning failure [in 26-42% of all weaning attempts (12-14)] or accidental extubation in up to 15% of cases (15).

- These patients have an increased risk of regurgitation because they traditionally are not fasted (considered "full stomach") (16).

- DA/Invasive equipment is not frequently immediately available in the ICU, and the use of EtCO₂ for confirmation of the correct ETT positioning is limited (17).

The addition of these factors may reflect in a greater need for multiple attempts at endotracheal intubation. According to Mort (19), it is observed that several attempts of intubation using DL are associated with a dramatic increase in the incidence of hypoxemia, regurgitation of gastric contents, aspiration, bradycardia, and cardiorespiratory arrest (Figure 1) in patients in a non-operating room environment (18).

Prediction of DA

Numerous clinical conditions predict a DA (20,21), summarized in Table 1.

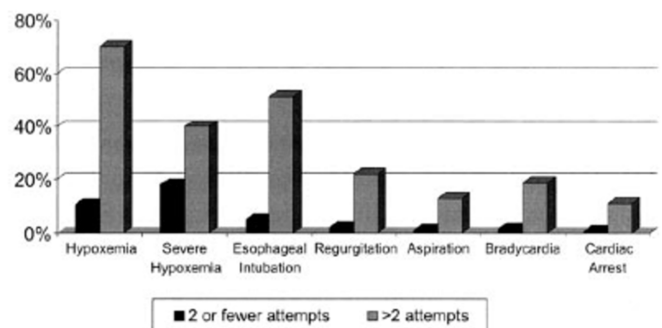


Figure 1: Graphic display of complications by intubation attempts

Table 1: Clinical conditions that predict a difficult airway (35,54)			
Anomalous facial anatomy	Limited mouth opening	Cervical restriction	Larynx/Pharynx anomalies
<ul style="list-style-type: none"> • Small mouth and/or macroglossia • Dental anomalies • Prognathism • Obesity • Advanced pregnancy • Acromegaly • Congenital syndromes (e.g., treacher collins syndrome) 	<ul style="list-style-type: none"> • Masseter spasm (dental abscess) • Temporomandibular joint dysfunction • Facial burns • Post-radiation fibrosis • Scleroderma 	<ul style="list-style-type: none"> • Obesity/short neck • Limited cervical mobility (e.g., ankylosing spondylitis) • Previous surgery of the cervical spine • Presence of cervical collar • Post-radiation fibrosis 	<ul style="list-style-type: none"> • High or anterior larynx • Deep vallecula • Anatomical changes of the epiglottis or hypopharynx • Subglottic stenosis

A previous history of difficult intubation or the presence of signs or symptoms suggestive of cervical/pharyngeal/mediastinal pathology is relevant in anticipating a likely difficulty in the airway. On the other hand, despite being universally used, it has not yet been demonstrated a significant positive predictive value for the use of common anatomical indices, such as inter-incisor distance, Mallampati index, cervical mobility, or distances between various cervical anatomical point (11,22-27). The low predictive value of individual anatomical indices has led to the structuring of combinations of indices and the creation of scores, also with variable sensitivity and specificity. Additionally, in the context of ICU, the use of these methods can be time-consuming and often impractical. A method for predicting DAs outside the operating room, called the MACOCHA score (Table 2) (28), has been described and has undergone external validation. To rule out the probability of a DA, a cut-off of 3 seems appropriate.

Considering that the prevalence of DA is challenging to establish among populations and most tests and scores have a low negative predictive value, it is accepted by several authors (29-33) that the systematic planning of an intubation strategy is crucial for addressing unexpected problems that may occur during the intubation attempt. The structured planning of this strategy is suggested in the form of an algorithm.

DA Algorithm in the ICU

Each patient poses a unique airway challenge, making the teaching of complex algorithms on airway management often unrealistic and counterproductive (34). While the ASA DA algorithm (4) is universally known and taught among anesthesiologists, it has faced various criticisms, being designed for the operating room environment and challenging to execute in emergencies. Additionally, it is not widely disseminated among nurses and non-anesthesiologist physicians, limiting communication and teamwork in an emergent situation (35). Therefore, many authors consider it unsuitable for difficult or emergent airway situations outside the operating room, particularly in locations such as the emergency room or the ICU (29,36).

Table 2: The MACOCHA score (28)

	Points
Factors related to the patient	
Mallampati ≥ 3	5
Obstructive Sleep Apnea Syndrome (OSAS)	2
Reduced cervical spine mobility	1
Reduced mouth opening (<3 cm)	1
Factors related to pathology	
Coma	1
Severe hypoxemia ($\text{SaO}_2 < 80\%$)	1
Factors related to the operator	
Non-anesthesiologist	1
Total	12

An alternative strategy aligning with the approach proposed by the DA Society (DAS) (31), considers three scenarios:

1. Anticipated DA

This represents the least lethal "scenario" since there is time to consider a strategy, optimize the situation, and obtain appropriate adjuvants/supplemental assistance. In this case, two fundamental questions must be addressed: "Should the patient be intubated awake, or can there be an anesthetic induction?" and "Which intubation technique should be used?"

- **Awake intubation:** It is more time-consuming, requires trained personnel, is less comfortable for the patient, and may need to be abandoned due to a lack of cooperation. However, it is significantly safer, considering the maintenance of pharyngeal and laryngeal muscle tone and spontaneous ventilation. It is commonly used in situations involving fiberoptic intubation and retrograde intubation.

- **Intubation under anesthetic induction:** This involves inducing deep anesthesia sufficient to allow for DL and orotracheal intubation without the use of muscle relaxants and optimally with the maintenance of spontaneous ventilation. Intubation without muscle relaxation can be facilitated by the prior application of lidocaine spray. Patient preparation, equipment readiness, and the involvement of all personnel are crucial in this scenario (Table 3).

2. Unanticipated DA

In this case, there is only a small time-window to address the problem, aiming to prevent hypoxemia, hypoventilation, hemodynamic instability, and potentially cardiorespiratory arrest (37). The patient is already anesthetised, often apnoeic, relaxed, and may have undergone several unsuccessful intubation attempts. If the appropriate equipment and assistance are not immediately accessible, there may not be time to obtain them! If a depolarizing relaxant, a short-acting non-depolarizing agent,

Table 3: Requirements for the approach to DA with intubation under anaesthesia induction, adapted from Lavery and McCloskey (11)

Fasted patient
Anti-acid therapy
Optimal positioning
Monitoring of vital signs and capnography
Availability of endotracheal tubes and laryngoscope blades in various shapes and sizes
Availability of adjunct devices, ideally bougies, stylets, introducers, laryngeal masks (of various sizes), or Combitube [®]
Availability of a cricothyroidotomy kit or mini-tracheostomy kit
Preoxygenation of the patient
Maintenance of spontaneous ventilation until the airway is secured
Use of bimanual laryngoscopy or BURP (Backward, Upward, Rightward, Pressure) maneuver if necessary
DA: Difficult airway

or a reversible relaxant has been used and ventilation is easy, it may be appropriate to allow the patient to regain consciousness, with the option to plan a delayed awake intubation. However, in most cases, due to the need to establish a definitive airway for respiratory failure, altered consciousness, or other reasons, alternative techniques to DL are often employed to improve the chances of visualising and intubating the trachea (38). The following are a set of techniques and devices alternative to DL. For a better understanding of their potential, it is suggested to search for illustrative videos online or attend a DA course.

Bimanual Laryngoscopy (BURP)

This corresponds to the initials of Backward, Upward, Rightward, Pressure, (BURP) which can improve the visualization of the vocal cords under DL (39), when performed by the laryngoscopist and subsequently maintained by the assistant.

Bougie or Modified Bougie (Frova Catheter)

Bougie is a malleable, thin, and elongated plastic cylinder that can have a blunt distal tip in the shape of a "hockey stick" to facilitate direction and entry through a less visible or even non-visible glottis (blind introduction). The correct placement of the Bougie in the tracheobronchial tree is revealed by transmitting the contact of the tip with the successive tracheal rings, which is felt as a series of bumps. At this point, the ETT can be introduced, according to the Seldinger technique (40) through the Bougie, which acts as an introducer/guide. It is, for many authors (41,42), the first alternative adjunct in a Ventilation-Associated Device (VAD) situation because it is cost-effective, disposable, enables ventilation (in the case of the Frova catheter), and has a quick learning curve.

Stylus with Light Source (Light Wand)

The stylus with a light source corresponds to a flexible introducer with an optical fiber light source, which is inserted into the ETT to later allow intubation when the light source is in the trachea. It is a device that facilitates blind intubation because it distinguishes the tracheal lumen (more anterior) from the esophageal lumen through transillumination of cervical tissues when the light source passes beyond the vocal cords (43). An important disadvantage is the requirement for low ambient lighting, which is not desirable (and often not possible) in the intensive care environment. Additionally, it is contraindicated in patients with anatomical airway alterations or cervical tissue. The intubation failure rate appears to be similar that of the lighted stylet.

Supraglottic Devices

- LMA®: The classic LMA (cLMA®) is a small rubber mask shaped like a spoon with an inflatable elliptical cuff, connected to a hollow plastic tube. It is blindly placed in the hypopharynx, adapting obliquely to the pharyngeal opening. Despite providing a seal for ventilation, the cLMA® does not protect against the

risk of aspiration. However, compared to intubation, it can be placed more successfully and quickly, especially by operators with limited training (44,45), making it useful as an alternative device in VAD situations.

- Modified laryngeal masks: The technology of laryngeal masks has seen significant differentiation in recent years, with various modified laryngeal masks available in the market. These include the ILMA®, Proseal LMA®, and several variations, including disposable formats.

The ILMA has a more rigid, angled, and larger-diameter tube with an insertion handle (see figure). These masks allow the introduction of a modified wire-reinforced endotracheal tube that can be inserted through the mask for blind intubation or with the assistance of a fiberoptic. Due to their characteristics, they can be used in trauma situations with suspected cervical injury or limited airway access (46). The Proseal LMA® (47) was introduced to overcome the risk of aspiration and improve adaptation to the anatomical structures of the hypopharynx. It features a larger and more concave mask, and the cuff is positioned posteriorly.

Additionally, it incorporates a working channel parallel to the tube, allowing the introduction of a suction catheter for esophageal content aspiration, thus limiting the risk of regurgitation.

Videolaryngoscopes: C-Mac, Glidescope®, McGrath®

Videolaryngoscopes are modified laryngoscopes that incorporate a rigid optical fiber with a camera at the distal end of the blade. The blade is inserted into the oral cavity along the midline and directed toward the base of the tongue until the epiglottis is visualized. The distal end of the endotracheal tube can then be directed through the glottis under indirect visualization. These devices appear to improve the approach to airway management in Anaesthesiology and Intensive Care, reducing the incidence of difficult laryngoscopy and intubation (48). A major disadvantage is their costliness.

Combitube® (Dual-Lumen Esophagotracheal Airway)

The Combitube® is a modified blind-insertion tube that includes an esophageal obturator and a tracheal tube (Figure 1). Regardless of its placement in the trachea or esophagus, it allows ventilation with partial protection against aspiration. Potential disadvantages include the inability to aspirate the trachea if the distal end is in the esophagus (more frequent position) and the possibility of airway trauma during placement. For these reasons, it is contraindicated in patients with known esophageal pathology, intact laryngeal reflexes, or after ingestion of caustic substances.

3. "Can't Intubate-Can't Ventilate"

This is an absolute emergency situation. In this scenario, it is crucial to remain calm and follow an appropriate algorithm

that includes only two options: a “minimally” invasive approach with a satisfactory method of ventilation without intubation, or an invasive approach with a decision for a surgical airway (cricothyroidotomy vs. emergency tracheostomy). The choice should depend on the operator's familiarity with the technique and the availability of materials/human resources in each institution.

Cognitive Aid: “The Vortex Approach” (29)

In an emergency, having a protocol for action serves to organise a team's response systematically and prevent delays or lapses in certain therapeutic options. However, adherence to guidelines may be challenging in a stressful environment with limited time. As discussed above, in an emergency, protocol-based action should be simple (for quick recall) and universal, shared by all team members, allowing for anticipating treatment priorities. In the case of DA, creating such guidelines is complicated by the existence of various possible devices and the understanding that the clinical context certainly influences the most appropriate approach. In this context, guidelines need to be both simple and robust to guide the approach in a wide range of situations. Despite this, the guidelines (4,31) from societies dedicated to DA remain relatively complex and are designed for the operating room environment.

Therefore, all ICU staff need a simple and effective cross-sectional mental model for DA management during a critical event. The Vortex cognitive model (29) is one such suggested method, conceptualizing the DA approach as a funnel based on the following assumptions:

The primary goal is to ensure that oxygen delivery to the alveoli is maintained, associated with airway patency (patient kept in the “Green Zone”). This can be achieved by:

1. Facial mask – Non-surgical extra-glottic airway,
2. LMA – Non-surgical supraglottic airway,
3. ETT – Non-surgical transglottic airway,
4. Surgical infra-glottic and definitive methods (surgical airway and definitive airway).

Preferably, up to three “optimized attempts” should be made to secure the airway with each of the non-surgical techniques described above.

The order in which each technique should be used depends on the operator and the airway maintenance objective (Figure 2).

The inability to establish airway patency after exhausting the previous possibilities should prompt an immediate transition to a surgical airway, regardless of SaO₂.

The “green zone” is conceptualized as a horizontal surface that reinforces the idea that in the presence of a difficult airway (VAD), there is no immediate imperative to proceed with successive airway manipulations. Instead, the focus is on ventilation/oxygenation, providing an opportunity to pause and devise a strategy while keeping the patient in a “safety zone”.

Proposal for an “Protocol” for Orotracheal Intubation in Intensive Care

It has recently been demonstrated that the use of an airway management protocol in intensive care has led to a reduction in complications associated with tracheal intubation (49). The protocol, the Montpellier algorithm, includes the interventions described in the Table 4. Implementing this protocol has resulted in a significant reduction in complications associated with intubation (9% vs. 21%) (49,50).

Table 4: Orotracheal intubation protocol in the ICU [modified from (49)]

Pre-intubation
<ol style="list-style-type: none"> 1. Presence of two operators 2. Administration of “Fluid Loading” (recommended 500 mL of 0.9% NaCl) in the absence of cardiogenic oedema 3. Preparation of long-term sedation and noradrenaline infusion 4. Pre-oxygenation for 3 minutes with NIV in case of respiratory failure (FiO₂ 100%, pressure support ventilation between 5-15 cmH₂O to achieve tidal volume between 6-8 mL/kg, and PEEP of 5 cmH₂O)
Peri-intubation
<ol style="list-style-type: none"> 5. Rapid sequence intubation: <ul style="list-style-type: none"> • Propofol 0.1 mg/kg or ketamine 1.5-3 mg/kg • Succinylcholine 1-1.5 mg/kg (in the absence of known allergy, hyperkalaemia, severe acidosis, neuromuscular disease, burns over 48 hours, spinal trauma, and organophosphate poisoning) • Rocuronium: 0.6-0.9 mg/kg in case of succinylcholine contraindication, prolonged stay in the ICU, or risk of neuropathy 6. Sellick maneuver (also known as cricoid pressure is used for endotracheal intubation to prevent the occurrence of gastroesophageal reflux)
Post-Intubation
<ol style="list-style-type: none"> 7. Immediate confirmation of tube placement by capnography 8. Immediate initiation of noradrenaline infusion if diastolic blood pressure <35 mmHg 9. Initiation of long-term sedation 10. Initiation of “protective ventilation”: Tidal volume 6-8 mL/kg, PEEP>5cm H₂O, respiratory rate 10-20 cycles/min, P_{plateau}<30 cmH₂O 11. Recruitment maneuver: CPAP 40 cmH₂O for 40s, FiO₂ 100% (if the patient does not have cardiovascular collapse) 12. Maintenance of cuff pressure at 25-30 cmH₂O
NIV: Non-invasive ventilation, CPAP: Continuous positive airway pressure, ICU: Intensive care unit, PEEP: Positive-end-expiratory pressure

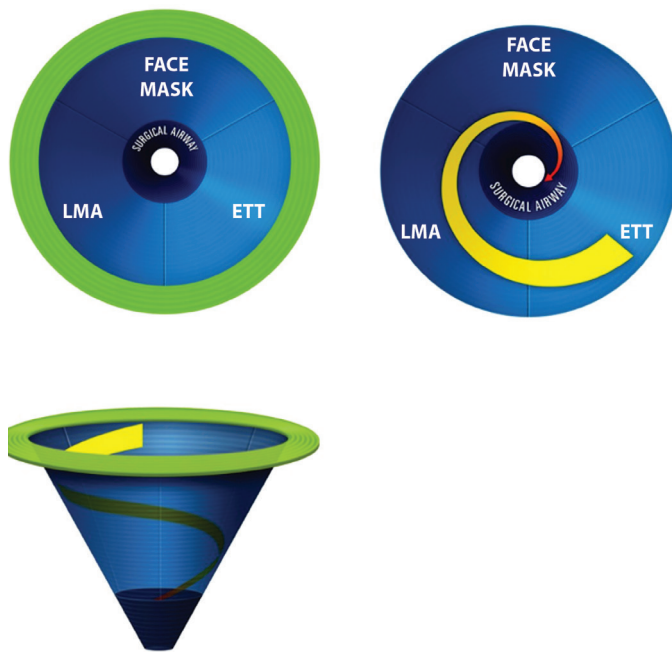


Figure 2: Concept of "Green Zone"

ETT: Endotracheal tube, LMA: Laryngeal mask airway

Delayed Sequence Intubation (DSI)

Unlike rapid sequence intubation, which involves the simultaneous administration of a hypnotic agent and a muscle relaxant without providing ventilation until endotracheal intubation, DSI involves the administration of specific sedative agents with minimal attenuation of spontaneous ventilation or airway reflexes. Another way to conceptualise DSI is to promote mild sedation of the patient while effectively pre-oxygenating under non-invasive ventilation. This technique often uses Ketamine and Continuous Positive Airway Pressure, as described in the Montpellier algorithm (49). After achieving $SpO_2 >95\%$, the muscle relaxant can be administered, and ETI can be performed. In the case of patients in respiratory failure, DSI appears to be a safe and effective alternative to conventional pre-oxygenation (51-54).

Best Practice Recommendations for Airway Management in the ICU [Adapted from the National Audit Project 4 (NAP4) Recommendations (1)].

The NAP4, conducted in the United Kingdom in 2011, was a national project to record all airway-related complications that occurred in the previous year. From this project, which is available for consultation, emerged best practice recommendations in the field of intensive care, described in the Table 5, aiming to

Table 5: NAP4 best practice recommendations for airway management in the ICU	
Capnography	Capnography should be used during endotracheal intubation in all critical patients, regardless of their hospital location. Continuous capnography should be used in all ICU patients who are intubated and ventilator-dependent (including those with tracheostomies). When capnography is not used in the aforementioned situations, there should be documentation of the clinical reason for non-use and regular review of the situation. Training for all ICU staff should include capnography interpretation. The focus of the training should be on airway identification or displacement, as well as recognition of the capnography waveform during cardiac arrest.
Intubation	An intubation checklist should be developed and used for all intubations of critically ill patients. The checklist should include alternative plans.
Anticipation of difficulty and planning	Each ICU should have an algorithm for airway management during intubation, extubation, and reintubation. Patients at risk of airway-related events should be identified early and clearly recognized by the staff. There should be a documented plan for these patients, including the primary plan and alternatives, as well as the necessary additional strategies and equipment. This information should be communicated and validated at each shift change.
Displacement of the endotracheal tube	Staff training should emphasize the recognition and risks of displacement of the endotracheal tube/tracheal cannula. This event is more common in obese patients, those with tracheostomies, during mobilisation, and when sedation is interrupted.
Obesity	Obese critically ill patients should be identified as individuals with an increased risk of airway complications and an elevated risk of associated morbidity (55).
Airway equipment	All ICUs should have immediate access to a difficult airway cart. This cart should have the same content and layout as the one in the operating room. The difficult airway cart should be checked regularly (56,57). A fiberscope should be immediately available for use in the ICU.
Cricothyrotomy	Training for the staff involved in advanced airway management should include regular practice of cricothyrotomies on manikins. Regular identification of anatomical landmarks should be encouraged, especially in obese patients.
Transfers	There should be recognition that intra or inter-hospital transfers are high-risk events, and it is recommended to assess the airway and establish an airway management plan before the transfer.
Staff	Specialty trainees responsible for managing critically ill patients should be proficient in basic management of emergency airways. Additionally, they should always have access to a senior professional with advanced airway expertise.
Training	Specialty trainees responsible for managing critically ill patients should learn basic emergency airway management. This training should include basic airway management, familiarity with algorithms for handling predictable complications, and the use/interpretation of capnography. This training should also serve to identify the limits of each trainee's experience and teach the early need for seeking help from more experienced clinicians. Team training and simulation should be included in this education. Regular audits of airway management issues and other critical events in the ICU should be conducted.

NAP: The National Audit Project 4, ICU: Intensive care unit

improve the quality of care and limit morbidity and mortality related to airway management.

Conclusion

If difficulty in endotracheal intubation is anticipated, consider the feasibility of an alternative initial approach. The use of ILMA, videolaryngoscopy, or bronchofibroscope is associated with high success rates but requires time and the patient's functional reserve.

If the lighted stylet is the chosen technique for initial intubation, it is important to note that the first attempt is always the best. After the second attempt, the risk of complications increases by 85%. Positioning should be optimised as much as possible, and pre-oxygenation is crucial.

Competent airway management depends on integrating individual knowledge, clinical judgment, appropriateness for the patient, and technical skills—factors that evolve throughout each professional's career.

Airway management is a team effort where everyone speaks the same language: training in cognitive tools among all team members and early recognition of the need for a senior anaesthesiologist is crucial to prevent fatal outcomes.

Airway management is not learned in theory: all techniques should be practised in elective settings (in the operating room) or in simulation. Attendance at a DA course is strongly recommended.

Ethics

Authorship Contributions

Surgical and Medical Practices: J.B.-E., B.C.M., Concept: M.K.B., B.C.M., Design: J.B.-E., B.C.M., Data Collection and/or Processing: E.K., M.K.B., Analysis and/or Interpretation: J.B.-E., M.K.B., Literature Search: E.K., B.C.M., Writing: J.B.-E., E.K.

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Short-Term Renal Function Outcomes after Renal Artery Stenting in Atherosclerotic Renal Artery Stenosis

Aterosklerotik Renal Arter Stenozunda Renal Arter Stentleme Sonrası Kısa-Dönem Renal Fonksiyon Sonuçları

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Abstract

Objectives: Renal artery stenosis (RAS) poses significant challenges due to decreased renal perfusion, leading to various disease processes. We aimed to evaluate the safety and effectiveness of renal artery stenting in patients with atherosclerotic RAS, focusing on early renal function changes and identifying factors influencing treatment response.

Materials and Methods: This single-center, retrospective, observational study included patients undergoing renal artery stenting for atherosclerotic RAS over a 10-year period. Clinical and procedural data were analyzed, and renal function outcomes were assessed at the 1-month follow-up. Statistical analysis was performed to identify correlations between patient characteristics, procedural factors, and treatment outcomes.

Results: Forty-nine patients were included, with a mean age of 67.08±8.73 years. Successful stenting was achieved in all patients, with no major adverse clinical events reported. At the 1-month follow-up, 67.3% of patients had stable renal function, while 12.2% showed improvement and 20.4% experienced worsening. A significant correlation was found between age and treatment response (p=0.045). However, no significant associations were observed between changes in renal function and other patient characteristics or procedural factors.

Conclusion: Renal artery stenting in patients with atherosclerotic RAS resulted in successful procedural outcomes with minimal complications. While age was identified as a significant predictor of treatment response, no other patient or procedural factors showed significant correlations with changes in renal function. Our findings emphasize the need for further research to refine patient selection criteria in this population.

Keywords: Renal artery stenosis, renal artery stenting, atherosclerotic RAS, renal function outcomes, patient selection

Öz

Amaç: Renal arter stenozu (RAS), azalmış renal perfüzyon nedeniyle çeşitli hastalık süreçlerine yol açarak önemli zorluklar teşkil etmektedir. Aterosklerotik RAS'li hastalarda renal arter stentlemenin güvenliğini ve etkinliğini değerlendirerek, erken dönem renal fonksiyon değişikliklerine odaklanmayı ve tedavi yanıtını etkileyen faktörleri belirlemeyi amaçladık.

Gereç ve Yöntem: Bu tek merkezli, retrospektif, gözlemsel çalışma, 10 yıllık bir dönemde aterosklerotik RAS için renal arter stentleme yapılan hastaları içermektedir. Klinik ve prosedürel veriler analiz edilmiş ve 1 aylık takipte renal fonksiyon sonuçları değerlendirilmiştir. Hasta özellikleri, prosedürel faktörler ve tedavi sonuçları arasındaki korelasyonları belirlemek için istatistiksel analiz yapılmıştır.

Bulgular: Kırk dokuz hasta dahil edilmiş olup, ortalama yaş 67,08±8,73 yıl olarak belirlenmiştir. Tüm hastalarda başarılı stentleme gerçekleştirilmiş ve majör advers klinik olay bildirilmemiştir. Bir aylık takipte, hastaların %67,3'ünde stabil renal fonksiyon gözlenirken, %12,2'sinde iyileşme ve %20,4'ünde kötüleşme görülmüştür. Yaş ile tedavi yanıtı arasında anlamlı bir korelasyon bulunmuştur (p=0,045). Ancak, diğer hasta özellikleri veya prosedürel faktörler ile renal fonksiyon değişiklikleri arasında anlamlı bir ilişki gözlenmemiştir.

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Sonuç: Aterosklerotik RAS'li hastalarda renal arter stentleme, minimal komplikasyonlarla başarılı prosedürel sonuçlar sağlamıştır. Yaş, tedavi yanıtının önemli bir belirleyicisi olarak tanımlanırken, diğer hasta veya prosedürel faktörler ile renal fonksiyon değişiklikleri arasında anlamlı bir korelasyon bulunamamıştır. Bulgularımız, bu popülasyonda hasta seçim kriterlerini iyileştirmek için daha fazla araştırma yapılması gerektiğini vurgulamaktadır.

Anahtar Kelimeler: Renal arter stenozu, renal arter stentleme, aterosklerotik RAS, renal fonksiyon sonuçları, hasta seçimi

Introduction

Renal artery stenosis (RAS) poses a significant clinical challenge, precipitating a decline in renal perfusion and initiating various pathological cascades (1). The condition directly induces ischemic atrophy due to reduced renal perfusion, while also triggering systemic hypertension and cardiovascular complications through the renin-angiotensin-aldosterone system and the systemic nervous system. These mechanisms collectively contribute to end-organ damage, including glomerulosclerosis (2).

Atherosclerosis stands out as the primary etiology of RAS, detectable on imaging in approximately 50% of patients with coronary artery disease (3). Atherosclerotic renovascular disease carries a substantial mortality rate, predominantly attributable to associated cardiovascular conditions (4-6). It ranks as the second most common cause of fibromuscular dysplasia (FMD) following atherosclerosis (3).

The clinical presentation of organ dysfunction resulting from impaired renal perfusion and its progression remains multifaceted and not entirely understood (4). Presently, the primary management approach for significant RAS primarily involves medical intervention with antihypertensive agents (7). While angioplasty without stenting suffices for FMD-induced RAS, the preferred approach in atherosclerotic stenosis involves concurrent stenting to mitigate potential recoil and restenosis post-angioplasty.

Renal artery stenting remains a contentious topic in the medical literature. Our study seeks to contribute to this ongoing discourse by evaluating the safety and efficacy of renal artery stenting in patients with atherosclerotic RAS and identifying subpopulations poised to derive the greatest benefit.

This single-center, retrospective, observational study aims to assess the early changes in renal function among patients undergoing renal stenting for atherosclerotic RAS at our institution over a decade-long period.

Materials and Methods

Patients aged 18 and above who underwent renal artery stenting at our institution between July 25, 2012, and October 7, 2022, due to RAS exceeding 50%, were included in this study. We opted not to stratify patients based on the degree of stenosis, encompassing all individuals with RAS greater than 50%, aiming to minimize exclusions during our retrospective review.

Exclusion criteria comprised patients with FMD, total arterial occlusion, spontaneous dissection, stenosis in a transplant or bypass graft anastomosis, abdominal aortic aneurysm larger than 45 mm in diameter, and those lacking follow-up after 1 month. This study adhered to the principles outlined in the Declaration of Helsinki.

Approval for the protocol was obtained from the Human Research Ethics Committee of Ankara University Faculty of Medicine (date: 28.01.2023, approval no.: İ02-73-23) the participating hospitals, and written informed consent was acquired from all patients before stent implantation.

Renal artery stenting decisions at our center were made through consensus between the interventional radiologist and the primary clinician following the patient. Stent implantation utilized a standard retrograde femoral approach. Stent deployment adhered to recommended pressure, with stent size selection based on visual assessment. Peri-procedural and post-procedural anticoagulant and antiplatelet therapy followed routine hospital practice and were at the discretion of the treating physician.

The primary endpoint, acute technical success, was defined as angiographic residual diameter stenosis <30%. Secondary endpoints encompassed major complications within 48 hours post-stent implantation and changes in renal function at the 1-month follow-up.

Renal function outcomes were categorized as improvement [$\geq 20\%$ increase in baseline estimated glomerular filtration rate (eGFR)], worsening ($\geq 20\%$ decrease in baseline eGFR), or stabilization (no deterioration).

Major clinical adverse events (MACE) included events necessitating additional procedures, prolonged hospitalization, or death, encompassing deaths within 30 days post-procedure or during hospitalization.

Statistical Analysis

Statistical analysis utilized SPSS version 23.0. Descriptive statistics were presented as mean \pm standard deviation or median (minimum-maximum) for numerical variables and as percentages for categorical variables. Non-parametric data underwent analysis using the Mann-Whitney U test, while categorical variables were assessed using the chi-square test or Fisher's exact test. Statistical significance was considered at $p < 0.05$.

Results

Demographic and clinical characteristics: A total of 49 patients were retrospectively evaluated, with a mean age of 67.08 ± 8.73 years. Among them, 34 (69.4%) were male, and 15 (30.6%) were female. Hypertension was prevalent in 40 (81.6%) patients, diabetes mellitus in 21 (42.9%), hyperlipidemia in 17 (34.7%), and atrial fibrillation in 4 (8.2%). Nineteen (38.8%) patients had a history of previous myocardial infarction. Regarding antihypertensive medication, 19 (38.8%) patients received monotherapy, 21 (42.9%) received combination therapy, and 9 (18.4%) did not use any hypertensive medication. Additionally, 15 (30.6%) patients were using statins, 11 (22.4%) were using insulin, 34 (69.4%) were using antiplatelets, and 2 (4.1%) were taking anticoagulants. The mean estimated eGFR before the procedure was 77.31 ± 36.98 , and the mean creatinine value was 1.35 ± 0.52 mg/dL.

Renal artery stenting was performed on the left side in 23 (46.9%) patients, on the right side in 19 (38.8%), and bilaterally in 7 (14.3%) patients. The mean stent diameter used was 5.54 ± 0.64 mm, with a mean stent length of 16.38 ± 5.36 mm. Successful stenting was achieved with less than 30% residual stenosis in all patients, and no major MACE were observed.

Thirty-three (67.3%) patients maintained stable renal function, while improvement was noted in 6 (12.2%) patients, and 10 (20.4%) patients experienced worsening post-stenting. No significant correlations were found between changes in renal function and patient characteristics or procedural data, including gender, comorbidities, medication use, pre-procedural renal function parameters, stent characteristics, or side of stenting (all $p > 0.05$).

At the 1-month follow-up, patients with improved renal function (12.2%) had a mean age of 63.17 ± 12.15 years, while those with stable renal function (67.35%) had a mean age of 67.00 ± 8.56 years, and patients with worsened renal function (20.4%) had a mean age of 69.70 ± 6.80 years. Statistical analysis revealed a significant correlation between age and treatment response ($p = 0.045$).

Discussion

RAS presents a complex clinical scenario characterized by diminished renal perfusion and subsequent renal dysfunction. Patients with RAS often exhibit parenchymal changes such as interstitial fibrosis, tubular atrophy, glomerulosclerosis, periglomerular fibrosis, and arteriolar abnormalities (8). The optimal approach to managing RAS, whether through medical or interventional therapy, remains a subject of debate in the literature (9,10).

The STAR trial, focusing on 140 patients over 2 years, did not demonstrate a clear benefit of stenting over medical treatment alone (11). Similarly, the ASTRAL trial involving 806 patients and the CORAL trial with 947 patients found no significant differences in renal or cardiovascular outcomes between stenting and medical therapy alone (1,12). Moreover, The STAR trial reported a significant increase in procedure-related complications (11). These trials collectively suggest that renal artery stenting may not provide additional benefits when added to high-quality medical therapy.

However, recent insights from the CORAL trial's 5-year follow-up introduced the urine albumin-to-creatinine ratio (UACR) as a potential marker for treatment response. This metric proposes that patients with RAS and healthy kidneys may benefit from stenting, while those with poor organ function, indicated by an elevated UACR, may not. Our study's correlation between age and treatment response aligns with this hypothesis, suggesting that younger patients with healthier kidneys may experience improved renal function following stenting (13).

Our study may contribute to the patient selection process in managing RAS with renal artery stenting. Notably, our findings indicate that, in experienced hands, the risk of complications can be minimal.

Study Limitations

Nevertheless, our study acknowledges several limitations, including its retrospective design, lack of stratification based on stenosis severity, and short-term follow-up. Additionally, the multifactorial nature of eGFR changes underscores the need for cautious interpretation. Similar to prior literature, our findings suggest that stent placement may not consistently improve early renal function, emphasizing the necessity for rigorous patient selection criteria. Incorporating patient age into these criteria may offer valuable insights into treatment response and guide personalized management strategies for atherosclerotic RAS.

Conclusion

Our study supports the safety and potential benefits of renal artery stenting in preventing kidney function decline in select patient populations. Determining factors such as UACR and age may be beneficial in selecting suitable candidates for stent intervention. Future studies should aim to address these limitations by employing rigorous patient stratification methods, longer follow-up periods, and comprehensive outcome assessments to provide further insights into the optimal management of RAS.

Ethics

Ethics Committee Approval: The study was carried out with the permission of Ankara University Faculty of Medicine Human Research Ethics Committee (date: 28.01.2023, approval no.: İ02-73-23, registration no: 2023/40).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients. However, patients' procedure consents were available.

Authorship Contributions

Surgical and Medical Practices: E.C.Ç., S.B., Concept: E.U.B., E.C.Ç., Ö.A.Ç., K.A., E.Ö., S.B., Design: E.U.B., E.C.Ç., Ö.A.Ç., K.A., E.Ö., S.B., Data Collection and/or Processing: E.U.B., E.C.Ç., Analysis and/or Interpretation: E.U.B., E.C.Ç., Literature Search: E.U.B., E.C.Ç., Writing: E.U.B., E.C.Ç.

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Vertebral Artery Origin Stenosis in Patients with Posterior Circulation Strokes Due to Large Artery Atherosclerosis

Büyük Arter Aterosklerozuna Bağlı Posterior Dolaşımda İnmesi Olan Hastalarda Vertebral Arter Orjin Stenozları

© Seyda Erdoğan¹, © Turgut Şahin¹, © Mine Hayriye Sorgun¹, © Tuğra Karaaslan¹, © Zerin Özaydın Aksun¹, © Eray Yalap¹,
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Abstract

Objectives: The origin of the extracranial vertebral artery (V1 segment) is a common site for large artery atherosclerosis (LAA). The aim of this study was to determine the risk factors, prevalence and prognosis of the patients presented with acute ischemic stroke due to vertebrobasilar atherosclerosis and additional V1 stenosis.

Materials and Methods: We reviewed the charts of 957 patients who were admitted with acute ischemic stroke between the dates January 2011 and May 2017, and selected cases with stroke related to posterior circulation (PC) atherosclerosis. The demographic data, risk factors, National Institutes of Health Stroke Scale (NIHSS) scores at admission, and modified Rankin scores (mRS) in the follow-up period were recorded.

Results: There were 80 (8.36%) patients with acute ischemic stroke in the PC due to LAA. Thirty (37.5%) patients [9 females (30%), mean age 67.4±14.3 years] had V1 stenosis. No between group differences in the history of vascular risk factors and mRS scores during the follow-up period were observed ($p>0.05$). In logistic regression analysis, the admission NIHSS score was higher in patients with V1 stenosis than others ($p=0.022$).

Conclusion: In our registry, more than one third of patients with acute PC stroke due to LAA had stenosis in the origin of the vertebral artery. The patients with coexisting V1 stenosis presented with relatively severe stroke.

Keywords: Vertebral artery origin, posterior circulation strokes, large artery atherosclerosis

Öz

Amaç: Ekstrakraniyal vertebral arterin orjini (V1 segmenti), büyük arter aterosklerozunun sık görüldüğü bir bölgedir. Bu çalışmanın amacı vertebrobaziler aterosklerozu ve ek olarak V1 stenozu nedeniyle akut iskemik inme geçiren hastaların risk faktörlerini, prevalansını ve prognozunu belirlemektir.

Gereç ve Yöntem: Ocak 2011 ile Mayıs 2017 tarihleri arasında akut iskemik inme nedeniyle başvuran 957 hastanın dosyaları incelendi ve posterior dolaşım aterosklerozuna bağlı inme geçiren hastalar çalışmaya dahil edildi. Demografik veriler, risk faktörleri, başvuru anındaki Ulusal Sağlık İnme Ölçeği (NIHSS) skorları ve takip dönemindeki modified Rankin scores (mRS) değerleri kaydedildi.

Bulgular: Büyük arter aterosklerozu nedeniyle arka sirkülasyonda akut iskemik inme geçiren 80 (%8,36) hasta vardı. [Otuz (%37,5) hastada 9 kadın (%30), ortalama yaş 67,4±14,3 yıl] V1 darlığı vardı. Vasküler risk faktörleri öyküsü ve takip süresi boyunca mRS skorları açısından gruplar arasında fark gözlenmedi ($p>0,05$). Lojistik regresyon analizinde V1 darlığı olan hastaların başvuru NIHSS skoru diğerlerine göre daha yüksekti ($p=0,022$).

Sonuç: Merkezimizde büyük arter aterosklerozuna bağlı akut posterior sirkülasyon inmesi geçiren hastaların üçte birinden fazlasında vertebral arter çıkışında darlık vardı. Eşlik eden V1 darlığı olan hastalar nispeten daha şiddetli inme ile başvurmuştu.

Anahtar Kelimeler: Vertebral arter orjini, posterior dolaşım inmeleri, büyük arter aterosklerozu

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Introduction

Prognosis and clinical management differ significantly among stroke subgroups according to anatomical localization and infarct mechanism in patients with acute ischemic stroke. One fifth of strokes and transient ischemic attacks (TIA) occur in the posterior circulation (PC) area (1). The most common causes of PC ischemia are large artery atherosclerosis (LAA), cardiac embolism and small vessel occlusion (2,3).

Anatomically, the vertebral artery is traditionally evaluated in four parts (V1-4). The first segment (V1) is the part from the origin of the vertebral artery to the foramen in the transverse processes of the fifth or sixth cervical vertebra. In the PC, atherosclerosis usually occurs at the origin of the vertebral artery. Autopsy and angiography studies have shown that up to 40% of patients with cardiovascular risk factors have stenosis or occlusion at the origin of the vertebral artery (2-4). Moreover, V1 segment stenosis of the vertebral artery accounts for almost 20% of PC strokes (2).

This study aimed to investigate the prevalence, demographic and clinical characteristics of ischemic stroke patients diagnosed with vertebral artery V1 stenosis due to LAA.

Materials and Methods

The medical records of patients hospitalized with a diagnosis of acute ischemic stroke at the Ankara University Faculty of Medicine Neurology Department between January 2011 and May 2017 were reviewed. Age, gender, drug history, vascular risk factors [hypertension (HT), diabetes mellitus (DM), hyperlipidemia (HL), atrial fibrillation (AF), coronary artery disease (CAD), congestive heart failure (CHF) and malignancy], history of stroke or TIA, history of myocardial infarction in the last month, recurrent stroke status, admission National Institutes of Health Stroke Scale (NIHSS) score, pre-stroke and follow-up modified Rankin scores (mRS), and laboratory results were recorded. The etiologic workup included cerebral and cervical vascular imaging studies [carotid Doppler ultrasonography, computerized tomography angiography, magnetic resonance angiography, or digital subtraction angiography (DSA)], transthoracic or transesophageal echocardiography, 24-hour cardiac rhythm monitoring, and laboratory tests for hypercoagulability and vasculitis. Automated Causative classification of stroke system was used to determine the etiological type of ischemic stroke (5). Patients with acute ischemic stroke in the PC due to LAA (PC infarction-LAA) were included in the study.

The Ankara University Faculty of Medicine Clinical Research Ethics Committee granted ethical approval for this study (date: 27.05.2019, approval no.: 10-772-19) and the study was

conducted in accordance with the ethical standards of the Declaration of Helsinki.

Statistical Analysis

The analysis of the data was made in the SPSS for Windows 15 package program. Descriptive statistics are shown as mean \pm standard deviation for variables with normal distribution, and as median (minimum-maximum) for variables with non-normal distribution, and nominal variables are shown as number of cases and percentage (%). The significance of the difference between the two groups in terms of means was investigated with the t-test, and the significance of the difference in terms of median values was investigated with the Mann-Whitney U test. Nominal variables were evaluated with Pearson's chi-square or Fisher's exact test. Logistic regression analysis was performed for the risk factors affecting the dependent variable. Results for $p < 0.05$ were considered statistically significant.

Results

We reviewed the charts of 957 patients who were admitted with acute ischemic stroke between January 2011 and May 2017. A total of 80 (8.36%) patients had acute ischemic stroke in the PC due to LAA.

Thirty (37.5%) patients [27 females (90%), mean age 67.4 ± 14.3 years] had symptomatic V1 stenosis and 15 (18.75%) patients [13 females (86.7%), mean age 68.2 ± 18.05 years] of them had isolated V1 stenosis.

We compared the patients with acute ischemic stroke in the PC due to LAA with and without V1 stenosis. No between group differences in history of vascular risk factors and mRS in the follow-up period were observed ($p > 0.05$). The admission NIHSS score was higher in patients with V1 stenosis ($p = 0.049$). Serum C-reactive protein (CRP) levels were higher in patients without V1 stenosis, whereas serum magnesium levels were higher in patients with V1 stenosis. The demographic data, clinical and laboratory results are summarized in Table 1.

The distribution of arteries with significant stenosis in the PC is shown in Table 2.

In logistic regression analysis, admission NIHSS scores and serum magnesium levels were still significantly higher in patients with V1 stenosis ($p < 0.05$) (Table 3). The mean admission NIHSS score \pm standard deviation in patients with coexisting V1 stenosis was 11.5 ± 11.7 , while it was 4.88 ± 4.55 in patients without V1 stenosis ($p = 0.001$). The admission NIHSS score was significantly higher in patients with coexisting V1 stenosis in logistic regression analysis ($p = 0.018$).

Table 1: Demographic and clinical characteristics of patients with acute posterior circulation stroke due to large artery atherosclerosis			
	PC-LAA with V1 stenosis n=30	PC-LAA without V1stenosis n=50	p value
Age, year, mean \pm SD	67.4 \pm 14.3	65.8 \pm 13.1	0.38
Sex, n (%)			
- Female	9 (30)	24 (48)	0.088
- Male	21 (70)	26 (52)	
Stroke/TIA, n (%)	21 (70)/9(30)	28 (56)/22 (44)	0.157
Medical history			
- Hypertension, n (%)	22 (73.3)	40 (80)	0.336
- Diabetes mellitus, n (%)	9 (30)	21(42)	0.102
- Atrial fibrillation, n (%)	1 (3.3)	1 (2)	0.137
- Hyperlipidemia, n (%)	10 (33.3)	15 (30)	0.472
- CAD, n (%)	4 (13.3)	14 (28)	0.105
- CHF, n (%)	0 (0)	3 (6)	0.239
- Previous TIA history, n (%)	2 (6.7)	1 (2)	0.208
- Previous stroke history, n (%)	3 (10)	10 (20)	0.741
Admission NIHSS, mean \pm SD	4.9 \pm 4.5	4.9 \pm 5.1	0.825
Median	5	3.5	0.049
(Min-Max)	(0-26)	(0-14)	
Hospital mortality, n (%)	4 (13.3)	8 (16)	0.105
Follow up mRS, Mean \pm SD	1.79 \pm 2.3	2.61 \pm 2.3	0.515
Median	1	1	
(Min-Max)	(0-6)	(0-6)	
Recurrent stroke, n (%)	2 (6.7)	8 (16)	0.762
LDL, mg/dL, mean \pm SD	112.38 \pm 50.2	120.24 \pm 49.6	0.967
CRP, mg/dL, mean \pm SD	8.74 \pm 5.92	16.97 \pm 16.19	0.017
Mg mg/dL, mean \pm SD	2.72 \pm 3.58	2.02 \pm 0.23	0.019

SD: Standard deviation, TIA: Transient ischemic attack, CAD: Coronary artery disease, CHF: Congestive heart failure, NIHSS: National Institutes of Health Stroke Scale, mRS: The modified Rankin scale, LDL: Low-density lipoprotein, CRP: C-reactive protein, Mg: Magnesium, Min-Max: Minimum-maximum, PC-LAA: Acute ischemic stroke in the posterior circulation due to large artery atherosclerosis

Table 2: Distribution of arteries with significant stenosis in patients with acute ischemic stroke in the posterior circulation due to large artery atherosclerosis			
	PC-LAA with V1 stenosis n=30	PC-LAA without V1 stenosis n=50	p value
Isolated V1 stenosis	15 (50%)	-	
V2 stenosis	14 (46.6%)	3 (6%)	<0.001
V3 stenosis	12 (40%)	1 (2%)	<0.001
V4 stenosis	14 (46.6%)	27 (54%)	0.5
BA stenosis	6 (20%)	8 (16%)	0.64
PCA stenosis	9 (30%)	12 (24%)	0.55

PC-LAA: Acute ischemic stroke in the posterior circulation due to large artery atherosclerosis, BA: Basiler artery, PCA: Posterior cerebral artery, V: Vertebral artery

Table 3: Logistic regression analysis of PC-LAA with V1 stenosis			
	Beta	95%, confidence interval	p value
Admission NIHSS, mean \pm SD	0.006	0.001-0.012	0.022
Mg mg/dL, mean \pm SD	0.051	0.036-0.066	<0.001

SD: Standard deviation, PC-LAA: Acute ischemic stroke in the posterior circulation due to large artery atherosclerosis, NIHSS: National Institutes of Health Stroke Scale

Discussion

Various vascular structures belonging to the intra- or extracranial as well as anterior or PC may be affected in ischemic stroke. Etiological, clinical and prognostic features may vary depending on the vascular structures affected by atherosclerotic stenosis (6). Investigating the subtypes of ischemic stroke according to the affected vessel and underlying causes may be beneficial in terms of better understanding the risk factors and clinical features of the disease.

In PC ischemic strokes, there may be different underlying causes, including cardio-embolism, LAA and small vessel disease (7). The rate of large vessel disease as the etiology of PC ischemic strokes varies among studies depending on the diagnostic criteria used and the diagnostic methods performed (8). Large artery disease was responsible for 32% of posterior cerebral artery territory infarcts in the New England Medical Center PC Registry (2).

LAA is defined as >50% stenosis or occlusion of a large cervical or cerebral artery (9). In the PC, atherosclerosis commonly occurs at the origin of the vertebral artery (7). However, atherosclerosis can also occur in the distal vertebral, basilar and posterior cerebral arteries. In this study, we focused on posterior system strokes due to LAA. We investigated whether there were differences in the demographic and clinical characteristics between patients with and without V1 stenosis.

Vertebral artery stenosis (24.8%) ranks second among extracranial stenosis after internal carotid stenosis (59.4%) (10). The rate of V1 stenosis among patients with acute ischemic stroke in the PC due to LAA was 37.5% in our registry. In a prospective cross-sectional study conducted in Iran examining 3703 acute stroke patients, vascular imaging with DSA was performed in 342 patients with large vessel disease, and stenosis was detected in the extracranial segment of the right and/or left vertebral artery in 32% of them (10). The researchers noted that these results were similar to the North American and European data. Similarly, in the Oxford Vascular Study, severe stenosis of the vertebral or basilar artery was responsible for 26% of patients with posterior system minor stroke or TIA (11).

Although male dominance was noted in patients with V1 stenosis (70% vs. 52%), no statistically significant difference was detected between the two groups in terms of age and gender. There was also no group difference in the history of vascular risk factors, including HT, AF, DM and HL as well as history of CAD and CHF. In this study, median admission NIHSS score was higher in patients with V1 stenosis ($p=0.049$) suggesting that stroke may be clinically more severe in patients with coexisting V1 stenosis. The higher frequency of additional vertebrobasilar stenosis (V2, V3 segment, basilar artery and posterior cerebral

artery) in half of the patients with V1 segment stenosis included in the study may be related to the higher severity of stroke and high NIHSS scores in this group.

Signs and symptoms seen in PC infarcts include dizziness, vertigo, dysarthria, diplopia, dysphagia, nausea or vomiting, impaired consciousness, weakness, ataxia and nystagmus (2,3). However, in our study, we did not analyze which symptoms and findings were responsible for the higher NIHSS scores in patients with V1 stenosis. Although patients with V1 stenosis had a higher admission NIHSS score, there was no difference between the two groups in terms of hospital mortality rates and mRS scores or recurrent strokes at follow-up. In patients without V1 stenosis, presentation with TIA was more common (46% vs. 30%). However, the difference between the two groups in terms of stroke or TIA presentation was not significant.

Interestingly, serum CRP levels were higher and serum magnesium levels were lower in patients without V1 stenosis when compared with patients with V1 stenosis. Both higher CRP and lower magnesium (Mg) levels may be associated with an increased risk for atherosclerosis (12,13). On the other hand, both may point to poor prognosis in patients with stroke (14-16). A recent study revealed that although admission NIHSS scores were similar between patients with normal and high CRP levels, high CRP levels could predict poor prognosis (15). In our study, the admission NIHSS score was lower in patients without V1 stenosis, even though serum CRP levels were higher and serum magnesium levels were lower. The outcomes were similar in both groups despite these differences.

Conclusion

This study is a retrospective study and included only a small number of patients from a single center; therefore, the results should be interpreted cautiously. However, we can conclude that PC stroke with coexisting V1 stenosis may be associated with stroke severity in the acute stage. The associations between localization of stenosis, stroke severity and serum biomarkers, including CRP and Mg levels need to be further investigated which may help to understand the pathogenesis and choose better prevention and treatment methods.

Ethics

Ethics Committee Approval: The Ankara University Faculty of Medicine Clinical Research Ethics Committee granted ethical approval for this study (date: 27.05.2019, approval no.: 10-772-19).

Informed Consent: This study is a retrospective study and included only a small number of patients from a single center; therefore, the results should be interpreted cautiously. However, we can conclude that PC stroke with coexisting V1 stenosis may be associated with stroke severity in the acute stage.

Authorship Contributions

Concept: S.E., C.T.I., M.H.S Design: S.E., C.T.I., M.H.S Data Collection and/or Processing: T.Ş., M.H.S., T.K., Z.Ö.A., E.Y., O.B., B.Ö., A.Y.Y., Z.Y., C.Ö., A.N., M.E., E.A., T.A., Analysis and/or Interpretation: M.E, Literature Search: S.E., C.T.I., Writing: S.E., C.T.I., M.H.S

Conflict of Interest: There is no potential conflict of interest to declare.

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Evaluation of Odontoid Process Bone Quality with Hounsfield Unit Values in the Adult Population

Erişkin Popülasyonda Hounsfield Ünitesi Değerleri ile Odontoid Proses Kemik Kalitesinin Değerlendirilmesi

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Abstract

Objectives: In this study, the aim is to investigate the changes in bone density and quality of the odontoid tip, neck and second cervical vertebral body located beneath the base of odontoid with advancing age.

Materials and Methods: Seven study groups were formed, each consisting of healthy individuals in the age ranges of 18-29, 30-39, 40-49, 50-59, 60-69, 70-79, and 80 years and above. The odontoid bone structure of each individual was identified on cervical computed tomography images in both sagittal and coronal planes. Mean Hounsfield unit (HU) values were calculated for the odontoid tip, odontoid neck, and the C2 body portion below the odontoid base areas in both midsagittal and midcoronal planes. The HU values were compared and analyzed.

Results: There is a significant, negative correlation between age and the HU values measured in the sagittal plane for the odontoid tip, odontoid neck, and C2 vertebral body portion under the odontoid base (the correlation coefficients are -0.795 r, -0.766 r, and -0.789 r, respectively). Similarly, there is a significant, negative correlation between age and the HU values measured in the coronal plane for the odontoid tip, odontoid neck, and C2 vertebral body portion under the odontoid base (the correlation coefficients are -0.836 r, -0.680 r, and -0.802 r, respectively). These results indicate that as age increases, the quality of the odontoid bone decreases.

Conclusion: The assessment of bone quality through computed tomography, based on HU values, reveals a significant decrease in the bone quality of both the odontoid bone and C2 vertebral body with increasing age.

Keywords: Odontoid bone, odontoid fractures, Hounsfield unit

Öz

Amaç: İlerleyen yaş ile birlikte odontoid proses fraktürlerindeki artışın kemik kalitesinin zaman içinde azalması ile ilişkili olabileceği gösterilmektedir. Bu çalışmada, ilerleyen yaşla birlikte odontoid proses, boyun ve ikinci servikal vertebra gövdesindeki kemik yoğunluğu ve kalitesindeki değişikliklerin araştırılması amaçlanmıştır.

Gereç ve Yöntem: Her biri 18-29, 30-39, 40-49, 50-59, 60-69, 70-79 ve 80 yaş ve üzeri sağlıklı bireylerden oluşan yedi çalışma grubu oluşturuldu. Her bireyin odontoid kemik yapısı bilgisayarlı tomografi görüntülerinde tanımlandı. Ortalama Hounsfield ünitesi (HU) değerleri odontoid proses, odontoid boynu ve C2 gövde kısmı için hem midsagittal hem de midkoronal planlarda hesaplandı. Elde edilen veriler söz konusu 7 grup arasında karşılaştırıldı ve istatistiksel olarak analiz edildi.

Bulgular: Yaş ile odontoid proses, odontoid boynu ve C2 vertebra gövdesi kısmı için sagittal düzlemde ölçülen HU değerleri arasında anlamlı, negatif bir korelasyon vardı (korelasyon katsayıları sırasıyla -0,795 r, -0,766 r ve -0,789 r'dir). Benzer şekilde, yaş ile odontoid ucu, odontoid boynu ve odontoid tabanının altındaki C2 vertebra gövdesi kısmı için koronal düzlemde ölçülen HU değerleri arasında anlamlı, negatif bir korelasyon vardı (korelasyon katsayıları sırasıyla -0,836 r, -0,680 r ve -0,802 r'dir). Bu sonuçlar, yaş arttıkça odontoid kemiğin kalitesinin azaldığını göstermektedir.

Sonuç: HU değerlerine dayalı olarak bilgisayarlı tomografi ile kemik kalitesinin değerlendirilmesi, artan yaşla birlikte hem odontoid kemiğin hem de C2 vertebra gövdesinin kemik kalitesinde önemli bir düşüş olduğunu ortaya koymaktadır.

Anahtar Kelimeler: Odontoid kemik, odontoid kırıklar, Hounsfield ünitesi

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Introduction

The odontoid process is a specific bony projection of the second cervical vertebra (C2), also known as axis, and it projects superiorly from the C2 vertebral body to articulate with the anterior arch of the first cervical vertebra (C1), also known as atlas (1). The joint between C1 and C2 is stabilized by numerous special and strong ligament structures, including the tectorial membrane, transverse ligament, alar ligaments, apical ligaments, and accessory ligaments (2). Bone and ligament structures located in the atlantoaxial region are crucial for maintaining the stability of this segment (3).

Fractures in the upper cervical region are a frequent consequence of cervical trauma, and odontoid fractures are present in approximately 18% of all cervical trauma cases (4). This percentage rises to over 50% in the population aged >80 years (4). The most commonly used classification for odontoid fractures today is the Anderson and D'Alonzo classification (4,5). Odontoid fractures are categorized as type 1 for odontoid tip fractures, type 2 for odontoid base fractures, and type 3 for fractures extending into the C2 vertebral body (4,5). Type 2 odontoid fractures represent the most prevalent subtype among these injuries (6).

The management of odontoid fractures is still not definitively established, and treatment selection varies depending on factors like fracture type, patient age, and the quality of the odontoid bone (7,8). The increased life expectancy has resulted in a higher prevalence of osteoporosis, leading to an elevated risk of fractures, particularly in the elderly population, due to the reduction in odontoid bone quality (8).

There are various radiological methods used to assess bone quality and strength, and one of the most commonly used and gold standart method is dual X-ray absorptiometry (DXA) (9). However, in recent years, the success and reliability of measuring bone Hounsfield unit (HU) values on computed tomography (CT) for assessing bone quality have been demonstrated, and calculating HU values has confidently become a method used to measure bone quality (10). There is a correlation between low bone HU values and osteoporotic fractures, screw loosening, and the development of pseudarthrosis risks. Therefore, in spinal surgery, HU values play a significant role in diagnosis, determining the treatment method, and follow-up (10). In this study, the age-related changes in odontoid bone HU values in the adult age groups will be investigated. Consequently, the alteration of odontoid fracture risk with age in adult population will be elucidated.

Materials and Methods

Study Population

This retrospective study was approved by Ankara University Human Research Ethics Committee (decision no.: İ10-705-23, date: 21.11.2023). The study population consists of 70 healthy adults (35 males, 35 females). The individuals included in the study were randomly selected. In the study, there are a total of 7 groups based on age: Group 1 (18-29 years), Group 2 (30-39 years), Group 3 (40-49 years), Group 4 (50-59 years), Group 5 (60-69 years), Group 6 (70-79 years), and Group 7 (80 years and older). For each group, 10 healthy individuals were randomly selected and included in the study.

Measured Parameters

The odontoid bone structure of each individual was identified on cervical CT images in both sagittal and coronal planes. Mean HU values were calculated for the odontoid tip, odontoid neck, and the C2 body portion below the odontoid base areas in both midsagittal and midcoronal planes (Figure 1). The obtained HU values were compared among the mentioned 7 groups, revealing intergroup differences and demonstrating the changes in odontoid bone quality with advancing age.

Statistical Analysis

The statistical analysis was conducted using the SPSS 22.0 software program for Windows. The results were evaluated at a 95% confidence interval, and a p value less than 0.05 was considered statistically significant. To investigate the correlation between age and odontoid bone HU values, both Pearson's correlation test and Spearman's rho correlation test were utilized.

Results

Groups 1, 2, 3, 4, 5, 6, and 7 consist of patients in the age groups of 18-29, 30-39, 40-49, 50-59, 60-69, 70-79, and >80, respectively. Each group includes 10 subjects, with 5 females and 5 males. The mean age values for individuals in groups 1, 2, 3, 4, 5, 6, and 7 are, respectively, 25, 34.9, 45.1, 54.7, 64.5, 73.9, and 84.3 years with standart deviations of groups were as follows: 2,9; 2,7; 2,8; 2,7; 2,2; 2,2; 2,2 respectively. The mean age value for all patients in the study population is 54.6.

For all patients in the study population, the mean sagittal plane HU values are 806.4 for the odontoid tip, 568.8 for the odontoid neck, and 561.6 for the C2 vertebral body area below the odontoid base. The mean coronal plane HU values for the same areas are 800.3, 559.2, and 563.1, respectively.

The distribution of mean HU values for the odontoid tip in the sagittal plane is examined based on groups, the values are



Figure 1: A) Midsagittal, and B) mid-coronal sections. The circles indicated by red arrows, from top to bottom, respectively, encompass the odontoid tip, odontoid neck, and the areas below the odontoid base

as follows: Group 1: 902.2, Group 2: 900, Group 3: 901.3, Group 4: 847.2, Group 5: 770.8, Group 6: 684.3, and Group 7: 639.6. Distribution of mean HU values for the odontoid neck in the sagittal plane across groups is as follows: Group 1: 666.3, Group 2: 636.3, Group 3: 618.8, Group 4: 606, Group 5: 570.4, Group 6: 477.8, and Group 7: 406.3. Mean HU values for the C2 vertebral body segment below the odontoid base were examined in the sagittal plane, and the distribution for each group is as follows: Group 1: 655.9, Group 2: 635.8, Group 3: 615.7, Group 4: 601.3, Group 5: 567.3, Group 6: 465.2, and Group 7: 390.6. The graph illustrating the distribution of sagittal plane HU values for the odontoid tip, odontoid neck, and C2 vertebral body in all patients included in the study is presented in Figure 2. Figure 2 demonstrates that HU values decrease with increasing age.

When examining the distribution of mean HU values for the odontoid tip in the coronal plane, Group 1 has a value of 895.6, Group 2: 904.1, Group 3: 899, Group 4: 836.4, Group 5: 762.6, Group 6: 681, and Group 7: 623.9. Examining the distribution of mean HU values for the odontoid neck in the coronal plane, Group 1 has a value of 611.7, Group 2: 612.3, Group 3: 618.9, Group 4: 602, Group 5: 564.3, Group 6: 496.9, and Group 7: 408.5. Examining the distribution of mean HU values for the C2 vertebral body located under the odontoid base in the coronal plane, Group 1 has a value of 660.1, Group 2: 633.2, Group 3: 615.5, Group 4: 600.1, Group 5: 573.7, Group 6: 463.9, and Group 7: 395.8. The graph illustrating the distribution of coronal plane HU values for the odontoid tip, odontoid neck, and C2 vertebral body in all patients included in the study is presented in Figure 3.

There is a significant, negative correlation between age and the HU values measured in the sagittal plane for the odontoid tip, odontoid neck, and C2 vertebral body portion under the

odontoid base (the correlation coefficients are -0.795 r, -0.766 r, and -0.789 r, respectively). Similarly, there is a significant, negative correlation between age and the HU values measured in the coronal plane for the odontoid tip, odontoid neck, and C2 vertebral body portion under the odontoid base (the correlation coefficients are -0.836 r, -0.680 r, and -0.802 r, respectively). These results indicate that as age increases, the quality of the odontoid bone decreases.

Discussion

Odontoid fractures are commonly encountered after the age of 65 and are the most frequent axis fractures in the

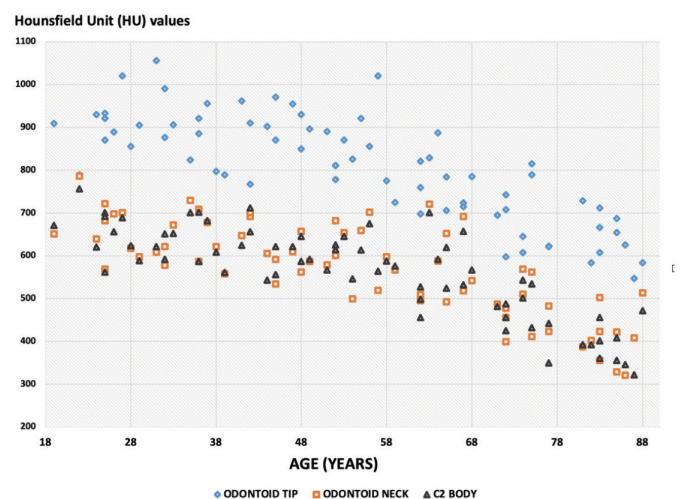


Figure 2: The distribution of sagittal plane Hounsfield unit values for the odontoid tip (blue rectangles), odontoid neck (orange squares), and C2 vertebral body under the odontoid base (black triangles) based on age
C2: Second cervical vertebra

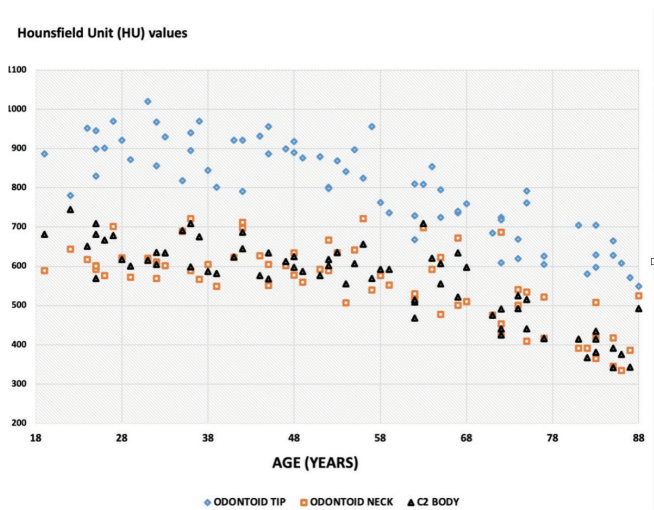


Figure 3: The distribution of coronal plane Hounsfield unit values for the odontoid tip (blue rectangles), odontoid neck (orange squares), and C2 vertebral body under the odontoid base (black triangles) based on age C2: Second cervical vertebra

elderly population (11). The treatment of these fractures is generally managed through surgical intervention or the use of cervical orthosis (11,12). In the elderly population, surgical treatment carries increased risks and lower success rates due to accompanying medical comorbidities and poor bone quality (11). Similarly, non-surgical treatment is more prone to non-union risks due to the same reasons (11). The surgical treatment of odontoid fractures is generally categorized into two main approaches: anterior and posterior techniques (13). The choice of approach for treatment is determined by considering various factors such as the direction of fracture extension, presence of accompanying osteoporosis, bone quality, and the age of the patient (13).

Clinically, lower bone mineral density and bone quality and accompanying osteoporosis is associated with a increased risk of bone fractures (14). To assess bone quality and measure bone mineral density, the most commonly used and widely accepted method today is DXA, considered the gold standard (15). However, numerous recent studies indicate that measurements of HU using CT are correlated with DXA and are highly successful in demonstrating bone quality, fracture risk, the presence of osteoporosis, or the existence of accompanying metabolic bone diseases (15-17). HU values, especially in the femoral neck and lumbar vertebrae, are calculated to investigate bone quality and mineral density, and its success in this regard has been widely recognized (18). HU values have been calculated to investigate the results of various techniques, including C1-C2 posterior fixation, pedicle and lateral mass screwing, translaminar screwing, and have been presented in the literature (16,19).

In the literature, there are many morphometric studies examining the anatomy of the C2 joint (20). In particular, odontoid fracture examination studies using multi dimensional and 3-dimensional CT reconstruction methods have an increasingly more popular place in the literature (21,22). These studies have pioneered radiomorphological studies, which are important in understanding the biophysics of odontoid fractures (23).

In this study, HU values were calculated for the odontoid parts corresponding to the bone regions used in the classification of odontoid fractures, and the changes in these values with increasing age were investigated. Thus, the regions with the highest bone quality of the odontoid bone were identified, and the decline in bone quality in advanced age was demonstrated.

Conclusion

The assessment of bone quality through CT, based on HU values, reveals a significant decrease in the bone quality of both the odontoid bone and C2 vertebral body with increasing age. This finding substantiates the increased occurrence of odontoid fractures in the elderly population when compared to younger individuals.

Ethics

Ethics Committee Approval: This retrospective study was approved by Ankara University Human Research Ethics Committee (decision no.: İ10-705-23, date: 21.11.2023).

Informed Consent: Retrospective study.

Authorship Contributions

Surgical and Medical Practices: B.C.A., Ü.E., Concept: Y.Ş.Ç., Design: Ö.M.Ö., Data Collection and/or Processing: E.B., Literature Search: M.Z., Writing: B.C.A., M.Z.

Conflict of Interest: According to the authors, there are no conflicts of interest related to this study.

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Total Neoadjuvant Tedavi Alan Rektum Kanseri Hastalarında Çinko Düzeyi ve Patolojik Yanıt İlişkisi

The Relationship Between Zinc Level and Pathological Response in Rectum Cancer Patients Receiving Total Neoadjuvant Therapy

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Öz

Amaç: Total neoadjuvan tedavi (TNT) rektum kanserlerinde altın standart olarak kullanılmaktadır. Çinkonun hücre siklusu üzerinde, hücre içi yollarla hücre proliferasyonu üzerinde etkili olduğu bilinmektedir. Çalışmamız çinko düzeyinin TNT alan rektum kanserli hastalarda yanıt ile ilişkisinin araştırılması amacıyla planlanmıştır.

Gereç ve Yöntem: Ankara Üniversitesi Tıp Fakültesi, Tıbbi Onkoloji Bilim Dalı'nda TNT almış rektum kanserli 29 hastanın bilgileri retrospektif olarak toplandı ve tedavi yanıtı ile ilişkisi değerlendirildi. İstatistiksel analiz klasik yöntemler ve Bayesci analiz ile yapıldı.

Bulgular: On sekiz erkek, 11 kadın olmak üzere çalışmaya 29 hasta dahil edildi. Ortanca yaş 66 olarak izlendi, histolojik olarak hastalardan 26'sı adenokarsinoma histolojisi olarak görüldü. Neoadjuvan tedavi olarak 22 hasta kısa kol radyoterapi ve kemoterapi, 7 hasta uzun kol radyoterapi ve kemoterapi aldığı görüldü. Tedaviye tam yanıt alınan hastalarda ortalama çinko düzeyi 89 µg/dL ve parsiyel yanıt alınanlarda ortalama 77 µg/dL olarak izlendi (p=0,07). Bayesci analizde sonuç orta değerlendirildi.

Sonuç: Çinko seviyesinin yüksek olması ile rektum kanserinde TNT yanıtının artabileceğine dair istatistiksel olarak anlamlı fark izlenmesine rağmen, elde edilen bulgular Bayesci analize göre ortadır.

Anahtar Kelimeler: Rektum kanseri, neoadjuvan tedavi, tedavi yanıtı, çinko

Abstract

Objectives: Total neoadjuvant therapy (TNT) is used as the gold standard in rectal cancers. It is known that zinc has an effect on the cell cycle, intracellular pathways and cell proliferation. Our study was planned to investigate the relationship between zinc level and response in rectal cancer patients receiving TNT.

Materials and Methods: Information of 29 patients with rectal cancer who received TNT treatment at Ankara University Faculty of Medicine, Department of Medical Oncology was collected retrospectively and its relationship with treatment response was evaluated. Statistical analysis was performed using classical methods and Bayesian analysis.

Results: A total of 29 patients, 18 males and 11 females, were included in the study. The median age was 66 years, and histologically, 26 of the patients were found to have adenocarcinoma histology. As neoadjuvant treatment, 22 patients received short-arm radiotherapy and chemotherapy, and 7 patients received long-arm radiotherapy and chemotherapy. The median zinc level in patients with a complete response to treatment was 89 µg/dL, and in those with a partial response, the median zinc level was 77 µg/dL (p=0.07). In Bayesian analysis, the result was evaluated moderately.

Conclusion: Although a statistically significant difference was observed indicating that TNT response in rectal cancer may increase with high zinc levels, the findings are moderate according to Bayesian analysis.

Keywords: Rectum cancer, neoadjuvant therapy, treatment response, zinc

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Giriş

Kolorektal kanser (KRK) dünyadaki üçüncü en sık kanser tipi olup ölüm nedenleri arasında ikinci sırada yer almaktadır (1). KRK sıklığı ve mortalitesi göz önüne alındığında, patogenezi ve tümör gelişimi üzerine çok sayıda klinik ve prekllinik çalışma yapılmıştır. Çinko çeşitli enzimlerde kofaktör olarak kullanılan bir eser elementtir ve intestinal mukoza korunmasında önemli olduğunu gösteren çalışmalar mevcuttur (2). Çinko homeostazının korunması ve yeterli günlük alımın sağlanmasının başta over kanseri olmak üzere kanser gelişiminin önlenmesinde ve prognozun iyileştirilmesinde faydasının olabileceğini gösteren çalışmalar mevcuttur (3).

Çinko-parmak proteinleri hücre siklusunda önemli bir rol oynamaktadır. KRK gelişiminde klasik WNT/AKT/ β -katenin yoluyla ZNRF3/RNF43, ZFP36, GATA6 gibi çinkoyu kofaktör olarak kullanan proteinler ile regüle edilmektedir (4). Bir çinko-parmak proteini olan ZNF217'nin KRK hastalarında aşırı ekspresyonunun bulunduğu, hücre migrasyonu ve invazyonunu artırdığı düşünülmektedir (5). Bununla beraber KRK hastalarında L3 çinko bağlayıcı domaine mutasyon olmasının KRK prognozunu kötü etkilediği gösterilmiştir (6). Tarihsel olarak çinko eksikliğinin kanser gelişiminde risk faktörü olduğunu gösteren çalışmalar mevcuttur (7). Ayrıca, çinko düzeylerinin kanserli over, pankreas, prostat, akciğer dokularında azaldığını gösteren çalışmalar mevcuttur (8). Özofagus kanseri modellemesinde, ratlarda çinko yüklemesi ile apoptozun indüklendiği ve kanser gelişiminin önüne geçildiği gösterilmiştir (9). Sağlıklı çinko homeostazının immün sistem ve savunma mekanizmalarında önemli olduğu düşünülmektedir (10).

Buna rağmen, yapılan bir çalışmada çinko dahil olmak üzere antioksidan özellik bulunduran mikronütrientlerin alımının sigara içenlerde KRK hastalık gelişiminde risk azaltmadığına dair bir görüş öne sürülmüştür (11). Ayrıca KRK dokusunda, kanserli olmayan dokulara göre çinko düzeyinin daha yüksek olduğunu gösteren çalışma mevcuttur (12).

Çinko düzeyleri ve kanser prognozu, kanserin önlenmesi ve tedavi yan etkilerinin azaltılması ile ilgili güncel literatürde çok sayıda çalışma bulunmaktadır. Buna rağmen total neoadjuvan tedavi (TNT) alan rektum kanseri hastalarında hastalık özellikleri ve tedavi yanıtı ile ilgili bir bilgi bulunmadığı için bu çalışma planlanmıştır.

Gereç ve Yöntem

Çalışma tek merkezli retrospektif kohort çalışması olarak planlandı. Ankara Üniversitesi Tıp Fakültesi, Tıbbi Onkoloji Anabilim Dalı poliklinik ve kliniklerinde rektum kanseri için TNT alan 18 yaş ve üzeri, çinko düzeyi ölçümü yapılmış hastalar dahil edildi. Dışlama kriterleri olarak ikinci malignite olması, preoperatif ve postoperatif patolojinin adenokarsinom veya

müsinöz karsinom dışı olarak sonuçlanmış olması, tanı anında evrelelendirmenin tam olmaması, total neoadjuvan protokolü bilinmemesi ve eksik verilerin %10'dan fazla olması olarak belirlendi. Hasta bilgilerine hastane bilgi yönetimi sistemi üzerinden ulaşıldı.

Tanı yaşı, hastanın cinsiyeti, komorbiditeleri, tanı tarihi, tanı patolojisi, tanı lokalizasyonu, tümör ilişkili özellikler, çinko seviyeleri, hastaların aldığı neoadjuvan tedaviler ve detayları, operasyon bilgileri ve operasyon patolojileri, nüks ve sağkalım bilgileri elektronik veri tabanına toplandı. Veri toplama aşamasında hastaların anonimliği korunması esas alındı, hasta ile ilgili herhangi bir kimlik bilgisi toplanmadı.

Çalışma protokolü için Ankara Üniversitesi Klinik Araştırmalar Etik Kurulu (tarih: 16.11.2023, karar no.: İ10-694-23) ve hastane başhekimliğinden onay alındı. Çalışma kişisel verilerin korunması kanunu, Helsinki bildirgesi ve etik kurallar çerçevesinde gerçekleştirildi.

İstatistiksel Analiz

İstatistiksel analizler için R4.1 (Viyana, Avusturya) kullanıldı. Kategorik değişkenler için ki-kare testi, normal dağılan verilerin analizleri için Student's t-testi, normal dağılmayan verilerin analizi için Wilcoxon ve Mann-Whitney U testi kullanıldı. Çinko düzeyi ve hastalık ilişkili parametrelerin ilişkisinin değerlendirilmesi için Bayesci istatistik analizi yapıldı, belirlenen kesme değerlerine göre Bayesci faktör (BF) hesaplandı. Tüm klasik istatistiksel analizlerde hasta sayısının azlığı nedeniyle p değeri sınırı 0,10 olarak belirlendi.

Bulgular

Çalışmaya toplam 29 hasta dahil edildi. Cinsiyete bakıldığında 18 hastanın (%62,1) erkek cinsiyette, 11 hastanın (%37,9) kadın cinsiyette olduğu gözlemlendi, cinsiyetler arasında belirgin fark izlenmedi ($p=0,26$). Ortanca yaş 66 olarak görüldü. Hastalardan 26'sı adenokarsinoma (%89,7) ve 3'ü müsinöz karsinom (%10,3) histolojisindeydi, adenokarsinom histolojisi anlamlı olarak fazlaydı ($p<0,01$). Tanı anında 26 hasta evre III (%89,7) ve 3 hasta evre II (%10,3) hastalık olarak değerlendirildi. Ortanca çinko seviyesi 82 mg/dL olarak izlendi. Neoadjuvan tedavi olarak 22 hasta (%70,9) kısa kol radyoterapi ve kemoterapi ve 7 hasta (%22,6) uzun kol radyoterapi ve kemoterapi almış olarak izlendi. Sadece 1 hasta mikrosatelit instabil olarak izlendi. Hastaların demografik bilgileri ve tedavi özellikleri Tablo 1'de belirtildi.

Çinko seviyelerinin, hastalık ve tedavi özellikleri ile karşılaştırılmasında *tümör, nod, metastaz-TNM* evresi II olan hastalarda ortanca çinko düzeyi 82 mg/dL, evre III olan hastalarda 79,5 mg/dL olarak görüldü, fark istatistiksel olarak anlamsız olarak gözlemlendi ($p=0,97$). Neoadjuvan tedaviye verilen yanıt incelendiğinde tam yanıt alan hastalarda çinko seviyesi ortanca 89 mg/dL ve parsiyel yanıt alınan hastalarda çinko

77 mg/dL olarak izlendi, fark anlamlı olarak değerlendirildi ($p=0,07$). TNT protokolü uzun kol radyoterapi ve kemoterapi olan hastalarda ortanca çinko düzeyi 77 mg/dL, kısa kol radyoterapi ve kemoterapi olan hastalarda 82,5 mg/dL olarak izlendi, fark istatistiksel olarak anlamsız ($p=0,70$) olarak değerlendirildi. Hastalık ve tedavi özellikleri ile çinko seviyesinin karşılaştırma bilgileri Tablo 2'de verildi.

Histolojik alt tiplere göre adenokarsinom izlenen hastalarda ortanca çinko seviyesi 79,5 mg/dL [minimum-maksimum (min.-maks.) 36-103], müsinöz karsinomda ortanca çinko seviyesi 87 mg/dL (min.-maks. 73-97) olarak izlendi, fark istatistiksel olarak

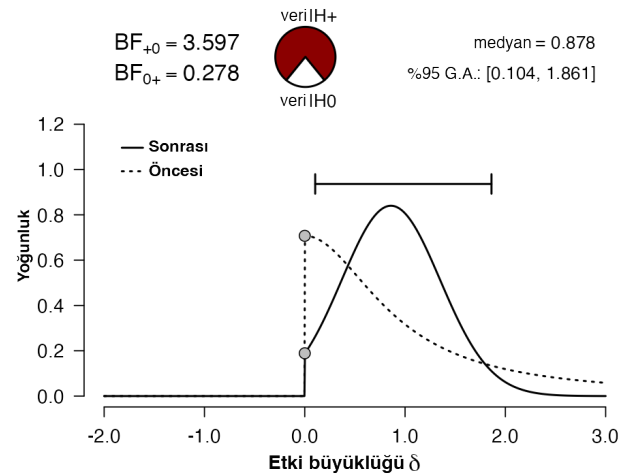
Tablo 1: Hastaların demografik bilgileri ve tedavi özellikleri (n=29)	
Cinsiyet	n (%)
Erkek	18 (%62,1)
Kadın	11 (%37,9)
Yaş (ortanca, çeyrekler arası aralık)	66 (56-70)
Histolojik tip	n (%)
Adenokarsinom	26 (%89,7)
Müsinöz karsinom	3 (%10,3)
Tanı TNM evresi	n (%)
II	3 (%10,3)
III	26 (%89,7)
Çinko seviyesi (ortanca, çeyrekler arası aralık)	82 (73-87)
Neoadjuvan tedavi	n (%)
Uzun kol radyoterapi + kemoterapi	7 (%24,1)
Kısa kol radyoterapi + kemoterapi	22 (%76,9)
Mismatch instabilitesi	n (%)
Mismatch stabil	23 (%95,8)
Mismatch instabilitesi-yüksek	1 (%4,2)
*Patolojik olarak bilinenlerde TNM: Tümör, nod, metastaz	

Tablo 2: Hastalık ve tedavi özellikleri ile çinko seviyesinin karşılaştırılması	
Hastalık ve tedavi özellikleri	Çinko düzeyi mcg/dL (ortanca, min.-maks.)
TNM evre	*p=0,97
II (n=3)	82 (66-87)
III (n=26)	79,5 (36-103)
Tümör regresyonu	*p=0,07
Tam yanıt (n=5)	89 (74-103)
Parsiyel yanıt (n=24)	77 (36-102)
TNT protokolü	*p=0,70
Uzun kol + KT (n=7)	77 (56-97)
Kısa kol + KT (n=22)	82,5 (36-103)
*Mann-Whitney U testi TNM: Tümör, nod, metastaz, TNT: Total neoadjuvan tedavi, min.-maks.: Minimum-maksimum	

anlamsız olarak görüldü ($p=0,35$). Yaş ile çinko düzeyi ilişkisi incelendiğinde, yaş arttıkça çinko seviyesinin azaldığı (Pearson korelasyon analizi $r=-0,30$) ve istatistiksel olarak anlamlı olduğu gözlemlendi ($p=0,10$).

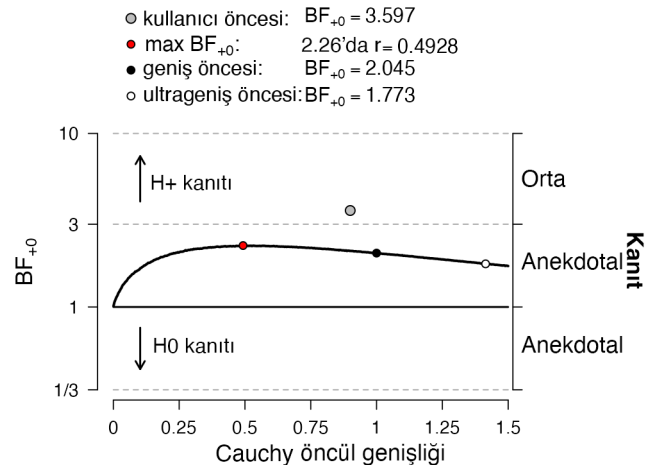
Tam yanıt alan hastalarda istatistiksel anlam gözlemlendiği için Bayesci istatistik analizi alındığında çinko düzeyi ve BF+0 değeri 3.597 olarak izlendi, analize bakıldığı zaman kanıt orta olarak izlendi. Bayesci analiz tanımlayıcıları ve BF analizi Şekil 1 ve 2'de belirtildi.

Sadece bir hastada nüks izlendi, nüks için geçen süre tanıdan itibaren 18 ay olarak görüldü, analize alınan örnekte herhangi bir ölüm izlenmedi. Ortanca takip süresi 17 ay (min.-maks. 4-49) olarak izlendi. Ölüm izlenmemesi nedeniyle sağkalım analizleri yapılmadı.



Şekil 1: Bayesian analizi

BF: Bayesci faktör, G.A.: Güven aralığı



Şekil 2: Bayesian tutarlılık

BF: Bayesci faktör

Tartışma

TNT, metastatik olmayan rektum kanserinde günümüzde ameliyat öncesi standart tedavi olarak kullanılmaktadır. Bu yaklaşımın standart tedavilerde üstün olduğu gösterilmiştir ve TNT ile elde edilen patolojik tam yanıt oranlarının artması yüz güldürücüdür. Bununla beraber patolojik tam yanıtta etki eden faktörler çok net olarak bilinmemektedir. Bu çalışmada çinko düzeylerinin TNT yanıtına etkisi araştırılması planlanmıştır.

Çinko takviyelerinin, diğer mikronütrientler ile birlikte kanser tedavisinde yan etkileri azalttığı bilinmektedir, bununla beraber tedavi ile ilişkisini değerlendiren birçok çalışma mevcuttur (8). Dhawan ve Cdahta (13) tarafından yazılan derlemede çinko takviyesi ile KRK gelişiminin önlenmesine katkı sağlanabileceği öne sürülmüştür. Çeşitli mekanizmalar üzerinden bu durum ilişkilendirilmeye çalışılmış ve bu konuda çelişkili sonuçlar elde edilmiştir. Hansen ve ark. (11) tarafından yapılan bir çalışmada KRK'li hastalarda, tütün kullanımı ile artan oksidatif stresin, antioksidan özellik bulunduran mikronütrientler ile önlenilebilirliğine dair bir kanıt bulunamamıştır. Fong ve ark. (9) tarafından özofagus kanseri modellenen bir çalışmada ise çinko eksikliği olan ratlarda özofagus kanser gelişiminin önlenmesi ve malignite potansiyeli taşıyan hücrelerde çinko yerine konulması ile apoptozun indüklendiği gözlenmiştir. Bu durum çinko-bağımlı proteinlerin apoptotik özelliklerinin çinko seviyesiyle direkt ilişkili olması ve bir anti-kanser mekanizma olarak apoptozun tekrar kullanıma girmesi olabilir. Bununla beraber, Grant (7) tarafından yapılan ekolojik besinsel çinko ve demir çalışmasında KRK ve diğer birçok kanserin gelişiminde çinkonun önleyici rol oynadığı gösterilmiştir. Buna karşıt olarak Kucharzewski ve ark. (14) tarafından yapılan çalışmada KRK'li dokularda, poliplere nazaran daha fazla çinko bulunduğu gösterilmiştir. Wan ve Zhang (2) tarafından yapılan bir derlemede ise çinko eksikliği ya da fazlalığı ile oluşan çinko homeostazının bozulmasının kanser, enflamatuvar barsak hastalığı gibi birçok kolorektal hastalık ile ilişkisine vurgu yapılmıştır. Yin ve ark. (3) tarafından over kanserli hastalarda yapılan çalışmada düşük çinko seviyelerinin kötü differansiasyonla ilgili olduğu gösterilmiştir.

Moleküler seviyede çinkonun kanser gelişiminde koruyucu ya da ilerletici etkisinin olabileceğini savunan çalışmalar bulunmaktadır. Loh (15) tarafından yazılan bir derlemede çinkonun p53 katlanmasında önemine ve kanserle ilişkisine vurgu yapılmış, uygun olmayan bağlanmaların kanseri tetikleyebileceği öne sürülmüştür. Børresen-Dale ve ark. (6) tarafından 1998'de yapılan çalışmada L3 çinko-bağlayıcı domain'de oluşan mutasyonların KRK'de kötü prognoz ile ilişkili olduğu gösterilmiştir. Bu mutasyonların bulunması durumunda çinko bağlanmasının bozulması ve çinko metabolizmasının bozulması kötü prognoz ile ilişkilendirilebilir. Zhang ve ark. (5) tarafından çinkonun sitotoksik dozlarda posttranslasyonel

etkisinin bulunduğu ve özellikle Dicer yolağının ekspresyonunu artırarak kanserli hücrelerde sitotoksik etkiyi indüklediği gösterilmiştir. Bununla beraber Iyer ve ark. (4) tarafından yazılan derlemede çinko-parmak proteinlerinin KRK'de rolünün olabileceğini savunulmuştur ve Qi ve ark. (16) tarafından bir çinko-parmak protein olan MCOLN1/TRPML1 ile çinko alımının kanserli hücrelerde otofajiyi tetiklediği gösterilmiştir. Zhang ve ark. (17) tarafından yapılan çalışmada bir çinko-parmak protein olan TRPV4'ün tedavi hedefi olarak kullanılabileceği öne sürülmüştür.

Çalışmanın Kısıtlılıkları

Çalışmamızın ana kısıtlılığı, çalışmamızın örneklem sayısının kısıtlı olmasıdır. Bunun nedeni çinko düzeylerinin rutin onkolojik takiplerde kullanılmaması, sadece çeşitli toksisiteler ve diğer medikal durumlarda istenmesi olabilir. Diğer kısıtlılıklar olarak çalışmamızın retrospektif olarak yürütülmesinden dolayı veri kısıtlılıkları olması, eksik verilerin olması, TNT alan hastaların sayısının azlığı, dokudaki çinko düzeyi ile ilişkinin bilinmemesi, istatistiksel analizlerin orta seviyede kalması olarak belirtilebilir. Bu nedenle çalışmamızın daha geniş bir popülasyonda, prospektif olarak, doku düzeyleri ve tedavi ile çinko düzeyindeki değişimlerinin değerlendirilmesi gerekmektedir.

Sonuç

Çinko seviyesinin yüksek olması ile rektum kanserinde TNT yanıtının artabileceğine dair istatistiksel olarak anlamlı fark izlenmesine rağmen, elde edilen bulgular Bayesci analize göre ortadır. Bu nedenle bir mikronütrient olarak çinkonun rektum kanseri tedavisinde önemini açıklamak üzere daha geniş ve detaylı çalışmalar gerekmektedir.

Etik

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Hasta Onayı: Retrospektif çalışma olduğundan hasta onamına gerek duyulmamıştır.

Yazarlık Katkıları

Konsept: E.C.E., M.Y., G.U., Dizayn: E.C.E., M.Y., Ç.T., Veri Toplama veya İşleme: E.C.E., M.Y., Ç.T., Analiz veya Yorumlama: E.C.E., M.Y., G.U., Literatür Arama: E.C.E., M.Y., G.U., Yazan: E.C.E., M.Y.

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A Correlation Study that Reveals the Relationship Between Countries' GDP, Frequency of Access to Clean Fuel, Level of PM2.5, and Death Rate Related to Air Pollution

Ülkelerin GSYİH'si, Temiz Yakıt Erişim Sıklığı, PM2.5 Düzeyi ve Hava Kirliliğine Bağlı Ölüm Hızı Arasındaki İlişkiyi Ortaya Çıkaran Bir Korelasyon Çalışması

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Abstract

Objectives: Air pollution is one of biggest environmental health problems and is responsible for 11.7% of deaths. It was aimed at examining the relationship between gross domestic product (GDP), the percentage of access to clean fuels, PM2.5 level, air pollution death rates.

Materials and Methods: This study is a correlational study. Data for 208 countries for 1990-2019 were accessed from "Our World in Data" web page in April-May 2023. Comparisons were made according to World Bank income groups.

Results: GDP per capita had a very strong positive correlation with percentage of access to clean/technological fuels ($r=0.915$), and a very strong negative correlation with indoor air pollution death rate ($r=-0.914$). There was a moderate negative correlation between GDP per capita and PM2.5 ($r=-0.470$). The average PM2.5 level had a moderate negative correlation with percentage of access to clean/technological fuel ($r=-0.445$), a moderate positive correlation with indoor air pollution death rate ($r=0.433$), and a strong positive correlation with outdoor air pollution death rate ($r=0.602$).

Conclusion: The percentage of access to clean/technological fuels has increased over the years, indoor air pollution death rate has decreased. It has been almost completely eradicated in high-income countries, but remains in low-income countries. By encouraging clean/technological heating and cooking methods, indoor air pollution death rate will no longer be a problem in any country. On the other hand, outdoor air pollution death rate is higher in countries with high PM2.5 levels. If policymakers reduce coal, oil consumption and prioritize clean energy, transportation, they can improve air quality by lowering PM2.5 levels.

Keywords: Indoor air pollution, outdoor air pollution, PM2.5, gross domestic product, clean fuel, World Bank country income groups

Öz

Amaç: Hava kirliliği en büyük çevre sağlığı sorunlarından biridir ve ölümlerin %11,7'sinden sorumludur. Gayri safi yurtiçi hasıla (GSYİH), temiz yakıtlara erişim yüzdesi, PM2.5 düzeyi ve hava kirliliğinden ölüm hızları arasındaki ilişkinin incelenmesi amaçlandı.

Gereç ve Yöntem: Bu çalışma korelasyonel bir çalışmadır. Nisan-Mayıs 2023'te "Our World in Data" web sayfasından 1990-2019 için 208 ülkeye ait veriye ulaşıldı. Karşılaştırmalar Dünya Bankası gelir gruplarına göre yapıldı.

Bulgular: Kişi başına düşen GSYİH, temiz/teknolojik yakıtlara erişim yüzdesi ile çok güçlü bir pozitif korelasyona ($r=0,915$) ve iç ortam hava kirliliği ölüm hızı ile çok güçlü bir negatif korelasyona ($r=-0,914$) sahipti. Kişi başına düşen GSYİH ile PM2,5 ($r=-0,470$) arasında orta düzeyde negatif korelasyon vardı. Ortalama PM2.5 düzeyi, temiz/teknolojik yakıtlara erişim yüzdesi ile orta derecede negatif korelasyona ($r=-0,445$), iç ortam hava kirliliği ölüm hızı ile orta derecede pozitif korelasyona ($r=0,433$) ve dış ortam hava kirliliği ölüm hızıyla güçlü pozitif korelasyona sahipti ($r=0,602$).

Sonuç: Yıllar geçtikçe temiz/teknolojik yakıtlara erişim yüzdesi arttı, iç ortam hava kirliliği ölüm hızı azaldı. Bu hız yüksek gelirli ülkelerde neredeyse tamamen ortadan kaldırıldı, ancak düşük gelirli ülkelerde varlığını sürdürüyor. Temiz/teknolojik ısıtma ve pişirme yöntemlerinin teşvik edilmesiyle,

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İç ortam hava kirliliğinden ölüm hızı artık hiçbir ülkede sorun olmayacak. Öte yandan PM2.5 seviyesinin yüksek olduğu ülkelerde dış ortam hava kirliliğinden ölüm hızı daha yüksektir. Politika yapıcılar kömür ve petrol tüketimini azaltır ve temiz enerji ile ulaşım öncelik verirlerse PM2.5 seviyelerini düşürerek hava kalitesini artırabilirler.

Anahtar Kelimeler: İç ortam hava kirliliği, dış ortam hava kirliliği, PM2.5, gayri safi yurtiçi hasıla, temiz yakıt, Dünya Bankası ülke gelir grupları

Introduction

Air pollution is the deterioration of the air content by pollutants such as heating, fuel, industrial activities, unplanned urbanization. Air pollution is one of the world's biggest environmental health problems. According to the Global Burden of Disease study of the Institute for Health Measurements and Evaluation, air pollution is responsible for 11.7% of deaths in the world (1). Air pollution; it is examined in two ways as outdoor and indoor air pollution.

Outdoor air pollution is caused by electricity generation, industrial emissions, vehicle exhaust, wind-blown dust and crop burning (2). According to the Global Burden of Disease study, 7.8% (4.5 million) of deaths are due to outdoor air pollution, and in some countries air pollution accounts for at least 10% of deaths. There are up to 10 times different death rates between countries. Rates increase as countries industrialize and move from low-income to middle-income, and are usually highest in middle-income countries (1). If air pollution death rates are to be reduced, both exposure should be reduced and health conditions should be improved (3).

There are two main outdoor air pollutants, ozone and particulate matter (PM). Mortality rates from PM pollution are higher than from ozone. What is meant here is "tropospheric ozone" found in the lower atmosphere near the surface. This should not be confused with the ozone layer in the stratosphere, which protects us from UV radiation (3). The main element of outdoor air pollution is PM, which is a mixture of solid and liquid, organic and inorganic particles. PM2.5 are fine particles that can be taken up by alveolar macrophages and endothelial cells in the lung and cause direct health effects (4). The World Health Organization (WHO) Global Air Quality Guidelines offer global guidance on thresholds and limits for key air pollutants that pose health risks, such as PM. So much so that WHO set out the annual average PM2.5 level up to 5 µg/m³ as the clean air threshold in 2021 (5).

Indoor air pollution is caused by the burning of solid fossil sources such as wood, coal, manure for cooking and heating. Burning such fuels, especially in underdeveloped countries, causes pneumonia, lung cancer, heart disease, stroke (6). According to the Global Burden of Disease study, 4.1% (2.3 million) of global deaths are caused by indoor air pollution. On the other hand, WHO predicted more deaths, announcing that 3.2 million people died from indoor air pollution in 2020 (7).

Only 60% of the world has access to clean fuel for cooking but this share is increasing (8).

Income is a strong determinant of energy access and fuel source choice. Low-income households mostly use traditional solid fuels such as wood and dung. As income increases, this energy mix shifts towards wood and coal. In higher-income countries, cleaner fuels such as natural gas and ethanol are often used instead of harmful fossil fuels. Electricity is mostly available at higher income levels. In countries with a per capita Gross Domestic Product (GDP) of less than 2,000 USD per year, access to clean energy in houses is less than 10% (8).

In this study, it is aimed at examining the relationship between the GDP of countries', the percentage of access to clean or technological fuels, outdoor PM2.5 levels, and air pollution death rates

Materials and Methods

This study is a correlational study. The data was obtained from the website <https://ourworldindata.org/> in the period of April-May 2023, and data for 208 countries in total were obtained. Data between 1990-2017 for the variable "PM2.5", and data between 1990-2019 for the variables "GDP per capita", "indoor, outdoor and total air pollution death rates", "percentage of access to clean/technological fuel" are included in the analysis (9). Comparisons were made according to World Bank country income groups (high-income, upper-middle-income, lower-middle-income, low-income) available on the same website.

Statistical Analysis

Statistical analysis were evaluated using the R 3.5.1. program. Descriptive values are expressed as number, percentage, mean (standard deviation), median, minimum-maximum. Continuous variables were compared with the non-parametric Kruskal-Wallis test, as they did not conform to the normal distribution in the evaluation made with visual-analytical tests, and the relationships between them were evaluated using the Spearman correlation test. The correlation coefficient is weak if $r=0.00-0.24$, moderate if $r=0.25-0.49$, strong if $r=0.50-0.74$, very strong if $r=0.75-1.00$ (10). The significance level was taken as $p<0.05$. Since the study was produced from publicly available data, no application was made to the ethics committee.

Results

Average values in the world between 1990–2019; GDP per capita was 13847.4 (1836.8) USD, indoor, outdoor, total air pollution death rates were 63.4 (22.1) (6.6% of deaths), 59.8 (1.1) (6.5% of deaths), 120.5 (22.2) (12.8% of deaths) per hundred thousand, respectively. Average PM2.5 level was 47.0 (2.1) $\mu\text{g}/\text{m}^3$ between 1990–2017. Average values in Türkiye between 1990–2019; GDP per capita was 18730,9 (5201,8) USD, indoor, outdoor, total air pollution death rates were 5.4 (6.8) (0.7% of deaths), 66.2 (7.8) (9.6% of deaths), 70.8 (13.9) (10.1% of deaths) per hundred thousand, respectively. Average PM2.5 level was 42.8 (1.4) $\mu\text{g}/\text{m}^3$ between 1990–2017. Average values in the world in 2019; GDP per capita was 16897,2 USD, indoor, outdoor, total air pollution death rates were 30.2 (4.1% of deaths), 57.4 (7.8% of deaths), 85.6 (11.7% of deaths) per hundred thousand, respectively. PM2.5 level was 45.5 $\mu\text{g}/\text{m}^3$ in 2017. Average values in Türkiye in 2019; GDP per capita was 28197,3 USD, indoor, outdoor, total air pollution death rates were 0.3 (0.1% of deaths), 53.7 (9.5% of deaths), 53.3 (9.5% of deaths) per hundred thousand, respectively. PM2.5 level was 44.3 $\mu\text{g}/\text{m}^3$ in 2017.

The average indoor air pollution death rates were 1.0 (0.8), 54.6 (31.9), 118.6 (35.5), 210.3 (36.3) per hundred thousand in high, upper-middle, lower-middle and low-income countries,

respectively. As income decreased, indoor air pollution death rate increased ($p<0.001$). The average outdoor air pollution death rates were 25.1 (7.8), 79.9 (5.9), 76.6 (9.8), 33.2 (5.8) per hundred thousand in high, upper-middle, lower-middle, and low-income countries, respectively ($p<0.001$). While outdoor air pollution death rate was higher in upper-middle and lower-middle-income countries than high and low-income countries, it was higher in low-income countries than high-income countries. As income decreased, total air pollution death rates increased ($p<0.001$). The average PM2.5 level were 15.9 (0.8), 45.2 (3.8), 62.2 (2.1) and 41.7 (1.5) $\mu\text{g}/\text{m}^3$ in high, upper-middle, lower-middle and low-income countries, respectively ($p<0.001$). In high-income countries, PM2.5 level was lower than other income groups. In addition, upper-middle income group and low-income group also had lower PM2.5 concentrations than lower-middle income group (Table 1).

Table 2 shows the correlation between GDP per capita and air pollution death rates, PM2.5 level and percentages of access to clean/technological fuel in the world between 1990–2017. GDP per capita had a very strong positive correlation with the percentage of access to clean/technological fuels ($r=0.915$), and a very strong negative correlation with indoor air pollution death rate ($r=-0.914$). There was a moderate negative correlation between GDP per capita and PM2.5 ($r=-0.470$). As GDP per capita increased, the percentage of access to clean/

Table 1: Comparison of GDP, air pollution death rates and PM2.5 levels among country income groups in the world in 2019–1990

World Bank income groups		GDP per capita (USD)	Indoor air pollution death rate [*]	Outdoor air pollution death rate [*]	Total air pollution death rate [*]	PM2.5 levels ($\mu\text{g}/\text{m}^3$) [#]
High Income	Mean (SD)	41437,0 (5593,2)	1.0 (0.8)	25.7 (7.8)	25.9 (8.6)	15.9 (0.8)
	Median	42677,0	0.7	23.8	24.4	16.2
	Range	32193,1–50491,8	0.3–3.0	14.9–39.1	15.1–41.9	14.5–17.0
Upper-Middle Income	Mean (SD)	10097,5 (3867,2)	54.6 (31.9)	79.9 (5.9)	130.9 (34.2)	45.2 (3.8)
	Median	8936,5	51.3	81.9	132.3	44.7
	Range	5857,8–17393,4	13.8–114.7	66.2–85.4	78.8–187.9	39.0–50.9
Lower-Middle Income	Mean (SD)	4552,9 (1299,0)	118.6 (35.5)	76.6 (9.8)	189.8 (25.9)	62.2 (2.1)
	Median	4205,1	119.6	74.7	188.6	62.3
	Range	3162,2–7115,2	59.5–171.0	62.0–91.9	145.9–227.9	9.0–66.0
Low Income	Mean (SD)	1556,5 (258,5)	210.3 (36.3)	33.2 (5.8)	240.2 (30.8)	41.7 (1.5)
	Median	1480,5	213.2	30.8	241.0	41.8
	Range	1229,4–2022,0	148.5–263.7	27.2–43.7	188.6–287.4	39.4–44.3
p value		<0.001	<0.001	<0.001	<0.001	<0.001
Total	Mean (SD)	13847,4 (1836,8)	63.4 (22.1)	59.8 (1.1)	120.5 (22.2)	47.0 (2.1)
	Median	13767,5	63.0	60.0	120.5	46.6
	Range	11097,3–16897,8	30.2–100.1	56.8–6.0	85.6–156.1	44.3–50.8
Türkiye	Mean (SD)	18730,9 (5201,9)	5.4 (6.8)	66.2 (7.8)	70.8 (13.9)	42.8 (1.4)
	Median	17610,3	2.0	64.7	66.0	42.6
	Range	12507,3–28318,4	0.3–24.5	53.7–79.0	53.3–102.4	40.6–45.4

SD: Standard deviation, GDP: Gross domestic product, *per hundred thousand, #1990–2017

Table 2: Correlation between GDP, air pollution death rates, PM2.5 levels and percentages of access to domestic clean fuel/technology in the world in 1990–2017

		GDP per capita (USD)	Access to clean fuel (%)	Indoor air pollution death rate	Outdoor air pollution death rate	PM2.5 level ($\mu\text{g}/\text{m}^3$)
GDP per capita (USD)	r	1,000				
	p	-				
Access to clean fuel %	r	0.915	1,000			
	p	<0.001	-			
Indoor air pollution death rate*	r	-0.914	-0.929	1,000		
	p	<0.001	<0.001	-		
Outdoor air pollution death rate*	r	-0.010	0.055	0.081	1,000	
	p	0.460	<0.001	<0.001	-	
Annual average PM2.5 level ($\mu\text{g}/\text{m}^3$)	r	-0.470	-0.445	0.433	0.602	1,000
	p	<0.001	<0.001	<0.001	<0.001	-

GDP: Gross domestic product, r: Correlation coefficient, p: Significance level, *per hundred thousand

technological fuel increased significantly, and as income and percentage of access to clean/technological fuels increased, indoor air pollution death rate and PM2.5 decreased. There was no significant correlation between GDP per capita and outdoor air pollution death rate. The average PM2.5 level had a moderate negative correlation with the percentage of access to clean/technological fuel ($r=-0.445$), a moderate positive correlation with indoor air pollution death rate ($r=0.433$), and a strong positive correlation with outdoor air pollution death rate ($r=0.602$). As PM2.5 level increased, indoor and outdoor air pollution death rates increased.

Figure 1 shows that as GDP per capita increases, the indoor air pollution death rate decreases.

Figure 2 shows that as the percentage of access to clean/technological fuel for cooking increases, the indoor air pollution death rate decreases.

According to Figure 3, as the PM2.5 increases, outdoor air pollution death rate also increases. The percentage of access to clean/technological fuels in the world has increased over the years, and indoor air pollution death rate has decreased. Despite the partial decrease in PM2.5 level, there is no significant decrease in outdoor air pollution death rate (Figure 4).

Discussion

The average indoor, outdoor and total air pollution death rates in the world were 63.4, 59.8 and 120.5 per hundred thousand in 1990–2019, respectively. Finally, the rates were 30.2, 57.4, 85.6 per hundred thousand in 2019, respectively. When the literature is examined; air pollution appears to be the second leading cause of death in Africa. There were 1.1 million deaths of which 697,000 indoor, 383,419 outdoor PM2.5 pollution, 11230 outdoor ozone pollution attributed to air pollution in Africa in

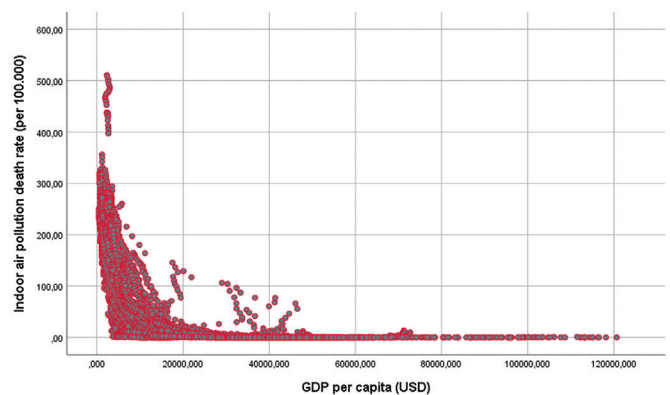


Figure 1: Relationship between GDP per capita and indoor air pollution death rate

GDP: Gross domestic product

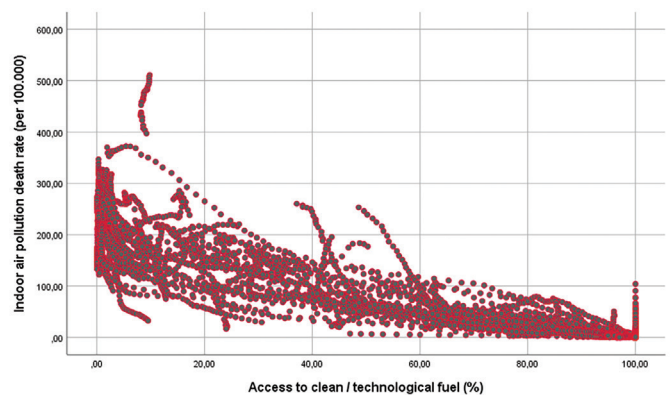


Figure 2: Relationship between percentage of access to clean/technological fuel for cooking and indoor air pollution death rate

2019. This was 16.3% of all deaths. Although indoor air pollution death rate have decreased, outdoor air pollution death rate have increased from 26 per 100,000 in 1990 to 29 per 100,000 in 2019, according to one study (2). The frequency in this study is lower than ours. In our study, while the outdoor air pollution death rate in Africa was 31.5 per hundred thousand in 1990, it was 46.1 in 2019. This difference may be due to the different countries in the sample. In our study, average indoor, outdoor and total air pollution death rates were 5.4 (0.7% of deaths), 66.2 (9.6% of deaths), 70.8 (10.1% of deaths) per hundred thousand in Türkiye between 1990-2019, respectively. Finally, the rates were 0.3 per hundred thousand (0.1% of deaths), 53.7 (9.5% of deaths), 53.3 (9.5% of deaths) in 2019, respectively. In studies conducted in different regions of Türkiye, the share of air pollution in deaths was found to be, 16.8% (4), 33.5% (4) and 29.2% (11). In our study, this percentage for Türkiye is 9.5% in 2019, and lower than the values in the studies above.

In the world, average PM2.5 level was 47.0 $\mu\text{g}/\text{m}^3$ between 1990-2017, and 45.5 $\mu\text{g}/\text{m}^3$ in 2017. In Türkiye, average PM2.5 level was 42.8 $\mu\text{g}/\text{m}^3$ between 1990-2017, and 44.3 $\mu\text{g}/\text{m}^3$ in 2017. In the literature, exposure to PM2.5 was high in many low and middle-income countries in Africa and Asia in 2017.

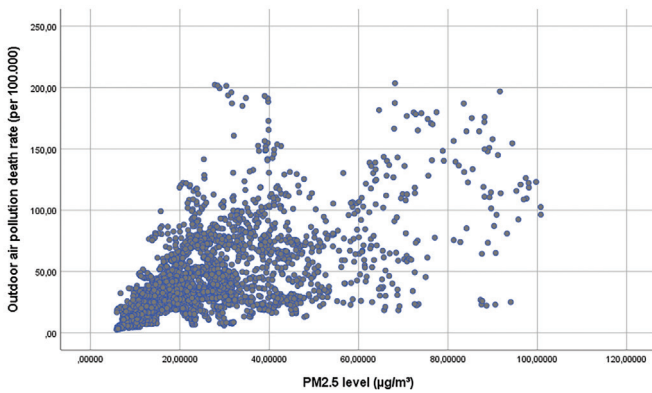


Figure 3: Relationship between annual average PM2.5 concentration and outdoor air pollution death rate

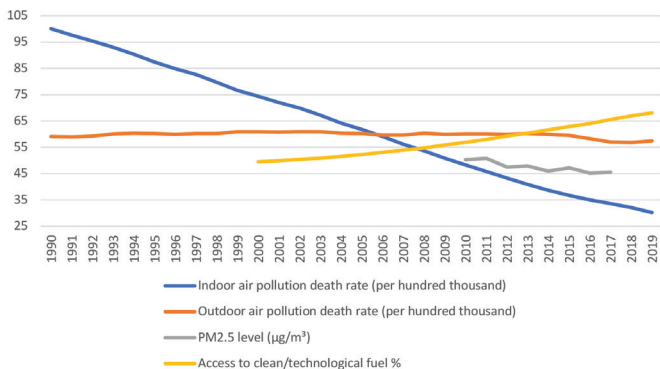


Figure 4: Changes in air pollution death rates, PM2.5 levels and percentages of access to clean/technological fuel over the years in the world

In particular, it was very high in North Africa, up to 200 $\mu\text{g}/\text{m}^3$, due to dry conditions with more sources of sand and dust. Whereas in Sweden it was 40 times lower at 5 $\mu\text{g}/\text{m}^3$ (4). Annual PM2.5 level in Sub-Saharan Africa was 45 $\mu\text{g}/\text{m}^3$ in 2019 (2). Many African countries had PM2.5 concentrations that exceeded the WHO guideline (12). The average annual PM2.5 level in China was 52.7 $\mu\text{g}/\text{m}^3$ in 2017, 9% lower than in 1990. In 2017, all Chinese population lived in areas that exceeded the WHO guideline of 10 $\mu\text{g}/\text{m}^3$, and 81.1% of them lived above the interim target of 35 $\mu\text{g}/\text{m}^3$ (13). The average PM2.5 level in houses was 51 $\mu\text{g}/\text{m}^3$. This was 10 times higher than the WHO recommended value. (14). According to the Global Study of Disease, Injury and Risk Factors, PM air pollution was the 4th risk factor for death and disability-adjusted life years in China (15). The Chinese Government has implemented a number of measures to reduce PM2.5 levels (16). As a result, PM2.5 levels have decreased in heavily polluted areas such as Beijing (17). Türkiye's 2017 PM2.5 level was high, although slightly below China's. For this reason, it is necessary to implement practices similar to those in China in our country.

According to the 2020 World Air Quality report of the Sweden-based IQAir group, PM2.5 was above the upper limit in 26 of 106 countries. The countries with the most polluted air were Bangladesh, Pakistan and India. Average PM2.5 was 77.1 in Bangladesh, 59.0 in Pakistan, 51.9 $\mu\text{g}/\text{m}^3$ in India. In the Virgin Islands, New Caledonia and Puerto Rico, where the air quality was highest, PM2.5 levels averaged 3.7 $\mu\text{g}/\text{m}^3$. Türkiye was the 46th most polluted country with an average PM2.5 level of 18.7 $\mu\text{g}/\text{m}^3$ (18). Within the scope of a joint project, 31,476 deaths in Türkiye in 2019 were associated with air pollution and it was calculated that these deaths could have been prevented if PM2.5 levels was at the standards set by WHO (19). According to the 2021 European PM2.5 air quality ranking, Türkiye ranked 7th with 20 $\mu\text{g}/\text{m}^3$. Finland was the only country to reach the 5 $\mu\text{g}/\text{m}^3$ limit set by WHO (20). The average PM2.5 level in 2019 determined for Türkiye in these two studies is half of the average value of the last 30 years in our study. Although PM2.5 levels have decreased in the last 30 years for our country, it is regrettable that our country is still at the top of the world rankings.

Indoor air pollution death rates increased significantly as income decreased. While the outdoor air pollution death rate was significantly higher in upper/lower-middle-income countries than in high/low-income countries, it was significantly higher in low-income countries than in high-income ones. As income decreased, the total air pollution death rate increased significantly. The literature on inequalities between countries in air pollution is limited (21,22). Most of the literature documents nationwide inequalities in the US, and indicates that those from low socioeconomic status are more exposed to pollution

than those from higher socioeconomic status (23–25). Evidence for European countries is limited and a mixed relationship is considered (26,27). Information is also limited for China and other low- and middle-income countries, where 91% (26%) of outdoor air pollution premature deaths occur (22,28). In 2016, increased PM levels were associated with 8.4% mortality in undeveloped and developing countries and 4.2% in developed countries (29). As a result, in our study, as the income situation worsens, indoor and total air pollution and deaths increase in parallel with the literature.

In this study, PM_{2.5} levels were found to be lower in high-income countries than in other groups. In addition, the upper-middle and low-income group also have lower PM_{2.5} concentrations than the lower-middle income group. As income increased, the annual average PM_{2.5} level decreased significantly. In China, a positive relationship was found between socioeconomic status and outdoor air pollution. PM_{2.5} concentrations in China were higher in high socioeconomic status than lower socioeconomic status, and in long-term urban residents than come rural to urban people (13). In Europe, it is estimated that approximately 60% of the population of high-income countries and 80% of the population of middle and low-income countries are exposed to PM_{2.5} levels above the WHO limit (29). Similar to our study in Europe, there is an inverse correlation between PM_{2.5} levels and income, while the opposite is true in China. The fact that the majority of China's population lives in industrial and economically developed big cities may cause more air pollution in high-income regions.

In this study as a result of the correlation analysis; as income increased, the percentage of access to clean/technological fuel increased, and the indoor air pollution death rate decreased. In addition, as the percentage of access to clean/technological fuel increased, the indoor air pollution death rate decreased. Indoor air pollution is the common form of air pollution in Africa. The highest rates in Africa were seen in countries with the lowest social development indices, similar to our study. Indoor air pollution accounted for more than 80% of disease damage in Ethiopia and Rwanda, but only half in more economically developed Ghana (2). As countries get richer, they begin to take measures to reduce air pollution and related deaths. Countries with a GDP per capita of 5–15 thousand USD (such as India) are in the first phase. Countries that have become richer and more competent (such as China, Türkiye) enter the second phase. At this stage, air pollution-related deaths are reduced by increasing environmental investments. Türkiye's air pollution deaths, which were 60–70 per hundred thousand in the 1990s, decreased to 40–50 in the 2010s (Türkiye's 2020 GDP per capita was 30,000 USD). The decline is more striking in Singapore, which is much richer than Türkiye, with air pollution deaths falling from 43 per

100,000 in 1990 to 20 in 2017 (Singapore's 2020 GDP per capita was 102,000 USD) (30). In these studies, similar to ours, it was observed that the death rate of air pollution decreased as the income level of the country increased.

In Africa, 60% of air pollution deaths are caused by indoor air pollution, and polluting fuels such as coal and kerosene are widely used. With the intervention of the government, non-governmental organizations and United Nations agencies, morbidity and mortality from air pollution in the home is decreasing, albeit slowly and sporadically. With exceptions like Nigeria, African countries haven't yet any precautions against the use of fossil fuels. Therefore, they have the opportunity to get rid of their dependence on oil and natural gas by investing in renewable energy and non-polluting technologies. Reducing dependence on fossil fuels, switching to non-polluting renewable energy sources such as solar, wind and hydroelectric, and improving public transportation are the main pollution prevention strategies (2). The proportion of households cooking with solid fuel in China decreased from 84.4% in 1990 to 61% in 2005 and 32.2% in 2017. The use of coal for cooking and heating has been banned in the areas around Beijing, and clean energy such as natural gas has been promoted in the country. The age-standardized death rate attributed to air pollution decreased by 60.6% in China between 1990 and 2017. The decrease for outdoor PM pollution is 12.0% and for indoor air pollution is 85.4%. In China, the age-standardized death rate attributed to PM decreased by 8.9% between 2013 and 2017. In addition, average PM_{2.5} concentrations decreased by 33.3% between 2013 and 2017 (31). As can be seen, both PM levels and air pollution death rates decrease as access to clean fuel increases.

Study Limitations

There are some limitations in this study. Only the relationships between income level/access to clean/technological fuel/PM_{2.5} levels and deaths due to air pollution was examined. As we know, there are many variables that have an effect on deaths, and the fact that these variables are not included in the analysis may lead to bias in the results.

Conclusion

In conclusion, there was a positive correlation between income and percentage of access to clean/technological fuels; there was a negative correlation between income and PM_{2.5}, death rate from indoor and total air pollution. As the percentage of access to clean/technological fuels increased, PM_{2.5} and indoor air pollution death rates decreased. There was a negative correlation between percentage access to clean/technological fuels and PM_{2.5} level; there was a positive correlation between PM_{2.5} level, indoor and outdoor air pollution death rates.

The percentage of access to clean/technological fuels in the world has increased over the years, and indoor air pollution death rate has decreased. Indoor air pollution death rate has a clear economic distinction. It has been almost completely eradicated in high-income countries, but remains an environmental and health problem in low-income countries. By encouraging clean/technological heating and cooking methods at houses, the indoor air pollution death rate will no longer be a problem in low-income countries. On the other hand, outdoor air pollution death rate is higher in countries with high PM2.5 levels. If policymakers reduce coal and oil consumption and prioritize clean air, energy and transportation, it will benefit air quality improvement.

Ethics

Ethics Committee Approval: Since the study was produced from publicly available data, no application was made to the ethics committee.

Informed Consent: This study is a correlational study.

Financial Disclosure: This study received no financial support.

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Clinical Efficacy and Safety of Using N-Butyl Cyanoacrylate in the Treatment of Perforator Vein Insufficiency

Perforatör Ven Yetmezliğinin Tedavisinde N-Butil Siyanoakrilat Kullanımının Klinik Etkinliği ve Güvenliği

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Abstract

Objectives: Venous insufficiency has traditionally been managed through various techniques, including surgical interventions and thermal ablation. A novel technique for venous insufficiency is non-thermal ablation using a vein sealing system, involving the endovenous delivery of N-butyl cyanoacrylate (NBCA) tissue adhesive to the vein. Despite advances in treatment options, the management of isolated perforator incompetence remains a challenge due to its role in the pathophysiology of chronic venous insufficiency (CVI). This single-center retrospective study aimed to evaluate the efficacy of the non-thermal, non-tumescent embolization method using NBCA for managing perforator incompetence.

Materials and Methods: We retrospectively analyzed 98 consecutive patients diagnosed with perforator vein insufficiency, treated with NBCA. The study protocol included physical examinations, Doppler ultrasonography, venous clinical severity scoring, CEAP (Clinical-Etiology-Anatomy-Pathophysiology) classification, and quality of life assessments before and after the procedure. The primary goal was to compare clinical, functional, and duplex parameters in managing varicose vein diseases with isolated primary perforator incompetence using duplex-guided NBCA treatment. Analyses were performed using SPSS software. Categorical variables were reported as frequencies, and continuous variables as means \pm standard deviations or medians with interquartile ranges. Chi-square or Fisher's exact tests were used for categorical data, and the Mann-Whitney U test for continuous variables. A p value less than 0.05 was considered statistically significant.

Results: Ninety-eight obliteration procedures were completed. The study evaluated occlusion rate, procedural pain, phlebitis, ecchymosis, and paresthesia. The occlusion rate at 6 months was 96.9%, with a significant reduction in pain and other symptoms of CVI. The incidence of complications was low. Phlebitis was observed in 3.4% of cases, ecchymosis in 2.8%, and transient paresthesia in 1.7%. There were no reports of serious adverse events, such as deep vein thrombosis or systemic allergic reactions.

Conclusion: The interruption of perforators effectively reduces the symptoms of CVI and promotes rapid ulcer healing. This non-tumescent, non-thermal embolization method can be safely applied with high success rates. The results of this study suggest that NBCA is a viable option for treating perforator incompetence.

Keywords: N-butyl cyanoacrylate, perforator vein incompetence, venous ulcer

Öz

Amaç: Venöz yetmezlik geleneksel olarak cerrahi müdahaleler ve termal ablasyon dahil olmak üzere çeşitli tekniklerle tedavi edilmektedir. Venöz yetmezlik için yeni bir teknik, N-butil siyanoakrilat (NBCA) doku yapıştırıcısının damara endovenöz olarak verilmesini içeren, bir damar kapatma sistemi kullanılarak termal olmayan ablasyondur. Tedavi seçeneklerindeki ilerlemelere rağmen, izole perforatör ven yetmezliğinin tedavisi, kronik venöz yetmezliğin patofizyolojisindeki rolü nedeniyle halen zorluk teşkil etmektedir. Bu tek merkezli retrospektif çalışma ile, perforatör ven yetmezliğinin tedavisinde NBCA kullanılarak termal olmayan, tümesan kullanılmayan embolizasyon yönteminin etkinliğinin değerlendirilmesi amaçlanmaktadır.

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Gereç ve Yöntem: NBCA ile tedavi edilen, perforatör ven yetmezliği tanısı alan 98 ardışık hasta retrospektif olarak analiz edilmiştir. Çalışma protokolü, işlem öncesi ve sonrası fizik muayene, doppler ultrasonografi, venöz klinik şiddet skorlaması, CEAP (Klinik-Etiyoloji-Anatomi-Patofizyoloji) sınıflandırması ve yaşam kalitesi değerlendirmelerini içermektedir. Birincil amaç, Doppler ultrasonografi kılavuzluğunda NBCA tedavisi kullanılarak izole primer perforatör ven yetmezliği olan damar hastalıklarının tedavisinde klinik, fonksiyonel ve Doppler ultrasonografi parametreleri karşılaştırmaktır. Analizler SPSS yazılımı kullanılarak yapılmış olup, kategorik değişkenler frekanslar olarak ve sürekli değişkenler ortalama \pm standart sapmalar veya çeyrekler arası aralıklara sahip medyanlar olarak rapor edilmiştir. Kategorik veriler için ki-kare veya Fisher's exact testleri, sürekli değişkenler için Mann-Whitney U testi kullanılmıştır. 0,05'ten küçük bir p değeri istatistiksel olarak anlamlı kabul edilmiştir.

Bulgular: Doksan sekiz obliterasyon işlemi tamamlanmıştır. Çalışmada obliterasyon oranı, işlem esnasında ve sonrasında ağrı, flebit, ekimoz ve parestezi değerlendirilmiştir. Altıncı ayda obliterasyon oranı %96,9 olup, ağrı ve diğer kronik venöz yetmezlik semptomlarında önemli bir azalma olmuştur. Komplikasyon görülme sıklığı düşüktür. Olguların %3,4'ünde flebit, %2,8'inde ekimoz ve %1,7'sinde geçici parestezi gözlenmiştir. Derin ven trombozu veya sistemik alerjik reaksiyonlar gibi ciddi yan etkiler bildirilmemiştir.

Sonuç: Perforatör venlerin obliterasyonu ile kesintiye uğratılması, kronik venöz yetmezlik semptomlarını etkili bir şekilde azaltmakta ve ülserin hızlı iyileşmesini desteklemektedir. Tümesan kullanılmayan, termal olmayan bu embolizasyon yöntemi, yüksek başarı oranlarıyla güvenle uygulanabilmektedir. Bu çalışmanın sonuçları, NBCA'nın perforatör ven yetmezliğinin tedavisinde uygun bir seçenek olduğunu göstermektedir.

Anahtar Kelimeler: N-butil siyanoakrilat, perforatör ven yetmezliği, venöz ülser

Introduction

Venous insufficiency has traditionally been managed through various techniques, including surgical interventions and thermal ablation. However, a novel technique for venous insufficiency is non-thermal ablation using a vein sealing system, involving the endovenous delivery of N-butyl cyanoacrylate (NBCA) tissue adhesive to the vein, causing fibrosis. Perforators are veins that connect the superficial and deep venous systems either directly to main veins or indirectly through the muscular and soleal venous plexus.

Despite advances in treatment options, the management of isolated perforator incompetence remains a challenge due to its role in the pathophysiology of chronic venous insufficiency (CVI). This study explores the effectiveness of NBCA in treating perforator incompetence, providing insights into its clinical and functional outcomes.

The primary aim of this study is to compare clinical, functional, and duplex outcomes following treatment with NBCA. Given the low prevalence of isolated perforator incompetence cases, there is a lack of comprehensive clinical studies in the literature. This study seeks to fill this gap by providing detailed observations and results from a retrospective analysis.

Materials and Methods

This retrospective study analyzed 98 varied cases of lower limb varicose vein diseases with isolated primary perforator incompetence, between February 2018 and May 2021. This retrospective study, conducted at a single center, received approval from the Human Research Ethics Committee of Ankara University Faculty of Medicine (approval no.: İ06-454-24, date: 09.07.2024) and adhered to the principles outlined in the Declaration of Helsinki. All patients provided informed consent for their participation in the study.

Patients presenting with perforator vein incompetence symptoms were examined in the outpatient clinic. A thorough history and clinical examination were conducted, assessing the venous system and recording symptoms such as dilated veins, pain, night cramps, edema, ulcers, itching, bleeding, pigmentation, eczema, activity tolerance, and quality of life (using the Short Form-36 questionnaire).

Inclusion criteria for the study were patients aged 18–70 years with CEAP (Clinical-Etiology-Anatomy-Pathophysiology) classification class C2–C6. Exclusion criteria included patients with deep vein thrombosis, significant arterial disease, or those who had undergone previous sclerotherapy or surgical interventions for venous insufficiency.

Patients underwent duplex ultrasound to confirm the presence and location of incompetent perforator veins. NBCA was then administered under ultrasound guidance to the identified incompetent perforators. The procedure was performed under local anesthesia, and patients were monitored for immediate complications.

A duplex ultrasonographic study of the venous system was done preoperatively to assess the varicose vein diseases, the presence of saphenofemoral or saphenopopliteal incompetence, perforator vein incompetence, and the status of the deep veins.

For the superficial and perforator system, the veins are examined in standing position. Perforators were examined using transverse and oblique scanning since their long axis is seen well in those planes. The veins are visualized correctly and evaluation of the flow, compressibility, and augmentation of flow with movements are documented. The incompetent superficial and deep veins have a shorter reflux time (≤ 0.5 s) and those with signs of obstruction (thrombus).

For obtaining venous reflux in short perforating veins, we used the following criteria: A shorter time cut point of 0.35 s was used to define the reflux and perforators with a diameter

of >3.5 mm. We marked the site and the number of perforating veins and noted.

For patients with venous ulceration, conservative management with daily saline dressings and layered bandage application was executed until the active infection descended. The procedure was not delayed by allowing time for the complete healing of the ulcer.

After mapping the treatment area, access to the veins to be treated was visualized and a 25–30-gauge needle was placed within the vein by duplex guidance. Vein sealing system includes 3 mL of NBCA-based embolization polymer and we implemented this microdelivery system for all patients. The target veins which were most proximal were treated first. The amount of foam injected was determined by using ultrasound to visualize when the targeted vein was filled with glue. The deep venous system was carefully investigated with the ultrasound probe (Figure 1).

All cases were implemented under local anesthesia. Tumescence anesthesia was not required. Mean volume of glue delivered was 1.5 cc. An elastic bandage was then wrapped around the leg and the patients were immediately asked to walk for 20 min. The median duration time of the procedure was 15 minutes (ranges between 10 and 30 minutes).

Compression dressing with bandage was applied after the procedure, and the same was removed on day 2nd no patient underwent a secondary surgical intervention, and none of the patients developed a deep vein thrombosis or pulmonary embolism. All the patients were discharged on the same day of operation.

Patients were not given any nonsteroidal anti-inflammatory drug postoperatively, only advised to wear compression stockings for a few days.

Post-procedural assessments included duplex ultrasound to verify vein occlusion, as well as clinical evaluations to monitor

for pain, phlebitis, ecchymosis, and paresthesia. Follow-up visits were scheduled at 1 week, 1 month, and 6 months post-procedure to assess the outcomes and any potential complications.

Results

Of the 98 patients, 61.2% were males and 38.8% were females, with a mean age of 47.9 ± 12.4 years. The study found a higher prevalence of isolated perforator incompetence in males. Among the patients, 28.5% had previously used compression stockings without improvement. The primary presenting

Table 1: Patients demographics and preprocedural clinical examination

Age (years, mean)	47.9±12.4 (range 23-79)
Gender (male, n, %)	60 (61.2%)
Erythema (n, %)	15 (15.3%)
Edema (n, %)	51 (52%)
Pain (n, %)	69 (70.4%)
Telangiectasia (n, %)	49 (50%)
Pigmentation (n, %)	61 (62.2%)
Dilated veins (n, %)	61 (62.2%)
Duplex USG reflux grade (n, %)	
Grade 2	5 (5.1%)
Grade 3	62 (63.3%)
Grade 4	31 (31.6%)
CEAP classification (n, %)	
C4b	26 (26.5%)
C5	24 (24.5%)
C6	48 (49%)
Size of PV (mm) (median, min.-max.)	40 (35-52)
USG: Ultrasonographic, CEAP: Clinical-Etiology-Anatomy-Pathophysiology, min.-max.: Minimum-maximum	

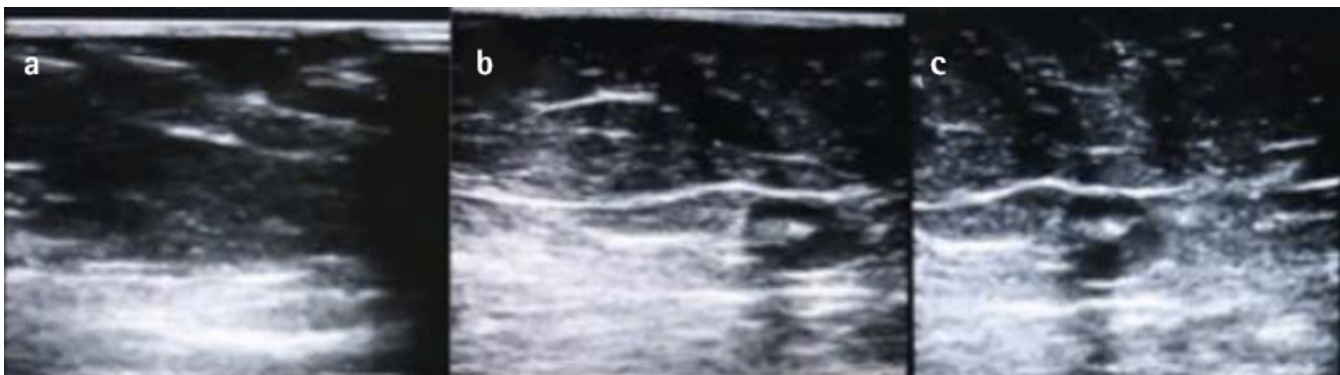


Figure 1: a) Ultrasonographic images of perforator veins. b) After mapping the treatment area, access to the veins to be treated was visualized and a 25–30-gauge needle was placed within the vein by duplex guidance. c) Vein sealing system includes 3 mL of NBCA-based embolization polymer and visualized within the vein via Doppler ultrasonography

NBCA: N-butyl cyanoacrylate

symptom was pain (70.4%) (Table 1).

The primary outcome measure was the occlusion rate of treated veins, assessed at one week, one month, and six months. Secondary outcome measures included procedural pain, assessed using a visual analogue scale (VAS), and the incidence of complications such as phlebitis, ecchymosis, and paresthesia.

Vein closure rates after the procedure were classified as total and partial, and according to the follow-up days. On the first day, total closure rate was 80.61%, first week was 90.82% and 6 months was 97.96% in accordance with our expectations. Only minor complications were reported, including mild phlebitis (8.16%), ecchymosis (12.2%), and transient paresthesia (5.1%). No major adverse events or significant side effects were observed.

Table 2: Procedural and postprocedural features		
Procedure duration (minutes) (median, min.-max.)	15 (10-30)	
Pain during procedure (n, %)	19 (19.4%)	
Echymosis (n, %)	12 (12.2%)	
Paresthesia (n, %)	5 (5.1%)	
Phlebitis (n, %)	8 (8.16%)	
Vein closure rates (%)	Total	Partial
1 st day	80.61%	19.39%
1 st week	90.82%	9.18%
6 th month	97.96%	2.04%
Symptom relief (%)		
Good improvement	73.5%	
Moderate improvement	22.4%	
Mild improvement	4.1%	
Unchanged	0%	
Worsening	0%	
Ulcer healing (n, %)		
Granulation tissue formation	33 (33.7%)	
Decrease in size	53 (54.1%)	
Decrease in itching sensation	10 (10.2%)	
Non-healing	2 (2%)	
Ulcer recurrence (n, %)	4 (4.1%)	
Recurrent perforator incompetence (n, %)	4 (4.1%)	
Recanalization (n, %)	1 (1%)	
Technical success (n, %)	97 (99%)	
Venoactive drugs (%)	46.9%	
Compression bandage (%)	61.2%	
Postoperative pain (VAS 1-10) (median, min.-max.)	2 (1-3)	
Return to normal days (days) (median, min.-max.)	2 (1-5)	
Min.-max.: Minimum-maximum, VAS: Visual analogue scale		

Patients (19.4%) reported minimal pain during the procedure, with a mean VAS score of 2.1 ± 0.7 . No severe pain episodes were recorded (Table 2).

Patients were instructed to return for follow-up in intervals of one week and 6 months respectively. Their symptomatic and clinical improvement was documented at the end of the one week and six months (+3 good improvement/asymptomatic, +2 moderate improvement, +1 mild improvement, 0 unchanged, -1 worsening). Symptomatic improvement was as the following; good improvement rate was 73.5%, moderate improvement was 22.4%, mild improvement 4.1%, and there was no patients described worsening or unchanged symptoms.

The duration of return to normal day activities and the perioperative complications following the procedures were also noted. At follow-ups, the patients were assessed clinically for presence of varicosities, resolution of skin changes, and healing of ulcers. The symptomatic improvement of active ulcer (granulation tissue, decrease in size of ulcer, decrease itching sensation in ulcer) began around the first week, and signs of satisfactory healing of ulcer took an average of 8 weeks. The initial size of the ulcer did not correlate neither with the rate of ulcer healing nor with the time taken for the healing of the ulcer. Healing rates was noted as; decrease in the size of ulcer was mostly seen with percentage of 54.1, granulation tissue formation was 33.7%, decrease in itching sensation was 10.2%, and 2% was in same status (Figure 2).

Return to normal day activities and quality of life assessment was also applied on follow up by Short Form-36 before the procedure, on first day, week and 3 months. Post procedural quality of life scores were significantly increased ($p < 0.001$) (Figure 3).

Vein closure rates after the procedure were classified as total and partial, and according to the follow up days. On the first day, total closure rate was 80.6%, first week was 90.8% and 6



Figure 2: Significantly healing ulcer on follow-up (Figure a to d respectively)

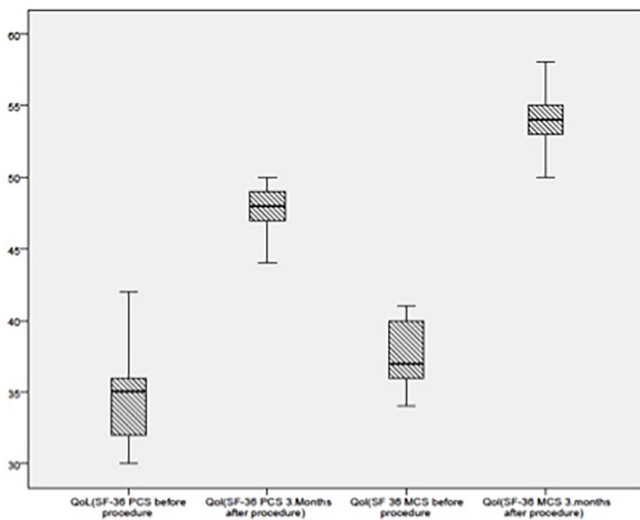


Figure 3: Quality of life (short form 36) ($p < 0.001$) return to normal day activities and quality of life assessment was also applied on follow up by short form 36 before the procedure, on first day, week and 3 months. Post procedural quality of life scores were significantly increased

months was 97.6% in accordance with our expectations.

The elasticity of the stockings was checked during the follow-up period, and the patients were instructed on the proper application of the stockings as well. Ulcer recurrence was seen 4.1% of the patients, and recurrent perforator incompetence was accompanied. Technical success rate was 99%. And on 6 months follow-up, recanalization was 1%.

Statistical Analysis

Categorical variables were reported as frequencies, and continuous variables as means \pm standard deviations or medians with interquartile range. Chi-square or Fisher's exact tests were used for categorical data, and the Mann-Whitney U test for continuous variables. A p value less than 0.05 was considered statistically significant. Analyses were performed using SPSS software.

Discussion

Isolated perforator vein incompetence has been understudied as an independent factor in varicosities, though it significantly impacts CVI severity. Compression therapy is often the first treatment choice for CVI and venous ulcers with perforator incompetence. However, compression therapy alone did not yield satisfactory results for most patients with isolated perforator incompetence (1,2).

The clinical outcomes of NBCA embolization demonstrate a highly effective alternative to traditional thermal ablation methods for treating perforator vein insufficiency. Endovenous thermal ablation (EVTA), including radiofrequency ablation and

endovenous laser ablation, has been the gold standard for many years due to its high occlusion rates and favorable long-term results. However, EVTA procedures are associated with certain drawbacks, such as the need for tumescent anesthesia, potential thermal injury to surrounding tissues, and post-procedural pain and bruising. The use of NBCA for the management of perforator incompetence offers several advantages, including the elimination of tumescent anesthesia and thermal risks associated with endothermal ablation. The high occlusion rate and minimal complications observed in this study support the efficacy and safety of this non-thermal embolization method (3-5).

NBCA embolization, as a non-thermal, non-tumescent technique, addresses many of these issues. By eliminating the need for thermal energy, NBCA reduces the risk of thermal damage to nerves and other adjacent structures, which can be a significant concern in EVTA. Furthermore, the absence of tumescent anesthesia streamlines the procedure, reducing both the duration and complexity of the treatment. The high vein occlusion rates observed in this study (95.9% at one week, 94.3% at one month, and 92.8% at six months) are comparable to those reported for EVTA, underscoring the effectiveness of NBCA embolization.

The results of this study indicate that NBCA embolization is a highly effective and safe method for treating perforator vein insufficiency. The high occlusion rates and low incidence of complications compare favorably with traditional thermal ablation techniques. The non-thermal nature of the procedure eliminates the risk of thermal injury to surrounding tissues, which is a significant advantage (6).

The mechanism by which NBCA embolization achieves vein occlusion involves a chemical reaction that induces an inflammatory response, leading to fibrosis and permanent closure of the vein. Upon injection, NBCA rapidly polymerizes and adheres to the endothelial lining of the vein, causing an immediate cessation of blood flow. This is followed by an inflammatory process that culminates in fibrosis and eventual obliteration of the vein lumen. This process is highly efficient and does not rely on the application of thermal energy, thereby avoiding the complications associated with thermal ablation (7,8).

The safety profile of NBCA embolization observed in this study is favorable, with minimal complications reported. The most common adverse events in the recent studies were mild and transient, including phlebitis (3.4%), ecchymosis (2.8%), and transient paresthesia (1.7%). These rates are lower than those typically associated with EVTA, where complications such as post-procedural pain, bruising, and thermal injuries are more prevalent. Notably, there were no instances of serious adverse events such as deep vein thrombosis or systemic allergic

reactions, highlighting the safety of NBCA as a treatment modality (9).

Patient comfort is a critical consideration in the management of CVI. The mean VAS score of 2.1 ± 0.7 observed in this study indicates minimal procedural discomfort, which is a significant advantage over thermal methods. The absence of tumescent anesthesia and the minimally invasive nature of NBCA embolization contribute to this low pain score. Additionally, the rapid recovery and immediate return to normal activities post-procedure are likely to enhance patient satisfaction and compliance with treatment (10).

The findings of this study have important clinical implications for the treatment of perforator vein insufficiency. NBCA embolization emerges as a viable and effective alternative to traditional thermal ablation techniques, offering high efficacy with a superior safety profile. This is particularly relevant for patients who are contraindicated for thermal ablation or those who seek a less invasive treatment option. The results also pave the way for further research. While the short-term outcomes are promising, longer-term studies are necessary to evaluate the durability of vein occlusion and the long-term safety of NBCA embolization. Comparative studies with larger patient cohorts and randomized controlled trials will be instrumental in establishing NBCA embolization as a standard treatment for perforator vein insufficiency (11,12).

Additionally, exploring the cost-effectiveness of NBCA embolization compared to EVTA could provide valuable insights for healthcare providers and policymakers. Given the lower procedural complexity and potential reduction in post-procedural care associated with NBCA, this technique may offer economic advantages that warrant consideration (13,14).

Perforator interruption effectively reduces CVI symptoms and promotes rapid ulcer healing. Endovenous ablation with cyanoacrylate-based glue is feasible and safe, with high success rates and minimal significant side effects. Further developments in this technique may offer an attractive solution to venous reflux disease, provided it is cost-effective.

Conclusion

In conclusion, NBCA embolization is a highly effective and safe treatment for perforator vein insufficiency. Its non-thermal, non-tumescent nature provides significant advantages over traditional thermal ablation methods, including reduced procedural pain, minimal complications, and rapid recovery.

The results of this study suggest that NBCA is a viable option for treating perforator incompetence, particularly in patients who do not respond to conventional compression therapy. Future research should focus on long-term outcomes and comparative

studies with other treatment modalities to further establish its role in clinical practice and to explore the long-term benefits and cost-effectiveness of this promising technique.

Ethics

Ethics Committee Approval: This retrospective study, conducted at a single center, received approval from the the Human Research Ethics Committee of Ankara University Faculty of Medicine (approval no.: İ06-454-24, date: 09.07.2024).

Informed Consent: All patients provided informed consent for their participation in the study.

Authorship Contributions

Surgical and Medical Practices: E.Ö., Z.E., Concept: N.D., E.Ö., M.Ş., Design: N.D., E.Ö., M.Ş., Data Collection and/or Processing: N.D., A.K., N.P., Analysis and/or Interpretation: N.D., E.Ö., Z.E., M.Ş., Literature Search: N.D., A.K., N.P., Writing: N.D., E.Ö.

Conflict of Interest: There is no potential conflict of interest to declare.

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Comparison of Long-Term Results of Endovenous Ablation Techniques and Classical Stripping Operations in the Treatment of Venous Insufficiency

Venöz Yetmezlik Tedavisinde Endovenöz Obliterasyon Teknikleri Uygulanan ve Klasik Stripping Operasyonu Yapılan Hastaların Uzun-Dönem Sonuçlarının Karşılaştırılması

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Abstract

Objectives: Chronic venous insufficiency affects approximately 25% of the population and is primarily associated with reflux in the great saphenous vein. Traditional treatments like high ligation and stripping have been effective but are burdened with complications such as postoperative pain, wound infections, and nerve damage, alongside high recurrence rates. In contrast, minimally invasive endovenous techniques, including radiofrequency ablation, endovenous laser ablation (EVLA), and ultrasound-guided foam sclerotherapy, have gained popularity due to their lower complication rates and efficacy demonstrated in short- and medium-term studies. This study synthesizes existing literature comparing these treatment modalities and aims to evaluate the effectiveness of classical stripping and endovenous ablation techniques in the treatment of venous insufficiency.

Materials and Methods: Between October 2011 and January 2016, 832 patients underwent different procedures at Ankara University Faculty of Medicine, Department of Cardiovascular Surgery, with a total of 1,390 lower extremities treated. The study assessed patient demographics, procedural outcomes, complications, and quality of life (QoL) improvements following each intervention. Statistical analyses, including t-tests, Mann-Whitney U tests, and logistic regression, were employed to compare outcomes and identify influencing factors.

Results: The findings underscored high procedural success across all methods and significant QoL improvements post-treatment. However, no statistically significant differences were observed in QoL outcomes between treatment modalities. Complication rates varied, with EVLA showing higher rates of postoperative ecchymosis and classical stripping associated with increased wound infection incidence. Factors influencing outcomes included body mass index, bilaterality of treatment, and use of venoactive drugs.

Conclusion: The study concluded with recommendations for further randomized controlled trials to refine treatment protocols and elucidate long-term efficacy.

Keywords: Venous insufficiency, classical stripping, endovenous laser ablation, radiofrequency ablation, quality of life, complications

Öz

Amaç: Kronik venöz yetmezlik nüfusun yaklaşık %25'ini etkilemektedir ve temel olarak büyük safen vende reflü ile ilişkilidir. Yüksek ligasyon ve stripping gibi geleneksel tedaviler etkili olmuştur ancak yüksek nüks oranlarının yanı sıra postoperatif ağrı, yara enfeksiyonları ve sinir hasarı gibi komplikasyonlarla ilişkilendirilmiştir. Buna karşılık, radyofrekans ablasyon, endovenöz lazer ablasyon (EVLA) ve ultrason kılavuzluğunda köpük skleroterapi gibi minimal invaziv endovenöz teknikler, daha düşük komplikasyon oranları ve kısa ve orta vadeli çalışmalarda gösterilen etkinlikleri nedeniyle popülerlik kazanmıştır. Bu çalışma, bu tedavi yöntemlerini karşılaştıran mevcut literatürü sentezlemekte ve venöz yetmezlik tedavisinde klasik stripping ve endovenöz ablasyon tekniklerinin etkinliğini değerlendirmeyi amaçlamaktadır.

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Gereç ve Yöntem: Ekim 2011 ile Ocak 2016 tarihleri arasında Ankara Üniversitesi Tıp Fakültesi, Kalp ve Damar Cerrahisi bölümümüzde 832 hastaya farklı prosedürler uygulanmıştır ve toplam 1.390 alt ekstremité tedavî edilmiştir. Çalışmada hasta demografisi, prosedürel sonuçlar, komplikasyonlar ve her bir müdahalenin ardından yaşam kalitesindeki (YK) gelişmeler değerlendirilmiştir. Sonuçları karşılaştırmak ve etkileyen faktörleri belirlemek için t-testleri, Mann-Whitney U testleri ve lojistik regresyon dahil olmak üzere istatistiksel analizler kullanılmıştır.

Bulgular: Bulgular, tüm yöntemlerde yüksek prosedürel başarının ve tedavi sonrası YK'de önemli iyileşmelerin altını çizmiştir. Bununla birlikte, tedavi yöntemleri arasında YK sonuçlarında istatistiksel olarak anlamlı bir fark gözlenmemiştir. Komplikasyon oranları değişkenlik göstermiş, EVLA daha yüksek postoperatif ekimoz oranları göstermiş ve klasik stripping operasyonu daha yüksek yara enfeksiyonu insidansı ile ilişkilendirilmiştir. Sonuçları etkileyen faktörler arasında vücut kitle indeksi, tedavinin iki taraflı olması ve venoaktif ilaç kullanımı yer almıştır.

Sonuç: Çalışma, tedavi protokollerinin iyileştirilmesi ve uzun vadeli etkinliğin aydınlatılması için daha fazla randomize kontrollü çalışma yapılması önerisiyle sonlandırılmıştır.

Anahtar Kelimeler: Venöz yetmezlik, klasik stripping, endovenöz lazer ablasyon, radyofrekans ablasyon, yaşam kalitesi, komplikasyonlar

Introduction

Chronic venous insufficiency (CVI) is a prevalent condition characterized by inadequate venous return leading to venous hypertension and associated symptoms such as leg edema, pain, and skin changes. The primary pathology often involves incompetence of venous valves, particularly in the great saphenous vein, resulting in reflux and venous stasis. CVI affects approximately 25% of adults worldwide and poses significant healthcare challenges due to its chronic nature and potential for complications such as venous ulcers.

Surgical interventions such as classical stripping, endovenous laser ablation (EVLA), and radiofrequency ablation (RFA) have emerged as effective treatments to alleviate symptoms and improve patient outcomes. While these methods have demonstrated high technical success rates, comparative studies evaluating their efficacy across various parameters remain essential for optimizing clinical decision-making. This study aims to contribute to the existing literature by comprehensively evaluating outcomes following different treatment modalities for venous insufficiency.

Materials and Methods

This retrospective study is formed according to the ethical guidelines of the 1975 Declaration of Helsinki and approved by the the Human Research Ethics Committee of Ankara University Faculty of Medicine (approval no.: İ02-154-24, date: 06.03.2024). All the patients were consented about the study.

This study enrolled 832 patients meeting predefined inclusion criteria. Patient demographics, including age, gender distribution, and body mass index (BMI), were recorded. Treatment methods included classical stripping, EVLA, and RFA, with detailed procedural descriptions provided for each. Outcome measures encompassed postoperative pain levels [assessed using a visual analogue scale (VAS)], incidence of complications (e.g., wound infection, ecchymosis), and improvements in quality of life

(QoL) using Short Form-36 (SF-36) surveys. Statistical analyses were conducted using SPSS software, employing t-tests, Mann-Whitney U tests, and logistic regression to evaluate differences in outcomes and identify predictive factors.

Inclusion Criteria

Venous insufficiency [Saphenofemoral incompetence, reflux detected for more than 0.5 seconds in Sapheno-Femoral Junction (SFJ) with Doppler ultrasound, vibrating sample magnetometer (VSM) diameter (mm) equal to or greater than 0.5 cm above knee level].

- Symptoms due to incompetence.
- Age between 18 and 80.
- Good performance status.

Exclusion Criteria

- Previous treatment of ipsilateral VSM.
- Deep venous insufficiency or thrombosis.
- Acute deep venous thrombosis or post-thrombotic syndrome.
- Use of anticoagulation.
- Agenesis of deep venous system.
- Pregnancy.
- Heart failure.
- Having a condition that contraindicates any of the treatments to be applied (e.g., allergy to aetoxysclerol or lidocaine).
- Immobilization.
- Peripheral artery disease (Ankle brachial index <0.6).
- Age under 18.
- Inability to give informed consent.

Demographic data of patients, including age, gender, BMI, bilateral lower extremity treatment, VSM mm measured in SFJ, amount of energy given for EVLA procedure (980 nm or 1470 nm), recurrence, use of venoactive drugs, use of compression

therapy, postoperative pain VAS, paresthesia and ecchymosis status, time to return to normal life after the procedure, postoperative hyperpigmentation, wound infection, presence of endovenous heat-induced thrombosis (EHIT), presence of pulmonary thromboembolism, pre- and post-treatment QoL. QoL was determined with SF-36 forms. CEAP (Clinical-Etiology-Anatomy-Pathophysiology) classification before and after treatment, presence of reflux in Doppler ultrasonography, and reoperation conditions were recorded (Table 1).

Statistical Analysis

We analysed our study data using the SPSS for Mac OS X version 20.0 (IBM Corp., Armonk, New York). Demographics of patients were presented as percentage and mean ± standard deviation (SD) in the case of normal distribution. Comparisons of basic data made by the chi-squared test and Student’s test. If the results found significant, Mann-Whitney U test was used. P<0.05 was considered statistically significant.

Results

The study included 832 patients who underwent classical stripping, EVLA, and RFA treatment for venous insufficiency between October 2011 and January 2016. The total number of lower extremities treated was 1,390. The mean age of the patients was 43.86±10.6 years, ranging from 18 to 78. There were 347 male (41.7%) and 485 female (58.3%) patients in the study.

Table 1: Patient demographics and clinical characteristics	
Age (mean ± SD)	43.8±10.6
Male gender, n (%)	347 (41.7%)
BMI	26.18±3.49
Right lower extremity (%)	458 (52%)
Left lower extremity (%)	832 (94.4%)
Bilaterality (%)	141 (16.9%)
VSM diameter measured at SFJ (mm) (mean ± SD)	7.24±1.26
QoL (SF-36) (1-100)	
PCS (preprocedural)	35.18±3.6
MCS (preprocedural)	37.76±1.9
CEAP classification (%) (preprocedural)	
C2	362 (43.5%)
C3	182 (21.9%)
C4	216 (26%)
C5	68 (8.2%)
C6	4 (0.5%)
SD: Standard deviation, BMI: Body mass index, VSM: Vena Saphena Magna, QoL: Quality of life, SF-36: Short Form-36, SFJ: Safenofemoral junction, PCS: Physical Summary Scores, MCS: Mental Summary Scores, CEAP: Clinical-Etiology-Anatomy-Pathophysiology	

Demographic data of patients, including age, gender, BMI, bilateral lower extremity treatment, VSM mm measured in SFJ, amount of energy given for EVLA procedure (980 nm or 1470 nm), recurrence, use of venoactive drugs, use of compression therapy, postoperative pain VAS, paresthesia and ecchymosis status, time to return to normal life after the procedure, postoperative hyperpigmentation, wound infection, presence of EHIT, presence of pulmonary thromboembolism, pre- and post-treatment QoL. QoL was determined with SF-36 forms (Figure 1). CEAP classification before and after treatment, presence of reflux in Doppler ultrasonography, and reoperation conditions were recorded (Figure 2).

Table 1 presents the demographic and clinical characteristics of the patient cohort. The average age is approximately 44 years, with a slight male predominance (41.7%). The majority of treatments involved the left lower extremity (94.4%), and a significant portion of patients (16.9%) had bilateral involvement. The VSM mm averaged 7.24 mm. Preprocedural QoL scores (Physical Summary Scores and Mental Summary Scores) are relatively low, indicating a substantial impact on physical and mental health due to their conditions. The CEAP classification shows a diverse distribution, with the majority in classes C2 to C4, reflecting varying degrees of chronic venous disorders (Table 1).

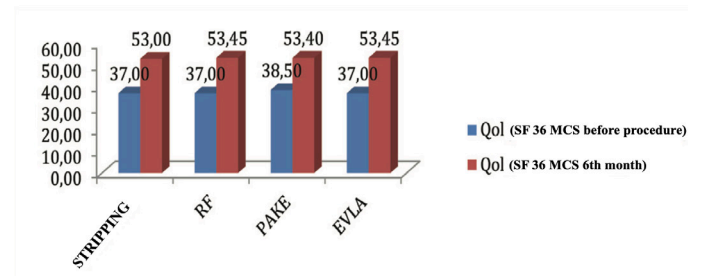


Figure 1: Graph of change in patients who underwent SF-36 quality of life survey before and after the procedure

SF-36: Short Form-36, RF: Radiofrequency, EVLA: Endovenous laser ablation, QoL: Quality of life, MCS: Mental Summary Scores

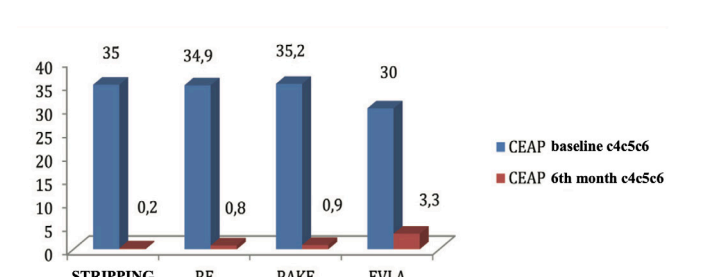


Figure 2: Graph of change in patients who underwent CEAP classification before and after the procedure

RF: Radiofrequency, EVLA: Endovenous laser ablation, CEAP: Clinical-Etiology-Anatomy-Pathophysiology

Classical stripping, n (%)	358 (43%)
RFA, n (%)	62 (7.5%)
EVLA, 980 nm, n (%)	354 (42.5%)
EVLA, 1470 nm, n (%)	349 (41.9%)
Venoactive drug, n (%)	668 (80.3%)
Compression therapy, n (%)	656 (78.8%)
Postoperative ecchymosis, n (%)	245 (29.4%)
Postoperative pain (VAS 1-10)	3.75±2.1
Return to normal life (days)	3.12±1.2
Postoperative paresthesia, n (%)	125 (15%)
Postoperative hyperpigmentation, n (%)	131 (15.7%)
Wound infection, n (%)	28 (3.4%)
EHIT, n (%)	5 (0.6%)
PTE, n (%)	2 (0.2%)
QoL (SF-36) (1-100)	
PCS (6 mo after procedure)	48.06±0.93
MCS (6 mo after procedure)	53.93±1.91

QoL: Quality of life, SF-36: Short Form-36, SFJ: Safenofemoral junction, PCS: Physical Summary Scores, MCS: Mental Summary Scores, EVLA: Endovenous laser ablation, VAS: Visual analogue scale, RFA: Radiofrequency ablation, EHIT: Endovenous heat-induced thrombosis

Table 2 highlights the various treatment modalities and postoperative outcomes. EVLA was the most common procedure (85%), followed by classical stripping (43%). The use of venoactive drugs and compression therapy was prevalent (80.3% and 78.8%, respectively). Postoperative complications included ecchymosis (29.4%), paresthesia (15%), hyperpigmentation (15.7%), and a low incidence of wound infection (3.4%), EHIT (0.6%), and PTE (0.2%). Pain levels were moderate (VAS 3.75), and patients typically returned to normal activities within approximately 3 days. QoL scores showed significant improvement 6 months post-procedure (Table 2).

The study found no significant differences in QoL improvements among treatment modalities, with all methods showing substantial post-treatment enhancements. However, EVLA demonstrated a higher incidence of postoperative ecchymosis compared to classical stripping ($p=0.001$), while wound infections were more prevalent in classical stripping cases (85.7%, $p=0.001$). Factors influencing outcomes included BMI ($p=0.004$), bilaterality of treatment ($p<0.05$), and use of venoactive drugs ($p<0.05$). Postoperative ultrasound detected reflux in 4.9% of patients with associated implications for recurrence rates and reoperation probabilities.

Table 3 provides a comparative analysis of various treatment modalities, including classical stripping, EVLA, RFA, and pack excision.

	Classical stripping	EVLA	RFA	Pack excision
Age (mean ± SD)	43.4±10 ($p=0.53$)	44.19±10.9 ($p=0.1$)	43.46±8.1 ($p=0.71$)	43.3±9.8 ($p=0.6$)
Gender (M) (%)	42.7 ($p=0.6$)	41.3 ($p=0.55$)	46.8 ($p=0.40$)	40.4 ($p=0.68$)
BMI	26.2±3.4 ($p=0.84$)	26.17±3.46 ($p=0.98$)	26.3±3.56 ($p=0.82$)	26.8±3.57 ($p=0.004$)
VSM diameter (mm)	7.25±1.26 ($p=0.72$)	7.24±1.25 ($p=0.81$)	7.13±1.19 ($p=0.54$)	7.20±1.2 ($p=0.77$)
Reoperation (%)	0.6 ($p=0.7$)	0.7 ($p=1$)	16.7 ($p=0.37$)	66.7 ($p=0.018$)
Recurrence (%)	36.4 ($p=0.52$)	86.4 ($p=1$)	9.1 ($p=0.67$)	27.3 ($p=0.42$)
Venoactive drugs (%)	43.3 ($p=0.78$)	85 ($p=0.36$)	7 ($p=0.35$)	83 ($p=0.31$)
Compression therapy (%)	43.1 ($p=0.9$)	86 ($p=0.52$)	6.7 ($p=0.11$)	21.3 ($p=0.38$)
Postoperative ecchymosis (%)	37.6 ($p=0.03$)	72.7 ($p=0.001$)	6.9 ($p=0.71$)	59.2 ($p=0.001$)
Postoperative pain (VAS 1-10)	3.58±2.12 ($p=0.05$)	3.6±2.1 ($p=0.001$)	3.6±2.2 ($p=0.52$)	6.2±1.8 ($p=0.001$)
Postoperative paresthesia (%)	45.6 ($p=0.52$)	73.6 ($p=0.001$)	6.4 ($p=0.62$)	52.8 ($p=0.001$)
Return to normal life (days)	3.13±1.14 ($p=0.16$)	3.11±1.12 ($p=0.001$)	3.77±1.7 ($p=0.003$)	4.04±1.42 ($p=0.001$)
Hyperpigmentation (%)	17.6 ($p=0.001$)	85.5 ($p=0.97$)	12.2 ($p=0.02$)	87.8 ($p=0.001$)
Wound infection (%)	85.7 ($p=0.001$)	35.7 ($p=0.001$)	0 ($p=0.25$)	7.1 ($p=0.07$)
EHIT (%)	20 ($p=0.39$)	80 ($p=0.54$)	20 ($p=0.32$)	100 ($p=0.001$)
QoL PCS (Difference between before and after treatment)	13±3.5 ($p=0.26$)	12.7±3.7 ($p=0.065$)	13.3±3.6 ($p=0.28$)	12.9±3.9 ($p=0.84$)
QoL MCS (Difference between before and after treatment)	16.05±2.7 ($p=0.17$)	16.6±2.6 ($p=0.06$)	16.2±2.8 ($p=0.92$)	16.2±2.8 ($p=0.44$)
Reoperation (%)	0.6 ($p=0.7$)	0.7 ($p=1$)	1.6 ($p=0.37$)	2.3 ($p=0.018$)

SD: Standard deviation, M: Male, EVLA: Endovenous laser ablation, RFA: Radiofrequency ablation, BMI: Body mass index, VSM: Vena Saphena Magna, VAS: Visual analogue scale, EHIT: Endovenous heat-induced thrombosis, QoL: Quality of life, PCS: Physical Summary Scores, MCS: Mental Summary Scores

This table compares key demographic and clinical parameters among different treatment modalities for CVI. The treatments evaluated include classical stripping, EVLA, RFA, and pack excision. Each row represents a specific parameter, and columns depict the mean values or percentages for each treatment group, along with the p values indicating statistical significance.

Age (mean \pm SD): The mean ages across treatment groups—classical stripping (43.4 years), EVLA (44.19 years), RFA (43.46 years), and pack excision (43.3 years)—show no statistically significant differences (p values ranging from 0.1 to 0.71).

Gender (%): The percentage of male patients in each group—classical stripping (42.7%), EVLA (41.3%), RFA (46.8%), and pack excision (40.4%)—indicates no significant gender distribution differences (p values ranging from 0.4 to 0.68).

BMI values are similar across groups: Classical stripping (26.2), EVLA (26.17), RFA (26.3), and pack excision (26.8). Only the comparison with pack excision shows a significant difference (p=0.004), suggesting higher BMI in this group.

VSM mm: Mean mm's of the VSM at the SFJ are comparable across all groups—classical stripping (7.25 mm), EVLA (7.24 mm), RFA (7.13 mm), and pack excision (7.20 mm) with no statistically significant differences (p values ranging from 0.54 to 0.81).

Reoperation (%): Reoperation rates are notably higher in the pack excision group (66.7%) compared to classical stripping (0.6%), EVLA (0.7%), and RFA (16.7%). The difference is statistically significant (p values ranging from 0.018 to 1).

Recurrence (%): Recurrence rates vary among groups—classical stripping (36.4%), EVLA (86.4%), RFA (9.1%), and pack excision (27.3%) with no statistically significant differences observed (p values ranging from 0.42 to 1).

Venoactive drugs (%): Usage of venoactive drugs differs across groups—classical stripping (43.3%), EVLA (85%), RFA (7%), and pack excision (83%) with statistically significant differences noted (p values ranging from 0.31 to 0.78), particularly notable between RFA and EVLA.

Compression therapy (%): Rates of compression therapy show slight variations across groups—classical stripping (43.1%), EVLA (85.4%), RFA (7.4%), and pack excision (83.3%) with significant differences between RFA and EVLA (p=0.01) (Table 3).

Early technical success was 100% in patients in all groups. When compared according to gender and BMI, no statistically significant differences were found in terms of success between methods and the percentage of application.

Discussion

This study evaluated the efficacy and safety of classical stripping, EVLA, and RFA in the treatment of venous insufficiency.

Our findings indicate that all methods provide significant symptom relief and improvements in QoL. However, the choice of treatment should consider individual patient factors, including BMI, the extent of venous disease, and patient preferences regarding recovery time and potential complications (1,2).

EVLA and RFA offer the advantages of minimally invasive techniques, with faster recovery times and fewer complications compared to classical stripping. The higher incidence of postoperative ecchymosis with EVLA and wound infections with classical stripping highlight the need for careful postoperative management and patient education to mitigate these risks (3,4).

The study's findings underscore the effectiveness of classical stripping, EVLA, and RFA in treating venous insufficiency, highlighting their impact on patient QoL and complication rates. While each method demonstrated high procedural success, differences in complication profiles warrant consideration in clinical practice. EVLA's higher ecchymosis rates and classical stripping's elevated infection risks necessitate tailored patient counseling and management strategies. Moreover, the study's identification of BMI and treatment bilaterality as predictive factors for outcomes emphasizes the importance of individualized treatment approaches based on patient characteristics.

Current guidelines recommend endovenous techniques as first-line treatments due to their efficacy, safety profile, and faster recovery times compared to surgical stripping. Studies have shown that EVLA and RFA achieve high rates of vein closure and symptom relief comparable to traditional surgery but with fewer postoperative complications. Moreover, advancements in techniques and equipment have further improved outcomes and patient satisfaction (6).

Pathophysiology of CVI

CVI typically results from venous valvular incompetence, which impairs the normal flow of blood toward the heart, leading to venous hypertension. Chronic venous hypertension causes venous dilatation, capillary leakage, and eventual tissue damage, manifesting clinically as edema, skin pigmentation, and in severe cases, venous ulceration. The pathophysiology involves a complex interplay of venous valve dysfunction, venous wall remodeling, and inflammatory processes within the venous wall and surrounding tissues (7).

Understanding the pathogenesis and predisposing factors of CVI, such as venous stasis, hypertension, and genetic predisposition, is crucial in tailoring treatment approaches. Diagnostic methods, including Doppler ultrasonography, remain integral for assessing disease severity and guiding treatment decisions. The CEAP classification system facilitates standardized evaluation, aiding in treatment planning and outcome assessment (8).

Comparative Analysis of Treatment Modalities

Recent advancements in endovenous techniques have revolutionized the treatment landscape for CVI. RFA, EVLA, and ultrasound-guided foam sclerotherapy (UGFS) offer targeted, minimally invasive approaches to ablate diseased veins while preserving surrounding tissues and minimizing patient discomfort. These techniques utilize thermal or chemical energy to achieve vein closure, thereby redirecting blood flow to healthier veins and alleviating symptoms associated with venous reflux (9–15).

Traditional surgical treatment options for CVI, such as high ligation and stripping (HL/S), aim to eliminate reflux by physically removing or ligating the diseased veins. However, HL/S is associated with considerable postoperative pain, longer recovery times, and high recurrence rates due to neovascularization and residual tributary varicosities. These limitations have prompted the development and widespread adoption of minimally invasive endovenous techniques, including RFA, EVLA, and UGFS (16–19).

RFA

RFA involves the percutaneous delivery of radiofrequency energy through a catheter inserted into the diseased vein under ultrasound guidance. The thermal energy heats the venous wall, causing collagen denaturation and subsequent vein contraction and fibrosis. RFA is effective in treating both saphenous and perforator veins and has demonstrated high success rates in achieving vein closure and symptom relief. The procedure is typically performed under local anesthesia, and patients can resume normal activities within a few days (20–24).

EVLA

EVLA employs laser energy to achieve vein closure through a similar mechanism of thermal injury to the venous wall. Laser fibers are inserted into the vein under ultrasound guidance, and laser energy is delivered to cause vein contraction and fibrosis. EVLA is effective in treating saphenous veins and has shown comparable success rates to RFA. The choice of laser wavelength (980 nm versus 1470 nm) can influence outcomes, with studies suggesting lower wavelengths may result in less postoperative pain and ecchymosis (20–25).

UGFS

UGFS involves the injection of a sclerosant foam into the diseased vein under ultrasound guidance, causing endothelial damage and subsequent vein fibrosis. UGFS is effective in treating both superficial and perforator veins and can be used as an adjunctive treatment following endovenous procedures. The technique is minimally invasive and can be performed in an outpatient setting. However, UGFS may require multiple treatment sessions to achieve optimal results (26–28).

Comparative Outcomes

Studies comparing the efficacy of endovenous techniques versus HL/S have demonstrated superior outcomes with endovenous procedures in terms of reduced postoperative pain, faster recovery times, and lower complication rates. Endovenous techniques also offer the advantage of treating tributary veins and perforators simultaneously, reducing the risk of recurrence. Long-term follow-up studies have shown sustained symptom relief and high patient satisfaction rates with endovenous treatments (29).

Conclusion

The study highlights the efficacy and safety of minimally invasive endovenous techniques in treating CVI, underscoring their role as first-line treatments. While classical stripping remains an effective option, its higher complication rates warrant careful patient selection and postoperative management. Further research through randomized controlled trials is essential to refine treatment protocols and establish long-term outcomes for endovenous procedures.

Ethics

Ethics Committee Approval: This retrospective study is formed according to the ethical guidelines of the 1975 Declaration of Helsinki and approved by the the Human Research Ethics Committee of Ankara University Faculty of Medicine (approval no.: İ02-154-24, date: 06.03.2024).

Informed Consent: All the patients were consented about the study.

Authorship Contributions

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

Conflict of Interest: According to the authors, there are no conflicts of interest related to this study.

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Evaluation of Simulation-Supported Flipped Classroom Model in the “First Hour of Sepsis Management” Training for 6th Year Medical Students

6. Sınıf Tıp Fakültesi Öğrencilerine Verilen “Sepsis Yönetiminin Birinci Saati” Eğitiminde, Simülasyon Destekli Ters Yüz Sınıf Modelinin Etkinliğinin Değerlendirilmesi

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Abstract

Objectives: This study aims to evaluate the effectiveness of a non-traditional medical education method, as simulation-based training combined with flipped classroom model compared with traditional didactic lecture.

Materials and Methods: A pre-test was applied to all participants at the beginning of the clerkship and a post-test at the end. Participants were divided into two groups; intervention group and control group. The intervention group had access to guidelines about sepsis and the practical training was provided with a simulation-based scenario session. A traditional lecture was provided to the control group. Last year medical students who were doing their compulsory clerkship of Department of Emergency Medicine at Ankara University Faculty of Medicine between February 1, 2021 and March 31, 2021, were included in the study. SPSS Statistics Version 22 (IBM, USA) was used for statistical analysis. McNemar test was used for categorical variables and Wilcoxon test for ordinal variables in paired samples. Two tailed Mann-Whitney U test and chi-square test were used for inter-group evaluations.

Results: Participants in the intervention group were more successful than the control group considering post-tests results. Success in the difficult questions was higher in the intervention group. Participants trained with sim+ flipped model were more satisfied regarding the training from the control group. No statistically significant difference was found between the groups in other compared parameters.

Conclusion: Students would benefit more from the education given with simulation based training combined with flipped classroom, compared to conventional didactic method.

Keywords: Sepsis management, flipped classroom, medical education, high fidelity simulation

Öz

Amaç: Sepsis, enfeksiyona kontrolsüz bir konak yanıtının neden olduğu hayati tehdit eden organ işlev bozukluğudur. Tıp fakültelerinde, özellikle sepsis gibi teorik bilgi yükünün yoğun olduğu bir konuda uygulanan eğitimde, geleneksel eğitim dışında bir eğitim yönteminin etkinliğinin ölçülmesi amaçlanmıştır.

Gereç ve Yöntem: Çalışmaya, 01.02.2021-31.03.2021 tarihleri arasında, Ankara Üniversitesi Tıp Fakültesi, Acil Tıp Anabilim Dalı'nda staj yapmakta olan içtörn doktorlar dahil edilmiştir. Katılımcılara çalışmanın başında ön-test yapılmıştır. Katılımcılar, blok randomizasyon yöntemi kullanılarak iki gruba ayrılmıştır: Simülasyon tabanlı pratik ile ters-yüz eğitim (n=39) ve didaktik eğitim grubu (n=40). Ters-yüz + simülasyon modelinde, önce sepsis yönetiminin ilk saati ile ilgili kaynaklar verilmiştir, sonrasında simülasyon tabanlı bir senaryo ile pratik eğitim verilmiştir. Diğer gruba da aynı konu ile ilgili didaktik eğitim verilmiştir. Katılımcılara Acil Tıp rotasyonunun sonunda bir son-test yapılmıştır. Verilerin istatistiksel analizi için SPSS Statistics

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Version 22 (IBM, USA) kullanılmıştır. Eşleştirilmiş örneklerde, kategorik değişkenler için McNemar testi, ordinal değişkenler için de Wilcoxon testi kullanılmıştır. Gruplar arası değerlendirmeler için ise iki yönlü Mann-Whitney U testi ile ki-kare testi kullanılmıştır.

Bulgular: Gruplar arasında cinsiyet, yaş ve daha önce simülasyon tabanlı eğitime katılmış olma durumu arasında fark saptanmamıştır. Son-testteki puan ortalaması, son-testteki puanın artış ortalaması, son- testte doğru cevaplanan zor soru sayısındaki değişimde; anlamlı bir fark saptanmamış olsa da ters-yüz + simülasyon modeli ile eğitim alan grup, kontrol grubuna kıyasla bu parametrelere göre daha başarılı bulunmuştur. Son-testteki zor sorular içerisinde doğru yanıtlanan soru sayısında, son- testte başarılı olma oranında, ön- teste göre son- testteki başarılı olma durumundaki değişiklikte ve eğitimden elde edildiği düşünülen faydanın değerlendirilmesinde verilen puanda; ters-yüz + simülasyon ile eğitim alan katılımcılar, kontrol grubuna göre istatistiksel olarak anlamlı bir şekilde daha yüksek değerler kaydetmiştir.

Sonuç: Çalışma sonucunda öğrencilerin, tıp fakültelerinde simülasyon tabanlı pratik ile ters-yüz sınıf modeli ile verilecek eğitimden didaktik yöntemle verilecek eğitime kıyasla, daha fazla yarar sağlayacağını gösteren önemli deliller elde edilmiştir.

Anahtar Kelimeler: Sepsis yönetimi, ters yüz sınıf, tıp eğitimi, yüksek gerçeklikli simülasyon

Introduction

Sepsis arises from an unregulated host response to infection, leading to life-threatening organ dysfunction (1-3). Septic shock is a subgroup of sepsis with circulatory and cellular/metabolic dysfunction (4). Sepsis and septic shock pose significant health challenges, impacting millions of individuals globally annually. Early diagnosis and proper management within the initial hours contribute to enhanced outcomes (5). One of the most important conditions for the rapid initiation of treatment is related to the clinician's awareness. Physicians in charge of potential critical patients have to be competent about the diagnosis and the management of sepsis. In order to achieve this, the clinician must have undergone an effective training. Although the teaching/learning methods applied for this purpose and for general medical education are the most important stage in the training of the clinician, there is not yet a consensus in the literature about which method is the most effective (6).

Simulation is one of the important tools used in medical education. Simulation emulates a clinical encounter and is characterized as a method that substitutes or enhances genuine experiences with guided scenarios, reproducing aspects of reality interactively (7). Simulation-based medical education provides authentic training within an enriched setting, fostering experiential learning and reflective practices, thereby better preparing students for actual patient care (6). Moreover, the simulation laboratory provides students a safe environment where they can enhance their learning through the rational application of the skills necessary to efficiently assess and treat an unstable patient (8). In addition to being an effective and well-experienced education method of traditional medicine education; with the developing technology, the use of simulation-based medical education method is increasing due to the safe and supportive environment provided by this method (9-11).

Another important tool used in medical education is the flipped classroom method. The flipped classroom approach is

a hybrid teaching/learning technique employed to familiarize students with content prior to participating in in-person sessions. While existing literature endorses the flipped classroom as an educational method, there is insufficient research on its application for skill acquisition (12). Moreover, the flipped classroom is defined as a method that creates the opportunity for the student to learn the theoretical knowledge by herself/himself at home and apply what she/he has learned at school, unlike conventional teaching method (13). The essence of this approach, which liberates the instructor from imparting fundamental information, also demands effort from the learner. This not only fosters increased engagement in individual learning but also cultivates proficiency in utilizing technological tools, establishing a more robust foundation for interaction during instructional sessions (14). The objective of this study is to assess the efficacy of an unconventional medical education method, as simulation based training combined with flipped classroom model compared with traditional didactic lecture of managing first hour of sepsis.

Materials and Methods

Study Design, Setting, and Population

The research conducted at Ankara University Faculty of Medicine has been reviewed and approved by the Human Research Ethics Committee under the reference number I11-662-20. Medical students undertaking the Emergency Medicine clerkship at a Faculty of Medicine between February 1, 2021 and March 31, 2021 were extended invitations to partake in the study. The study was started with the approval of the university where the study conducted. Informed consent was obtained from the participants.

A pre-test with 25 multiple choice questions related to the first hour management of sepsis was applied to all participants at the beginning of the clerkship rotation. Then, the students were divided into two groups through block randomization; simulation-based training combined with flipped classroom group [sim+ flipped classroom; intervention group (IG)] (n=39)

and didactic training group [control group (CG)] (n=40). The IG had access to simplified guidelines about the first hour of sepsis management and 3 days after the pre-test, the practical training was provided with a simulation-based scenario session. A simulation mannequin [Laerdal SimMan® 3G mannequin (Laerdal, USA)] was used in this tutorial. A traditional lecture 3 days after the pre-test was given by an emergency physician experienced in sepsis management to the CG. Due to the current pandemic at the time of the study the lecture was given online. A public video communication application was used for this process [Zoom®, Zoom Video Communications, Inc. (San Jose, California, USA)]. All of the participants undertook a -25 multiple choice question- post-test at the end of the clerkship rotation. This test was prepared with the same questions as the pre-test, however the placement of the questions and their answers choices differed from the pre-test. A score over 60 out of 100 was considered successful. Besides total scores, the ability to answer correctly to the most difficult questions was evaluated. Criteria for a question to be considered as a difficult one was to have an item difficulty index ≤ 0.29 . The item difficulty index of the questions was calculated through the utilization of the Henryson method (15). Out of 25 questions, 4 questions were mentioned as most difficult ones. The Delta value of difficult questions were evaluated for each participant. The delta value was defined as; (number of questions answered correctly out of 4 difficult questions in the post-test)- (number of questions answered correctly out of 4 difficult questions in the pre-test). Along with the post-test, the participants were asked to determine their degree of satisfaction and presumed benefit from the training. Visual analog scale from 0 to 10 was used for this evaluation.

Data Analysis

Statistical analysis of the obtained data was conducted using SPSS Statistics Version 22 (IBM, USA). A power analysis of independent sample t-tests, with an alpha level of 0.05, an effect size of 0.50, and a power of 0.80, indicated a required total sample size of -72. McNemar test was used for categorical variables and Wilcoxon test for ordinal variables in paired samples. Inter-group assessments were conducted using the two-tailed Mann-Whitney U test and chi-square test.

Results

Of the 88 last-year medical students enrolled in the clerkship, 79 willingly joined the study. All participants provided their informed consent. They were randomly assigned to the IC (n=39) and to the CG (n=40). Two students from the CG could not complete the study because of absenteeism on examination day (Figure 1).

The average age of the participants was 25.23 (0.43), 56% of the students enrolled were female and 95% of them did not have any experience in simulation practice (Table 1).

Participants' post-tests' mean scores were higher in both IG and CG. Students who were in the flipped classroom and had simulation practice had a higher increase in post-tests' scores compared to the ones who underwent the didactic lecture. The delta value of the most difficult 4 questions in the IG was found to be significantly higher than the control group ($p=0.048$). Participants trained with sim+ flipped model were more satisfied regarding the training from the control group (Table 2).

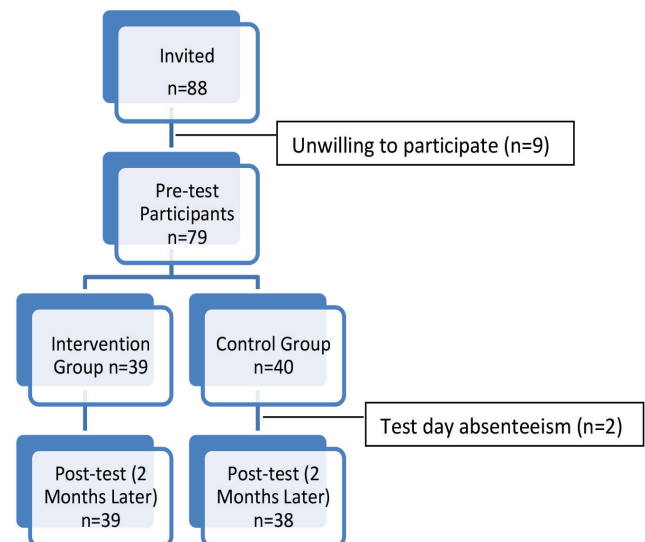


Figure 1: Flowchart of the study

Table 1: Demographic data and previous participation status of the groups			
Parameters	Intervention group	Control group	p value
Age (years) Mean (\pm SD)	25.23 (\pm 0.43)	25.16 (\pm 0.32)	0.983
Gender, n (%)			
Female	22 (56)	18 (47)	0.497
Male	17 (44)	20 (53)	
Previous simulation experience, n (%)			
No	37 (95)	36 (95)	1.000
Yes	2 (5)	2 (5)	

SD: Standard deviation

Table 2. Comparison of the learning outcomes and satisfaction level

Parameters	Intervention group ^a	Control group ^a	p value
Pre-test score	53.1±8.1	54.7±8.5	0.43
Post-test score	69±12.4	63.9±13.7	0.14
Delta value between the tests	15.9±14.2	9.16±13.4	0.083
Number of correct answers out of the 4 difficult questions			
At pre-test	0.64±0.843	0.68±0.775	0.649
At post-test	2.21±0.894	1.68±1.118	0.025*
Delta value of the difficult questions	1.564±1.119	1±1.315	0.048*
Success over test score "60/100"			
At pre-test			
<60/100	27 (69%)	23 (61%)	0.479
≥60/100	12 (31%)	15 (39%)	
At post-test			
<60/100	5 (13%)	13 (34%)	0.03*
≥60/100	34 (87%)	25 (66%)	
Increase in the success over the score "60/100"			
Yes	22	12	0.024*
No	17	26	
Degree of satisfaction from the learning methodology	9.05±1.05	6.7±2.19	<0.001*

^aNumerical data were presented as mean ± standard deviation and categorical data were represented as frequency (%).
^{*}p value <0.05 is considered statistically significant

Discussion

Sepsis, emerging from a spectrum of endemic and epidemic diseases, has left a deep imprint on the course of human history. Today, sepsis continues to significantly contribute to illness and death on a global scale. The exact number of people affected by sepsis is not known. In addition, the increase in antimicrobial resistance and nosocomial sepsis has been a concern; researches suggest 10 million people worldwide will die from health-related infections each year by 2050's (16).

During the past several years, numerous extensive studies have demonstrated the crucial role of prompt diagnosis and management in the successful treatment of sepsis. The Surviving Sepsis Company provides valuable resources for enhancing the diagnosis and treatment of sepsis, particularly in cases of severe sepsis and septic shock in patients. Nevertheless, based on existing scientific evidence, a substantial portion of patients, around 30% to 40%, does not receive care, and an estimated 20% to 25% of the administered care may be unnecessary or potentially harmful for the patient (17).

Therefore, correct and on-site management of sepsis patients will protect the health system and humanity from the burden of serious morbidity and mortality due to sepsis. For prompt and accurate management of sepsis, health-care providers, especially doctors, should receive an effective and adequate

education about sepsis. In the current study, learners trained with sim+flipped classroom method on the management of the first hour of sepsis showed better post-tests results than the CG.

Pre-test and post-tests comparison are instruments useful to measure changes and knowledge gains. According to our results, mean scores in the post-test, were higher in the IC with a mean score of 69 than in the CG with a score 63.1, however this difference showed no statistically significant difference (p=0.14). It has been observed that some of the similar studies in the literature have superior results for IG and some for CG (18,19).

The delta value of difficult questions was found to be statistically significantly higher in the participants in the IG (p=0.048). Similarly, Liebert et al. (20) evaluated the efficacy of a flipped classroom method applied in surgical clerkships of third year medical students. Their results showed a significant increase in mean delta values for each module after flipped classroom training.

Participants were considered successful or unsuccessful according to their scores in the pre-test and post-test respectively ≥60 and <60. No significant difference was found between the IC and the CG for the pre-test (CG= 15, IG= 12) (p=0.479). However, participants became successful in the post-test in both groups (CG= 25, IG= 34) (p=0.03). In a research conducted by Zhao et al. (21) and published in 2020, which the combined problem-based with case-based learning method was

compared with traditional education, the difference between the participants' post-test success was examined. Similar to our study, the group who underwent traditional education was found to be more unsuccessful in the post-test, however the difference between the two groups was not statistically significant (21).

Many studies comparing simulation based education with traditional education have shown medical students to score equivalent or higher on post-tests (22-25). Learning through didactic methods primarily relies on explicit memory, involving the direct recall of previously acquired information. Practical training using simulation facilitates the formation of implicit memory originating from subconscious cognitive processes. Implicit memory is activated through the observation of cues and their association with suitable actions, as opposed to the direct presentation of information through oral or written means. Given the extensive preclinical content, students frequently encounter challenges in determining how to allocate their time and efforts. After experiencing simulations rooted in authentic clinical scenarios, students can grasp the significance and practical relevance of delving more profoundly into the simulated subjects (26).

In comparing teaching/learning methods, besides performance or score improvement it is important to assess whether the method provided appeared beneficial to the participants. For this purpose, the students who participated to the study were asked to score the benefit they thought they received from the training, along with the post-test. We used a visual analog scale, who perceived the benefit at the highest level were asked to give 10 points, and those who perceived the least level of benefit were asked to give 0 point. Considering the mean scores given by the participants (CG= 6.7, IG= 9.05), it was determined that the IG reported a statistically significant higher level of benefit compared to the CG ($p<0.001$). In a study published by Ramnanan and Pound (27), the students were satisfied with the use of activities based on small group discussions in face-to-face sessions of flipped classroom model; in addition, it was concluded that these sessions helped to increase their motivation to learn, increase their participation level and increase their interest in the subject (27). However, in a study conducted by Fahy et al.(28), certain limitations of the flipped classroom method were identified, especially among reserved students hesitant to engage in discussions with their peers during class sessions.

Study Limitations

This study was conducted at a single center with a limited number of participants; therefore, the results need to be validated in randomized multicenter studies. Another issue that should be emphasized is that traditional education was given

online, not face-to-face, due to the current COVID-19 pandemic at the time of the study. This study, centered around sepsis management, consequently, its results cannot be extrapolated to encompass all of medical education.

Conclusion

Although our study was carried out with a limited number of participants (n=77) in a single center, some important evidences were obtained showing that students would benefit more from the education given with simulation based training combined with flipped classroom in medical schools, compared to conventional didactic method. Considering all the parameters in this study, although the flipped classroom method was found to be more successful than the didactic method for the management of the first hour of sepsis, multicenter studies with larger samples are needed on this subject.

Ethics

Ethics Committee Approval: The research conducted at Ankara University Faculty of Medicine has been reviewed and approved by the Human Research Ethics Committee under the reference number 111-662-20.

Informed Consent: Informed consent was obtained from all the participants before conducting the study.

Authorship Contributions

Surgical and Medical Practices: A.G., S.G., A.B.O., M.G.E., Concept: A.G., A.K., M.G.E., Design: A.G., A.K., A.B.O., M.G.E., Data Collection and/or Processing: A.G., Analysis and/or Interpretation: A.G., A.K., S.G., O.P., M.G.E., Literature Search: A.G., A.K., A.B.O., Writing: A.G., A.K.

Conflict of Interest: Each author declares the absence of any commercial affiliations (e.g., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that could potentially create a conflict of interest related to this article.

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Predictive Value of ARISCAT Risk Index in the Development of Postoperative Pulmonary Complications After Major Abdominal Cancer Surgery

Majör Abdominal Kanser Cerrahisi Sonrası Postoperatif Pulmoner Komplikasyon Gelişmesinde ARISCAT Risk İndeksinin Prediktif Değeri

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Abstract

Objectives: The ARISCAT risk assessment score is a seven-variable regression model that divides patients into low, moderate, and high-risk groups in terms of developing postoperative pulmonary complications (PPC). In this study, we aimed to assess the predictive value of the ARISCAT score in major abdominal cancer surgery patients since they are considered to be vulnerable to postoperative complications.

Materials and Methods: A total of 410 patients aged >18 years old with American Society of Anesthesiologists (ASA) I-IV were included. Demographic data, body mass index, smoking status, ASA scores, preoperative hemoglobin levels, pulmonary disease history in the last 30 days, location of surgical incision (lower-upper abdominal), type of surgery (laparoscopic or open), emergency or elective, and operation times of patients were recorded.

Results: Age, smoking, higher ASA score, type of operation, preoperative pulmonary dysfunction, and higher ARISCAT scores were found to be related with PPC ($p<0.05$). A positive correlation was found between ARISCAT score and PPC ($p<0.05$). Elderly, lower preoperative SpO_2 , surgeries with upper incision site, emergency surgeries were found to be associated with increased risk of developing PPC. Age was found to have the strongest relationship among the variables.

Conclusion: We found that the ARISCAT risk score was a strong predictor of the development of PPC after major abdominal cancer surgery.

Keywords: Complications, postoperative, pulmonary, scoring methods

Öz

Amaç: ARISCAT risk skoru, postoperatif pulmoner komplikasyon (PPK) gelişimi açısından hastaları düşük, orta ve yüksek riskli gruplara ayıran yedi değişkenli bir regresyon modelidir. Bu çalışmada, ARISCAT risk skorunun majör abdominal kanser cerrahisi geçiren hastalarda prediktif değerini araştırmaktır.

Gereç ve Yöntem: On sekiz yaş üstü, Amerikan Anestezistler Derneği (ASA) I-IV olan toplam 410 hasta çalışmaya dahil edildi. Demografik veriler, vücut kitle indeksi, sigara öyküsü, ASA skorları, ameliyat öncesi hemogloblin düzeyleri, son 30 gün içindeki akciğer hastalığı öyküsü, cerrahi insizyonun yeri (alt-üst karın), ameliyatın türü (laparoskopik veya açık), acil veya elektif ve hastaların operasyon süreleri kaydedildi.

Bulgular: Yaş, sigara kullanımı, yüksek ASA skoru, operasyon tipi, preoperatif akciğer fonksiyon bozukluğu ve yüksek ARISCAT skorlarının PPK ile ilişkili olduğu belirlendi ($p<0.05$). ARISCAT puanı ile PPK arasında pozitif korelasyon bulundu ($p<0,05$). Yaşlılarda, ameliyat öncesi SpO_2 'nin düşük olması durumunda, üst kesi yeri olan ameliyatlarda, acil ameliyatlarda PPK gelişme riskinin arttığı gözlenmiştir. Değişkenler arasında PPK gelişmesiyle en güçlü ilişki hastanın yaşı olduğu tespit edilmiştir.

Sonuç: ARISCAT risk skorunun majör abdominal kanser cerrahisi sonrası PPK gelişmesini tahmin etmede güçlü bir öngörücü olduğunu tespit ettik.

Anahtar Kelimeler: Komplikasyon, postoperatif, pulmoner, skrolama yöntemi

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Introduction

Postoperative pulmonary complications (PPC) are quite common and one of the important causes of postoperative morbidity and mortality (1). While the rate of mortality and morbidity is 14–30% in patients with PPC, it is 0.2–3% in patients without PPC. The incidence of PPC in non-cardiac surgery has been reported between 2% and 19%, and it is more common than cardiac complications (2,3). PPCs continue to be an important cause of unexpected intensive care admissions and long-term hospital stays (4).

Major abdominal cancer surgery is a very common type of surgery, and the rate of PPC development is expected to be higher due to the immunodeficiency of the cancer itself, decreased physiological reserve or complicated long surgical procedures. In the literature, the incidence of PPC development after major abdominal surgery has been reported as 5.8% (5).

In this study, our primary aim was to investigate the effectiveness of the ARISCAT risk scoring index in predicting the development of PPC in patients undergoing major abdominal cancer surgery. Secondary purposes were to show the relationship of PPCs with parameters such as radiotherapy/chemotherapy history, operation type and duration, demographic characteristics, pulmonary function status, length of hospital stay and 30-day mortality.

Materials and Methods

After ethical approval from University of Health Sciences Türkiye, Ankara Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital Clinical Research Ethics Committee (approval no.: 2019-11/459, date: 20.11.2019, trial registry: NCT04663958), between December 2020–June 2021, 420 patients over the age of 18 with an American Society of Anesthesiologists (ASA) score of 1–4, who were planned for major abdominal cancer surgery in the general surgery, urology and gynecological oncology departments with general anesthesia were included in the study prospectively and observationally, and informed consent forms were signed by all patients. Pregnant patients, patients with acute or chronic respiratory disease, previously intubated patients, patients who underwent surgery due to previous surgical complications, patients with severe cardiovascular disease or severe hemodynamic instability, and patients given regional anesthesia were excluded from the study. The study was conducted in accordance with the Helsinki Declaration–2013.

ARISCAT risk assessment scores were calculated by evaluating the patients preoperatively. ARISCAT risk scoring system is one of the most important measurement tools which is simple to implement, inexpensive, and widely used

in the evaluation of PPC at the bedside (4). The ARISCAT risk assessment score (The Assess Respiratory Risk in Surgical Patients in Catalonia: Evaluating respiratory risk in surgical patients in Catalonia) has seven variables (age, preoperative SpO₂, preoperative anemia, lung infection presence in the last month, duration of operation, operation procedure, surgical incision site) that divides patients into low, medium and high risk groups, which is a risk scoring tool. A score of <26 is considered low risk, a score of 26–44 is considered medium risk, and a score >45 is considered high risk (Table 1) (2).

The patients were followed during the post-anesthetic care unit and hospital stay, and the presence of PPC was evaluated, and the time to discharge was recorded. On the 30th day after discharge, the patients were called by phone and the presence of mortality was questioned.

PPC are defined by the development of one of the following novel findings. This definition is based on the

Table 1: The ARISCAT risk assessment score		
Risk factors	Risk score	
Age		
≤50	0	
51–80	3	
>80	16	
Preoperative O₂ saturation		
≥96	0	
91–95	8	
≤90	24	
Respiratory infection in the last month		
	17	
Preoperative anemia (hemoglobin ≤10 g/dL)		
	11	
Surgical incision		
Peripheral	0	
Upper abdominal	15	
Intrathoracic	24	
Duration of surgery		
≤2 hours	0	
2–3 hours	16	
>3 hours	23	
Operation procedure		
Elective	0	
Emergency surgery	8	
Risk class	Total risk score	Pulmonary complications rates
Low	<26	1.6%
Intermediate	26–44	13.3%
High	≥45	42.1%

European Perioperative Clinical Outcome Definitions (EPCO) (6). Unscheduled emergency re-intubation and previously intubation before intensive care unit admission, which are not included in the EPCO definitions, are also included in this classification (Table 2).

Statistical Analysis

Research data was uploaded to the computer and evaluated by means of "SPSS (Statistical Package for Social Sciences) for Windows 20.0 (SPSS Inc, Chicago, IL)". Mean, standard deviation, ratio and frequency values were used in the descriptive statistics of the data. The distribution of variables was checked with the Kolmogorov-Smirnov test. Mann-Whitney U test and independent samples t-test were used to analyze quantitative data, chi-square test was used to analyze qualitative data, and Fisher's exact test was used when chi-square conditions could not be met. Logistic regression was performed to investigate the effect level, odds ratios (OR), 95% confidence interval (CI), and receiver operating characteristic (ROC) analysis were used to estimate the relationship between PPC and other variables. P value <0.05 was considered statistically significant. In order to decide on the sample size, a literature review was conducted and power analysis was performed. The overall incidence of PPC was found to be 5.8% in previous studies (6). For the simplest within-group and between-group comparisons, the sample size with an effect value determined for a statistical power of 0.90 at the alpha=0.05 level was calculated as n=405 (G*Power 3.1.9.7). The n=410 patients collected for this study is more than sufficient for the purpose of the study.

Results

Of the 420 patients included in the study, 6 were excluded because they did not sign the written consent and 4 patients were excluded due to lack of data (Figure 1). Statistical analysis of a total of 410 patients was performed. PPC was detected in 12.4% (n=51) of 410 patients who underwent major abdominal cancer surgery, and PPC was not detected in 87.6% (n=359) (Table 3). According to these data, a significant difference was found between the patients with and without PPC in terms of age, smoking, ASA score, operation type, pulmonary function status and ARISCAT scores (p<0.05).

The mean ARISCAT score of 359 patients without PPC was 33.62, and of the 51 patients with PPC was 49.07 (Table 4). The most common complication was pneumonia, which was observed in 23 (5.6%) patients, and then atelectasis 19 (4.6%), respiratory failure 15 (3.6%), pleural effusion 14 (3.4%), ongoing postoperative intubation after surgery 6 (1.5%), pulmonary embolism 4 (1%), unplanned emergency reintubation 4 (1%), pneumothorax 3 (0.7%) and ARDS 2 (0.5%).

While the mean ARISCAT score of 12 (23.5%) patients with one PPC was 39.7 ± 12.13 , the mean ARISCAT score of the patients with four PPCs was 59.5 ± 2.12 . A positive statistical significance (p<0.005) was found between the development of more than one PPC in the same patient and the ARISCAT score (Table 4).

According to this study, ROC analysis was performed to determine the cut-off points in terms of low, medium and high

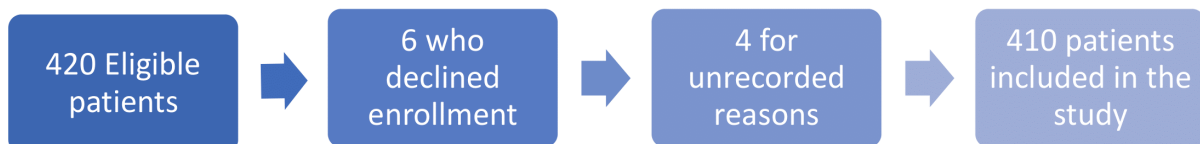


Figure 1: Recruitment flowchart

Table 2: Definitions of postoperative pulmonary complications	
Respiratory failure	When postoperative PaO ₂ <60 mmHg on room air, a ratio of PaO ₂ to inspired oxygen fraction <300 or arterial oxyhemoglobin saturation measured with pulse oximetry <90% and requiring oxygen therapy
Respiratory infection	When a patient received antibiotics for a suspected respiratory infection and met at least one of the following criteria: new or changed sputum, new or changed lung opacities, fever, leukocyte count >12,000/μ
Aspiration pneumonitis	Acute lung injury after the inhalation of regurgitated gastric contents
Pleural effusion	Chest X-ray demonstrating blunting of the costophrenic angle, loss of the sharp silhouette of the ipsilateral hemidiaphragm in upright position, evidence of displacement of adjacent anatomical structures, or (in supine position) a hazy opacity in one hemithorax with preserved vascular shadows
Pneumothorax	Air in the pleural space with no vascular bed surrounding the visceral pleura
Atelectasis	Lung opacification with a shift of the mediastinum, hilum, or hemidiaphragm toward the affected area, and compensatory over inflation in the adjacent non atelectatic lung
Bronchospasm	Newly detected expiratory wheezing treated with bronchodilators
Acute respiratory distress syndrome	The presence of diffuse bilateral infiltrates on chest radiograph no signs of minimal left atrial overload within 7 days after surgery, PaO ₂ /FiO ₂ [†] : ≤300

[†]Partial pressure of oxygen, [‡]Inspired oxygen concentration

Table 3: Demographic characteristics and distribution of ARISCAT scores in patients with and without postoperative pulmonary complications				
	Total n=410 (%)	PPC		p value
		Yes n=51 (12.4)	No n=359 (87.6)	
Age (years) Mean ± SD	60.69±11.9	66.4±11.98	59.9±11.7	0.001*
Gender, n (%)				
Woman	225 (54.9)	n=29 (12.8)	n=196 (87.2)	0.440†
Man	185 (45.1)	n=22 (11.9)	n=163 (90.1)	
BMI (kg/m²) n (%)				
0-20 (kg/m ²)	42 (10.2)	6 (14.2)	36 (85.8)	0.815†
21-35 (kg/m ²)	336 (82)	42 (12.5)	294 (87.5)	
>35 (kg/m ²)	32 (7.8)	3 (9.3)	29 (91.7)	
Smoking, n (%)		Yes, n (%)	No, n (%)	
0 packs/year	218 (53.2)	19 (8.7)	199 (91.3)	0.005†
1-20 packs/year	62 (15.1)	9 (14.5)	53 (85.5)	
21-40 packs/year	94 (22.9)	12 (12.7)	82 (87.3)	
41-60 packs/year	35 (8.5)	11 (31.4)	24 (68.6)	
61-80 packs/year	1 (0.2)	n <2	n <2	
ASA scores (%)		Yes, n (%)	No, n (%)	
I	13 (3.2)	n <2	13 (100)	<0.001†
II	190 (46.3)	9 (4.7)	181 (95.3)	
III	188 (45.9)	30 (15.9)	158 (84.1)	
IV	19 (4.6)	12 (63.1)	7 (36.9)	
Type of operation n (%)		Yes, n (%)	No, n (%)	
Emergency	38 (9.3)	18 (47.3)	20 (52.7)	<0.001†
Elective	372 (90.7)	33 (8.8)	339 (91.2)	
Chemotherapy history in the last 1 year n (%)		Yes, n (%)	No, n (%)	
Yes	92 (22.4)	9 (9.7)	83 (90.3)	0.381†
No	318 (77.6)	42 (13.2)	276 (86.8)	
Radiotherapy history in the last 1 year n (%)		Yes, n (%)	No, n (%)	
Yes	51 (12.4)	5 (9.8)	46 (90.2)	0.655†
No	359 (87.6)	46 (12.4)	313 (87.2)	
Pulmonary function n (%)		Yes, n (%)	No, n (%)	
No dyspnea	324 (79)	31 (9.5)	293 (90.5)	<0.001†
Dyspnea with exercise	80 (19.5)	16 (20)	64 (80)	
Resting dyspnea	3 (0.7)	2 (66.6)	n<2	
Always dyspnea	3 (0.7)	2 (66.6)	n<2	
ARISCAT risk classification		Yes, n (%)	No, n (%)	
Low risk <26	91 (22.2)	2 (2.1)	89 (97.9)	<0.001†
Medium risk <26-44	214 (52.2)	18 (8.4)	196 (91.6)	
High risk <44	105 (25.6)	31 (29.5)	74 (70.5)	

Values are mean ± SD, PPC: Postoperative pulmonary complication, n: Number of patients, %: Column percentage, *Mann-Whitney U test, †Pearson chi-square test, ‡Fisher's Precision test (p<0.005)
SD: Standard deviation, BMI: Body mass index, ASA: American Society of Anesthesiologists Classification

risk according to the ARISCAT risk scores of patients with PPC, and ARISCAT scores were found to be 29 and 44 [77.6% (95% CI; 71%-85%)]. In this case, as a result of the analysis obtained, 0-29 low risk value; 29-44 were considered as medium risk factors and >44 as high-risk factors. In Figure 2, the ROC analysis graph for the sensitivity and specificity values of the cutoff notes was given. Logistic Regression analysis was performed to determine the effect power of the ARISCAT variables used to

determine the risk of PPC in patients. The full model including the variables in the ARISCAT scale was found to be statistically significant (p<0.001).

Surgical incision site, preoperative SpO₂ value, the type of surgical procedure was found to be statistically significant (p<0.05) in the development of PPC (Table 5). The age was found to be the strongest predictor of the occurrence of PPC. When all other items in the scale were kept under control, it was observed

that 51–80 years of age increased the probability of PPC 3 times (OR=3.37) and that age >80 increased 14 times (OR=13.694).

The incidence of PPC was higher in emergency surgeries, open surgical procedures, upper abdominal incisions, and low preoperative SpO₂ and hemoglobin values. There was no statistically significant difference between the duration of surgery and PPC. While patients who did not develop PPC stayed in the hospital for 8.6±4.32 days, this period was found to be 12.9±9.22 days in patients who developed PPC. The duration of stay in the postoperative care unit was 17.9±5 and 82.7±147.6 hours, respectively (Table 6). A positive and significant relationship was found between the length of hospital stay-postoperative care unit stay and PPC (p<0.001).

Fourteen (3.4%) deaths were detected in the 30-day period in 410 patients included in the study. While there were 13

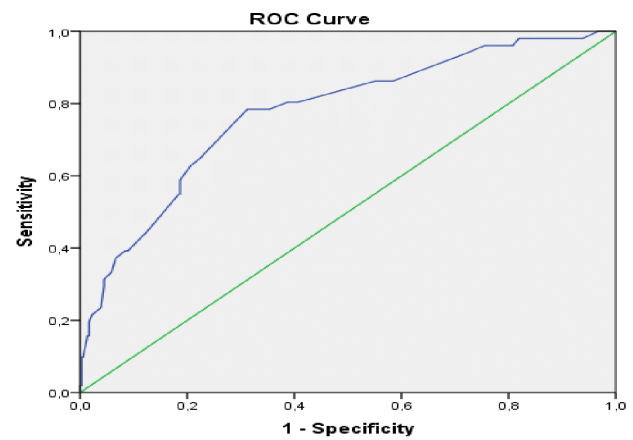


Figure 2: Receiver operating characteristic analysis result
ROC: Receiver operating characteristic

Table 4: Relationship between ARISCAT score and number of postoperative pulmonary complications			
Number of PPCs	ARISCAT mean score ± SD	n (%)	p value
1	39.7±12.13	12 (23.5)	0.008*
2	50.04±14.8	23 (45.2)	
3	54.07±17.6	14 (27.4)	
4	59.5±2.12	2 (3.9)	
Total	49.07±15.6	51 (100)	

Values are mean ± SD, *Spearman-rho test
SD: Standard deviation, n: Number of patients, PPC: Postoperative pulmonary complication

Table 5: Power of ARISCAT risk index to predict the development of postoperative pulmonary complications								
	S.E.	Wald	p value	OR	B	Risk scores	95% CI for odds ratio	
							Low	High
Age								
<50		10.050	0.007					
51-80	0.669	2.761	0.009	3.37	0.437	4	0.819	11.263
>80	0.853	9.403	0.002	13.694	1.706	17	2.571	72.934
Preoperative SpO₂								
>96		5.550	0.005					
91-95	0.456	0.088	0.042	1.145	0.673	7	0.468	2.797
<90	0.577	4.133	0.027	3.232	2.038	20	1.043	10.013
Pulmonary infection in the last month	1.106	0.152	0.697	0.650	0.431	4	0.074	5.676
Preoperative anemia Hb <10 g/dL	0.449	360	0.549	0.764	0.269	3	0.317	1.841
Surgical incision site								
Peripheral								
Upper abdominal	356	9.441	0.002	2.989	1.095	11	1.487	6.011
Operation time								
<2 hours	0.703	1.152	0.283	2.127	1.085	10	0.536	8.439
2-3 hours	0.742	2.141	0.143	2.960	0.331	3		
>3 hours								
Type of procedure								
Elective								
Emergent	0.439	17.497	0.000	6.263	1.835	19	2.651	14.797

SE: Standard error, Wald: Wald test, OR: Odds ratio, B: Beta, CI: Confidence interval, SpO₂: Peripheral oxygen saturation, Hb: Hemoglobin

(25.5%) deaths in 51 patients who developed PPC, 1 (0.2%) died in 359 patients who did not develop PPC. A statistically significant relationship ($p < 0.001$) was found between PPC and 30-day mortality.

Discussion

This is the first observational study to investigate the effectiveness of ARISCAT in predicting the occurrence of PPC after major abdominal cancer surgery to our knowledge. PPC was detected in 12.4% of the patients, and a positive correlation was found between the increase in ARISCAT score and the development of PPC. Among the independent variables, age, preoperative SpO₂, surgical incision site and operation procedure (elective/emergency) were effective factors in predicting the development of PPC, and age was found to be the strongest variable.

Canet et al. (2) reported the rates of PPC development as 1.6% in the low-risk group, 13.3% in the intermediate-risk group, and 42.1% in the high-risk group according to the ARISCAT scores. In another study examining renal transplant

patients, PPC was observed in 75% of the patients in the high-risk group and 19.5% of the patients in the intermediate-risk group (7). In our patient group, a significant positive correlation was found between the ARISCAT score and the development of PPC. The ARISCAT scores were found to be 29 and 44 as a result of the ROC analysis performed to determine the cut-off points of the patients in terms of low, medium and high risk, which is similar to other studies (2,8,9). Canet et al. (2) found the incidence of PPC development as 39.6% in cardiac surgery, 31.4% in thoracic surgery, 7.2% in abdominal surgery and 5.8% in vascular interventions. It has been shown that the incidence of PPC is inversely proportional to the distance of the incision line from the diaphragm, and a similar result was observed in our study (3,10).

Postoperative pneumonia is a common pulmonary complication after thoracic or non-thoracic surgery (11,12). Arozullah et al. (13) found the incidence of postoperative pneumonia to be 1.5% in their study in which they evaluated multifactorial risks to prevent postoperative pneumonia in patients who underwent non-cardiac surgery. In our study, the most common PPC was found to be pneumonia with a rate

Table 6: Relation of perioperative data with postoperative pulmonary complications

		PPC			p value
		Yes n (%)	No n (%)	Total	
Premedication	Yes	30 (9.6)	282 (90.4)	312 (100)	0.002*
	No	21 (21.4)	77 (78.5)	98 (100)	
Incision site	Upper abdomen	31 (20)	124 (80)	155 (100)	0.001*
	Lower abdomen	9 (7.1)	118 (92.9)	127 (100)	
	Laparoscopic	11 (8.5)	117 (91.5)	128 (100)	
Duration	<2 hour	4 (8.8)	41 (91.2)	45 (100)	0.746†
	2-3 hour	30 (12.9)	202 (87.1)	232 (100)	
	>3 hour	17 (12.7)	116 (87.3)	133 (100)	
Preoperative SpO ₂ (mean ± SD)		91.9±4.53	94.01±2.3		0.002*
Surgical Procedure	Elective	33 (8.9)	339 (91.1)	372 (100)	0.000*
	Emergent	18 (47.4)	20 (52.6)	38 (100)	
Type of surgery	Open	40 (14.2)	243 (85.8)	283 (100)	0.146†
	Laparoscopic	11 (8.7)	116 (91.3)	127 (100)	
Hemoglobin (mean ± SD)		11.64±2.17	12.7±2.11		0.004†
Total		51 (100)	359 (100)	410 (100)	

Values are mean ± SD, *Pearson chi-square, †Fisher's exact test, ‡Mann-Whitney U test
PPC: Postoperative pulmonary complication, n: Number of patients, %: Column percentage, SpO₂: Peripheral oxygen saturation, SD: Standard deviation

Table 7: Relationship between length of stay in hospital and postoperative care unit with postoperative pulmonary complications

	Total (n=410)	PPC Yes (n=51)	PPC No (n=359)	p value
Length of hospital stay (days) mean ± SD	9.15±5.37	12.9±9.22	8.6±4.32	0.001*
Postoperative care (hours) mean ± SD	26±56	82.7±147.6	17.9±5	0.000*

Values are mean ± SD, †Mann-Whitney U test
n: Number of patients, PPC: Postoperative Pulmonary Complication, %: Column percentage, SD: Standard deviation

of 5.6%. Some differences in the frequency of all PPCs in the literature might be related to the heterogeneity of the patient populations, the type of surgery and the variability of the definitions used in the studies (14).

Age is an important factor in the development of postoperative complications, and Canet et al. (2) determined the age of 80 as a deviation point at which PPCs increase significantly (9). In our study, we observed that the frequency of PPC increased significantly over the age of 80. It has been suggested that decrease in physiological reserve with advancing age, high airway closure capacity and low ventilation/perfusion ratios lead to hypoxia among the potential mechanisms.

The SpO₂ value is included in the ARISCAT risk score parameters as it may reflect both respiratory and cardiovascular functional status. In our study, we found that SpO₂ was also found to be an effective predictor. Many studies indicated that smoking was an important risk factor in the development of PPC (11). Although it is known that the risk of PPC increases 6 times in smokers compared to those who have never smoked before, it has been suggested in recent publications that this rate is lower in those who started smoking in the last year before surgery (15). In our study, a positive and significant correlation was found between the increase in the amount of smoking and PPC. Yang et al. (5), in their multicenter study, in which they retrospectively analyzed 165196 cases, reported that there was a positive correlation between the presence and severity of respiratory distress in patients and PPC. Although different results were reported in the studies (2,7,16,17), a positive and significant correlation was found between the ASA values of the patients and PPC in this study ($p<0.001$).

There is no conclusive level of evidence that obesity increases PPCs. In obese individuals, decreased chest wall and lung compliance and functional residual capacity are observed (18). Yang et al. (5) found a significant relationship between BMI and PPC. There were also several studies showing that the risk of PPC did not increase with obesity (19,20). In our study, no significant relationship could be demonstrated between BMI and PPC.

Preoperative anemia (hemoglobin <10 g/dL⁻¹) has been defined as a poor prognosis marker in postoperative and intensive care patients. It was reported that even mild anemia might cause an increase in 30-day mortality and cardiac complications (21). Canet et al. (2) found that preoperative anemia increased the development of PPC 3 times. In our study, in the logistic regression analysis used to determine the effects of the independent ARISCAT variables in the development of PPC, preoperative anemia could not be defined as a strong factor. However, there was a significant difference in hemoglobin levels between patients with and without PPC ($p<0.005$). For this reason, we think that preoperative anemia should be evaluated

in the early period, especially in risky patient groups, and attention should be paid to its perioperative management.

Emergency surgery is the independent risk factor that contributes most to the development of PPC (22). These patients are generally hypovolemic, have poor vital signs and need active resuscitation. Canet et al. (2) showed that the risk of PPC increased 2.2 times in patients who were operated on urgently (2). Perilli et al. (8) reported the incidence of PPC in patients undergoing major abdominal surgery as 7% in elective cases and 33% in emergency cases. In our study, these rates were found to be 8.9% and 47.4%, respectively. The fact that our patient population was cancer patients and the increased frailty levels and co-morbidities related to cancer might have caused the difference in the results. McAlister et al. (23) stated that the duration of the operation longer than 2.5 hours increased the incidence of PPC development 3.3 times. In our patients who underwent major abdominal cancer surgery, no significant relationship could be demonstrated between the duration of the operation and the development of PPC. It was thought that the fact that the time was evaluated in only three categories might have affected the difference between cancer surgeries that lasted much longer than 3 hours.

The surgical incision site plays an important role in the evaluation of PPCs. In ARISCAT risk scoring, the incision sites are defined as thoracic, upper abdominal and peripheral and do not contain information about laparoscopic methods. PPC most commonly develops after thoracic and upper abdominal surgeries. The incidence of PPC varies inversely with the distance of the incision site to the diaphragm (3). In our study, similar to the literature, PPC was mostly observed after upper abdominal incision.

It was shown that the duration of intensive care and hospitalization was significantly prolonged in patients with PPC ($p<0.001$). Smith et al. (24) reported that PPCs increased the length of hospital stay up to 17 days in patients who underwent laparotomy. Similar results have been shown in other studies (11,14,25). In our study, the group with the highest 30-day mortality was the group that developed PPC ($p<0.001$) and a similar result was observed by Canet et al. (2).

Study Limitations

The fact that there is no definition of ARISCAT score in laparoscopic interventions. Therefore, we scored laparoscopic procedures as peripheral surgeries and our definition of laparoscopic procedures might have an impact on the results. However, we thought that this effect would not cause a significant change in our results due to the absence of large abdominal incisions that caused postoperative pain and difficulty in mobilization and the speed of the healing process in laparoscopic procedures. We added emergency re-intubation and continuation of intubation after surgery to the EPCO criteria used in the evaluation of PPCs. Although this change

in definition might make a difference in developing PPC types, it did not affect the correlation between PPC frequency and ARISCAT scores. In addition, clinically insignificant atelectasis might have been overlooked, since routine chest radiographs were not requested from every patient who was operated on.

Conclusion

In our study, we found that the ARISCAT risk scoring index was significantly effective in predicting the development of PPC in patients undergoing major abdominal cancer surgery. Among the independent variables, age, preoperative SpO₂, surgical incision site and type of operation procedure were important factors, and age was found to be the strongest variable. Revealing the potential risk factors for the development of PPC will contribute to the early determination of preventive strategies and the effective use of health resources, especially in cancer patients with high frailty. In future studies, simple-to-use, bedside preoperative tests such as ARISCAT should be developed, and targets for identifying patient and surgical risk factors and improving perioperative care should be determined.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the University of Health Sciences Türkiye, Ankara Dr. Abdurrahman Yurtaslan Oncology Training and Research Hospital Clinical Research Ethics Committee (approval no.: 2019-11/459, date: 20.11.201).

Informed Consent: Informed consent forms were signed by all patients.

Authorship Contributions

Surgical and Medical Practices: M.K.Ş., S.A., Concept: M.K.Ş., S.A., G.O., S.Ü., Design: M.K.Ş., S.A., G.O., S.Ü., Data Collection and/or Processing: M.K.Ş., S.A., Analysis or Interpretation: M.K.Ş., S.A., G.O., S.Ü., Literature Search: M.K.Ş., S.A., G.O., S.Ü., Writing: M.K.Ş., S.A., G.O., S.Ü.

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Renal Metastasis from a Primary Hepatic Neuroendocrine Tumor: A Case Report and Literature Review

Primer Karaciğer Nöroendokrin Tümörünün Böbrek Metastazı: Nadir Olgu ve Literatür Taraması

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Abstract

Neuroendocrine tumors (NET) are a diverse collection of neoplasms with varying biological characteristics, histologic patterns, and therapeutic responses. We present a rare case of a 41-year-old female who was diagnosed with a primary NET of the liver and had multiple kidney and bone metastases. Primary hepatic NETs are rare, and metastasis to the kidney makes this case one of the few in the literature. The patient was admitted to the hospital because of pain in the lower extremities. Several imaging examinations revealed multiple lesions in the bone, kidney, and liver. Sandostatin and Denosumab treatments are started against the tumor and bone metastases. At first, the team thought the case was a NET of the liver and synchronous renal cell carcinoma. However, after the total excision of the kidney, pathology was reported as the NET metastasis to the kidney. Despite showing regression in bone metastases, the lesion in the the liver has advanced. ¹⁷⁷Lu-DOTATATE treatment was added to the current treatment regimen. Renal metastasis from a primary hepatic NET can be challenging to diagnose and treat. Since there are no guidelines specifically designed for this type of case, multiple treatment modalities must be discussed with a multidisciplinary team to choose the best option for patients.

Keywords: Neuroendocrine tumor, primary hepatic neuroendocrine tumor, renal metastasis, sandostatin

Öz

Nöroendokrin tümörler (NET), değişen biyolojik özelliklere, histolojik yapılar ve terapötik yanıtlara sahip çok çeşitli neoplazmalar koleksiyonudur. Bu makalede karaciğerde primer NET tanısı alan, çok sayıda böbrek ve kemik metastazı bulunan 41 yaşında kadın hastayı sunuyoruz. Primer hepatik NET'ler nadirdir ve böbreğe metastaz olması durumu daha da nadir hale getirir. Hasta alt ekstremitte ağrısı nedeniyle hastaneye başvurdu. Çeşitli görüntülemelerde kemik, böbrek ve karaciğerde çok sayıda lezyon ortaya çıktı. Tümör ve kemik metastazlarına karşı Sandostatin ve Denosumab tedavilerine başlandı. Ekip ilk başta vakanın karaciğerde nöroendokrin bir tümör ve senkron renal hücreli karsinom olduğunu düşündü. Ancak böbreğin total eksizyonu sonrasında patoloji, NET'in böbreğe metastazı olarak rapor edildi. Kemik metastazlarında gerileme görülmesine rağmen karaciğerdeki primer lezyonu ilerledi. Mevcut tedavi rejimine ¹⁷⁷Lu-DOTATATE tedavisi eklendi. Primer hepatik NET'ten kaynaklanan renal metastazın teşhis ve tedavisi zor olabilir. Bu tip vakalar için özel olarak tasarlanmış bir kılavuz bulunmadığından, hastalar için en iyi seçeneğin seçilebilmesi için birden fazla tedavi yönteminin multidisipliner bir ekiple tartışılması gerekir.

Anahtar Kelimeler: Nöroendokrin tümör, primer karaciğer nöroendokrin tümörü, böbrek metastazı, sandostatin

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Introduction

Neuroendocrine tumors (NETs) are a diverse collection of neoplasms with varying biological characteristics, histologic patterns, and therapeutic responses. NETs are commonly seen in the gastrointestinal system, especially in the small intestine and pancreas. Primary hepatic NETs (PHNETs) are exceedingly rare tumors that cause challenges in diagnosis (1). Kidney metastases are exceedingly rare in NET, especially if the primary site is the liver (2). Here, we present a rare case of a 41-year-old female who was diagnosed with a primary NET of the liver and had multiple kidney and bone metastases.

Case Presentation

The patient was admitted to the orthopedics department because of pain in the lower extremities. Magnetic resonance imaging (MRI) showed a 63 mm heterogenous lesion in the lower segment of the right kidney, a 24x36 mm heterogenous lesion with cystic structures was found in the left proximal femur, and a 42x76 mm similar lesion was detected in the right proximal femur (Figure 1H). Abdominal MRI with intravenous (IV) contrast showed multiple lesions in different segments of the liver, with the largest one being a 35 mm well-circumscribed hypervascular lesion in segment VIII (Figure 1D). In addition, the MRI revealed a semisolid lesion in the posterior part of the right

kidney containing cystic structures with several retroperitoneal enlarged lymph nodes, which resembled renal cell carcinoma (Figure 1F).

Furthermore, fluorodeoxyglucose (FDG) positron emission tomography (PET) showed a 50x30 mm lesion with pathological FDG absorption in the proximal part of the right femur, liver, kidney and multiple lytic lesions in C7, TH5, TH11, and S1 vertebrae (Figure 1A-C, E, G). Tru-cut biopsy was done for the lesions in the liver, and the results were consistent with a grade 1 NET. In the liver tru-cut biopsy sample, a neoplasm consisting of monotonous epithelial cells separated from the liver parenchyma with smooth borders is observed. Neoplastic cells, forming an organoid pattern, have oval or round nuclei with no visible nucleoli and eosinophilic granular cytoplasm (Figure 2). No mitotic figure is seen. No necrosis is observed. Immunohistochemical staining was done and demonstrated CK8/18 and Synaptophysin positive, PAX8, and GATA3 negative neoplastic cells (Figure 2). The proliferative index of the tissue provided by Ki-67 labeling was less than 2% (Figure 2). Furthermore, GA-68 DOTA PET was done to determine the possibility of Sandostatin treatment. GA-68 DOTA PET results showed high-level somatostatin receptor expression in lesions at the liver, vertebrae, and femur (Figure 1). Denosumab 120 mg once in 4 weeks for bone metastases and Sandostatin 30 mg once in 4 weeks treatments were started. Palliative radiotherapy was done for the lesions on the proximal femur. After several

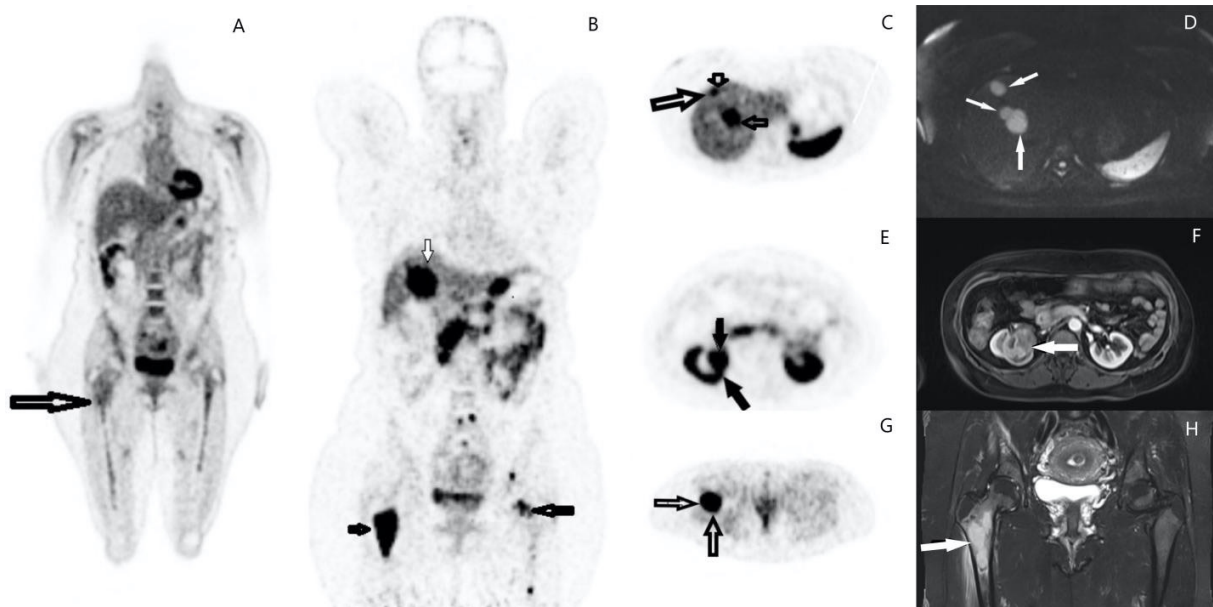


Figure 1: Tumoral masses in the liver, right renal cystic metastasis, and most of the bone metastasis are negative in FDG PET (A) and positive in ^{68}Ga -DOTATATE PET (B). 2 Liver lesions in VIII segment showing intense ^{68}Ga -DOTATATE uptake in axial Ga DOTATATE PET MIP image (C) and strongly restricted diffusion in diffusion-weighted axial MRI (D). Contrast-enhanced axial T1A FS MRI (F) images and axial MIP DOTA PET images (E) demonstrate a right renal cystic metastatic lesion with a great avidity for ^{68}Ga -DOTATATE. The largest bone metastasis is located in the right femoral neck, causing surrounding soft tissue edema and cortical thinning; coronal T2A FS MRI (H). Intramedullary tumor showing metabolic activity both in FDG-PET/CT (A) and ^{68}Ga -DOTATATE PET/CT (B, G)

PET: Positron emission tomography, CT: Computed tomography, MRI: Magnetic resonance imaging, MIP: Maximum intensity projection, FDG: Fluorodeoxyglucose

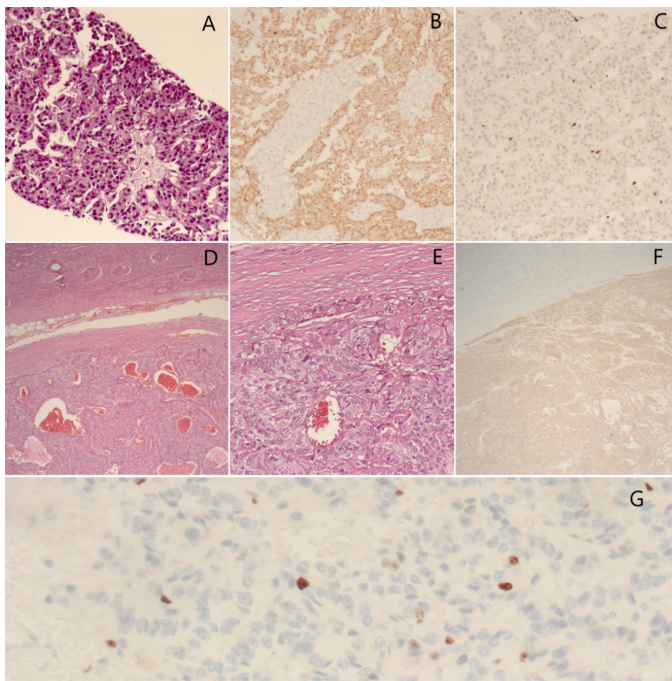


Figure 2: A) Tru-cut biopsy specimen, liver, hematoxylin eosin stain. B) Tru-cut biopsy specimen, liver, synaptophysin stain. C) Tru-cut biopsy specimen, liver, Ki-67 stain. D) Nephrectomy material, right kidney neuroendocrine tumor, hematoxylin-eosin stain 4x. E) Nephrectomy material, right kidney, neuroendocrine tumor hematoxylin-eosin stain 20x. F) Nephrectomy material, right kidney, neuroendocrine tumor synaptophysin stain. G) Nephrectomy material, right kidney, neuroendocrine tumor Ki-67 stain

months, laparoscopic right radical nephrectomy surgery was done with suspicion of renal cell carcinoma. Pathology reported a single Grade 1 NET. In the nephrectomy material, an intrarenal solid tumor with a diameter of 65 mm was observed in the lower pole. A neoplasm consisting of monotonous epithelial cells forming an organoid pattern, separated from the renal parenchyma by smooth borders, was observed (Figure 2). Neoplastic cells had oval or round nuclei with no visible nucleoli and large eosinophilic granular cytoplasm without necrosis (Figure 2). The mitotic index is counted as 0-1/10 HPF. Immunohistochemical staining was done and demonstrated CK8/18 and Synaptophysin positive, PAX8, and GATA3 negative neoplastic cells (Figure 2). The proliferative index of the tissue provided by Ki-67 labeling was less than 2%. Follow-up imaging demonstrated a heterogeneous response to the treatment, a GA-68 DOTATATE PET/computed tomography (PET/CT) was obtained after seven months and showed an obvious enlargement noted in the high-grade somatostatin receptor-expressing lesions in the VIII segment of the liver (Figure 3A-C). In contrast, MRI showed partial regression in the dimensions, T2A signal intensity, and metabolic activity of right femoral metaphyseal metastasis (Figure 3A, D, E). ¹⁷⁷Lutetium-Dotatate treatment was added to the current drugs. The patient currently comes for control visits without any complications.

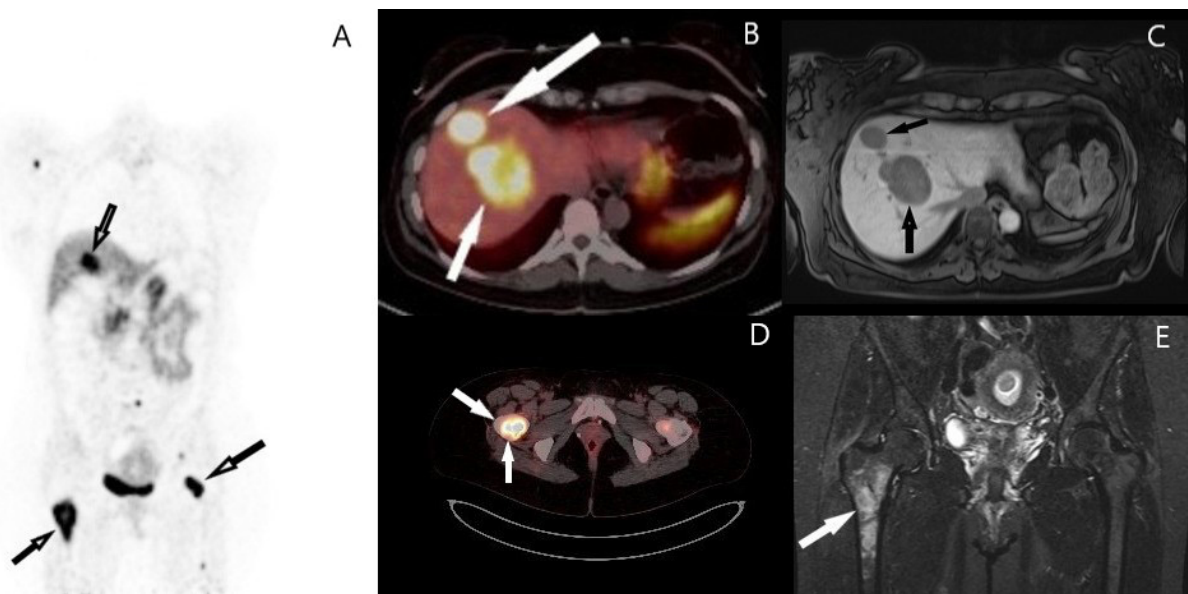


Figure 3: Heterogeneous metabolic response in ⁶⁸GA-DOTATATE PET/CT obtained 7 months after treatment. Obvious enlargement was noted in the high-grade somatostatin receptor expressing lesions in the VIII segment of the liver; Coronal view DOTA PET (A), DOTA PET fused axial image (B), Late liver phase postcontrast T1W axial MRI obtained with hepatospecific contrast agent (C). Partial regression was observed in the dimensions, T2A signal intensity and metabolic activity of right femoral metaphyseal metastasis; Fused posterior DOTA PET image (D), Coronal T2A FS MRI (E)

PET: Positron emission tomography, CT: Computed tomography, MRI: Magnetic resonance imaging

Discussion

PHNET are incredibly uncommon, and not many studies have been done to analyze the features and available treatments. PHNETs generally do not secrete hormones (2). The World Health Organization developed the NET categorization system in 2010, and it is based on pathological findings, including cell morphology, the number of mitotic cells found in ten high-power fields of view, and the Ki-67 index (3). NET tumors of the pancreas and gastrointestinal tract (GEP-NETs) can be divided into three categories based on this classification system: low malignancy (grade 1), moderate malignancy (grade 2), and high malignancy (grade 3). The tumor was grade 1 in our patient according to the classification.

With only around 200 reported PHNET cases globally, the diagnosis and treatment can be challenging. PHNETs can resemble other hepatic tumors radiologically so it is difficult to differentiate them preoperatively. CT with IV contrast and MRI with gadolinium can be helpful in showing tumor enhancement by featuring tumor vascularity (4). Immunostaining is one of the best tools to diagnose PHNETs since more than 70 percent of the tumors are positive for various hormones irrelevant of the functionality status (4). Neuroendocrine markers like hydroxyindoleacetic acid (5-HIAA) and serum chromogranin A can also assist to diagnose NET, but they are usually elevated in extrahepatic carcinoids rather than PHNETs (5). Although there are a few cases reported in the literature that show renal metastasis from rectal, ileal, and bronchial NETs, to our knowledge this is the first case that reports renal and bone metastasis from a PHNET (1,6-9).

Less than 1% of all NETs are found in the genitourinary tract, and the kidney is an incredibly uncommon location, accounting for 5-19% of them. Even less common are metastatic renal NETs from other main organs (1). Even though there is very little data regarding the management of renal metastasis of carcinoids because of their rarity, there are some papers regarding primary renal NET (PRNETs) that can give physicians some opinion. Romero et al. (10) investigated 56 reported cases and found that the median age of the patients with PRNETs was 49. 17.8% of the reported cases were present in horseshoe kidney. Only 12.7% of the cases showed classical neuroendocrine syndromes, and 45.6% of the cases were metastatic at the time of first diagnosis, which may suggest that there are challenges in early diagnoses of PRNETs. They found that significant negative prognostic factors are: age greater than 40 years, tumor size greater than 4 cm, purely solid tumors on the cut surface, mitotic rate higher than 1/10 high power fields, metastasis at initial diagnosis, and tumors extending throughout the renal capsule (10).

Most critically, renal NET need to be distinguished from renal cell carcinoma and from benign renal tumors such as

oncocytoma, angiomyolipoma, or malacoplakia. The primary form of treatment for renal carcinoids, like with other carcinoids, is surgical resection (6). In our case, the lesion was thought of as renal cell carcinoma at first until the post-operative pathological report.

Treatment methods for NET are improving day by day. While surgery is counted as the best treatment option for solitary PHNETs, metastatic cases like ours are not the best candidates for resection (4,11). The 5-year survival rate was found 74% in patients who had undergone liver resection for the solid PHNET (4). Somatostatin analogs remain the first-line treatment for functional and non-functional NET because It has been demonstrated that somatostatin possesses all four regulatory roles: endocrine, paracrine, neurocrine, and autocrine (12). In addition, Stueven et al. (13) reported that while initially used in the treatment of carcinoid syndrome to inhibit the release of neuropeptides or bioactive amines, several trials meanwhile revealed an effect of somatostatin analogs on tumor cell proliferation. We used Sandostatin (octreotide) for the initial treatment of the patient.

GA-68 Dotatate PET/CT scan is widely used to detect the feasibility of somatostatin analog treatment in early-stage NET. Lee et al. (14) found that GA-68 DOTATATE PET/CT independently predicted early failure on SSA monotherapy in patients with well-differentiated grade 1-2 GEP-NET. Thus, Routine GA-68 DOTATATE PET/CT has excellent sensitivity for quickly identifying patients who are not expected to benefit from SSA therapy. We also used a GA-68 DOTATATE PET/CT scan before starting Sandostatin treatment.

In addition to Sandostatin, Denosumab treatment was added to the patient's treatment regimen to target the bone metastases. A helpful phase 3 trial done by Lipton et al. (15) reported that in individuals with advanced cancer and bone metastases, denosumab outperformed zoledronic acid in preventing skeletal-related events with favorable safety and convenience.

Novel approaches are emerging for the treatment of NET. ¹⁷⁷Lutetium-Dotatate treatment is one of them. ¹⁷⁷Lutetium-Dotatate approved by the FDA after the NETTER-1 trial and outcome data from a large European registry. The drug's mechanism is evident in its structure, which consists of a somatostatin analog (octreotide) that binds to only cells that express the somatostatin receptor and a chelated beta-emitting isotope called ¹⁷⁷Lu. Due to its potential to promote tumor cyto-reduction, which is uncommon compared to other available treatments, and provide sustained disease control, ¹⁷⁷Lu-DOTATATE stands out as a unique addition to the treatment arsenal for gastroenteropancreatic NETs (16). We added ¹⁷⁷Lu-DOTATATE treatment to the patient's current treatment regimen after the treatment progression of the primary tumor.

There are other promising minimally invasive treatment modalities like trans-arterial chemoembolization, systemic chemotherapy, and local ablation, but none of them showed favorable results in terms of long-term survival (17).

Future research on the demographical, clinicopathological, and survival data with a large sample size of PHNETs would give a valuable understanding for clinicians.

Conclusion

To conclude, PHNETs are sporadic tumors, and metastasis to the kidney makes it even more uncommon. Renal metastasis from a PHNET tumor can be challenging to diagnose and treat. Since there are no guidelines specifically designed for these types of cases, multiple treatment modalities must be discussed with a multidisciplinary team to choose the best option for patients.

Ethics

Informed Consent: Informed consent was obtained from the patient.

Authorship Contributions

Surgical and Medical Practices: A.A., T.H., N.A., G.A., A.H., E.S., Concept: A.I., A.A., E.S., G.A., Design: A.I., A.A., E.S., A.H., Data Collection and/or Processing: A.I., T.H., N.A., Literature Search: A.I., N.A., T.H., G.A., A.H., Writing: A.A., A.I.

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Suprapubik Doku Defekti ile Başvuran Munchausen Sendromlu Hasta: Olgu Sunumu

A Patient with Munchausen Syndrome Presenting with Suprapubic Tissue Defect: A Case Report

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Öz

Munchausen sendromu nadir görülen, hastanın bilinçli olarak hasta rolü oynadığı, tamamen kendi oluşturduğu yapay, tekrarlı ve abartılı bir fiziksel ya da ruhsal hastalık veya yaralanma sebebi ile sürekli ilgi ve genellikle girişimsel tıbbi tedavi arayışı içinde olduğu psikiyatrik bir hastalıktır. Bu olgu sunumunda daha önceden lökosit adezyon defekti düşünülen ancak devamında Munchausen sendromu tanısı konan, suprapubik alandaki cerrahi insizyonun tekrarlı dehissansı ile kliniğimize refere edilen ve kliniğimizce debridman ve primer onarım yapılan hastanın anlatıldığı nadir görülen bir olgu sunulmaktadır.

Anahtar Kelimeler: Lökosit adezyon defekti, dehissans, Munchausen sendromu, kronik yara

Abstract

Munchausen syndrome is a rare psychiatric disorder in which the patient consciously plays the role of the patient and seeks constant attention and often interventional medical treatment due to an artificial, repetitive and exaggerated physical or mental illness or injury that is completely self-created. In this case report, we present a rare case of a patient who was previously thought to have leukocyte adhesion defect, but was subsequently diagnosed with Munchausen syndrome. The patient was referred to our clinic with recurrent dehiscence of the surgical incision in the suprapubic area, and debridement and primary repair was performed.

Keywords: Leukocyte adhesion defect, dehiscence, Munchausen syndrome, chronic wound

Giriş

Munchausen sendromu 1951 yılında Richard Asher tarafından tanımlanmıştır (1). Hastalık ismini Rus ordusu ile katıldığı savaşlar ile ilgili abartılı ve uydurma macera öyküleri ile ünlenen Alman aristokrat Baron Karl Friedrich Hieronymus Freiheiss von Munchausen'den (1720-1797) almaktadır (1,2). Hastalar genellikle akut prezentasyonlu ilginç hastalıklar ve enfeksiyon, bozulmuş yara iyileşmesi, ağrı, kanama, kaynağı belirsiz ateş gibi cerrahi branşları da ilgilendiren semptomlarla

birden çok hastaneye başvurmaktadır (1). Hastalar çok sayıda ve bazen hayati tehlikeye neden olabilecek operasyonlar geçirebilmektedirler (1). Hastalar tıbbi öykülerini doktorları yanıltmak adına tamamen ya da kısmen uydurabilmekte, laboratuvar değerlerine müdahale edebilmekte veya gerçek doku defektlerine neden olabilmektedir (1,3). Organ amputasyonlarına ve gereksiz ilaç kullanımına neden olarak sağlık kuruluşlarına, hastalara ve cerrahi branş doktorlarına önemli derecede iş yükü getirebilen bu sendromda en önemli basamak hastaların erken tanısının yapılabilmesidir (1,4).

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Olgu Sunumu

On beş yaşında kadın hasta kliniğimiz çocuk sağlığı ve hastalıkları immünoloji bölümüne karın ön duvarında tekrarlı doku defekti nedeni ile başvurdu. Hastanın anamnezinden hastanın 5 yaşında başlayan şiddetli idrar yolu enfeksiyonu öyküsü ve bu nedenle 2 defa yatışı verilerek intravenöz antibiyoterapi ile takip edildiği öğrenildi. Tekrarlı idrar yolu enfeksiyonu etiyojisi sırasında lökosit adezyon defekti tip 1 tanısından şüphelenilen hastanın 7 yaşında bilateral vezikoüretal reflü nedeni ile bilateral üreteroneostostomi operasyonu geçirdiği öğrenildi. Yaklaşık 6 yıl herhangi bir semptomu olmadan takip edilen hastanın 6. yılın sonunda operasyon sahasında doku defekti geliştiği ve bu nedenle yeniden yara yeri debridmanı ve onarımı operasyonu geçirdiği öğrenildi. Hastanın yara yerinde bir süre sonra yeniden doku defekti geliştiği ve en sonucusu kliniğimize başvurusundan 2 hafta önce olmak üzere toplamda 3 defa debridman ve yara yeri revizyonu operasyonu geçirmek zorunda kaldığı öğrenildi. Hastanın gestasyonel öyküsünde ise hastanın 39 yaşında anneden G3Y3 olarak 28 haftalık iken sezaryen ile doğduğu öğrenildi. Hastanın annesi ile babası arasında akrabalık öyküsü olmadığı ve kendisinden büyük 2 erkek kardeşinde herhangi bir sağlık problemi bulunmadığı öğrenildi. Yapılan fizik muayenede inspeksiyonunda suprapubik alanda yaklaşık 10 cm uzunluğunda insizyon skarı ve insizyon hattının sağ lateralinden orta hatta uzanan yer yer akıntılı 3 cm boyutunda doku defekti görülmekteydi. Hastanın insizyon hattı etrafı yer yer eritemliydi. Palpasyonda deri altı apseyi akla getirecek fluktuasyon, ağrı veya hassasiyet gibi bulgular mevcut değildi. Hastanın son operasyonu sırasında yara yerinden alınan dış merkez patolojisi "hipertrofik skar, akut enflamasyon, iltihabi granülasyon dokusu" olarak raporlanmıştı. Hastanın çocuk hastalıkları kliniğinde yatışı sırasında istenen laboratuvar değerlerinden kanama parametreleri, tam kan sayımı, albümin değeri ve immünglobulin (Ig) G, IgA, IgM değerleri normal aralıktaydı. Hastanın C-reaktif protein değeri 0,3 mg/L (N<0,1 mg/L) olarak normal değerler arasındaydı. Aynı zamanda hastanın doku defektinden alınan yara kültüründe üreme olmamıştı. Hastadan istenen yüzeyel doku ultrasonografi sonucu "deri ve deri altı dokular arasında serbest ya da loküle sıvı izlenmemiştir. İnsizyon hattı sağ lateral kesimi deri düzeyinde açık izlenmektedir." olarak raporlanmaktaydı. Hastadan yara iyileşmesini bozduğu düşünülerek istenen çinko değeri de normal değerlerin üzerindeydi. Hastadan yine çocuk hastalıkları kliniğince istenen alt abdomen bilgisayarlı tomografi sonucu ise "suprapubik bölgede orta hat ve sağında deri ve deri altı dokuyu ilgilendiren defektif görünüm, apse veya yabancı cisim saptanmamıştır." olarak raporlanmıştı. Hastanın çocuk cerrahisi ekibince yatak başı alınan patoloji spesimeni kliniğimiz patoloji bölümüne incelenmiş ve "hafif şiddette non-spesifik kronik enflamasyon bulguları, yağ nekrozu ve fibrinden zengin

iltihabi eksuda" olarak raporlanmıştı. Bu süre zarfında hastanın yara kültürü yenilenmiş ancak yine üreme olmamıştı. Hasta kliniğimize karın ön duvarında tekrarlı doku defekti onarımı nedeni ile danışıldı.

Hasta bu aşamadan sonra karın ön duvarında tekrarlı doku defekti ön tanısı ile genel anestezi ile onarım için hazırlandı. Hastadan istenen tam kan sayımı, tam biyokimya, koagülasyon parametreleri ve viral marker testleri normal sınırlardaydı. Hastaya debridman ve fasiyokütan flep ile onarım uygulandı. Hastanın insizyon hattından alınan spesimen doku kültürü olarak mikrobiyoloji laboratuvarına ve patolojik incelemeye gönderildi. Hastanın insizyon hattına intraoperatif olarak negatif basınçlı yara tedavisi (NBYT) uygulandı. Hastanın NBYT pansumanı postoperatif 3. günde sonlandırıldı. Hastanın yara yerinde herhangi bir komplikasyon görülmemesi üzerine hasta antibiyotik ve antienflamatuvar ilaçları reçete edilip poliklinik kontrolleri düzenlenerek taburcu edildi. Hastadan intraoperatif olarak alınan spesimenin patolojik incelemesi "ülserasyon, iltihabi granülasyon dokusu, sütür artıklarına karşı gelişmiş yabancı cisim tipi iltihabi olay, yağ nekrozu bulguları" olarak raporlandı. Hastanın intraoperatif doku kültüründe üreme olmadı. İzlemede hastanın ek şikayeti olmadı ve komplikasyon izlenmedi. Hasta kronik yara etiyojisi açısından yeniden değerlendirildiğinde mevcut doku defekti için herhangi bir neden bulunamadı. Hastanın patoloji raporunda spesifik bir bulgu olmaması ve buna ek olarak hastanın utangaç, sessiz tavırları ve şüpheli davranışları nedeni ile Munchausen sendromu ön planda tutuldu. Bu nedenle hasta taburculuk sonrası çocuk ruh sağlığı bölümüne konsülte edildi ve tedavisine ilgili bölüm tarafından devam edildi.

Hastanın preoperatif görünümü Şekil 1'de gösterilmiştir.

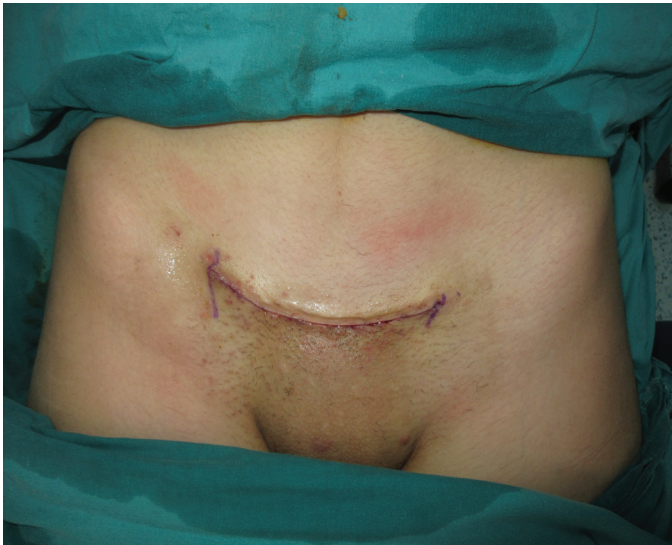
Hastanın intraoperatif görüntüleri Şekil 2, 3 ve 4'te gösterilmiştir.



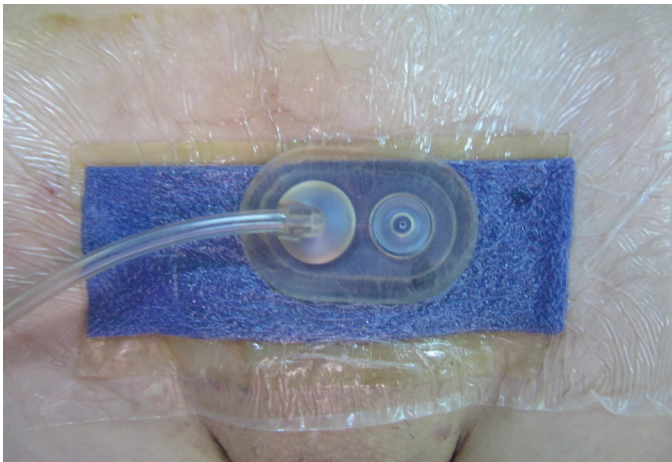
Şekil 1: Hastanın preoperatif görünümü



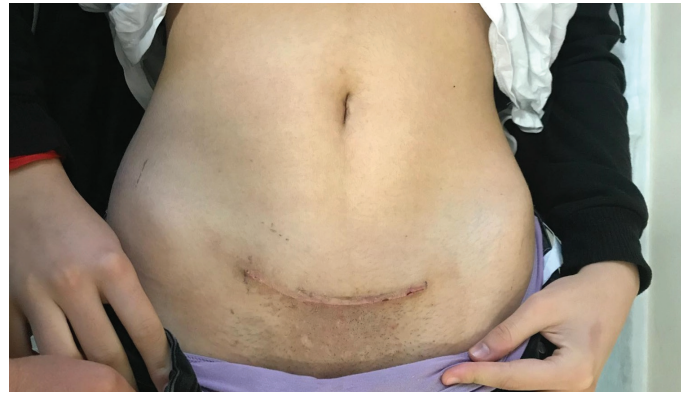
Şekil 2: Hastanın debridman sonrası intraoperatif erken dönem görünümü



Şekil 3: Hastanın primer onarım sonrası intraoperatif geç dönem görünümü



Şekil 4: Hastaya intraoperatif olarak uygulanan negatif basınçlı yara tedavisi sonrası görünümü



Şekil 5: Hastanın postoperatif 1. ay görünümü

Hastanın postoperatif 1. ay kontrolünde ek şikayetinin olmadığı ve yarasının tamamen iyileştiği görüldü.

Hastanın postoperatif 1. ay görünümü Şekil 5'te gösterilmiştir.

Tartışma

Pediyatrik hasta popülasyonu düşünüldüğünde deri yapısı ve fizyolojisi erişkinlere benzer olmasına rağmen pediyatrik deri, yetişkin derisine göre daha hassas ve frajildir (5). Pediyatrik deride bağışıklık yanıtı, olgunlaşmamış enflamatuvar hücreler ve daha az sayıda kemik iliği progenitör hücresi nedeniyle daha az gelişmiştir (5). Bu nedenle pediyatrik hastaların, özellikle de yenidoğanların mikroorganizmalara karşı tepkileri zayıftır (5). Buna karşılık çocuklarda yara enfeksiyonlarının genel fizyolojik durumdan ziyade operasyon sırasındaki faktörlerle ilişkili olduğu da belirtilmektedir (6). Pediyatrik kronik yara ayırıcı tanısında otoimmün hastalıklar, bası yaraları, koagülasyon bozuklukları, çeşitli dermatitler, sigara söndürülmesi benzeri ihmal ve istismarlar gibi çok geniş spektrumda nedenler bulunmaktadır (7). Olgu sunumundaki hastada operasyon öncesi alınan doku patolojisinin normal olması ve hasta öyküsü öncelikli tanıda Munchausen sendromunu düşündürmüştür.

Kronik bir hastalık olan Munchausen sendromunun dahil olduğu yapay bozukluklar için DSM-IV-TR tanı kriterlerine göre 3 ana klinik bulgu mevcuttur. Bunlar hastanın kendisi tarafından yapay fiziksel veya psikolojik semptomların üretilmesi, hasta rolünün benimsenmesi ve hastanın kendisi veya bir başkası için ekonomik kazanç, yasal sorumluluklardan kaçma, fiziksel iyilik gibi dış kazanımların olmamasıdır (1). Yine DSM-IV-TR Munchausen sendromunu "fiziksel veya psikolojik bulgu veya semptomların kasıtlı olarak oluşturulması veya varmış gibi davranılması" olarak tanımlamaktadır (8). Olgu sunumunda bahsedilen hastada Munchausen sendromu tanısı için gerekli üç tanı kriteri de sağlanmaktadır.

Munchausen sendromunun benzer somatoform bozukluklarından ayrılması gerekmektedir. Somatizasyon

bozukluğunda ve konversiyonda hastalar semptomları tamamen bilinçdışı nedenlerle ve istemsiz olarak yapmaktadırlar. Hastalar gerçekten hasta olduklarına inanmaktadırlar ve organik bir patoloji olmadan duygusal stres ve çatışmalarını fiziksel bulgular olarak yansıtmaktadırlar (1,9). Tamaruzda ise hastaların semptomları oluşturmada ekonomik kazanç, yasal sorumluluklardan kaçma veya korunma gibi sekonder kazançlar rol oynamaktadır. Hastaların sekonder kazanç ihtiyacı kalmadığında semptomlar da kaybolmaktadır. Hastalar bilinçli ve istemli olarak hasta taklidi yapmaktadırlar. Bu iki patoloji arasında bir spektruma sahip olan yapay bozukluklarda ve ona dahil olan ve bu gruptaki en uç noktayı oluşturan Munchausen sendromunda semptomlar bilinçaltı dürtüler ile bilinçli ve istemli şekilde ortaya çıkmaktadır. Ancak tamaruzdaki gibi sekonder dış kazançlar söz konusu değildir ve hastalar bu semptomlara neden sebep olduklarını bilmemektedirler (9).

Bu hastalar genellikle tanı alamadığından Munchausen sendromunun prevalansı tam olarak bilinmemekle birlikte 1.200 hastalık bir çalışmada psikiyatri konsültasyonu istenen hastalarda fiziksel semptom içeren yapay bozukluk oranı %0,8 olarak belirlenmiştir (1).

Munchausen sendromu 20:1 oranında kadınlarda daha sık görülmekte ve %30-70'e varan oranlarda intihar ile sonuçlanabilmektedir (10). Hastaların yaklaşık olarak %50'sinin sağlık çalışanı veya sağlık çalışanı yakını olması dikkat çekmektedir (11). Bu hastalar kendi hastalıkları hakkında geniş bilgiye sahip olabilmektedirler (8). Olgu sunumunda bahsedilen hastanın kadın olması ile literatüre uymaktadır. Munchausen sendromunda hastalar borderline kişilik bozukluğuna benzer davranış değişiklikleri gösterebilmektedir. Ancak borderline kişilik bozukluğunda hasta kendine zarar verse bile bunu saklamamakta ve bu durumu kendi çıkarı için kullanmamaktadır (11). Hastanın, doktorunun tanı ve tedavi aşamalarında yaşadığı zorluktan alınan zevk hastanın bilinçsiz sadistik davranışlarını, kendine zarar verip girişimsel tanı ve tedavilere maruz kalarak fiziksel ızdıraba maruz kalması da mazoşistik davranış paternini açıklamaktadır (4,10).

Munchausen sendromu genellikle apendektomi ve kolesistektomi gibi abdominal operasyonlar ile sonuçlansa da bu sendrom post-travmatik ve cerrahi kesileri de komplike edebilmektedir (1). En sık görülen olgulardan biri olan tekrarlı kronik iyileşmeyen ülserler malignensi, enfeksiyon, vaskülit, otoimmün hastalıklar veya yara iyileşmesini bozan metabolik hastalıklar ile karışabilmektedir (12).

Vücutta elle ulaşılabilen, ağrıya çok hassas olmayan alanlara yerleşmiş, özellikle gecikmiş yara iyileşmesinin olduğu yüzeysel yaralarda veya cerrahi kesilerde yabancı cisim bulunması, keskin sınırlı veya dairesel yeni kesiler, çok sayıda tırnak izi veya delik olması, taze kanama alanlarının bulunması durumunda

Munchausen sendromundan şüphelenilebilir (10). Hastanın birden fazla merkezde çok sayıda operasyon geçirmesi, radyolojik herhangi bir bulgunun eşlik etmemesi ve devamında hızlı bir iyileşme sürecinin ardından açıklanamayan doku defektinin tekrarlaması halinde Munchausen sendromundan şüphelenilmelidir (8,13). Hastanın pansumanını bilerek bozması ya da kirletmesi ve bu yolla yara yeri enfeksiyona neden olması da şüphe uyandırıcıdır (1,10). Hastanın kendine zarar verdiğinin kesin kanıtı olmasa da olgu sunumunda bahsedilen hastaya yara yeri revizyonu öncesi Munchausen sendromu tanısı koyulmuştur. Yaraya NBYT uygulanarak hastanın yarasına müdahalesinin önüne geçilmiş ve yara iyileşme süreci hızlandırılmıştır (14). NBYT ile hastanın yara yerine müdahalesine engel olunduktan sonra yara hızlı ve komplikasyonsuz bir biçimde iyileşmiştir.

Hastalarda daha önceden geçirilmiş bir psikiyatrik bozukluk olması, herhangi bir risk faktörü olmamasına rağmen bilateral olabilen iyileşmeyen yaralar, yara yerinden tekrarlı kanama olması, çok sayıda başarısız operasyon öyküsü ve hastanın hasta rolünü benimseyip cerrahi girişimler gibi tanısız ve terapötik yöntemler ile hastanede kalmaya devam etmek istemesi gibi ipuçları tanıda önem kazanmaktadır (1). Lezyonun görünüşü, lokalizasyonu, histopatolojik bulguları ve doğal süreci arasında uyumsuzluk halinde Munchausen sendromu ayırıcı tanıda akla gelmelidir (4). Olgu sunumunda bahsedilen hastanın patolojik incelemesinde spesifik bir hastalığa ait bir bulgunun olmaması, hastane yatışı sırasındaki aşırı utangaç ve sessiz tavrı Munchausen sendromu tanısını güçlendirmektedir.

Munchausen sendromu tanısı bir ekartasyon tanısı olduğundan en kısa sürede tanı konmalıdır (4). Tanı konar konmaz hastanın ileri tanısız ve terapötik girişimsel uygulamalara maruz kalması engellenmeli ve psikiyatrik muayeneye yönlendirilmelidir. Ancak bu kötü prognozlu hastalığın kesin bir tedavisi bulunmamakla beraber farmakoterapiye aile terapisi ve davranışsal tedavi eklenmektedir (8,9). Olgu sunumunda bahsedilen hasta yara yeri iyileşmesinin ardından çocuk ruh sağlığı bölümüne konsülte edilmiş ve hastaya ilgili bölüm tarafından aile terapisi planlanmıştır.

Sonuç

Munchausen sendromu %1'den daha nadir görülse de her plastik cerrahın aklında olması gereken, özellikle postoperatif dönemde tanısı zor konan bir hastalıktır. Medikolegal açıdan doktorların kendilerini güvence altına almaları adına hastaların medikal kayıtları tutulmalı, gerekirse geçmiş medikal kayıtları dikkatlice incelenmelidir (9). Tedavide amaç yara iyileşmesini sağlamak ve hastanın sahte cerrahi döngülerini kırmaktır (1,15). Hastalığın geç tanısının getirdiği ekonomik yük düşünüldüğünde bulgular ve tanının uyuşmamasından şüphelenilen hastalarda mutlaka interdisipliner bir tedavi planı yapılmalı ve hastalar direnç gösterse bile psikiyatrik muayeneden geçirilmelidir (4,10).

Etik

Hasta Onayı: Hastadan yazılı ve sözel olarak aydınlatılmış onam alınmıştır.

Yazarlık Katkıları

Cerrahi ve Medikal Uygulama: A.Ö., B.K., Konsept: B.K., Dizayn: B.K., Veri Toplama veya İşleme: A.Ö., Analiz veya Yorumlama: B.K., Literatür Arama: A.Ö., Yazan: A.Ö., B.K.,

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