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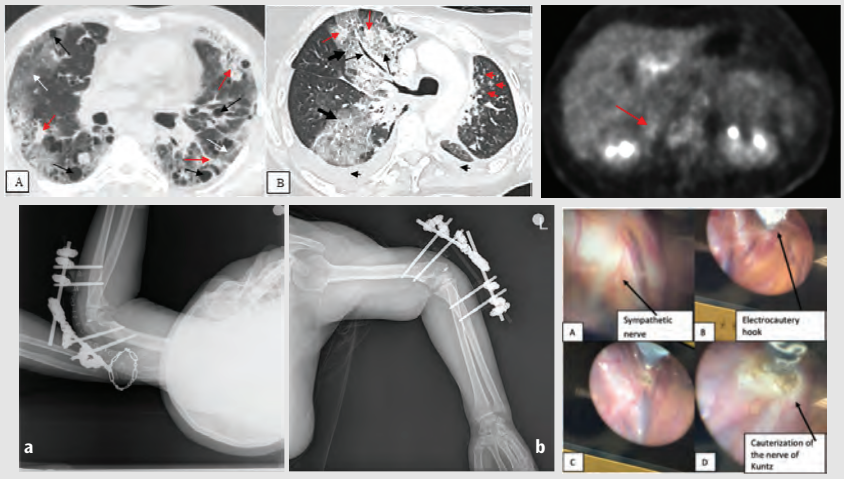

Highlights

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European Archives of Medical Research (Eur Arch Med Res) is the scientific, peer-reviewed, open access publication of University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital. The journal is a quarterly publication, published on March, June, September, December. The publication language of the journal is English.

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Abstract: An abstract should be submitted with all submissions except for Letters to the Editor. The abstract of Original Articles should be structured with subheadings (Objective, Methods, Results, and Conclusion). Please check Table 1 below for word count specifications.

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Original Articles: This is the most important type of article since it provides new information based on original research. The main text of original articles should be structured with Introduction, Methods, Results, Discussion, and Conclusion subheadings. Please check Table 1 for the limitations for Original Articles.

Statistical analysis to support conclusions is usually necessary. Statistical analyses must be conducted in accordance with international statistical reporting standards (Altman DG, Gore SM, Gardner MJ, Pocock SJ. Statistical guidelines for contributors to medical journals. Br Med J 1983: 7; 1489-93). Information on statistical analyses should be provided with a separate subheading under the Materials and Methods section and the statistical software that was used during the process must be specified.

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Units should be prepared in accordance with the International System of Units (SI).

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Review Articles: Reviews prepared by authors who have extensive knowledge on a particular field and whose scientific background has been translated into a high volume of publications with a high citation potential are welcomed. These authors may even be invited by the journal. Reviews should describe, discuss, and evaluate the current level of knowledge of a topic in clinical practice and should guide future studies. The main text should contain Introduction, Clinical and Research Consequences, and Conclusion sections. Please check Table 1 for the limitations for Review Articles.

Case Reports: There is limited space for case reports in the journal and reports on rare cases or conditions that constitute challenges in diagnosis and treatment, those offering new therapies or revealing knowledge not included in the literature, and interesting and educative case reports are accepted for publication. The text should include Introduction, Case Presentation, Discussion, and Conclusion subheadings. Please check Table 1 for the limitations for Case Reports.

Case Series: The Case Series section reports a series of 2-6 similar cases. The cases should address a challenging diagnostic and/or therapeutic problem with possible solutions to help clinicians in managing these cases. Case series must be accompanied with a comprehensive review of literature. It should include six authors maximum. Structure of manuscript should include Introduction, Case Series, Discussion, Conclusion. It should have 3-5 keywords maximum. Please check Table 1 for the entire limitations for Case Series.

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Image(s): The number of images is left to the discretion of the author. (See Original article section)

Figure Legend: Reference citations should appear in the legends, not in the abstract. Since there is no manuscript text, the legends for illustrations should be prepared in considerable detail but should be no more than 500 words total. The case should be presented and discussed in the Figure legend section.

References: Maximum eight references (see Original article section).

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Tables

Tables should be included in the main document, presented after the reference list, and they should be numbered consecutively in the order they are referred to within the main text. A descriptive title must be placed above the tables.

Abbreviations used in the tables should be defined below the tables by footnotes (even if they are defined within the main text).

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Type of manuscript	Word limit	Abstract word limit	Reference limit	Table limit	Figure limit
Original Article	3500	250 (Structured)	40	6	7 or total of 15 images
Review Article	5000	250	80	6	10 or total of 20 images
Case Report	1000	200	15	No tables	10 or total of 20 images
Letter to the Editor	500	No abstract	5	No tables	No media

Tables should be created using the "insert table" command of the word processing software and they should be arranged clearly to provide easy reading. Data presented in the tables should not be a repetition of the data presented within the main text but should be supporting the main text.

Figures and Figure Legends

Figures, graphics, and photographs should be submitted as separate files (in TIFF or JPEG format) through the submission system. The files should not be embedded in a Word document or the main document. When there are figure subunits, the subunits should not be merged to form a single image. Each subunit should be submitted separately through the submission system. Images should not be labeled (a, b, c, etc.) to indicate figure subunits. Thick and thin arrows, arrowheads, stars, asterisks, and similar marks can be used on the images to support figure legends. Like the rest of the submission, the figures too should be blind. Any information within the images that may indicate an individual or institution should be blinded. The minimum resolution of each submitted figure should be 300 DPI. To prevent delays in the evaluation process, all submitted figures should be clear in resolution and large in size (minimum dimensions: 100 × 100 mm). Figure legends should be listed at the end of the main document.

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When a drug, product, hardware, or software program is mentioned within the main text, product information, including the name of the product, the producer of the product, and city and the country of the company (including the state if in USA), should be provided in parentheses in the following format: "Discovery St PET/CT scanner (General Electric, Milwaukee, WI, USA)"

All references, tables, and figures should be referred to within the main text, and they should be numbered consecutively in the order they are referred to within the main text.

Limitations, drawbacks, and the shortcomings of original articles should be mentioned in the Discussion section before the conclusion paragraph.

References

While citing publications, preference should be given to the latest, most up-to-date publications. If an ahead-of-print publication is cited, the DOI number should be provided. Authors are responsible for the accuracy of references. Journal titles should be abbreviated in accordance with the journal abbreviations in Index Medicus/ MEDLINE/PubMed. When there are six or fewer authors, all authors should be listed. If there are seven or more authors, the first six authors should be listed followed by "et al." In the main text of the manuscript, references should be cited using Arabic numbers in parentheses. The reference styles for different types of publications are presented in the following examples.

Journal Article: Stephane A. Management of Congenital Cholesteatoma with Otoendoscopic Surgery: Case Report. Turkiye Klinikleri J Med Sci 2010;30:803-7.

Book Section: Suh KN, Keystone JS. Malaria and babesiosis. Gorbach SL, Barlett JG, Blacklow NR, editors. Infectious Diseases. Philadelphia: Lippincott Williams; 2004.p.2290-308.

Books with a Single Author: Sweetman SC. Martindale the Complete Drug Reference. 34th ed. London: Pharmaceutical Press;2005.

Editor(s) as Author: Huizing EH, de Groot JAM, editors. Functional reconstructive nasal surgery. Stuttgart-New York: Thieme;2003.

Conference Proceedings: Bengisson S. Sothemin BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sept 6-10; Geneva, Switzerland. Amsterdam: North-Holland;1992. pp.1561-5.

Scientific or Technical Report: Cusick M, Chew EY, Hoogwerf B, Agrón E, Wu L, Lindley A, et al. Early Treatment Diabetic Retinopathy Study Research Group. Risk factors for renal replacement therapy in the Early Treatment Diabetic Retinopathy Study (ETDRS), Early Treatment Diabetic Retinopathy Study Kidney Int: 2004. Report No: 26.

Thesis: Yılmaz B. Ankara Üniversitesindeki Öğrencilerin Beslenme Durumları, Fiziksel Aktiviteleri ve Beden Kitle İndeksleri Kan Lipidleri Arasındaki Ilişkiler. H.Ü. Sağlık Bilimleri Enstitüsü, Doktora Tezi. 2007.

Manuscripts Accepted for Publication, Not Published Yet: Slots J. The microflora of black stain on human primary teeth. Scand J Dçent Res. 1974. Epub Ahead of Print Articles: Cai L, Yeh BM, Westphalen AC, Roberts JP, Wang ZJ. Adult living donor liver imaging. Diagn Interv Radiol 2016 Feb 24. doi: 10.5152/dir.2016.15323. [Epub ahead of print].

Manuscripts Published in Electronic Format: Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis (serial online) 1995 Jan-Mar (cited 1996 June 5):1(1): (24 screens). Available from: URL: http:/ www.cdc.gov/ncidodlEID/cid.htm.

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CONTENTS

REVIEW

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An Overview of Anesthetic Agents used in Anesthesia Practices

Münire Canan Çiçek[1], Rasim Onur Karaoğlu[1], Mehmet Nuri Yakar[2], Namigar Turgut[1]

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Abstract

The process, which started with the discovery of the anesthetic properties of diethyl ether by William Morton in 1846, as the beginning of anesthesia and inhalation anesthesia in the medical world, continued to develop with the discovery of many anesthetic agents. Sevoflurane and desflurane were developed towards the end of the 1960s. They are among the most preferred inhalation anesthetics today. Intravenous anesthetics also continue to evolve with the advancement of pharmacology. New agents will allow us to leave the traditional understanding of anesthesia in the background and allow us to respond more appropriately to the increasing elderly population and increasing population with minimal effects on recovery time and cardiovascular side effects.

Keywords: Inhalation anesthetics, intravenous anesthetics, general anesthesia

INTRODUCTION

The process, which started with the discovery of the anesthetic properties of diethyl ether by William Morton in 1846, as the beginning of anesthesia and inhalation anesthesia in the medical world, continued to develop with the discovery of many anesthetic agents such as chloroform, ethylene, cyclopropane, and nitrous oxide (N_2O) (1,2). After the use of halothane in the clinic in 1957, surgical anesthesia was started, and methoxyflurane was discovered in 1960. After the occurrence of halothane-induced hepatotoxicity and methoxyflurane-induced nephrotoxicity, enflurane was synthesized in 1963 and its isomer isoflurane was synthesized in 1965 in line with the need for new anesthetics (2,3). Sevoflurane and desflurane were developed towards the end of the 1960s. They are among the most preferred inhalation anesthetics today (2). Intravenous (i.v.) anesthetics also continue to evolve with the advancement of pharmacology. First generation i.v. agents for anesthesia induction and maintenance date back to the introduction of thiopental in the 1930s as an alternative to inhaled agents. Since then, barbiturates, propofol, ketamine, etomidate, benzodiazepines and dexmedetomidine represent i.v. anesthetic and sedative agents.

New agents will allow us to leave the traditional understanding of anesthesia in the background and allow us to respond more appropriately to the increasing elderly population and increasing population with minimal effects on recovery time and cardiovascular side effects.

1. Inhalation Anesthetics

1.1. N_2O, dinitrogen monoxide, nitrogen protoxide

N_2O is an inorganic inhalation agent that is colorless, odorless or sweet-smelling, non-irritating to tissues, non-flammable but capable of supporting (4). It does not undergo biotransformation, does not bind to hemoglobin, and is transported by dissolving in the blood (4). Its elimination is the opposite of uptake and distribution. Its low solubility enables rapid elimination (4,5). N_2O, which was defined by Sir Humphry Davy as "laughing/giggle gas", was not used for anesthesia in the first half of the 19th century, but began to be used for analgesic purposes in

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clinical medicine and dentistry (6). It is the least effective of the available inhalation agents because it requires a concentration of 104% to reach the Minimum Alveolar Concentration (MAC). Its low potency and its both anesthetic and analgesic activities cause it to be preferred as an adjuvant in balanced anaesthesia (7). It helps anesthesia induction by reducing the MAC value of the agent it is used with due to both primary and secondary gas effects. By inhibiting methionine synthase, it impairs vitamin B12 and folate metabolism (7). Most of the side effects of N_2O are due to the irreversible inhibition of methionine, folate, and vitamin B12, which plays an important role in DNA synthesis (8). With long-term N_2O application, conditions such as megaloblastic anemia, neurological toxicity and teratogenicity, immunodeficiency and impaired wound healing can be observed (7). In large-scale studies performed in non-cardiac surgeries, there are different opinions about whether there is an increase in the risk of cardiovascular complications such as myocardial infarction and venous thromboembolism in the postoperative period (8-10). Some studies have shown that N_2O increases pulmonary arterial pressure, and its use should be avoided in patients with pulmonary hypertension (10,11). The low blood-gas partition coefficient of N_2O causes it to replace nitrogen and oxygen in hollow chambers in the body, including the lungs. Such a high diffusion capacity can lead to diffusion hypoxia and an increase in the existing pneumothorax area during its elimination from the body (7,12). In order to prevent diffusion hypoxia, 100% oxygen should be given to the patient in the first few minutes following the discontinuation of N_2O therapy (4). In terms of postoperative complications such as pneumonia, pneumothorax or pulmonary embolism, the ENIGMA-I study showed statistically significant results in patients receiving N_2O, while there was no statistically significant increase in respiratory events in patients receiving N_2O in the ENIGMA-II study (8,9). Although studies show that the development of postoperative cognitive dysfunction is not observed in patients using N_2O, there is not enough research in this area (13). In recent years, recreational abuse of N_2O has become increasingly common. N_2O abuse can damage multiple systems, especially the nervous system, and the exact mechanism of its toxicity is controversial (14,15). It can be used in obstetric gynecology due to its analgesic effects (10,16). Due to its possible neurotoxic effects, its use in the first trimester is not recommended (17).

1.2. Isoflurane ($C_3H_2ClF_5O$, methyl ethyl ether)

Isoflurane is a non-flammable volatile anesthetic with a pungent ether-like odor and is the structural isomer of enflurane (18). Its pungent odor limits its induction by inhalation (19). Its effect in the central nervous system (CNS) strengthens GABA and glycine receptor activities, while it inhibits receptor activity in NMDA glutamate receptor subtypes (19). Although it has a minimal effect on the left ventricle, it can cause a dose-dependent decrease in systemic vascular resistance (SVR) with the β-adrenergic stimulation it causes, resulting in a decrease in preload and thus cardiac output. Compensation for the decreased cardiac output can be achieved with the increase in heart rate caused by it (18,19). A decrease in SVR may cause coronary dilatation, leading to what is known as the "coronary steal phenomenon" (18,19). It should be kept in mind that all halogenated volatile anesthetics, including isoflurane, may cause malignant hyperthermia in patients with a personal or family history (18-20). In studies, there are also animal models showing that both i.v. and inhalation anesthesia promotes neuronal apoptosis (21,22). Due to the different biological systems, it is difficult to transfer the neurotoxic effects of volatile anesthetics from animals to humans (19). This leads to more research on the known neuroprotective and neurotoxic effects of volatile anesthetics (19). Recent studies have shown that isoflurane has neuroprotective properties. Especially in studies with neonatal hypoxic ischemic brain injury, it has been found that early isoflurane treatment has neuroprotective effects (23,24).

1.3. Sevoflurane ($C_4H_3F_7O$, methyl isopropyl ether)

Sevoflurane, discovered in 1971, is a halogenated volatile anesthetic that is used for the induction and maintenance of general anesthesia in pediatric patients and in inpatient or outpatient surgery in adults (25). It can provide hypnosis, amnesia, analgesia, akinesia, and autonomic blockade during surgical and procedural interventions (25). It has a colorless volatile form with a mild pleasant odor (26). Although its working mechanism is not clear, it shows its effect similar to other volatile anesthetics by increasing the activity of inhibitory postsynaptic receptors such as GABA and glycine in the CNS or by suppressing excitatory stimuli such as NMDA (18,25). It causes a dose-dependent decrease in blood pressure and cardiac output by reducing SVR (25). Like all volatile anesthetics, it is irritant in terms of respiratory tract, can trigger cough and laryngospasm, but these properties are rarely observed due to its sweet smell and less sharpness compared to others (25). By causing dose-dependent vasodilation in the cerebrovascular area, it increases cerebral blood flow and intracranial pressure, while decreasing cerebral metabolic rate (25). Sevoflurane is an agent with a potential theoretical risk of developing hepatotoxicity, nephrotoxicity, and neurotoxicity (25). In recent studies, it has been reported that sevoflurane reduces myocardial ischemia-reperfusion injury and infarct size (27). In addition, there is evidence that it can reduce neuronal damage and cerebral ischemia-reperfusion damage

due to its anti-inflammatory and neuroprotective effects (28-30). It contributes to the preservation of neurocognitive skills by reducing neuron apoptosis and antioxidant stress (31). Like other volatile anesthetics, sevoflurane is metabolized in the liver by a specific cytochrome enzyme (CYP-2E1) (19). Hepatotoxicity has been reported very rarely due to the low percentage of metabolized sevoflurane (32,33). Today, there are studies reporting that it is used for sedation in intensive care units as well as being used as a maintenance in general anesthesia (34).

1.4. Desflurane ($C_3H_2F_6O$, methyl ethyl ether)

Desflurane was synthesized in the 1970s. Its only structural difference from isoflurane is that it contains fluorine atoms instead of chlorine. This minor change causes the vapor pressure of desflurane to be 681 mmHg at 20 °C and boiling at room temperature in high altitude regions. A pressure-temperature controlled vaporizer specific to desflurane was developed due to this feature (18,35). Due to its sharp smell, it is preferred for anesthesia maintenance rather than induction. It is very slightly soluble in blood due to its blood/gas partition coefficient of 0.42. This feature causes rapid induction and recovery (18,35). Similar to sevoflurane and isoflurane, a decrease in blood pressure and a minimal increase in heart rate are observed with a decrease in SVR (35). Dilation of cerebral arteries causes a decrease in cerebral metabolic rate and an increase in intracranial pressure (35). In recent studies, it has been reported that delirium and respiratory complications may be encountered more frequently than other agents, especially in the pediatric population (36-38). In studies on the geriatric population, it was determined that postoperative recovery was faster when desflurane was used (39).

1.5. Xenon (Xe)

Xe is a colorless, odorless, non-explosive noble gas first discovered in 1898 for use in spacecraft and flashlights (40). Its anesthetic effect was first discovered after "poisoning" in deep-sea divers in hyperbaric conditions and was first applied as an anesthetic by Stewart Cullen in 1951 (40). It is thought to show its effect by competitive inhibition with glycine and through NMDA receptor antagonism (40). It is obtained from the atmosphere after a very expensive distillation process and special anesthesia devices are used for its application (18). Side effects frequently associated with the use of Xe gas for inhalation as a general anesthetic in the literature include increased intracranial pressure, bradycardia, nausea and vomiting (41-43). It has a pharmacokinetic profile suitable for anesthesia with its very low blood-gas partition coefficient (Xe: 0.115, N_2O, 0.47; sevoflurane, 0.65; desflurane, 0.42), regardless of exposure time (44). Since it is excreted from the lungs without biotransformation by the kidney or liver systems, it is thought that it may be preferred in some patients in whom liver or kidney functions are reduced (44). Due to its hemodynamic stability, recent studies have shown its superiority in cardiac and non-cardiac major surgeries, especially in the elderly population, in terms of postoperative cognitive dysfunction and rapid postoperative recovery. It is environmentally friendly and has no ozone-depleting effect, but its high cost is an important limiting factor in clinical practice (45).

2. Intravenous Anesthetics

The main effect of i.v. anesthetics is sedation and hypnosis caused by CNS depression. Their effects begin quickly, most of them are more lipid soluble and have a high cerebral perfusion rate. The end of their effects is the result of redistribution. They can be used alone in short interventions, as balanced anesthesia with inhalation anesthetics or as total i.v. anesthesia with opioids.

2.1. Barbiturates

Barbiturates depress the reticular activating system, reduce intracranial pressure in clinical doses, and do not have muscle relaxant properties. They are used in status epilepticus because of their anticonvulsant effects.

The sodium salts of barbiturates are water-soluble but markedly alkaline and relatively unstable. The anesthetic effects of barbiturates are culminated by the reduction of the drug from the central lipophilic brain tissues to the peripheral lean muscle compartments. They cause further reduction in cerebral oxygen consumption, so the decrease in cerebral blood flow is not harmful, they can protect the brain against transient focal ischemia attacks. Although the general idea is to cause hyperalgesia after barbiturate administration, recent studies question this situation. Past studies evaluating the effects of thiopental on pain are conflicting (46). Recent studies have shown that thiopental has a neuroprotective effect on postoperative neurological complications (47,48). The use of new barbituric acid derivatives as antioxidant, antibacterial and anti-proliferative agents has become questionable (49-52).

2.2. Benzodiazepines

Benzodiazepines bind to a different site of the same receptor groups as barbiturates in the CNS. Binding to the $GABA_A$ receptor, benzodiazepines increase the frequency of opening of associated chloride ion channels. Their chemical structure consists of a benzene ring and a seven-membered diazepine ring. Substitutions at various positions on these rings affect potency and biotransformation.

Metabolites of benzodiazepine biotransformation are excreted mainly in the urine. Prolonged sedation may be observed in patients with renal failure due to the accumulation of alpha hydroxymidazolam, a conjugated metabolite of midazolam (53). It has minimal cardiovascular depressant properties, arterial blood pressure, cardiac output, and peripheral vascular resistance are usually slightly reduced. Cerebral oxygen consumption decreases cerebral blood flow and intracranial pressure, but not as much as barbiturates. It has been shown that long-term use of benzodiazepines leads to irreversible cognitive dysfunction and dementia, especially in elderly patients (54-58). There are studies related to malignancy surgery, suggesting that midazolam may have an antineoplastic effect through different mechanisms (59-62). Remimazolam is an ultra-short-acting benzodiazepine derivative due to its rapid onset, rapid recovery time and degradation by non-specific tissue esterases (63-65).

Remimazolam effects are achieved by binding to the standard benzodiazepine site on the $GABA_A$ receptor (66). It has a superior safety profile with features such as minimal cardiorespiratory side effects, no injection pain, and metabolism unaffected by liver or kidney function. Although many areas of use are foreseen, including anesthesia induction and maintenance, and sedation in intensive care patients, its cost-effectiveness limits the use of the drug.

2.3. Ketamine

Ketamine, an NMDA antagonist, inhibits the effects of excitatory neurotransmitters in the CNS. Functionally, it separates the thalamus from the limbic cortex. While some neurons of the brain are inhibited, others are tonically excited. Clinically, this dissociative state of anesthesia causes patients to appear conscious but unable to evaluate and respond to sensory input. Even subteratopic doses of ketamine can be hallucinogenic, clinically it is administered with small doses of midazolam for amnesia and sedation. It is a good option for i.v. anesthesia in patients with hypovolemia and trauma, in whom ketamine's tendency to produce sympathetic stimulation is particularly beneficial. It is a stereoisomer. The S isomer is superior to the R isomer with its increased anesthetic potency and decreased psychomimetic side effects (67,68). The accepted conventional belief about ketamine is that ketamine increases cerebral oxygen consumption, cerebral blood flow, and intracranial pressure. Although this situation limits its use in intracranial traumas and intracranial space-occupying lesions, recent publications question these effects of ketamine (69-71).

2.4. Etomidate (R 16659)

Etomidate depresses the reticular activating system and mimics the inhibitory effects of GABA. Etomidate (R 16659) is a potent $GABA_A$ receptor agonist. Like ketamine, it is racemic. Unlike barbiturates, it has disinhibitory effects on parts of the nervous system that control extrapyramidal motor activity, so myoclonus is seen between 30-60% in induction. It has been shown that dexmedetomidine can effectively prevent the incidence of etomidate-induced myoclonus (72). Cardiovascular effects are minimal. Compared to other agents for rapid serial intubation, it is a superior agent in terms of hemodynamic stabilization (73,74). It decreases cerebral metabolic rate, cerebral blood flow and intracranial pressure. Postoperative nausea and vomiting are more common than barbiturates and propofol, and it has no analgesic effect. Since induction doses of etomidate temporarily inhibit the enzymes involved in the synthesis of cortisol and aldosterone, it has been observed that it causes adrenocortical suppression, especially in cases of long-term infusion, especially in patients with sepsis (75). ABP-700, newly developed in drug studies, is an etomidate analogue with a short half-life due to its rapid degradation and inactive metabolites. Although the frequency of nausea, vomiting and adrenocortical suppression is less than that of etomidate, the incidence of involuntary muscle movements and seizures is not less than etomidate, which limits the use of ABP 700 for now (76-79).

2.5. Propofol ($C_{12}H_{18}O$, 2,6 diisopropylphenol)

Propofol allosterically increases the binding affinity of GABA to the $GABA_A$ receptor. It consists of a phenol ring to which two isopropyl groups are attached. It has been shown in many studies to reduce postoperative complications and oxidative stress, which leads to faster recovery, and may therefore be the induction agent of choice in the right clinical setting (80,81). When used for long-term sedation, lipemia causes metabolic acidosis and propofol infusion syndrome with death, especially in children and young adults (82). It has been shown that chemotherapeutic drugs can enhance their anti-neoplastic effect and inhibit tumor growth and metastasis in in vivo animal models (83,84).

The pharmacological activity of fospropofol, a prodrug of propofol, results from its degradation by alkaline phosphatase and the release of its active molecule propofol. Compared to propofol, the duration of peak effect is longer. Therefore, side effects such as hypotension and respiratory depression are less common in patients compared to the propofol bolus. Another advantage of propofol is that it does not cause a burning

sensation in i.v. administration, but the paresthesia and itching sensation after drug administration and the late onset of its effect limit its clinical use (85-87).

2.6. Dexmedetomidine ($C_{13}H_{16}N_2$)

Dexmedetomidine is a potent selective α2 agonist agent with sedative, analgesic and anxiolytic properties. It has a short distribution half-life of six minutes. Despite the side effects of hypotension and bradycardia, it is quite safe for short-term sedation. Its use in patients in the process of weaning from mechanical ventilation in the intensive care unit is very important in terms of patient comfort (88). Its use as a sedative agent in perioperative and intensive care units may provide advantages, especially in elderly patients, by reducing the incidence of postoperative delirium and shortening the discharge time (89-91). Although recent studies give different results regarding its effects on malignancy progression, they emphasize that it facilitates metastasis due to inducing angiogenesis (91-93).

CONCLUSION

As a conclusion; the process, which started with the discovery of the anesthetic properties of diethyl ether by William Morton in 1846, as the beginning of anesthesia and inhalation anesthesia in the medical world, continued to develop with the discovery of many anesthetic agents. New agents will allow us to leave the traditional understanding of anesthesia in the background and allow us to respond more appropriately to the increasing elderly population and increasing population with minimal effects on recovery time and cardiovascular side effects.

Ethics

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

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Early and Mid-term Results Following Surgery of Elbow Fractures with the Terrible Triad

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Abstract

Objective: This study aimed to evaluate the mid-term results of patients with dislocated fractures around the elbow with the terrible triad who were treated with an elbow external fixator together with internal fixation and ligament repair.

Methods: The study included patients who underwent surgery for a diagnosis of a terrible triad between January 2009 and January 2015. A total of 14 patients were diagnosed with terrible triad and were operated with an elbow external fixator additional to internal fixation and ligament repair.

Results: The mean follow-up period was 27 months (range, 22-38 months). According to the Mayo elbow performance score, 10 patients were evaluated as excellent, 2 as good and 2 as poor. The flexion ROM were mean 118° (range, 115°-122°), and extension ROM was mean 26° (range, 20°-32°). Flexion contracture was determined of mean 15° (range, 10°-20°) and extension contracture of mean 7.5° (range, 5°-10°). Full bone union was observed radiographically in all patients.

Conclusion: In fractures around the elbow diagnosed with terrible triad, the combination of internal fixation with elbow external fixator provided the possibility of starting elbow joint movements in the early period and the mid-term results obtained were pleasing.

Keywords: Elbow, fracture, external fixator, terrible triad

INTRODUCTION

Bone fractures and ligamentous structure injuries accompanying complex elbow dislocations are significant causes of elbow instability. These are injuries that can cause problems at the treatment stage when accompanied by various clinical problems (1,2).

The aim of treatment for complicated elbow dislocations is to be able to obtain a stable joint that provides good functional status following early surgical reconstruction (3,4).

This study aimed to evaluate the functional results of patients with dislocated fractures around the elbow with the terrible triad who were treated with an elbow external fixator together with internal fixation and ligament repair.

METHODS

Approval for this retrospective study was granted by the University of Health Sciences Turkey, Okmeydani Training and Research Hospital Local Ethics Committee (no: 48670771-514,10). The study included patients who underwent surgery for a diagnosis of a terrible triad. Between January 2009 and January 2015.

A total of 14 patients were diagnosed with terrible triad and were operated with an elbow external fixator additional to internal fixation and ligament repair (Table 1). The patients had non-comminuted radial head fractures that involve <40% articular surface and type I-II coronoid fractures. Patients were excluded from the study if they had a stable elbow fracture, neurovascular injuries, or elbow fracture following a congenital disease.

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On postoperative day 3rd, elbow joint movements were started in all patients as tolerated. For each of the 14 patients included in the study, a record was made of age, gender, mechanism of injury, concomitant injuries, early and late postoperative radiographs and computed tomography images, the total follow-up period, time from trauma to surgery, early and late postoperative complications and time to union (Figure 1).

Table 1. Demographic features and clinical measurements of the patients

Gender (M/F)	14/0
Mean age (years)	34 (24-48)
Mean follow-up period (months)	27 (22-38)
Mean time from trauma to surgery (hours)	36 (24-48)
Mean follow-up period with external fixator (weeks)	5 (4-6)
Mean VAS score	8 (7-9)
Mean elbow flexion angle (degrees)	118.60°+2.3 (range, 115°-122°)
Mean elbow flexion contracture angle (degrees)	15°+3.5 (range, 10°-20°)
Mean elbow extension angle (degrees)	7.5°+1.4 (range, 5°-10°)
M: Male, F: Female, VAS: Visual analog scale	

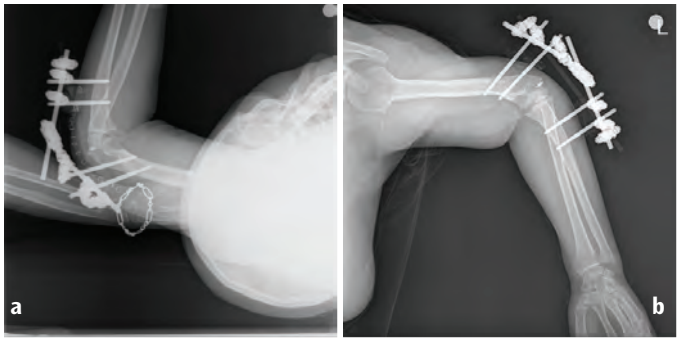


Figure 1. a, b) Postoperative X-rays of one of our patients

Statistical Analysis

Descriptive statistical methods such as mean, standard deviation, median, frequency and ratio were applied while evaluating the study data.

Surgical Technique

All the patients were operated on under general anesthesia by different surgeons in our hospital. For radius head fracture restoration and lateral collateral ligament (LCL) injury reconstruction, either a Kocher or Kaplan incision was used, depending on the surgical plan. In patients with a multi-fragmented radius head, a radius head prosthesis was used. In patients with a radius head that could be restored, fixation with screws only or with plate and screws was applied. LCL repair was applied with the aid of suture anchors. Under fluoroscopic guidance, a K-wire was placed in the lateral plane to pass the midpoint of the condyles then 2x4 mm Schanz screws were placed from the lateral of the distal humerus followed by 2x4 mm Schanz screws in the lateral plane from the proximal ulna. Fixation was then provided by placing an elbow external fixator so that the K-wire was at the hinge point of the humerus condyles. After checking the stability and bleeding, the layers were closed appropriately. No early postoperative complications were observed in any patient.

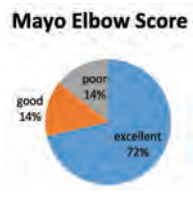
RESULTS

The 14 cases included in the study were male with a mean age of 35.7+8.9 years (range, 24-48 years). The mean time from trauma to surgery was 36+6.6 h (range, 24-48 hours) and the mean follow-up period was 27.6+4.7 months (range, 22-38 months). The mechanism of trauma was a workplace accident in 3 cases (21.4%) and a fall from height in 11 cases (78.6%). Head trauma was determined in 1 patient (9%), and sub trochanteric femur fracture in 2 patients (18%) who fell from height. The patient suffered from a workplace accident and had no additional injuries.

The follow-up time with external fixator was mean 5 weeks +0.8 (range, 4-6 weeks). After the removal of the external fixator, the mean visual analog scale (VAS) score was 8+0.78 (range, 7-9). According to the Mayo elbow performance score, 10 patients were evaluated as excellent, 2 as good and 2 as poor (Table 2). The elbow flexion angle was mean 118.60°+2.3 (range, 115°-122°). Flexion contracture was determined to mean 15°+3.5 (range, 10°-20°) and extension contracture of mean 7.5°+1.4 (range, 5°-10°). Full bone union was observed radiographically in all patients (Figure 2). Infection in 2 of the patients with an open fracture was eradicated with antibiotherapy without the need for removal of the implant. In 2 patients (5%) with an open fracture who did not respond to antibiotherapy, the radius head prosthesis was removed at 6 months postoperatively because

Table 2. Mayo elbow score

	n	%
Excellent	10	71.4
Good	2	14.3
Poor	2	14.3
Total	14	100



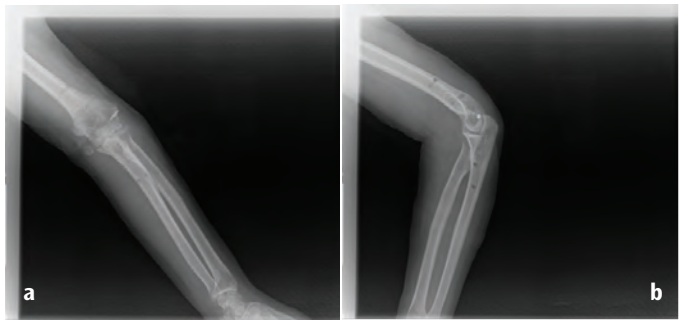


Figure 2. a, b) Full bone union was observed radiographically in all the patients

of infection. Apart from these 2 patients where the radius head prosthesis was removed, no postoperative instability was observed. No postoperative complications of neurovascular deficit or heterotrophic ossification developed. The superficial pin tract infection was seen in the pins placed in the humerus in 4 patients and this responded to oral antibiotic treatment in all cases.

DISCUSSION

The aim of the treatment of complicated elbow injuries should be to obtain stable joint restoration by providing full joint range of motion (3,5,6). It is usually difficult to achieve this as different procedures must be used for the restoration of the bones and when a wide surgical dissection is necessary, more invasive surgical methods are required. The use of minimally invasive methods is recommended, which will provide mobilization and stability for treating complicated elbow fractured dislocations (3,6,7).

With the consideration of a minimally invasive approach, elbow external fixator treatment was combined with ligament repair and internal fixation for the patients in this study. No difference was observed between the early postoperative and mid-term results.

The hinged external fixator (HEF) is an effective, minimally invasive method that can be used to create a stable joint at a good level of function in terrible triad injuries and complicated elbow fracture dislocations. HEF provides good protection during the healing process in patients where ligament repair has been achieved. In this study, the VAS pain score and Mayo performance score evaluations were consistent with the literature (2,3,6).

The gold standard treatment in complicated elbow fracture dislocations is restoration, with repair made of capsular and ligament structures with internal fixation (3,4). The gold standard treatment for complex fractures around the elbow is internal fixation and stable reconstruction. Elbow external fixators are used in several complex injuries (8). In this study, an elbow external fixator was used alone in patients diagnosed with the terrible triad and mid-term successful results were obtained.

There are difficulties in the combination of multiple surgical procedures and the treatment of fractures around the elbow joint (9). In this study, despite several difficulties in the application of the elbow external fixator, no major complications developed in any patient in the current study.

Instability is generally seen after reconstruction of bone and ligamentous structures in complicated elbow fracture dislocations, which leads to terrible triad injury dislocations. The treatment results of these injuries do often not please, with post-traumatic instability, joint stiffness and early joint arthrosis often seen (5,10). In patients with elbow dislocation diagnosed with a terrible triad, it has been reported that the use of plaster cast for immobilization could prevent early mobilization and increases the risk of joint contracture and stiffness (11-15). It has been reported in the literature that patients with terrible triad diagnosis experience pain and restricted joint movement (16-18). In the present study, restricted movement was determined in only 2 patients.

Unstable elbows are often treated with the application of a plaster cast following primary ligament and bone repair. Ligament repair may not provide sufficient stabilization for early active movement. As plaster cast immobilization does not permit early movement, there is an increased risk of joint stiffness forming leading to joint contracture (9,11-13). Therefore, the HEF is an effective treatment method for complicated elbow dislocations. Successful early results have been reported in the literature from the use of an elbow fixator for early movement (17). Consistent with the data in the literature, the early and mid-term results of the current study patients were successful.

During rehabilitation of an elbow fixed with an elbow external fixator, the elbow is stabilized against the varus stress formed associated with the weight of the forearm when the shoulder is in abduction. As this stabilization was provided in this series, open surgical approaches, which lead to fibrosis and heterotrophic calcification, could be avoided, The HEF, when applied centralized to provide medial collateral ligament and LCL isometry, reduce scar formation by allowing early mobilization (18). No scar formation was observed in the current study patients, which was consistent with the literature.

The most important complications of the surgical treatment of patients with terrible triad of symptoms are heterotrophic ossification, joint stiffness, nerve injury and recurrent subluxation or dislocation (18).

Previous studies have shown that excessive dissection and a late start to movement lead to heterotrophic ossification and elbow stiffness. In this study, as movements were started early and minimally invasive surgical dissection was performed, no heterotrophic ossification was observed.

There are inherent difficulties in the application of an elbow external fixator to fractures around the elbow. However, it has been shown that when the HEF technique is applied appropriately, taking the anatomical regions into consideration, no complications develop (19). As the fixator was applied to the patients in the current study taking the technical properties into consideration, no associated complications were observed. A superficial infection encountered in 2 patients was successfully treated with antibiotherapy.

In many studies, while the elbow flexion and extension degree of movement after removal of the fixator in most cases are good in the early period (18,20), the mid-term results of the current study were also seen to be good.

Study Limitations

The limitations of the current study are that the number of patients was low and there was no long-term follow-up.

CONCLUSION

In fractures around the elbow diagnosed with terrible triad, the combination of internal fixation with elbow external fixator provided the possibility of starting elbow joint movements in the early period and the mid-term results obtained were pleasing. Therefore, this can be considered a good option during the initial treatment.

Ethics

Ethics Committee Approval: Approval for this retrospective study was granted by the University of Health Sciences Turkey, Okmeydani Training and Research Hospital Local Ethics Committee (no: 48670771-514,10).

Informed Consent: All the patients participating in the study were informed about the study and informed consent was obtained.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.Ç.T., E.Te., Concept: A.Ç.T., Design: B.K., Data Collection or Processing: B.K., Analysis or Interpretation: H.G., Writing: E.T., B.K.

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

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ORIGINAL ARTICLE

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Long Term (4 years) Refractive Outcomes of Eyecryl® Phakic Intraocular Lens Implantation in Myopia

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Abstract

Objective: To evaluate the long term (4 years) outcomes of Eyecryl phakic intraocular lens (pIOL) implantation in myopia.

Methods: Medical records of patients, who had implantation of Eyecryl pIOL implantation were retrospectively reviewed. Patients with a follow up period of 4 years were included in the study. Refractive results, endothelial cell density, vault, and complications were evaluated.

Results: Preoperative and postoperative spherical equivalent of manifest refraction were -12.98±3.05 and -0.72±0.86 D, respectively. The efficacy index was 1.05±0.45 and safety index was 1.51±0.53. Preoperative corrected distance visual acuity (CDVA) was 0.26±0.15. Postoperative uncorrected and CDVA were 0.27±0.21 and 0.10±0.10 respectively at the last visit (4 years). The mean vault was 570±155 µ at the first month and decreased to 500±133 µ at the 4th year. Endothelial cell loss was 3.9% in the first 2 years. No significance difference was seen between 2nd and 4 years ($p>0.005$). No significant cataract formation was seen.

Conclusion: Eyecryl pIOL implantation for the correction of myopia may be a safe and effective surgical procedure.

Keywords: Myopia, refractive surgery, phakic intraocular lens

INTRODUCTION

Methods used for the surgical correction of refractive errors are, corneal refractive surgery, clear lens extraction and phakic intraocular lens (pIOL) implantation (1-3). pIOLs are used especially when the corneal refractive surgical techniques are impossible, as in the high myopic patients. Maintenance of accommodation and better quality of vision, when compared with corneal surgeries the main advantages (4). The efficacy and safety of some models of anterior and posterior chamber pIOLs have been reported (5-11).

Eyecryl® pIOL (Biotech Vision Care, Ahmedabad India) is a relatively newer posterior chamber pIOL. It is a hydrophilic acrylic, single piece, foldable, plate haptic pIOL placed in the ciliary sulcus. It has an aspheric optics (4.65 to 5.50 mm) with zero aberration. The optic has a 320 µm central hole to improve the aqueous humor circulation. Early results of the efficacy and safety of these lenses are promising (11-13). However, the long-term refractive results and complications are not known.

In this study, we evaluated the long term (4 years) efficacy and safety of Eyecryl® posterior chamber pIOL implantation in patients with high myopia.

METHODS

This study was designed and conducted in accordance with the Declaration of Helsinki and ethics committee approval was obtained from the Ethics Committee for Clinical Research of Taksim Training and Research Hospital (decision no: 35, date: 05.02.2020). Inclusion criteria were Eyecryl® pIOL implantation and a follow-up for at least 4 years. The exclusion criteria were age <20 and preexisting ocular pathology. Patients with retinal

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breaks were also excluded. Informed consent was obtained from all patients before the surgery.

Preoperative and postoperative uncorrected visual acuity (UDVA) and corrected distance visual acuity (CDVA) were measured using an LCD chart and a digital phoropter. Scheimpflug camera combined with Placido-disk corneal topography (Sirius, Costruzione Strumenti Oftalmici, Firenze, Italy) was used for topography and pachymetry mapping as well as anterior chamber depth and horizontal white-to-white measurements. Endothelial cell count was measured using a specular microscope (CEM-530; Nidek Co. Ltd., Aichi, Japan) at annual visits. In all postoperative visits, the pIOL vault (the distance between pIOL and the crystalline lens) was measured using an anterior segment optical coherence tomography (OCT) device (Visante OCT, Carl Zeiss AG, Germany).

Power calculation for the pIOL was performed using the modified vergence formula provided by the manufacturer. Our goal in this study was to achieve emmetropia in all cases. All surgeries were performed with sub-tenon anesthesia. Two side-port incisions and a 2.8 mm clear corneal temporal incision were created. The anterior chamber was filled with a cohesive ophthalmic viscosurgical device (OVD) (Provisc; Alcon Laboratories Inc, Fort Worth, TX, USA). The pIOL was loaded onto the cartridge-injector system provided by the manufacturer and it was injected into the anterior chamber through the 2.8 mm temporal incision. Its haptics were placed under the iris one by one. The OVD was washed out of the anterior chamber by simple irrigation. The incisions were hydrated with balanced salt solution.

Statistical Analysis

Statistical analysis was performed using SPSS software (version 21.0; IBM, Armonk, NY). Mean, standard deviation, minimum-maximum (min-max), and frequency values were used in descriptive statistical analyses. Kolmogorov-Smirnov test was used to analyze the distribution of variables. The efficacy (postoperative UDVA/preoperative CDVA) and safety (postoperative CDVA/preoperative CDVA) indices were calculated for each patient. Visual acuity were converted to logMAR for statistical analysis. A paired samples t-test was used to compare the preoperative and postoperative measurements. A p value <0.05 was considered statistically significant.

RESULTS

Thirty six eyes of 18 patients were included in the study. Thirteen (72%) patients were women, 5 (28%) patients were men. The mean age of patients was 32.67±7.33. Preoperative spherical equivalent (SE) was (-12.98±3.05) and eighty-one percent of the eyes were between -10.00 and -20.00 D. Preoperative patient characteristics are shown in Table 1.

Visual Acuity, Efficacy, and Safety

The intended target was emetropia in all cases. The mean CDVA was 0.26±0.15 logMAR preoperatively. Postoperative UDVA was 0.27±0.21 logMAR and CDVA was 0.10±0.10 logMAR at 4 years postoperatively. At 4 years follow up the efficacy index (postoperative UDVA/preoperative CDVA) was 1.05±0.45. Figure 1A shows patients with preoperative CDVA and postoperative UDVA. Change in the best CDVA of the patients at the end of 4 years, compared to preoperative period is shown in Figure 1B. The safety index (postoperative CDVA/preoperative CDVA) was 1.51±0.53 at the last follow-up. Twenty four (66.7%) patients gained one or more Snellen lines of CDVA. Twelve (33.3%) patients corrected vision remained unchanged and no Snellen loss was seen.

Figure 1C shows the attempted versus achieved refractive correction. The mean SE at the end of 4 years was -0.72±0.86 (-3.38-0.25) D. 86% of patients was with in ±1.00 D and 64% of patients within ±0.50 D, respectively (Figure 1D).

Figure 1F shows the stabilitity of manifest refraction throughout follow-up period. The SE was -0.43±0.58 D at the first year and 0.72±0.86 D at the fourth year (p<0.005, paired samples t-test, 2-tailed p value).

Figure 2 shows the changes in central endothelial cell density (ECD). The mean preoperative ECD was 2742.83±316 cells/mm^2. At first year it was 2609±325 cells/mm^2, and 2608±323 at 2 years. For the first two year the mean endothelial cell loss was

Table 1. Preoperative patient characteristics

	Mean ± SD	Minimum	Maximum
Age (years)	32.67±7.33	23	49
SE (D)	-12.98±3.05	-7.00	-20,00
Cylinder (D)	-0.99±0.66	0	2.00
CDVA (logMAR)	0.26±0.15	0.52	0
WTW (mm)	11.73±0.26	11.27	12.10
ECD (cells/mm^2)	2742±316.53	2062	3189
ACD (mm)	3.67±0.18	3.28	4.01
Mean Sim K (D)	44.38±1.98	38.82	47.28
IOP (mmHg)	14.6±2.46	10.00	21.00
AL (mm)	27.97±1.27	24.15	29.61
Corneal thickness (µ)	530.46±35.49	452	595

SE: Spherical equivalent, CDVA: Corrected distance visual acuity, WTW: White to white, ECD: Endothelial cell density, ACD: Anterior chamber depth, Sim K: Simulated keratometry, IOP: Intraocular pressure, AL: Axial lenght, SD: Standard deviation

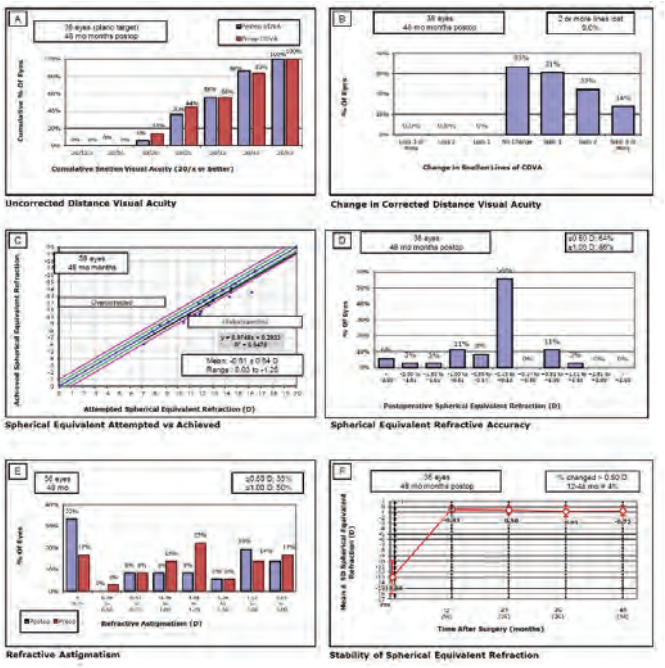

Figure 1. A) Cumulative uncorrected and corrected distance visual acuity (UDVA and CDVA, respectively), B) change in CDVA, C) spherical equivalent of attemted versus achieved refraction, D) accuracy of spherical equivalebt refraction, E) preand postoperative refractive astigmatism, F) accuracy of spherical equivalent refraction
UDVA: Preoperative and postoperative uncorrected visual acuity, CDVA: Corrected distance visual acuity

3.9% ($p<0.0001$). The fourth year ECD was 2505±303 cells/mm^2, and no significant cell loss ($p>0.05$) was seen between 2nd and 4th years.

Figure 3 shows the mean vault of the pIOL during follow-up period. The mean vault was 570±155 µ at the first month, decreased to 520±141 µ and 500±133 µ (min: 220; max: 790) at the 1th and 4th years, respectively (repeated measures ANOVA, $p<0.001$).

There were no cases of anterior subcapsular cataracts or opacities. No other intraoperative or postoperative complications were observed.

DISCUSSION

In this study, we analyzed the long-term refractive results of Eyecryl® pIOL implantation by using efficacy, safety, stability and predictability. At four years, we found that 64% of the patients were within 0.50 D of emmetropia. Mean SE changed from -0.43±0.58 D at the first year to 0.72±0.86 D at the fourth year ($p<0.005$, paired samples t-test, 2-tailed p value). The regression of the refractive effect was an expected finding in this population and probably results from the elongation of axial length. However, axial length measurements were not a

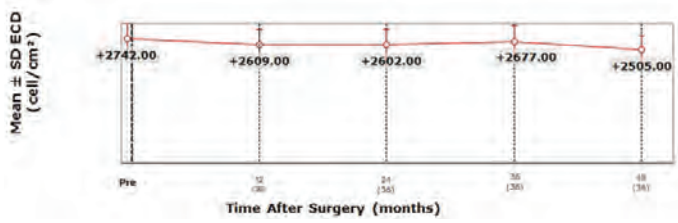

Figure 2. Endothelial cell density during follow-up

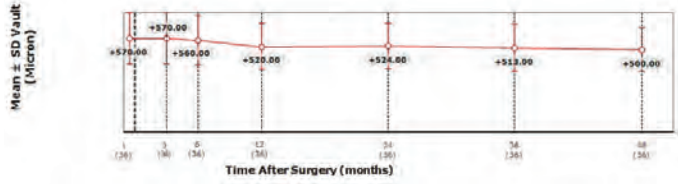

Figure 3. Mean vault during follow-up period

part of preoperative and postoperative examinations. Thus, it was impossible to evaluate axial length in this study. In high myopic patients, manifest refraction may be difficult to obtain due to a combination of low visual acuity of the patient and aberrations and minimizing effect of trial lenses. This may result in postoperative refractive surprise as manifest refraction is the most important variable in the pIOL power calculation. In addition, myopia is generally progressive and SE increases with time. In this study, preoperative SE was -12.98±3.05 and 81% of the eyes were between -10.00 and -20.00 D. Thus, early postoperative refractive surprises or an increase in myopia during long term follow-up were expected findings in this study.

However, despite the progression of myopia, the efficacy index was 1.05±0.45. An efficacy index >1 means that the mean postoperative UCVA in this study was better than mean preoperative CDVA even at postoperative 4 years despite residual postoperative refractive errors. This was a result of improved CDVA in this study as indicated by the safety index, which was 1.51±0.53 at four years. It is well-known that a definite improvement in CDVA is seen after the surgical correction of high myopia and 35-100% of the eyes experience 1 or more lines of CDVA (6,14-20). Although pIOL used in this study was different, 24 (67%) patients showed 1 or more line gain.

Vault is the distance between the pIOL and crystalline lens. It is closely related to the appropriate sizing of the pIOL to the posterior chamber. When the vault is too low or too high, it can cause some complications, such as cataract formation, pupillary block, pigment dispersion and glaucoma (20-23). In our study, the mean vault was 531±134 (min: 220, max: 790) within normal limits. We did not see any complication related to vault problems.

Endothelial cell loss is one of the biggest problems pIOL implanted patients. It is reported to be between 6.2%- 9.5 in some long-term studies of icl implantation (6,9,24,25). Urdem and Agca (12) in their 2 years-follow up study of Eyecryl® pIOL reported 4.51% endothelial cell loss at first year and no significant difference in the second year. In our study, for the first two years, the mean endothelial cell loss was 3.9% ($p<0.0001$). The fourth year ECD was 2505±303 cells/mm^2, and no significant cell loss ($p>0.05$) was seen between 2nd and 4th years.

The formation of cataracts is a well-known complication of pIOL implantation, with a reported incidence of 1.6% to 18.3% after ICL implantation (9,26). It is usually in the form of anterior subcapsular cataract, and its incidence increases with increasing follow-up period (26). Older age, low vault are the main contributing factors (9,24). The design and material properties of the pIOL may also have an effect. In our study, no cataract formation was observed at 4 years follow up.

Pupillary block, angle narrowing due to a high vault, or chronic pigment dispersion may result in increased IOP after PIOL implantation (27,28). As there is a central hole in the optics of the lens, a pupillary block is unlikely in Eyecryl® pIOL implanted eyes and we did not see a pupillary block in this study. Also, no patient developed glaucoma due to angle narrowing and or pigment dispersion.

The study population consists of high myopic (probably degenerative myopic) patients. A higher retinal detachment risk should be considered in this population. However, we did not observe any retinal complications. This may be due to the limited number of patients or exclusion of patients with a retinal break.

Study Limitations

The major limitation of this study was its retrospective nature. Axial measurements were excluded from our postoperative routine measurements. Thus, it was impossible to analyze the relationship between the axial lengths and myopic shift during the follow-up period. Also, the number of eyes is not high enough to evaluate the relatively rare complications such as cataracts.

CONCLUSION

In conclusion, we have retrospectively evaluated our long term (4 years) results of Eyecryl® pIOL implantation. The results were promising in terms of efficacy and safety indices. No serious complication was seen during follow-up time. Studies with larger patient groups and longer follow-up periods are required.

Ethics

Ethics Committee Approval: Ethics Committee for Clinical Research of Taksim Training and Research Hospital (decision no: 35, date: 05.02.2020).

Informed Consent: Written informed consent was obtained from the patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

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

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

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ORIGINAL ARTICLE

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The Relationship Between Fear of COVID-19, Fear of Death and Anxiety in the Accompanists of Patients Diagnosed with COVID-19

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Abstract

Objective: The coronavirus disease-2019 (COVID-19) outbreak emerged in China in December 2019 and has spread throughout the world, including Turkey. During the pandemic, both the fear of infection that could result in death and the action plans implemented had negative effects on the mental health of the people. The aim of this study was to evaluate the relationship between the fear of COVID-19, anxiety, and fear of death in the accompanists of patients diagnosed with COVID-19 who are receiving treatment in inpatient clinics.

Methods: Fifty six accompanists of hospitalized patients with a diagnosis of COVID-19 were included in the study. The Fear of COVID-19 scale, the Templer death anxiety scale ve the Hamilton anxiety rating scale was used as data collection tools in the study. IBM 21.0 software was used to analyze the data.

Results: Fifty six people included in the study were between the ages of 18-75 (mean age 41.07). Because of the study, it was found that the presence of anxiety increases the fear of COVID-19 by 6.5 units, the presence of fear of death increases the fear of COVID-19 by 5.2 units and the presence of both fears increases the fear of COVID-19 by 11.7 units.

Conclusion: Relatives of people diagnosed with COVID-19 become more vulnerable to the negative psychological effects of the pandemic due to the fear of losing their loved ones and having a higher risk of getting the disease than other people. The families of COVID-19 patients should also be evaluated when preparing mental health programs.

Keywords: Accompanists, anxiety, COVID-19, fear of death

INTRODUCTION

Coronavirus outbreak first appeared in Wuhan, China's Hubai Region, in December 2019 (1), and spread rapidly in China and other countries (2). With globalization, the spread of pathological agents has become easier, resulting in the pandemics (3).

In Turkey, the first coronavirus disease-2019 (COVID-19) case was identified in March 2020, and after the first death was subsequently reported on March 17, 2020. In Turkey's pandemic plan, teams were formed to take the necessary measures and conduct the work. Starting from March 2020, working hours became more flexible, compulsory weekend curfews and curfews for citizens under the age of 20 and over the age of 65 were imposed, inter-city travel restrictions were implemented, and mass gatherings were prohibited. As of June 2020, with the normalization process, some of these prohibitions were lifted by taking certain measures (4).

Fear of infection is very common during a pandemic (5). On an individual level, it can trigger feelings of despair, sickness, and death. Fear is usually a primitive emotion and it occurs despite a real or perceived threat. Some physiological signs, such as increased heart rate, muscle tension, and accelerated respiration, prepare the body to find a solution despite danger. However, fear reveals changes in the cognitive system, such as distraction (6). Additionally, during infectious disease outbreaks, individuals can misinterpret health stimuli such as worsening

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mental health, bodily senses, and changes due to fear. People may misinterpret harmless bodily senses or changes as signs of infection, which could lead them to be redundantly anxious (7).

Nationwide measures and compulsory curfew implementation can lead to mass hysteria, anxiety, and stress accompanied by loss of control and feeling trapped. The necessity of separation from the family, the uncertainty of the progression of the disease, the insufficiency of basic necessities, financial loss, increased risk perception resulting from uncertain information, and inappropriate communication with the media in the early stages of the pandemic could enhance this situation (8-10). People were also worried that the health system would not be able to cope with the COVID-19 outbreak due to the lack of sufficient hospital beds and ventilators for the number of estimated COVID-19 cases increase during the outbreak (5).

Accompanists of COVID-19 patients were included in this study. These people have been in contact with the COVID-19 pathogen for a long time without protective measures. The relationship between death anxiety and fear of COVID-19 with anxiety was evaluated in these individuals. We believe that these variables will help the mental health follow-up studies of society during the pandemic.

METHODS

This study was conducted between August 10 and September 10, 2020, using the quantitative research method, cross-sectional method. Accompanists of patients receiving treatment in inpatient clinics who were diagnosed with COVID-19 were included in the study.

People over the age of 18 who agreed to participate, who had sufficient cognitive ability to answer the questions and answered all the questions, and who were not diagnosed with COVID-19 or who tested negative/not yet received their test results were included in this study. Individuals who had been diagnosed with COVID-19 or who had recovered from COVID-19 were excluded.

Participants filled in the following forms prepared by us: Socio-demographic data form, the fear of COVID-19 scale (FCS), the Templer death anxiety scale (DAS), and the Hamilton anxiety rating scale (HAM-A).

Socio-demographic Data Form

The form prepared by the researchers includes information such as age, gender, educational and marital status, occupation, income perception, the presence of a chronic disease, voluntary or compulsory quarantine period, number of people living in the house and the number of children.

The Fear of COVID-19 Scale

It was developed by Ahorsu et al. (11) in 2020. It is a one-dimensional seven-item Likert-type scale. The highest score that can be obtained from the scale is 35 and a higher score indicates higher fear from COVID-19. The scale is correlated with perceived insecurity, hospital anxiety, and depression (11). Turkish validity and reliability study by Haktanir et al. (12). In this study, the Cronbach's alpha value was found as 0.86 (12).

The Templer Death Anxiety Scale

It was developed by Templer in 1970. In a Turkish validity and reliability study were carried out by Şenol (13) in 1989. This scale measures anxiety and fears of the individual about death and the risk of death of oneself. It is a 15 item scale answered as true-false. The highest score that can be obtained from the scale is 15 and a higher score indicates higher death anxiety. It could be evaluated that people who have an average score of 7 or higher have more death anxiety (14). Şenol (13) applied a reliability study, which was conducted with the "Test-Retest" method, twice with an interval of 3 weeks. The correlation between both application scores was found 0.86 (14). Templer, following the same method in the reliability study, found the "Test-Retest" reliability as 0.83 (15).

The Hamilton Anxiety Rating Scale

It was developed by Hamilton (16) in 1959. The Turkish validity and reliability study was conducted by Yazıcı et al. (17). It is one of the most frequently used scales to determine the levels of anxiety in studies on anxiety disorders. This was based on expert ratings (17). Regarding the evaluation of the scores obtained from the scale; 0-5 is considered no anxiety, 6-14 is considered minor anxiety, 15 and above is considered major anxiety. In this study, we considered 15 and above as anxiety (18). Yazıcı et al. (17) reported a mean correlation coefficient of 0.72 for individual items and 0.94 for a total score.

Approval of the Ministry of Health (approval code: T10_51_47) and University of Health Sciences Turkey, Prof. Dr. Cemil Tascioglu City Hospital Research Ethics Committee (approval code: 48670771-514.10) was obtained. Verbal and written consent was obtained from the participants by providing detailed information before completing the questionnaire forms.

Statistical Analysis

In this study, to conduct statistical analysis, IBM 21.0 SPSS 21 software was use. to First, descriptive analysis was carried out to demonstrate the frequency distribution of socio-demographic variables. Also, chi-square test was performed to investigate the relationship of demographic variables to HAM-A and DAS.

Then, the normal distribution was checked to determine which comparison analysis will be used. It was determined that the use of parametric tests was suitable for this. Finally, multiple linear regression analysis was performed to measure the effect of variables on each other.

RESULTS

The participants were 56 individuals between the ages of 18 and 75. The socio-demographic characteristics of the participants in this study appear in Table 1.

The socio-demographic distribution of the participants, chi-square analysis was performed to determine whether there was a relationship between these variables and HAM-A (Table 2). These variables statistically significantly predicted fear of COVID-19 F(52): 3.955, p< 0.0001, R2: 0.543. R square value showed that about 54% of the variance in fear of COVID-19 is explained by the eleven predictor variables. The β values indicated the relative impact of the variables, so, HAM-A had the greatest influence on fear of COVID-19 (β: 5.50, t(52): 2.91, p<0.01) and followed by DAS (β: 3.70, t(52): 2.15, p<0.05) (Table 3).

Also, chi-square analysis was performed to determine whether there was a relationship between these variables and DAS. Looking at the analysis result, it was seen that there was no relationship between DAS and socio-demographic variables since the p value is greater than the significance level (p=0.05) for all variables.

We examined independent sample t-test to reveal the difference between those the ages of 18-49 and those over the age of 50 according to the FCS. The results indicated that people who the ages of 18-49 (n=40, M: 17.62) had significantly different total scores than those over the age of 50 (n=66, M: 13.37), t(13.487): 2.10, (p=0.001). In other words, people between the ages of 18-49 are more afraid of COVID-19 than people aged 50 and over.

Following the analysis of the differences for these socio-demographic variables, to reveal differences between individuals with and without DAS according to FCS, we carried out independent sample t-test. The results showed that people with DAS (n=31, M: 19.66) had significantly different total scores than people who without it (n=25, M: 12.39), t(5.77): -4.49, (p=0.000). In other words, people with death anxiety are more afraid of COVID-19 than those without it.

Finally, we conducted independent sample t-test to demonstrate the difference between people who have HAM-A and those have not. The results indicated that people who have HAM-A score (n=14, M: 21.35) had significantly different total scores than

Table 1. Socio-demographic characteristics of participants

	Total sample: 56	
	Frequency (n)	Percent (%)
Age		
Mean (SD)	41.07 (±12.78)	
Range	18-75	
Number of persons at home		
Mean (SD)	3.59 (±1.24)	
Range	2-7	
Number of children		
Mean (SD)	1.5 (±1.4)	
Range	0-5	
Maximum stay at home		
Mean (SD)	26.31 (±25.58)	
Range	2-120	
Gender		
Male	24	42.9
Female	32	57.1
Marital status		
Married	34	60.7
Single	18	32.1
Separated	3	5.4
Occupation status		
Employed	29	51.8
Unemployed	27	48.2
Income perception		
Very bad	3	5.4
Bad	17	30.4
Middle	33	58.9
Good	3	5.4
People who have COVID-19		
Spouse	14	25
Child	6	10.7
Parents	25	44.6
Parents-in-law	3	5.4
Sibling	2	3.5
Caregiver	4	7.1
Grand parents	1	1.8
Chronic disease		
Heart disease	3	5.4
Respiratory disease	2	3.6
Hypertension	4	7.1
Diabetes mellitus	1	1.8
Hepatitis B	2	3.6
Endometrium cancer	1	1.8
None	43	76.8
Education time		
Mean (SD)	9.58 (±5.24)	

COVID-19: Coronavirus disease-2019, SD: Standard deviation

Table 2. Relationship between socio-demographic variables and HAM-A

Variables		Hamilton anxiety scale	
		No	Yes
Gender	Male	18 (42.9%)	6 (42.9%)
	Female	24 (57.1%)	8 (57.1%)
	p value	1.00	
Marital status	Married	27 (64.3%)	7 (50.0%)
	Single	12 (28.6%)	6 (42.9%)
	Separated	24.8%	1 (7.1%)
	p value	0.69	
Occupation status	Employed	19 (45.2%)	10 (71.4%)
	Unemployed	23 (54.8%)	4 (28.6%)
	p value	0.12	
Income perception	Very bad	2 (4.8%)	1 (7.1%)
	Bad	13 (31.0%)	4 (28.6%)
	Middle	25 (59.5%)	8 (57.1%)
	Good	2 (4.8%)	1 (7.1%)
	p value	0.96	
People who have COVID-19	Spouse	11 (26.8%)	3 (21.4%)
	Child	5 (12.2%)	1 (7.1%)
	Parents	17 (41.5%)	8 (57.1%)
	Parents-in-law	2 (4.9%)	1 (7.1%)
	Sibling	2 (4.9%)	0 (0%)
	Caregiver	4 (9.8%)	0 (0%)
	Grand parents	0 (0.0%)	7 (1%)
	p value	0.42	
Age	18-49	27 (64.3%)	13 (92.9%)
	+50	15 (35.7%)	1 (7.1%)
	p value	0.047*	
Number of person at home	≤4	30 (71.4%)	14 (100%)
	≥5	12 (28.6%)	0 (0%)
	p value	0.026*	
Number of children	≤2	28 (66.7%)	14 (100%)
	≥3	14 (33.3%)	0 (0%)
	p value	0.012*	
Maximum stay at home	≤60	37 (92.5%)	13 (92.9%)
	≥61	3 (7.5%)	1 (7.1%)
	p value	1.00	
Chronic disease	Yes	10 (23.8%)	3 (21.4%)
	No	32 (76.2%)	11 (78.6%)
	p value	1.00	
Education time	≤10	21 (51.2%)	20 (57.1%)
	≥11	8 (48.8%)	6 (42.9%)
	p value	0.76	

*p<0.05 (p value significant), COVID-19: Coronavirus disease-2019, HAM-A: Hamilton anxiety rating scale

people who did not (n=42, M: 14.76), t(0.017): -3.44, (p=0.000) (Table 4).

In of these analyses, we conducted correlation analysis to evaluate the relationships between HAM-A, DAS, and FCS. According to correlation analysis, while there was no significant relation between HAM-A and DAS, there was a positive and significant relation between FCS and HAM-A (r=0.410, p<0.01), also there was a positive and significant relation between FCS and HAM-A (r=0.522, p<0.01).

Multiple regression was carried out to predict fear of COVID-19 from HAM-A and DAS. These variables statistically significantly predicted fear of COVID-19 F(55): 15.785, p<0.0001, R2: 0.350. R square value showed that about 35% of the variance in fear of COVID-19 is explained by the two predictor variables. The β values indicated the relative impact of the variables, so, HAM-A had the greatest influence on fear of COVID-19 (β: 6.47, t(55): 4.15, p<0.001) and followed by DAS (β: 5.20, t(55): 2.92, p<0.01). In other words, whether an individual has the HAM-A is the highest contributing (6.48) predictor to explain the fear of COVID-19, and the next is whether an individual has the death anxiety cut-off score (5.20). The direction of influence for the two is positive (Table 5).

In addition to the explanation above, having the HAM-A increases the fear of COVID-19 by approximately 6.5 units, and having the DAS increases the fear of COVID-19 by 5.2 units.

DISCUSSION

Studies conducted worldwide have clearly revealed that facing an unexpected threat has negative psychological effects on individuals. Many different variables affect people's mental health. Socio-demographic variables are one of these conditions. In our study, we found that some socio-demographic variables were associated with fear of coronavirus, anxiety, and fear of death.

We found that the anxiety levels were higher in individuals under the age of 50 compared with individuals over the age of 50. Similarly, in a study conducted with many participants online in China, mental health symptoms were reported to be more common under the age of 40. In that study, in the younger group, the presence of symptoms was explained with the use of social media and wider access to misleading information on the Internet. The importance of obtaining the right information during the pandemic process has been emphasized (19). In another article, it was stated that negative information about infection increases the perception of personal risk and causes

Table 3. Comparing to socio-demographic variables, HAM-A, DAS according to FCS				
Variables	**β**	**SE**	**t**	**p**
(Constant)	13.085	9.069	1.443	0.157
HAM-A	5.504	1.885	2.919	0.006**
DAS	3.769	1.748	2.156	0.037*
Age	-0.045	0.080	-0.560	0.579
Gender	4.019	1.855	2.166	0.036*
Educational status	-0.354	0.178	-1.987	0.054
Occupation	-0.994	1.852	-0.537	0.594
Marital status	-2.907	1.708	-1.702	0.097
The number of children	0.189	0.783	0.242	0.810
Number of people living in the house	0.338	0.687	0.493	0.625
Income perception	1.561	1.328	1.176	0.247
Voluntary/compulsory quarantine period	-0.079	0.035	-2.225	0.032*
Presence of a chronic disease	0.474	2.302	0.206	0.838
R^2: 0.543; F: 3.955; p<0.001				
*p<0.05, **p<0.01. Dependent variable: FCS, independent variable: DAS, HAM-A, socio-demographic variables. HAM-A: Hamilton anxiety rating scale, DAS: Death anxiety scale, FCS: Fear of COVID-19 scale, SE: Standard error of mean				

Table 4. Comparing to ages, maximum stay at home, chronic disease, DAS, HAM-A according to FCS					
Groups	**n**	**Mean**	**SD**	**t**	**p**
Those between the ages of 18-49	40	17.62	7.62	2.105	0.001*
Those over the age of 50	16	13.37	4.08		
Those stay home for up to 60 days	50	16.64	7.06	0.239	0.491
Those stay at home for more than 60 days	4	15.75	8.46		
Chronic disease yes	13	17.76	7.24	0.792	0.546
Chronic disease no	43	16.00	7.00		
DAS high	31	19.667	6.92	-4.49	0.000*
DAS low	25	12.360	4.75		
HAM-A high	14	21.35	6.59	-3.443	0.002*
HAM-A low	42	14.76	6.97		
*p<0.05 (p value significant), DAS: Death anxiety scale, HAM-A: Hamilton anxiety rating scale, FCS: Fear of COVID-19 scale					

Table 5. Predictor of FCS				
Variables	**β**	**SE**	**t**	**p**
(Constant)	11.527	1.170	9.853	0.000***
DAS	5.209	1.782	2.923	0.005**
HAM-A	6.471	1.552	4.169	0.000***
R^2: 0.350, F: 15.785, p<0.001				
**p<0.01, ***p<0.001. Dependent variable: FCS, independent variable: DAS, HAM-A. FCS: Fear of COVID-19 scale, DAS: Death anxiety scale, HAM-A: Hamilton anxiety rating scale, SE: Standard error of mean				

nervousness or fear (20). In another study in Spain, it was stated that young people between the ages of 18-25 had more anxiety, and the importance of adding programs to reduce stress symptoms in education programs was mentioned (21).

We found that although the increase in the level of anxiety was more evident in younger people, fear of COVID was higher in adults over the age of 50. It has been reported in the literature that older age groups are at higher risk in terms of depression and anxiety due to reasons including quarantine enforcement and the presence of additional diseases (22). The reason for the increased fear of COVID in older people may be the selected population composed of accompanists. In general information about the disease, the fact that the disease prognosis is worse in the older population compared to the younger population may appear as a fear of coronavirus more specifically in this age group. In our study, we could not find a relationship between age and the duration of the quarantine. However, we found a relationship between the duration of quarantine and the fear of COVID. This situation might be explained by the voluntary quarantine practices of people with fear of COVID.

In our study, we could not find a difference between genders there was in the study conducted in Spain (21). Differently, a large-scale study in China reported higher mental health symptoms in men (19). Studies have defined male gender as a poor prognostic factor in terms of the course of infection (23). The difference in results could be due to the selection of different sample groups and to some sample groups not having information about the virus.

In numerous studies, it has been reported that quarantine practices have negative effects on mental health. This situation has been attributed to fear of infection, reduced flow of information, and insufficient access to main resources. Interestingly, we could not find a difference in terms of the quarantine period and the fear of COVID-19. It was thought that this situation may be related to the period of the study (the summer period, during the normalization process, in which there was a perception that the infection was partially under control), as well as the state policy to provide basic necessities during the quarantine period.

Interestingly, while we could not find a relationship with the quarantine period, we found higher anxiety levels in participants with fewer children and live with fewer people. This situation might be related to social isolation. Crowded families who live in the same house may be changing their focus due to both social support and the presence of other people they should take care of.

In our study, we found a relationship between fear of COVID-19 and anxiety, and fear of COVID-19 and fear of death. Additionally, we found that if an individual has anxiety, it increases the fear of COVID-19 by 6.5 units, the fear of death by 5.2 units, and if an individual has both anxiety and fear of death, it increases the fear of COVID-19 by 11.7 units. Studies have reported that the family members and friends of COVID-19 patients are prone to mental health disorders, and 50% of their family members have mild to severe mental health symptoms (19). It has also been noted that a traumatic event experienced by a loved one plays a triggering role in mental health disorders (24,25). Furthermore, relatives of patients with COVID may also have a fear of being infected, quarantined, or stigmatized. All these situations can exacerbate mental health problems (10,26). Supporting this argument, Tsang et al. (20) stated that approximately 50% of the family members of the infected person had psychological problems. They also emphasized that this situation is related to feelings of stigmatization (20).

Because to the prevalence of the infection, all resources are allocated to the treatment of the disease, or the studies have focused more on the public and healthcare professionals. However, relatives of those diagnosed with COVID-19 face both the fear of losing their loved ones and the risk of getting the disease themselves. Therefore, they become more vulnerable to the negative psychological effects of the pandemic than other people. COVID-19 patients and their families should also be evaluated in terms of social and psychological aspects. Early strategies are required to prevent and treat the psychological effects of the COVID-19 outbreak. As it was stated in several studies, there is a need for planning for the prevention and treatment of mental health problems caused by the pandemic (27). Accordingly, many studies conducted in different sample groups will be required.

Study Limitations

Our study has limitations, such as the small sample size and the use of this sampling regression analysis.

CONCLUSION

The presence of contamination risk in filling the scales by meeting face to face with the participants limited reaching more participants. There is a need for numerous studies on the near-term and long-term effects of pandemics on mental health.

Ethics

Ethics Committee Approval: Approval of the Ministry of Health (approval code: T10_51_47) and University of Health Sciences Turkey, Prof. Dr. Cemil Tascioglu City Hospital Research Ethics Committee (approval code: 48670771-514.10) was obtained.

Informed Consent: Verbal and written consent was obtained from the participants by providing detailed information before completing the questionnaire forms.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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ORIGINAL ARTICLE

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Single-port Endoscopic Thoracic Sympathectomy in Cases of Primary Hyperhidrosis: Single-center Experience

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Abstract

Objective: Pathological excessive sweating that can occur in specific parts for else throughout the body is known as hyperhidrosis. Although there are different medical and surgical options, medical treatment applied to many patients provides temporary relief. With advances in surgical techniques, the most commonly used surgical treatment method is endoscopic thoracic sympathectomy (ETS). In this study, we examined the results of ETS operations performed in our clinic considering the current literature.

Methods: Between 15.03.2011 and 30.10.2020, 45 single-port ETS operations were performed on 23 patients due to palmar and/or axillary hyperhidrosis. Patients' demographic data, complaints, complications, therapeutic results, and post-treatment satisfaction were evaluated.

Results: Thirteen of the 23 patients were male and 10 were female, with average age of 25. Ten patients were operated for palmar hyperhidrosis, two for axillary hyperhidrosis, and 11 for axillary and palmar hyperhidrosis. Forty-five thoracic sympathectomy operations were performed with bilateral single port ETS in the same session in all but one of the 23 patients. Mean operative time was 28 min, and hospitalization time was 1.1 (0-8) days. Two patients exhibited compensatory sweating during follow-up, and one patient showed rebound sweating. At follow-up, 91% of patients (21) were satisfied with their operations.

Conclusion: Endoscopically-assisted single-port thoracic sympathectomy appears to be a reliable and practicable technique for treating hyperhidrosis, with effective results, high patient satisfaction, and early discharge time. We believe that the most important advantages of this technique are an early return to normal life, less pain, and a positive return to social life.

Keywords: Hyperhidrosis, thoracoscopy, thoracic sympathectomy

INTRODUCTION

Pathological excessive sweating exceeding normal limits is known as hyperhidrosis (HH). This can develop in specific regions, or throughout the body. There are two types of HH. The pathological state characterized by excessive sweating alone unassociated with any underlying disorder is known as primary HH, whereas HH associated with another underlying condition is known as secondary HH. Secondary HH is more common in individuals with a body mass index >28. Other frequently encountered secondary causes of HH include hyperthyroidism, diabetes mellitus, pheochromocytoma, and infection. A lack of distinction between daytime and nighttime sweating is typical. The etiology of primary HH is still unclear. Excessive sweating in the body or in a few regions thereof occurs involuntarily when the individual feels under psychological stress and in certain seasons. Sweating in primary HH does not occur during nocturnal sleep. The incidence of this form in the community is 1-3% (1,2). The prevalence of primary HH is equal in both genders, but increases in early adulthood (2). It tends to start in early childhood, severity worsens in puberty, and the incidence decreases progressively with age (3,4).

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Treatment of HH depends on the type. Treatment with secondary HH targets the underlying disease. Various medical and surgical options are available for treating primary HH, although medical treatment applied in several cases produces temporary improvement. Oral anticholinergic drugs, topical agents, iontophoresis, and botulinum toxin injections can be employed as medical treatments (5). The most widely employed surgical option as surgical techniques have improved is endoscopic thoracic sympathectomy (ETS) (6). ETS is normally performed using a double port, although it can now be performed with a single port due to increased experience. This study aims to report our experience of ETS surgery with a single port applied in cases of primary HH, with a discussion of the current literature.

METHODS

Approval for the study was granted by the Kahramanmaras Sutcu Imam University Ethical Committee (session 2021/04, decision no: 15, dated: 25.01.2021). The research was performed incomplianc with the 1975 Declaration of Helsinki through a retrospective examination of the records of patients undergoing ETS with a single port due to palmar and/or axillary HH in the Kahramanmaras Sutcu Imam University Medical Faculty Thoracic Surgery Clinic between 15.03.2011 and 30.10.2020. Before the sympathectomy surgery, the risks of the surgery were explained to all patients and an informed consent form was obtained by signature. All patients' demographic data, symptoms, thoracic sympathectomy sites, complications, treatment outcomes, and post-treatment satisfaction were evaluated.

Surgical Procedure

Patients were placed in a semi-sitting position with both upper extremities in 90-degree abduction. The procedure was performed with patients under general anesthesia using a double-lumen endotracheal tube. Following single-lung ventilation, a 1 cm skin incision was made to the midaxillary line, and the thoracic cavity was entered through a blunt dissection. A port was installed in the hemothorax scheduled for the procedure. Depending on the patient's symptoms, the second sympathetic ganglion was resected in the presence of facial HH, the third and fourth sympathetic ganglia if palmar HH was present, and the fourth and fifth ganglia in case of axillary HH by cauterization with an electrocautery hook passed through the camera without the need for a second incision (Figure 1). The objective was to prevent recurrence following sympathectomy by cauterizing alternative sympathetic nerve connections such as the nerve of Kuntz. Following this procedure, anelaton catheter was inserted inside the lung through the port entrance, while the other end was placed inside a container filled with saline solution. The procedure was maintained until the air outflow ended through ventilation of the lung. Following air outflow termination, the catheter was withdrawn and the entry site was sutured. The same procedure was also performed on the other hemothorax in patients under going bilateral thoracic sympathectomy. The procedure was concluded with the installation of a chest tube. Patients were evaluated with postoperative lung X-rays taken in the operating room and sent to the ward.

Statistical Analysis

Statistical analysis was performed on IBM SPSS 25 for Windows software. Continuous variables were expressed as mean ± standard deviation. Categorical variables were analyzed using Fisher's Exact test and were expressed as frequency and percentage values.

RESULTS

Thirteen of the 23 patients with a mean age of 25 years (17-36) operated due to HH at the Kahramanmaras Sutcu Imam University Thoracic Surgery Department were men, and 10 were women (Table 1). Ten patients were operated for palmar HH, two for axillary HH, and 11 for both palmar and axillary. Bilateral thoracic sympathectomy was performed on all 23 patients, with

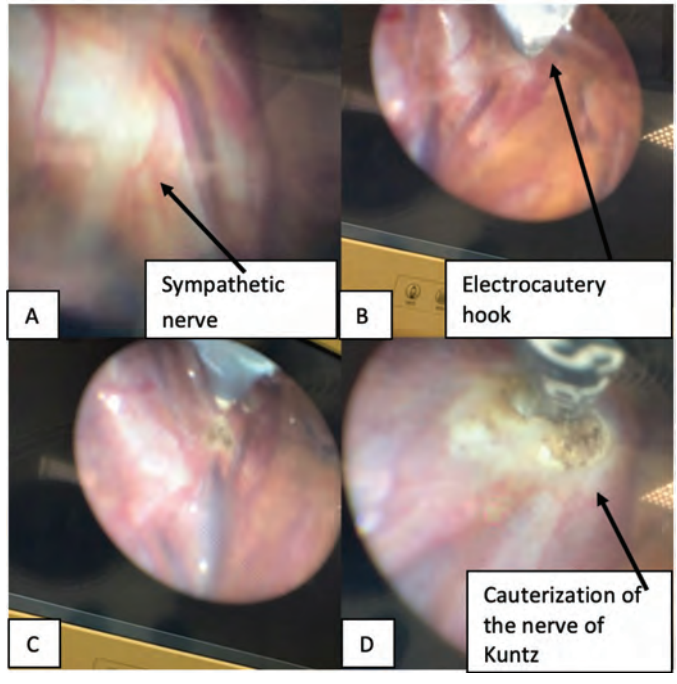

Figure 1. Images of the endoscopic thoracic sympathectomy operation (A: Endoscopic image of the sympathetic nerve, B: Image of the electrocautery hook capable of being passed through the camera, C: Cauterization of the sympathetic nerve with the electrocautery hook, D: Cauterization of the nerve of Kuntz)

one exception, using the single-port ETS method in the same session, 45 thoracic sympathectomies thus being carried out (Table 2).

The mean operative time was 28 min, and mean length of hospital stay was 1.1 days (0-8). All patients apart from one were transferred to the chest surgery ward without requiring chest tube insertion. Three patients were discharged on the same day, and 19 following control X-ray on the first day postoperatively. Primary repair using mini-axillary thoracotomy was performed on one patient due to parenchymal laceration during single-port ETS due to pulmonary parenchymal adhesion to the chest wall. The operation was concluded following the insertion of a chest tube. The patient was discharged on the eighth day with removal of the chest tube. Patients attended clinical following-ups 10 days, and two and 12 months after discharge.

No mortality occurred in the operated patients. Compensatory sweating was determined at follow-ups in two patients. This was in the inguinal region alone in one patient and in the inguinal region and back in the other. Sweating in the inguinal region improved spontaneously after the second month, while the other patient's symptoms resolved in the postoperative 12th month. Rebound sweating occurred in one patient, but improved without intervention after the third week. Recurrence was observed in one patient during postoperative follow-ups. Repeat left-side ETS was performed in the sixth month postoperatively in this case.

When asked about their satisfaction with the procedure during postoperative follow-ups, 21 (91%) expressed postoperative satisfaction with thoracic sympathectomy using ETS. The other two patients were the case with compensatory sweating resolving on the 12th month, and the case undergoing mini thoracotomy due to parenchymal laceration.

Table 1. Demographic data and clinical outcomes

Age	25 (17-36)
Gender M/F	13/10
Operative time (min)	28
Length of hospitalization (days)	1 (0-8)
Complications	
Compensatory sweating	2
Parenchymal laceration	1
Rebound sweating	1
Follow-up duration (months)	12

M: Male, F: Female

Table 2. Operation indications and resection levels

Indication	No	Levels
Hand sweating	10	T3-4
Axillary sweating	2	T4-5
Hand and axillary sweating	11	T3-5

DISCUSSION

The first sympathectomy in HH was reported by Kotzaref in 1920 (7). However, the size of the incision prevented the operation from being widely performed in subsequent years. The first endoscopic treatment of HH with the entry into surgical practice of closed surgical techniques was performed by Hughes in 1942 (8). Closed endoscopic procedures became more widely performed in the 1980s and gradually came to replace open surgery (9). ETS is a surgical technique of proven efficacy in cases of HH that fail to respond to medical treatment (10). Its efficacy for treating HH, its reliability, and the use of a small incision, have made the procedure a well-tolerated option for treating the (10,11). ETS was initially performed with two or three ports, but due to increasing experience, it has now become possible with only a single port. ETS surgery has been performed with a single port for the last decade in our clinic.

ETS is not only frequently employed for treating HH, but also in Reynaud's disease, reflex sympathetic dystrophy, and upper extremity ischemia. Selecting the endoscopic thoracoscopic approach in preference of top thoracotomy, or open surgery, provides greater patient comfort with both less muscle tissue damage and a smaller incision. This means the patient feels less pain in the postoperative period, increases patient satisfaction and contributes to a more rapid return to social life (12,13). Ninety-one percent of patient satisfaction was determined in thoracic sympathectomy operations performed with the ETS method and a single port in this study. We think that this high patient satisfaction rate can be attributed topatients experiencing less pain due to a smaller incision and lower tissue trauma with the single port ETS method, and to their early return to working and social life by being discharged on the same or the next day.

There are various operation application types in ETS. These differences derive from different thoracic entry sites or from the surgeon's use of different sympathetic nerve blocks (1,14). The thoracic sympathetic consists of 10-12 ganglia and extends beneath the parietal pleura on both sides of the spinal cord. ETS surgery is performed by interrupting the ganglia at predetermined levels and the branches between then (1,14). Although different methods with different names are employed, the essential aim is to interrupt the sympathetic chain. Removal by severing the sympathetic ganglion from above and below is

defined as sympathectomy, damaging the sympathetic ganglion by using ultrasound or laser is defined as ablation, attaching a clip over the desired ganglion in the sympathetic trunk is known as clipping, and clipping the ganglion in the sympathetic trunk from above and below is defined as sympathetic blockage. In our clinic, we perform thoracic sympathectomy with the ETS method and a single port by interrupting the sympathetic ganglion using the ablation technique with an electrocautery hook. One previous study determined no significant difference in terms of operation-related risk and/or patient satisfaction between different techniques including ablation, cutting, and clipping (15).

While the optimal level for sympathetic chain resection is still unclear, the T3 or T3-4 ganglia are recommended in palmar HH, T4 in axillary HH, and T2 in facial HH (16). In this study, ablation was applied to the T3 and T4 ganglia for palmar HH, and to the T4-T5 ganglia for axillary HH. Family histories are present in 12.5-56.5% patients (14). Cerfolio et al. (2) described the best patient group for treatment as individuals with symptom onset before the age of 16, without sweating during sleep, and without bradycardia or other additional diseases. Adolescence has been described as the ideal age for surgery in patients with HH. However, studies have revealed no significant difference in terms of surgical outcomes between adolescence and patients over 40 or under 14 (17,18). The essential aim of HH surgery is to achieve a dry skin with as few complications as possible. The objective must be to perform blockage at the appropriate level to achieve this balance. However, results are not always at the desired level, and complications capable of causing the patient to regret having undergone surgery can even develop (19). Postoperative dissatisfaction was determined in two cases in this study, one in which parenchymal laceration developed, and one with compensatory sweating.

The reasons for surgical failure and recurrence of the disease include anatomical variations of the sympathetic nerve, pleural adhesions, inability to clearly visualize the nerve due to excess adipose tissue, and insufficiency of the sympathetic incision because of venous structures in the proximity of the sympathetic canal (20). The most common complication of ETS is compensatory sweating, the prevalence of which among all different surgical approaches ranges between 3% and 98% (2,21). In this complication, sweating increases abnormally in the lower part of the line passing between the nipples (22). Compensatory sweating is also the principal cause of postoperative regret. Of the two cases in which compensatory sweating developed in this study, the symptoms resolved spontaneously in one in the second postoperative month, while the other patient's symptoms persisted for 12 months. Rebound sweating is a non-permanent complication that resolves within 30 days and that consists of slight moisture in the early postoperative period (Table 3). This should not be interpreted as a recurrence. It is thought to be associated withtransient neurotransmitter release from the nerve end exposed to postganglionic degeneration (22). Rebound sweating developed in one patient in our series, but resolved entirely in the third week.

Another complication is excessively dry hands that can result in cracks in the palms, especially in cold weather. Dry hands are reported to be less common in patients in whom T4 is employed in preference to T3 in sweating of the hands (22). Another complication is Horner syndrome resulting from perioperative stellar ganglion damage in the C8-T1 junction. Although now not frequently seen, it was once one of the most frequent complications. The likelihood of development is higher in interventions at the T2 level or above in patients presenting with facial sweating. The prevalence is 0.7-5.6%. The effect may be transient in some patients, but can also produce permanent injury. However, the incidence has decreased as surgical interventions are increasingly performed to lower levels and to increased surgical experience (22). Horner syndrome was not encountered in any of our patients. Complications developing following thoracic sympathectomy are shown in Table 3. As with all interventional procedures, patients must be given comprehensive information and their consent must be obtained in terms of potential complications before ETS surgery (23).

Although tube thoracostomy is not currently required following thoracic sympathectomy using the ETS method, it is required in pneumothoraces, which develop at a rate of 4-6%. Pneumothorax is most frequently caused by parenchymal adhesions (22). Parenchymal adhesions were present in two cases in this study. Primary repair with axillary mini-thoracotomy associated with parenchymal laceration was required in one patient. In the other case, although bilateral sympathectomy was planned, no

Table 3. Sympathectomy complications

Postoperative complications	Perioperative complications
Compensatory hyperhidrosis	Vascular bleeding
Gustatory sweating	Parenchymal laceration
Phantom sweating	Rhythm changes (bradycardia-tachycardia)
Recurrence	Plexus brachialis damage linked to surgical position
Rebound sweating	-
Horner syndrome	-
Hydro-hemo-pneumothorax	-

intervention was performed on the side with adhesion, while endoscopic sympathectomy was applied to the other side, and tube thoracostomy was not required.

CONCLUSION

ETS has been increasingly applied for treating HH with satisfactory results and low complication rates recently. We believe that the advantage of the single port endoscopic sympathectomy we performed is that it allows the operation with a single small incision, less pain and less scarring, resulting in higher satisfaction in patients and their return to social life earlier.

Ethics

Ethics Committee Approval: Approval for the study was granted by the Kahramanmaras Sutcu Imam University Ethical Committee (session 2021/04, decision no: 15, dated: 25.01.2021).

Informed Consent: Informed consent form was obtained by signature.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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Evaluation of Compliance to Diabetes Treatment, Care Standards in Diabetes Treatment and Follow-up and Awareness of Patients

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Abstract

Objective: Diabetes is a lifelong disease caused by the deficiency or ineffectiveness of insulin hormone. The aim of diabetes treatment is to keep blood sugar regulated thus improving quality of life and preventing the development of long-term complications. In this study, the sociodemographic characteristics that cause diabetes regulation and the complications that may occur because of the disease are examined. We compared the regulation of diabetes and complications and awareness by determining the complications, awareness of patients and the other factors that affect the regulation of diabetes.

Methods: A questionnaire form was applied to 216 patients with diabetes older than 18 years old who applied to the Endocrinology, Diabetes and Internal Medicine outpatient clinics of Okmeydani Training and Research Hospital. Data on sociodemographic information, awareness levels, the values and factors effecting the disease regulation and complications were analyzed.

Results: 58.7% of the patients were female and 41.3% were male. 70.8% of the patients were over 50 years old. 26.3% of the patients did not have any graduation and 49% were primary school graduates. 48.6% of the patients had an income level of 2,000 TL and below. The rate of patients with regulated HbA1c was 30.5%. The rate of patients using insulin was 54.6%. In our study, the mean HbA1c of the retinopathy group was found to be significantly higher than that of the non-retinopathy patients, but there was no significant difference between HbA1C levels and nephropathy. The awareness points of the HbA1c group, which were not regulated, were significantly lower than the ones in the regulated group.

Conclusion: Determining the factors affecting diabetes regulation, the presence of complications and awareness levels play an important role in the follow-up and treatment of diabetes.

Keywords: Diabetes mellitus, complication, related factors, awareness, diabetes

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disorder in which the organism cannot make sufficient use of carbohydrates, fats, and proteins due to insulin deficiency or disorders in the effect of insulin. It is important to inform and educate health workers and patients to reduce the risk of acute complications and to prevent long-term treatment costs and most importantly, chronic (retinal, renal, neural, cardiac, and vascular) complications (1). The awareness level of patients with DM increases the compliance of the treatment and thus the treatment success. Especially in diseases such as diabetes, where the patient himself is a part of the treatment, it is of great importance in terms of awareness, compliance and treatment success. Our aim is to regulate blood sugar in patients and to prevent future complications and related mortality and morbidity. For this reason, awareness is of great importance to ensure that the treatment given to the patient is used properly and that the patients comply with the

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recommendations for lifestyle changes. Simultaneously, the internet can be a powerful support for diabetes nutrition, self-care and self-management. In our study, sociodemographic features, awareness levels, the frequency of macrovascular and microvascular complications, which are of great importance in the control with diabetes, and the effects of the recommendations presented in the follow-up of the patients on the control with diabetes were compared.

METHODS

A questionnaire was applied to 216 patients who were admitted to the endocrinology, Internal Medicine and Diabetes Outpatient Clinics of University of Health Sciences Turkey, Okmeydani Health Application and Research Center with a diagnosis of DM for more than 6 months, who were older than 18 years, who were pregnant and had no previous history of gastrointestinal system surgery. A questionnaire was prepared as our data collection tool. After sociodemographic characteristics such as age, sex, weight, height, body mass index (BMI), education level, income level, smartphone and internet usage, type of diabetes treatment, type, and year of DM, presence of micro and macrovascular complications and treatment and in the follow-up, the suggestions and applications to the branches related to the complications were questioned. Simultaneously, albumin/creatinine ratios in the spot urine, epidermal growth factor receptor (GFR), low-density lipoprotein, fasting blood sugar and HbA1c levels were recorded. In the last part of the study, parameters were determined by questions about the level of awareness of patients, smoking, diabetes education, exercise, and nutrition recommendations, blood sugar measurement at home and frequency of admission to the physician.

The Ethical Committee approved this study at University of Health Sciences Turkey, Okmeydani Health Application and Research Center on 21.11.2017 no: 48670771-514.10. All patients were informed and consent forms were obtained.

Statistical Analysis

Statistical analysis in this study were performed using the Number Cruncher Statistical System (NCSS) 2007 Statistical Software (Utah, USA) package program.

In the power analysis performed using the G*power 3.1 program related to our study, the effect size for HbA1c ≤7 among the study groups was found to be 0.10 (Quality of Care for Patients with Type 2 Diabetes Mellitus in Dubai: A HEDIS like assessment) (alpha error probability: 0.05); the total number of patients required to be taken in total was found to be at least 160 in the sample size analysis performed with a power value of 0.80.

In addition to descriptive statistical methods (mean, standard deviation, frequency and percentage distributions) in the evaluation of data, we used

- One-Way analysis of variance for intergroup comparison of normally distributed variables (One-Way ANOVA),

- Independent t-test for comparison of paired groups,

- Mann-Whitney U test for comparing non-normally distributed variables between binary groups.

RESULTS

There was a statistically significant difference between the HbA1c averages of no graduation, primary school, high school and university groups ($p<0.001$). HbA1c averages of the no graduation group were found to be significantly higher than the high school and university groups ($p<0.001$, $p=0.001$). HbA1c averages of the primary school group were found to be statistically higher than the high school and university groups ($p=0.006$, $p=0.033$). There was no statistically significant difference between the other groups ($p>0.05$).

The mean HbA1c of the smartphone users was found to be statistically lower than the ones who don not use smartphones ($p<0.001$) (Table 1).

The mean HbA1c of the internet users was found to be significantly lower than the patients who did not use internet ($p=0.002$) (Table 1).

A statistically significant difference was observed between the HbA1c averages of the income groups <1,000 TL, 1,000-2,000 TL, 2,000-3,000 TL, 3,000-5,000 TL, and >5,000 TL ($p=0.0001$) (Table 1). HbA1c averages of <1,000 TL income group were found to be significantly higher than the income groups 2,000-3,000 TL, 3,000-5,000 TL, and >5,000 TL ($p=0.006$, $p=0.012$), HbA1c averages of the income group 1,000-2,000 TL were found to be statistically higher than the income groups 2,000-3,000 TL, 3,000-5,000 TL, and >5,000 TL ($p<0.001$, $p=0.002$), there was no statistically significant difference between the other groups ($p>0.05$) (Table 1).

The mean HbA1c of the dietary group was significantly lower than that of the non-dietary group ($p<0.001$) (Table 2).

A statistically significant difference was observed between the mean HbA1c of the exercise groups not doing, once a week and >2 times a week ($p<0.001$). The HbA1c averages >2 times a week were found to be significantly lower than those who did not exercise ($p<0.001$), and no statistically significant difference was observed between the other groups ($p>0.05$) (Table 2).

The mean HbA1c of oral antidiabetic (OAD) users was significantly lower than those without OAD (p=0.023) (Table 2).

The mean HbA1c levels of the insulin users were significantly higher than those of the non-insulin users (p<0.001) (Table 2).

The mean HbA1c of the group that used treatment regularly was significantly lower than that of the group that uses treatment irregularly (p<0.001) (Table 2).

The mean HbA1c of the DM year ≤10 group was found to be significantly lower than the DM year >10 group (p=0.004) (Table 2).

There was a statistically significant difference between the mean HbA1c of diabetic retinopathy (DRP) unknown, none and existing groups (p=0.019). The mean HbA1c of the DRP existence group was found to be significantly higher than the no DRP group (p=0.01), but no statistically significant difference was observed between the other groups (p>0.05) (Table 3).

No statistically significant difference was observed between the mean of the control visit recommendations for the branches about DM complications of the ≤7 HbA1c and >7 HbA1c groups (p=0.703) (Table 4).

The mean examination score for the branches with DM complications in the >7 HbA1c group was statistically significantly lower than that in the ≤7 HbA1c group (p=0.013) (Table 4).

Table 1. Comparison of mean HbA1c levels and demographic characteristics

		n	HbA1c	p
Age	**20-40**	21	7.96±1.9	0.284
	41-50	42	8.68±2.37	
	51-60	67	7.87±1.53	
	61-70	58	8.27±2.03	
	>71	28	8.44±2.4	
Sexuality	**Female**	127	8.12±1.96	0.389
	Male	89	8.36±2.07	
Education status	**No graduation**	57	9.04±2.13	**<0.001**
	Primary school	106	8.33±1.97	
	Collage	43	7.2±1.44	
	University	10	6.62±0.78	
Smart phone usage	**Not using**	136	8.63±2.11	**<0.001**
	Using	80	7.51±1.59	
Internet usage	**Not using**	163	8.46±2.05	**0.002**
	Using	53	7.47±1.67	
Income status	**<1,000 TL**	12	9.43±3.13	**<0.001**
	1,000-2,000 TL	93	9.1±1.94	
	2,000-3,000 TL	59	7.46±1.29	
	3,000-5,000 TL	39	7.25±1.52	
	>5,000TL	13	7.08±2.06	

The awareness score averages of >7 HbA1c groups were significantly lower than the ≤7 HbA1c group (p<0.001) (Table 4).

DISCUSSION

Turkish Diabetes Epidemiology Study (TURDEP) is the most comprehensive research guideline in which epidemiological diabetes is examined nationally. According to TURDEP I and II, diabetes is seen more frequently in women in our country and 58.7% of the participants were women in our study (Table 1). When the TURDEP II results are examined, cigarette consumption has decreased from 30% to 17.3% in the last 12 years. The smoking rate of the patients in our study was found to be 26% (2).

Although type 2 diabetes may be seen in young people, although less frequently, it is usually seen in the population aged 40 years and over. In an other study, the mean age of type 2 diabetic patients was found to be 53.99±7.75 (3). In our study, 70.8% of

Table 2. Comparison of clinical features and mean HbA1c levels

		n	HbA1c	p
BMI	<20 BMI	7	7.67±2.22	0.117
	20-25 BMI	28	7.42±1.33	
	25-30 BMI	72	8.37±2.23	
	>30 BMI	109	8.36±1.95	
Diet	Not in diet	89	9.39±2.13	**<0.001**
	In diet	127	7.39±1.42	
Exercise	None	119	8.91±2.12	**<0.001**
	Once in a week	6	8.27±2.14	
	2 or more times in a week	91	7.30±1.41	
OAD	Not using	33	8.94±1.95	**0.023**
	Using	183	8.08±1.99	
Insulin	Not using	98	7.2±1.4	**<0.001**
	Using	118	9.06±2.05	
Treatment regularity	Regularly	33	10.52±1.79	**<0.001**
	Irregularly	183	7.8±1.75	
DM age	≤10 years	149	7.95±1.89	**0.004**
	>10 years	67	8.80±2.14	
DM type	Type I	9	8.77±1.76	0.401
	Type II	207	8.19±2.02	
FPG	≤120	65	6.67±0.9	<0.001
	>120	151	8.87±1.98	
LDL	≤100	9	7.87±1.87	**0.166**
	>100	207	8.31±2.05	

BMI: Body mass index, OAD: Oral antidiabetic, DM: Diabetes mellitus, FPG: Fasting plasma glucose, LDL: Low-density lipoprotein

Table 3. Comparison of systemic features and mean HbA1c levels

		n	HbA1c	p
DNP	**Unknown**	14	8.02±2.01	0.506
	None	154	8.11±1.99	
	Microalbuminuria	23	8.63±2.21	
	Proteinuria	14	8.93±1.9	
	Renal failure	11	8.22±1.92	
DRP	**Unknown**	38	8.51±1.99	**0.019**
	None	128	7.91±1.82	
	Exist	50	8.78±2.34	
Diabetic neuropathy	**Unknown**	127	8.33±1.99	0.285
	None	74	7.94±1.92	
	Exist	15	8.64±2.51	
Chronic ischemic heart disease	**None**	162	8.23±1.95	0.850
	Exist	54	8.17±2.2	
HT	**None**	128	8.13±1.99	0.463
	Exist	88	8.34±2.04	
CVD	**None**	205	8.19±1.97	0.412
	Exist	11	8.7±2.72	
PAD	**None**	214	8.19±1.99	0.057
	Exist	2	10.9±3.39	
Diabetic foot	**None**	213	8.18±1.98	**0.026**
	Exist in past and healed	1	13.3±	
	Still exist	2	9.45±1.34	
Diabet education	**None**	178	8.38±2.01	**0.008**
	Exist	38	7.43±1.8	
Weight loss advice	**No**	5	6.86±1.81	0.127
	Yes	211	8.25±2	
Diet advice	**No**	3	7.5±2.07	0.535
	Yes	213	8.23±2.01	
Exercise advice	**No**	7	7.34±1.52	0.243
	Yes	209	8.24±2.02	
Smoking cessetion advice	**Yes**	47	8.95±1.96	**0.017**
	No	9	8.14±1.33	
	Not using	160	8±2.01	
Frequency of physician control	**0-3 months**	125	7.81±1.93	**0.004**
	3-6 months	57	8.64±2	
	6-12 months	21	9.1±1.96	
	>12 months	13	8.84±2.08	
Home blood glucose measurement	**No**	40	8.64±2.19	0.136
	Yes	176	8.12±1.96	

DN: Diabetic nephropathy, DRP: Diabetic retinopathy, HT: Hypertension, CVD: Cardiovascular disease, PAD: Peripheral artery disease

the patients with diabetes were found to be over 50 years of age (Table 1).

Another study found that most patients had a low educational level and had a disease duration of more than 5 years (3). The patients in our study had similar characteristics in this respect (Table 2).

HbA1c averages of patients with smartphone and internet usage were lower than those without use (Table 1). In a study by Grant et al. (4), it was found that those who did not use the internet were older and had lower education levels and therefore, some differences were found in treatment and complications.

As it is known, factors such as high income level, diet and exercise have positive effects on diabetes regulation. The mean HbA1c levels of the groups with an income of 2,000 TL or more, who paid attention to their diet and fed regularly and exercised 2 or more times a week were found to be significantly lower than the other groups (Tables 1, 2). In a meta-analysis, positive effects of diet and exercise on type 2 DM were reported (4). In a study by Houle et al. (5), it also shows that low education and socioeconomic factors have negative effects on diabetes regulation.

There is strong and consistent evidence that obesity management can delay the transition from prediabetes to type 2 diabetes and is useful for treating type 2 diabetes (6). In our study, the presence of BMI above 25 and more was significantly higher in the HbA1c >7 group than in the HbA1c ≤7 group, and the mean BMI of patients who have HbA1c above 7 was significantly higher than the other group (Table 2). In another study, Oğuz et al. (7) it has been stated that obesity is a major problem in providing diabetes regulation.

Diabetes age and regular use of treatment are important factors for diabetes regulation. In our study, the mean HbA1c levels were lower in the group receiving regular treatment and in the group with DM age less than 10 years compared to the other groups (Table 2). Simultaneously, the mean year of DM was significantly lower in patients with regulated HbA1c than non-regulated ones (Table 2). In a study by Ahmad et al. (8), each 1 year increase in the duration of DM was associated with a 5% reduction in the probability of achieving target glycemic control. In another study, HbA1c levels showed a significant increase as diabetes duration increased (9).

In our study, the percentage of patients with regulated HbA1c levels was found to be 30.5%. In a study by Oğuz et al. (7), the percentage of patients with regulated HbA1c was 36%.

Table 4. Comparison of awareness and complication scores in between blood glucose regulation groups				
	All patients n=216	**≤7 HbA1c n=71**	**>7 HbA1c n=145**	**p**
Control visit advice for complications	1.79±1.15	1.83±1.16	1.77±1.14	**0.703**
Control visit for complications	4.58±3.31	5.39±3.41	4.18±3.19	**0.013**
Awareness score	4.29±3.38	5.69±3.4	3.61±3.17	**<0.001**

DRP is one of the common complications of diabetes. In our study, the incidence of retinopathy was found to be 23.1% (Table 3). In a study conducted in 2016, retinopathy was associated with advanced age, early onset of the disease, longer disease duration, uncontrolled blood sugar, hypertension and insulin use, and the presence of neuropathy and nephropathy and retinopathy was found to be 36.4% (10).

Another important complication associated with diabetes is nephropathy. In a study in Albania, the prevalence of microalbuminuria in patients with type 2 diabetes was 26.3%. Ahmed et al. (10) found a rate of 16.6% patients with microalbuniria. In our study, the rate of microalbuminuria was 10.6%, the rate of macroalbuminuria was 6.4% and patients with GFR below 60 were 5% (Table 3). In our study groups, differences in disease regulation rates and disease duration were thought to be effective the differences between the results determined in the literature.

According to the data of a study conducted in our country dealing with the relationship between target glycemic values and complication frequencies; there was a weak positive correlation between diabetic nephropathy and retinopathy rates and mean HbA1c values, but no statistically significant correlation was found between microalbuminuria and neuropathy rates (11). In our study, the mean HbA1c values of the group with DRP were significantly higher than those without DRP, but no significant difference was found between HbA1c levels with and without DNP.

In terms of control visit frequency for complications, the mean HbA1c levels of the 0-3 months group were found to be significantly lower than those of the other groups (Table 4). In another study, they also mentioned that HbA1c monitoring frequency is associated with diabetes control (12).

The awareness level of diabetes patients is a critical factor in reaching the target glycemic values in the disease. Awareness also plays an important role in preventing complications and achieving treatment success. In our study, a significant relationship was found between the awareness questionnaire score and the regulation of the disease (Table 4). Awareness of the non-regulated HbA1c group was significantly lower than that of the regulated group (Table 4). Increasing the awareness of patients in a chronic disease such as diabetes will make a significant contribution to the regulation of diabetes.

CONCLUSION

It is also important to achieve the goals of glycemic control and to identify other factors that are effective in preventing complications.

As mentioned in our study, the factors that are adversely affecting diabetes regulation, such as; low level of education and income, advanced age of diabetes, the use of technological devices such as smart phones and the internet, frequency of physician control, smoking and obesity, will create serious complications in the short and long term and will also cause serious economic burden is obvious.

With the help of larger studies, it is possible to achieve clearer and more effective results and thus, short- and long term complications of diabetes can be prevented using both conventional and technological methods and to increase the quality of life of patients and decrease the economic burden of diabetes.

Ethics

Ethics Committee Approval: The Ethical Committee approved this study at University of Health Sciences Turkey, Okmeydani Health Application and Research Center on 21.11.2017 no: 48670771-514.10.

Informed Consent: All patients were informed and consent forms were obtained.

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Authorship Contributions

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

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Comparison of the Efficacy of Endoscopic and Microscopic Type 1 Tympanoplasty

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Abstract

Objective: To compare the graft success rates and hearing gains of patients who underwent endoscopic and microscopic tympanoplasty.

Methods: A total of 90 patients, 45 patients who underwent endoscopic tympanoplasty and 45 patients who underwent microscopic tympanoplasty between 2014 and 2019, were included in the study. Patients' age, gender, operation side, perforation location, graft material type, graft placement type, preoperative, and postoperative audiological findings and graft success were compared in the two groups.

Results: There was no significant difference between the two groups in terms of age, gender, operation side, perforation location and the way the graft was placed ($p>0.05$). There was a difference between the two groups in terms of the graft material used. The mean hearing gain was found statistically significant in the audiological evaluations performed before and after the operation in both groups ($p<0.001$), but there was no difference between the groups ($p=0.222$). When the graft success rates were compared between the two groups, no statistically significant difference was found ($p=0.748$).

Conclusion: There is no difference between endoscopic tympanoplasty and microscopic tympanoplasty operations in terms of graft success rates and hearing gain. Both methods are effective and safe methods to use in chronic otitis media surgery.

Keywords: Endoscopic tympanoplasty, microscopic tympanoplasty, tympanoplasty, chronic otitis media

INTRODUCTION

Chronic otitis media (COM) is one of the most common otological problems with permanent changes in the tympanic membrane and/or middle ear structures. It is generally divided into two subgroups as with and without cholesteatoma. Tympanoplasty is the surgical reconstruction of the tympano-ossicular system, which includes canaloplasty, meatoplasty, myringoplasty, and ossiculoplasty (1). The tympanoplasty procedure has been performed microscopically for many years. However, with the development of endoscopic instruments, especially since the 90's, the endoscopic tympanoplasty procedure has been used with increasing acceleration and its popularity has increased recently (2,3).

During microscopic surgery, the surgical field view is limited to the narrowest part of the external ear canal, while in endoscopic surgery, this narrow area is bypassed and a wide view of the surgical field is provided even with 0° endoscopes. In microscopic tympanoplasty, retroauricular or endaural incisions are usually made to expand the view of the surgical field and canaloplasty may be required when necessary. However, one of the most important advantages of endoscopic tympanoplasty is that it can be performed transcanally without the need for any incision or canaloplasty, deep and corner areas that are difficult to see with a microscope can be easily seen, and it is a less invasive procedure (3-5). The greatest advantage of microscopic tympanoplasty is that it allows the use of 2 hands together at the same time (6).

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Although the rate of successful closure of the tympanic membrane perforation in microscopic tympanoplasty varies between 83%-100% in the literature, these rates are between 80%-100% in endoscopic tympanoplasty (7). In this study, we aimed to compare the results of endoscopic and microscopic type 1 tympanoplasty and examine the graft success rate and the changes in the hearing of the patients.

METHODS

Forty five patients [5 females, 20 males; endoscopic tympanoplasty (ET) group] who underwent endoscopic type 1 tympanoplasty and 45 patients [22 females, 23 males; microscopic tympanoplasty (MT) group] who underwent microscopic type 1 tympanoplasty in the ENT Clinic of Haseki Training and Research Hospital between January 2014 and December 2019, in 90 patients were analyzed retrospectively. Ethics committee approval of the study was obtained from the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital Local Ethics Committee (date: 14.05.2020, decision no: 2020-57). Patients with cholesteatoma and otosclerosis who underwent ossiculoplasty in the same session and revision operations were excluded from the study. Age, gender, side of the perforation, location of the perforation, average air-bone conduction gap in the preoperative and postoperative 3rd month, mean hearing gain, the graft material used in the operation and the success rates of the graft in the postoperative follow-ups were evaluated. Hearing thresholds were calculated by taking the averages of 500 Hz, 1000 Hz and 2000 Hz in the audiogram. All patients underwent type 1 tympanoplasty under general anesthesia. A retroauricular or endaural approach was used in patients who underwent microscopic tympanoplasty. During endoscopic tympanoplasties standard endoscope assisted transcanal tympanoplasty was performed. Perforations were grouped according to their anatomical location as central-marginal and anterior-posterior-inferior. The temporal fascia, perichondrium, tragal cartilage, or conchal cartilage were used as graft materials in all operations. The grafts were placed as underlay or over-underlay. Postoperative routine control of the patients was carried out in the 1st week, 3rd week, 3rd month and 6th month. Complete closure of the perforation in these controls was defined as graft success.

Statistical Analysis

SPSS 15.0 for Windows program was used for statistical analysis. Descriptive statistical methods were given the number and percentage for categorical variables; mean, standard deviation, minimum, maximum, and median for numerical variables. The rates in the groups were compared using the chi-squared test. Since the numerical variables did not provide normal distribution condition, the comparisons of the two groups were made using the Mann-Whitney U test. Dependent group analyzes were performed using the paired t-test when the differences in numerical variables provided the normal distribution condition and the Wilcoxon test when the normal distribution condition was not met. The statistical significance level was set as $p<0.05$.

RESULTS

A comparison of the demographic and clinical characteristics of the patients in the ET group and in the MT group is shown in Table 1. The mean age of the ET group was 31.4±12.6 (range 18-63 years) while the mean age of the MT group was 32.5±11.2 (range 18-60 years). There was no statistical difference between the two groups in terms of age ($p=0.387$). There were 20 males (44.4%), 25 females (55.6%) in the ET group; 23 males (51.1%), 22 females (48.9%) in the MT group and there was no significant difference in terms of gender ($p=0.527$). While 17 left ears (37.8%) and 28 right ears (62.2%) were operated in the ET group; 20 left ears (44.4%) and 25 right ears (55.6%) were operated in the MT group and there was no significant difference between the groups in terms of the operated side ($p=0.520$).

Perichondrium was used in 19 patients (42.2%), tragal cartilage in 17 patients (37.8%), the fascia in 7 patients (15.6%) and conchal cartilage in 2 patients (4.4%) who underwent endoscopic tympanoplasty. However, perichondrium was used in 3 patients (6.7%), tragal cartilage in 6 patients (13.3%), the fascia in 14 patients (31.1%) and conchal cartilage in 22 patients (48.9%) who underwent microscopic tympanoplasty. A statistically significant difference was found between the two groups in terms of the graft materials used ($p<0.001$).

In the ET group, the grafts of 20 patients (44.4%) were placed as underlay, while 25 patients' grafts (55.6%) were placed as over-underlay. In the MT group, the grafts of 14 patients (31.1%) were placed as underlay, while 31 patients' grafts (68.9%) were placed as over-underlay. There was no significant difference between the two groups in terms of graft placement position ($p=0.192$).

The perforations of the patients who underwent endoscopic tympanoplasty were posteriorly located in 19 patients (42.2%), anteriorly located in 15 patients (33.3%) and inferiorly located in 11 patients (24.4%). Simultaneously, 40 of the perforations (88.9%) were central perforation while 5 of them (11.1%) were marginal. The perforations of the patients who underwent microscopic tympanoplasty were posteriorly located in 24 patients (53.3%), anteriorly located in 7 patients (15.6%) and inferiorly located in

14 patients (31.1%). While 39 of the perforations (86.7%) were central perforation, 6 of them (13.3%) were marginal. There was no significant difference between the two groups in terms of the location of the perforations (p=0.146 and p=0.748).

In the controls performed in the postoperative 6th month, the graft success rate in the ET group was found 86.7% (39 of 45 patients). The graft success rate in the MT group was found 88.9% (40 of 45 patients). No statistically significant difference was found between the two groups in terms of graft success rate (p=0.748) (Table 2).

The average preoperative air-bone conduction gap was 20.4±9.7 in the ET group. In the postoperative 3rd month measurements, it was found 13.2±10.7 (Table 2). The mean hearing gain in the ET group was statistically significant (p<0.001) (Table 3). While the average preoperative air-bone conduction gap was 20.6±8.8 in the MT group, it was found 10.4±9.9 in the measurements at the postoperative 3rd month (Table 2). The mean hearing gain in the MT group was found to be statistically significant (p<0.001) (Table 3). However, when the mean hearing gains were compared between the ET and MT groups, no statistically significant difference was found (p=0.222) (Table 2).

DISCUSSION

Tympanoplasty is a term used to describe the surgical procedure performed not only for reconstructing the tympanic membrane,

Table 1. Comparison of the preoperative clinical characteristics of patients

		Endoscopic tympanoplasty	Microscopic tympanoplasty	p
Gender n (%)	Male	20 (44.4)	23 (51.1)	0.527
	Female	25 (55.6)	22 (48.9)	
Age mean ± SD (min-max)		31.4±12.6 (18-63)	32.5±11.2 (18-60)	0.387
Graft type n (%)	Tragal	17 (37.8)	6 (13.3)	**<0.001***
	Conchal	2 (4.4)	22 (48.9)	
	Fascia	7 (15.6)	14 (31.1)	
	Perichondrium	19 (42.2)	3 (6.7)	
Operation side n (%)	Left	17 (37.8)	20 (44.4)	0.520
	Right	28 (62.2)	25 (55.6)	
Graft position n (%)	Underlay	20 (44.4)	14 (31.1)	0.192
	Overlay	0 (0.0)	0 (0.0)	
	Over-underlay	25 (55.6)	31 (68.9)	
Perforation location n (%)	Posterior	19 (42.2)	24 (53.3)	0.146
	Anterior	15 (33.3)	7 (15.6)	
	Inferior	11 (24.4)	14 (31.1)	
Perforation type n (%)	Central	40 (88.9)	39 (86.7)	0.748
	Marginal	5 (11.1)	6 (13.3)	

*p<0.05, SD: Standard deviation, min: Minimum, max: Maximum

Table 2. Comparison of audiological results and graft success

		Endoscopic tympanoplasty	Microscopic tympanoplasty	p
Average preoperative air-bone conduction gap Mean ± SD (min-max/median)		20.4±9.7 (3-43/20)	20.6±8.8 (5-40/20)	0.689
Average postoperative air-bone conduction gap Mean ± SD (min-max/median)		13.2±10.7 (0-41/10)	10.4±9.9 (0-40/8)	0.095
Mean hearing gain Mean ± SD (min-max/median)		7.1±6.9 (-16-18/7)	9.9±11.7 (-19-36/10)	0.222
Graft success n (%)	Yes	39 (86.7)	40 (88.9)	0.748
	No	6 (13.3)	5 (11.1)	

SD: Standard deviation, min: Minimum, max: Maximum

Table 3. Comparison of hearing gain			
	Average preoperative air-bone conduction gap	Average postoperative air-bone conduction gap	p
Endoscopic tympanoplasty mean ± SD	20.4±9.7	13.2±10.7	**<0.001***
Microscopic tympanoplasty mean ± SD	20.6±8.8	10.4±9.9	**<0.001***
*p<0.05, SD: Standard deviation, min: Minimum, max: Maximum			

but also to remove middle ear pathologies such as COM, cholesteatoma and ossicular chain problems.

With the invention of binocular microscopes, ear surgery has undergone a great change and the foundations of modern otology have been laid. Then, with the introduction of rigid endoscopes, modern otology has passed to another stage. In 1978, Eichner (8) introduced the use of a 2.7 mm diameter and high resolution rigid endoscope for autological examination. Since el-Guindy's (9) first publication in 1992, endoscopes are now widely used in tympanoplasty. While the most important advantages of microscopic ear surgery are that both hands can be used simultaneously, it provides stereoscopic vision and requires a shorter training period, the most important disadvantage is that it cannot provide sufficient vision of the hidden areas in the middle ear without performing canaloplasty, particularly in patients with narrow and curved external auditory canal (10-12). These hidden areas, which cannot be seen easily with a microscope, have been easily accessible without canaloplasty with rigid endoscopes. However, working with one hand, difficulty in using endoscopes at the beginning of the training and not providing stereoscopic guidance are important disadvantages of endoscopic ear surgery (12,13).

In studies in the literature, many publications have shown that endoscopic tympanoplasty takes less time than microscopic tympanoplasty (11,14). As the most important reason for this, it has been advocated that there is no need for suturing in endoscopic tympanoplasty at the end of the operation.

Choi et al. (15) compared the results of endoscopic and microscopic tympanoplasty in their study published in 2017 and found no difference between the two groups in terms of graft success rate. Likewise, Shakya et al. (16) compared the graft success rate in endoscopic and microscopic tympanoplasty, achieved a success rate of 91.42% in both groups and found no significant difference in graft success rate between the groups. In our study, the graft success rate was 86.7% in the endoscopic tympanoplasty group, while it was 88.9% in the microscopic tympanoplasty group and no significant difference was found between the two groups (p=0.748).

Güler and Özcan (17) found a mean hearing gain of 12.8 dB and 12.4 dB, respectively, in their study comparing endoscopic and microscopic techniques and found no significant difference in gain between the two groups. Gulsen and Baltacı (14) found a mean hearing gain of 19.4 dB in endoscopic tympanoplasty and 18.7 dB in microscopic tympanoplasty and they found no significant difference in terms of hearing gain between the two techniques. In both studies, postoperative hearing gain was found to be significant in both techniques. In our study, the mean hearing gain was found to be 7.1 dB in the endoscopic tympanoplasty group and 9.9 dB in the microscopic tympanoplasty group. While the hearing gain in both groups was statistically significant (p<0.001), no significant difference was found when the mean hearing gain was compared between the two groups (p=0.222).

The biggest disadvantage of endoscopic tympanoplasty is the difficulty of working with one hand. Working with one hand, especially in the case of bleeding, makes the operation difficult and can prolong the duration of the surgery. However, with sufficient practice and experience, these disadvantages can be manageable.

We think that it is important to start tympanoplasty training with microscopic tympanoplasty first and to switch to endoscopic tympanoplasty after gaining the necessary experience because endoscopic surgeries require more experience.

Study Limitations

The main limitation of the study is that there was a statistically significant difference between the microscopic and endoscopic tympanoplasty groups in terms of the graft materials used. Further studies with a larger sample of patients and using the same graft materials are needed to confirm the data presented in this work.

CONCLUSION

When the results of our study and other studies in the literature are evaluated, there is no difference between the two techniques in terms of graft success rate and average hearing gain in both endoscopic and microscopic tympanoplasty. Although studies

in the literature have shown that endoscopic tympanoplasty shortens the operation time, it requires more experience due to the difficulty of working with one hand. After gaining the necessary experience, we believe that endoscopic tympanoplasty may be preferred more frequently by surgeons as it provides a better surgical field view, is less invasive and short operation time.

Ethics

Ethics Committee Approval: Ethics committee approval of the study was obtained from the University of Health Sciences Turkey, Istanbul Haseki Training and Research Hospital Local Ethics Committee (date: 14.05.2020, decision no: 2020-57).

Informed Consent: Informed consent was obtained from all the patients included in the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.U., O.Ü., G.G., Y.B., Concept: S.U., O.Ü., Design: O.Ü., G.G., Y.B., Data Collection or Processing: G.G., Y.B., Analysis or Interpretation: O.Ü., G.G., Y.B., Literature Search: O.Ü., G.G., Y.B., Writing: S.U., O.Ü.

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ORIGINAL ARTICLE

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The Relationship Between the First Trimester Pregnancy Loss and Maternal Serum 25-Hydroxyvitamin D Level. A Case-control Study

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Abstract

Objective: Following the discovery of 25-hydroxyvitamin D [25(OH)D] receptor expression in the reproductive system organs and placenta, many studies exploring the relationship between pregnancy complications and 25(OH)D is being performed. In this study, we examined serum 25(OH)D levels in early pregnancy loss.

Methods: Patients who were in 20-30 years old age range whose body mass index >25 and <30, between April 2019 and January 2020 were included in the study at the Clinic of Obstetrics and Gynecology of University of Health Sciences Turkey, Prof. Dr. Cemil Tascioglu City Hospital in Istanbul/Turkey. Those who had miscarriage within the first 10 weeks (as a study group) and those who were diagnosed within the first 10 weeks and continued their pregnancies as live pregnancies after the 10th week (as a control group) were included in the study as two groups. Cases where the pregnancy was conceived through artificial reproductive technology, cases with a history of recurrent pregnancy losses, cases with chronic diseases and cases treated for imminent abortion were excluded. First prenatal visit 25(OH)D levels were retrospectively extracted from the hospital medical records.

Results: A statistically significant difference was observed between the 25(OH)D levels in women with an early pregnancy loss and 25(OH)D levels in women with an ongoing healthy pregnancy ($p<0.01$). The mean 25(OH)D level was found to be 8.61 ng/mL in the spontaneous pregnancy loss group; whereas, the mean level was found to be 16.61 ng/mL in the control group. As of this significance, a cut-off value for 25(OH)D levels was calculated using receiver operator characteristic curve analysis (sensitivity 94%, specificity 74%). Additionally, among other factors, older paternal age and vaginitis were also correlated with early pregnancy loss.

Conclusion: Our results show that 25(OH)D deficiency may play a role in early pregnancy loss. 25(OH)D may be a useful marker in predicting and preventing early pregnancy loss.

Keywords: Pregnancy loss, early, pregnancy trimester, first, 25(OH)D, miscarriage, spontaneous abortion

INTRODUCTION

Early pregnancy loss is the most common early pregnancy complication and is observed in approximately 30% of all pregnancies. This incidence decreases to 10% when evaluated as clinically recognized pregnancies (1). It is difficult to measure the full burden of miscarriage and is related to how early women realize their pregnancy. However, it is difficult to distinguish between abortion and stillbirth and the concept of early pregnancy is not fully clarified, and differences between studies make it difficult to give a clear incidence of miscarriage. Early pregnancy loss (miscarriage) is defined as a non-viable empty intrauterine gestational sac or a gestational sac containing an embryo or fetus without fetal heart activity within the first 10 0/7 weeks of gestation (2). In recent studies, modifiable factors like advanced maternal age, prepregnancy body mass index (BMI) and alcohol consumption have been emphasized (3-5). Although the cause of most miscarriages is unknown, it is likely due to

This study was derived and produced from Dr. Buse Kurtdereli thesis raw data in the field of gynecology and obstetrics in 2019.

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the complex interplay between parental age, genetic, hormonal, immunological and environmental factors (6).

The fetus is characterized as a semi-allograft which is incapable of survival if there is no maternal immune tolerance. 25-hydroxyvitamin D [25(OH)D] is a fat-soluble steroid prohormone mainly synthesized in the lower layers of the skin epidermis through a chemical reaction that depends on ultraviolet B radiation by sun exposure, and it can also be ingested from the diet and from supplements (7). Although the main function of 25(OH)D is on calcium metabolism and bone mineralization, recent studies have noted the expression of 25(OH)D receptors in peripheral and central organs that regulate the female reproductive system such as the uterus, ovary, placenta, pituitary gland and hypothalamus (8). Correlations between low levels of 25(OH)D and adverse outcomes of pregnancy such as preeclampsia, gestational diabetes mellitus, fetal growth restriction and preterm labor have been shown (9-11). This study aimed to compare the 25(OH)D levels in women having a first trimester pregnancy loss with the 25(OH)D in women ongoing a healthy first trimester pregnancy.

METHODS

Forty women with early pregnancy loss and 62 women with a healthy ongoing first trimester pregnancy seen between April 2019 and January 2020 at the Clinic of Obstetrics and Gynecology of University of Health Sciences Turkey, Prof. Dr. Cemil Tascioglu City Hospital (formerly known as Okmeydani Education and Research Hospital) in Istanbul/Turkey were included in this retrospective case-control study. Women aged 20-30 years and having a single pregnancy less than 10 weeks of gestation according to transvaginal ultrasound (TVUSG) or the last menstrual period and admitted to the hospital for antenatal care were included in the study population.

Women without any chronic disease like diabetes, hypertension, hypo or hyperthyroidism, a history of 2 or more previous miscarriages, consanguineous marriage, multiple pregnancies, ectopic pregnancies, pregnancies conceived through artificial reproductive technology, patients with a BMI less than 25 or greater than 30, Rh incompatibility, any confirmed chromosomal abnormality in either one of the couples, vitamin D supplement use and patients using any medications other than only folic acid were excluded from the study.

Comprehensive gynecology and obstetric history was conducted. Patient ID number, hospital registry number, age, height, weight, education level, gravidity, parity, smoking, and alcohol intake history, any vaginal bleeding or vaginitis episodes during the current pregnancy, a history of pelvic surgery, sexual intercourse history in the current pregnancy, paternal age, blood group and Rh status and consanguine marriage if present, were recorded.

Miscarriage was defined as confirmation of a pregnancy with a crown-rump length (CRL) of 7 mm or greater without cardiac activityor an empty gestational sac measuring 25 mm or greater in mean gestational sac diameter according to the guidelines of the Royal College of Obstetricians and Gynecologists (12). When these ultrasonographic criteria were not met but when there were findings suspicious for pregnancy failure, additional criteria from the Society of Radiologists in Ultrasound Multispecialty Panel on Early First Trimester Diagnosis of Miscarriage and Exclusion of a Viable Intrauterine Pregnancy (13) were considered:

- Absence of embryo with heartbeat 2 weeks or more after a scan that showed a gestational sac without a yolk sac.

- Absence of embryo with heartbeat 11 days or more after a scan that showed a gestational sac with a yolk sac.

Gestational age was calculated from the date of the last menstrual period and verified by ultrasound findings. If the patient could not recall or was not sure of the first day of her last menstrual period, or had irregular cycles, CRL was used to determine the gestational age. Speculum was examined in patients with vaginal bleeding to check the cervical status and identify the bleeding. Ultrasonographic evaluation of the pregnancy allowed us to document intrauterine pregnancy, measure CRL, evaluate gestational sac, yolk sac, fetal cardiac activity, and visualize any subchorionic hematoma. The control group consisted of patients with a live pregnancy whose gestational week was less than 10 weeks according to the last menstrual period and confirmed by TVUSG.

The medical records and laboratory results of the pregnant women who met the inclusion criteria were checked and extracted from the hospital database. Pregnant women who had routine first prenatal care visit laboratory workup results (complete blood count, biochemistry, 25(OH)D, vitamin B12, folate, blood group, and Rh type) were included in the study.

The study was approved by the University of Health Sciences Turkey, Okmeydani Training and Research Hospital Ethics Committee in April 2019 (no: 4867071-514.10, approval number: 1216). All participants provided informed written consent if they agreed to participate after oral description of the study.

Statistical Analysis

Descriptive statistical methods (mean, standard deviation, median, frequency, ratio) as well as the Shapiro-Wilk test for

normally distributed data and box plot graphs for visualization were used. Mann-Whitney U test was used for comparing of non-normally distributed data between groups. Student's t-test was used for comparison of normally distributed data, Chi-square test, Fisher's Exact test and Fisher-Freeman-Halton test were used for comparing categorical data. Cut-off value for 25(OH)D levels was determined by receiver operator characteristic (ROC) curve analysis as for determination of the most appropriate cut-off value in a diagnostic test. P<0.05 was considered statistically significant.

RESULTS

A total of 102 patients, 62 in the control group and 40 in the study group, were included in the study. No significant difference was observed between the mean ages of the control group and the study groups (26.21±3.01 vs. 26.33±3.2, respectively; p=0.750). When the ages of the husbands were analyzed, it was realized that the mean husband age of the group with early pregnancy loss was significantly higher than the mean husband age of the control group (32.3±5.71 and 30.18±4.59, respectively; p=0.041). BMI, gravidity, parity in the two groups did not have a statistically significant differences (p=0.278, p=0.099, p=0.517; respectively) (Table 1). Vaginitis was significantly higher among women with early pregnancy loss (p=0.003). Sexual intercourse during pregnancy, folic acid usage, Rh incompatibility and consanguineous marriage status did not show statistically significant differences between the two groups (p>0.05) (Table 1).

A statistically significant difference was observed between vitamin D levels of the two groups; 25(OH)D levels of the early pregnancy loss group were significantly lower than those of the control group [miscarriage mean 8.61 mcg/L (21.4 nmol/L) vs. non-miscarriage mean 16.61 mcg/L (41.43 nmol/L); p=0.001, Studen's t-test]. Folate, PTH and vitamin B12 levels were not significantly different between the two groups (p>0.05) (Table

Table 1. Demographic characteristics of patients

	Total (n=102)		**Abort group (n=40)**	**Alive group (n=62)**	**p value**
Age*	26.21±3.01		26.33±3.2	26.13±2.91	0.750[a]
BMI*	22.86±1.99		23.13±2.00	22.68±1.99	0.278[a]
Gravida*	2.55±1.26		2.83±1.38	2.37±1.16	0.099[b]
Parity*	1.13±1.35		1.86±1.02	1.78±1.43	0.087[b]
Educational status n (%)	Illiterate	7 (6.9)	4 (10)	3 (4.8)	0.517[c]
	Primary school	34 (33.3)	16 (40)	18 (29)	-
	Middle school	27 (26.5)	8 (20)	19 (30.6)	
	High school	19 (18.6)	6 (15)	13 (21)	
	Graduate	15 (14.7)	6 (15)	9 (14.5)	
Partner age*	31.01±5.14		32.3±5.71	30.18±4.59	**0.041**[a]
Alchol status; n (%)	No		40 (100)	62 (100)	-
Smoking status; n (%)	No		30 (75.0)	54 (87.1)	0.118[c]
	Yes		10 (25.0)	8 (12.9)	
Vaginitis; n (%)	No		30 (75.0)	59 (95.2)	**0.003**[c]
	Yes		10 (25.0)	3 (4.8)	
Sexual intercourse during pregnancy n (%)	No		7 (17.5)	11 (17.7)	0.975[c]
	Yes		33 (82.5)	51 (82.3)	
Folic acid usage n (%)	No		21 (52.5)	39 (62.9)	0.297[c]
	Yes		19 (47.5)	23 (37.1)	
Rh incompatibility n (%)	No		40 (100)	60 (96.8)	0.519[d]
	Yes		0 (0)	2 (3.2)	
Consanguineous marriage status n (%)	No		40 (100)	61 (98.4)	1.000[d]
	Yes		0 (0)	1 (1.6)	

[a]Student's t-test,[b] Mann-Whitney U test,[c] Chi-square test, [d] Fishers Exact test. Bold text p value is statistically significant, *Data are given as mean ± standard deviation. BMI: Body mass index

2). However, phosphorous levels showed significant differences between the groups, where levels in the early pregnancy loss group were significantly higher than the levels in the control group (miscarriage median 4.18 mg/dL vs. non-miscarriage median 3.46 mg/dL; p=0.043, Mann-Whitney rank-sum test). A cut-off value of 12.5 mcg/L for 25(OH)D levels in women with early pregnancy loss and 25(OH)D levels in women with a healthy pregnancy was determined. For this 12.5 mcg/L cut-off value, sensitivity and specificity were 95% and 74.19%, respectively, with a positive predictive value of 70.37% and a negative predictive value of 95.83%. The area under the curve was calculated as 90.1% in the ROC curve used to determine the cut-off value (Tables 3, 4, Figure 1). The difference observed between the two groups at this cut-off value of 12.5 g/L for vitamin D levels was statistically significant (p=0.001) (Figure 1).

DISCUSSION

In this study, we attempted to reveal any relationship between early pregnancy loss and low levels of 25(OH)D, which is a predictable, preventable and treatable condition. Our study results demonstrate a significant difference between the 25(OH)D levels of women with an early pregnancy loss and the 25(OH)D levels of women without an early pregnancy loss.

Andersen et al. (12) found an association with low maternal serum 25(OH)D levels and the first trimester pregnancy loss in their cohort study on 1,683 patients. The authors attribute the beneficiary effects of 25(OH)D to its regulation of the innate and adaptive immune system. In a small Danish controlled cohort study (13). Three women who had miscarriage during the second trimester of pregnancy had a lower 25(OH)D than 84 controls who completed their pregnancy.

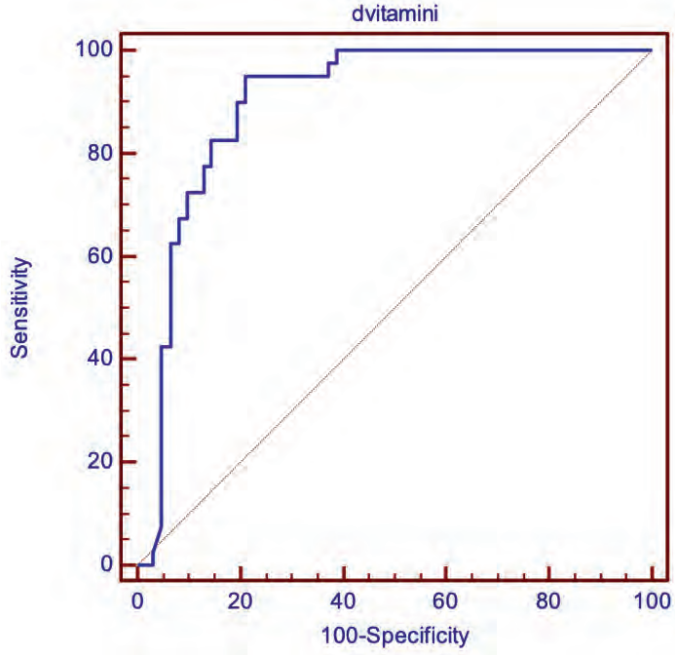

Figure 1. ROC curve for 25(OH)D2
ROC: Receiver operator characteristic, 25(OH)D: 25-hydroxyvitamin D

Conversely, in a randomized controlled trial of pregnant women taking different doses of vitamin D supplements (400, 2000, or 4000 IU of vitamin D 3 per day until delivery), 25(OH)D levels at the 12th week of pregnancy. There was no significant difference in l25(OH)D concentrations [circulating 25(OH)D level mean ± standard deviation; 61.2±27.1, 57.5±22.4, 59.8±25.4, respectively) at 12 weeks gestation when women who experienced pregnancy loss were compared with women who gave birth to a live baby (14). In a cohort study from Australia, when vitamin D levels at 10-14 weeks of pregnancy were compared among 3,714 women with healthy pregnancies and 39 women with pregnancy losses no significant difference was observed with mean 25(OH)D concentrations of 56.9 nmol/L [95% confidence interval (CI): 43.9, 70.8] vs. 53.5 nmol/L (95% CI: 42.4, 61.7) (15). In our study, we found that 25(OH)D was related to miscarriage in the first trimester. It is possible that 25(OH)D plays a protective role against miscarriage.

Discussions on vitamin D deficiency as a global public health problem continue to be relevant due to low levels of serum 25(OH)D in a vast number of studies conducted worldwide. Prevailing low 25(OH)D levels, especially in pregnant women and neonates is keeping drawing attention (16).

Nevertheless, Dietary Reference Intake (DRI) recommendations for daily intake of vitamin D by the US Institute of Medicine (IOM) and Health Canada is 600 IU/day; these DRIs being based on maintaining bone health, do not provide recommendations on health issues besides maintaining skeletal health (17). Although a 2016 update of a Cochrane Systematic Review and some other current reviews propose that vitamin D supplement

Table 2. Evaluations of blood biochemical measurements

	Abort group (n=40)*	Alive group (n=62)*	p value
25(OH)D (µg/L)	8.61±2.42	16.61±6.12	**0.001**[a]
Hemoglobin (g/L)	12.71±1.04	12.07±1.38	0.014[a]
Folate (mcg/L)	16.69±5.33	14.55±5.11	0.077[b]
PTH (pcg/mL)	36.17±17.29	36.62±17.03	0.997[b]
P (mg/dL)	4.18±2.37	3.46±0.54	**0.043**[b]
B12 (ng/L)	178.33±60.53	198.98±66.76	0.257[b]

[a]Student's t-test, [b]Mann-Whitney U test, *Data are given as mean ± standard deviation. PTH: Parathormone, P: Phosphorus, B12: Vitamin B12, 25(OH)D: 25-hydroxyvitamin D

Table 3. Diagnostic screening tests and ROC curve results for vitamin D measurement							
Diagnostic scan					**ROC curve**		
Cutt-off	**Sensitivity**	**Specifity**	**PPV**	**NPV**	**AUC**	**95% CI**	**p value**
≤12.5	95.00	74.19	70.37	95.83	0.901	0.838- 0.963	0.001
PPV: Positive predictive value, NPV: Negative predictive value, CI: Confidence interval, AUC: Area under curve, ROC: Receiver operator characteristic							

Table 4. Relationship between groups and 25(OH)D2 measurement					
	25(OH)D2 (cut-off value 12.5)				p value*
	>12.5		≤12.5		
	n	%	n	%	
Alive group	46	95.8	16	29.6	**0.001**
Abort group	2	4.2	38	70.4	
*Pearson's chi-squared test, 25(OH)D: 25-hydroxyvitamin D					

during pregnancy may lower the incidence of pre-eclampsia and fetal growth restriction, no high-quality evidence for significant effects on other maternal and fetal outcomes could be found (18-20).

Ergocalciferol (vitamin D2) absorbed through diet and cholecalciferol (vitamin D3), mainly synthesized in the skin by UV rays, are converted to 25(OH)D in the liver, 25(OH) D is later transformed into the most active form 1,25-OH 2D, primarily in the kidneys. 25(OH)D is the major circulating form of vitamin D, but its activity is less than 1% of 1,25-OH 2D, the most active form of vitamin D. Serum concentration of 25(OH)D is currently the main indicator of vitamin D status. It reflects vitamin D produced endogenously through sun exposure and that obtained from foods and supplements (21).

ACOG (22) has emphasized that measuring serum 25(OH)D levels would be an acceptable indicator of the vitamin D status of pregnant women. However, there is no consensus on what a healthy serum level should be. Generally, for optimal skeletal health, a minimum serum level is considered as 20 ng/mL (50 nmol/L) (23). However, some researchers have stressed in a serum level of at least 32 ng/mL (80 nmol/L) (24). In 2010, the Food and Nutrition Board of the National Academies' IOM stated that a daily intake of 600 IU of vitamin D would be sufficient during pregnancy and lactation (25).

Over the past decades, there has been growing research on the potential links between 25(OH)D and major human diseases and clinical conditions. Dark skin pigmentation, insufficient sun exposure, inadequate dietary intake are major reasons for 25(OH)D deficiency (26). 25(OH)D metabolism during pregnancy is still less clear than in the non-pregnant state and is under ongoing research.

The immunomodulator effect of vitamin D on the endometrium that secures implantation, may imply that in 25(OH)D deficiency or insufficiency, dysfunction through the implantation process may be responsible for early pregnancy losses and late placental dysfunctions (27). Additionally, fetal rejection that may occur during this period because the conceptus may be considered a semi-allograft, will not occur due to the effects of 25(OH)D on the immune system. Consequently, the immunomodulator and the anti-inflammatory properties of 25(OH)D play an important role in preventing early pregnancy losses (28).

In a study of 133 women with 3 or more consecutive pregnancy losses, those with 25(OH)D levels less than 30 ng/mL (75 nmol/L) had a significantly higher prevalence of auto- and cellular immune abnormalities (29). Similarly, various *in vitro* studies have illustrated that in the endometrial cells of women with spontaneous recurrent abortions, 1,25(OH)2D3 plays an essential role in cytokine regulation (30).

Vitamin D receptor is expressed in many cell types and controls antigen-receptor signalization and T-cell activation (31). It has also been demonstrated that the active form of 25(OH)D inhibits the secretion of proinflammatory cytokines such as tumor necrosis factor-alpha, interleukin-6, and interferon-gamma in the placenta (32).

1,25(OH)2D3, the active form of 5(OH)D, has potent anti-inflammatory effects at the maternal-fetal interface, by decreasing the T helper cell type 1 (Th1)/Th2 ratio, suppressing Th17 cell activity, and increasing T regulatory cell production (33). Animal studies have shown that treatment with vitamin D regulates endometrial decidualization (34). *In vitro* studies on trophoblasts cultured from human placenta revealed that 1,25(OH)2D3 stimulated estradiol and progesterone secretion in trophoblasts (35). It has also been demonstrated that 1,25(OH)2D3 is involved in HOXA10 expression, a key target gene in the implantation process (36).

Some study findings suggest that women with sufficient levels of 25(OH)D are more likely to achieve clinical pregnancy following in vitro fertilisation (8). Bacterial vaginosis, which has been shown to be associated with adverse pregnancy outcomes, mostly with preterm birth, has also been shown to be associated with low vitamin D levels (37). Many studies have demonstrated

that vitamin D deficiency may play a role in recurrent pregnancy losses. Still, it may seem compulsive to presume an active role for vitamin D at the maternal-fetal immunologic interface leading to pregnancy loss.

We found that vitamin D levels were low both in the study group and in the control group of our study. We assume that these low levels are due to the low economic profile of our patient group, leading to nutritional deficiencies and most of the patient population choosing to dress according to religious restrictions leading to limited sun exposure.

Study Limitations

The limitations of our study are the retrospective design of the study, the small number of participants, the likely confounding factors resulting from the low socioeconomic profile of the participants, and the serum vitamin D measurements not being cleared of seasonal variations.

CONCLUSION

As a result, we found that women with the first trimester pregnancy losses had much lower serum 25(OH)D levels of <12.5 ng/mL. These findings suggest that vitamin D plays a protective role in preventing pregnancy losses. Randomized controlled trials are needed to test the protective effect of vitamin D supplements for low levels of 25(OH)D during early pregnancy or even in the preconception period.

Ethics

Ethics Committee Approval: The study was approved by the University of Health Sciences Turkey, Okmeydani Training and Research Hospital Ethics Committee in April 2019 (no: 4867071-514.10, approval number: 1216).

Informed Consent: All participants provided informed written consent if they agreed to participate after oral description of the study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: B.K., O.Ş., V.M., Concept: B.K., O.Ş., V.M., Design: B.K., O.Ş., V.M., Data Collection or Processing: B.K., O.Ş., V.M., Analysis or Interpretation: B.K., O.Ş., V.M., Literature Search: B.K., O.Ş., V.M., Writing: B.K., O.Ş., V.M.

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ORIGINAL ARTICLE

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Effects of a COVID-19 Pandemic on Breast Cancer Management

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Abstract

Objective: The coronavirus disease-2019 (COVID-19) pandemic caused some difficulties in the management of breast cancer, so we examined the effect of this challenging condition on the diagnosis and treatment of breast cancer.

Methods: In this study, the 26 month period from March 2019 to April 2021 was divided into two periods according to the start date of the pandemic. The previous 13 months were defined as A, the next 13 months as B, and the first 3 months of both periods were defined as A* and B*. All patients diagnosed with breast cancer were evaluated retrospectively based on hospital records, in terms of some characteristics like histopathological, and molecular subtypes of the tumor, primary systemic treatment (PST) frequency and its model, axillary staging method before PST, and surgical method. The results were evaluated with the chi-square test, and $p>0.05$ was statistically significant.

Results: All patients were female, 356 cases were in the A period, 30.3% of them had PST as neoadjuvant chemotherapy (NAC) and 37% (n=40) had sentinel lymph node biopsy before PST. There were 281 patients in period B, 116 cases received PST (41.2%); NAC and neoadjuvant endocrine therapy (NET) were staged radiologically and cytologically if necessary. When the findings of periods A and B (and A*-B*) were compared, the difference in PST in B compared to period A was statistically significant ($p=0.005$), insignificant for NAC ($p=0.849$), and highly significant for axillary approach and NET ($p=0.000$). In period B, more breast-conserving surgery (BCS) was applied, which may have been due to more initiation of PST. Overall, results in A* and B* were broadly similar to periods A and B.

Conclusion: During the COVID-19 pandemic, some adjustments were made in breast cancer management plans. PST was applied more often, NET became an option to start treatment, the axillary staging was performed based on a non-invasive method and surgically, BCS was performed more frequently.

Keywords: COVID-19 outbreak, breast cancer, primary systemic therapy, neoadjuvant chemotherapy, sentinel lymph node biopsy

INTRODUCTION

The severe acute respiratory syndrome-coronavirus-2 outbreak has created some unexpected challenges in healthcare around the world. There are still disruptions in health services in all countries that still prevail and can be fatal, especially in conditions that affect the immune system, such as cancer. The risk of morbidity and mortality with the transmission of coronavirus disease-2019 (COVID-19) infection is 4.5 times higher than that in the general population (1).

However, early diagnosis and treatment are particularly important for cancer patients and should not be delayed or compromised. For this reason, some changes have been made to the standard care for breast cancer patients to refrain from the risk of infection, and relevant guidelines have been prepared (1-3).

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More than 600 newly diagnosed breast cancer patients apply to the oncology clinic of our hospital every year, more than half of them are treated by the breast surgery department of the surgery clinic, and their treatment is planned by discussing the case in the breast tumor council after preliminary diagnostic procedures are achieved. But when the epidemic started, our hospital was been organized as a COVID-19 center, when the first case was identified in our country namely in March 2020. Accordingly, health services and work plans have changed, elective surgeries have been cut for a short while, and there are still some restrictions. During this period, some changes were made in the treatment planning and application in patients with breast cancer.

In this study, we reviewed the effect of the pandemic on the diagnosis and treatment of breast cancer in our center in terms of the number of patients, the way of starting the treatment, the choice of neoadjuvant chemotherapy (NAC) or neoadjuvant endocrine therapy (NET) for primary systemic treatment (PST), the approach to the axilla, and the surgical technique, by comparing these parameters with those of the previous similar time.

METHODS

According to "March 2020" the Start date of the Pandemic, the 26-month between March 2019 and April 2021 were divided into two periods. The 13-month period before March 2020 was defined as periods 'A' and the 13 months after that as period 'B.'

We also aimed to examine whether the effects of uncertainties and restrictions in the B period, especially in the first months of the pandemic, were different in the first 3 months compared to the whole process. As result, the first 3 months of periods A and B were handled separately as A* and B*.

The study was approved by the Ethics Committee of the Universtiy of Health Sciences Turkey, Prof. Dr. Cemil Tascioglu City Hospital, with the decision dated 07.01.2021-271.

Statistical Analysis

All patients diagnosed with breast cancer were analyzed retrospectively using breast cancer board records. The number of patients, whether the patients were metastatic at the time of diagnosis, the histopathological structure, and molecular subtype of the tumor, the selected model as PST and its frequency of use, sentinel lymph node biopsy (SLNB) for axillary staging before PST, and the surgical method were examined. The results were analyzed with the chi-square test, and a p-value of <0.05 was statistically significant.

RESULTS

Our study population consisted of female patients with a mean age of 61 years (22-91) in period A, and 59.5 years (30-88) in period B. When analyzed according to the histopathological structure of the tumor, an equal number of patients with ductal carcinoma *in situ* was in A and B periods the same (n=27), but rates of them were 7.5%-9.6% respectively. In periods A, and B respective number of patients received the diagnosed with lobular carcinoma [n=16 (4.5%) vs. n=24 (8.5%)], and invasive ductal carcinoma [n=313 (88%) vs. n=230 (81.9%)] (Table 1).

We also defined breast cancer patients according to their molecular subtypes. In periods A, and B, respective numbers of patients had luminal A [n=210 (63.8%) vs. n=147 (57.9%)], luminal B [n=20 (7.9%) vs. n=20 (7.9%), HER-2 (+) [n=61 (18.6%) vs. n=55 (21.6%)], triple-negative breast cancer [n=38 (11.6%) vs. n=32 (12.6%)]. The results of the two periods were found to be similar in terms of histopathological structure.

In period A, 15, and in period B, 12 patients had metastatic breast cancer at their first admission with a similar metastatic breast cancer detection rate (4.2%) (Table 2).

In period A, 356 patients had newly diagnosed breast cancer, and 30.3% (n=108) had received all PST all in the form of PST. Before PST, 40 (37%) cases had undergone SLNB.

In period B, the total number of patients decreased by 22% to 281, and 116 (41.3%) patients were started on PST. In the PST group 10 (3.5%) patients received NET, and 106 (37.8%) PCT. SLNB was not applied to any patient in period B before PST. In

Table 1. Histopathologic characteristics of tumors and patients'

Characteristics of tumor and patients	A	B
Age (median)	61	59.5
DCIS	27	27
Lobular	16	24
Ductal	313	230
Total	356	281

DCIS: Ductal carcinoma *in situ*

Table 2. Specific characteristics of the tumors

Molecular subtype of tumor	A	B
Luminal A	210	147
Luminal B	20	20
HER-2 (+)	61	55
Triple-negative	38	32
Total	356	281
M+	**15**	**12**

the comparison of these periods, the rates of receiving PST and NAC was found to be borderline significant (p=0.005), while the intergroup difference was found to be highly significant (p=0.000) in terms of receiving NET and SLNB for axillary staging before PST (Table 3).

The total number of patients in A* was 75, and in B* 79. In periods A* and B *, the same number of patients (n=20) were started on NAC, in period B a slightly higher number of patients (53% vs. 38.3%) received NAC, but without any statistically significant intergroup difference (p=0.0849). In A*, 12 patients underwent SLNB before PST, while SLNB was not performed in B* with a highly significant intergroup difference (p=0.000), (Table 4).

Our patients were also analyzed according to the surgical procedures; mastectomy (Mx) or breast-conserving surgery (BCS) they had undergone in periods A and B. In period A 232 (71%) of the 334 cases were treated with BCS, while Mx was applied to 102 patients for treatment (n=96; 27%) or prophylaxis (n=6; 1.8%) In period B, a total of 228 patients underwent surgery, including BCS (n=181: 79%) and Mx (n=47: 21%). Within the first 3 months, BCS was performed for 57 (24%), and Mx for 20 (21%) patients in A*, while in B* 40 (22%) patients received BCS, and Mx was performed for 13 (27%) patients (Table 5).

Six patients who have diagnosed in period A and completed PST did not want to wait on days when surgical procedures were limited in our hospital and were operated on other centers. In period B, 4 patients died from COVID.

Table 3. First line of treatment and staging of axille before treatment

First line of treatment and approach to axilla	A	B	p
PST	108	116	0.005
NAC	108	106	0.005
NET	0	10	0.000
SLNB	40	0	0.000
Total	356	281	-

PST: Primary systemic therapy, NAC: Neoadjuvant chemotherapy, NET: Neoadjuvant endocrine therapy, SLNB: Sentinel lymph node biopsy

Table 4. Comparison PST and SLNB between in A* and B* period

	A*	B*	p
PST	20	20	0.849
SLNB	12	0	0.000

PST: Primary systemic therapy, SLNB: Sentinel lymph node biopsy

Table 5. The surgical method used in both period and A*and B*

Surgical method	A* (%)	A	B* (%)	B
BCS	57 (24.5)	232	40 (22)	181
Mx	20 (21)	96	13 (27)	47
Prophylactic Mx	3 (3.75)	6	0 (0)	0
Total	80	334	53	228

BCS: Breast-conserving surgery, Mx: Mastectomy

DISCUSSION

The COVID pandemic has caused some problems in the field of health apart from itself. It directly affected health services, patients, and healthcare workers. Knowing that it is necessary to avoid risks while planning the treatment of our patients, we tried overcoming them with the least morbidity, especially for patients with breast cancer. Our hospital has been organized as a COVID-19 center since March 2020, when the first case was identified in our country, and elective surgeries were interrupted for a while and continued partially for a certain period.

The risk of morbidity and mortality with the transmission of COVID-19 infection in cancer patients is 4.5 times higher than that in the general population (1). For this reason, some changes have been made in the standard care that avoids the risk of infection for breast cancer patients in the world and in our country, and guidelines have been prepared to that end (1,2).

According to the current staging method of breast cancer, treatment should be started according to the molecular subtype. The first step of treatment option is general surgery or PST, according to criteria such as hormone receptor status, tumor size, axillary involvement, nuclear grade of the tumor, Ki-67 proliferation index, which is evaluated individually in each patient. Triple-negative and cERB 2 (+) cases are the most common patients in whom PST is started because these patients respond well or even completely to treatment. Luminal A-B tumors respond less to PST, but less surgery in these conditions necessitated some changes in treatment planning (1-3).

In our country, a study was initiated to provide a consensus on what can be done in order not to disrupt breast cancer treatment in the first days of the pandemic (3). In this study, where we also participated in, 46 statements related to 28 different case scenarios were voted electronically by a panel consisting of 51 surgeons and medical oncologists with the necessary skills and experience in breast cancer management, using the Delphi method. While 37 of them reached a consensus in the first round as acceptance or rejection, nine of them were put to vote as the required decision threshold could not be reached in the second

round. At the end of two rounds, a statement was approved as a proposal for each of the 14 case scenarios.

For patients with node-negative, small-sized triple-negative, HER-2-positive, and luminal A-like tumors, the consensus was that neoadjuvant systemic therapy should be administered until conditions improve for surgical treatment. Panelists also agreed to expand systemic therapy for patients with clinically and completely responsive HER-2-positive and luminal B-like tumors after application of neoadjuvant systemic therapy (3).

While evaluating our patients, we considered the current conditions, the Turkish consensus report, and the other guidelines; we postponed reconstructive surgery, benign breast surgeries, those with low-grade malignancy, and only operated on cancers that should not be delayed. The breast cancer council did not take a break from its work at our hospital, it continued online for the first 3 months, then in accordance with the pandemic measures and with the participation of as few specialists as possible from all departments.

We had to use the resources of the operating room very sparingly, during the 2nd and 3rd waves, (December 2020 and April 2021), the operating room was converted into an intensive care unit (4). Based on these challenging conditions, and up-to-date information, we reduced the number of invasive procedures.

In the period when the working hours in the operating room were very restricted, PST was brought to the agenda in the Tı-T2 HER-2 negative luminal A and B patients, for whom we did not routinely prefer. As well as NET became an option in treatment, it was chosen as the PST before surgery; NET came to the fore with only extremely limited indications previously ie. for only those who could not receive NAC or had no chance for surgery. Before and during period A, SLNB for axillary staging was being applied before PST, although with gradually decreasing frequency. The SLNB procedure before PST was not applied anymore in period B because of its decreasing use and overwhelming information indicating that the surgical procedure increased morbidity, and that radiological evaluation and then, if necessary, biopsy yielded comparable results (2,3).

In this way, the number of intraoperative frozen examinations decreased. The reduction of frozen procedures to be studied in fresh material with a high risk of contamination and working with cytological samples fixed with 70% alcohol also reduced the risk exposed by pathology department workers.

With the pandemic, interruptions, and disruptions were seen in cancer screening programs worldwide, and the number of newly diagnosed breast cancer patients decreased compared to the period A. Corsi et al. (1) reported an approximately 32% decrease in the rates of newly diagnosed breast cancers in their breast cancer clinics "a non-COVID center" compared to the same period as the previous year (93 vs. 63).

In another study conducted in France, a decrease of 43.5% was reported during the pandemic (5). In our study, a 22% decrease was noted between periods A and B. The first 2 months were conducted in the studies conducted in Italy and France. The pandemic started earlier in Italy and France and led to serious disruptions in health services. Our country was relatively more prepared against a pandemic. In these two studies, authors reported that elective surgery was not performed in the first month, while in our hospital, cancer surgery continued, albeit to a limited extent.

Curigliano et al. (6) listed suggestions on how breast cancer treatment should be performed in this process. Accordingly, there are 4 categories in health services; emergency, high, medium, and low priority; breast cancer is in the high and medium-risk group. The authors emphasize that cancer patients should be treated in clean hospitals or departments with meticulously careful use of resources. In our hospital, a vertical structuring plan was applied during the COVID process, and the departments allocated to COVID patients in our hospital, which consists of five blocks, and the entrance and exit of other departments and the work schedules of the employees were arranged separately (4).

Similar recommendations were made to surgeons in the guide written by Curigliano et al. (6) and in the Turkish consensus report (3). These recommendations concern basic patients whose NAC was completed, and emphasize performing emergency-priority surgeries, but postponing surgeries to be performed for benign conditions, esthetic indications, oncoplastic procedures larger than level 1, and reconstruction plans. We followed these rules. While prophylactic Mx and reconstruction were performed in 6 patients in period A, none of the patients included in this study in period B underwent these surgeries.

The study by Rocco et al. (7), it was aimed to evaluate how breast surgeons adapt their surgical activities due to the rapid spread of COVID-19 around the world. A panel of 12 breast surgeons from the most affected areas of the world held a virtual meeting on April 7, 2020, and a web-based questionnaire was designed to assess changes in surgical practices to be carried out by breast surgeons from various countries. The virtual meeting showed that different countries and regions are experiencing different stages of the pandemic. Surgery was given priority to patients with aggressive disease who were not candidates for PST, patients with the progressive disease under neoadjuvant systemic therapy, and those who completed neoadjuvant therapy.

Although 100 breast surgeons who participated in this survey favored traditional standards for treating potentially fatal diseases such as breast cancer, it was concluded that as the situation worsened, alternative strategies should be adopted. In a consensus study conducted in our country, it was observed that surgeons participating from different centers were not willing to postpone surgery in the first round of voting (3).

Physicians dealing with breast cancer in China, the origin of the COVID-19 pandemic, emphasized that the timing of the surgery should be decided according to factors such as the severity of the pandemic and the allocation of medical resources in their study, where they sought an answer to the question of how to manage the treatment in this period. For this purpose, by presenting a short algorithm, surgical candidates who received the diagnosed with T1N0 tumors were allocated for surgery, and patients with breast cancers at T2 and N1 and above stages were allocated as PST candidates (8).

Sheng et al. (9), on the other hand, have stated that cancer treatment has changed during the COVID-19 pandemic, and doctors must carefully weigh the risks and benefits of administering immunosuppressive therapy during the pandemic. They have emphasized that tumor biology should guide breast cancer treatment planning, and genomic tumor profiling should be used more often with a resultant increase in the use of PST. Our practice and data also support this view.

NET, which was not preferred previously as a primary treatment, found supporters in this period. According to a survey by Park et al. (10), conducted with 114 physicians from 29 states in the USA, including 42 (37%) medical oncologists, 14 (12%) radiation oncologists, and 58 (51%) surgeons, most of these participants were "rarely" using NET for ER. + Breast cancer before the COVID-19 pandemic. In this process, 54% of them recommended using NET until surgery, while 46% suggested that they could delay the surgery for 2 months without NET. The preferred NET regimen was tamoxifen for premenopausal and an aromatase inhibitor for postmenopausal women. In this study, it was also argued that NET also reduces the rates of axillary surgery and that axillary surgery may not be required after the NET, which changes the clinical scenario of a patient with micrometastasis in the sentinel lymph node as the duration of drug administration is prolonged (10).

In a study presented at the 2020 San Antonio Breast Cancer Virtual Symposium, it was reported that rates of interest in and acceptance of NET by both physicians and patients during the pandemic period increased compared to the previous period, and NETwas started in 36 patients in this small series of 45 patients to act as a bridge until surgery (11). In the series we presented, we found that while NET was not performed as PST in any patient in period A, NET was administered to 10 patients (8.6%) in period B. Although we do not have a prediction about the effect of NET on axillary surgery, this issue is worth examining in a larger series.

The use of radiotherapy as a PST option during the pandemic period has been discussed both in our country and in the world, but any different application specific to this period has not been made.

As for the effect on the COVID-19 pandemic in the choice of technique in patients who can undergo surgery, a surgical technique can be chosen in a way that does not prolong the duration of surgery and hospitalization at times and places where surgery can be performed. In a study in which the results of 64 breast centers in England were compiled, it was reported that 62% of 957 patients who underwent surgery during this period underwent BCS and 37% had a Mx (2).

To summarize, in this study 108 (30.33%) patients received PST in period A and 116 (41.3%) patients in period B. Despite a 22% decrease in the total number of cases between periods A and B, the increase in the rate of PST was found to be significant. Before PST, SLNB was performed in period A, albeit in decreasing numbers, it was not performed in period B.

While NET was planned as the only treatment option for patients who could not receive anesthesia in period A, it was applied as the first treatment choice in period B and to save time until surgery.

Study Limitations

In our opinion, the weakness of this study was that it could not be determined whether there was a delay in the initial diagnosis. Our hospital is not a screening center, only registered women and women who apply themselves are included in the screening group for breast cancer. Other studies conducted during the epidemic will be useful to learn the effects in terms of early diagnosis.

CONCLUSION

During the ongoing COVID-19 pandemic, the breast cancer council of our hospital is still carrying on and makes its decisions, as always, with the "tailoring management" in addition to considering the working schedules of the clinics. Breast surgery for benign conditions, prophylactic and reconstructive surgery were not performed. Prominent differences were observed between periods A and B about PST, where is planned more

frequently when surgery is limited, including NET as PST, probably due to this, BCS was applied more.

The approach to the axilla has changed significantly. In patients with breast cancer, the axillary staging is currently performed only by radiological and cytological examinations in our clinic.

Ethics

Ethics Committee Approval: The study was approved by the Ethics Committee of University of Health Sciences Turkey, Prof. Dr. Cemil Tascioglu City Hospital, with the decision dated 07.01.2021-271.

Informed Consent: Obtained from all patients and available in their files.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: S.G., A.M.P., B.D.Y., P.Ö.Y., M.M.A., A.A., Concept: S.G., B.D.Y., Design: S.G., B.D.Y., Data Collection or Processing: S.G., A.M.P., P.Ö.Y., A.A., Analysis or Interpretation: S.G., A.M.P., P.Ö.Y., M.M.A., A.A., Literature Search: S.G., A.M.P., Writing: S.G., A.M.P.

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ORIGINAL ARTICLE

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Congenitally Short Pedicles; as an Underlying Cause of Lumbar Spinal Stenosis

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Abstract

Objective: A major element of developmental anatomical abnormalities associated with congenital lumbar spinal stenosis is congenitally shortened pedicles. We analyzed the role of congenitally shortened pedicles in LSS by quantitatively analyzing the antero-posterior midsagittal diameter of the spinal canal and the pedicle lengths on lumbar magnetic resonance imaging (MRI).

Methods: The lumbar MRI database of our hospital was retrospectively searched for terms' lumbar spinal stenosis, spinal stenosis and stenosis' in patients older than 18 years between January 2020 and January 2021. Midsagittal AP diameters of the lumbar spinal canal were measured at L2, L3, L4, and L5 levels on sagittal T2w images. Patients having at least one level of AP diameter equal to or less than 12 mm were considered as having LSS and included in the study group. After exclusions, 19 patients met the criteria and additional measurements were made for the pedicle lenght. They were compared with 76 control subjects.

Results: The rate of AP diameter being 12 mm or less at all levels was statistically significantly higher in the LSS group. The mean length of pedicles at the L2, L3, L4 and L5 levels in the LSS group was significantly shorter. The cut-off value for the pedicle length at the L2 level in the diagnosis of LSS was ≤8.7 mm. This was ≤9.7 for L3 level, ≤9.5 for L4 level and ≤10.1 for L5 level.

Conclusion: Decrease in pedicle length is proportionally associated with reduced diameter of the spinal canal resulting in CCS. Furthermore, the congenitally shortened pedicles give the canal a flattened appearance. The other-discriminating feature is that narrowing of the spinal canal is usually distributed throughout the lumbar spine. We found greater threshold values for shortened pedicles associated with decreased spinal canal AP diameter than found in other studies in the literature. In conclusion, the congenitally shortened pedicle plays an important role by increasing the likelihood of symptomatic presentations in LSS patients.

Keywords: Short pedicle, lumbar spinal stenosis, congenital stenosis

INTRODUCTION

Spinal stenosis is characterized by the narrowing of the spaces for the neural and vascular elements in the spinal canal to the point where it can exert pressure on the nerves running through the spine. It is subdivided based the relevant anatomical regions into central canal stenosis (CCS), lateral (recess) stenosis (LS) and foraminal stenosis (FS). The most commonly affected region is the lumbar spine followed by the cervical spine (1). CCS in the lumbar spine can cause impingement on the nerves of the cauda equina or on the thecal sac itself, resulting in debilitating buttock or lower extremity pain, with or without accompanying low back pain. Symptoms of lumbar radiculopathy may also be present when the lateral recess and neural foramen are stenosed. Lumbar spinal stenosis (LSS) is the most common cause for lumbar spinal surgery in elderly patients older than 65 years (2,3). However, because of the lack of universally accepted radiological diagnostic criteria, the exact epidemiology is difficult to determine. Nonetheless, radiological examinations are the key non-invasive tests for the diagnosis (2,4). Magnetic resonance imaging (MRI) is the most commonly preferred modality of choice with its excellent soft tissue resolution that demonstrates

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the thecal sac and the neural elements in the neuroforamina. On lumbar MRIs, absent fluid around the cauda equine and osseous/soft tissue hypertrophic degenerative changes, including degenerative disc disease, facet joint hypertrophy and ligamentum flavum hypertrophy are qualitative indicators of CCS. These degenerative changes are prominent imaging findings responsible for the acquired, degenerative form of LSS (DLSS). However, the presence of developmental anatomical abnormalities of the spinal canal can increase the likelihood of LSS with minimal, less severe degenerative changes. This type of LSS, which is less common than its degenerative form, is named as congenital LSS (CLSS) (5,6). Therefore, patients with DLSS may have a preexisting developmentally narrowed canal when they are treated at later ages (7,8). A major element of these developmental anatomical abnormalities is congenitally shortened pedicles (9). In this study, we analyzed the role of congenitally shortened pedicles in LSS by quantitatively analyzing the antero-posterior (AP) midsagittal diameter of the spinal canal and the pedicle lengths on lumbar MRIs.

METHODS

Study Population

The lumbar MRI database of our hospital was retrospectively searched for the terms' LSS, spinal stenosis and stenosis' in the reports of adult patients (older than 18 years) in one year period between January 2020 and January 2021, until a study group of 19 patients and a control group of 76 patients were formed. Patients with severe degenerative changes, lumbar spondylolisthesis, history of trauma, infection, and tumor interfering with the central canal diameter, and patients with achondroplasia and lumbar spinal surgery for any reason were not included. Ethics approval was obtained from the University of Health Sciences Turkey, Prof. Dr. Cemil Tascioglu City Hospital Local Institutional Review Board (no: E-48670771-514.99, date: 18.04.2022). Two radiologists with more than 20 years (H.Ö.) and 7 (B.E.) years of radiology experience, respectively, evaluated the examinations in consensus. All were examined on 1.5 T or 3.0 T MR scanners and included sagittal T1w and T2w images, and axial T2w images of the lumbar spine.

Midsagittal AP diameters of the lumbar spinal canal were measured at the L2, L3, L4, and L5 levels on sagittal T2w images. Patients having at least one level of AP diameter equal to or less than 12 mm were considered as having LSS and included in the study group. Among the study patients, the values smaller than 10 mm were accepted as absolute LSS and the values between 10 and 12 were accepted as relative LSS. Nineteen patients met the criteria in whom additional measurements were made for the pedicle length on the sagittal T2w images. They were compared with 76 control subjects between the ages of 20-40 with normal AP diameters (>12 mm) of the lumbar spine at all four levels.

Statistical Analysis

While evaluating the findings obtained in the study, IBM SPSS Statistics 22 program was used for statistical analysis. The conformity of the parameters to the normal distribution was evaluated with the Shapiro-Wilks test. While evaluating the study data, in addition to descriptive statistical methods (mean, standard deviation, frequency), Student's t-test was used for comparisons of normally distributed parameters between two groups, and Mann-Whitney U test was used for comparisons between groups of parameters that did not show normal distribution. Continuity (Yates) correction and Fisher's Exact test were used to compare qualitative data. The most appropriate cut-off point was chosen on the basis of the ROC curve analysis. Statistical significance was defined at $p<0.05$.

RESULTS

The study was conducted with 95 subjects, 53 (55.8%) men and 42 (44.2%) women, whose ages ranged from 20 to 79, with a mean age of 37.19±13.95 years. The subjects were evaluated under two groups as "LSS" (n=19) and "control" (n=76). The mean age of the LSS group was statistically significantly higher than that of the control group ($p=0.000$; $p<0.05$). There was no statistically significant difference between the groups in terms of gender distribution ($p>0.05$) (Table 1).

The mean AP diameter at the L2 level of the control group was 20.04±2.74, and 12.93±2.03 in the LSS group. The rate of AP diameter being 12 mm or less at the L2 level in the LSS group (31.6%) was statistically significantly higher than that in the control group (0%) ($p=0.000$; $p<0.05$). The rate of having AP diameter of 10 mm or less at the L2 level was higher than in the LSS group (5.3%) than in the control group (0%) but, this was not statistically significant ($p>0.05$). The mean AP diameter at the L3 level of the control group was 18.61±2.93 mm and it was

Table 1. Evaluation of groups in terms of age and gender

	LSS	Control	p
Age mean ± SD (median)	58.74±16.01 (62)	31.80±5.96 (35)	[1]0.000*
Gender n (%)			
Male	10 (52.6%)	43 (56.6%)	[2]0.959
Female	9 (47.4%)	33 (43.4%)	

[1]Mann-Whitney U test, [2]Continuity (Yates) correction, *p<0.05, SD: Standard deviation, LSS: Lumbar spinal stenosis

11.48±2.10 mm in the LSS group. The rate of having AP diameter of 12 or less at L3 level in the LSS group (63.2%) was statistically significantly higher than that in the control group (0%) (p=0.000; p<0.05). The rate of having AP diameter of 10 mm or less at the L3 level in the LSS group (31.6%) was statistically significantly higher than that in the control group (0%) (p=0.000; p<0.05). The mean AP diameter at the L4 level of the control group was 17.62±2.48, and 11.09±2.04 in the LSS group. The rate of having AP diameter of 12 mm or less at the L4 level in the LSS group (57.9%) was statistically significantly higher than the control group (0%) (p=0.000; p<0.05). The rate of having AP diameter of 10 mm or less at the L4 level in the LSS group (47.4%) was statistically significantly higher than the control group (0%) (p=0.000; p<0.05). The mean AP diameter at the L5 level of the control group was 17.10±2.48, and 12.51±2.33 for the LSS group. The rate of having AP diameter of 12 mm or less at the L5 level in the LSS group (36.8%) was statistically significantly higher than the control group (2.6%) (p=0.000; p<0.05). The AP diameter in these 2 patients was 11.99 mm. The rate of having AP diameter of 10 mm or less at the L5 level in the LSS group (21.1%) was statistically significantly higher than that in the control group (0%) (p=0.000; p<0.05) (Table 2).

The mean length of pedicles at the L2, L3, L4, and L5 levels of the cases in the LSS group were statistically significantly shorter than that in the control group (p=0.000; p<0.05) (Table 3). In the diagnosis of LSS, the ROC curve was drawn for the pedicle length at the L2 level (Figure 1). The area under the curve was 0.961 and its standard error was 0.01. The area under the ROC curve was found to be significantly higher than 0.5 (p=0.001; p<0.05). The cut-off point determined for the pedicle length at the L2 level in the diagnosis of LSS was ≤8.7 mm. The sensitivity of this value was 89.5% and the specificity was 92.1%. The rate of having pedicle length of 8.7 mm or less at the L2 level in the LSS group (89.5%) was statistically significantly higher than that in the control group (7.9%) (p=0.000; p<0.05) In the diagnosis of LSS, the ROC curve was drawn for the pedicle length at the L3 level (Figure 2). The area under the curve was 0.917 and its standard error was 0.02. The area under the ROC curve was found to be significantly higher than 0.5 (p=0.001; p<0.05). The cut-off point determined for the pedicle length at the L3 level in the diagnosis of LSS was ≤9.7 mm. The sensitivity of this value was 94.7% and the specificity was 77%. The rate of having pedicle length of 9.7 mm or less at the L3 level in the LSS group (94.7%) was statistically significantly higher than that in the control group (23%) (p=0.000; p<0.05). In the diagnosis of LSS, the ROC curve was drawn for the pedicle length at the L4 level (Figure 3). The area under the curve was 0.919 and its standard error was 0.02. The area under the ROC curve was found to be significantly higher than 0.5 (p=0.001; p<0.05). The cut-off point determined for the pedicle length at the L4 level in the diagnosis of LSS was ≤9.5 mm. The sensitivity of this value was 84.2% and the specificity

Table 2. Evaluation of groups in terms of AP diameter measurements being shorter than 10 and 12 mm

		Control (n=76)	LSS (n=19)	Total (n=95)	
Spinal AP diameter		n (%)	n (%)	n (%)	p
L2	<12	0 (0%)	6 (31.6%)	6 (6.3%)	0.000*
L2	<10	0 (0%)	1 (5.3%)	1 (1.1%)	0.200
L3	<12	0 (0%)	12 (63.2%)	12 (12.6%)	0.000*
L3	<10	0 (0%)	6 (31.6%)	6 (6.3%)	0.000*
L4	<12	0 (0%)	11 (57.9%)	11 (11.6%)	0.000*
L4	<10	0 (0%)	9 (47.4%)	9 (9.5%)	0.000*
L5	<12	2 (2.6%)	7 (36.8%)	9 (9.5%)	0.000*
L5	<10	0 (0%)	4 (21.1%)	4 (4.2%)	0.000*

Fisher's Exact test, *p<0.05, LSS: Lumbar spinal stenosis, AP: Antero-posterior

Table 3. Evaluation of groups in terms of pedicle length measurements

	LSS	Control	
Pedicle	Mean ± SD	Mean ± SD	p
L2	7.64±0.92	10.14±1.27	0.000*
L3	8.22±1.05	10.64±1.55	0.000*
L4	8.52±1.15	11.09±1.56	0.000*
L5	8.82±1.41	11.92±1.86	0.000*

Student t-test, *p<0.05, LSS: Lumbar spinal stenosis, SD: Standard deviation

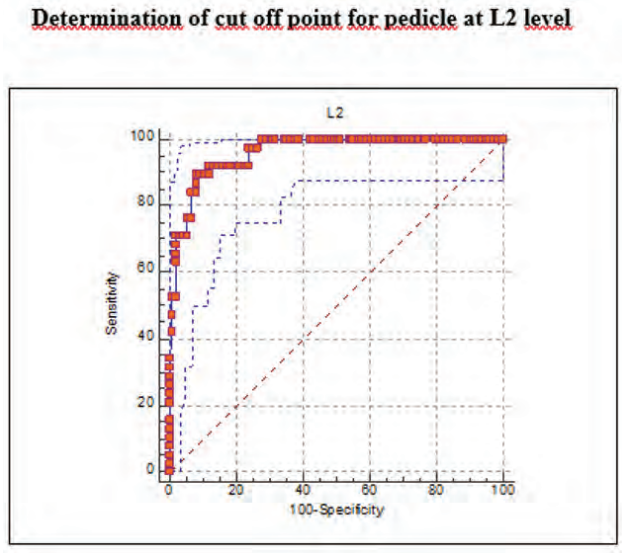

Figure 1. ROC curve for the pedicle length at L2 level in the diagnosis of LSS
LSS: Lumbar spinal stenosis, ROC: Receiver operating characteristic

was 87.5%. The rate of having pedicle length of 9.5 mm or less at the L4 level in the LSS group (84.2%) was statistically significantly higher than that in the control group (12.5%) (p=0.000; p<0.05). In the diagnosis of LSS, the ROC curve was drawn for the pedicle length at the L5 level (Figure 4). The area under the curve was 0.921 and its standard error was 0.02. The area under the ROC curve was found to be significantly higher than 0.5 (p=0.001; p<0.05). The cut-off point determined for the pedicle level at the L5 level in the diagnosis of LSS was ≤10.1 mm (Table 4). The sensitivity of this value was 86.8% and the specificity was 82.9%. The rate of having pedicle length of 10.1 mm or less at the L5 level in the LSS group (86.8%) was statistically significantly higher than the control group (17.1%) (p=0.000; p<0.05).

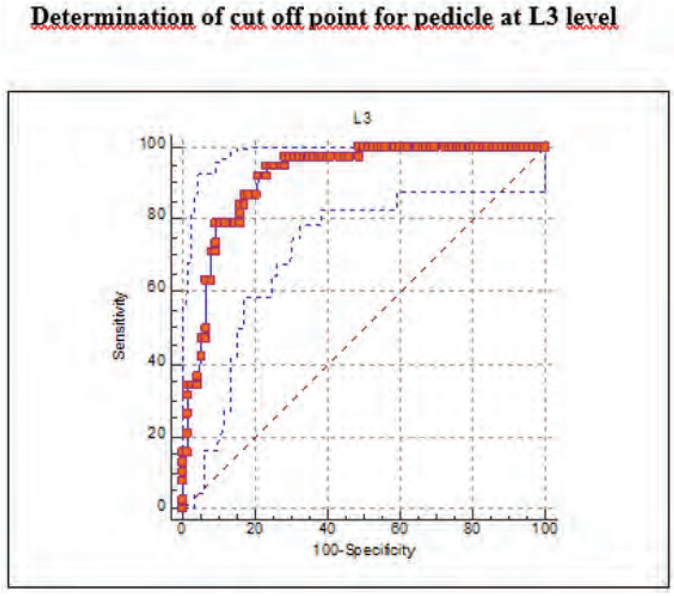

Figure 2. ROC curve for the pedicle length at the L3 level in the diagnosis of LSS
LSS: Lumbar spinal stenosis, ROC: Receiver operating characteristic

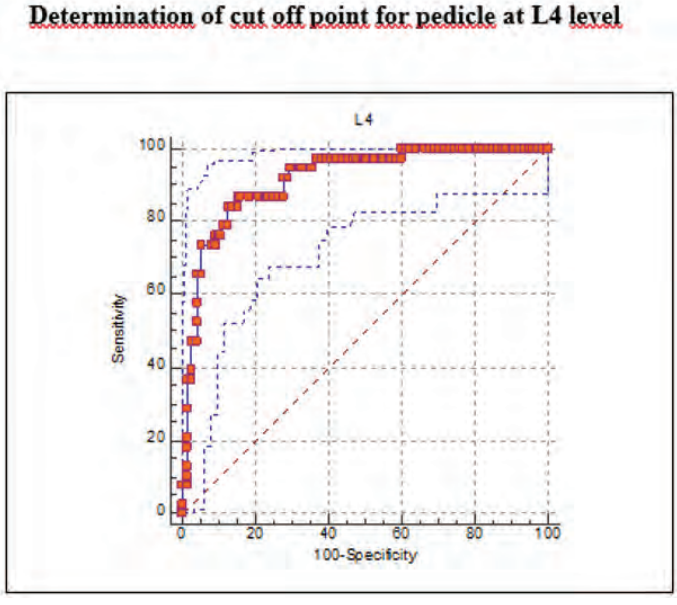

Figure 3. ROC curve for the pedicle length at the L4 level in the diagnosis of LSS
LSS: Lumbar spinal stenosis, ROC: Receiver operating characteristic

DISCUSSION

LSS is a common cause of lumbar spinal surgery in patients with leg and low back pain. However, there is a lack of universally accepted radiological diagnostic criteria for LSS due to significant variability regarding the relationship between the imaging findings and the clinical symptoms. Fourteen different semiquantitative or qualitative radiologic criteria that were identified in a systematic review [according to the involved anatomic spaces including criteria for CCS, lateral (recess) stenosis, and FS] showed remarkable variability based on the subjectivity of the evaluation of the interpreter (10). Quantitative measurements of LSS also showed great variability among the results of different studies in the literature. AP and transverse diameters of the spinal canal with regard to its shape were reported as a reliable indicator for CCS (11,12). In the Delphi survey, the highest rated quantitative criterion for CCS was the AP diameter of the osseous canal (13). Epstein et al. (14) found the lower limit of normal for a sagittal canal diameter of approximately 15 mm. A mean AP canal diameter of 14.1 mm was identified by Schonstrom et al. (15) on computed tomography scans. Sortland et al. (16) determined that 10.5 mm in extension was the lower value of the normal by describing

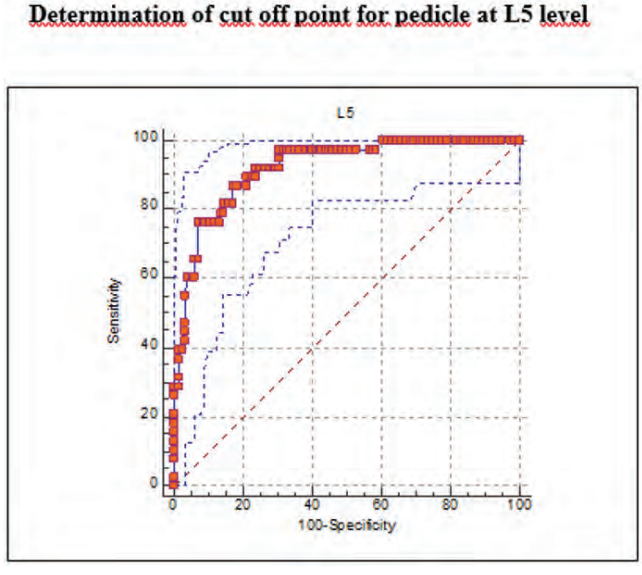

Figure 4. ROC curve for the pedicle length at the L5 level in the diagnosis of LSS
LSS: Lumbar spinal stenosis, ROC: Receiver operating characteristic

improved myelographic techniques with flexion-extension views. In a systematic review which identified 10 different quantitative parameters to measure LSS, the AP mid-sagittal diameter <10 mm was found to be one of the most frequently reported criteria (17). Verbiest divided LSS into two subgroups as absolute stenosis having an AP diameter <10 mm and relative stenosis as AP diameter between 10 and 12 mm (18,19). We also measured the midsagittal AP diameter in lumbar MRI to define CCS, and we accepted a central canal diameter of <10 mm as absolute LSS and diameters between 10 and 12 mm as relative LSS (Figure 5). It is well known that evidence of lumbar spondylosis (LS) usually accompanies LSS in varying degrees. However, in congenitally stenotic patients, the spinal canal is primarily narrowed by an anatomical abnormalities that increase the likelihood of neural compression with fewer, less severe degenerative spondylotic changes. These patients are at a disadvantage because a small disc bulge may convert them from asymptomatic to severely symptomatic LSS, which is probably present at earlier ages than the degenerative form. The most common cause of the congenital narrowing of the spinal canal is short pedicles. The decrease in pedicle length is proportionally associated with reduced diameter and cross-sectional area of the spinal canal resulting in CCS, which is the pertinent feature in CLSS due to short pedicles. Furthermore, there are additional unique features of the spinal canal in these congenitally stenotic patients with short pedicles that differentiate them from their primarily degenerative counterparts. First, the congenitally shortened pedicles give the canal a flattened (compressed) appearance compared to the more round shape of the spinal canal in healthy patients (Figure 6). This is referred to as trefoil-shaped bony spinal canal, particularly when the lateral recesses are also stenosed (12,20). The other-discriminating feature of CLSS is that narrowing of the spinal canal is usually distributed throughout the lumbar spine as opposed to the DLSS in which the stenosis is often limited to a single level, reported much more frequently at L4-5 level (Figure 7) (19,21). In their comparative study of 15 patients with CLSS, Singh et al. (9) reported a shorter pedicle length with a critical cutoff value of 6.5 mm and proportionally decreased cross-sectional area of the spinal

Table 4. Evaluation of the pedicle measurements of the groups in terms of the rate of being shorter than the cut-off values

		Control (n=152)	LSS (n=38)	Total (n=190)	
Pedicle		**n (%)**	**n (%)**	**n (%)**	**p**
L2	≤8.7	12 (7.9%)	34 (89.5%)	46 (24.2%)	0.000*
L3	≤9.7	35 (23%)	36 (94.7%)	71 (37.4%)	0.000*
L4	≤9.5	19 (12.5%)	32 (84.2%)	51 (26.8%)	0.000*
L5	≤10.1	26 (17.1%)	33 (86.8%)	59 (31.1%)	0.000*

Continuity (Yates) correction, *p<0.05, LSS: Lumbar spinal stenosis

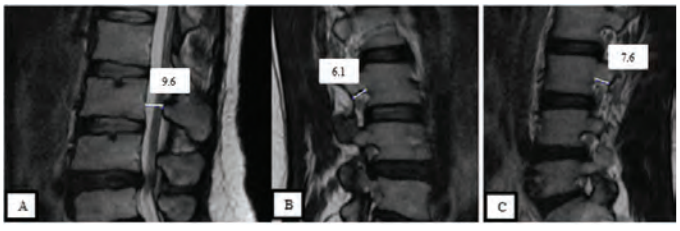

Figure 5. A-C) Sagittal T2w MR images of a 32-year-old female demonstrating the decreased AP diameter of the lumbar spinal canal at the L3 level (A) and associated short pedicle lengths in both the right (B) and the left (C) side
MR: Magnetic resonance, AP: Antero-posterior

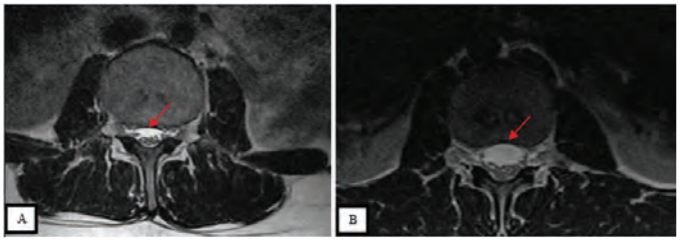

Figure 6. A) Axial lumbar T2w MR image of a 32-year-old female with short pedicles shows a compressed appearance of the lumbar spinal canal (A, arrow) B) axial lumbar T2w MR image of a 22-year-old female with normal pedicle lengths shows a more rounded (non-compressed) appearance of the lumbar spinal canal (B, arrow)
MR: Magnetic resonance

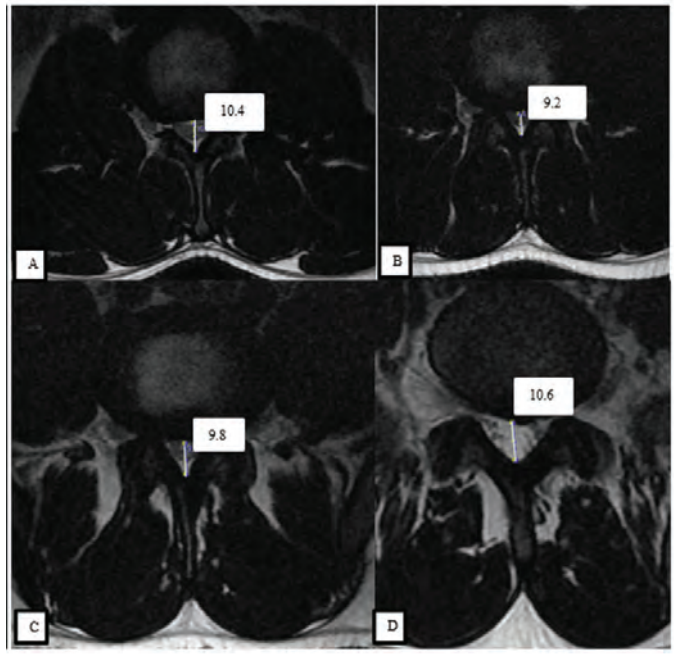

Figure 7. Axial T2w MR images of a 20-year-old male with short pedicles showing the long segment of narrowing of the central spinal canal at all four levels; L2-L3 (A), L3-L4 (B), L4-L5 (C) and L5-S1 (D). The associated compressed appearance of the central spinal canal is noted
MR: Magnetic resonance

canal in congenitally stenotic patients in contrast to the control group subjects with pedicle lengths closer to 9 mm. Although, the preoperative MRI and plain radiographs of the congenitally stenotic patients were evaluated, the major limitation of this study was that all congenitally stenotic patients in this study were treated surgically, i.e. these patients aforementioned in this study represent severely symptomatic patients. However, congenital stenosis does not correspond only to the extreme end of the narrowing requiring surgical treatment, but includes a spectrum of changes with increasing clinical severity. We found greater threshold values for shortened pedicles associated with decreased spinal canal AP diameter than found in this study. We think that this is because our study group consisted of patients with lumbar spinal canal diameter less than 12 mm, who were considered stenotic, but did not require surgical management because to the lack of significant degenerative changes made them not significantly symptomatic. However, less severe degenerative hypertrophic changes may convert them into severely symptomatic states than expected.

Our study stands out with its following features; first, we included congenitally stenotic patients who were not surgically treated to obtain the cut values associated with decreased midsagittal AP diameter at the lumbar spine. However, as one of the shortcomings of this study, we did not compare patients with symptomatic CLSS to asymptomatic CLSS to determine the phenotypic differences that may result in/or correlate with the symptoms. Additionally, we did immeasure the transverse diameter of the spinal canal in our study. In this regard, Singh et al. (9) found no notable difference in the transverse diameter of the canal and concluded that the reduction in cross-sectional area is mainly due to the reduced AP diameter of the lumbar spinal canal. Another shortcoming is that we did immeasure the diameters of the lumbar vertebral bodies to evaluate if the congenitally shortened pedicles are also associated with smaller vertebral bodies. We believe that our results will contribute to the understanding of CLSS and conducting further studies regarding the limitations of our study.

CONCLUSION

LSS is an important cause of low back and leg pain. In patients suffering from LSS, the congenitally shortened pedicle plays an important role by increasing the likelihood of symptomatic presentations in less severe degenerative changes compared to with normal individuals. Additionally, since it is more often multilevel pathology defining this subgroup of stenotic patients is also important in the management approaches.

Ethics

Ethics Committee Approval: Ethics approval was obtained from the University of Health Sciences Turkey, Prof. Dr. Cemil Tascioglu City Hospital Local Institutional Review Board (no: E-48670771-514.99, date: 18.04.2022).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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ORIGINAL ARTICLE

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Clinical Issues in Tibia Shaft Fractures Performed Fasciotomy: A 4 Year Follow-up Study

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Abstract

Objective: The only known effective treatment for acute compartment syndrome is fasciotomy. Our aim is to present a long-term analysis of the clinical problems encountered by patients who underwent fasciotomy after suspicion of acute compartment syndrome with a tibial shaft fracture.

Methods: Thirty-three patients who were treated between 2013 and 2017, with at least 4 years of follow-up, and who remained after the exclusion criteria, were included in the study.

The total number of operations, total hospitalization time, and return to work time, second and 4th year visual analog scale (VAS) score in the crus area for pain assessment, second and 4th year American Orthopedic Foot & Ankle Association scala (AOFAS) score for ankle functionality, second and 4th year knee injury and osteoarthritis outcome score, short version (KOOS-PS) score for knee functionality parameters were obtained from the medical records of the patients. Information was added on whether the patients had complaints about the appearance of the fasciotomy area and whether they had changed their clothes for this situation.

Results: The mean time to return to work of the patients was 9.0±2.7 months. A significant difference was observed between the VAS and AOFAS scores of the patients in the 2nd year compared to the fourth year (<0.001, <0.001). Postoperative 4th year VAS, AOFAS and KOOS-PS scores of patients who developed pseudoarthrosis did not differ significantly from those of other patients (p=0.41, p=0.51, p=0.62).

Conclusion: The coexistence of tibial shaft fracture and fasciotomy can clinical cause problems affecting the social life of patients. It appears that clinical and functional scores are affected more significantly in the short term. We believe that patients should be informed about these issues at the beginning of treatment.

Keywords: Fasciotomy, tibia, fracture, acute compartment syndrome

INTRODUCTION

Acute compartment syndrome is a serious health issue that can result in severe morbidity if treatment is delayed (1). Fasciotomy is the only known effective treatment method for acute compartment syndrome (2). Clinically, acute compartment syndrome is most commonly associated with tibial shaft fractures and the coexistence of these two appears to be associated with poor clinical outcomes (3).

There are few studies in the literature examining the clinical long-term follow-up of these patients following fasciotomy treatment (3,4). Our hypothesis is that although the clinical problems of these patients are more evident in the early period, these problems are less effective in the long term. Our aim is to present a long-term analysis of the clinical problems encountered by patients who underwent fasciotomy after suspicion of acute compartment syndrome with a tibial shaft fracture.

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METHODS

After receiving Ethics Committee approval from the University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital (number: E-48670771-514.10), 76 fasciotomy performed tibia fractures between 2013 and 2017 were retrospectively analyzed. Inclusion criteria included being over the age 18, having at least four years of follow-up, having no additional injuries in the same extremity, having no neurological injuries and not having acute bone loss. Twelve patients without adequate medical records, 3 patients who had Gustillo-Andersen type 3c fractures, 1 patient who was under the age of 18, one patient who had peroneal nerve injury, one patient with acute death, and 25 patients without a tibial shaft fracture were excluded. The remaining 33 patients were included in the study.

The same surgical team operated on all the patients (T.O.B., M.A., A.C.T., A.Y.). The same team-decided fasciotomy in all the patients due to a suspicion of acute compartment syndrome. Pain, swelling, paresthesia, presence of pain with passive stretch were used as suspicious findings (5). All patients had a single lateral incision 4 compartment fasciotomy (6). The Tasarım Medical TF-ERS Rail Fixator® was applied to all patients using 6 mm Schanz nails from the medial side of the tibia to parallel to the posterior surface of the tibia, with at least three Schanz placed proximal and distal to the fracture line. The treatment of the fracture with this fixator was planned and it was applied to bridge the entire tibia (7).

All patients received traditional wet-to-dry dressings after fasciotomy (8), as well as the first generation cephalosporin and aminoglycoside prophylaxis. Debridement was performed if necessary at the 48th hour examination after clinical follow-up. The debridements were performed in the operating room under general anesthesia. If there was no microorganism growth in the culture taken between 5 and 7 days and the skin examination was appropriate, the wound was closed with split-thickness skin grafting (9). When there was microorganism growth in the culture, the closure operation was postponed and appropriate antibiotic therapy was started. Fasciotomy closure operations were performed by the plastic surgeons of our hospital.

Union times were calculated from the control roentgenograms of the patients. Delayed union was defined as the failure of fracture union by 20 weeks and nonunion was defined as a lack of union at 36 weeks and failure of the progression of fracture callus over a 6 week (3). Patients who nonunion, required additional surgical procedures. Deformity analyses were performed using the tibia anatomical axis from the patients' radiographs after union for deformity measurement. The shortness of more than 10 mm, a coronal angulation of more than 5 degrees, and a sagittal angulation of more than 10 degrees were deemed unacceptable and classified as deformity (10). Three senior orthopedic surgeons who did not perform the surgery evaluated the radiographs and their joint decisions were used as the basis. Preoperative and postoperative radiographic measurements were performed using the imaging software named INFINITT PACS (Picture Archiving and Communication Systems) version 3.0.11.4 (BN13)® used in our hospital.

Patients started isometric exercises and exercises for joint range of motion on the 1st postoperative day and continued isometric exercises until their fasciotomy was closed. Following the closure of the fasciotomy, isokinetic and muscle-strengthening exercises were initiated and continued until the return of the work.

Age, gender, fracture type, type of injury, soft tissue injury according to Gustillo-Andersen classification, infection development, causative microorganism if infection developed, the total number of operations, total hospitalization time, and return to work time, visual analog scale (VAS) score in the crus area for pain assessment, 2nd year American Orthopedic Foot & Ankle Association scala (AOFAS) score for ankle functionality, 2nd year knee injury and osteoarthritis outcome score, short version (KOOS-PS) score for knee functionality parameters were obtained from the medical records the patients. As time to return to work; It was determined as being able to start the profession before the trauma in people with a profession, and being able to do their daily work fully in people without a profession. The patients' most recent (minimum 48 months) VAS, AOFAS, and KOOS-PS scores were obtained by calling their registered phones and interviewing them. They were asked again during the interview if they had any complaints about the appearance of the fasciotomy area and if they had changed their any clothing modification due to this situation.

Statistical Analysis

The SPSS Windows version 24.0 package program was used for statistical analysis. Mean ± standard deviation was given for numerical variables as descriptive statistics and number and percentage values were given for categorical variables. The compliance of the data to a normal distribution was tested with the Shapiro Wilk test. Student's t-test was performed for the normally distributed features in comparison of numerical data in 2 independent groups while Mann-Whitney U test was performed for non-normally distributed features. The relationship of two independent variables at the categorical measurement level with other was tested using the chi-square test and Fisher's Exact test. A p value of <0.05 was considered statistically significant.

RESULTS

Of the patients, 30 (90.1%) were male and 3 (9.1%) were female. The mean age was 29.3±8.5. The mean duration of follow-up was 59.3±11.8 months.

According to the Arbeitsgemeinschaft für Osteosynthesefragen classification, the fracture types of the patients were A2 5 (15.1%), A3 10 (30.3%), B1 7 (21.2%), B2 6 (18.1%), B3 1 (3%), C2 2 (6.06%), C3 2 (6.06%). Eight (24.2%) of the patients suffered additional injuries, without the same extremity. Twenty-eight (84.8%) of the patients were involved in traffic accidents, two (6%) had fallen from a height, two (6%) had a gunshot injury, and one (3%) had crush-type injuries.

There were 24 (72.7%) closed fractures and 9 (27.3%) open fractures among the fractures. According to the Gustillo Andersen classification, 5 (55.5%) of the fractures were type 1, 1 (11.1%) were type 2, and 3 (33.3%) were type 3a. It was observed that patients with open fractures required statistically significantly higher rates of infection and debridement than patients with closed fractures ($p<0.001$, $p<0.001$). However, the rates of pseudoarthrosis in patients with open fractures were not significantly different from those in the other patients ($p=0.104$) and there was no significant difference in clinical VAS, AOFAS and KOOS-PS scores at the end of the fourth year ($p=0.41$, $p=0.51$, $p=0.62$).

The patients' average hospital stay after the first operation was 20.3±6.1 days, and the average total hospitalization time for fractures was 24.3±10.1 days. Debridement was required in 10 (30.3%) of the patients, and the duration of hospital stay (31.7±8.5) was significantly longer in these patients ($p<0.001$). The patients had undergone an average of 4.05±1.5 operations because of this fracture. In patients whose fasciotomy wounds required debridement before closure, the total number of operations was 6±1.05 ($p<0.001$).

The patients' average union time was 7.03±2.3 months. While 12 (36.3%) patients had delayed union, 10 (30.3%) patients required a second operation for nonunion, 6 (60%) of these patients were treated with tibial intramedullary nailing, and 4 (40%) patients were treated with Ilizarov type circular external fixator applications. The duration of hospitalization, return to work and the number of operations they underwent were significantly higher in those operated for non-union ($p<0.001$, $p<0.001$, $p<0.001$).

The patients' average time to return to work was 9.0±2.7 months.

While all patients had paresthesia in the fasciotomy area, 4 (12.1%) had dysesthesia in the fasciotomy area that required medical treatment, and 3 (18.1%) had dysesthesia in the donor area. While 16 (48.4%) of the patients stated that they were uncomfortable with the appearance of the wound, 5 (31.2%) of these patients stated that they had modified their clothes so that the wounds were not visible.

Cultures from 7 (21.2%) patients showed growth before their fasciotomy was closed. *Klebsiella* spp. growth was observed in 3 (42.8%) patients, *Staphylococcus aureus* growth in 3 (42.8%) patients, and *Pseudomonas aeruginosa* growth in 1 (14.2%) patient, and they were all treated with antibiotics and debridement. No patient had osteomyelitis.

Five (15.1%) of the patients had received medical treatment multiple times for peroneal tendonitis. The rate of developing dysesthesia following debridement or in patients who developed an infection in the fasciotomy area was not significantly different from that of other patients ($p=0.36$, $p=0.13$). However, the frequency of tenosynovitis problems was found to be significantly higher in both groups of patients who underwent debridement and developed an infection ($p<0.001$, $p<0.001$). Patients with recurrent tenosynovitis had significantly lower AOFAS scores at 2nd and 4th years ($p<0.05$). Table 1 shows the postoperative VAS, AOFAS, and KOOS-PS scores for the second and fourth years.

While the VAS scores of patients who required pseudoarthrosis surgery were significantly higher in the second year ($p<0.05$), no significant difference in the AOFAS or KOOS-PS scores was observed in the second year ($p=0.56$, $p=0.64$). Table 2 compares some parameters and clinical scores of patients who require pseudoarthrosis surgery with those of other patients.

There were no clinical complaints about the deformities in any of the five patients who had residual deformities. Patients' deformities were observed to be 10 degrees valgus in two patients, 1.5 cm shortness in two patients, and 7 degrees valgus and 1.5 cm shortness in one patient. Table 3 compares the clinical scores of patients with deformities to those of other patients.

Table 1. Comparison of the 2nd and 4th year postoperative clinical results of the patients

Mean ± SD*	Postoperative 2nd year	Postoperative 4th year	p**
VAS	3.06±0.9	1.9±1.04	**<0.001**
AOFAS	71.8±5.2	80.6±7.1	**<0.001**
KOOS-PS	72.2±4.8	76.9±16.6	0.13

*SD: Standard deviation, **Mann-Whitney U test. VAS: Visual analog scale, AOFAS: American Orthopedic Foot & Ankle Association scala, KOOS-PS: Knee injury and osteoarthritis outcome score, short version

Table 2. Some parameters of patients undergoing pseudoarthrosis surgery compared with other patients			
Mean ± SD*	**Pseudoarthrosis (+)**	**Pseudoarthrosis (-)**	**p****
Hospital stay (day)	35.2±6.6	20.8±6.3	**<0.006**
Return to work (month)	12.2±2.2	7.7±1.7	**<0.001**
Number of operations	5.3±1.5	3.5±1.1	**<0.002**
VAS***	2.1±0.5	2±1.1	0.68
AOFAS***	77±3.6	82.2±7.8	0.56
KOOS-PS***	73.9±6.6	73.9±6.6	0.72
*SD: Standard devitation, **Mann-Whitney U test, ***Postoperative 4th year. VAS: Visual analog scale, AOFAS: American Orthopedic Foot & Ankle Association scala, KOOS-PS: Knee injury and osteoarthritis outcome score, short version			

Table 3. Comparison of clinical scores of patients with and without deformity			
Mean ± SD*	**Deformity (+)**	**Deformity (-)**	**p****
VAS***	2.2±0.8	1.9±1.0	0.71
AOFAS***	75.6±1.6	82±9.2	0.11
KOOS-PS***	76.2±6.6	79.8±9.3	0.58
*SD: Standard devitation, **Mann-Whitney U test, ***Postoperative 4th year. VAS: Visual analog scale, AOFAS: American Orthopedic Foot & Ankle Association scala, KOOS-PS: Knee injury and osteoarthritis outcome score, short version			

DISCUSSION

The association of tibial fracture and compartment syndrome with poor clinical outcomes is mentioned in the literature (3). Although factors such as delayed rehabilitation processes, fasciotomy wounds, and skin graft problems, a high rate of pseudoarthrosis, and infection development are thought to contribute to these poor outcomes, there are no conclusive results in the literature (4). We think that our study examines the clinical and social problems of injury well in the medium-long term. We think that it is especially important to show an increase in clinical scores in the long term.

When closing the fasciotomy wound, split-thickness skin grafts are commonly used (9). This surgical procedure is associated with various issues, including poor appearance and pain in the fasciotomy area (9). In fact, this out-of-favor appearance may lead to avoidance of displaying the fasciotomy area and associated clothing modifications (11). This appears to be one of the important social issues confronting patients who have undergone fasciotomy. Although paresthesia at the fasciotomy area is generally well tolerated, dysesthesia is a significant clinical issue that may contribute to patient dissatisfaction (12). Tendon problems in the fasciotomy area appear to have a negative impact on clinical scores in both our study and the literature (13). The closure of the fasciotomy wound with a split-thickness skin graft may be a situation that adversely affects both social and clinical scores in the mid-long term. Although it has been reported in the literature that primary closure is associated with better clinical outcomes, it is impossible to apply it in every case (14). Therefore, primary closure may be a good option in appropriate cases.

Although nonunion and infection are more common in the association of fasciotomy and tibial shaft fracture, there appears to be no significant difference in the patients' clinical scores in the long term (15). Clinical scores are lower in the early period due to long treatment periods (4). This effect was more pronounced in our study, particularly in patients who developed pseudoarthrosis. Fasciotomy may affect the clinical scores of tibial shaft fractures, particularly in the early stages.

The aim of our technique, with the rail external fixator placed on the medial side of the tibia, is to reduce the possibility of deep infection in a patient with a fasciotomy wound (16), obtain a stable fixation, and make fasciotomy wound care easier (17). However, this system appears less stable against valgus forces generated by the cruris posterolateral compartment (18). As a result, a mild valgus deformity may be observed (18). However, for at least four years, these deformities do not appear to have a negative effect on clinical outcomes. In the case of compartment syndrome and tibial shaft fracture, this technique may provide safe and functional results in terms of bone infection.

Because of the additional surgical procedures required, fasciotomy appears to significantly increase both the duration of hospital stay and the cost (19). In our study, patients who required debridement stayed in the hospital for significantly longer. The higher infection rate in patients with open fractures may increase the cost of debridement and anti-biotherapy protocols. When the frequency of delayed union, nonunion, and the associated repetitive examinations, as well as longer labor loss, is added to this situation, the cost increase to both social institutions and the patient may become more clear. Since cost-related information could not be obtained from the medical records of the patients, we could not perform a cost analysis in

our study. We think that these results are valuable for our study and we think that this is an important shortcoming of our study.

Study Limitations

The limitations of our study were that it is a retrospective study, the relatively short follow-up period, the absence of a comparison group, the small number of cases, and the fasciotomy indication based on clinical findings. Determining the diagnosis of compartment syndrome with absolute values may be a method to prevent unnecessary fasciotomy and related morbidity (20,21). However, it is available in a limited centers due to its dependence on technical equipment (21). Therefore, many studies in the literature are based on clinical observations in the diagnosis of acute compartment syndrome (3,7,17,22).

CONCLUSION

As a result; the coexistence of tibial shaft fracture and fasciotomy can cause problems affecting the social life of patients. It appears that clinical and functional scores are affected more significantly in the short term. We believe that patients should be informed about these issues at the beginning of treatment.

Ethics

Ethics Committee Approval: University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital Ethics Committee approval was obtained (number: E-48670771-514.10).

Informed Consent: Written informed consent forms of all patients who were treated were obtained and recorded.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: T.O.B., M.A., A.Ç.T., A.Y., M.Y., N.E., Concept: T.O.B., E.İ.G., M.A., A.Y., N.E., H.G., Design: T.O.B., E.İ.G., M.A., A.Y., N.E., H.G., Data Collection or Processing: T.O.B., A.Ç.T., M.Y., N.E., Analysis or Interpretation: T.O.B., E.İ.G., A.Ç.T., M.Y., N.E., H.G., Literature Search: T.O.B., A.Ç.T., M.Y., N.E., Writing: T.O.B., A.Y., N.E.

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

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ORIGINAL ARTICLE

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Clinical and Radiological Findings of COVID-19 Pneumonia in Immunodeficient Patients: A Single Center Retrospective Analysis

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Abstract

Objective: Various chest computed tomography (CT) manifestations of coronavirus disease-2019 (COVID-19) pneumonia have been reported in immunocompetent patients. In immunodeficient patients, the clinical manifestations and chest CT imaging findings may differ from usual patterns and may cause mistakes in the diagnosis and management. We evaluated the chest CT manifestations in patients with immunosuppression from various causes and to compare with those seen in immunocompetent patients.

Methods: Forty-four immunodeficient and 44 immunocompetent patients with positive real-time reverse transcriptase-polymerase chain reaction test for severe acute respiratory syndrome-coronavirus-2 having suspicious chest CT manifestations were included and the chest CT images were retrospectively evaluated. The making manifestations were divided as typical findings including ground-glass opacity (GGO)and/or consolidations, air bronchogram sign, crazy paving pattern, microvascular dilatation, halo sign&reverse halo signs and atypical findings including bronshiectasia, tree in bud appearance, pulmonary nodules, pleural effusion and cavitation.

Results: There were 28 males and 16 females in the immunodeficient group and 27 males and 17 females in the control group. A statistically significant difference was found in terms of the length of hospital stay and mortality. The most frequent symptom was fever in immunodeficient patients, while it was dyspnea in the control group. The most common underlying cause for immunosuppression was receiving chemo-radiotheraphy, and the lung&gastric cancers were the most common. In terms of CT features, GGO was the most common finding. A significant difference was found in crazy paving pattern and peripheral-subpleural distribution. Atypical findings were detected significantly higher in immunodeficient patients. When all patients considered together, there was a significant association between mortality and tree-in-bud appearance, pleural effusion, bronchiectasis.

Conclusion: In our study, there was an increased risk of more severe COVID-19 disease and a higher mortality rate in immunodeficient patients. Radiologists should consider COVID-19 pneumonia in cases of rare, atypical and vague CT findings in immunodeficient patients. Since the course of COVID-19 pneumonia may be more severe in immunodeficient patients, being aware of rare atypical findings will decrease morbidity and mortality rates.

Keywords: COVID-19, immunodeficiency, pneumonia

INTRODUCTION

The coronavirus disease-2019 (COVID-19) presents mild-to-moderate upper and lower respiratory tract manifestations in most of the cases. However, particularly older patients or patients with underlying chronic disease progress to severe pneumonia associated with massive alveolar damage and acute respiratory failure. Moreover, as the pandemic progressed, various other systems like musculoskeletal system, central nervous system have been shown to be involved (1,2). Definitive diagnosis requires a positive real-time reverse transcriptase-polymerase chain reaction (rRT-PCR) test on respiratory specimens (3). Although, chest computed tomography (CT) is not recommended in the

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diagnosis and screening of the patients due to its lower specifity, it plays an important role with a low rate of missed diagnosis by revealing the abnormalities immediately. Various chest CT findings have been reported in COVID-19 patients, of which some are typical and frequently observed findings while others are atypical and rare. As shown in many studies and our previous studies, multifocal ground glass opacities (GGOs) with peripheral/subpleural distribution and accompanying areas of consolidation are the most frequently observed scenerio in immunocompetent patients. Additionally, perilesional/intralesional microvascular dilatation, halo and reversed halo signs have been reported as quite characteristic CT features of COVID-19 pneumonia, observed more commonly than non-COVID-19 viral pneumonia (4-6). However, in immunodeficient patients the clinical manifestations and chest CT imaging findings may differ from these usual patterns and may cause mistakes in the diagnosis and management. In this study, we evaluated the chest CT imaging findings seen in patients with immunodeficiency from various causes and to compare with those seen in immunocompetent patients.

METHODS

Between 16 March-30 May 2020, 88 patients (44 immunodeficient and 44 immunocompetent) with positive rRT-PCR test for severe acute respiratory syndrome-coronavirus-2 having uspicious chest CT imaging findings of COVID-19 pneumonia (typical or atypical) were included in the study and the chest CT images were retrospectively evaluated. The exclusion criteria included a paucity of clinical or radiological data, a significant artifact on CT images and being under the age of 18. The radiological findings have been divided as typical findings including GGOs and/or consolidations (non-lobar/non-segmental), air bronchogram sign, crazy paving pattern, microvascular dilatation, halo sign and reverse halo sign and atypical findings including bronshiectasia, tree in bud appearance, pulmonary nodules, pleural effusion and cavitation. Additionally, the distribution of the pneumonic infiltration, presenting symptoms, underlying causes of the immunodeficiency and comorbidities of the patients were recorded. Mortality rates and the length of hospital stay were used as clinical markers. Chest CT images were evaluated in consensus by two experienced radiologists (NK and BE).

Statistical Analysis

Statistical significance level was set as $p<0.05$.

RESULTS

There were 28 male and 16 female patients in the immunodeficient group and 27 male 17 female patients in the control group. The mean age of the immunodeficient group was 58.6±12.17 versus 58.9±10.9 years in the control group. There was no significant difference between the two groups in terms of age and gender. Accompanying comorbidities in patients are shown in (Figure 1). Nineteen (43.1%) patients in the immunodeficient group and 3 (6.8%) patients in the immunocompetent group died during hospital stay and the rest of them were discharged. Additionally, the mean length of hospital stay was 16.13±14.15 days in immunodeficient patients and 10.18±5.87 in the control group. A statistically significant difference was found between the two groups in terms of the length of hospital stay and mortality ($p=0.012$ and $p<0.001$, respectively) The most frequent symptom was fever (54.5%) in immunodeficient patients, whereas it was dyspnea (84.1%) in the control group and there was a statistically significant difference in symptoms including fever, dyspnea, and confusion between the two groups ($p=0.005$, $p=0.005$, and $p=0.049$, respectively) (Table 1). The most common underlying cause for immunodeficiency was receiving chemo-radiotheraphy for cancer, and the lung &gastric cancers were the most common (13.6% and 9.1%, respectively) (Table 2). In terms of CT features, GGO was the most common finding and was detected in all chest CT scans (Figures 2-4). A significant difference was found in crazy paving pattern and peripheral-subpleural distribution of lesions between the two groups ($p=0.031$ and $p=0.006$, respectively) (Figure 3). Atypical findings, including bronchiectasis, pulmonary nodules, tree-in-bud appearance, and pleural effusion were detected statistically significantly higher in immunodeficient patients ($p=0.002$, $p=0.047$, $p<0.001$ and $p=0.001$, respectively) (Figures 2, 3, 5-7). When all patients were considered together, there was a significant association between mortality and tree-in-bud appearance, pleural effusion, bronchiectasis (each of $p<0.05$). In addition to these atypical findings, air bronchogram sign was associated with mortality ($p<0.05$) (Table 3).

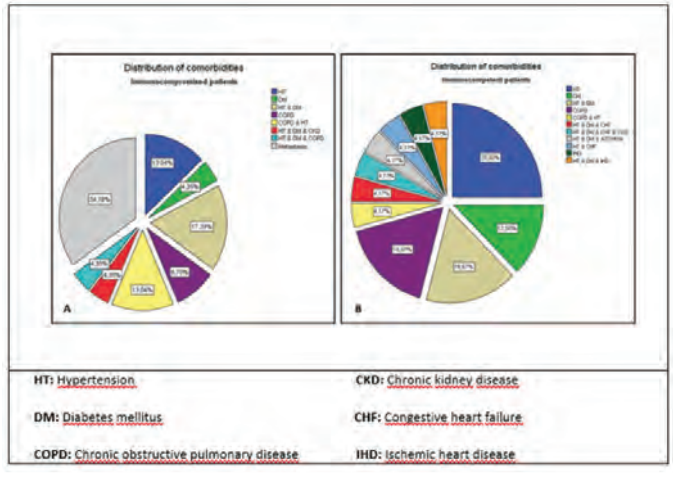

Figure 1. Distribution of comorbidities for both groups of the patients

Table 1. Demographics, prognosis and initial symptoms of the patients			
	Immunocompromised patients (n=44, %)	**Immunocompetent patients (n=44, %)**	**p values**
Demographic			
Gender			
-Male n (percentage)	28 (63.6%)	27 (61.3%)	p=0.826
-Female n (percentage)	16 (36.3%)	17 (38.6%)	
Age (years)			
-Range	30-77	33-86	p=0.898
-Mean (± SD)	58.6±12.17	58.9±10.9	
Prognosis			
Length of hospital stay			
-Mean (± SD)	16.13±14.15 (1-73)	10.18±5.87 (3-30)	**p=0.012***
Survey (mortality)			
- n (percentage)	19 (43.2%)	3 (6.8%)	**p<0.001***
Symptoms			
Fever: n (percentage)	24 (54.5%)*	11 (25%)	**p=0.005***
Dyspnea: n (percentage)	25 (56.8%)	37 (84.1%)*	**p=0.005***
Cough: n (percentage)	17 (38.6%)	16 (36.4%)	p=0.826
Fatigue: n (percentage)	11 (25%)	6 (13.6%)	p=0.177
Loss of taste or smell: n (percentage)	12 (27.3%)	6 (13.6%)	p=0.113
Nausea and vomiting: n (percentage)	5 (11.4%)	2 (4.5%)	p=0.237
Myalgia: n (percentage)	9 (20.5%)	7 (15.9%)	p=0.580
Headache: n (percentage)	1 (2.3%)	1 (2.3%)	p=1.000
Confusion: n (percentage)	6 (13.6%)*	1 (2.3%)	**p=0.049***

*There was statistically significant relationship between two groups (p value <0.05), SD: Standard deviation

Table 2. The cause of immunosuppression in the patients	
Underlying causes for immunosuppression	**Frequency n=44, (100%)**
Lung cancer: n (percentage)	6 (13.6%)
Gastric adenocarcinoma: n (percentage)	4 (9.1%)
Non-Hodgkin lymphoma: n (percentage) Multiple myeloma: n (percentage) Acute myeloid leukemia: n (percentage)	Each of 3 (6.8%)
Breast cancer: n (percentage) Esophageal cancer: n (percentage) Endometrial cancer: n (percentage) Pancreatic cancer: n (percentage) Unknown primary: n (percentage)	Each of 2 (4.5%)
Hepatocellular cancer: n (percentage) Renal cell carcinoma: n (percentage) Liver transplantation: n (percentage) Cholangiocellular cancer: n (percentage) Testicular tumor: n (percentage) Femur osteosarcoma: n (percentage) Glioblastoma multiforme: n (percentage) HIV: n (percentage) HIV+ lung cancer: n (percentage) Malignant melanoma: n (percentage) Bladder cancer: n (percentage) Myastenia gravis: n (percentage) Hairy cell leukemia: n (percentage) Tongue cancer: n (percentage) Thrombocytosis disease: n (percentage)	Each of 1 (2.3%)

DISCUSSION

Immunodeficiency is one of the important underlying conditions that may be associated with a more severe course of most viral infectious pneumonia, including influenza (7). It could also be pre prepared for COVID-19. However, there are currently limited data on the prognosis, clinical presentations and the CT imaging findings of the disease in immunodeficient patients, which may differ from those seen in immunocompetent adults. Reported studies also have conflicting results. Some studies have shown that the mortality and morbidity of COVID-19 is higher in immunodeficient patients due to the higher levels of viral load (8-10), while other studies reported no statistically significant risk of more severe COVID-19 in these patients (11). Previously, some viral respiratory infections were shown to be associated with more severe manifestations in patients on long-term immunosuppressive medications (12,13). A prospective cohort monitoring COVID-19 cases throughout China revealed poorer outcomes from COVID-19 in patients with cancer with a higher risk of severe events including admission to the intensive care unit, requiring invasive ventilation, and death compared with patients without cancer (14). However, any significant differences were not found in the study by Miyashita et al. (15) regarding COVID-19 mortality among 334 patients with cancer compared with those without cancer. Moreover, as the pandemic progresses corticosteroids decreases mortality in patients with severe COVID-19 pneumonia, implying a favorable effect of suppressed immune response during the disease (16). In COVID-19, a hyperinflammatory state with increased levels of cytokines, including IL-6, is generated and

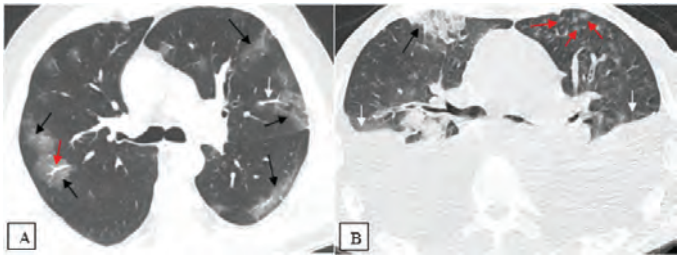

Figure 2. Axial CT images showing. A) Multifocal/multilobar GGOs with predominantly peripheral in distribution (A, black arrows) in a 61-year-old immunocompetent male patient presenting with cough, myalgia, and dyspnea, who had no comorbidities and who was discharged from the hospital 19 days later. Note also the perilesional (A, white arrow) and intralesional (A, red arrow) microvascular proliferation and B) A patchy peripheral GGO with superimposed areas of consolidations in the right middle lobe (B, black arrow) in a 69-year-old immunocompromised male patient presenting with cough, fatigue, and fever, who had a history of gastric cancer and died 24 days after being hospitalized for COVID-19 pneumonia. Note the presence of obvious bilateral pleural effusion (B, white arrows) in this immunocompromised patient in addition to multiple small centrilobular nodules with tree-in-bud appearances (B, red arrow) in the left lung, which was probably associated with bacterial superinfection

GGOs: Ground glass opacities, COVID-19: Coronavirus disease-2019, CT: Computed tomography

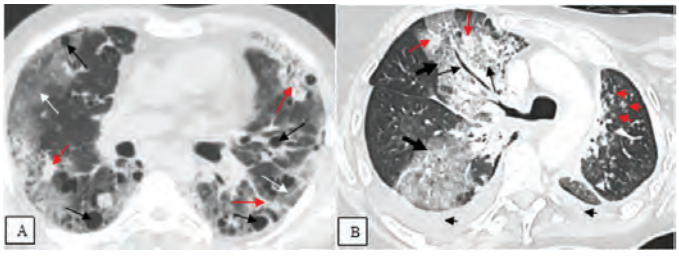

Figure 3. Axial CT images showing. A) Bilateral patchy and confluent GGOs predominantly peripheral in distribution (A, white arrows) mixed with areas of irregular consolidations (A, red arrows) in a 43-year-old immunocompromised male patient presenting with fever, cough, confusion, and dyspnea, who had testicular carcinoma with pulmonary metastases and died 9 days after being hospitalized for COVID-19 pneumonia. Note also the multiple pulmonary metastases seen as cystic lesions following chemotherapy (A, black arrows). B) Unilateral GGOs without peripheral predominance (B, thick black arrows) associated with areas of superimposed consolidations (B, red arrows) and reticulation resulting in crazy paving pattern (B, black arrow) and an air bronchogram sign (B thin black arrow) in the right lung in a 49-year-old immunocompromised female patient presenting with dyspnea, myalgia and fever, who had a history of lung cancer with liver metastases and died 7 days after being hospitalized for COVID-19 pneumonia. Note the presence of bilateral moderate pleural effusions (B, black arrowheads) and multiple small centrilobular nodules with tree-in- bud appearances (B, red arrowheads) in the left lung, which was probably associated with bacterial superinfection. The interlobar pleural thickening is also seen (B, white arrowhead)

GGOs: Ground glass opacities, COVID-19: Coronavirus disease-2019, CT: Computed tomography

suggested as an endogenous pathway in the pathophysiology of both pulmonary damage and multiorgan complications

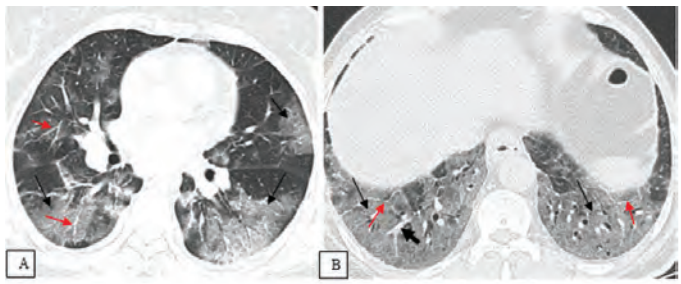

Figure 4. Axial CT images showing. A) bilateral patchy multifocal GGOs predominantly peripheral in distribution (A, black arrows) in a 56-year-old immunocompetent female patient presenting with cough and dyspnea, who had a history of hypertension, type 2 diabetes mellitus and asthma, who was discharged from the hospital 7 days after being hospitalized for COVID-19 pneumonia. Note also the intralesional microvascular dilatations (A, red arrows). B) Bilateral GGOs involving wide areas in the lower lobes (B, black arrows) associated with intralesional microvascular dilatation (B, thick black arrow) in a 61-year-old immunocompetent male patient presenting with dyspnea and cough, who died 30 days after being hospitalized for COVID-19 pneumonia. Note also the presence of fibrotic streaks associated with the GGOs (B, red arrows)

GGOs: Ground glass opacities, COVID-19: Coronavirus disease-2019, CT: Computed tomography

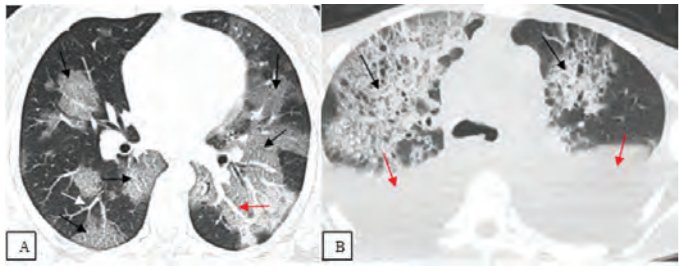

Figure 5. Axial CT images showing. A) multifocal peripheral and central/peribronchovascular GGOs superimposed with reticularion resulting in crazy paving pattern (A, black arrows) in a 33-year-old immunocompetent patient presenting with cough, dyspnea, and chest pain, who had a history of the atrial septal defect and who was discharged 15 days after being hospitalized for COVID-19 pneumonia in a 55-year-old immunocompromised patient presenting with fever, cough, dyspnea, and weakness. Note also the perilesional (A, white arrow) and intralesional (A, red arrow) microvascular dilatations B) Bilateral consolidative opacities at the circumferences of structural damaged emphysematous pulmonary parenchyma, which is more prominent in the right lung (B, black arrows). Note the presence of bilateral pleural effusion (B red arrows) in this immunocompromised patient presenting with fever, dyspnea, and cough who had a history of essential thrombocytosis and died 15 days after being hospitalized for COVID-19

CT: Computed tomography, GGOs: Ground glass opacities, COVID-19: Coronavirus disease-2019

of the disease, which is known as a cytokine storm. This could be expected to be less likely and milder in severity in immunodeficient patients (17-20). Similarly, the evaluation of 110 immunodeficient patients with COVID-19 obtained from a systematic review of 16 articles revealed that immunodeficient

patients seemed to have a favorable course (21). Additionally, a statistically significant risk of severe COVID-19 was not found among immunodeficient patients in a meta-analysis from China (22). However, the lack of a normal immune response can also be associated with the lack of protective antiinflammatory effects and higher possibility of developing co-infections in this

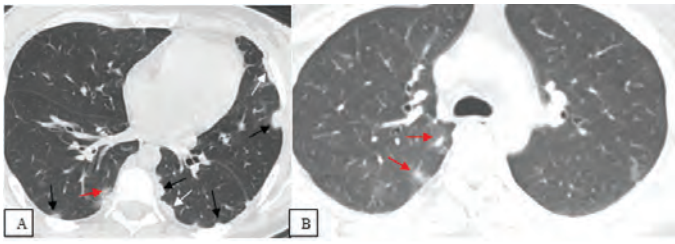

Figure 6. Axial CT images showing. A) Bilateral nodular pulmonary infiltration predominantly peripheral in distribution (A, black arrows) in a 30-year-old immunocompromised female patient presenting with cough, fatigue, and nausea who had a history of esophageal cancer and was discharged from the hospital 8 days after being hospitalized for COVID-19 pneumonia. Note also the subpleural GGOs (A, red arrow) and consolidations (A, white arrows). B) GGOs surrounding the nodular consolidations in the right lower lobe resulting in halo sign (B, red arrow) in a 51-year-old immunocompromised female patient presenting with fever and dyspnea, who had a history of diffuse large B-cell non-Hodgkin lymphoma was discharged from the hospital 10 days after being hospitalized for COVID-19 pneumonia

CT: Computed tomography, GGOs: Ground glass opacities, COVID-19: Coronavirus disease-2019

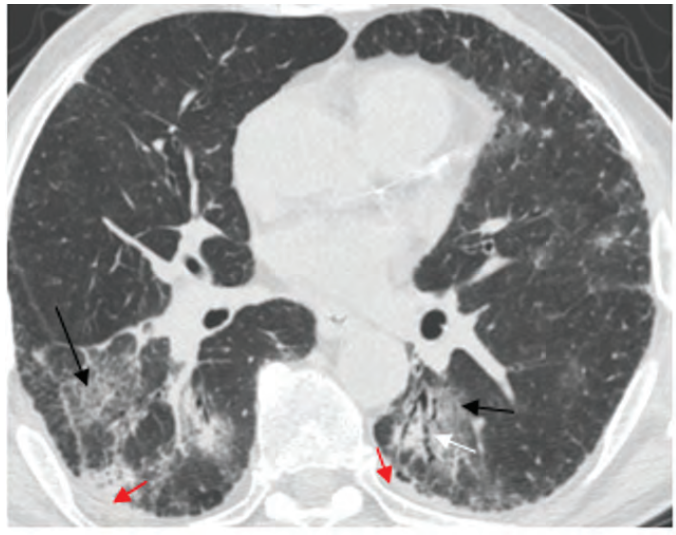

Figure 7. Axial CT image showing irregular consolidative infiltration in association with patch bilateral GGOs (black arrows) in a 71-year-old immunocompromised male patient presenting with dyspnea and fatigue who had a history of lung cancer, hypertension, type 2 diabetes mellitus and who was discharged from the hospital 14 days after being hospitalized for COVID-19 pneumonia. Note also bilateral small amounts of pleural effusion (red arrows) and the irregularly dilated bronchioles (bronchiectasis) (white arrow) in association with the pneumonic infiltration in the left lower lobe

CT: Computed tomography, GGOs: Ground glass opacities, COVID-19: Coronavirus disease-2019

Table 3. Chest CT findings of the patients

Chest CT findings	Immunocompromised patients (n=44, %)	Immunocompetent patients (n=44, %)	p values
Typical findings			
GGO: n (percentage)	44 (100%)	44 (100%)	*
GGO + consolidation: n (percentage)	30 (68.2%)	23 (52.3%)	0.127
Crazy paving pattern: n (percentage)	20 (45.5%)	30 (68.2%)	**0.031****
Air bronchogram: n (percentage)	22 (50%)	16 (36.4%)	0.197
Halo sign: n (percentage)	13 (29.5%)	10 (22.7%)	0.467
Microvascular dilatation: n (percentage)	13 (29.5%)	16 (36.4%)	0.496
Reversed halo sign: n (percentage)	0 (0%)	0 (0%)	*
All lobes involvement: n (percentage)	37 (84.1%)	40 (90.9%)	0.334
Peripheral-subpleural involvement: n (percentage)	37 (84.1%)	44 (100%)*	**0.006****
Peribronchovascular involvement: n (percentage)	35 (79.5%)	31 (70.5%)	0.325
Atypical findings			
Bronchiectasis: n (percentage)	13 (29.5%)	2 (4.5%)	**0.002****
Pulmonary nodules: n (percentage)	11 (25%)	4 (9.1%)	**0.047****
Tree-in-bud appearance: n (percentage)	18 (40.9%)	1 (2.3%)	**<0.001****
Pleural effusion: n (percentage)	18 (40.9%)	4 (9.1%)	**0.001****
One lobe involvement: n (percentage)	7 (15.9%)	4 (9.1%)	0.334
Cavitation: n (percentage)	0 (0%)	0 (0%)	*
Distribution of lesions			
One lobe involvement: n (percentage)	7 (15.9%)	4 (9.1%)	0.334
All lobes involvement: n (percentage)	37 (84.1%)	40 (90.9%)	0.334
Peripheral-subpleural distribution: n (percentage)	37 (84.1%)	44 (100%)*	**0.006****
Peribronchovasculary distribution: n (percentage)	35 (79.5%)	31 (70.5%)	0.325

* It was not statistically calculated, ** There is statistically significant difference between two groups. CT: Computed tomography, GGO: Ground glass opacity

patient group, which may be associated with higher mortality. A large retrospective national cohort study from Spain showed that immunodeficient patients hospitalized with COVID-19 have higher odds of in-hospital death and complications than immunocompetent patients. These groups were reported as the vulnerable population for complicated COVID-19 and suggested to be closely monitored (23). Similarly, our study revealed a significantly higher mortality rate in immunodeficient patients than in the immunocompetent patients, regardless of the age. When we looked at the underlying causes for immunodeficiency in our patients, the most common were being under treatment for cancer, which may be the reason for this higher mortality. Some recent reports revealed a similarly high mortality rate in cancer patients with COVID-19 (24). Reports regarding the chest CT imaging findings in immunodeficient patients with COVID-19 pneumonia are scarce in the current literature. Severe pulmonary sequelae has been reported in a 12-year-old child with primary immunodeficiency during the follow-up of COVID-19 pneumonia (25). Bilateral GGOs with multiple nodules complicated with pneumothorax, pneumomediastinum and pneumopericardium has been reported in a 28-year-old woman with a medical history of combined variable immunodeficiency under treatment with intravenous immune globulin (26). In the study by Abrishami et al. (27) most chest CT findings in kidney transplant recipients on immunosuppression were found to be similar to those from other adult studies for the general population. They only reported unilateral involvement and consolidation as slightly more frequent in their patients (27). In our study, the most common chest CT finding was also GGO with or without accompanying consolidations, which is the most frequent imaging finding of COVID-19 in general population reported in the literature. However, in our study, the crazy paving pattern, which is consistent with the progressive phase of the disease was observed statistically significantly higher in the immunocompetent group. Peripheral/subpleural distribution of the infiltration was also observed significantly higher in immunocompetent patients. A significant correlation was found between the immunodeficient patient group and atypical radiological findings, including bronshiectasia, tree in bud appearance, pulmonary nodules, and pleural effusion. Our study also revealed a significant association between mortality and atypical findings, which were statistically significantly more frequent in immunodeficient patients.

Study Limitations

The limitations of our study included, the limited number of patients, the retrospective nature of the study, not being able to evaluation in terms of superinfection, which may be a confounder of the chest CT findings observed, particularly immunodeficient patients who may be more susceptible to secondary bacterial infections.

CONCLUSION

In our study, it was determined that there was an increased risk of more severe COVID-19 disease and a higher mortality rate in immunodeficient patients. Radiologists should consider COVID-19 pneumonia in cases of rare, atypical and vague CT findings in immunodeficient patients. Since the course of COVID-19 pneumonia may be more severe in immunodeficient patients, the detection of chest CT findings of the diagnosed patients and knowing the typical and atypical findings will decrease morbidity and mortality rates with a more accurate interpretation.

Ethics

Ethics Committee Approval: This study was approved by the Clinical Research Ethics Committee of University of Health Sciences Turkey, Prof. Dr. Cemil Taşcıoğlu City Hospital (no: 48670771-514.10).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

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

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

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CASE REPORT

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Hyaline-vascular Adrenal Castleman's Disease Mimicking an Adrenal Neoplasm

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Abstract

Castleman's disease (CD), also known as angiofollicular lymph node hyperplasia, is an uncommon, benign B-cell lymphoproliferative disorder. Adrenal CD is an extremely rare lesion of the adrenal gland that mimics other adrenal neoplasms reported only in a few cases in the literature. We presented a large-sized right adrenal CD, which was found incidentally in a 46-year-old male patient during the evaluation for coronavirus disease-2019 pneumonia. Although imaging features overlap with other hypervascular adrenal neoplasms, CD should also be considered in the differential diagnosis of the adrenal masses, particularly when it is relatively well defined with homogenous attenuation and enhancement despite its large size.

Keywords: Castleman's disease, adrenal neoplasm, hypervascular adrenal mass

INTRODUCTION

Castleman's disease (CD), also known as angiofollicular lymph node hyperplasia, is an uncommon, benign B-cell lymphoproliferative disorder that preserves the lymph node architecture. The mediastinum is the most common part of involvement, however anywhere in the body can be involved, including both nodal, and extranodal sites (1). These lesions are rarely reported in the literature as a mimicked of other neoplasms of the associated organs, including a mimicked of a gastric submucosal leiomyoma, a mass of pancreatic head, a mesenteric mass, or a mimicked of renal cell carcinoma (2-4). We present a large-sized right adrenal CD which was found incidentally in a 46-year-old male patient during the evaluation for coronavirus disease 2019 (COVID-19) pneumonia.

CASE PRESENTATION

A 46-year-old male patient with a 25 pack-year smoking history was admitted to our hospital with suspicion of COVID-19. On the upper abdominal images of the chest computed tomography (CT), a 56x30 mm sized relatively well-defined soft tissue density lesion compressing the inferior vena cava was incidentally established at the right adrenal location. Only the medial limb of the adrenal gland was visible and the interface of mass with the remaining parts of the adrenal gland could not be discerned (Figure 1). The density of the mass on non-contrast CT was incompatible with a lipid-rich adenoma. On wash-out imaging, progressive enhancement was observed as opposed to that expected from lipid-poor adenoma and pheochromocytoma. There was no associated retroperitoneal lymph nodes or peritoneal thickening around the mass. Magnetic resonance imaging (MRI) did not show the characteristic bright T2w signal intensity of the pheochromocytoma. On chemical shift imaging, there was no signal drop in the out of phase images to suggest intravoxel (intracellular) lipid (Figure 2). He had no history of malignancy. At that time, positron emission tomography-CT reported minimally increased fluorodeoxyglucose (FDG) uptake (maximum standardized uptake value: 3.5) (Figure 3). With the suspicion of malignancy, surgical excision with inevitable right adrenalectomy was performed. Histopathological evaluation of

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the lesion revealed hyalin vascular type adrenal CD (Figure 4). Informed consent has been taken from the patient.

DISCUSSION

CD is a rare benign lymphoproliferative disease with not well-known etiology and pathogenesis, although chronic low-grade inflammatory states and autoimmunity have been suggested (5). There are two distinct clinical subtypes including the unicentric (localized) CD and multicentric CD. Unicentric CD is more common occurring usually in young adults and is usually asymptomatic, if there are no symptoms resulting from the localized pressure of the mass. In our patient, the right adrenal mass was incidentally found during the evaluation of COVID-19 pneumonia at the upper abdominal images included to the chest CT. On the other hand, the multicentric CD, which occurs more commonly in older patents is a systemic disease associated with a poor prognosis (6,7). The histopathological variants are hyaline vascular type, plasma cell type, and mixed-type. While the unicentric CD occurs in the form of a hyaline vascular type, which is seen in about 90% of the cases, most of the multicentric CD demonstrates the plasma cell type (5,7). Reported in only a few cases in the literature, adrenal CD is an extremely rare mass lesion of adrenal gland mimicking other adrenal neoplasms (8,9). The hyaline vascular type is characterized with a high number of blood vessels in relation with abnormal lymphoid follicles in contrast to the plasma cell type, which is associated with little number of vessels along with mature plasma cells (4). Because to the rarity of the adrenal CD and the absence of well defined specific radiological imaging findings, the preoperative diagnosis is very difficult. On radiological imaging, the unicentric hyalin vascular type CD is seen as a solitary mass usually homogenous in attenuation with prominent and usually homogenous contrast enhancement due to its highly

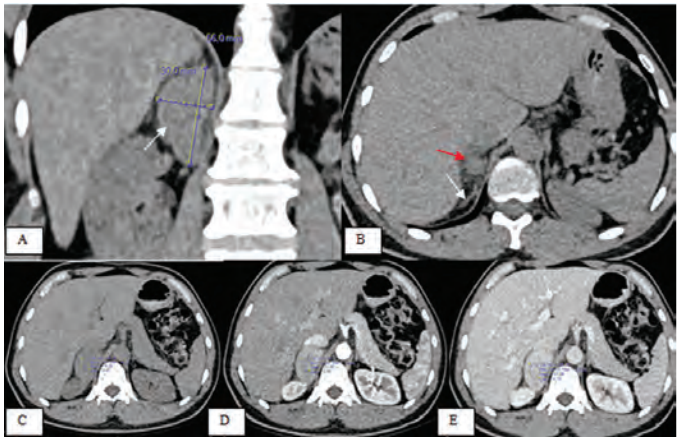

Figure 1. (A, B) Non-contrast CT images showing the right adrenal mass-measuring 56x30 mm on coronal image (A, arrow). On axial images the lateral limb of the right adrenal gland is shown, but corpus of the rest of the gland was not visible (B, white arrow). The part of the mass that should not be discerned from the adrenal gland is shown (B, red arrow). (C-E) Contrast washout CT scan demonstrates soft tissue density of the lesion on non-contrast CT (C) and progressive enhancement during the arterial (D) and venous (E) phases
CT: Computed tomography

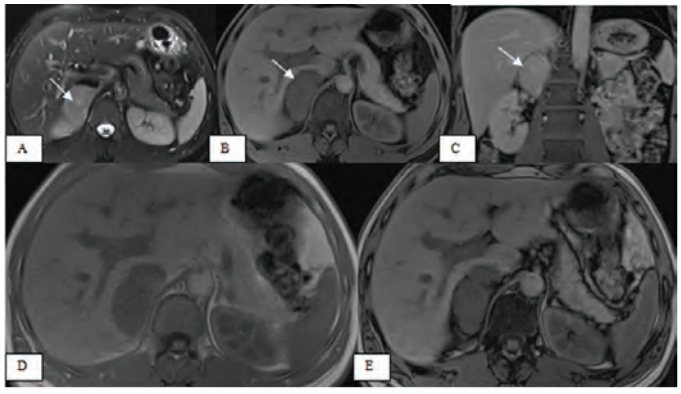

Figure 2. Magnetic resonance imaging showing the mass on T2w image having high signal intensity relative to the liver but not as much as expected from a pheochromocytoma (A, arrow). Precontrast T1w (B, arrow) and postcontrast T1w (C) images show homogenous enhancement of the lesion (C, arrow). There was no drop in signal intensity out of phase imaging (A; in phase and B; out of phase)

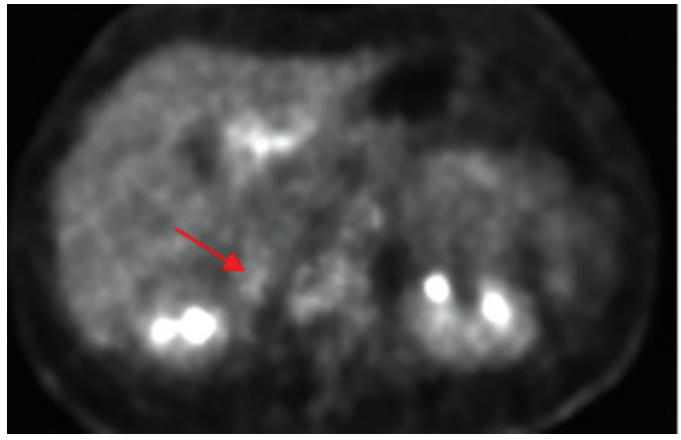

Figure 3. FDG-PET/CT showing minimally increased focal FDG uptake at the central part of the lesion (arrow)
FDG: Fluorodeoxyglucose, PET: Positron emission tomography, CT: Computed tomography

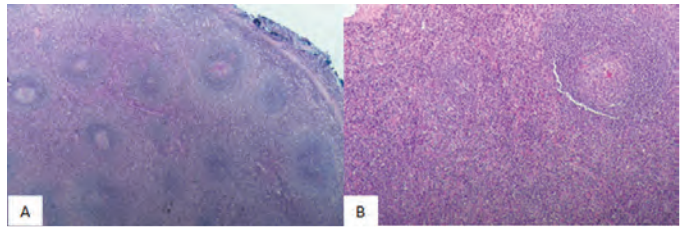

Figure 4: Microscopic appearance of the lesion (A) hematoxylin-eosin stain X 40 and (B) hematoxylin-eosin stain X 100 show lymphoid follicles with small hyalinized germinal centers and a broad mantle zone in association with prominent vascular proliferation in interfollicular areas

vascular nature. Although adrenal cortical carcinoma and pheochromocytoma generally have generally heterogeneous attenuation and enhancement pattern, large CD lesions with necrotic parts may also show heterogeneous enhancement and should be considered in the differential diagnosis. In some case reports, peripheral rim like enhancement has been shown in association with marked peripheral capillary vessels seen on the microscopic evaluation of hyalin vascular CD. In these case reports, peritoneal thickening surrounding the mass has also been demonstrated and attributed to reactive peritoneal hyperplasia (9,10). Some internal calcifications may also present in the hyalin vascular CD. In our patient, the right large-adrenal mass showed soft tissue density on non-enhanced CT images without any peritoneal thickening and internal calcifications. Washout CT imaging and MRI have revealed progressive intense enhancement during arterial and venous phases. Additionally, the density on early phases was not as high as was expected from a pheochromocytoma. The absence of intracellular lipid has also been verified by chemical shift MRI with a demonstration of the absence of a signal drop on the opposite phase. Minimal FDG uptake was present. Although there were no areas of hemorrhage or necrosis as expected from such a large adrenal cortical carcinoma or there was no history of primary malignancy to suggest metastasis, due to the overlapping imaging findings, histopathological diagnosis was needed.

CONCLUSION

Adrenal CD is an extremely rare lesions of the adrenal gland. Although imaging features overlap with other adrenal neoplasms, CD should also be considered in the differential diagnosis of the adrenal masses, particularly when it is relatively well defined with homogenous attenuation and enhancement despite its large size.

Ethics

Informed Consent: Informed consent has been taken from the patient.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Concept: B.E., S.D.Ö., D.A., H.Ö., Design: B.E., S.D.Ö., D.A., Data Collection or Processing: B.E., T.O.K., İ.M., Analysis or Interpretation: B.E., H.Ö., Literature Search: B.E., T.O.K., Writing: B.E., İ.M.

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

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

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CASE REPORT

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Signet Ring Basal Cell Carcinoma: An Extraordinary Case

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Abstract

Basal cell carcinomas are slow-growing, locally aggressive tumors arising from the interfollicular epidermis and/or hair follicle. Here, a 74-year-old man presented with an irregular nodule 2.5x2 cm in size on the left ala of the nose for 3 years. On light microscopy the signet ring cell configuration was observed among neoplastic cells focally (in some areas). The most prominent feature was cells containing large eosinophilic, pink, eccentric intracytoplasmic inclusions that compress the nuclei to the cell border. The cell inclusions did not stain with periodic acid schiff and alcian blue pH 2.5. The tumor cells were positive for Ber-EP4 but negative for S-100.

Keywords: Signet ring cell, basal cell carcinoma, dermatopathology

INTRODUCTION

Basal cell carcinomas (BCCs) are slow-growing, locally aggressive tumors originating from interfollicular epidermis and/or hair follicle (1). It is the most common malignancy in fair skinned populations worldwide and has many histological variants including nodular, superficial, basosquamous, infiltrating etc. (1). Although there is no specific statistical ratio regarding its prevalence in the literature, we know that signet ring cell BCC is a very rare variant of BCC that tumor cells contain large, pink, eosinophilic, eccentric intracytoplasmic inclusions that crescentically compress nuclei to the cell border (2).

CASE PRESENTATION

A 74-year-old man presented with an irregular nodule 2.5x2 cm in size on the left ala of nose for 3 years. The patient was evaluated as fitz patrick type 3 on physical examination. The lesion was diagnosed as BCC by incisional biopsy and than a wide excision was performed.

Histopathological and Immunohistochemical Findings

On light microscopy the tumor consists of islands of basaloid cells with peripheral palisading, clefts separating neoplastic epithelium and intervening fibroblastic stroma (retraction artefact) (Figure 1). Signet ring cell configuration was observed among neoplastic cells focally. The most prominent feature was cells containing large eosinophilic, pink, eccentric intracytoplasmic inclusions, which compress the nuclei in a few lobules (Figure 2A-C). The cell inclusions did not stain with periodic acid schiff (PAS) (Figure 3) and alcian blue pH 2.5 (Figure 4). Tumor cells were positive for Ber-EP4 (Figure 5) but negative for S-100 except for some

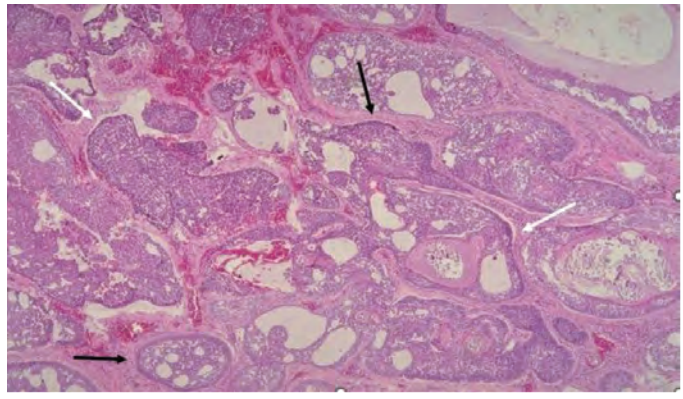

Figure 1. Peripheral palizading basaloid cells (black arrows), clefts seperating neoplastic epitelium and intervening fibroblastic stroma (white arrows), hematoxylin and eosin, X40

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cells corresponding to Langerhans cells, which are scattered within tumor islands (Figure 6).

DISCUSSION

Although BCC is the most common cutaneous malignancy, signet ring cell BCCs are rare in routine and our case was not a pure signet ring cell variant as well. At this point, the overall pattern of the neoplasm becomes the most important diagnostic criterion for histological evaluation (3). Although the characteristic features are well-known of BCC, pathologists may consider metastasis of an adenocarcinoma when observing signet ring cells in a skin

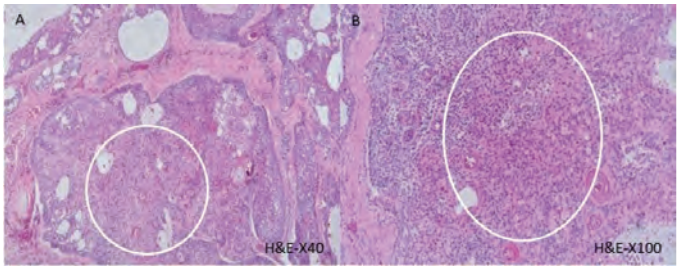

Figure 2. A, B) Signet ring cell configuration among neoplastic cells focally (white circles)

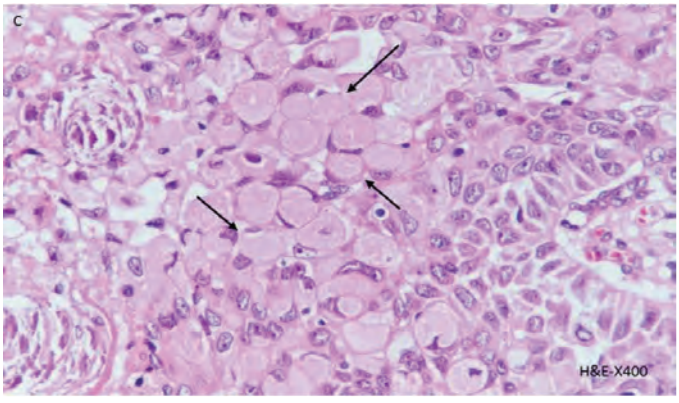

Figure 2. C) The cells containing large, pink, eccentric intracytoplasmic inclusions that compress the nuclei (black arrows)

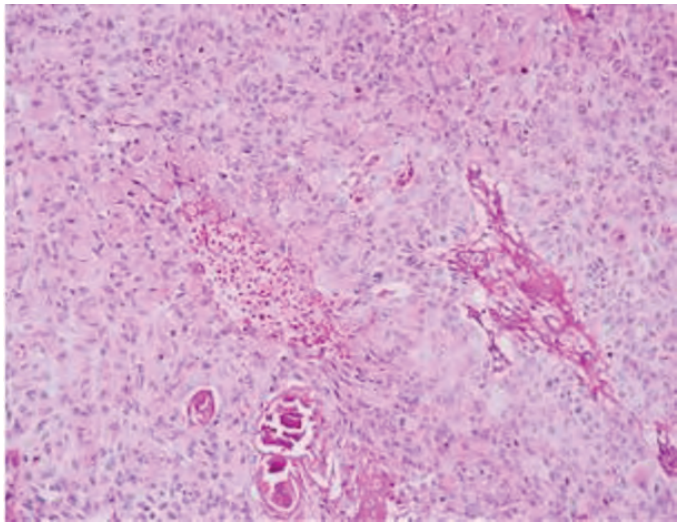

Figure 3. Signet ring tumor cells are negative for PAS, x100
PAS: Periodic acid schiff

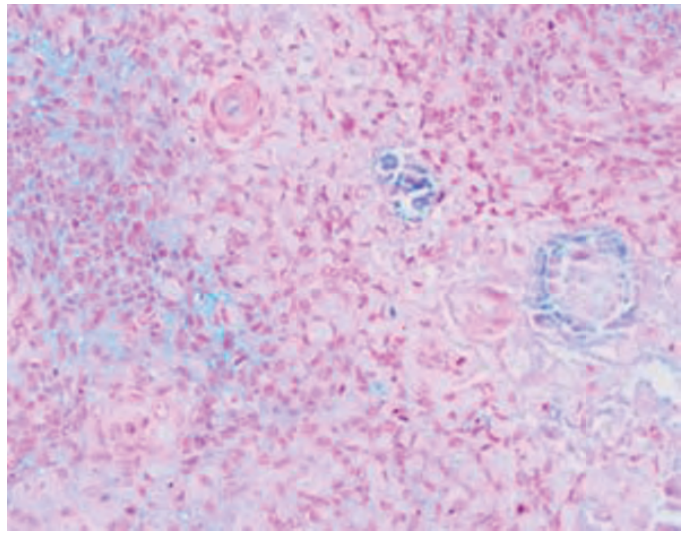

Figure 4. Signet ring tumor cells are negative for Alcian blue pH 2,5, X200

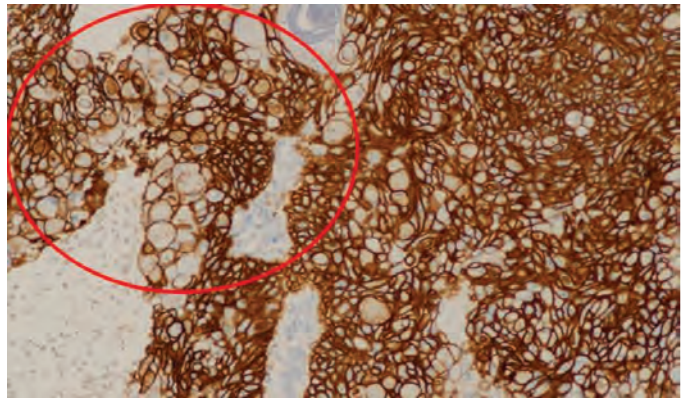

Figure 5. Tumor cells were positive for Ber-EP4. Signet ring cell group also positive for Ber-EP4 (red circle), X100

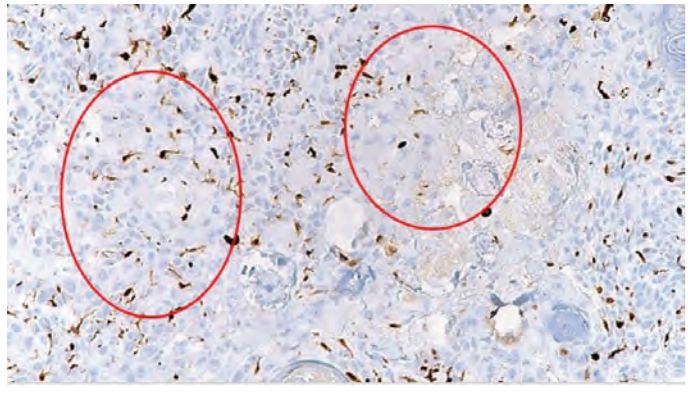

Figure 6. Tumor cells are negative for S-100 except for some cells corresponding to Langerhans cells which are scattered within tumor islands, X200

neoplasm. Nuclear pleomorphism, hyperchromatism, mitotic activity, a type of infiltration (e.g. diffuse patern supports metastasis), and clinical correlation could help to distinction between metastasis and BCC (4). In cutaneous metastases of visceral adenocarcinomas, there is nuclear displacement because of cytoplasmic musin deposition, which giving signet ring shape to the cell. Therefore, neoplastic cells are stained with PAS and D-PAS (3). In metastatic lesions, typically there is a diffuse dermal infiltrate. Additionally the overlying epidermis is intact and there is an underlying spared zone of uninvolved dermis which is called grenz zone (5). Also the neoplastic cells are generally positive for carcinoembryonic antigen (3). Primary cutaneous signet ring cell neoplasms can also be seen like trichilemmal carcinoma, signet ring cell lymphoma, signaling ring cell squamous cell carcinoma (SCC), sebaceous carcinoma, signet ring melanoma except for metastatic adenocarcinomas (5). In trichilemmal carcinoma, there are foci of keratinization, PAS-positive tumor cells, lobular architecture composed of large atypical cells with clear cytoplasm and prominent nucleoli. This neoplasm is usually deeply seated with no connection to the epidermis and there is no normal pilar structures (6). In signet ring cell lymphomas, tumor cells may have abundant clear or vacuolated cytoplasm that giving shape to cell signet ring appearance mostly because of the abnormal membrane recycling or secretion of immunoglobulin and either B or T-cell markers are positive immunohistochemically (7,8).

In signet ring cell SCCs are negative for BREP4 and CD10 (9). In sebaceous carcinomas are characterized by lobular formations of sebaceous and undifferentiated basaloid cells. Also, the sebaceous cells show foamy, microvesicular cytoplasm instead of a signet ring shape (6). Sebaceous carcinoma shows immun reactivity for CKPAN, EMA, adiphopilin and perilipin (10). Signet ring melanoma stain for melanocyte markers such as HBM-45, Melan-A, and S-100.

To sum up, signet ring cells are uncharacteristic of any particular primary or secondary cutaneous neoplasm. We attach great importance to histomorphology in the differential diagnosis since BCC has well-known diagnostic criteria such as peripheral palisading, retraction artefact, tumor nests. We report this case due to the limited number of studies in the literature about signet ring cell BCC.

CONCLUSION

This case report and similar studies could make it easier to recognize this tumor. Further studies including more cases would be necessary to clarify the clinical behavior and nature of signaling ring cell BCCs.

Ethics

Informed Consent: Patient consent could not be received from the patient due to the retrospective design of the study.

Peer-review: Internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Ö.Y., B.A., S.A.A., Concept: Ö.Y., B.A., S.A.A., Design: Ö.Y., B.A., S.A.A., Data Collection or Processing: Ö.Y., B.A., S.A.A., Analysis or Interpretation: Ö.Y., B.A., S.A.A., Literature Search: Ö.Y., B.A., S.A.A., Writing: Ö.Y., B.A., S.A.A.

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

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