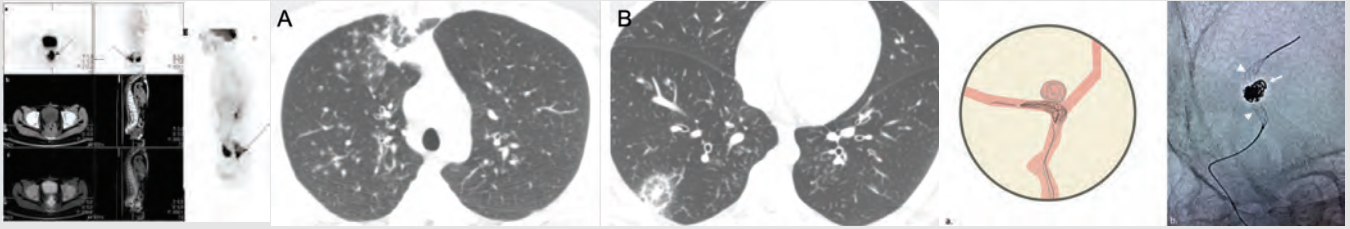


# European Archives of Medical Research

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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
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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.

## INSTRUCTIONS TO AUTHORS

All acronyms and abbreviations used in the manuscript should be defined at first use, both in the abstract and in the main text. The abbreviation should be provided in parentheses following the definition.

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.

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**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.

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Slots J. The microflora of black stain on human primary teeth. *Scand J Dent 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].

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### REVISIONS

When submitting a revised version of a paper, the author must submit a detailed "Response to the reviewers" that states point by point how each issue raised by the reviewers has been covered and where it can be found (each reviewer's comment, followed by the author's reply and line numbers where the changes have been made) as well as an annotated copy of the main document. Revised manuscripts must be submitted within 30 days from the date of the decision letter. If the revised version of the manuscript is not submitted within the allocated time, the revision option may be canceled. If the submitting author(s) believe that additional time is required, they should request this extension before the initial 30-day period is over.

Accepted manuscripts are copy-edited for grammar, punctuation, and format. Once the publication process of a manuscript is completed, it is published online on the journal's webpage as an ahead-of-print publication before it is included in its scheduled issue. A PDF proof of the accepted manuscript is sent to the corresponding author and their publication approval is requested within 2 days of their receipt of the proof.

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# European Archives of Medical Research

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# Interventional Radiology: The Invisible Part of the Iceberg

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## Abstract

T-Tube occlusion removal under fluoroscopy was introduced by Alexander R. Margulis in 1967 and the placement of vascular prosthesis by Dotter in 1969. Thereafter, rapid developments in minimally invasive treatment methods occurred in the field of “interventional radiology,” including the dazzling developments in the vascular, non-vascular, and neurointerventional fields. Radiologists primarily receive diagnostic radiology training, thus they are very skillful in using these treatment methods. Routine procedures in most countries include biopsies, drains, angiographies, venous dialysis catheters, port placement for chemotherapy, ablative treatments, etc. Additionally, some treatment methods continue to become widespread such as temporary intracranial stents, flow-diverter stents, middle cerebral artery embolization for chronic subdural hematoma, thyroid ablation and embolization, cryoablation, chemosaturation, bariatric embolization, uterine fibroid embolization, fallopian tube recanalization, hemorrhoidal embolization, varicocele treatment, prostatic artery embolization, and geniculate artery embolization. Continuous developments in the field of new interventional radiological treatment have been improving since the writing of this review.

**Keywords:** Interventional radiology, biopsy, angiography, endovascular treatment

## INTRODUCTION

### Temporary Intracranial Stents

Coiling with the double stent technique in intracranially located wide neck aneurysms increases the efficiency of the procedure and provides a more robust operation (1,2). However, double stents may increase the occurrence of side effects. Complications have been reported in a 2-12.7% rating (3,4). Thereupon, solutions to reduce the stent load were considered and temporary stents started to develop.

Temporary stents include new temporary bridging devices that are developed to cover the aneurysm neck during coiling. Comaneci device (Rapid Medical, Yokneam, Israel) (Figure 1) and PulseRider (Cerenovus, New Brunswick, NJ), as well as solitaire FR revascularization device (Medtronic), are in use. Temporary device usage instead of a second stent deployment can be a straightforward alternative in overcoming potential difficulties (5).

### Flow-Diverter Stents

Flow-diverter devices (FDD) are new-generation stents that are placed in the parent artery at the aneurysm neck level to disrupt the intra-aneurysmal flow, both provide significant rheologic effects with potential changes in the transmural pressure gradient and progressively create an intra-aneurysmal thrombosis, thus offering good support for the neointima development (6).

The following are the approved five types of intracranial aneurysm treatment: Silk (Balt Extrusion, Montmorency, France), Pipeline Embolization Device (PED) (Covidien, Mansfield, MA, USA), p64 Flow-Modulation Device (Phoenix, AZ, USA), Flow Re-direction Endoluminal Device (Microvention, Tustin, CA, USA), and Surpass Flow-Diverter (Surpass; Stryker Neurovascular, Fremont, CA, USA).

The PED (Chestnut Medical Technologies, Menlo Park, CA) was the first commercially available FDD. Pipeline received



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the Conformité Européene mark in June 2008 and entered the market after receiving the Food and Drug Administration approval on April 6, 2011. Since then, exponential growth has been witnessed in technological advancements in flow-diverter stent (7). In addition, modeling stents can be used to support FDDs according to the configuration of aneurysms (Figure 2).

FDDs are rapidly becoming a suitable alternative to the traditional endosaccular treatments for uncoilable aneurysms. Among all saccular aneurysms, those with large necks and low dome-to-neck ratio should preferably be treated by FDDs because they respond less favorably to other treatments.

### Middle Meningeal Artery (MMA) Embolization

MMA embolization has emerged as a promising treatment for chronic subdural hematoma (cSDH). cSDH incidence increase with increasing antiplatelet and anticoagulant use and the aging population (8). Spontaneous resolution of cSDH is rarely seen and mainly reported for patients with thrombotic thrombocytopenic purpura (9). Craniotomy or burr-hole irrigation and drainage are considered the gold standard for symptomatic cSDH. However, 5-30% of operative cases are associated with hematoma recurrence (10-15).

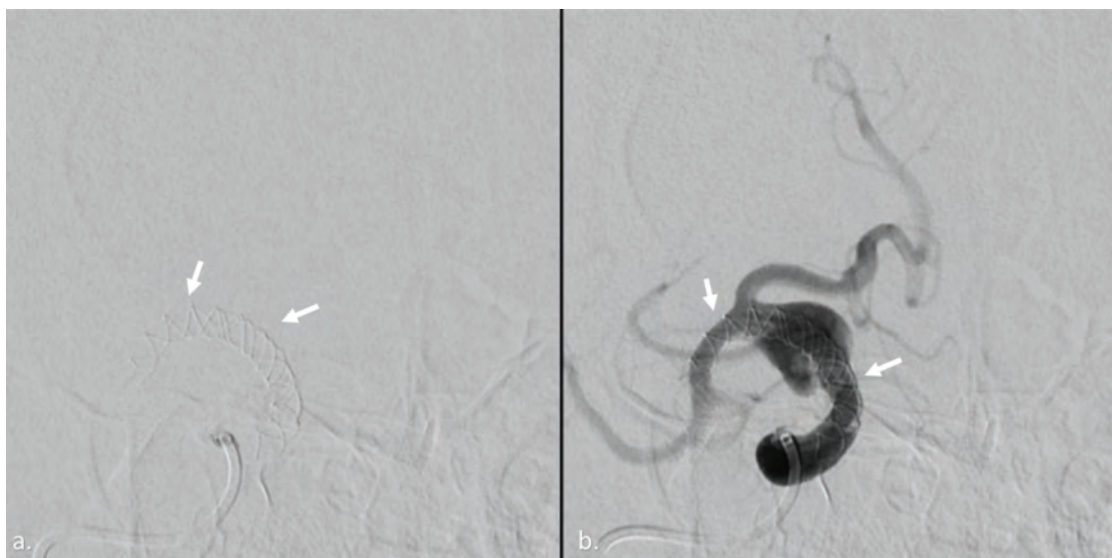


a.



b.

**Figure 1.** (a, b) The schematic diagram shows the (a) fluoro images of Comaneci device-assisted (arrowheads) coiling (arrow). After the coiling, the Comaneci device is pulled out



a.

b.

**Figure 2.** (a, b) The digital subtracted angiography images show the flow-diverter device (arrows) through the saccular aneurysm

Repeated recurrence is potentially due to the failure of surgical evacuation alone to address the underlying pathophysiologic mechanism of cSDH formation, which involves the formation of fragile capillaries along the subdural membrane encapsulating the collection (16-18). Endovascular embolization of the MMA has been proposed as a minimally invasive method to permanently address the vascular supply of cSDH. Preliminary studies have evaluated the safety and efficacy of MMA embolization as a standalone procedure and in combination with surgical evacuation, with encouraging results (19) (Figure 3).

### Thyroid Ablation and Embolization

Surgery is the primary therapeutic approach in benign and malign thyroid nodules; however, thermal ablation techniques and thyroid artery embolization procedures are the more recently used minimally invasive interventional radiological treatment options as a comparable alternative to the surgery in nodular thyroid diseases management (20-24). Moreover, recent studies showed that thermal ablation procedures are effective in papillary microcarcinoma of the thyroid gland (23,25). As a comfortable treatment option, thermal ablation procedures started to also be frequently preferred by patients. Compared with surgical procedures, thermal ablation techniques appear as treatment methods that take a very short time, are easily applied and repeated, and most importantly, thyroid function-preserving treatment options (26). Additionally, thermal ablative procedures are the novel alternatives of radioactive iodine treatment in patients with autonomously functioning thyroid nodules (27). During patient follow-up, the greatest volume reduction is usually observed within the first month after ablation, followed by a more gradual decrease (28). Several sessions are needed, especially in patients suffering from cosmetic problems and

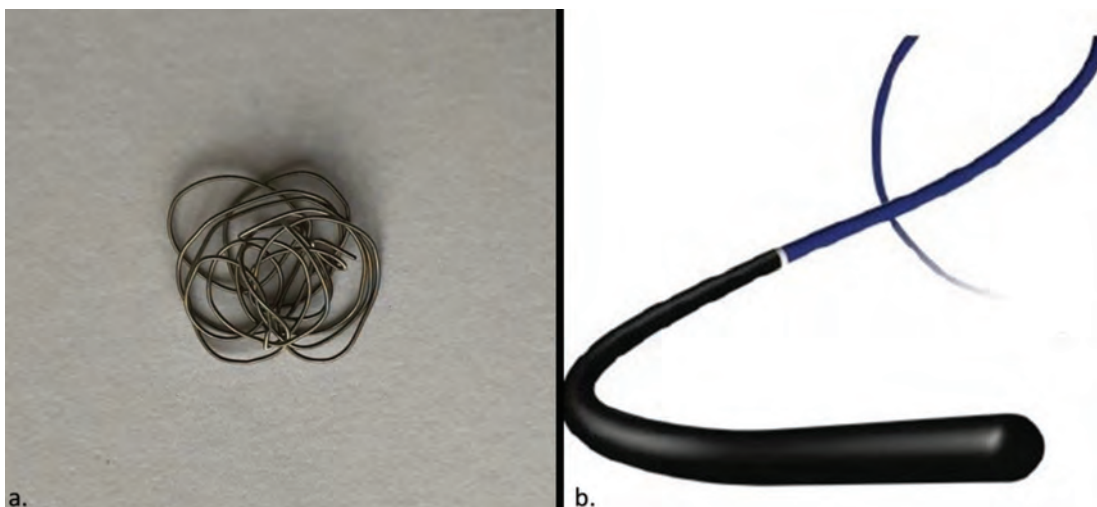
patients with large nodules, to achieve complete ablation. Some complications, such as pain, voice change, skin burn, hematoma, and thyroid function disorders, have been reported in the literature; however, most patients recovered without any permanent sequela (28,29) (Figure 4).

### Cryoablation

Cryoablation is one of the minimally invasive tumor ablation techniques, which is used in the daily practice of interventional radiology, especially for the liver, kidney, lungs, breast, and soft tissue masses (30-35). The specially designed ablation probes, which are called cryoprobes, are used during the procedure. The basic principle of the system refers to the use of thermal energy in low temperatures to achieve tumor cell destructions by freezing and thawing. This process occurred in different mechanisms, such as mechanical, osmotic, ischemic, and immunologic (36,37). The most prominent advantage of cryoablation over other thermal ablation procedures, like radiofrequency (RF) or microwave (MW) ablation, is the real-time ablation zone observation, which is called an ice ball even in different radiological guidance. This issue would make the ablation session safer by avoiding non-target ablation and minimizing complications. Contrarily, longer ablation time and smaller ablation zone are the main disadvantages of this technique compared to MW and RF ablations (38). Besides the most common complication after an ablation treatment due to the systemic response, which is a post-ablation syndrome, a more severe clinical condition, called cryoshock, that encompasses coagulopathy and multiorgan failure could rarely occur (39).

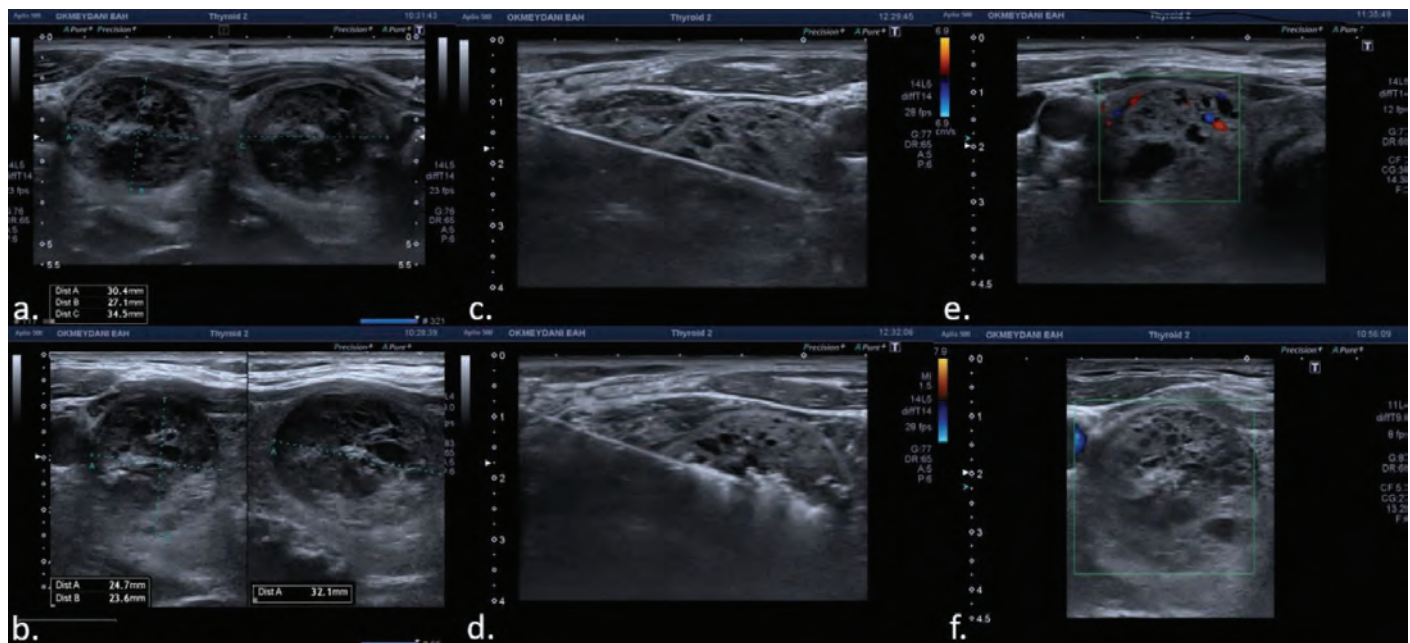
### Chemosaturation

Besides primary tumors, the liver is among the organs with frequent metastasis (40). Surgical treatments, such as resection



**Figure 3.** (a, b) One of the most common embolic materials is coils (a), which are deployed through small-size microcatheters (b)





**Figure 4.** (a-f) Ultrasound-guided microwave ablation treatment of an autonomously functioning thyroid nodule (c-d). Compared to preprocedural volume (a), approximately 40 percent of reduction was achieved after the procedure (b). The Doppler signal on admission (e) was not seen anymore (f). The clinical conditions of the patient recovered and the thyroid functions were within normal limits

and transplantation, can be performed in primary and suitably metastatic tumors. Additionally, some interventional radiological procedures, such as local ablative and transarterial treatments, can be performed in patients who are not suitable for surgery and/or as part of combined treatments (40). Moreover, chemosaturation is another interventional radiological procedure for disease control, with prolonged survival, symptom palliation, and quality of life improvement in patients with primary liver tumors and liver metastases that cannot be surgically treated (40). This method aimed to expose the liver to the chemotherapeutic agent as intensely as possible, by delivering a high concentration of chemotherapeutic agent (melphalan) to the liver tissue through the arterial vascular inlet and taken out to the extracorporeal area by venous outlet before it reaches the systemic circulation. After the chemotherapeutic agent is cleared by the hemofiltration system, the blood flow is directed to the systemic circulation through second venous access. In this way, the liver tissue reaches intense chemotherapeutic concentrations in contrast to the very low concentrations in the systemic circulation (41). The effectiveness of chemosaturation has been demonstrated in the treatment of hepatocellular carcinoma, malignant melanoma metastasis, neuroendocrine tumor metastases, and cholangiocellular carcinoma that are not suitable for surgery and unresponsive to other treatments (41-45). Some studies and case reports reported that stable disease was observed in some other metastatic tumor treatments (41,44).

Patients with Child-Pugh B or C, proven portal hypertension, history of transient ischemic attack, left ventricular ejection fraction of <50%, bodyweight of <35 kg, history of gastrinoma, and those incompatible with general anesthesia constitutes the unsuitable group for the procedure, as well as general angiography contraindications (41). More studies are needed to compare the technique with other treatment options.

### Bariatric Embolization

Obesity, which is common worldwide, is one of the important health problems that affect mortality and morbidity (46). The surgical approach is the standard treatment method in patients with obesity; however, transarterial embolization has become one of the alternative treatment options in selected patients. The method named bariatric arterial embolization in the literature is based on the catheterization of the left gastric and gastroepiploic arteries, accompanied by the main femoral artery access and the administration of embolic agents at these levels. The left gastric artery provides gastric fundus nutrition, thus reducing most of the ghrelin release from this level after embolization is theoretically planned (47). As a result of the decreased ghrelin level, weight loss is achieved in patients by reducing hunger at the hypothalamic level (48).

Studies are ongoing in the literature; however, significant results have been obtained according to the published preliminary reports of the GET LEAN study, in which patients' weight loss,



quality of life, and appetite hormone levels are evaluated after 1-year follow-up (49). The preliminary results of the study conducted by Bai et al. (50) in China reported a significant decrease in subcutaneous fat tissue during follow-up in magnetic resonance imaging while providing safety and efficacy results that support other studies. In addition, the BEATLES study is still in progress and will be completed in 2023 as a randomized and placebo-controlled study that includes the 12-month follow-up results of the bodyweight changes in 59 patients in the study (51).

### **Uterine Fibroid Embolization**

Most of the uterine fibroids, which constitute the most common uterine tumor in females of reproductive age, are asymptomatic and do not require treatment (52). Hysterectomy is a curative treatment method for the treatment of fibroids that cause mass effects and bleeding-related symptoms (52) but is not an appropriate treatment method for patients who consider having a child of reproductive age (53). Myomectomy is the uterine-sparing surgical method that can be applied in this patient group (53). As an alternative to these surgical treatments, uterine fibroid embolization, which is a minimally invasive interventional method together with percutaneous ablation, is a treatment method that includes the embolization of appropriate vessels that feeds the fibroid through the common femoral artery and from the bilateral uterine arteries and collateral pathways (54). Treatment indication includes patients with fibroid-related menometrorrhagia, pelvic pain, pelvic pressure sensation due to the mass effect of myoma, sudden urination, frequent urination, incontinence retention, and hydronephrosis (54). The procedure is contraindicated in patients with pregnancy and suspected pelvic gynecological malignancy, as well as general angiographic procedure contraindications. The procedure should not be preferred in patients who plan for pregnancy within 2 years, since patients who underwent myomectomy have a higher chance of pregnancy during this period (53,54). Studies show that uterine fibroid embolization procedure treats symptoms that are related to menometrorrhagia and with mass effect at the same level as surgical treatments (54,55). In addition, studies compared long-term results with surgery and revealed procedure effectiveness. Results of short and long-term studies (level A evidence level) revealed that uterine fibroid embolization is accepted as an effective and safe treatment method in selected patients who want to preserve their uterus (52,54,56).

### **Fallopian Tube Recanalization (FTR)**

FTR is the reopening of the fallopian tubes with the help of microcatheters and micro guidewires, which the interventional radiologist places into the vagina and cervix.

The microcatheter is inserted through the fallopian tube over a micro guidewire and clears any blockages in the fallopian tubes and restores the connection between the uterus and the abdominal cavity. This procedure is used to treat infertility caused by a blockage in the proximal fallopian tubes. Knowing the patient's menstrual cycle and ovulation timing is important to optimize pregnancy outcomes following FTR. FTR contraindications include active pelvic infection, pelvic malignancy, or pregnancy (57).

Technical success of FTR is noted in up to 100% of cases (58,59), with the postprocedural re-occlusion rate of 20-50% (60). The pregnancy rate in 1-year following FTR is approximately 41%, with the successful delivery of full-term infants in 84% of pregnancies (59). The global pregnancy and delivery rates for in vitro fertilization (IVF) are 24.0% and 17.6%, respectively and for intracytoplasmic sperm injection (ICSI) is 26.2% and 19.0%, respectively (61). Therefore, FTR should be considered and offered to patients who present with infertility secondary to proximal fallopian tube obstruction, particularly when they wish to pursue natural methods of conception before IVF or ICSI.

### **Hemorrhoidal Embolization**

Hemorrhoidal disease is an important health problem that causes deterioration in the psychological and physical conditions of patients in the anorectal region. Today, most patients benefit from local treatments, but 10% of patients are treated with surgery (62). Endovascular hemorrhoidal embolization, called the emborrhoid technique in the literature, has emerged as a promising minimally invasive alternative method to surgical treatment (63). Clinical studies determined the main indication for emborrhoid method as patients with grade 1-3 bleeding hemorrhoids (64). The technique is performed by angiography after access from the patient's right main femoral artery, accompanied by the superior rectal artery that originates from the inferior mesenteric artery branch, and the medial rectal artery that commonly originates from the internal iliac artery. It involves embolizing agent injection by selecting those vessels. Medial rectal artery variation is seen in a wide range of 12-97% and may originate from the internal pudendal artery or the inferior gluteal artery. The classifications of rectal vascularity defined the types in which the medial rectal artery is dominant in arterial nutrition (65,66). This anatomical variation significantly affects the success of embolization. Robust literature data were obtained for the safety and efficacy of the technique from 7 studies that are conducted with a total of 230 cases and between 2014 and 2021 (66). El Tawab et al. (67) reported

anal pain in 27 (81%) of 33 patients after embolization, with self-limited symptoms and no complications in the follow-up. The literature reported a clinical success range of 63-97%. The important factors affecting clinical success are the variability in the defecation habits and diets of patients after the treatment and their compliance with the primary medical treatment.

The current data and the number of patients in studies are still very small; however, endovascular embolization is a promising treatment for patients with comorbidities who are not suitable for surgical treatment or with other primary pathology at the anorectal level compared with other surgical treatment methods (67).

### **Treatment of Varicocele**

Varicocele, defined as dilatation and venous insufficiency in the pampiniform plexus, is a health problem seen in approximately 15% of the adult male population (68). Varicocele, which is the most common cause of male infertility, constitutes the cause in 30-40% of patients who are investigated for primary infertility that reaches 85% in the patient group presenting with secondary infertility. Various surgical methods can be used in varicocele treatment (68). Varicocele embolization is an alternative procedure to surgery, in which the gonadal veins are reached via the main femoral vein or the internal jugular vein and incompetent vein embolization is performed using various embolizing agents (69). Varicocele embolization was initially a treatment method used in patients with recurrent varicoceles after surgery or those with spermiograms that did not improve in the third month after surgery; however, it has now become the primary treatment method for varicocele (54). Patients with testicular pain and edema, varicocele-induced infertility, postoperative recurrent varicocele, and testicular atrophy in the pediatric population are suitable for the procedure (70). Numerous studies showed that varicocele embolization is a more comfortable and minimally invasive interventional method that improves spermiogram pain and increases pregnancy rates, with lower complications and faster recovery time (68-70).

### **Prostatic Artery Embolization (PAE)**

PAE is a technique that results in prostatic artery occlusion, which most commonly originates from a branch of the internal iliac artery using particular embolic agents, such as polyvinyl acetate or microspheres. Due to ischemia in the prostate, apoptosis is triggered in the glandular cells that shrink/soften the prostate gland associated with the improvement of lower urinary tract symptoms (LUTS). Moreover, decreased density of  $\alpha$ -1 adrenergic receptors by cell death leads to relaxation of smooth muscles

that contribute to clinical improvement (71). Patients who cannot tolerate or with failed medical treatment can have PAE, especially, patients with very large prostate volume ( $>100\text{ cm}^3$ ), multi-comorbidities, prostatic hemorrhage, and indwelling foley catheters.

PAE is a minimally invasive procedure and is performed on an outpatient basis. Patients return to normal activities in a shorter period and complication rates are fewer in PAE compared to surgical methods. In addition, erectile and ejaculatory dysfunctions are less frequently seen (72). Compared with surgical methods, LUTS reduction is similar in PAE; however, improvements in peak flow rate, post-void residual volume, and prostate volume are less. PAE is recommended as a safe and acceptable minimally invasive treatment for appropriately selected patients using the Society of Interventional Radiology (SIR) guidelines (73). Further, SIR recommends PAE as a treatment option for patients with large prostate volume ( $>100\text{ cm}^3$ ) and acute or chronic urinary retention.

### **Geniculate Artery Embolization (GAE)**

GAE is a new procedure that is performed in mild and moderate knee osteoarthritis (OA) refractory to the medical treatment for pain management. In this procedure, genicular arteries in the knee region, where patients mostly suffer pain, are determined by digital subtraction angiography and are embolized by using embolic agents like particles, polyvinyl alcohol, or imipenem/cilastatin. Many studies were reported to understand the mechanism of knee pain in OA. The most important theory is inflammatory mediator-associated neurosensitization. Increased sensory nerves and neoangiogenesis caused by inflammatory mediators, which are released from the affected knee, play an important role in this mechanism. As microtrauma and inflammation persist, sensorial nerves are easily activated (74). Consequently, patients suffer from pain in minimal movement or even at rest. In GAE, pain control is expected by embolizing those neoangiogenic vessels. GAE is indicated in patients who are non-responsive to medical treatments and minimally invasive procedures, such as intraarticular glucocorticoid/hyaluronic acid injections. These minimally invasive procedures can provide short-term pain relief. Therefore, GAE can be offered to these patients as an alternative treatment before surgery.

A recent meta-analysis that included 11 studies with a median follow-up time of 6-12 months analyzed the visual analog score (VAS) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores (75). Statistically, significant decreases are reported in both VAS and WOMAC scores starting from 1 to 12 months after GAE. Very few studies reported

minor complications according to the SIR guidelines and no studies showed major complications. Likewise, a statistically significant decrease in the need for pain medications (opioids and non-steroid anti-inflammatory drugs) is reported in these studies. A recent randomized controlled trial (RCT) compared the effectiveness of GAE to placebo (76) and reported a statistically significant decrease in both VAS and WOMAC scores in patients who underwent GAE procedure, without any improvement in pain scores in the placebo group. RCTs on the safety and effectiveness of GAE are ongoing and, undoubtedly, GAE has great potential in the management of moderate OA.

### Ethics

**Peer-review:** Internally peer-reviewed.

### Authorship Contributions

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

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# Etiological Evaluation of Infants with Wheezing

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## Abstract

**Objective:** Patients with recurrent wheezing should be evaluated for asthma and the differential diagnosis should be posed carefully. The study aimed to evaluate the demographic and etiological characteristics of patients presenting with recurrent wheezing less than 3 years.

**Methods:** Ninety-two children with wheezing were included in this retrospective study at the University of Health Sciences Turkey, Dr. Sami Ulus Maternity Outpatient Clinic, Children's and Diseases Training and Research Hospital, Ankara, Turkey between March 2009 and March 2010. The demographic characteristics, number of wheezing episodes over the last year, the number of hospitalizations, and eosinophil counts were recorded.

**Results:** The mean age of the participants was 19.9+9.4 months and the youngest patient was 6 months old. The sample population included seventy (70) boys. The etiologic evaluation of the study population included 42 patients with atopic wheezing, 28 patients with gastroesophageal reflux (GER), and 23 patients with a viral associated wheezing. Eosinophilia was not statistically significant in patients with a family history of atopy (18 patients) related to those with no family history of atopy.

**Conclusion:** In this study, the most prevalent etiological factor was atopy, followed by GER and viral agents, respectively. The definition of children with wheezing includes diseases with different pathophysiology, course, and prognosis. Children with non-atopic wheezing may develop chronic lung inflammation similar to asthma. It is necessary to identify these disorders early enough via monitoring closely and managing adequately. Obtained from the thesis titled, "Is there a diagnostic value of high-sensitivity C-reactive protein in wheezing infants?"

**Keywords:** Wheezing infant, asthma, eosinophilia, etiology

## INTRODUCTION

Wheezing is a high-frequency polyphonic whistling sound, which is usually caused by irregular airflow in narrowing bronchial lumen caused by bronchospasm, mucosal edema, and inflammation (1). Although it can be heard at any age, it is most common in infancy. The prevalence of wheezing ranges between 4-32% in infancy (2). An infant with wheezing can be defined as the occurrence of at least 3 lower respiratory tract infections with wheezing (first episode before 1 year of age) in the first 2 years of life (3).

Recurrent childhood wheezing is often associated with recurrent upper respiratory tract infection (2). Lower respiratory tract infections (bronchiolitis, pneumonia), gastroesophageal reflux

(GER), aspiration, congenital malformations (vascular ring, tracheoesophageal fistula, esophageal cyst), bronchiectasis, cystic fibrosis, bronchopulmonary dysplasia, bronchiectasis, congenital heart diseases, foreign body aspiration are the other origins of wheezing in infancy (4). Wheezing in early childhood can be classified into 3 subgroups namely early transient wheezing, late-onset wheezing, and persistent wheezing (5,6).

The differential diagnosis of asthma should be posed in a patient below 3 years presenting recurrent wheezing after exclusion of other possible etiologies (5). Wheezing attacks in early childhood may be the first sign of asthma, and it is important to determine the patients at risk of asthma by evaluating hereditary and environmental risk factors; thus, initiating treatment early enough for effective disease control (6). Eosinophils, mast cells,



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lymphocyte mediators, and cytokines released from these cells are responsible for chronic inflammation in the pathogenesis of asthma. Eosinophils play an important role in asthmatic chronic inflammation (7). Although there are studies evaluating factors that play a role in the development of childhood asthma, its real cause is still unclear.

This study aimed to evaluate the demographic and etiologic characteristics of patients with recurrent wheezing under the age of 3 years, related to the eosinophil counts and IgE levels, according to the asthma predictive index (API) and the presence of a family history of atopy, respectively.

## METHODS

Ninety-two wheezy children were included in this retrospective study at the University of Health Sciences Turkey, Dr. Sami Ulus Maternity Outpatient Clinic, Children's and Diseases Training and Research Hospital, Ankara, Turkey between March 2009 and March 2010. The inclusion criteria for the group were as follows: (i) Age between 6 and 36 months; and (ii) wheezing episodes during the last 12 months. The exclusion criteria were: (i) any evidence of bacterial infection, body temperature  $>39^{\circ}\text{C}$ , white blood cell count  $>20.000/\mu\text{L}$ , predominantly neutrophilia on a peripheral blood smear, positive throat, urine, or blood cultures; (ii) pleural effusion, lobar consolidation other than lung hyperinflation, interstitial infiltration, and peribronchial thickening on chest X-ray; (iii) inflammatory disease, obesity, heart disease, or diabetes mellitus.

Age, sex, passive smoking exposure, family history of atopy, number of attacks in the last year, the number of hospitalizations, white blood cell count, and eosinophils (evaluated at 4% or more in peripheral smear) were recorded. The patients were grouped according to the modified API criteria (8). Serum total immunoglobulin E (IgE) was evaluated on nephelometry (Siemens Healthcare Diagnostics, Deerfield, Germany), and readings  $>2$  standard deviation (SD) were considered high with respect to age.

In patients with treatment failure, a detailed evaluation was performed for differential diagnosis (sweat test, cardiac evaluation, thorax CT, immunodeficiency tests) and these cases were excluded from the study.

### Statistical Analysis

All results were analyzed using Statistical Package for Social Sciences version 22-SPSS 22 (SPSS, Chicago, IL, USA). Categorical variables are described as percentages and numbers while continuous variables were expressed as minimum, maximum,

and mean  $\pm$  SD. The chi-squared and Mann-Whitney U tests were used for non-normally distributed variables. Student's t-test was used to compare normally distributed parametric data. Statistical significance was set at  $p<0.05$ . The Spearman correlation test was used to evaluate the potential correlations between variables.

## RESULTS

The mean age of the 92 patients included in this study was  $19.9\pm 9.4$  months and the youngest patient was 6 months old. Demographic characteristics of the study participants are reported in Table 1. The presence of a family history of atopy was revealed (maternal asthma in 6 cases, maternal allergic rhinitis in 4 cases, paternal asthma in 3 cases, paternal allergic rhinitis in 2 cases, asthma in the brother in 3 cases) in 18 cases (19.6%).

There was no statistically significant difference between the frequency of wheezing attacks and the number of hospitalizations in patients with smoking exposure compared to non-smokers ( $p=0.5$ ). There was no statistically significant difference between the frequency of wheezing attacks and the number of hospitalizations in preterm cases compared to term cases ( $p=0.8$ ).

The etiological evaluation of the cases is displayed in Table 2. The mean number of wheezing attacks was  $5\pm 1.4$  (4-12), 51 patients (55%) were hospitalized at least once within the last 12 months of the study period. Elevated IgE levels were detected in 39 (42%) and eosinophilia in 20 (21%) cases. Fifty-one (55%) of the patients have been treated in the last 3 months. Treatment

	n (%)
<b>Gender</b>	
Male	70 (76)
<b>Gestational age</b>	
Term	79 (85)
Smoking exposure	47 (51)
Pet feeding	7 (7)
Presence of atopy in family members	18 (19.6)
Asthma predictive index positivity	42 (45)

	n (%)
Patients with atopic wheezing	42 (45)
Patients with gastroesophageal reflux	28 (30)
Patients with viral induced wheezing	23 (25)

options for the positive cases were as follows: 27 (29%) cases were managed with inhaled corticosteroids, 18 (19%) cases with leukotriene antagonists and meanwhile, 6 (6%) patients with combined inhaled corticosteroids and leukotriene antagonists.

Eosinophilia or IgE elevation was not statistically significant in 18 patients with a family history of atopy compared to those without an atopic family history ( $p=0.053$  and  $p=0.844$ ). Mean eosinophil percentages of cases with familial atopy was  $4.08\pm 3.15$ , and mean eosinophil percentages of cases without familial atopy was  $2.41\pm 1.50$ .

Eosinophil percentages of the patients with a family history were statistically significantly higher than those without familial atopy in family members ( $p=0.001$ ). No correlation was found between eosinophilia and IgE elevation. There was a moderate correlation between IgE and Eosinophilia levels in patients with a family history of atopy ( $r=0.579$ ,  $p=0.012$ ).

## DISCUSSION

Ninety-two wheezy children were consequently enrolled in this study at the University of Health Sciences Turkey, Dr. Sami Ulus Maternity Outpatient Clinic, Children's and Diseases Training and Research Hospital, Ankara, Turkey between March 2009 and March 2010. The most common etiological factor was atopy, followed by GER and viral agents, respectively. The mean age of the study subjects was  $19.9\pm 9.3$  months and the youngest patient was 6 months old. The mean number of wheezing attacks was  $5\pm 1.4$ .

Boys constituted the majority of our study participants, which is inconsistent with the literature (2). In a study by İnal et al. (9) 60% of the cases were male. This male/female ratio was similar to our study.

Possible explanations of this male predominance could be relative airway obstruction, delayed immune maturation, low lung capacity, high airway resistance, or hormonal or vascular/bronchial tone differences.

In our study, 14% of the cases were preterm. No statistically significant difference was observed between the preterm and term infants in terms of frequency of attacks and the number of hospitalizations. Although preterm infants may have a more severe risk of developing bronchiolitis, they are more likely to receive Respiratory Syncytial Virus Ig prophylaxis and their families are more conscious.

Because GER is an important disease that increases wheezing, the diagnosis and treatment of GER should not be overlooked in patients with recurrent wheezing. GER is one of the major

concomitant diseases in infants with wheezing; thus, it is important to educate families about GER regarding the importance of treatment (10). In this study, GER was detected in 28 cases (30%). GER should be investigated especially in patients with a history of vomiting, wheezing, and increased cough after feeding and night coughs. In a study evaluating infants between 3 and 48 months with recurrent wheezing episodes in Turkey, the frequency of reflux was revealed to be 21.1% (4).

Differential diagnosis of wheezing is important and will improve the treatment success, and also has an important role in the case follow-ups. In patients resistant to the treatment, tuberculosis, cystic fibrosis, congenital lung malformations, and congenital heart diseases should be considered in the differential diagnosis (11,12). In our study, cases with therapeutic failure were evaluated for possible etiological factors, and patients with underlying disorders were excluded from the study.

Some studies endorse the idea that smoking exposure is an important risk factor for wheezing in the prenatal and postnatal periods. In our study, smoking exposure was disclosed in 47 cases (51.1%). Contrary to other literature, the frequency of wheezing attacks and hospitalization were not increased due to smoking exposure. When smoking at home was investigated in detail, it was disclosed that none of the smokers were the mothers of the cases. Additionally, most of the smokers smoked on the balcony (40 cases) and some of them changed their clothes after smoking (10 cases). These factors may explain the fact that the number of episodes and the frequency of hospitalizations were not different from those of non-smokers. Feeding a pet is known to increase the frequency of wheezing (8). In our study, detailed statistical analysis could not be performed due to the limited number of participants involved in pet feeding.

Eosinophilia or IgE elevation was not statistically significant in 18 cases with a family history of atopy related to those without atopy in family members ( $p=0.053$  and  $p=0.844$ ). But eosinophil percentages of the patients with the presence of atopy in family members were found to be significantly higher than those without a family history of atopy ( $p=0.001$ ). Although higher eosinophilia was detected in peripheral blood in atopic wheezing infants, this difference was not statistically significant compared to their non-atopic counterparts. This finding suggests that the pathological changes in asthma-like remodeling in wheezing infants without atopy inconsistent with the literature.

Bronchial biopsy disclosed a significantly higher basal membrane thickness and eosinophilic inflammation increases with increasing basal membrane thickness in patients with recurrent wheezing (13,14). In the study by Turato et al. (15) it was reported

that basal membrane thickness and eosinophil count were significantly higher in preschool children with wheezing without atopy than in the control group.

## CONCLUSION

In summary, the definition of wheezy children includes diseases with different pathophysiology, course, and prognosis. It is necessary to differentiate these diseases in the early stages and provide adequate follow-up and management approaches. Moreover, it should be noted that children with non-atopic wheezing may develop chronic lung inflammation similar to asthma.

### Ethics

**Ethics Committee Approval:** Retrospective study.

**Informed Consent:** Retrospective study.

**Peer-review:** Internally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: H.S.Ş., Concept: H.S.Ş., Design: Ö.V., Data Collection or Processing: Ö.V., H.S.Ş., Analysis or Interpretation: H.S.Ş., Literature Search: H.S.Ş., Ö.V., Writing: H.S.Ş., Ö.V.

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# Comparing BST-CarGel® with Hyalofast for the Treatment of Hyaline Cartilage Defects

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## Abstract

**Objective:** This study aimed to evaluate the clinical and radiological results of patients with medial femoral condyl defect who were treated with microfracture technique added with BST-CarGel® or Hyalofast as a scaffold at the end of surgery.

**Methods:** A total of 12 patients who had undergone microfracture surgery added with BST-CarGel® or Hyalofast as a scaffold were evaluated. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score was clinically evaluated, and the area measurement and depth and underlying structures (AMADEUS) score and defect filling were radiologically evaluated.

**Results:** The mean patient age was  $49.66 \pm 6.31$  years, and the mean follow-up time was  $21.75 \pm 7.72$  months. Seven patients also received BST-CarGel®, and five received Hyalofast at the end of surgery. The improvement of the WOMAC score, AMADEUS score, and defect filling after treatment were significant compared with preoperative data ( $p < 0.001$ ). No difference was found clinically and radiologically between the BST-CarGel® or Hyalofast group.

**Conclusion:** Microfracture treatment supplemented with BST-CarGel® or Hyalofast scaffolds at the end of surgery is a safe and helpful treatment for cartilage defects.

**Keywords:** Hyaline cartilage defect, microfracture, scaffold, BST-CarGel®, Hyalofast

## INTRODUCTION

Cartilage lesions more commonly occur with aging. Cartilage lesions are believed to progress to degenerative osteoarthritis. Because of pain, stiffness, movement limitation, decreasing quality of life, and progression to osteoarthritis, chondral defects are predisposed to surgery (1). Traditionally, hyaline cartilage surgeries can be performed with osteochondral replacement (2) or cartilage regeneration by autologous chondrocyte implantation (3). The advantage of these techniques are related to the use of mature autologous cartilage cells. Donor-site pathology, discontinuity in the orientation of the cartilage plugs, and fibrocartilage in the gaps are disadvantages of the osteochondral replacement technique (2). Moreover, the need for two operative procedures and higher costs, are disadvantages of autologous chondrocyte implantation (4). The

microfracture technique is another treatment method for chondral defects, which was described by Steadman et al. (5). This technique is based on bone marrow stimulation (5). The microfracture technique promotes the migration of mesenchymal stem cells for the maintenance of the cartilage in the articular surface. This technique forms fibrous cartilage that is not as durable as the hyaline cartilage (6).

Complications of hyaline cartilage-based surgeries and the decreased durability of the fibrous cartilage provided by the microfracture technique prompted tissue engineering professionals to strengthen the fibrous cartilage formed after microfracture. The application of scaffolds to microfracture surgery reduces this deficiency by strengthening the quality of the formed fibrous cartilage (7,8). Of these scaffolds, BST-CarGel® (Bio-Orthopaedics Division, Piramal Life Sciences, Mumbai,



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India) stabilizes the microfracture-based blood clot by dispersing a soluble polymer scaffold containing chitosan throughout the blood and implanting the mixture over marrow access holes in a cartilage lesion (9). Another example of these scaffolds is Hyalofast (Fidia Advanced Biopolymers, Abano Terme, Italy), in which hyaluronan is one of the principal component of the articular cartilage matrix (4,10). Hyalofast promotes the release of collagen from the chondrocytes to maintain the extracellular matrix (10).

With the BST-CarGel® surgical technique, the surgeon must wait until the liquid form of the scaffold has coagulated. To achieve clotting, the defect must be parallel to the ground and the defect must allow the pooling of the liquid in the defect area during surgery. In the presence of a groove at the defect or the defect was not parallel to the ground during the clotting process, the liquid scaffold would certainly flow out of the microfracture area. However, Hyalofast is not a liquid scaffold. Thus, in our clinic, we prefer the BST-CarGel® if the defect allows pooling of the liquid scaffold. Otherwise, Hyalofast scaffold was preferred.

Because of the revealed advantage of using scaffolds, we use them in our clinic practice within its indication (1,5,6,9,11). BST-CarGel® and Hyalofast were previously compared with the microfracture technique. In this study, we aimed to present and compare the clinical and radiological results of our patients to whom these two scaffolds were added.

## METHODS

The study began after it was granted permission by the Local Ethics Committee of Giresun University Giresun University Clinical Research (no: 90139838-000-E.28161, 2019-56). We retrospectively evaluated the patients who were threatened for grade 3-4 cartilage lesions of the knee joint according to the Outerbridge Arthroscopic Grading System. We investigated the patients who underwent cartilage implantation using BST-CarGel® or Hyalofast between March 2016 and March 2018 in Giresun University Hospital. The inclusion criteria, patients older than 40, patients with medial femoral condyl lesions, and patients in whom BST-CarGel® or Hyalofast was added to the microfracture surgery. The exclusion criteria were as follows: Patients with trauma, patients with additional surgeries such as osteotomy, anterior cruciate ligament reconstruction or meniscal repair, patients with additional lesions at other surfaces of the knee, patients with rheumatic diseases, patients who have <1 year of follow-up, and patients whose data could not be reached.

For the clinical evaluation, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores were taken

before surgery and at the last follow-up. For the radiologic evaluation, magnetic resonance imaging (MRI) sections which were taken before surgery and at the last follow-up were evaluated according to the area measurement and depth and underlying structures (AMADEUS) (12).

## Surgical Technique

All procedures were performed under spinal anesthesia and tourniquet. Standard anterolateral and anteromedial arthroscopic portals were used. Microfracture was performed as previously described (5). After obtaining the microfracture, a mini arthrotomy was performed by extending the anteromedial portal for the application of the scaffolds. The surgical techniques for BST-CarGel® (13) or Hyalofast (14) were similar as previously described. The choice of the used scaffold was based on the structure of the cartilage defect. We used the liquid BST-CarGel® if the defect allows for pooling of the fluid; otherwise, Hyalofast was used. Before all applications of the scaffolds, the microfracture area was wiped and dried with sponge via mini arthrotomy formed by extending the anteromedial arthroscopy portal. Briefly, BST-CarGel® was prepared with 4.5 mL of venous blood. Then, BST-CarGel® was injected into the microfracture area. After injection of BST-CarGel®, we waited for 15 min for the blood clot, and Hyalofast was prepared using a template of the microfracture area intraoperatively. Finally, Hyalofast was impregnated with venous blood and then placed to the microfracture area. The scaffolds were controlled in terms of stabilization after tourniquet was terminated. At the follow-up, the same rehabilitation protocol was implemented in all patients (15).

Complex meniscal tears were treated with partial meniscectomy before performing microfracture.

## Evaluation of MRI

Knee MRI of patients were taken on a 1.5 Tesla MR device [MAGNETOM Aera®; Siemens Healthcare, Erlangen, Germany]. Images for all patients were uploaded to a radiology work station (syngo.via, Siemens AG, Erlangen, Germany) on the hospital's PACS system and then evaluated. The sagittal and coronal T2 images were used for measurements. The measurements were performed by the consensus of the two authors. Evaluations were made according to AMADEUS score as previously described (12). In addition, we compared the defect filling according to the "area measurement" criteria of the AMADEUS score.

## Statistical Analysis

In this study, statistical analysis was made by using "SPSS Statistics version 23 (IBM Corp., NY, USA)". The Shapiro-Wilk test

was used to test for the normality of the variables. Independent samples t-test and paired sample t-tests were used to compare the means. Arithmetic mean and standard deviations were used as descriptive statistics. Besides, an alpha of 0.05 was used as the cutoff for significance.

## RESULTS

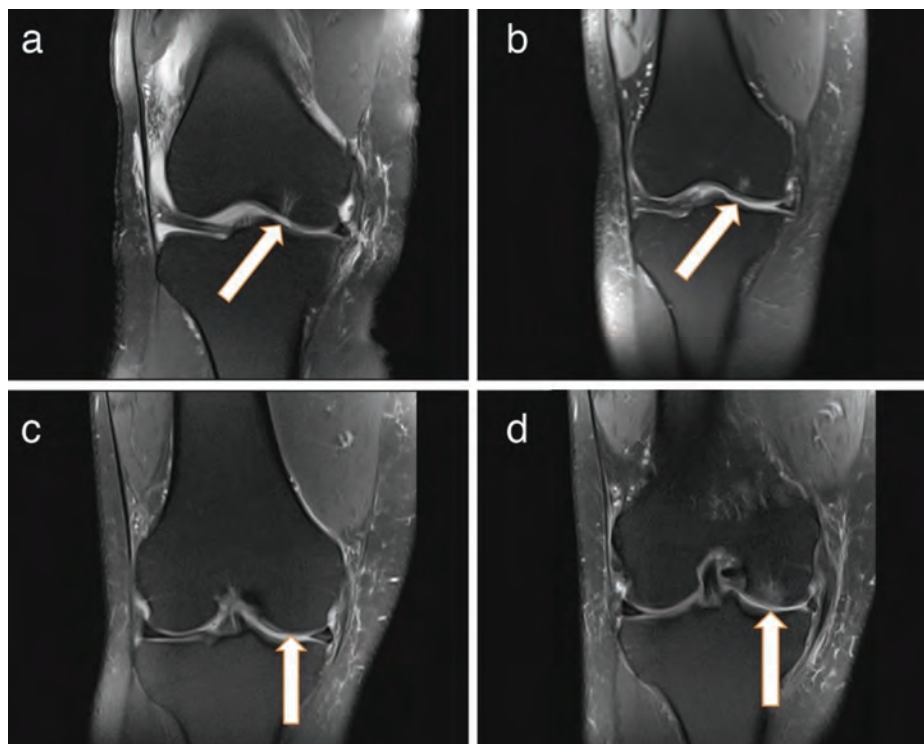
Between March 2016 and March 2018, 12 (7 male, 5 female) patients had received microfracture treatment at medial femoral condyl with BST-CarGel® or Hyalofast. The mean age of all patients were  $49.66 \pm 6.31$  years, with a mean follow-up duration  $21.75 \pm 7.72$  months. No significant difference was found according to independent sample t-test applications [sig. (p)=0.843>0.01 and sig. (p)=0.937>0.01, respectively] between the BST-CarGel® and Hyalofast groups in terms of their mean age [BST-CarGel®:  $49 \pm 6.48$  (n=7) year, Hyalofast:  $50.6 \pm 6.69$  (n=5)] and follow-up duration (BST-CarGel®:  $22 \pm 8.10$  months; Hyalofast:  $21.4 \pm 8.08$  months). The clinical and radiological data of the patients are given in Table 1. MRI sections are shown at Figure 1.

The preoperative and postoperative changes in the WOMAC score, radiological AMADEUS score, and defect filling of all patients are separately analyzed with the paired samples t-test, because each data set has normal distribution and interdependence. In the

test carried out according to the 5% significance level of paired samples, the sig values for each pair are  $<0.05$  ( $0.000 < 0.05$ ). The progression in the WOMAC score, radiological AMADEUS score, and defect filling at the last follow-up were significant according to the paired sample t-test applications in all patients ( $p < 0.001$ ;  $p < 0.001$ ;  $p < 0.001$ , respectively; Table 1).

The preoperative and postoperative changes in the WOMAC score, radiological AMADEUS score, and defect filling of the BST-CarGel® group were separately analyzed with the paired samples t-test, because each data set has normal distribution and interdependence. In the test carried out according to the 5% significance level of the paired samples, the sig values of for each pair were  $<0.05$ . The increase in the WOMAC score, radiological AMADEUS score, and defect filling at the last follow-up were significant according to the paired sample t-test applications in the BST-CarGel® group ( $p < 0.001$ ;  $p < 0.001$ ;  $p < 0.01$ , respectively; Table 1).

The preoperative and postoperative changes in the WOMAC score, radiological AMADEUS score, and defect filling of the Hyalofast group were separately analyzed with the paired samples t-test, because each data set has a normal distribution and interdependence. In the test performed according to the 5% significance level of the paired samples, the sig. values of for each pair are  $<0.05$ . The progress of the WOMAC score, radiological



**Figure 1.** (a, b) Hyalofast group. (c, d) BST-CarGel® group. (a, c) Preoperative sections; arrows indicate the cartilage defected area. (b, d) Postoperative sections; arrows indicate the thickening of the healed cartilage

AMADEUS score, and defect filling at last follow-up were significant according to the paired sample t-test applications in the Hyalofast group ( $p < 0.01$ ;  $p < 0.001$ ;  $p < 0.01$ , respectively; Table 1).

The preoperative and postoperative differences in the WOMAC score or radiological AMADEUS score or defect filling between the BST-CarGel® group and Hyalofast group were analyzed with the independent sample t-test separately, because each data set has normal distribution and independence of each other. In Table 1, in the analysis performed according to the 5% significance level, all p values were  $< 0.05$  for comparisons. According to statistical test results, no significant difference was found between the means of preoperative and postoperative data between the BST-CarGel® group and Hyalofast group ( $p > 0.05$ ; Table 1).

Of all patients, nine had complex meniscal tear at the medial menisci. Complex meniscal tears were treated via partial meniscectomy.

## DISCUSSION

In this study, we investigated the results of patients who were treated by the microfracture technique and supplemented with BST-CarGel® or Hyalofast scaffolds at the end of the surgery. The WOMAC clinic score and radiological AMADEUS score before surgery and at the last follow-up showed a significant improvement ( $p < 0.001$ ) (Table 1). The preoperative and postoperative comparisons of BST-CarGel® and Hyalofast groups

were not significant according to the WOMAC score, radiological AMADEUS score, and defect filling ( $p > 0.05$ ) (Table 1).

Stanish et al. (1) presented the clinic and radiologic results of patients who received BST-CarGel® and isolated microfracture. Of their 80 patients, 40 were treated by microfracture only, and the remaining 40 received BST-CarGel®. All patients clinically improved in their series compared with their preoperative condition. No significant clinical difference was found between groups according to the WOMAC score. The BST-CarGel® group had better radiological improvement according to MRI. Shive et al. (9) published their experience with BST-CarGel® compared with isolated microfracture in 2015. Microfracture with and without BST-CarGel® showed superiority compared with preoperative conditions. The clinical and radiological results of Shive et al. (9) were similar with those of Stanish et al. (1). Buda et al. (4) presented the results of patients with microfracture added with Hyalofast. They found similar results to Stanish et al. (1) and Shive et al. (9) in terms of clinical improvement. In the current study, we found radiological and clinical progress preoperatively to postoperatively, as in the literature.

The use of scaffolds probably helps mesenchymal stem cells to differentiate to more durable cartilage (10). The histological studies of Hyalofast (4,10) and BST-CarGel® (11) at cartilage repair showed a more durable cartilage repair. The clinical success achieved may be due to the microfracture treatment and/or the scaffolds used. Clinical studies that compared microfracture treatment with and without scaffolds showed the same clinic improvement, but the scaffold groups showed

**Table 1. Clinic and radiological outcomes of the patients**

		All patients (BST-CarGel® + Hyalofast) (n=12)	BST-CarGel® group (n=7)	Hyalofast group (n=5)	<sup>a</sup> p
		Mean ± SD	Mean ± SD	Mean ± SD	
AMADEUS	Preoperative	56.18±6.68	54.28±7.86	54±5.47	<b>0.946</b>
	Postoperative	83.75±8.56	81.42±8.99	87±7.58	<b>0.287</b>
	Δ AMADEUS difference	-29.58±8.38	-27.14±7.55	-33.00±9.08	-
	<sup>b</sup> p	<b>&lt;0.000**</b>	<b>&lt;0.000**</b>	<b>0.001**</b>	-
WOMAC	Preoperative	29.26±10.77	28.91±13.47	29.76±6.79	<b>0.901</b>
	Postoperative	89.89±4.71	89.98±4.01	89.76±6.07	<b>0.939</b>
	Δ WOMAC difference	60.62±10.92	-61.07±13.60	-60.00±7.05	-
	<sup>b</sup> p	<b>&lt;0.000**</b>	<b>&lt;0.000**</b>	<b>&lt;0.000**</b>	-
Defect filling	Preoperative	2.24±0.95	2.35±1.12	2.1±0.73	<b>0.664</b>
	Postoperative	0.88±0.28	0.89±0.3	0.85±0.29	<b>0.811</b>
	Δ Defect filling difference	1.36±0.70	1.45±0.86	1.24±0.47	-
	<sup>b</sup> p	<b>&lt;0.000**</b>	<b>0.004**</b>	<b>0.004**</b>	-

<sup>a</sup>Independent samples test, <sup>b</sup>Paired samples test, \*\* $p < 0.0$ , SD: Standard deviation, AMADEUS: Area measurement and depth and underlying structures, WOMAC: The Western Ontario and McMaster Universities Osteoarthritis Index

better radiological improvement. BST-CarGel® and Hyalofast do not only induce the quality of fibrous cartilage but also increase the amount of filling in the defected area (1,4,10,11). Previous studies have demonstrated the increased quality of the newly formed fibrous cartilage and increased clinical satisfactory with BST-CarGel® or Hyalofast (1,4,13,16-18). These studies have presented short- and mid-term results (1,4,9,11,16-18). We believe that the major clinical reflection of these studies would be seen in the long-term. Recently, Solheim et al. (19) compared the long-term results of OATS and microfracture. Solheim et al. (19) reported that the survival of the hyaline cartilage-based treatment OATS is better than the fibrous cartilage-based treatment with the microfracture technique. However, as the clinical, radiological, and histological studies of Hyalofast or BST-CarGel® for cartilage repair showed more durable cartilage repair (1,4,6,9-11), the follow-up durations of the aforementioned studies are still shorter than that of hyaline-based treatments (19). The studies put forth the improvement at the filling of the cartilage defect in the scaffold group compared with the microfracture group, despite the lack of difference in the clinic outcomes between the groups (1,9,11). Thus, studies have presented the long-term results of patients who used scaffolds (1,4,9,11).

Therefore, cartilage scaffolds are not only used in the knee. Some studies have shown the superiority of the cartilage scaffolds for hyaline cartilage defects in the synovial joints other than in the knee joint (20-22). The success of adding scaffolds at the lower extremity cartilage repair (1,4,9,11,20-22) can put forth the importance of increased quality of repair tissue. Scaffolds serve as a plug at the microfracture area. Moreover, the scaffolds may provide the same height level between the clot and the healthy hyaline cartilage border.

The most important difference of our study group from the literature is the application of Hyalofast with venous blood instead of mesenchymal stem cells obtained from the iliac crest as in the routine technique. The phenotype and differentiation potential of the cells at the distal femur are similar to those of bone marrow-derived mesenchymal stem cells from the iliac crest (23). Thus, we targeted the benefit of stem cells in those who come by microfracture surgery. Thus, a less invasive technique was applied to the patients. In the BST-CarGel® technique, venous blood is used routinely. The use of the venous blood for the scaffolds made the approaches of BST-CarGel® and Hyalofast more similar to each other. Thus, the techniques were similar as much as possible, except for the used scaffolds. The tourniquet was removed after the scaffold-supported plugs hardened. In terms of instability of the used scaffolds, such as separation from

the microfracture area, we controlled every case intraoperatively after terminating the tourniquet. The incision was closed after being sure of the stability of the used scaffolds.

### Study Limitations

The limitations of this study are on the low sample size, short follow-up time, and lack of histological results. Another important limitation is the lack of microfracture only group. Because the superiority of adding scaffolds to the microfracture treatment was shown previously, we have not included any patient group in which microfracture was performed alone.

## CONCLUSION

The addition of BST-CarGel® or Hyalofast to microfracture surgery is beneficial clinically and radiologically. To compare the long-term results of these two scaffolds with microfracture alone and/or hyaline cartilage-based treatment, further studies are needed.

### Ethics

**Ethics Committee Approval:** The study began after it was granted permission by the Local Ethics Committee of Giresun University Giresun University Clinical Research (no: 90139838-000-E.28161, 2019-56).

**Informed Consent:** Informed consent form was obtained from all patients.

**Peer-review:** Externally and internally peer-reviewed.

### Authorship Contributions

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

**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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# Do Maternal Blood Parameters Affect Fetal Birth Weight?

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## Abstract

**Objective:** Perinatal morbidity and mortality increase significantly in newborns with low birth weight (LBW). Maternal total protein, albumin, hemoglobin (Hb), hematocrit (Hct), red blood cell (RBC), and electrolyte values may affect the birth weight of the baby.

**Methods:** This study included 363 pregnant women who consulted the Gynecology Department of Okmeydanı Training and Research Hospital between July 2018 and December 2018 and gave birth between 37 and 42 gestational weeks. Newborns were divided into three groups:  $\leq 2500$  g, 2500-4000 g, and  $\geq 4000$  g. The relationship between birth weight and maternal Hb, Hct, RBC, total protein, albumin, and electrolytes values taken just before birth was examined.

**Results:** No significant difference was found between the three groups in terms of gravida, parity, abortus numbers, gestational weeks and age of the patients, maternal blood total protein, albumin, Hb, Hct, calcium, sodium, potassium, and chloride values. RBC values were significantly lower in the  $\leq 2500$  g group ( $p=0.046$ ), whereas maternal blood magnesium values were significantly higher ( $p=0.026$ ). When the relationship between severe anemia and fetal weight was examined, LBW was significant in the group with Hb  $< 7.4$  ( $p=0.004$ ).

**Conclusion:** Maternal RBC levels were low, but magnesium levels were high in pregnant women who gave to LBW infants, and the LBW rate was high in the group with severe anemia. However, possible physiological changes that occur during pregnancy should be considered.

**Keywords:** Fetal birth weight, maternal anemia, maternal albumin, maternal electrolytes, maternal protein, maternal red blood cell

## INTRODUCTION

Healthy nutrition during pregnancy aims for the birth of a healthy fetus that has reached term and for a good lactation process after birth.

A baby's weight at birth is affected by many social, economic, genetic, maternal, and environmental factors. Perinatal morbidity and mortality increase significantly in newborns with low birth weight (LBW). Although the LBW rate is as low as 6-7% in all newborns, 2/3 of all neonatal deaths occurred in babies with LBW (1).

Fetal birth weight is dependent on many factors related to the mother, such as height, pre-pregnancy weight, body mass index, weight gained during pregnancy, and number of calories in their diet. Studies have suggested that maternal total protein and albumin levels and maternal anemia may be effective in

determining LBW. However, only a few studies have shown the relationship between maternal blood electrolyte levels and obstetric outcomes (2).

Maternal nutrition is extremely important, both for the fetus and the mother. Rates of fetal anomalies, abortus, stillbirth, LBW, and perinatal mortality increase in maternal malnutrition conditions. Especially for newborns with LBW, possible risk factors include low pre-pregnancy body mass index, maternal malnutrition, smoking, and alcohol consumption, which may then cause impaired growth and cognitive functions in later years (3).

In this study, we investigated the effect of total protein, albumin, hemoglobin (Hb), hematocrit (Hct), red blood cell (RBC), and electrolyte values on the birth weight of term newborns.



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## METHODS

This study included 363 pregnant women who consulted the Gynecology Department of Okmeydani Training and Research Hospital between July 2018 and December 2018 and gave birth between 37 and 42 gestational weeks. Patients with maternal systemic disease, maternal TORCH group of infectious diseases, diabetes mellitus, gestational diabetes, preeclampsia, smoking habits, and multiple pregnancies were not included. Blood was drawn from patients just before birth, and their Hb, Hct, RBC, total protein, albumin, sodium, potassium calcium, magnesium, and chloride values were examined. In each case, gravida, parity, abortus numbers, age, gestational week, birth weight, fetal sex, and delivery type were recorded. Macrosomia was defined as fetal weight >4000 g, and LBW as fetal weight <2500 g. After birth, newborns were divided into three groups:  $\leq 2500$  g, 2500-4000 g, and  $\geq 4000$  g.

Pregnant women with Hb levels  $M11$  g/dL and Hct levels <33 were evaluated as “anemic”. Additionally, all values were examined in three groups, which were determined as (Hb <7.4), (7.4  $\leq$  Hb  $\leq$  9.5), and (Hb >9.5), to showcase the degree of anemia present.

Pregnant women with total protein levels <6.4 g/dL were considered “hypoproteinemic”, while those with albumin levels <3.4 g/dL were considered “hypoalbuminemic”.

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of the University of Health Sciences Turkey, Prof. Dr. Cemil Tascioglu City Hospital (date: 28/09/2020, no: 48670771-514.10-335). Written informed consent was obtained from patients who participated in this study.

### Statistical Analysis

All information obtained in the study was entered into SPSS version 25.0 (IBM Corp. Armonk, NY, USA). Descriptive statistics were used to calculate the frequency (n), percentage (%), central tendency (mean, median, and mode), and dispersion (range, variance, standard deviation, maximum, and minimum) for each variable when appropriate. Continuous data were evaluated by the Kolmogorov-Smirnov test to establish that if they are parametric or non-parametric. Then, One-Way ANOVA test (parametric) or Kruskal-Wallis test (non-parametric) were used as appropriate if there were more than two groups. As a post-hoc test, Tukey’s test was used. The chi-squared test was used in categorical variables. Pairwise comparisons with adjusted p values (Bonferroni method) were applied as the post-hoc test in significant factors identified in the chi-square test. A p value <0.05 was considered significant.

## RESULTS

In this study, 43 pregnant women (11.84%) who gave birth to infants with birth weight <2500 g (group 1), 273 pregnant women (75.20%) who gave birth to infants with birth weight between 2500 and 4000 g (group 2), and 47 pregnant women (12.94%) who gave birth to infants with birth weight >4000 g (group 3) were included. Demographic characteristics and obstetric results are shown in Table 1. No significant difference was found between the three groups in terms of gravida, parity, and abortion numbers. No significant difference was noted between the weeks of gestation and ages of the patients ( $p=0.101$  and  $p=0.251$ , respectively). The rate of delivering a male baby in group 3 was significantly higher than that in the other two groups ( $p<0.001$ ; difference was between group 1 and group 3 and between group 2 and group 3). Regarding delivery types, the rate of cesarean section in group 1 were significantly higher than that in the two groups ( $p<0.001$ , difference was between group 1 and group 2, between group 1 and group 3, and between group 2 and group 3). No significant difference was found between the three groups upon the examination of the maternal blood total protein, albumin, Hb, Hct, calcium, sodium, potassium, and chloride values (Table 2). The difference between the RBC values among the three groups was significant (One-Way ANOVA,  $p=0.046$ ). In the post-hoc tests, this difference was between group 1 and group 3 (Tukey test,  $p=0.048$ ). RBC values in group 1 were lower than the values in group 3. The difference between the maternal blood magnesium levels among the three groups was significant (One-Way ANOVA,  $p=0.026$ ). In the post-hoc tests, the difference in magnesium levels was between group 1 and group 2 (Tukey test,  $p=0.031$ ). Magnesium values in group 1 were higher than that in group 2.

The groups that comprised patients with Hb <11 g/dL and Hct < below 33 were re-examined to investigate the relationship between maternal anemia and birth weight. No significant difference was found between the three groups ( $p=0.494$ ,  $p=0.731$ , respectively). To examine the relationship between maternal hypoproteinemia and birth weight, the group with albumin levels <3.4 g/dL and total protein levels <6.4 g/dL was re-evaluated, and no significant difference was noted between the three groups ( $p=0.725$ ,  $p=0.445$ , respectively) (Table 3).

As regards the relationship between severe anemia and fetal weight, a fetal weight of  $\leq 2500$  g was significant in the group with Hb <7.4 ( $p=0.004$ ) (Table 4).

## DISCUSSION

Observational studies have tried to examine the relationship between the amount of fat that the mother consumed during pregnancy and her gestational weight gain (4). In a review that included 200 articles, the relationship between maternal nutrition and birth outcome depended on biological, socioeconomic, and demographic factors (5).

With the physiological changes that occur during pregnancy, lipids, fat-soluble vitamins, and some carrier proteins increase; while the glomerular filtration increases, albumin, water-soluble vitamins, amino acids, and mineral levels decrease. The plasma volume starts to increase between the 6<sup>th</sup> and 8<sup>th</sup> weeks of pregnancy and reaches 1500 mL at the 34<sup>th</sup> week (6). Although a deficiency in protein intake during pregnancy causes LBW in mice, sheep, and pigs, it is still debated in humans (7). Hb,

**Table 1. Demographic characteristics and obstetric outcomes**

	Group 1 ≤2500 g n=43	Group 2 2500-4000 g n=273	Group 3 ≥4000 g n=47	p
Age	29 (18-44)	26 (18-44)	27 (19-45)	0.251 <sup>a</sup>
Gestational week	38 (36.4-41.4)	39.1 (37-41.5)	39.5 (37.2-42.3)	0.101 <sup>a</sup>
Gravidity	3 (1-5)	2 (1-8)	3 (1-7)	0.104 <sup>b</sup>
Parity	1 (0-4)	1 (0-5)	1 (0-6)	0.066 <sup>b</sup>
Abortus	0 (0-2)	0 (0-3)	0 (0-3)	0.085 <sup>b</sup>
Gender				
Male	17 (39.5%)	119 (43.6%)	36 (76.6%)	<0.001 <sup>b,*</sup>
Female	26 (60.5%)	154 (56.4%)	11 (23.4%)	
Vaginal delivery	15 (34.9%)	180 (65.9%)	23 (48.9%)	-
Cesarean delivery	28 (65.1%)	93 (34.1%)	24 (51.1%)	<0.00b <sup>**</sup>
Repeats	16 (37.2%)	53 (19.4%)	10 (21.2%)	-
Progress failure	-	11 (4%)	3 (6.4%)	-
Cephalopelvic disproportion	-	8 (2.9%)	1 (2.1%)	-
Fetal distress	8 (18.6%)	13 (4.8%)	3 (6.4%)	-
Macrosomia	-	-	5 (10.6%)	-
Malpresentation	4 (9.3%)	8 (2.9%)	2 (4.3%)	-

<sup>a</sup>Kruskal-Wallis median (minimum-maximum), <sup>b</sup>Chi-square test, \*Difference was between group 1 and group 3 and between group 2 and group 3, \*\*Difference was between group 1 group 2, between group 1 and group 3, and between group 2 and group 3

**Table 2. Comparisons of protein, blood count parameters and electrolytes among birth weight groups**

		Group1 ≤2500 g	Group 2 2500-4000 g	Group 3 ≥4000 g	p
Protein	Total protein	6.60±0.49	6.54±0.43	6.48±0.42	0.467 <sup>a</sup>
	Albumin	3.34 (2.40-3.90)	3.4 (2.13-4.1)	3.38 (2.8-3.85)	0.4 <sup>b</sup>
Blood count parameters	Hemoglobin	11.70 (4.8-14.4)	11.8 (7.5-15.1)	11.8 (8.8-13.8)	0.736 <sup>b</sup>
	Hematocrit	34.8 (16.7-41.9)	34.9 (24.3-43.8)	35.4 (28.7-40.8)	0.497 <sup>b</sup>
	Red blood cells	4.08±0.47	4.15±0.38	4.28±0.36	0.046 <sup>a,*</sup>
Electrolytes	Calcium	8.76±0.43	8.71±0.57	8.87±0.38	0.165 <sup>a</sup>
	Magnesium	2.04±0.28	1.95±0.19	2±0.23	0.026 <sup>a,**</sup>
	Sodium	136 (131-140)	136 (126-142)	136 (132-140)	0.81b
	Potassium	4.09 (3.42-5.14)	4.06 (3.12-5.21)	4.1(3.78-4.99)	0.206 <sup>b</sup>
	Chlorine	105.08±2.36	105.03±2.34	104.9±1.97	0.922 <sup>a</sup>

<sup>a</sup>One-Way ANOVA [parametric-mean (standard deviation)], <sup>b</sup>Kruskal-Wallis [non-parametric-median (minimum-maximum)], \*Difference was between group 1 and group 3 (Tukey test p=0.048), \*\*Difference was between group 1 and group 2 (Tukey test p=0.031)

**Table 3. Comparison of anemia, hypoproteinemia, and hypoalbuminemia**

	≤2500 g	2500-4000 g	≥4000 g	p	
Hemoglobin	<11	11	80	10	0.494 <sup>a</sup>
	≥11	32	193	37	
Hematocrit	<33%	11	73	10	0.731 <sup>a</sup>
	≥33%	32	200	37	
Albumin	<3.4	24	136	25	0.725 <sup>a</sup>
	≥3.4	19	137	22	
Total protein	<6.4	14	99	21	0.445 <sup>a</sup>
	≥6.4	29	174	26	

<sup>a</sup>Pearson chi-square test

**Table 4. Comparison of anemia levels\***

Hb <7.4	Group 1	Group 2	Group 3
7.4 ≤ Hb ≤ 9.5	2 (4.7%)	0	0
Hb: 9.5-11	2 (4.7%)	15 (5.5%)	2 (4.3%)
Hb <7.4	39 (90.7%)	258 (94.5%)	45 (95.7%)

\*Chi-square test, p=0.004, Hb: Hemoglobin

iron, and albumin levels were evaluated in a study conducted in Korean pregnant women, and the logistic regression analysis revealed that Hb and albumin levels had the most important predictive value in determining LBW (2).

During pregnancy, there is a physiological decrease in Hct levels because the increasing plasma volume is disproportionate to the erythrocyte volume. Normally, physiological hemodilution occurs in every pregnancy. Anemia during pregnancy was defined by the Centers for Disease Control and Prevention in 1989 as Hb value <11 g/dL or Hct <33% in the 1<sup>st</sup> and 3<sup>rd</sup> trimesters of pregnancy and Hb <10.5 g/dL or Hct <32% in the second trimester. According to the World Health Organization in 2001, anemia during pregnancy is defined as Hb <11 g/dL for all three trimesters (8,9). In our study, we accepted the upper limit of the Hb value as 11 g/dL and Hct as 33%. Hb levels in the first trimester indicate maternal nutritional status and have a positive correlation with newborn weight. However, the effect of maternal hemodilution on fetal growth in the second and third trimesters is more important. Since there is insufficient hemodilution in pregnant women with chronic malnutrition, infants had LBW (2,10).

In the present study, no relationship was found between Hb and Hct values and birth weight. Msolla and Kinabo (11) found a positive correlation between Hb levels in the last trimester and birth weight in their study. Thus, the rates were significant than those with Hb <7.4 gr/dL who gave birth to babies with

weighing <2500 g, whereas those with Hb >9.5 gr/dL gave birth to babies with weighing >3000 g. Moreover, babies of mothers with anemia had lower birth weights than non-anemics (11). In the present study, the number of patients with severe anemia was significantly low. However, in accordance with the literature, the rate of newborns with LBW was significantly higher in those with Hb <7.4 g/dL. Besides, the rate of newborns weighing >4000 g was higher in the group with Hb of 9.5-11 g/dL. In a randomized controlled study, iron replacement to pregnant women until the 28<sup>th</sup> gestational week reduced LBW but did not prevent third-trimester anemia. Moreover, the authors stated that third-trimester anemia was not significant in determining the birth weight and that iron supplementation caused an increase in the birth weight of the baby by passing iron to the fetus (12). Studies have also stated that taking iron supplements during pregnancy causes oxidative damage (2,13). In a study conducted on 622 pregnant women, a decrease of 21 g in newborn weight was observed with a 1 g/dl decrease in maternal Hb, and a relationship between maternal anemia and low/insufficient birth weight was found (14). In a study of 2006-2010 data in Finland, a relationship was found between maternal anemia and adverse perinatal outcome, especially in multiparous pregnant women. This relationship was not found in nulliparas (15).

RBCs are oxygen-carrying cells. Low RBC levels indicate anemia or blood loss, while their numbers increase with heavy exercise and high altitude. Drugs that cause hemolysis may also reduce the erythrocyte count. In our study, the pregnant women had no history of such drug use, but RBC counts were significantly lower in the LBW group and were significant.

Additional protein is required for the growth and development of the fetus, uterus, placenta, and breasts. Some authors reported that a woman giving birth at term has a daily protein requirement of 6 g, and the amount of protein stored is between 925 and 1000 g (16). Studies have also revealed that birth weight increases in pregnancy women with high total protein and albumin levels and reported a relationship between large-for-gestational-age newborns and low serum albumin levels (17,18). However, some studies have reported that maternal albumin and protein levels do not affect fetal weight (7,19,20). In our study, albumin and total protein levels did not affect fetal weight.

Pregnant women need 20-30 g of calcium in total. Most of this is stored in fetal bone in the late period of pregnancy and is mobilized for fetal development. Taking calcium supplements during pregnancy prevents low gestational weight, birth weight <2500 g, and infants' risk hypertension in the future

by lowering the blood pressure of the fetus. Moreover, taking calcium supplements during pregnancy reduces pregnancy-induced hypertension only in women who receive a low amount of calcium (21). In previous studies, a significant relationship was found between neonatal weight and energy, protein, and calcium intake in the third trimester (22,23). The 2007 Cochrane review covers 12 studies on calcium. Regarding calcium supplementation, a decrease in the risk of preeclampsia was reported in 12 studies and a decrease in the risk of high blood pressure was reported in 11 studies compared with placebo. Maternal death and serious morbidity risk decreased in four studies. No effect on preterm birth or stillbirth was found (24). In our study, no significant difference was observed in maternal calcium values between the LBW group and other groups. In a study investigating maternal calcium, zinc, iron, and magnesium levels, significantly higher values of electrolytes, except magnesium, were found in umbilical cords of babies with normal birth weight compared with the babies with LBW (25). In the Cochrane review of seven studies, oral magnesium supplements before 25 gestational weeks decreased the frequency of preterm births, infants small for gestational age, and babies with LBW. In addition, the risk of hospitalization and antepartum hemorrhage was reduced in pregnant women. However, no studies have presented high-quality evidence to support the use of magnesium supplementation (26). In an animal study, magnesium restriction did not affect birth weight. However, if the restriction continued during the postnatal lactation period, the offspring is weaned and the bodyweight decreased (27). In our study, maternal blood magnesium level was significantly higher in the LBW group compared with the normal weight group.

Maternal plasma sodium concentrations decrease slightly as a result of pregnancy, and potassium concentrations do not change. A significant decrease was found in sodium, and potassium plasma levels in pregnant animals on a low-sodium diet increased (28). Moreover, pregnant rats on a low-sodium diet in the last 7 days of pregnancy experienced plasma expansion and fetal growth restriction. This study may be considered a simple animal model examining the relationship between maternal plasma volume and fetal growth (29). Chloride is the main anion in extracellular liquid and plays a role in the adjustment of osmotic pressure and anion-cation balance. Very few reports revealed the importance of chloride in pregnancy. Most studies are related to the amount of chloride in drinking water. In Italy, Fabiani et al. (30) examined the amount of chloride in drinking water and the obstetric outcome on pregnant women and did

not find a relationship between LBW and preterm delivery. In addition, no relationship was found between maternal sodium, potassium, and chloride values and fetal weight in our patient group.

## CONCLUSION

The effect of anemia, hypoproteinemia, and changes in maternal electrolyte levels on maternal and fetal outcomes should be evaluated according to etiology. In our study, maternal RBC levels were low, magnesium levels were high in pregnant women who gave birth with LBW, and the LBW rate was high in the group with severe anemia. Physiological changes that may occur during pregnancy should be given primary consideration. The interpretation of the results of our study is difficult because of differences in the characteristics, diagnostic criteria, and threshold value of the studied group of pregnant women. However, prospective studies with large patient groups and evaluations of all perinatal results are needed.

## Ethics

**Ethics Committee Approval:** Ethics Committee of the University of Health Sciences Turkey, Prof. Dr. Cemil Tascioglu City Hospital (date: 28/09/2020, no: 48670771-514.10-335).

**Informed Consent:** Written informed consent was obtained from patients who participated in this study.

**Peer-review:** Externally peer-reviewed.

## Authorship Contributions

Surgical and Medical Practices: S.G., E.A., B.C., M.E., H.A.Ş., O.Ş., V.M., Concept: S.G., E.A., M.E., V.M., Design: S.G., B.C., O.Ş., Data Collection or Processing: S.G., M.E., H.A.Ş., Analysis or Interpretation: S.G., E.A., B.C., Literature Search: S.G., B.C., V.M., Writing: S.G., H.A.Ş., O.Ş.

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# Effect of Pretreatment with Cilostazol on Spinal Cord Ischemia-reperfusion Injury in Rats

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## Abstract

**Objective:** Following the aortic aneurysm repair surgery, ischemic spinal cord injury is a substantial complication which may lead to paraplegia. This study aims to explore the protective effect of cilostazol, which is a phosphodiesterase type-3 inhibitor, against ischemic/reperfusion-induced spinal cord injury that is experimentally forged in medulla spinalis of rats.

**Methods:** A total of 24 rats were separated into three workgroups. The control group (n=8); the ischemic group (n=8), in which aortic clamping was performed without cilostazol administration; and finally the cilostazol-administered group (n=8). Each mouse was subjected to induced ischemia for 45 min by clamping of the abdominal aorta. Afterwards, blood build up was provided by de-clamping. Serial assessments of motor and sensory functions of all rats were performed prior to the operation and, at 24 and 48 h of reperfusion, using the Tarlov and LeMay scores. Later on, spinal cord tissues were collected for histopathologic examination.

**Results:** Tarlov scores at postoperative hours 24 and 48 tend to be significantly higher in the cilostazol-treated group than in the non-treated ischemia group (3.13±0.64 versus 1.25±0.71, p=0.0029 for the 24<sup>th</sup> hour; 2.75±0.71 versus 0.38±0.52, p=0.0016 for the 48<sup>th</sup> hour). LeMay scores at postoperative hours 24 and 48 were as well significantly higher in the cilostazol-treated group than in the non-treated ischemia group (9.13±1.13 versus 4.50±0.76, p=0.0018 for the 24<sup>th</sup> hour; 9.00±1.20 versus 3.75±0.89, p=0.0018 for the 48<sup>th</sup> hour). Histologic outcomes were strongly correlated to the neurologic outcomes.

**Conclusion:** These results suggest that pre-ischemia cilostazol treatment has a protective effect against ischemia/reperfusion-induced spinal cord injury.

**Keywords:** Ischemia/reperfusion, spinal cord injury, cilostazol, rat, animal model

## INTRODUCTION

Due to the medulla spinalis's exposure of temporary or permanent ischemia during the surgery, paraplegia is undoubtedly one of the most important emerging and undesirable complications that might result after thoracoabdominal aneurysm repair surgeries (1). Lintott et al. (2) reported the frequency of paraplegia occurrence due to extended clamp durations, dissection, and

rupture. Eventhough every procedure has been performed during surgery to ensure continuous perfusion of the medulla spinalis, paraplegia could be inevitable (3,4). The damage mechanism caused by the reperfusion after ischemia is not clearly known. Increase in lipid peroxidation after reperfusion and neuronal damage secondary to fiber degeneration and results in loss of motor functions.



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Cilostazol is known as a selective inhibitor of cyclic nucleotide phosphodiesterase 3 (PDE3) (5). Intracellular cyclic adenosine monophosphate (cAMP) levels increase due to the inhibition of PDE3 activity and the decrease in cAMP degradation which results in diminished thrombocyte aggregation and vasodilatation. Besides, the pleiotropic effects of cilostazol have been used for the prevention of clinical disorders like recurrent stroke, coronary artery disease, and peripheral occlusive disease (6,7). The pre-clinical studies where vasodilator and antiplatelet effects of cilostazol were presented are the determinants of these indications (5-7). This study explores the prophylactic properties of cilostazol on neurobehavioral disorders and histopathological changes observed due to experimentally induced ischemic/reperfusion in spinal cord injury on rats.

## METHODS

Istanbul University Animal Experiments Local Ethics Committee approval were obtained during the study (decision no: 145, date: 09.11.2009). The rats were exposed to 12 h of daylight as well as 12 h of darkness cycle. The shelter environment temperature was (20 °C-22 °C) and humidity was (50-60%) where standard rat feed and enough water was provided as well.

### Experimental Design

5 mg/kg xylazine (Rompun, Bayer, Istanbul, Turkey) and 60 mg/kg ketamine (Ketalar, Parke-Davis Eczacibasi, Istanbul, Turkey) were both used simultaneously for anesthesia. No mechanical ventilator was needed to support the animals' respiration during the experiment. A single 15 mg/kg dose of cefazolin (Cefamezin, Eczacibasi, Istanbul, Turkey) was administered in the postoperative period. During the experiment, these mice were administered 0.9% NaCl intravenously for volume replacement. After sterilization of the operation site, the abdominal aorta was attained via a transperitoneal approach through a 10-cm incision from the midline.

The cross clamp was placed after 100 U/kg systemic heparinization for anticoagulation. The aorta was cross-clamped by the use of aneurysm clips. During the procedure a surgical microscope was used. These clips were placed below the renal artery and above the iliac bifurcation. After 45 min, follows removal of the cross clamp. With the help of 4-Fr indwelling catheters placed beneath and above the clamp, distal and proximal aortic pressures were monitored. The incision was closed in layers. The control group was subjected to the exact surgical procedure except for aortic cross clamping. Before being placed in their cages.

The rodents were placed in a plastic box at 28 °C for 3 h to recover after the surgery.

Study groups: Twenty-four wistar-Albino male rats (weight 370-480 g) were divided into three different groups, as follows:

1. Sham group (n=8): The operation was performed with similar conditions except for aortic clamping.
2. Ischemia group (n=8): The operation was performed with similar conditions including aortic clamping for 45 min.
3. Cilostazol group (n=8): Cilostazol (100 mg/kg), dissolved in dimethyl sulfoxide, was injected intraperitoneally 2 h prior to operation. The surgery was performed in similar conditions including aortic clamping for 45 min.

### Evaluation of the Neurobehavioral Outcome

Evaluations of the motor and sensory functions in the hind limbs of the rats was performed prior to surgery and after 24<sup>th</sup> and 48<sup>th</sup> hours of reperfusion. While measuring, it was assessed using the LeMay score and Tarlov scale (8,9). The Tarlov motor scale is read as follows: 0, complete paraplegia; 1, slight movement in the joint; 2, enough mobility in the joint but an inability to stand; 3, able to stand and able to walk; and 4, complete recovery. The LeMay score was calculated using a 15-point spinal cord performance scale. Motor-sensory deficits of the animals are evaluated using an index for each animal at each point in time (Appendix 1). The maximum deficit calculated by the LeMay score was 15. The rats (n=8 per group) were assigned to be killed after the second neurobehavioral assessment (48<sup>th</sup> hour). The rodents were killed by a high dose injection of sodium pentothal (200 mg/kg). The rapidly collected spinal tissues were placed in 10% formaldehyde at 4 °C for 48 h.

### Histopathological Analysis

Spinal cord samples were taken out from the 10% formaldehyde after 48 h fixation period. The specimens were dehydrated by placing them in 95% alcohol for 30 min, then four changes were applied for 1 h each in 100% alcohol and five changes of toluene for 1 h each in a vacuum at 37 °C. After the spinal cords were infiltrated with paraffin, they were embedded in paraffin at 60 °C under vacuum and pressure. Transverse sections have been examined with a microtome. Five-micrometer sections were obtained through the spinal cord. Sections were deparaffinized and stained with cresyl violet, hematoxylin & eosin, Luxol Fast Blue staining (to check for the integrity of the myelin structure) and studied using light microscopy. Histopathologic changes of the ventral motor horn cells in medulla spinalis were scored on a 3-point scale for motor deficits, myelin injury, edema,

ependymal cell injury, vasocongestion as follows: 0, no damage; 1, mild lesion (<10%) observed; 2, a moderate lesion (10% to 50%) observed; 3, a severe lesion (>50%) observed. A blind study was done with the neuropathologist who was unaware of the experimental conditions.

### Statistical Analysis

The results obtained were reported as means  $\pm$  standard deviation. Data analysis was performed using the Statistical Package for Social Sciences version 14.0. Non-parametric tests such as Mann-Whitney U tests, Kruskal-Wallis tests, Spearman's correlation analyses, linear regression analysis, and paired Wilcoxon tests were carried out. Bonferroni correction was used where appropriate. P values of less than 0.05 were considered statistically significant.

## RESULTS

The surgery was well tolerated by every mice. The mean proximal arterial pressure and mean distal arterial pressure values revealed no difference among study groups ( $p=0.840$ , and  $p=0.982$ , respectively) (Table 1).

Arterial pressure	Sham group	Ischemia group	Cilostazol group	p value
Mean proximal arterial pressure, mmHg	79.38 $\pm$ 1.06	79.13 $\pm$ 0.83	79.25 $\pm$ 1.04	$p=0.840$
Mean distal arterial pressure, mmHg	10.88 $\pm$ 0.83	10.75 $\pm$ 1.04	10.75 $\pm$ 1.04	$p=0.982$

Groups	Tarlov score 24 h	<sup>a</sup> p value	Tarlov score 48 h	<sup>a</sup> p value
Sham	3.75 $\pm$ 0.46	Group 1 vs. 2, $p=0.014$	3.88 $\pm$ 0.35	Group 1 vs. 2, $p=0.0010$
Ischemia	1.25 $\pm$ 0.71	Group 2 vs. 3, $p=0.0029$	0.38 $\pm$ 0.52	Group 2 vs. 3, $p=0.0016$
Cilostazol	3.13 $\pm$ 0.64	Group 1 vs. 3, $p=0.1354$	2.75 $\pm$ 0.71	Group 1 vs. 3, $p=0.0105$
	** $p<0.001$		** $p<0.001$	

\*\*p value obtained from the Kruskal-Wallis test, <sup>a</sup>p value obtained after performing the Bonferroni-adjusted Mann-Whitney U-test

Groups	Lemay score 24 h	<sup>a</sup> p value	Lemay score 48 h	<sup>a</sup> p value
Sham	13.00 $\pm$ 1.31	Group 1 vs. 2, $p=0.0019$	12.75 $\pm$ 1.49	Group 1 vs. 2, $p=0.0018$
Ischemia	4.50 $\pm$ 0.76	Group 2 vs. 3, $p=0.0018$	3.75 $\pm$ 0.89	Group 2 vs. 3, $p=0.0018$
Cilostazol	9.13 $\pm$ 1.13	Group 1 vs. 3, $p=0.0026$	9.00 $\pm$ 1.20	Group 1 vs. 3, $p=0.0036$
	** $p<0.001$		** $p<0.001$	

\*\*p value obtained through the Kruskal-Wallis test, <sup>a</sup>p value obtained after conducting the Bonferroni-adjusted Mann-Whitney U-test

For each group, neurological examinations were performed during the 24<sup>th</sup> and 48<sup>th</sup> hours. For each group, Tarlov scores (Table 2) and LeMay scores (Table 3) revealed no difference between two-time points (24<sup>th</sup> and 48<sup>th</sup> hours of reperfusion) ( $p=0.07368$  and  $p=0.160$ , respectively).

Histopathological analysis revealed a significant difference among study groups ( $p<0.05$ ) (Table 4). While no significant damage was observed in the neurons in the sham-operated animal group, neuronal damage was detected in the control group rodents.

On the contrary, pretreatment with cilostazol was found to significantly reduce the histologic changes. Motor deficits, myelin injury, ependymal cell injury, and vasocongestion were found to be significantly lower in the cilostazol-treated group than in the non-treated ischemic group ( $p=0.0079$ ,  $p=0.0023$ ,  $p=0.0200$ , and  $p=0.0104$ , respectively). Regarding edema, both groups did not differ from each other significantly ( $p=0.1268$ ) (Table 4) (Figure 1-3).

## DISCUSSION

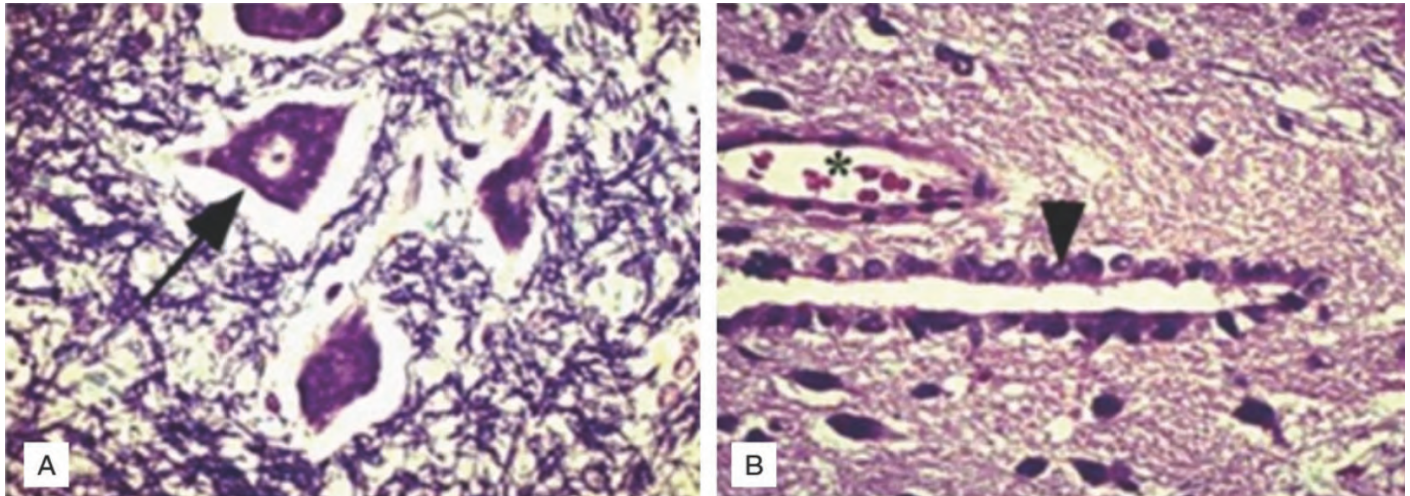
In this study, the transient ischemia-induced spinal cord ischemia (SCI) was significantly attenuated in rats that received cilostazol, (a type III phosphodiesterase inhibitor) compared with control animals. Cilostazol also prevented histologic changes induced by the transient ischemia, such as motor deficits, myelin injury, ependymal cell injury, and vasocongestion, both 24 and 48 h after the ischemia.

Ischemic spinal cord injury secondary to clamping the aorta may occur during thoracoabdominal aortic aneurysm and

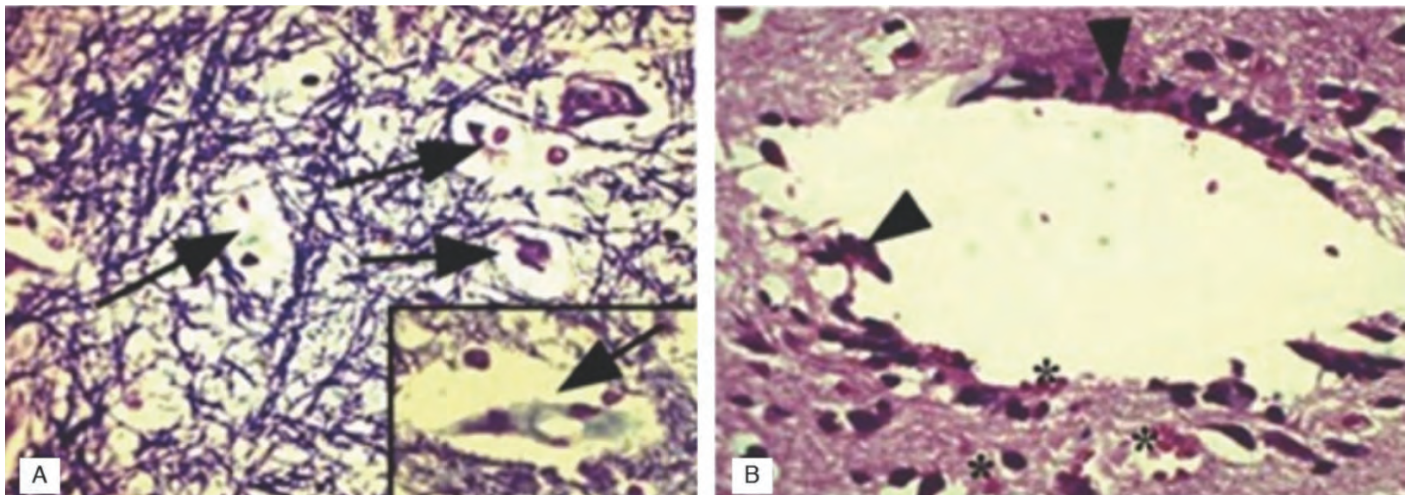


dissecting operations. As a result, paraplegia may develop. In experimentally induced SCI, while oxidative stress does not permit antioxidant activity, local antioxidants protect the neural tissue from oxidative stress. Reperfusion occurs 1-2 days after SCI, exacerbating the neural damage (8-10).

It is well known that, oxidative stress triggers the lipid peroxidation cascade resulting in cell membrane damage after a couple of days following SCI (11,12). Treatments which decrease oxidative stress might provide benefit for neurological diseases (13). The central nervous system which is well recognized for its rich lipid composition is more prone to damage as a result of



**Figure 1.** Group 1 (control group); normal morphology (A), nerve cells (arrow) (B), ependymal cells (arrowhead) and vascular structure (\*) are observed. (A) Luxol fast blue (Kluver Berrare) stain x100; (B) hematoxylin & eosin stain x100; insert: x400



**Figure 2.** In group 2 (ischemia group); (A) damaged nerve cells (arrow), diminished myelination, (A) damaged ependymal cells (arrowhead) and vasocongestion (\*) are seen. (A) Luxol fast blue (Kluver Berrare) stain x100; (B) hematoxylin & eosin stain x100; insert: x400

Table 4. Comparison of histopathological score among groups					
Groups	Motor deficits	Myelin injury	Edema	Ependimal cell injury	Vasocongestion
Group 1	0.00±0.00	0.13±0.35	0.13±0.35	0.13±0.35	0.00±0.00
Group 2	2.25±0.46	2.13±0.35	1.75±0.71	2.63±0.52	2.50±0.53
Group 3	1.25±0.46	1.13±0.35	1.13±0.35	1.75±0.46	1.38±0.52
Group 1 vs. 2	p=0.0006	p=0.0007	p=0.0020	p=0.0010	p=0.0008
Group 2 vs. 3	p=0.0079	p=0.0023	p=0.1268	p=0.0200	p=0.0104
Group 1 vs. 3	p=0.0006	p=0.0023	p=0.0023	p=0.0013	p=0.0007

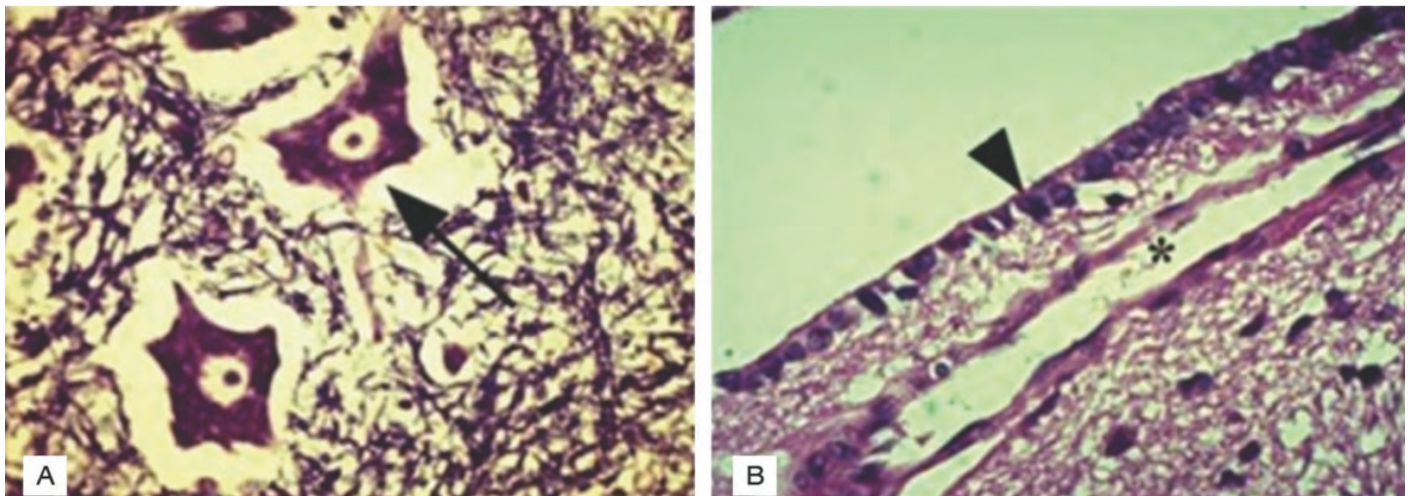


lipid peroxidation resulting from free radicals. The purpose of neuroprotection is to prevent neurons from lipid peroxidation occurring after SCI (14).

This study discloses a neuroprotective effect of cilostazol in an *in vivo* SCI model. To protect the spinal cord from the ischemic damage due to distal aortic perfusion, drainage of the cerebrospinal fluid, reimplantation of the intercostal arteries, and pharmacological treatments have been used. Many pharmacological agents like; magnesium, calcium channel blockers, opioid receptor antagonists, corticosteroids, free radical cleaners, sodium channel blockers, cyclosporin A, N-methyl-D-aspartate receptor antagonists, and thyrotropin-releasing hormone are used in the prophylaxis of SCI (15). Reperfusion occurs in 1-2 days following SCI. While the oxygen provided by the reperfusion ensures neural revival, catalysis some enzymatic oxidative reactions at the same time. Reactive oxygens resulted from oxidation reaction, causes DNA fragmentation by starting apoptosis (16). In one of their studies, Lee et al. (17) had applied cilostazol after they had occluded the middle cerebral artery for 2 h. From the samples obtained after 24-48 h of reperfusion, they realized that the DNA fragmentation has been significantly suppressed. It has been declared that, DNA chain breakdown is elicited by excessive poly(ADP-ribose) polymerase (PARP) activity which is a nuclear protein, resulting from ischemia/reperfusion. Thus, leading to necrosis (18). In another study, it is been determined by an enzyme analysis performed that with a low  $IC_{50}$  value of cilostazol, PARP is inhibited. Besides, cilostazol reduced the PARP activity in the rat's cerebral cortex exposed to ischemic-reperfusion damage and improved the product of activated PARP (19). Matsumoto et al. (20) reported that cilostazol inhibits the procoagulant activity caused by thrombin and this inhibition

is dependent on cilostazol concentration. With various studies, it has been disclosed that cilostazol has a protective effect against damages caused by transient or chronic cerebral ischemia. It is been revealed by the studies performed in rats that, cilostazol inhibited apoptotic and oxidative cell death, decreased gray and white matter damage thus substantially decreased ischemic brain infarction after 24 h from focal cerebral ischemia (21,22). With their studies performed in rats, Lee et al. (23) have scanned with magnetic resonance imaging that cilostazol had decreased the brain edema caused by ischemic infarction. Cilostazol prevented cognitive disorder devisal in rats where chronic cerebral hypoperfusion had been created with common carotid artery ligation and protected rats from the formation of white matter lesions (24).

The rat model used in our study was inspired by the rat model of LeMay et al. (9). The rat model involving aortic clamping is well established and has been previously used for testing the potential neuroprotective effect of drugs (25). In all rats where aortic cross clamp have been applied under normothermia, the observed paraplegia paced quite heavily. Thus, the study has a high repeatability ratio. The arterial vascularization of the spinal cord is very similar in rats. Both have heterosegmental aorta and some anterior radicular arteries (26). Recent experiments revealed that 45 min of aortic occlusion resulted in complete loss of evoked motor potentials and paraplegia (27). Thus, it is likely that the marked reduction in neuronal damage was affiliated to improved spinal cord function. The histopathological evaluation includes neuronal and axonal damage as well as microglial infiltration. The control group had no spinal injury. Interestingly, the cilostazol-treated group has significantly better histopathological results compared to the



**Figure 3.** In group 3 (cilostazol group); (A) normal nerve cells (arrow), (B) almost normal ependymal cells (arrowhead) and vascular structure (\*) are observed. (E) Luxol fast blue (Kluver Berrare) stain x100; (B): hematoxylin & eosin stain x100; insert: x400

sham-operated group. These results suggest that cilostazol may also have beneficial effects in protecting the intact and fully healthy spinal cords. It is believed that this effect is achieved by reducing oxidative stress. This study also evaluated the motor and sensory functions in the hind limbs of rats during the 24<sup>th</sup> and 48<sup>th</sup> hour of reperfusion, using the Tarlov scale and the LeMay score. Regarding postoperative 24<sup>th</sup> and 48<sup>th</sup> hour measurements, both LeMay and Tarlov scores have been ascertained as high in the group treated with cilostazol with respect to the ischemia group. However, when the control group is compared with the cilostazol treatment group, it has been ascertained that there is no difference in Tarlov scores obtained in 24 h.

As a result of this study, it could be assumed that; the motor functions of hind limbs of rats which had received cilostazol treatment, are healed with respect to the neurological examination done on rats after ischemic-reperfusion. With reference to these results, our hypothesis has been verified. As neurological scores of the mice in the control group were higher with respect to the cilostazol group, we think that cilostazol alone is not sufficient for the treatment of motor function disorders caused by the SCI-reperfusion damage. The beneficial effect of cilostazol was also confirmed by a histopathological study.

### Study Limitations

In this study, only functional outcomes and histopathological parameters were evaluated. The lack of biochemical and immunohistochemical assessment is the major pitfall of our study.

## CONCLUSION

In a clinically relevant rat model of aortic cross-clamping, cilostazol given before ischemia markedly reduced morphological spinal cord injury. It could be said that cilostazol might have a healing effect on the motor functions in rats caused by the spinal cord damage as a result of ischemic-reperfusion, though relying on the literature evidence bespoken. However, more scientific research is needed on this subject.

### Ethics

**Ethics Committee Approval:** Istanbul University Animal Experiments Local Ethics Committee approval were obtained during the study (decision no: 145, date: 09.11.2009).

**Informed Consent:** There is no need.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: Ü.K.K., G.E.Ş., Concept: Y.K., Design: Y.K., Data Collection or Processing: Ü.K.K., Analysis or Interpretation: G.E.Ş., Literature Search: Ü.K.K., Writing: Ü.K.K., G.E.Ş.

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

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Appendix 1. Spinal performance scale		
Variable		Score
Walking with lower extremities	Normal (symmetrical and coordinated ambulation)	4
	Toes flat under body when walking. but ataxia present	3
	Knuckle walking	2
	Movement in lower extremities but inability to knuckle walk	1
	No movement drags lower extremities	0
Horizontal rope	Grasps rope and pulls up with lower extremity	3
	Grasps rope without pulling	2
	Unable grasp rope	1
	Does not raise lower extremity	0
45 °C Bar	Grasps bar for >10 s	3
	Grasps bar for 5-10 s	2
	Grasps bar for <5 s	1
	No attempt to grasp bar	0
Pain sensation	Normal. withdrawal to toe pinch	2
	Squeals to toe pinch but does not withdraw	1
	No reaction to toe pinch	0
Rotating screen	Grasps screen to 180° for >5 s	3
	Grasps screen to 180° for <5 s	2
	Grasps screen past 270° but not to 180°	1
	Falls from vertical screen	0
Total score		15



# The Efficacy of <sup>18</sup>F-FDG PET/CT in Detecting Colorectal Cancer Recurrences

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## Abstract

**Objective:** Early diagnosis of recurrent colorectal cancer (CRC) has an impact on the patient's survival and quality of life. This study aimed to determine the efficacy of <sup>18</sup>F-fluorodeoxyglucose (<sup>18</sup>F-FDG) positron emission tomography/computed tomography (PET/CT) imaging in restaging patients with previously operated CRC, with elevated tumor markers and/or suspicious, equivocal, or pathological conventional imaging modality findings.

**Methods:** Data of 75 patients (42 males, 33 females) with CRC were retrospectively analyzed. All patients had undergone an operation, with suspicion of recurrence because of elevated tumor markers and/or equivocal or pathological conventional imaging modality findings during follow-up. Only patients, who have undergone conventional imaging methods (CIM) (e.g., CT and magnetic resonance imaging) and/or with serum tumor marker (carcinoembryonic antigen) measurements done within the first month preceding the PET/CT scan, were included in the study.

**Results:** Recurrence was confirmed in 58 patients with the clinical follow-up or pathological findings after the <sup>18</sup>F-FDG PET/CT imaging. The sensitivity, specificity, accuracy, and positive and negative predictive values of <sup>18</sup>F-FDG PET/CT in the diagnosis of CRC recurrence were 93.1%, 88.2%, 92%, 96.4%, and 78.9%, respectively. The <sup>18</sup>F-FDG PET/CT was superior to CIM and serum carcinoembryonic antigen (CEA) measurements in detecting recurrent diseases in patients with CRC.

**Conclusion:** The <sup>18</sup>F-FDG PET/CT imaging was efficient for early detection of patients with recurrent CRC having elevated serum CEA levels. The overall success of the <sup>18</sup>F-FDG PET/CT in detecting recurrences in patients with elevated CEA levels and negative, equivocal and/or pathological findings of conventional imaging modalities was 70.6%. PET/CT exhibited a 93% success in detecting the recurrence in cases referred to <sup>18</sup>F-FDG PET/CT depending on suspicious findings on CIM and/or elevated CEA results. In our study, the <sup>18</sup>F-FDG PET/CT has changed the disease management in 33.3% of patients.

**Keywords:** Colorectal cancer, recurrence, metastasis, positron emission tomography, carcinoembryonic antigen

## INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer both in men and women and comprises 10% of all cancers (1). Despite radical surgery combined with chemotherapy and radiotherapy, the recurrence rate is 40-50% (2,3). Recurrences are most commonly localized to a single organ, such as the liver, or an anatomic region, such as the pelvis (4,5). The outcome

of CRC has significantly improved with the introduction of metastasectomy for isolated liver involvement treatment and effective chemotherapeutic agents (6-8). Surgery for single-site was reported as 23-27% in the 5-y disease-free survival (4,5). Therefore, early diagnosis of the recurrent disease has an impact on the patient's survival and quality of life. Before the introduction of <sup>18</sup>F-fluorodeoxyglucose (<sup>18</sup>F-FDG) positron



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emission tomography/computed tomography (PET/CT), postoperative evaluation of patients with CRC was done by physical examinations, colonoscopy, and conventional imaging methods (CIM), such as ultrasound, CT, and magnetic resonance imaging (MRI), to confirm recurrence, especially with increased carcinoembryonic antigen (CEA) levels. These techniques had limitations in distinguishing between postsurgical anatomic changes and scarring after radiation and residual or recurrent disease (9). The <sup>18</sup>F-FDG PET/CT was a widely accepted imaging method in the management of a variety of neoplastic diseases, including CRC. Many studies demonstrated the value of the PET in the diagnosis of CRC recurrence in the postoperative period (10,11). The present study retrospectively evaluates the efficacy of <sup>18</sup>F-FDG PET/CT in the restaging of patients who were previously operated on due to CRC, with elevated CEA levels, and/or suspicious, equivocal, or pathological CIM findings.

## METHODS

### Patients

A total of 75 patients, wherein 42 were male and 33 were female, with a mean age of 62.1 years (range 30-82 years), suspected with recurrent CRC, who underwent PET/CT scanning from September 2007 to April 2009, were retrospectively reviewed. All patients had undergone an operation and presented with a suspicion of recurrence because of elevated tumor markers and/or equivocal or pathological CIM findings during follow-up. Only patients who had undergone CIM (CT, MRI) and/or had serum tumor marker (CEA) measurements done within the first month preceding the <sup>18</sup>F-FDG PET/CT scan were included in the study.

The <sup>18</sup>F-FDG PET/CT scan results, conventional imaging studies, and CEA levels were compared with the histopathological findings or follow-up results for 6-19 months.

This study was carried out with the approval decision of Okmeydani Training and Research Hospital Clinical Research Ethics Committee dated April 20, 2009, and numbered 260. Consent was obtained from all patients who were scanned.

Demographic details of patients are presented in Table 1.

### PET/CT Scan

PET/CT studies were carried out using an integrated PET/CT scanner, consisting of a full-ring HI-REZ LSO PET and a six-slice CT (Siemens Biograph 6; Siemens, Chicago, USA). Patients were instructed to fast for at least 6 h before the <sup>18</sup>F-FDG injection. Blood glucose levels were measured before the study and <sup>18</sup>F-FDG injections were given only when the blood glucose levels were below 11.11 mmol/L. Patients were injected with 296-555

MBq of <sup>18</sup>F-FDG according to body weight. Whole-body imaging commenced 60±5 min after the <sup>18</sup>F-FDG injection. The CT portion of the study was done without an intravenous contrast medium, just to define anatomical landmarks and make attenuation corrections on PET images. CT was first acquired with the following parameters: 50 mAs, 140 kV, and 5-mm section thickness. Whole-body CT was performed in a craniocaudal direction. PET images were acquired in a three-dimensional mode, from the base of the skull to the mid-thigh, with 5-7 bed positions of 3 min each, and PET data were collected in a caudocranial direction. The cranium was also included if any known or suspicious brain metastasis were observed. After the acquisition was over, a quick evaluation of images was done and additional regional delayed spot images were obtained in cases with suspicious <sup>18</sup>F-FDG uptake especially at the colon segments. The CT data were matched and fused with the PET data.

### Image Analysis

PET images were visually interpreted by three experienced nuclear medicine physicians about PET/CT fusion and CT images. Differences were settled by consensus reading. Positive PET findings were defined as the focal accumulation of <sup>18</sup>F-FDG

Table 1. Demographic details of patients	
<b>Characteristics</b>	
Total number of patients	75
<b>Age (years)</b>	
Mean	62.1
Range	30-82
<b>Gender</b>	
Male	42
Female	33
Time from the initial diagnosis to recurrence (months)	25.7±22.1 (3-118)
<b>Number of patients according to tumor localizations</b>	
Ascending colon and cecum	15 (20%)
Transverse colon	2 (3%)
Descending colon	7 (9%)
Sigmoid colon	4 (5%)
Rectosigmoid	9 (12%)
Rectum	38 (51%)
<b>Tumor histopathology</b>	
<b>Non-mucinous adenocarcinoma</b>	
Well-differentiated	10 (14%)
Moderately differentiated	53 (76%)
Poorly differentiated	7 (10%)
<b>Mucinous adenocarcinoma</b>	
	5 (7%)



above the normal level of surrounding tissue, excluding the physiologically increased uptake.

### Statistical Analysis

All obtained data in the study were recorded in the Microsoft Office Excel 2003 for Windows program. Statistical Package for the Social Sciences 16.0 for Windows was used for statistical evaluation and analysis. Data are expressed as means  $\pm$  standard deviation. Sensitivity and specificity, as well as positive and negative predictive values [(PPV and NPV), respectively] and accuracies of the <sup>18</sup>F-FDG PET/CT, CIM, and CEA measurements, were determined.

## RESULTS

Of the 75 patients, 37 (49%) had colon cancer and 38 (51%) had rectal cancer. A recurrence was eventually diagnosed in 58 of 75 patients (77.3%). The duration between the treatment (surgery and/or chemotherapy and/or radiotherapy) and the detection of recurrence in these patients was 25.7 months on average (range 3-118 months). Of the 75 patients, 30 (40%) patients diagnosed with recurrence were histopathologically confirmed following surgery or biopsy and 45 (60%) patients were confirmed with results from follow-up. Of the 75 patients referred to us with the suspicion of recurrence, 19 (25%) had elevated CEA levels, 24 (32%) had only suspicious CIM findings, and 29 (39%) had both. Three patients (4%) were referred to <sup>18</sup>F-FDG PET/CT scan since the complaints and physical findings raised suspicion of recurrence even without marker levels and CIM finding abnormality.

Serum CEA levels were above normal in 48 (64%) patients and within the normal range in 27 (36%) patients. CIM findings were pathologically positive or suspicious for pathology in 53 (71%) patients and without any abnormality in the remaining 22 (29%) patients.

Among the 87 confirmed metastatic lesions detected in 58 patients with recurrence, 23 local recurrences, 24 liver metastases, 13 lung metastases, 9 serosal implants in the abdomen, 8 lymph node metastases in the abdomen, 5 bone metastases, 4 mediastinal lymph node metastases, and 1 peritoneal carcinomatosis were found.

Of the 58 patients with recurrence, <sup>18</sup>F-FDG PET/CT accurately detected the lesion in 54 patients. Of the 17 patients who were proven to have no metastasis, the <sup>18</sup>F-FDG PET/CT was truly negative in 15 patients. The recurrent CRC evaluation revealed sensitivity, specificity, accuracy, PPV, and NPV of <sup>18</sup>F-FDG PET/CT of 93.1%, 88.2%, 92%, 96.4%, and 78.9%, respectively.

Of the 48 patients with above-normal serum CEA levels, the recurrent disease was confirmed in 42 patients. In 6 patients who were proven to have no metastatic disease, serum CEA levels were above normal, leading to false-positive results. Of the 27 patients with normal CEA levels, 11 had no recurrent disease, whereas 16 had recurrent disease. Therefore, the sensitivity, specificity, accuracy, PPV, and NPV of serum CEA levels were calculated as 72.4%, 64.7%, 70.6%, 87.5%, and 40.7%, respectively.

Of the 75 patients included in the study, CIM was reported suspicious, equivocal, and pathological in 53 patients. The CIM detected the recurrence correctly in 45 of these 53 patients, but lesions were reported as positive in 8 patients, although with no recurrent disease. Among the 22 patients who were evaluated as normal on CIM, 9 had no recurrent disease, yielding true-negative results, whereas 13 patients were reported as normal, which led to false-negative results. The recurrent evaluation calculated the sensitivity, specificity, accuracy, PPV, and NPV of CIM as 77.5%, 52.9%, 72%, 84.9%, and 40.9%, respectively.

The liver was the site of metastasis in 24 of 58 patients with recurrent disease. The sensitivity, NPV, and accuracy of <sup>18</sup>F-FDG PET/CT in the evaluation of hepatic metastases were 100%, 100%, and 95%, respectively. Similarly, the serum CEA levels in the 24 patients with liver metastases were elevated showing sensitivity, NPV, and accuracy of 100%, 100%, and 85%, respectively. The CIM were true-positive in 19 of 24 patients and false-negative in 5, yielding a sensitivity of 79% and accuracy of 68%.

Local recurrences were found in 23 of 58 patients with recurrent disease. The sensitivity, NPV, and accuracy of the <sup>18</sup>F-FDG PET/CT in the evaluation of local recurrence were 100%, 100%, and 95%, respectively. The serum CEA levels were elevated in 17 of 23 patients with local recurrences and gave false-negative results in 6 patients; showing a sensitivity, specificity, and accuracy of 73.9%, 64.7%, and 70%, respectively. Meanwhile, the CIM yielded true-positive results in 16 of 23 patients and false-negative results in 7 patients resulting in sensitivity, specificity, and accuracy of 69.5%, 52.9, and 62.5% in the evaluation of local recurrences, respectively.

The <sup>18</sup>F-FDG PET/CT detected 36 of 40 extrahepatic metastases correctly, thus lesion-based sensitivity, specificity, and accuracy were 90%, 88.2%, and 89.4%, respectively. Serum CEA levels were elevated in 17 of 29 patients with extrahepatic metastases and normal values were detected in the remaining 12 patients, yielding false-negative results. The patient-basis sensitivity, specificity, and accuracy of CEA levels in the evaluation of extrahepatic metastases were calculated as 58.6%, 64.7%, and 60.8%, respectively. CIM accurately detected 28 out of 40

extrahepatic metastatic foci, whereas false-negative in 12 patients. Therefore, the lesion-based sensitivity, specificity, and accuracy were calculated as 70%, 52.9%, and 64.9%, respectively.

Table 2 shows the comparative results of PET/CT, CIM, and serum CEA measurements.

Among the patients referred to <sup>18</sup>F-FDG PET/CT, increased CEA levels were found in 48 (64%) patients and abnormal CIM findings in 53 (71%) patients. All of the three modalities were true-positive in 28 (49%) patients. In 13 (22%) patients, <sup>18</sup>F-FDG PET/CT and CEA measurements were true-positive, whereas CIM was false-negative. In 13 (22%) patients, <sup>18</sup>F-FDG PET/CT and CIM were true-positive but CEA measurements were false-negative. The CIM correctly detected the recurrence in 3 (5%) patients, whereas <sup>18</sup>F-FDG PET/CT and CEA were false negatives. In 1 (2%) patient, CIM and CEA measurements were true-positive, whereas the <sup>18</sup>F-FDG PET/CT was false-negative. No recurrence was detected in 3 patients referred with suspicious physical examination findings.

## DISCUSSION

In our study, <sup>18</sup>F-FDG PET/CT correctly identified the recurrent disease in 54 out of 58 patients and yielded true-negative results in 15 of 17 patients without recurrent disease. Therefore, the sensitivity, specificity, accuracy, PPV, and NPV of <sup>18</sup>F-FDG PET/CT were found as 93.1%, 88.2%, 92%, 96.4%, and 78.9%, respectively. Thus, this study showed the superiority of <sup>18</sup>F-FDG PET/CT since these values were 72.4%, 64.7%, 70.6%, 87.5%, 40.7% and 77.5%, 52.9%, 72%, 84.9%, and 40.9% for serum CEA measurements and CIM, respectively.

One of 4 patients with false-negative results had normal serum tumor marker levels and was referred to PET/CT for the

evaluation of lung nodules detected with CT. No pathological FDG uptake in the nodules was observed on the PET/CT. The patient's clinical follow-up in the following months confirmed the suspicion of lung metastasis. This patient had rectal mucinous carcinoma, of which FDG affinity is low. The second patient who had undergone partial colectomy and liver metastasectomy for colon adenocarcinoma was referred to PET/CT for investigation of the free fluid in the abdomen detected in the MRI. The free fluid in the abdomen showed no abnormal <sup>18</sup>F-FDG uptake on PET/CT imaging, but the investigation of ascites fluid revealed adenocarcinoma. The third patient with mucinous adenocarcinoma had a mass lesion in the rectus abdominis without <sup>18</sup>F-FDG uptake. The last patient with false-negative showed no FDG uptake at the millimetric nodular lesions in the lungs probably due to the low affinity for FDG and/or resolution limitations. On clinical follow-up, the lesions were found to be metastatic nodules in the lungs.

One of the patients with a false-positive result had a mass lesion in the presacral space, strongly suggestive of recurrence on PET/CT, but the histopathology revealed exudative material. In the second false-positive case, widespread abnormal FDG uptakes were found in the liver on PET/CT images, suggestive of metastasis but the histopathology revealed active chronic hepatitis.

Approximately, in two-thirds of patients with CRC, serum CEA levels are increased with a specificity of 70-84% (12,13). Rocklin et al. (14) and Carlsson et al. (15) showed in their studies that CEA itself alone is superior to other biochemical tests in detecting recurrences. Wanebo et al. (16) prospectively examined many laboratory and radiological studies used in the follow-up of patients with colon and rectal cancer, and they detected the recurrences with elevated levels of CEA in 89% of patients. Serum CEA may show the recurrence earlier than all other diagnostic methods and symptoms (17). Serial CEA measurements are used in the follow-up of recurrence rather than clinical evaluation. However, the accuracy in the detection of locoregional recurrence and lung metastasis is not as high as it is in liver metastases (18). CIM can localize recurrences only 3-9 months after following the elevated CEA (12,19).

The sensitivity, NPV, and accuracy of serum CEA in detecting liver metastases are found as 100%, 100%, and 85%, respectively. Meanwhile, the accuracy of serum CEA value in detecting local recurrence and extrahepatic metastasis is found as 70% and 60.8%, respectively. The current study, as mentioned in the literature (18), shows that elevated values of serum CEA are highly indicative of liver metastases, whereas normal CEA does

**Table 2. Comparative results of PET/CT, CIM, and serum CEA measurements on patient-based analysis**

	PET/CT	CIM	Elevated serum CEA levels
Sensitivity (%)	93.1	77.5	72.4
Specificity (%)	88.2	52.9	64.7
PPV (%)	96.4	84.9	87.5
NPV (%)	78.9	40.9	40.7
Accuracy (%)	92	72	70.6
True-positive (n)	54	45	42
True-negative (n)	15	9	11
False-positive (n)	2	8	6
False-negative (n)	4	13	16

PPV: Positive predictive value, NPV: Negative predictive value, CIM: Conventional imaging methods, PET/CT: Positron emission tomography/computed tomography, CEA: Carcinoembryonic antigen

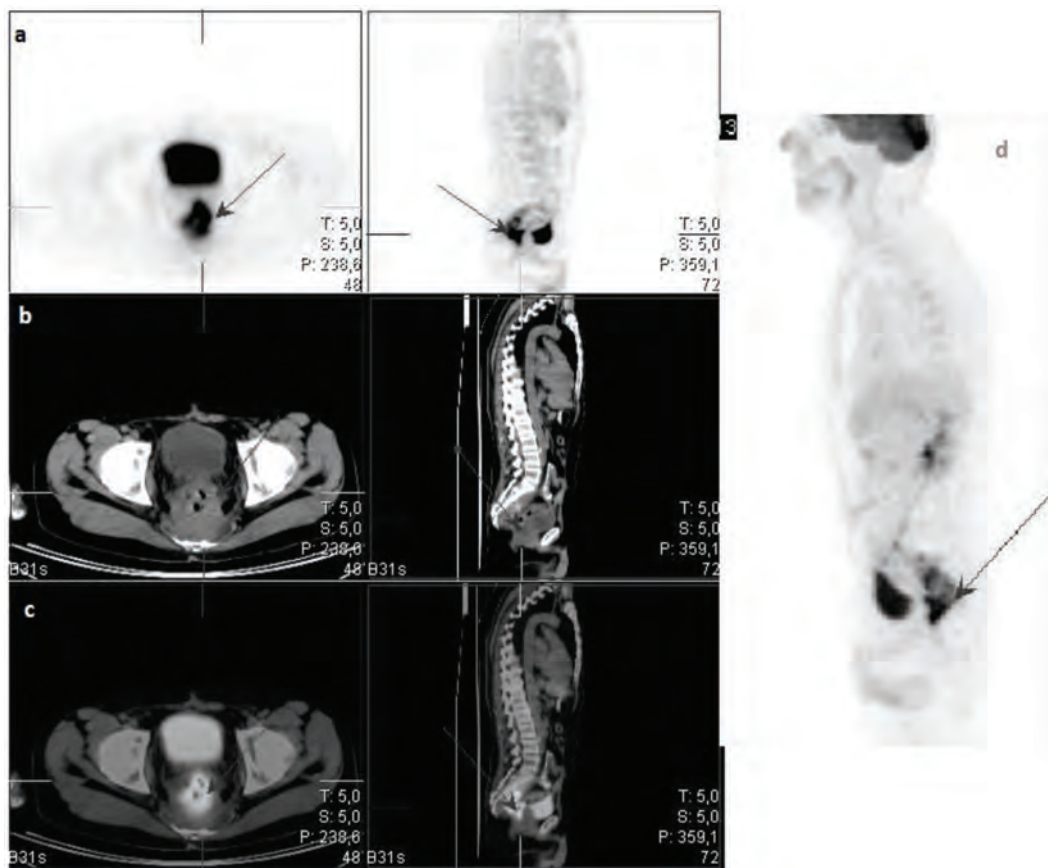
not rule out extrahepatic disease and local recurrence. In our study, CEA's NPV for local recurrence and extrahepatic metastases are calculated as 64.7% and 47.8%, respectively.

In patients presenting with high serum CEA levels and presacral mass, CIM has difficulty in differentiating the recurrence from fibrotic/scar tissue (20). The <sup>18</sup>F-FDG PET/CT imaging not only has a very important role in distinguishing between local recurrence and scar tissue after surgery/radiotherapy but also allows the detection of unpredictable distant metastases (21,22). The <sup>18</sup>F-FDG PET/CT has a sensitivity of 90% and specificity of 94% in detecting pelvic recurrence (20). Huebner et al. (23) reported in their meta-analysis that <sup>18</sup>F-FDG PET/CT has a sensitivity of 97% and specificity of 76%. In detecting local recurrences, the <sup>18</sup>F-FDG PET/CT showed sensitivity, PPV, and NPV of 90%, 88%, and 92%, respectively, whereas the sensitivity of CT/colonoscopy was reported as 71% (24).

In this study, all cases identified by the CIM as false positives consisted of postoperative fibrosis, scarring, and

postradiotherapy changes. The CIM yielded false-negative results, especially for extrahepatic metastases. In the present study, <sup>18</sup>F-FDG PET/CT correctly identified all 23 local recurrences and showed sensitivity, NPV, and accuracy of 100%, 100%, and 95%, respectively (Figure 1). Serum CEA levels were elevated in 17 of 23 patients with confirmed local recurrences and false-negative in 6 cases, yielding 73.9% sensitivity, 64.7% specificity, and 70% accuracy. CIMs were true-positive in 16 of 23 patients and false-negative in 7 patients, thus showing sensitivity, specificity, and accuracy of 69.5% 52.9%, and 62.5%, respectively. Our study results showed the superiority of <sup>18</sup>F-FDG PET/CT in detecting local recurrences following the literature findings.

When hematogenous dissemination is concerned, the primary site of metastasis for colorectal carcinoma is the liver (25). Liver metastases developed within 5 years in 50% of patients who had undergone curative surgery (26), and the only way to prolong the survey is by resecting the hepatic metastases (25). To be resectable, the hepatic metastases should be confined to one lobe, should be 1-4 in number, and without any other distant



**Figure 1.** <sup>18</sup>F-FDG PET/CT images of a 51-year-old patient who had undergone a miles operation for colorectal cancer 5 years ago and was referred to PET/CT for differentiation between scar tissue and local recurrence when CT detected a soft tissue mass at the presacral area. Serum CEA levels were normal. Axial PET (a), CT (b), fusion (c), and lateral MIP (d) images of the patient showed increased FDG uptake in the soft tissue mass at the presacral area consistent with metastasis (arrows)

<sup>18</sup>F-FDG: <sup>18</sup>F-fluorodeoxyglucose, PET/CT: Positron emission tomography/computed tomography, CEA: Carcinoembryonic antigen, MIP: Maximum intensity projection

metastatic site or metastatic lymphadenopathy (27). Only 10-20% of the hepatic metastases could be candidates for surgical resection (28). After curative surgical excision, 5-year survival and 5-year disease-free survival were reported to be 33-40% and 22%, respectively (3,26). The underlying reason for this relatively short duration of disease-free survival is the presence of occult cancer foci that are not detected in patients initially believed to be candidates for curative resection. The <sup>18</sup>F-FDG PET/CT is an important imaging modality in terms of its high sensitivity in detecting liver metastases, as well as detecting unpredictable metastatic disease (25). In most patients who are planning to undergo partial liver resection, CT is used to detect any extrahepatic diseases. However, either extensive disease discovered during laparotomy or the recurrent hepatic or extrahepatic diseases emerging shortly after surgery during follow-up necessitates more effective presurgical imaging to prevent unnecessary surgery.

In our study, the <sup>18</sup>F-FDG PET/CT correctly identified all 24 liver metastases with a sensitivity, specificity, NPV, and accuracy of 100%, 88.2%, 100%, and 95%, respectively. In the same way, in all 24 patients with confirmed liver metastasis, serum CEA levels were higher with sensitivity, accuracy, and NPV of 100%, 100%, and 85%, respectively. The CIM was true-positive in 19 out of 24 patients and false-negative in 5 patients yielding a sensitivity of 79% and accuracy of 68%. Therefore, in our study, <sup>18</sup>F-FDG PET/CT showed a very high sensitivity in detecting liver metastases.

The PET/CT was found to be more sensitive than CIM in detecting extrahepatic metastases (94% vs. 67%) (24). Delbeke et al. (29) reported in their study that PET/CT had a sensitivity of 100% and accuracy of 92% in the demonstration of extrahepatic metastases, whereas these values for CT were 71% and 74%, respectively. Peritoneal and mesenteric metastases with small volume are often missed with CT, whereas <sup>18</sup>F-FDG PET/CT can easily detect these lesions unless they are very small (<1 cm) (29).

In the present study, the <sup>18</sup>F-FDG PET/CT correctly identified the extrahepatic metastases in 36 out of 40 lesions, showing a sensitivity of 90%, specificity of 88.2%, and accuracy of 89.4% (Figure 2). Serum CEA levels were high in 17 out of 29 patients with extrahepatic metastases and its sensitivity, specificity, and accuracy were found as 58.6%, 64.7%, and 60.8%, respectively. Meanwhile, CIM detected 28 out of 40 extrahepatic metastatic foci, thus yielding a sensitivity, specificity, and accuracy of 70%, 52.9%, and 64.9%, respectively. In our study, the <sup>18</sup>F-FDG PET/CT's superiority to CIM was most prominent in detecting extrahepatic metastases.

All methods were true-positive in 28 (49%) patients. Elevated serum CEA levels and positive <sup>18</sup>F-FDG PET/CT results were seen in 13 (22%) patients, whereas CIM was false-negative in these patients. Contrarily, both <sup>18</sup>F-FDG PET/CT and CIM were true-positive in 13 (22%) patients when CEA gave false-negative results. Therefore, <sup>18</sup>F-FDG PET/CT exhibited a 93% success rate in detecting recurrence in cases referred to <sup>18</sup>F-FDG PET/CT depending on suspicious CIM findings and/or elevated CEA results.

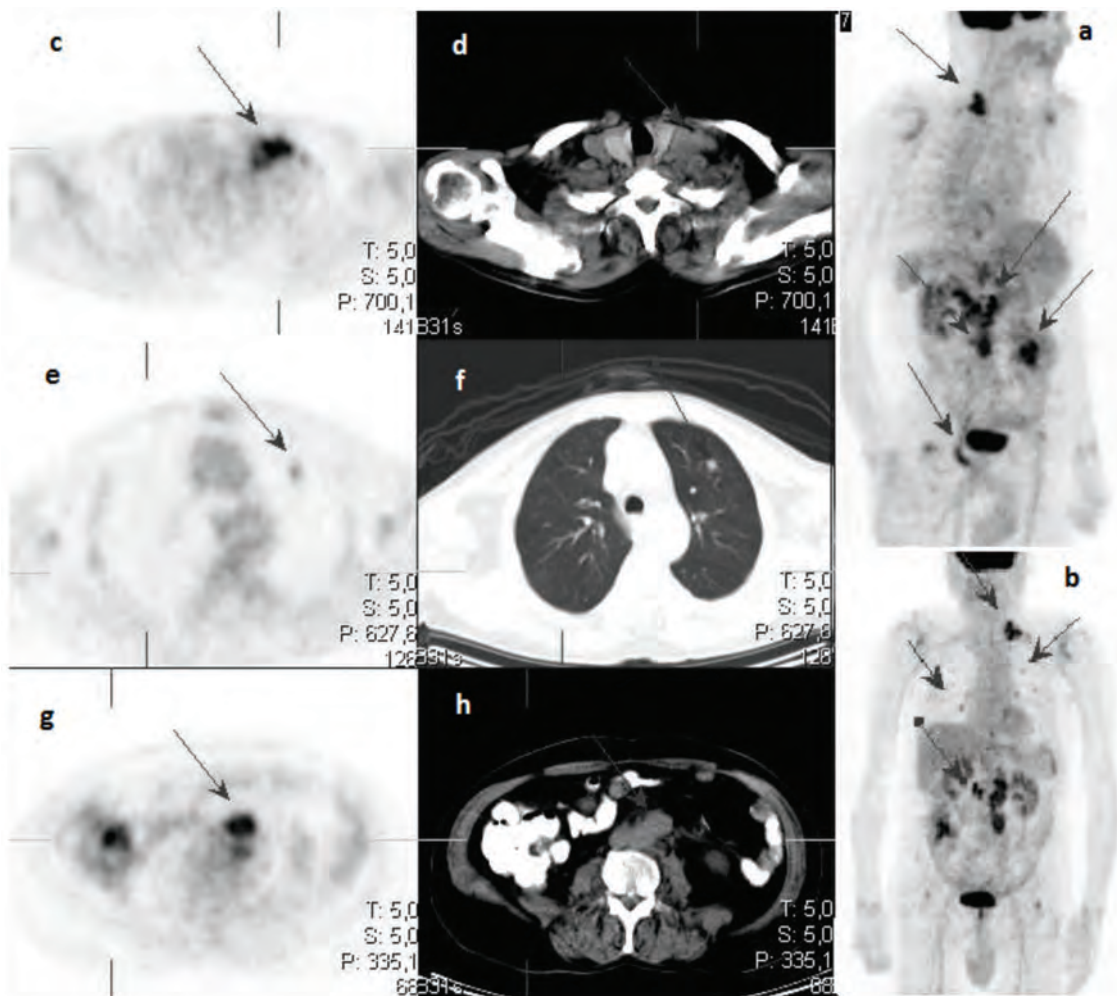
The most important consequence of this high rate of metastases detection is changing the treatment protocol. Demonstrating unexpected metastatic lesions on <sup>18</sup>F-FDG PET/CT in patients who were assumed to have limited metastatic disease before metastasectomy might change the treatment protocol of patients with a ratio of 13-32% (21,29).

In our study, the <sup>18</sup>F-FDG PET/CT detected extrahepatic foci of metastases in 7 patients, thus 6 patients underwent chemotherapy instead of liver metastasectomy. In another patient with high CEA values, whose CIM was reported as normal, metastatic foci were found in the abdomen, and similarly, chemotherapy was initiated. Additionally, 3 out of 5 patients, whose liver metastases were not detected with CIM, underwent metastasectomy. In the other 2 patients, multiple metastases were detected in the liver, and chemotherapy was applied. In 7 patients with local recurrence, the <sup>18</sup>F-FDG PET/CT correctly identified the lesions, whereas CIM could not differentiate the lesions from postoperative fibrosis/scarring, and consequently 3 patients were scheduled for radiotherapy and 4 underwent surgery. In addition, 6 of 17 cases without the recurrent disease (except true-negative patients detected by CIM and PET/CT together), PET/CT yielded true-negative results and reported normal. Therefore, <sup>18</sup>F-FDG PET/CT has changed the management of patients in 25 out of 75 cases (33.3%).

## CONCLUSION

In conclusion, recurrent CRC was detected by <sup>18</sup>F-FDG PET/CT with high sensitivity and specificity as compared with the CIM. Our study results revealed the superiority of <sup>18</sup>F-FDG PET/CT in detecting local recurrences of CRC following the literature findings. The <sup>18</sup>F-FDG PET/CT showed a very high sensitivity in detecting liver metastases but its superiority to CIM was most prominent in detecting extrahepatic metastases. The <sup>18</sup>F-FDG PET/CT has also substantially changed the management of patients. Our study revealed that CEA is highly sensitive in detecting liver metastases, but normal serum CEA levels do not rule out extrahepatic diseases and local recurrences. Recurrence





**Figure 2.** <sup>18</sup>F-FDG PET/CT images of a 74-year-old patient, who had undergone low anterior resection operation for rectal cancer 2 years ago and was referred to PET/CT for evaluation of the paraaortic lymph nodes detected with CT. Serum CEA levels were normal. Lateral (a) and anterior (b) MIP images showed pathologically increased FDG accumulations at the left supraclavicular region, nodules in both lungs, and intraabdominal paraaortic lymph nodes consistent with metastasis. Selected axial PET and CT images of the patient showed increased FDG uptake at the left supraclavicular region (c, d), at a pulmonary nodule in the left lung (e, f), and lymph nodes located in the left paraaortic region (g, h) (arrows)

<sup>18</sup>F-FDG: <sup>18</sup>F-fluorodeoxyglucose, PET/CT: Positron emission tomography/computed tomography, MIP: Maximum intensity projection, CEA: Carcinoembryonic antigen

was detected by <sup>18</sup>F-FDG PET/CT imaging in 70.6% cases with elevated serum CEA levels and negative, equivocal and/or pathological findings of CIM.

The <sup>18</sup>F-FDG PET/CT exhibited a 93% success rate in detecting recurrences in cases referred to <sup>18</sup>F-FDG PET/CT depending on suspicious findings on CIM and/or elevated CEA results.

### Ethics

**Ethics Committee Approval:** This study was carried out with the approval decision of Okmeydani Training and Research Hospital Clinical Research Ethics Committee dated April 20, 2009, and numbered 260.

**Informed Consent:** Consent was obtained from all patients who were scanned.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Concept: A.K.U., T.Ö., Design: A.K.U., T.K.G., F.Ö., T.Ö., Data Collection or Processing: A.K.U., T.K.G., F.Ö., Analysis or Interpretation: A.K.U., Literature Search: A.K.U., T.K.G., F.Ö., T.Ö., Writing: A.K.U.

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# Comparison of the Effects of Aerobic and Isokinetic Exercise Programs on Muscle Power, Cardiovascular Fitness, and Quality of Life in Multiple Sclerosis Patients: A Prospective, Randomized, Controlled Trial

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## Abstract

**Objective:** This study aimed to evaluate the effects of aerobic and isokinetic rehabilitation exercise programs on muscle power, cardiovascular fitness, and quality of life (QoL) in multiple sclerosis (MS) patients.

**Methods:** A total of 40 MS patients who enrolled in a rehabilitation center were included. Twenty patients were randomly assigned to the aerobic exercise group (AEG), and 20 to the isokinetic exercise group (IEG). Patients in both groups participated in a rehabilitation program for 3 days per week for 8 weeks. In the AEG, walking treadmills were adjusted to the maximum speed at which a person could walk, and a 30-45-min run-walk exercise was performed. The patients in the IEG pedaled on a bicycle ergometer. The primary outcome measures were exercise capacity, muscle strength, cardiovascular fitness, and QoL.

**Results:** In IEG, post-treatment exertion values improved significantly for all parameters except maximum achievable heart rate ( $p < 0.05$ ). The post-treatment values for all QoL assessments also improved significantly compared to pre-treatment values in the AEG ( $p < 0.05$ ). No significant differences in post-treatment values were observed between the two exercise groups ( $p > 0.05$ ).

**Conclusion:** Exercise increases muscle strength, functionality, and QoL of MS patients if preventive measures and appropriate precautions, such as selecting exercises suitable for the functional condition of the patient are used.

**Keywords:** Aerobic, isokinetic, exercise, multiple sclerosis, quality of life

## INTRODUCTION

Clinical signs can change during the course of multiple sclerosis (MS), causing muscle weakness and decreasing functional capacity, cardiac endurance, and quality of life (QoL) (1-3).

Muscle weakness affects many people with MS (4). Muscle weakness causes restrictions in daily life activities and decreases functions, such as walking, climbing up and down, sitting, and standing, and negatively affects participation in life and limits independence. This causes a further decrease in activity levels,



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particularly due to cardiopulmonary capacity, and a significant decrease in physiological condition (5,6).

Until the end of the past century, MS patients were advised not to exercise because symptoms resulting from increased body temperature and nerve cell fatigue during exercise were thought to worsen any long-term benefit (7). However, current studies have reported that exercise should be encouraged due to its positive effects on muscle strength, endurance, and QoL (8-10).

Many studies have shown that physical activity increases cardiovascular capacity and muscle strength and that aerobic exercise (AE) and resistance training are beneficial. Additionally, MS patients can tolerate high-intensity interval exercise (11-15). Although there is no consensus on an exercise program, AE, or isokinetic exercise (IE), or different modifications can be used as therapy for MS patients. According to the needs of the patient, one or more of these exercises may be preferred to improve muscle strength, endurance, and functional capacity (16,17).

While low-medium intensity AE in MS patients improves cardiopulmonary capacity and reduces fatigue, IE, which includes device-supported effective strengthening exercises that can be performed by applying force at different angular speeds and all degrees of motion, improve muscle strength, balance, and independent walking ability in MS patients (18-20).

The participation of MS patients in physical activities is a useful rehabilitation approach to manage symptoms without causing fatigue. It is important to encourage physical activity and strengthening exercises in MS patients (21,22). No randomized prospective study has compared the results of AE and IE training in MS patients.

This study aimed to evaluate and compare the effectiveness of IE and AE on muscle strength, cardiovascular system, and QoL in MS patients.

## METHODS

This study adhered to all relevant tenets of the Declaration of Helsinki and was approved by the University of Health Sciences Turkey, Okmeydani Training and Research Hospital Ethical Review Board (approval number: 128) and is registered at ClinicalTrials.gov (ref. NCT03805061). A minimum of 20 participants was needed for each group, with a 5% difference, and 80% power with a large effect size. Forty patients with MS aged 18-65 years who were being followed at the outpatient physical medicine and rehabilitation clinic were included in this study. Patients included in the study signed an "informed consent form".

Patients with a clinically definite diagnosis of MS according to the Poser criteria, disease duration of at least 1 year, and who could read and understand the MSQoL-54 questionnaire were enrolled. Patients who had a surgical operation on the knee joint in the last 3 months associated with an MS attack, a non-MS musculoskeletal disease (congenital anomaly or limb amputation), comorbid neurological (Parkinson's or Alzheimer's disease or polyneuropathy), and/or vestibular system disease, non-MS chronic systemic disease (diabetes mellitus, chronic obstructive pulmonary disease, hypertension, hyperlipidemia, serious cardiac disease, or malignancy), or other condition that would affect QoL, as well as those who were pregnant, were excluded from the study.

Descriptive information, such as age, gender, height, weight, occupation, marital status, and educational status, was recorded on a patient evaluation and follow-up form. Information about the disease, such as disease history, age at diagnosis, disease duration, type of disease, number of attacks, number of attacks per year, and symptoms that caused the patient to visit the health institution at the beginning of the disease, was collected individually. Motor, visual, and sensory symptoms; bladder and intestinal complaints; sexual problems; paroxysmal complaints; and cognitive or general dysfunction were assessed. Treatments used previously or currently and rehabilitation programs implemented up to the time of evaluation were also recorded.

The Expanded Disability Status scale (EDSS) score was determined by a trained and experienced specialist who had previously used the EDSS for treatment. These scores were employed as a measure of physical disability.

Each patient's QoL was assessed using the MSQoL-54 questionnaire. This scale is comprised of 54 questions and evaluates 12 areas: General health, energy and fatigue, role restriction due to physical problems, pain, physical-sexual-social-cognitive functioning, health concerns, QoL, emotional well-being, and role restrictions due to emotional problems. Subjects were asked to complete the questionnaire on their own.

Muscle strength was assessed using a hand-held muscle test, and isokinetic muscle strength was measured using a numerical classification of the Medical Research Association with a Humac Norm isokinetic dynamometer (Computer Sports Medicine Inc., Stoughton, MA, USA). Isokinetic test data obtained during measurements at two angular velocities included the following:

- Quadriceps peak torque (PT) value [Newton meters (Nm)]
- Hamstring PT value (Nm)
- Hamstring/quadriceps (H/Q) ratio



The PT-to-body mass index ratio (PT/BMI) was calculated by dividing the maximal torque values by the bodyweight of each patient. Muscle capacity reflects the muscle strength produced by the musculoskeletal system and is often measured in peak force.

Cardiopulmonary capacity indicates the body's capacity to endure long-term exercise and is usually measured by peak oxygen consumption ( $\text{VO}_2\text{max}$ ) (9,23,24).

Exercise capacity was assessed using the NoravTrackmaster TMX 425 treadmill exercise device using the modified Bruce protocol. Indirect maximum  $\text{VO}_2$  ( $i\text{VO}_2\text{max}$ ) and metabolic equivalent values were calculated using the heart rate obtained during submaximal treadmill exercise. The target heart rate, calculated as  $(220\text{-age}) \times (0.70)$ , was used to calculate 70-80% of each patient's maximum heart rate. For those exhibiting low sensitivity to exercise and low heat resistance, this figure was multiplied by 65%.

Functional capacity was measured by asking patients to walk at a comfortable pace as quickly as possible for 6 min in the hospital hallway along a 20-m ASTA flat track. The distance traveled in 6 min. was recorded in meters.

All participants were randomly assigned to two groups using a computer-generated block randomization list that was initiated by an independent individual not involved in patient treatment.

Of the 40 participants, 20 were randomly assigned to the AE group (AEG), and 20 to the IE group (IEG). Patients in both groups participated in a rehabilitation program for 3 days per week for 8 weeks. In the AEG, we carried out the AE daily protocol reported by Petajan et al. (25). According to that protocol, each training session was comprised of a warm-up at 30% of maximum  $i\text{VO}_2\text{max}$  for 5 min, followed by 60% of  $i\text{VO}_2\text{max}$  for 30 min and a 5-min cool down period. The walking treadmills were adjusted to the maximum speed at which a person could walk, and a 30-45-min run-walk exercise was performed according to the progressive training method. The patients in the IEG pedaled on a bicycle ergometer for 5 min at low resistance as a warm-up exercise before starting the exercise, and 5-10 min of stretching exercises were performed to cool down after the exercise. The IE program was comprised of 10 repetitions at 60°/sec, 90°/sec, 120°/sec, and 10 at 180°/sec, with a 30-sec rest period between sets. All patients in both groups were assessed before and after treatment.

All participants were analyzed and evaluated at the beginning and the end of the study. The data obtained were recorded, and the study was terminated.

## Statistical Analysis

Analyses were performed using SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA.) To compare the two groups, Student's t-test was used for normally distributed independent numerical variables, and the Mann-Whitney U-test was used for non-normally distributed independent numerical variables. Between-group comparisons of categorical variables were made using the chi-square or Fisher's tests. Pearson's and Spearman's correlation analyses were used to determine if any of the factors significantly affected the outcomes. Using the independent sample t-test and Cohen's d-value that a large effect on the physical health in MS ( $d=0.87$ ) with a total sample size of 40 participants, power was estimated at 84% at a significance level of  $\alpha=0.05$  (26). In addition, a regression model was created for the MSQoL-54 using variables that were significant. P values  $<0.05$  were considered significant.

## RESULTS

Of the 60 MS patients admitted to our outpatient clinic, 20 were excluded from the study because of respiratory system problems (3 cases), branch block (2 cases), issues with the resting electrocardiogram (1 case), and a delay in intraventricular conduction (1 case); 1 each had intracranial sinus thrombosis, polio sequelae, pregnancy, and breast cancer; 2 had a congenital hip dislocation, and 5 reported a history of MS attack in the last 3 months; 2 patients refused to participate in the study. Of the 40 MS patients included in the study, 13 (32.5%) were male, and 27 (67.5%) were female (Figure 1).

Of the 20 patients in the AEG, 14 were female and 6 were male, and their mean age was  $39.2\pm 6.0$  years. Of the 20 patients in the IEG, 13 were female and 7 were male, and their mean age was  $37.7\pm 9.7$  years. No significant differences were observed in the mean age or sex ratio of the study groups ( $p=0.561$ ,  $p=0.736$ ). The mean height of the patients in the AEG was  $165.3\pm 9.4$  cm, mean weight was  $73.4\pm 12.9$  kg, and mean BMI was  $26.9\pm 3.4$   $\text{kg/m}^2$ . The mean height of the patients in the IEG was  $162.4\pm 10.1$  cm, weight was  $67.5\pm 10.8$  kg, and BMI was  $26\pm 3.8$   $\text{kg/m}^2$ . No significant differences were observed between the groups in mean height, weight, or BMI ( $p=0.361$ ,  $p=0.125$ ,  $p=0.411$ ). Twenty (50%) of the cases were smokers. Twenty-five patients (62.5%) were receiving immunomodulatory treatment. Two patients had undergone an MS rehabilitation program since the diagnosis. The disease duration of the patients in the AEG was  $6.9\pm 4.4$  years, and the mean EDSS was  $1.6\pm 1.3$ . The disease duration in the IEG was  $5.8\pm 4.4$  years, and the mean EDSS was  $1.7\pm 1.5$ . No significant differences were observed between the groups ( $p=0.334$ ,

p=0.912). MS was diagnosed in 5 first-degree relatives and 2 second-degree relatives. The age at MS diagnosis was 32.3±8.7 years in the AEG and 31.9±9.6 years in the IEG (p=0.652). The mean number of attacks in the last 2 years was 1.8±0.9 in the AEG and 1.6±1.03 in the IEG (p=0.512).

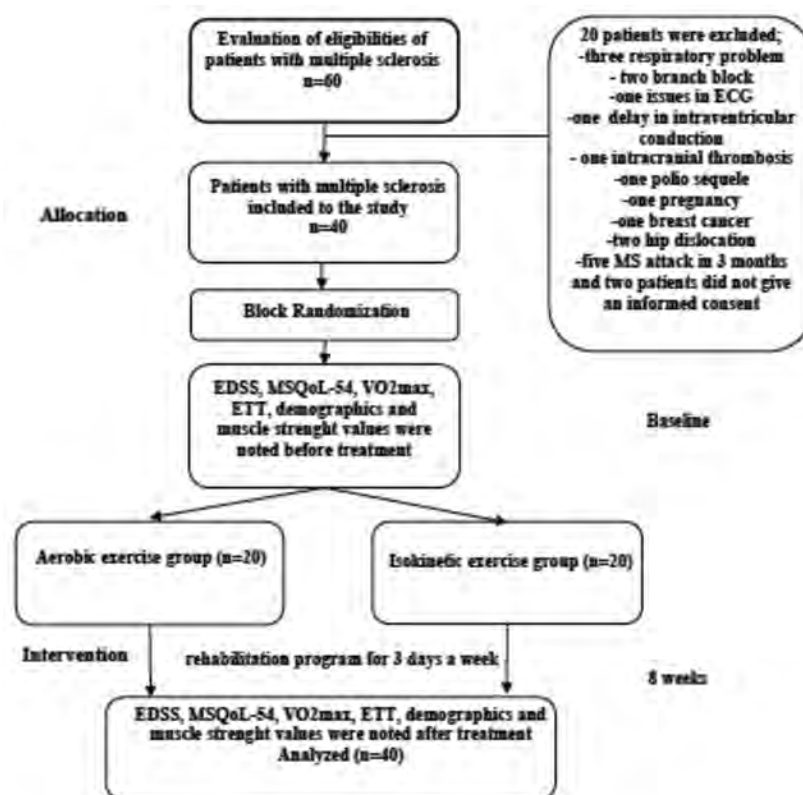
Ten patients were civil servants (25%), 13 were housewives (32.5%), 8 were sitting workers (20%), 5 were standing workers (12.5%), and 4 were tradesmen (10%).

When education levels were examined, 18 (45%) were primary school graduates, 5 (12.5%) were secondary school graduates, 11 (27.5%) were high school graduates, and 6 (15%) had higher education. No significant differences were observed between the groups in pre-treatment effort, muscle strength, or the MSQoL-54 assessments (Table 1).

The total MSQoL-54 score was 68.5±15.1 for males and 54.4±17.2 for females. The MSQoL-54 physical sub-scale scores were 69±13.5

	AE (± SD)	IE (± SD)	p
60°/sec PT (extensor)	88.7±33	93.6±40.9	0.679
60°/sec PT (flexor)	45.5±22.9	47±24.2	0.841
60°/sec H/Q	0.5±0.1	0.5±0.1	0.590
60°/sec PT/BMI	111.5±49.3	136.1±65.5	0.188
180°/sec PT (extensor)	42.3±17.5	45.3±26.7	0.672
180°/sec PT (flexor)	20.8±11.6	22.3±18.9	0.665
180°/sec H/Q	0.5±0.2	0.5±0.2	0.885
MSQOL-54 (total)	56±19.2	61.8±16.1	0.326
MSQOL-54 (physical)	58.3±19.2	62.3±14.3	0.463
MSQOL-54 (cognitive)	54±23.7	60.9±18.2	0.318

AE: Aerobic exercise, IE: Isokinetic exercise, H/Q: Hamstring/quadriceps ratio, BMI: Peak torque-to-body mass index ratio, MSQOL-54: Multiple Sclerosis Quality of Life-54 questionnaire, PT: Peak torque, SD: Standard deviation



**Figure 1.** The flowchart diagram of this study

ETT: Exercise tolerance test, MSQOL-54: Multiple Sclerosis Quality of Life-54 questionnaire, EDSS: The Expanded Disability Status scale

for males and  $56.4 \pm 17$  for females. The MSQoL-54 cognitive sub-scale scores were  $67.4 \pm 16.9$  for males and  $52.9 \pm 21.7$  for females. Significant differences were observed between genders before treatment ( $p=0.021$ ;  $p=0.030$ ;  $p=0.048$ , respectively). No significant difference in the MSQoL-54 total scores was observed according to educational status ( $p=0.349$ ). Furthermore, the total, physical, and cognitive QoL scores did not differ according to occupational status ( $p=0.083$ ;  $p=0.427$ ;  $p=0.150$ , respectively). The MSQoL-54 score was negatively correlated with the EDSS score and positively correlated with  $VO_2$ max, exercise tolerance test (ETT) time, 6-min walking distance, and  $60^\circ/\text{sec}$  and  $180^\circ/\text{sec}$  PT/BMI scores before treatment (Table 2).

In the AEG, the differences between pre-treatment and post-treatment exercise test scores were significant for all evaluations, except  $60^\circ/\text{sec}$  flexor PT,  $60^\circ/\text{sec}$  H/Q, and  $180^\circ/\text{sec}$  H/Q. Post-treatment evaluations revealed significant improvements in all other measures. The post-treatment values for all QoL assessments also improved significantly compared to the pre-treatment values in the AEG (Table 3).

In the IEG, post-treatment exertion values improved significantly for all parameters, except maximum achievable heart rate. Significant changes were detected in all muscle strength measures, except  $60^\circ/\text{sec}$  flexor PT,  $60^\circ/\text{sec}$  H/Q, and  $180^\circ/\text{sec}$  H/Q. Significant improvements were observed in all other

evaluations, including the QoL assessments, compared to pre-treatment values (Table 4). No significant differences were observed between the groups after treatment for measures of stress, muscle strength, or the MSQoL-54 (Table 5).

The two groups did not differ significantly in terms of changes between pre- and post-tests of stress, muscle strength, or the MSQoL-54 (Table 6).

## DISCUSSION

Petajan et al. (25) carried out an exercise program (EP) for MS patients and described the duration and goals of this program in detail. According to this EP, moderate-intensity aerobic activity for an average of 30 min twice per week and strengthening exercises involving major muscle groups twice per week were recommended for individuals with MS. We carried out a lower extremity strengthening program in the AEG for 30 min 3 times per week, and repeatedly in the IEG 3 times per week at determined angles. None of the patients in either group dropped out of their EPs due to fatigue or any other reason. All patients continued to perform their exercises on the specified days and completed the EP.

An IE study conducted by Lambert et al. (27) employed two MS groups and a control. Using a Cybex Norm dynamometer, the

**Table 2. The pretreatment values of the MSQoL-54, age, disease duration, number of attacks in the last two years, EDSS, effort capacity and muscle strength relationship**

		MSQoL 54 (total)	MSQoL-54 (physical)	MSQoL-54 (cognitive)
Age	r	-0.056	-0.171	0.031
	p	0.742	0.298	0.850
Disease duration (years)	r	-0.097	-0.055	-0.059
	p	0.569	0.740	0.723
Last 2 years attack issue	r	-0.218	-0.356	-0.128
	p	0.201	<b>0.028</b>	0.444
EDSS	r	-0.547	-0.553	-0.471
	p	<b>&lt;0.001</b>	<b>&lt;0.001</b>	<b>0.002</b>
VO <sub>2</sub> maximum	r	0.453	0.228	0.524
	p	<b>0.005</b>	0.164	<b>0.001</b>
ETT duration (sec)	r	0.445	0.327	0.433
	p	<b>0.006</b>	<b>0.042</b>	<b>0.006</b>
6 min walking distance	r	0.461	0.375	0.430
	p	<b>0.004</b>	<b>0.019</b>	<b>0.006</b>
60°/sec PT/BMI	r	0.594	0.517	0.475
	p	<b>&lt;0.001</b>	<b>0.001</b>	<b>0.002</b>
180°/sec PT/BMI	r	0.434	0.348	0.403
	p	<b>0.007</b>	<b>0.030</b>	<b>0.011</b>

PT/BMI: Peak torque-to-body mass index ratio, MSQoL-54: Multiple Sclerosis Quality of Life-54 questionnaire, ETT: Exercise tolerance test, EDSS: Expanded Disability Status scale

**Table 3. The pretreatment and posttreatment values of the stress-test evaluations, muscle strength assessments, and quality of life in the aerobic exercise group**

	Before treatment ( $\pm$ SD)	After treatment ( $\pm$ SD)	p
TA systolic	126 $\pm$ 17	121.5 $\pm$ 15.4	<0.001
TA diastolic	75.5 $\pm$ 7.7	72.9 $\pm$ 7.2	<0.001
Resting heart rate	86.3 $\pm$ 9.5	83 $\pm$ 9.3	<0.001
Maximum heart rate	146.5 $\pm$ 16.1	141.8 $\pm$ 17.5	0.003
VO <sub>2</sub> maximum	24.8 $\pm$ 11.1	30.7 $\pm$ 10.1	0.004
MET	8.1 $\pm$ 4.3	8.9 $\pm$ 2.9	0.039
ETT duration (sec)	606 $\pm$ 208.5	751.7 $\pm$ 176	0.001
60°/sec PT (extensor)	88.7 $\pm$ 33	96.4 $\pm$ 38.3	0.009
60°/sec PT (flexor)	45.5 $\pm$ 22.9	50.2 $\pm$ 22.7	0.071
60°/sec H/Q	0.5 $\pm$ 0.1	0.5 $\pm$ 0.1	0.210
60°/sec PT/BMI	111.5 $\pm$ 49.3	121.6 $\pm$ 51	0.025
180°/sec PT (extensor)	42.3 $\pm$ 17.5	53.3 $\pm$ 20.2	<0.001
180°/sec PT (flexor)	20.8 $\pm$ 11.6	26 $\pm$ 12.9	0.036
180°/sec H/Q	0.5 $\pm$ 0.2	0.5 $\pm$ 0.2	0.915
6 minutes walking distance	459 $\pm$ 90.8	491.5 $\pm$ 79.9	<0.001
MSQOL-54 (total)	56 $\pm$ 19.2	58.5 $\pm$ 19.5	<0.001
MSQOL-54 (physical)	58.3 $\pm$ 19.2	61.3 $\pm$ 18.7	<0.001
MSQOL-54 (cognitive)	54 $\pm$ 23.7	56.2 $\pm$ 24	<0.001

H/Q: Hamstring/quadriceps ratio, BMI: Body mass index ratio, MSQOL-54: Multiple Sclerosis Quality of Life-54 questionnaire, PT: Peak torque, TA: Tension arterial, ETT: Exercise tolerance test, MET: Metabolic equivalent value, SD: Standard deviation

**Table 4. The pretreatment and posttreatment values of the exercise tests, muscle strengths, quality of life in the isokinetic exercise group**

	Before treatment ( $\pm$ SD)	After treatment ( $\pm$ SD)	p
TA systolic	123.9 $\pm$ 15.5	120.1 $\pm$ 15.8	<0.001
TA diastolic	75.6 $\pm$ 6.7	73.1 $\pm$ 7.1	0.001
Resting heart rate	86.2 $\pm$ 9.3	82.9 $\pm$ 10.4	0.001
Maximum heart rate	141.4 $\pm$ 19.4	140.4 $\pm$ 19.1	0.609
VO <sub>2</sub> maximum	25.4 $\pm$ 9.7	29.4 $\pm$ 11.6	0.007
MET	7.3 $\pm$ 2.9	8.7 $\pm$ 3.3	<0.001
ETT duration (sec)	595.8 $\pm$ 209.9	698.4 $\pm$ 292.7	0.002
60°/sec PT (extensor)	93.6 $\pm$ 40.9	103.3 $\pm$ 41.2	0.032
60°/sec PT (flexor)	47 $\pm$ 24.2	52.9 $\pm$ 25.1	0.065
60°/sec H/Q	0.5 $\pm$ 0.1	0.5 $\pm$ 0.1	0.855
60°/sec PT/BMI	136.1 $\pm$ 65.5	152.1 $\pm$ 65.4	0.006
180°/sec PT (extensor)	45.3 $\pm$ 26.7	55.9 $\pm$ 27.6	<0.001
180°/sec PT (flexor)	22.3 $\pm$ 18.9	30.7 $\pm$ 22.1	0.002
180°/sec H/Q	0.5 $\pm$ 0.2	0.5 $\pm$ 0.2	0.672
6 minutes walking distance	461.4 $\pm$ 95.8	496.3 $\pm$ 101.6	<0.001
MSQOL-54 (total)	61.8 $\pm$ 16.1	63.8 $\pm$ 16.4	0.001
MSQOL-54 (physical)	62.3 $\pm$ 14.3	64.4 $\pm$ 14.7	<0.001
MSQOL-54 (cognitive)	60.9 $\pm$ 18.2	63.1 $\pm$ 18.7	0.001

H/Q: Hamstring/quadriceps ratio, PT/BMI: Peak torque-to-body mass index ratio, MSQOL-54: Multiple Sclerosis Quality of Life-54 questionnaire, PT: Peak torque, TA: Tension arterial, ETT: Exercise tolerance test, MET: Metabolic equivalent value, SD: Standard deviation



	Aerobic exercise ( $\pm$ SD)	Isokinetic exercise ( $\pm$ SD)	p
TA systolic	121.5 $\pm$ 15.4	120.1 $\pm$ 15.8	0.735
TA diastolic	72.9 $\pm$ 7.2	73.1 $\pm$ 7.1	0.947
Resting heart rate	83 $\pm$ 9.3	82.9 $\pm$ 10.4	0.975
Maximum heart rate	141.8 $\pm$ 17.5	140.4 $\pm$ 19.1	0.803
VO <sub>2</sub> maximum	30.7 $\pm$ 10.1	29.4 $\pm$ 11.6	0.600
MET	8.9 $\pm$ 2.9	8.7 $\pm$ 3.3	0.820
ETT duration (sec)	751.7 $\pm$ 176	698.4 $\pm$ 292.7	0.808
60°/sec PT (extensor)	96.4 $\pm$ 38.3	103.3 $\pm$ 41.2	0.586
60°/sec PT (flexor)	50.2 $\pm$ 22.7	52.9 $\pm$ 25.1	0.728
60°/sec H/Q	0.5 $\pm$ 0.1	0.5 $\pm$ 0.1	0.659
60°/sec PT/BMI	121.6 $\pm$ 51	152.1 $\pm$ 65.4	0.109
180°/sec PT (extensor)	53.3 $\pm$ 20.2	55.9 $\pm$ 27.6	0.741
180°/sec PT (flexor)	26 $\pm$ 12.9	30.7 $\pm$ 22.1	0.414
180°/sec H/Q	0.5 $\pm$ 0.2	0.5 $\pm$ 0.2	0.767
MSQOL-54 (total)	58.5 $\pm$ 19.5	63.8 $\pm$ 16.4	0.379
MSQOL-54 (physical)	61.3 $\pm$ 18.7	64.4 $\pm$ 14.7	0.572
MSQOL-54 (cognitive)	56.2 $\pm$ 24	63.1 $\pm$ 18.7	0.324

AE: Aerobic exercise, IE: Isokinetic exercise, H/Q: Hamstring/quadriceps ratio, PT/BMI: Peak torque-to-body mass index ratio, MSQOL-54: Multiple Sclerosis Quality of Life-54 questionnaire, PT: Peak torque, TA: Tension arterial, ETT: Exercise tolerance test, MET: Metabolic equivalent value, SD: Standart deviation

	Aerobic exercise change ( $\pm$ SD)	Isokinetic exercise change ( $\pm$ SD)	Change difference	p
TA systolic	4.5 $\pm$ 2.7	3.9 $\pm$ 1.7	0.600	0.407
TA diastolic	2.6 $\pm$ 1.8	2.5 $\pm$ 2	0.100	0.601
Resting heart rate	3.4 $\pm$ 2.9	3.3 $\pm$ 3.7	0.050	0.419
Maximum heart rate	4.7 $\pm$ 6	1.0 $\pm$ 8.6	3.650	0.177
VO <sub>2</sub> maximum	5.9 $\pm$ 8.1	4.0 $\pm$ 8.8	1.871	0.746
MET	0.8 $\pm$ 3.6	1.6 $\pm$ 1.8	0.772	0.652
ETT duration (sec)	145.7 $\pm$ 174	102.6 $\pm$ 263.2	43.050	0.839
60°/sec PT (extensor)	12.2 $\pm$ 7.7	18.9 $\pm$ 9.7	2.000	0.065
60°/sec PT (flexor)	11.1 $\pm$ 4.8	13.4 $\pm$ 5.9	1.150	0.768
60°/sec H/Q	0.0 $\pm$ 0.1	0.0 $\pm$ 0.1	0.026	0.899
60°/sec PT/BMI	10.2 $\pm$ 18.7	16 $\pm$ 23.4	5.850	0.405
180°/sec PT (extensor)	11.1 $\pm$ 7.6	10.6 $\pm$ 8.9	0.500	0.478
180°/sec PT (flexor)	10.4 $\pm$ 5.2	8.4 $\pm$ 13	3.250	0.795
180°/sec H/Q	0.0 $\pm$ 0.2	0.0 $\pm$ 0.2	0.027	0.988
MSQOL-54 (total)	2.5 $\pm$ 1.7	2.0 $\pm$ 1.8	0.528	0.791
MSQOL-54 (physical)	3.0 $\pm$ 2.7	2.1 $\pm$ 1.3	0.943	0.465
MSQOL-54 (cognitive)	2.2 $\pm$ 1.7	2.2 $\pm$ 2.3	0.049	0.508

AE: Aerobic exercise, IE: Isokinetic exercise, H/Q: Hamstring/quadriceps ratio, PT/BMI: Peak torque-to-body mass index ratio, MSQOL-54: Multiple Sclerosis Quality of Life-54 questionnaire, PT: Peak torque, TA: Tension arterial, ETT: Exercise tolerance test, MET: Metabolic equivalent value, SD: Standart deviation

researchers tested five repetitions of knee extensor and flexor exercises at 30°/sec, 60°/sec, 90°/sec, 120°/sec, and 180°/sec angular speeds, two at submaximal and three at maximal effort. They measured the PT values after applying the IE program. Extensor and flexor values at all speeds were divided into those for the dominant and the non-dominant lower limbs. The results revealed no significant difference in power generation between the dominant and non-dominant extremities in either group. However, significant differences in non-dominant limb extension and dominant and non-dominant flexion values were found in both groups. We used the extensor and flexor muscles of both lower extremities at the commonly preferred angular velocities of 60°/sec and 180°/sec for the muscle strength measurement but did not apply the dominant-non-dominant distinction.

In a study by Gehlsen et al. (28), 10 MS patients with EDSS scores <6 underwent an aquatic EP for 10 weeks. They then used a Cybex II isokinetic dynamometer at 60°/sec, 120°/sec, and 180°/sec to assess muscle strength. They measured the PT values of the knee joint flexor and extensor muscles at 240°/sec and 300°/sec and found a significant increase in the PT values of the knee extensor muscles. In contrast, in our study, a significant increase in 60°/sec and 180°/sec PT extensor and 180°/sec PT flexor muscle strength was detected in both exercise groups before and after the treatment (Table 5, 6). In agreement with our results, Hameau et al. (7) found an increase in knee extensor muscle strength after their rehabilitation program.

Romberg et al. (8) evaluated QoL, gait, and muscle strength after a 23-week AE program performed at home with 91 MS patients whose initial EDSS scores were 1.0-5.5. They reported a significant increase in those parameters but detected no change in  $VO_2$ max values. In our study, mean  $VO_2$ max before and after treatment improved significantly in both groups (Table 5, 6). In a 4-week study of a bicycle ergometer EP, Mostert and Kesselring (9) reported that the aerobic capacity of the exercise group increased significantly ( $VO_2$ max, +13%; working capacity, +11%), in agreement with our results. We found a significant increase in the mean 6-min walking distance at the end of treatment (Table 5, 6).

In our study, the MSQoL-54 values were positively correlated with  $VO_2$ max, the EDSS score, ETT duration, 6-min walking distance, and the 60°/sec and 180°/sec PT/BMI (Table 3). Similarly, the study by Petajan et al. (25), investigated the effects of exercise on QoL in MS patients. Patients with a mean EDSS score of  $3.8 \pm 0.3$  exhibited significant improvements in  $VO_2$ max values, from a mean of  $24.2 \pm 0.2$  to  $29.4 \pm 1.3$ , as a result of a 15-week EP. They also reported significant improvements in QoL.

In another study, 49 patients with a mean EDSS score of  $5.1 \pm 1.4$ , who were diagnosed with MS according to the Poser criteria, exercised 1 day per week for 6 weeks. The Barthel Index (BI) and Fatigue Severity Scale scores were evaluated before and after the study, and the Borg Scale scores were evaluated based on manual muscle strength, 10-m and 20-m walking times, and MSQoL-54 results. The results showed a 3.6% increase in the BI in the exercise group. A significant increase in muscle strength (+4.3%) was observed in the exercise group, as well as significant decreases in the 10-m and 20-m walking times. A 9.8% increase in the physical health score and a 7.7% increase in the physical functioning score were detected on the MSQoL-54 sub-scores (11). We also found significant increases in the 6-min walking distance, muscle strength, and MSQoL-54 scores in both exercise groups (Table 3, 4).

Fatigue associated with low QoL is one of the most important reasons restricting people's participation in daily life activities by reducing their work performance. Somatic symptoms in MS are also at the forefront (29-31). Fatigue in MS and increases in body temperature or ambient temperature increase the sensitivity of demyelinated myelin sheaths, slows down nerve conduction, and worsen symptoms (32). This can be a limiting factor for physical activity. Exercise should be done by reducing heat production to prevent exacerbating the symptoms. Submaximal exercise is ideal for MS patients, as it does not increase fatigue or body temperature. While the cardiopulmonary exertion rate is 70-80% in the healthy population, a value of 65% of the  $VO_2$ max is recommended for MS patients when aerobic exercises are performed 3 or more times per week (23,24). In our study, exercise was performed at 60% of  $iVO_2$ max without increasing body temperature.

Muscle weakness in the upper limbs alone is uncommon, as weakness usually occurs in the lower limbs (5,6,33). We also detected no muscle weakness in the upper extremities. Muscle strength was evaluated using a manual muscle test and classified according to the EDSS score. Exercises intended to increase muscle strength and function should be done daily. Prolonged strengthening exercises are thought to cause fatigue and decrease functional capacity in MS patients. Although exercises to increase muscle strength are generally reported to offer minimal benefits, recent studies have reported positive results (34-36). Nevertheless, patients should be warned about intense activity, and the need for frequent breaks during exercise should be emphasized (37).

Despite that many studies have shown the benefits of exercise in MS patients, this patient population is less active due to

movement disorders, difficulties with tasks that they have accomplished before, or fatigue and balance problems. Exercise is a useful rehabilitation strategy for MS patients to regain function, optimize QoL, and increase participation in daily life activities. Although there are individual differences at each level of disability, patients should be supported and encouraged to exercise.

### Study Limitations

Several limitations of our study should be mentioned. Our inclusion and exclusion criteria were standard factors and valid in all studies. The limitations of this study included the lack of a long follow-up period and no double-blindness.

### CONCLUSION

We examined the contribution of exercise to muscle strength, functional capacity, and QoL in MS patients and compared two exercise approaches. The results will contribute to the existing literature in this area. Exercise has not been recommended for MS patients because it was thought to increase body temperature and fatigue level. Our results indicate that exercise increases muscle strength, functionality, and QoL if preventive measures and appropriate precautions are taken, such as selecting exercises suitable for the functional condition of the patient, including AE, such as cycling and walking, and IE that does not result in fatigue.

### Ethics

**Ethics Committee Approval:** This study adhered to all relevant tenets of the Declaration of Helsinki and was approved by the University of Health Sciences Turkey, Okmeydanı Training and Research Hospital Ethical Review Board (approval number: 128) and is registered at ClinicalTrials.gov (ref. NCT03805061).

**Informed Consent:** Patients included in the study signed an “informed consent form”.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

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

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# Effects of Concentrated Growth Factor and Hyaluronic Acid in an Experimental Model of Acute Traumatic Tympanic Membrane Perforation

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## Abstract

**Objective:** The aim of this study is to investigate the efficacy of concentrated growth factor (CGF) and hyaluronic acid (HA) application on the healing of acute tympanic membrane (TM) perforation.

**Methods:** A total of 30 male albino rats were included in the study. The animals were randomly divided into three groups with 9 rats in each group (A, B, C). A CGF was applied to the perforated TMs of rats in group A. A gelfoam particle soaked in 1% hyaluronan was applied to the perforations in group B. The rats in group C were left to heal spontaneously. All rats were kept under control for 21 days. TM healing was evaluated. On the 21<sup>st</sup> day, all rats were decapitated for histopathological evaluation.

**Results:** In group A, 18 of the 18 TM perforations were closed and the mean healing time was 12.11 days. In group B, 18 of the 18 TM perforations were closed and the mean healing time was 15.05 days. In group C, 16 of 18 TM perforations were closed and the mean closure time was 17.11 days. There was a statistically significant difference in the mean TM closure time in all groups at the end of the 21<sup>st</sup> day ( $p=0.001$ ).

**Conclusion:** In this study, we used autologous CGF and HA in the treatment of acute TM perforations in rats. We observed that the application of both products was a more effective method than the control group. We think that using these methods, which are easy, inexpensive, and have low patient morbidity, as graft or graft support in chronic TM perforations will be beneficial and successful results will increase.

**Keywords:** Concentrated growth factor, hyaluronic acid, tympanic membrane

## INTRODUCTION

Tympanic membrane (TM) perforation often has different causes, such as trauma and infection. If the perforation is not healed, important problems such as chronic otitis media and hearing loss may occur. The reported incidence of TM perforation ranged from 1% to 4% (1). Perforations often heal spontaneously unless chronic inflammation develops; however, with chronic perforation, surgical repair is usually required (2).

In traumatic perforations, especially when less than a quarter of the membrane is perforated, approximately 90% of them heal spontaneously, while grafting is often required to repair large perforations (3).

Healing of perforated TM after acute trauma includes epithelial proliferation and migration, fibroblast proliferation, angiogenesis, and tissue remodeling. The epithelial layer first forms a bridge over the wound, the surface of the fibrous layer



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is closed, and the TM takes its final form (4). Different cytokines and growth factors are released from the wound site during the acute stage of wound healing. Many otolaryngologists perform microsurgical procedures to accelerate the healing process. These include early patching, surgery, and use of biomaterials such as hyaluronate, epidermal growth factor (EGF), fibroblast growth factor, platelet-derived growth factor, and transforming growth factor (5,6). Autogenous materials may be used more frequently in TM repairs because of their positive effects on wound healing quantity and quality. Various animal experimental studies have examined the effects of these growth factors on wound healing. These studies have helped us learn the healing process of TM perforations in humans.

This study aimed to investigate the effectiveness of concentrated growth factor (CGF) and hyaluronic acid (HA), which can be obtained by a simple and inexpensive method, on the healing of acute TM perforation.

## METHODS

This study was approved by the Animal Research Ethics Committee of Bezmialem Vakif University Medical Faculty (approval date: 21.03.2019, approval no. 2019/91). Thirty male albino rats with bilateral normal TM (weight, 250-300 g) breeding in the multidisciplinary research laboratories were examined and included in the study.

### Concentrated Growth Factor Preparation

Of the 30 animals, three were used for CGF preparation. Then, 4 mL of intracardiac blood were collected from the three rats and placed in test tubes without anticoagulants. These tubes were centrifuged (MEDIFUGE TM, Silfradent Srl, S. Sofia, Italy) at 2700 rpm for 2 min, 2400 rpm for 4 min, 2700 rpm for 4 min, and 3 min at 3000 rpm. The aim was to obtain a dense fibrin matrix containing growth factors at a higher rate by centrifuging the samples at different speeds and times. After the procedure, four layers were obtained from bottom to top: Red blood cell layer, growth factor and stem cell layer (CGF), buffy coat layer, and serum layer. Then, the CGF gel layer was separated using sterile surgical scissors and placed over the target site (7).

### Surgical Procedure

The animals were randomly divided into three groups with nine rats in each group (groups A-C). Ketamine hydrochloride (40 mg/kg) and xylazine hydrochloride (5 mg/kg) were administered intraperitoneally to anesthetize all animals. In the otomicroscopic examination, a perforation was created using a pike in the posterosuperior quadrant of both TMs in all rats.

CGF was applied to the perforated ears in group A. A 1.5-2 mm-diameter gelfoam particle soaked in 10  $\mu$ L of 1% hyaluronan (Healon, Pharmacia AB, Sweden) was applied to the perforations in group B. No intervention was made to the perforated ears in group C, and they were left to heal spontaneously. All rats were observed in their groups in cages with access to water and food. The animals were examined microscopically daily under inhaled isoflurane anesthesia until the animals were sacrificed or 21 days had passed to define the time of perforation closure.

### Histopathological Examination

On day 21, after intraperitoneal pentobarbital injections (80 mg/kg), all rats were decapitated. Their external ears were separated from the osteocartilaginous connections, and each bulla was opened. TMs were removed together with the bone annulus. All ear samples were stored in 10% formaldehyde solutions and sent to the pathology laboratory for histological evaluation. In total, 52 surgical specimens fixed in formaldehyde were decalcified in formic acid. Sections were embedded in paraffin. Tissue blocks were cut into 5-mm-thick slides, treated with hematoxylin and eosin, and then examined under a light microscope. Fibrosis, neovascularization, inflammation, and edema in tissue samples were evaluated in histopathological examination. All examinations were performed by the same pathologist without knowing which tissue sample belonged to which group. Changes in parameters were scored as (-), (+), (++) or (+++). Negative showed no change; (+), (++) and (+++) scores showed mild, moderate, and significant changes, respectively. No rats died during the study period.

### Statistical Analysis

In the evaluation of the study findings, IBM SPSS Statistics 22 (IBM Corp., Armonk, NY, USA) program was used for statistical analysis. While evaluating the study data, the conformity of the parameters to the normal distribution was evaluated with the Shapiro-Wilk test. In addition to statistical methods (mean, standard deviation, and frequency), the Kruskal-Wallis test was used for the comparison of the parameters that did not show a normal distribution in the comparison of quantitative data, between more than two groups. The chi-square test was used to compare qualitative data. Significance was evaluated at the level of  $p < 0.05$ .

## RESULTS

The closure process of TMs was examined microscopically for 21 days in a total of 27 rats. In group A, 18 of the 18 TM perforations in which CGF was applied were closed, and the mean healing

time was 12.11 days. In group B, 18 of the 18 TM perforations in which HA was applied were closed, and the mean healing time was 15.05 days. In group C, whose perforations were left to spontaneous heal, 16 of 18 TM perforations were closed, and the mean closure time was 17.11 days (Table 1). One of the rats in the control group, which was left to heal spontaneously, did not heal in both TMs.

The mean closure times were evaluated in all groups after 21 days, and a significant difference was observed ( $p=0.001$ ) (Table 1). When the difference in the mean closure time between the groups was compared, it was shorter in group A than in groups B and C, and the differences were found significant ( $p=0.004$ ,  $p=0.001$ , respectively). It was also slightly shorter in group B than in group C ( $p=0.037$ ) (Table 1). Histopathological evaluation initiated after 21 days of TM recovery evaluation revealed no significant difference between all animal groups in terms of edema, neovascularization, fibrosis, and inflammation parameters (Table 2).

## DISCUSSION

TM perforations in humans appear in various sizes depending on the causes, such as infections, accidents, explosion, slap injury, or instrument-induced injury. Even a very small perforation can negatively affect people's daily quality of life. Approximately 90% of TM perforations heal spontaneously within 7-21 days, depending on their size (4). Following an acute trauma to the TM, an exudative reaction begins first at the edges of the perforation. After a while, a keratin migration starts from the external squamous epithelial layer of the TM to the center of the perforation. Crust layer formation protects the underlying tissue, providing a suitable basis for cell migration and the healing process. Closure of the TM defect initially occurs through the keratin layer, then squamous epithelial cells fuse, and a supporting connective tissue closes the perforation (8).

At present, myringoplasty is an effective procedure commonly used to repair TM perforations. Many graft types are used in myringoplasty. These grafts should be biocompatible and easy to obtain. In perforation repair, while autografts (temporal muscle

fascia, tragal cartilage, and fat tissue), gel films, and paper patches are used for stromal support, silver nitrate cauterization and trichloride acetic acid can be applied to the perforation borders. The TM structures of humans and rats have similar histological features (9). Considering that similar results can be obtained in humans, rats are generally used in experimental studies on TM. Animals studies have shown the presence of stem cells in the annulus and manubrium malleus of TM. These cells are involved in the repair of TM owing to their high proliferation properties (4). Platelet-rich products are used in many areas in graft and wound treatment, as they promote accelerated angiogenesis, chemotaxis, mitosis, and proliferation of stem cells (10). To benefit from the effects of these products in wound healing, many types of platelet concentrate products have been used for years. These products take various names depending on their contents, centrifugation methods, and presence or absence of an anticoagulant in the production techniques. Platelet-rich plasma (PRP), platelet-rich fibrin (PRF), and CGF are some of these products. Studies on topical HA, EGF, PRP, PRF, and many other product applications have been reported in the treatment of traumatic TM perforations (11). Yeo et al. (12) reported that mouse TM perforations showed better closure than the control group with the application of a 2- $\mu$ g platelet-derived growth factor. Mondain et al. (13) showed that the application of fibroblast growth factor to mouse TM perforation resulted in faster closure. By contrast, O'Daniel et al. (14) studied pigs and showed that EGF receptors are present in all three TM layers, especially the squamous epithelial layer.

PRP and PRF were first defined by Dohan et al. (15) by dividing them into two different groups according to their production methods and contents. El-Anwar et al. (16) performed tympanoplasty with conchal cartilage for dry and large perforated TM 64 patients. In half of the cases, they applied PRP during the procedure. They observed a higher graft retention rate and a lower infection rate in the PRP group. Another similar study showed better graft success rates using PRP-impregnated gel foam in tympanoplasty (17). Erkiyet et al. (18) applied PRP to perforated TMs in rats and reported that PRP had positive effects on healing and shortened the recovery time. The main

**Table 1. Closure time of the study and control groups**

	Closure time (day)					p	Pairwise comparisons of the groups
	n (ear)	Minimum	Maximum	Mean	SD		
Group A (CGF)	18	9	15	12.11	1.94	0.001	Group A-B; $p=0.004$ Group B-C; $p=0.037$ Group A-C; $p=0.001$
Group B (HA)	18	11	17	15.05	1.55		
Group C (control)	16	12	20	17.11	1.68		

Kruskal-Wallis test  $p<0.05$ , Pairwise comparison: Mann-Whitney with Bonferroni correction, SD: Standard deviation, CGF: Concentrated growth factor, HA: Hyaluronic acid

generations of autologous platelet concentrate produced by centrifugation of venous blood at different rates are PRP, PRF, and CGF. CGF, which is the newest autologous platelet concentrate, was first described by Sacco (19). The rationale for this product is related to the *in situ* administration of multiple autogenous growth factors, as well as specific fibrin scaffold formation. Lei et al. (20) conducted a comparative study between advanced PRF (A-PRF), a variant of PRF, and CGF. They showed that A-PRF had a looser fibrin network than CGF, and stimulation of a sustained release of growth factor for 10 days was comparable in both products. Another comparative study showed that platelet and growth factor concentrations in A-PRF were comparable to CGF, but A-PRF and CGF had higher platelet and growth factors than PRP and plasma-rich growth factors (21). Contents of PRF and CGF are similar, but CGF is rich in growth factors and has a denser fibrin matrix. These materials have properties that increase soft tissue and bone healing (22). Membranes obtained from these biomaterials can be used as graft material in otological applications such as TM repair. CGF or PRF is preferred over PRP because no anticoagulants are added, and their membranes provide better biomechanical resistance. This event is valuable in terms of graft survival.

Ensari et al. (23) used PRF as graft material in rats and reported that the mean recovery time of TM perforation was  $10.3 \pm 2.18$  days in the study group and  $17 \pm 2.40$  days in the control group ( $p < 0.05$ ). Gür et al. (24) applied PRF in 30 of 60 patients with acute TM trauma and applied paper patches to the other 30 patients. They observed perforation closure in 93% of the patients in the PRF group and 83% of the patients in the paper group. They did not observe a significant difference in the healing rates of TMs. They reported 7.8 as the mean closure time of TMs in the PRF group. In addition, Habesoglu et al. (25) reported that the use of PRF in acute traumatic TM perforations resulted in significantly better recovery rates and times. In our study, we examined the healing process of TM perforations we have created in 18 rats for 21 days to observe the effect of CGF on traumatic TM perforation. Subsequently, 18 of the 18 TM perforations in which we applied CGF were closed, and the mean recovery time was 12.11 days. In the control group, whose perforations were left to heal spontaneously, 16 of 18 TM perforations were closed, and the mean closure time was 17.11 days (Table 1). A significant difference was found between the two groups in terms of mean recovery times of TM ( $p = 0.001$ ).

**Table 2. All rats were sacrificed on day 21: Histopathological evaluation of TMs**

	Group A (CGF)		Group B (HA)		Group C (control)		p
	n	%	n	%	n	%	
<b>Edema</b>							
-	11	61.1	15	83.3	15	83.3	0.052
+	6	33.3	-	-	2	11.1	
++	1	5.6	3	16.7	1	5.6	
+++	-	-	-	-	-	-	
<b>Neovascularization</b>							
-	16	88.9	17	94.4	18	100	0.347
+	2	11.1	1	5.6	-		
++	-	-	-	-	-		
+++	-	-	-	-	-		
<b>Fibrosis</b>							
-	-	-	5	27.8	6	33.3	0.113
+	11	66.7	10	55.6	9	50	
++	4	22.2	3	16.7	3	16.7	
+++	3	11.1	-	-	-	-	
<b>Inflammation</b>							
-	18	100	18	100	17	94.4	0.361
+	-	-	-	-	1	5.6	
++	-	-	-	-	-	-	
+++	-	-	-	-	-	-	

Chi-squared test  $p < 0.05$ , TMs: Tympanic membrane, CGF: Concentrated growth factor, HA: Hyaluronic acid



CGF, like other platelet concentrate products, accelerates wound healing, because it contains growth factors and cytokines. Since it is an autologous product, it does not pose a risk of infection and immune response. It also slowly releases growth factors into the environment through the fibrin network. It is easy and inexpensive to obtain (26). Recent studies with CGF are mostly on dental operations and bone tissue, and there are very few studies on TM. Sohn et al. (26) used CGF for maxillary sinus augmentation as well as implant surgery. They showed that CGF has an accelerating effect on new bone formation and soft tissue healing. In another case report, sinus perforation was treated with CGF, and new bone formation was demonstrated in the control evaluation performed with radiological examinations 6 months later (27). Talaat et al. (28) applied PRP, PRF, and CGF to the defects in 20 patients with bone defects caused by mandibular lesions. As a result, they reported that CGF is an economical and safe product that accelerates new bone formation. Topkara et al. (29) performed an animal study and showed that the viability of chopped cartilage covered with fascia, which is one of the important camouflage materials in rhinoplasty surgery, will increase when used with CGF. Zhao et al. (30) performed repeated local injections of CGF in patients with septal mucosal defects after rhinoplasty, and they observed complete closure in all patients, indicating that this technique is an easy and convenient procedure. Many surgeons have used adipose tissue as a graft, especially in the repair of small TM perforations. Fat graft myringoplasty is also a cost-effective, simple, and non-invasive surgery for TM perforations. However, fat grafting is a surgical procedure, albeit a minor one. CGF membrane application does not require any surgical procedure, and a blood sample from the patient is sufficient. In addition, CGF has a protective effect against infections.

Since fibrin obtained from platelet-rich materials contains proinflammatory cytokines, an increase in inflammation and fibrosis rates is expected in the areas where it is applied (31). Hu et al. (32) added PRP, PRF, and CGF to adipose tissues taken from rats and examined histologically. They observed richer vascularity and less fibrosis in the CGF added group compared with the PRP and PRF groups. Erkilet et al. (18) evaluated the improvement of TM perforations in rats in which PRP was applied, although it was not significant, fibroblastic reaction and neovascularization were higher in the study group on day 7. Ensari et al. (23) evaluated the perforated TMs of the rats to which they applied PRF, and they reported that neovascularization was more frequent days 3, 5, and 7, although it was not significant in the study group ( $p>0.05$ ). Herein, we performed the histopathological evaluation in the last week of our study. When

the tissues were taken for histopathological examination on day 21, no significant difference was found between all animal groups in terms of edema, neovascularization, fibrosis, and inflammation parameters (Table 2). In other studies, significant differences were found compared with the control groups in terms of these parameters; no difference was found between the groups because our histopathological evaluation was performed at a later stage.

HA, which is routinely used in ophthalmologic surgery because of its viscoelastic properties, is involved in various processes of early wound healing such as cell migration, organization of granulation tissue in cell proliferation, moderation of the inflammatory response, and angiogenesis (33,34). Local application of HA has positive effects in closing TM perforations in tympanoplasty and in reducing the length of hospital stay and cost (35). These effects regulate the healing of the fibrous layer by preventing dehydration of the perforation margins, providing a supportive environment for the keratin and hyperplastic epithelium that occurs during the healing process, and regulating functions such as mobility and phagocytic properties of polymorphonuclear leukocytes (36). Ozturk et al. (37) performed an experimental animal study with 24 male rats; they divided the rats into three groups as control rats, MeroGel rats, and daily topical HA rats. Perforations were closed in 70.8%, 91.7%, and 100% in the control, MeroGel rats, and daily HA rats, respectively. They reported that the main role of HA in repairing the TM is to provide a moist, wound-healing environment to aid in the healing process. Kaur et al. (38) used topical application of 1% sodium hyaluronate to repair human chronic TM perforations and reported that 86.7% (26/30) of the patients responded positively to the treatment. Rivas Lacarte et al. (39) reported that with the topical application of 1% sodium hyaluronate in 16 patients with chronic TM perforations, the perforation size reduced in 12 (75.0 %) patients; 6 (37.5 %) of whom showed complete healing, and 4 (25.0 %) showed no healing. Güneri et al. (6) evaluated the improvement of TM perforations with HA in another experimental animal study. While the mean closure time of TM perforation was  $8.6\pm 2$  days in the HA-treated group, it was  $15\pm 2$  days in the control group ( $p=0.0432$ ). Similarly, in our study, all TM perforations were closed in HA rats, but the mean closure time was 15.5 days. In our control group, this period was 17.11 days ( $p=0.037$ ). We think that these differences in mean recovery times are attributed to the number of rats used, localization of the perforations on the TM, and amount of HA applied. These findings obtained from rat studies suggest that HA application will have positive effects on the healing of acute traumatic TM perforations. In

addition, a study on wound healing has shown that a moist wound environment accelerates the healing of both acute and chronic wounds and promotes the growth of new tissue (40). Therefore, generally speaking, topical application of HA in the repair of traumatic TM perforation may exhibit a better healing state, thanks to the moist environment it provides.

## CONCLUSION

Few studies have focused on the use of PRF or CGF in the repair of TM perforations. In our study, we used autologous CGF membrane and HA in the treatment of acute perforations in rats. The application of both products was a more effective method than the control group. With these methods, which are easy, inexpensive, and have low patient morbidity, as graft or graft support in chronic TM perforations will be beneficial and promote successful results. The development of biological materials can assist or, in appropriate cases, replace conventional myringoplasty in repairing chronic TM perforations.

## Ethics

**Ethics Committee Approval:** This study was approved by the Animal Research Ethics Committee of Bezmialem Vakif University Medical Faculty (approval date: 21.03.2019, approval no. 2019/91).

**Informed Consent:** Animal experiments.

**Peer-review:** Externally peer-reviewed.

## Authorship Contributions

Concept: H.S., Y.A., Y.U., Design: H.S., Y.U., Data Collection or Processing: Ö.İ.B., S.K., Analysis or Interpretation: Y.A., S.Ş.E., D.H., G.B., Literature Search: S.K., D.H., Y.U., Writing: H.S., Y.A.

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# “Reversed Halo” Sign on Chest Computed Tomography in COVID-19 Pneumonia

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## Abstract

**Objective:** The reversed halo sign (RHS) is a rare finding of chest computed tomography (CT) for coronavirus disease-2019 (COVID-19) pneumonia. This study aimed to examine the frequency and characteristics of RHS in chest CT examinations of patients with reverse transcription-polymerase chain reaction (RT-PCR)-confirmed COVID-19, to evaluate the relationship between this finding and the clinical course, and to contribute to the differential diagnosis.

**Methods:** Chest CT data of 1500 patients who had positive RT-PCR tests for suspected COVID-19 pneumonia between March 16, 2020, and April 26, 2020, were evaluated retrospectively. This study included 49 patients with RHS. Patients were classified into two groups as the home-treated group and hospitalized group. The number of RHS; their craniocaudal, lobar, and peripheral-central distribution; morphological features of the wall structure; change over time; and additional findings were evaluated.

**Results:** Of the patients with RHS, 27 (55%) were treated at home, while 22 (45%) were treated in the hospital. The number of RHS lesions was higher in the hospitalized group. Lower zone involvement and predominance were common in both groups. The home-treated group mostly had oval-shaped lesions (44%), while oval- and round-shaped lesions were common in the hospitalized group (55%). The wall thickness of the reversed halo ring was greater in the hospitalized group. Incomplete ring morphology was common in both groups. Laboratory examinations showed a significant difference between the groups in terms of the monocyte counts and C-reactive protein and D-dimer levels ( $p=0.04$ ,  $p=0.002$ , and  $p=0.023$ , respectively).

**Conclusion:** RHS plays an important role in the differential diagnosis of COVID-19 pneumonia from other diseases based on its characteristic distribution pattern and morphological features.

**Keywords:** Reversed halo sign, COVID-19 pneumonia, computed tomography

## INTRODUCTION

The coronavirus, which emerged in the city of Wuhan in China, has caused a respiratory tract disease called coronavirus disease-2019 (COVID-19), and it gained a pandemic status from the World Health Organization on March 11, 2020 (1). Although it most frequently presents with signs of lower respiratory tract infections such as fever, cough, and shortness of breath, clinical findings vary widely depending on the age of the patients and comorbid factors (2). Chest computed tomography (CT) plays an

important role in both the diagnosis and follow-up in cases with suspected COVID-19 pneumonia (3).

In the literature, the typical involvement pattern of the lung parenchyma has been described as bilateral, multifocal, peripherally located, predominantly in the lower zone, irregularly shaped ground-glass opacities, or crazy-paving pattern characterized by interlobular septal thickening accompanied by ground-glass pattern and ground-glass opacities accompanied by consolidations. Cavitating lesions, halo sign, pleural, and



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pericardial effusion, pleural thickening, and lymphadenopathy are among the findings less frequently reported (4,5).

The reversed halo sign (RHS), also known as the atoll sign and the fairy ring sign, is a chest CT finding characterized by focal ground-glass opacity surrounded by a complete or incomplete ring of consolidation in the lung parenchyma. Although rare, this finding has been previously reported in the chest CT of COVID-19 pneumonia cases (6,7).

This study aimed to contribute to the diagnosis of COVID-19 and shed light on the differential diagnosis by examining the chest CT scans of patients with reverse-transcription-polymerase chain reaction (RT-PCR)-confirmed COVID-19 and to evaluate the frequency and characteristics of the RHS in these cases, the disease stage at which the sign is observed, and the clinical course of the patients with this sign.

## METHODS

The study was approved by the Ethics Review Board of University of Health Sciences Turkey, Prof. Dr. Cemil Tascioglu City Hospital (approval no: 48670771-514.10), and written informed consent was obtained from all participants who were briefed about the study. The study was conducted in accordance with the principles of the Declaration of Helsinki.

### Patient Selection

Chest CT scans of 1,500 patients with positive RT-PCR tests performed for suspected COVID-19 pneumonia between March 16, 2020, and April 26, 2020, were retrospectively evaluated. Forty-nine patients with RHSs on chest CT were included in the study. Laboratory results such as C-reactive protein (CRP), D-dimer, lactate dehydrogenase, oxygen saturation (SpO<sub>2</sub>), and lymphocyte, monocyte, and neutrophil counts of the patients were also evaluated. Patients were divided into two groups according to the treatment and follow-up protocols, namely, home-treated and hospitalized groups (service-intensive care unit follow-up).

### CT Protocol and Imaging Evaluation

Chest CT scans were obtained using a Philips Ingenuity 128 Slice CT machine (Philips, Amsterdam, Netherlands), without the use of an intravenous contrast agent. Scans were completed in the supine position in a single breath-holding period with both lungs covering the area from the apices of the lungs to the costodiaphragmatic sinuses. Chest CT acquisition parameters included tube voltage of 120 kV, tube current of 200 mAs, pitch of 1.375, field of view of 512 mm, and section thickness of 1.25 mm. The number of RHSs and their localization according to the

lung lobes and central/peripheral localization, morphological findings such as regularity/irregularity of the wall structure and wall thickness, complete/incomplete ring structure, nodular/reticular structure, their change over time, other patterns of COVID-19 pneumonia, and additional findings such as lymphadenopathy and pleural effusion were evaluated in the study. Images were evaluated separately by two radiologists experienced in thoracic radiology, and a decision was made with consensus.

### Statistical Analysis

Statistical analyses were performed using SPSS version 22.0 statistical software IBM SPSS Statistics for Windows, version XX (IBM Corp., Armonk, N.Y., USA). The relationship between categorical data was evaluated using the chi-square test. The compliance of the data to normal distribution was determined by the Kolmogorov-Smirnov test. Student's t-test was used for the comparison of the means of two independent groups that follow a normal distribution, while the Mann-Whitney U test was used for data that deviated from the normal distribution. For the evaluation of relationships between continuous data, the Pearson's correlation test was used for data with normal distribution, while the Spearman correlation test was used for data that deviated from the normal distribution. The results are assumed to be statistically significant when p value is less than 0.05.

## RESULTS

A total of 49 patients [20 (41%) were female and 29 (59%) were male] were included in this study. Of these patients, 27 (55%) were treated at home, while 22 (45%) were hospitalized. The mean age of all patients was 46.06±14.1 years. The mean age of the hospitalized group was 55.6±14.2 years, while that of the home-treated group was 38.8±9 years. The mean hospitalization period was 13.9±12.7 days [range: (2, 58) days]. Regarding additional diseases in both groups, 26 (53%) patients had no additional disease, four (8%) had hypertension, and three (6%) had both diabetes and hypertension. The remaining patients had other diseases such as hypothyroidism, epilepsy, chronic renal failure, asthma, and cardiovascular disease.

Table 1 shows the symptoms, SpO<sub>2</sub>, lactate dehydrogenase level, CRP level, and neutrophil, lymphocyte, and monocyte counts upon admission. Cough was the most common symptom in the home-treated and hospitalized groups (70% and 60%, respectively). Regarding symptoms, a significant difference was found only in the presence of dyspnea (p=0.02), with unsurprisingly higher frequency in the hospitalized group. Symptoms such as sore throat, loss of appetite, abdominal pain,

and diarrhea were not detected at the first admission in any of the patients in the home-treated group. In addition, cough and fatigue symptoms at the first admission were more common in the home-treated group, but the difference was not significant ( $p>0.05$ ).  $SpO_2$  was lower in the hospitalized group than in the home-treated group, but the difference was not significant ( $p>0.05$ ). The difference between the laboratory test results of the groups in terms of the CRP level, D-dimer level, and monocyte count was significant ( $p=0.002$ ,  $p=0.023$ , and  $p=0.04$ , respectively).

The localization and morphological characteristics of the RHS are given in Table 2. The frequency of the RHSs was higher in the hospitalized group than in the home-treated group [95% confidence interval (CI) 3.77-9.63; 3.16-5.64, respectively]. In regards to craniocaudal distribution, involvement of the lower zone was more common than involvement of the other zones in both groups. In addition, no significant difference was found between the two groups in terms of the craniocaudal distribution ( $p>0.05$ ). The bilateral incidence rate of the disease was high in both groups. Regarding the lobar distribution of the disease, involvement of the lower lobes of the right and

left lungs (82% and 78%, respectively) was more frequent in all patients. In the morphological examination of the reversed halo lesion, the lesion was most frequently oval-shaped in the home-treated group (44%), while lesions were oval and round in the hospitalized group (55%). Considering the ring structure of the RHS, the wall thickness was greater in the hospitalized group; however, the difference was not significant ( $p>0.05$ ). Incomplete ring morphology of the lesion was common in both groups.

The 95% CIs for all variables of interest are presented in Table 1 and 2. An appreciable overlap was found in the CIs (e.g., cough, fatigue, and  $SpO_2$ ) of the corresponding variables in both groups when the results are not significant (i.e.,  $p>0.05$ ). These intervals are mostly disjoint (e.g., dyspnea, CRP, D-dimer, and number of reversed halo lesions) when the results are significant (i.e.,  $p\leq 0.05$ ).

## DISCUSSION

The RHS is a rare finding in various diseases and at different disease stages. In our study, the lesions characterized with the RHS in COVID-19 pneumonia were mostly peripheral, localized in the lower lobe, irregularly contoured, oval-shaped, had a central

**Table 1. Distribution of symptoms and laboratory markers in both groups of patients with reversed halo signs**

Symptoms	Home-treated patients (n=27)		Hospital-treated patients (n=22)		All patients (n=49)	
	Number (proportion)	95% CI	Number (proportion)	95% CI	Number (proportion)	95% CI
Cough	19 (0.70)	0.53-0.88	13 (0.59)	0.39-0.80	32 (0.65)	0.52-0.79
Fatigue	10 (0.37)	0.19-0.55	7 (0.32)	0.12-0.51	17 (0.35)	0.21-0.48
Fever	6 (0.22)	0.07-0.38	6 (0.27)	0.09-0.46	12 (0.24)	0.12-0.37
Sore throat	0 (0.0)	0.00-0.00	2 (0.09)	-0.03-0.21	2 (0.04)	-0.01-0.10
Dyspnea	3 (0.11)	-0.01-0.23	7 (0.32)	0.12	10 (0.20)	0.09-0.32
Nausea/vomiting	2 (0.07)	-0.02-0.17	2 (0.09)	-0.03-0.21	4 (0.08)	0.00-0.16
Loss of appetite	0 (0.0)	0.00-0.00	2 (0.09)	-0.03-0.21	2 (0.04)	-0.01-0.10
Back pain	1 (0.04)	-0.03-0.11	2 (0.09)	-0.03-0.21	3 (0.06)	-0.01-0.13
Abdominal pain	0 (0.0)	0.00-0.00	1 (0.05)	-0.04-0.13	1 (0.02)	-0.02-0.06
Diarrhea	0 (0.0)	0.00-0.00	1 (0.05)	-0.04-0.13	1 (0.02)	-0.02-0.06
Asymptomatic	2 (0.07)	-0.02-0.17	1 (0.05)	-0.04-0.13	3 (0.06)	-0.01-0.13
<b>Laboratory findings</b>	<b>Mean (SD)</b>	<b>95% CI</b>	<b>Mean (SD)</b>	<b>95% CI</b>	<b>Mean (SD)</b>	<b>95% CI</b>
$SpO_2$ (%)	96.1 (3.1)	94.93-97.27	90.36 (16.9)	83.3-97.42	93.5 (11.6)	90.25-96.75
CRP	6.6 (6.5)	4.15-9.05	94.9 (79)	61.89-127.91	75.3 (78.8)	53.24-97.36
D-dimer	155.5 (6.3)	153.12-157.88	1380.3 (1623.7)	701.8-2058.8	1263.7 (1583.8)	820.24-1707.16
LDH	214.3 (28)	203.74-224.86	245.1 (53.9)	222.58-267.62	241.2 (52)	226.64-255.76
Neutrophil $10^3/\mu L^*$	5.5 (2.9)	4.41-6.59	4.8 (2.2)	3.88-5.72	5.2 (2.6)	4.47-5.93
Lymphocyte $10^3/\mu L^*$	1.6 (1.3)	1.11-2.09	2.7 (4.2)	0.94-4.46	2.1 (2.9)	1.29-2.91
Monocyte $10^3/\mu L^*$	0.3 (0.1)	0.26-0.34	0.5 (0.2)	0.42-0.58	0.4 (0.2)	0.34-0.46

\*Reference values: Neutrophil: 2-7, lymphocyte: 0.8-4, monocyte: 0.12-1.2, 95% CI are for the symptom proportions and laboratory marker values, \*\*Difference statistically significant ( $p<0.05$ ),  $SpO_2$  (%): Oxygen saturation, SD: Standard deviation, CI: Confidence interval, CRP: C-reactive protein, LDH: Lactate dehydrogenase

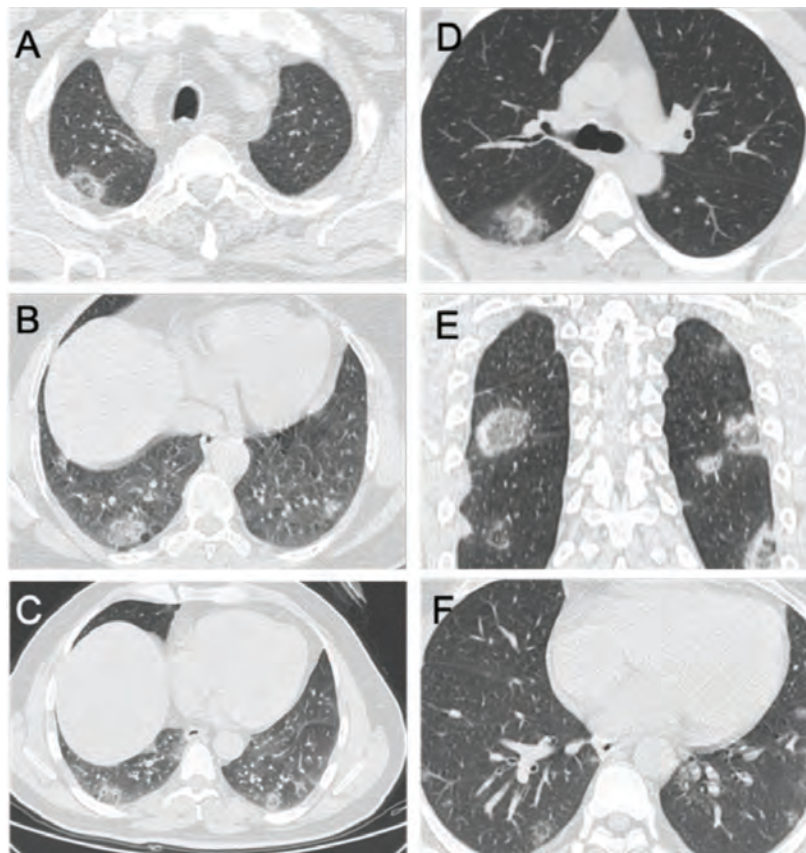
reticular pattern, and had an incomplete ring presentation (Figure 1). Although the RHS is considered specific for organized pneumonia, it was detected in approximately 19% of cryptogenic organized pneumonia cases (Figure 2) (8). In the differential diagnosis of diseases with this finding, a pleural-based RHS is predominantly located in the lower lobe (especially in the costodiaphragmatic angle); the triangular-pyramidal wedge-shaped configuration suggests pulmonary embolism (Figure 3) (9); the presence of a nodular pattern in the wall and central part suggests granulomatous diseases such as tuberculosis and sarcoidosis (Figure 4) (10); predominant upper lobe involvement, thick ring structure, and presence of accompanying pleural effusion suggest fungal infections (11).

This study analyzed two groups of patients with COVID-19 divided according to the follow-up protocol (home vs. hospital). A significant difference was found in the lung parenchymal infiltration between the two groups; however, no significant difference was found in the reversed halo lesion load. In both groups, the lesion pattern in the lung parenchyma, excluding the RHS, was most frequently consolidations accompanying ground-glass opacities, which is in line with the literature. The frequency of consolidations tends to increase, especially in patients followed in the hospital and those with severe clinical and laboratory findings. This may suggest that the situation may result from the progression of ground-glass opacities to consolidations.

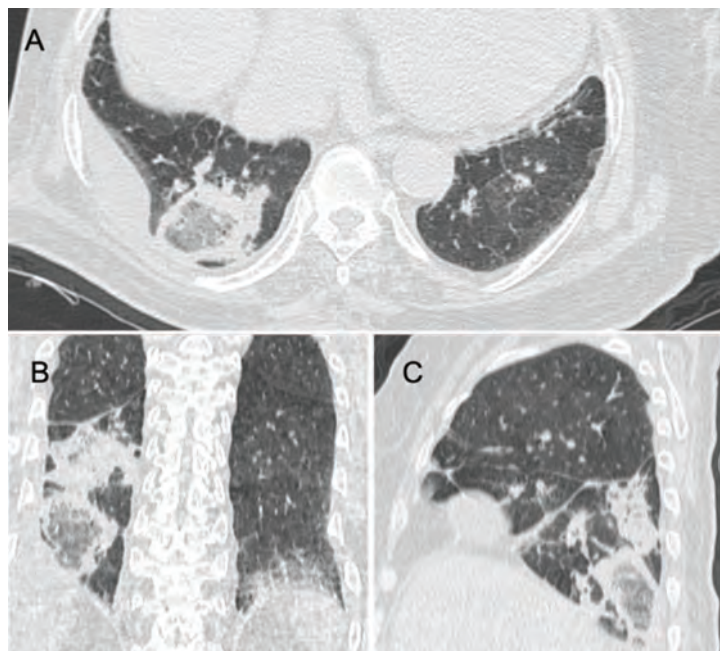
**Table 2. Morphological features, localization, and distribution of the lesion in both groups of patients with reversed halo signs**

	Home-treated patients (n=27)		Hospital-treated patients (n=22)		All patients (n=49)	
	Number (proportion)	95% CI	Number (proportion)	95% CI	Number (proportion)	95% CI
<b>Craniocaudal distribution</b>						
Upper zone	3 (0.11)	-0.01-0.23	4 (0.18)	0.02-0.34	7 (0.14)	0.04-0.24
Middle zone	7 (0.26)	0.09-0.42	3 (0.14)	-0.01-0.28	10 (0.20)	0.09-0.32
Lower zone	13 (0.48)	0.29-0.67	9 (0.41)	0.20-0.61	22 (0.45)	0.31-0.59
Diffuse involvement	4 (0.15)	0.01-0.28	6 (0.27)	0.09-0.46	10 (0.20)	0.09-0.32
<b>Laterality</b>						
Unilateral	3 (0.11)	-0.01-0.23	2 (0.09)	-0.03-0.21	5 (0.10)	0.02-0.19
Bilateral	24 (0.89)	0.77-1.01	20 (0.91)	0.79-1.03	44 (0.90)	0.81-0.98
<b>Lobar distribution</b>						
RUL	14 (0.52)	0.33-0.71	14 (0.64)	0.44-0.84	28 (0.57)	0.43-0.71
RML	3 (0.11)	-0.01-0.23	7 (0.32)	0.12-0.51	10 (0.20)	0.09-0.32
RLL	21 (0.78)	0.62-0.93	19 (0.86)	0.72-1.01	40 (0.82)	0.71-0.92
LUL	8 (0.30)	0.12-0.47	10 (0.45)	0.25-0.66	18 (0.37)	0.23-0.50
LLL	19 (0.70)	0.53-0.88	19 (0.86)	0.72-1.01	38 (0.78)	0.66-0.89
<b>Lesion morphology</b>						
<b>Shape</b>						
Round	6 (0.22)	0.07-0.38	6 (0.27)	0.09-0.46	12 (0.24)	0.12-0.37
Oval	12 (0.44)	0.26-0.63	4 (0.18)	0.02-0.34	16 (0.33)	0.20-0.46
Round and oval	9 (0.33)	0.16-0.51	12 (0.55)	0.34-0.75	21 (0.43)	0.29-0.57
<b>Ring structure</b>						
Incomplete	16 (0.59)	0.41-0.78	9 (0.41)	0.20-0.61	25 (0.51)	0.37-0.65
Complete	6 (0.22)	0.07-0.38	4 (0.18)	0.02-0.34	10 (0.20)	0.09-0.32
Incomplete and complete	5 (0.19)	0.04-0.33	9 (0.41)	0.20-0.61	14 (0.29)	0.16-0.41
	<b>Mean (SD)</b>	<b>95% CI</b>	<b>Mean (SD)</b>	<b>95% CI</b>	<b>Mean (SD)</b>	<b>95% CI</b>
Number of reversed halo lesions	4.4 (3.3)	3.16-5.64	6.7 (7)	3.77-9.63	5.4 (4.4)	4.17-6.63
<b>Lesion wall thickness</b>	4.1 (1.6)	3.50-4.70	4.2 (2.4)	3.20-5.20	4.2 (2)	3.64-4.76

95% CI are for the symptom proportions and laboratory marker values, SD: Standard deviation, CI: Confidence interval, RUL: Right upper lobe, RML: Right middle lobe, RLL: Right lower lobe, LUL: Left upper lobe, LLL: Left lower lobe



**Figure 1.** Cases with findings of COVID-19 pneumonia on chest CT with positive reverse-transcription-polymerase chain reaction results. Chest CT images of a 68-year-old male patient reveal peripherally located ground-glass opacity areas and multiple reversed halo signs of different sizes (A-C). Other patients demonstrated lesions characterized with the reversed halo sign in the superior segment of the right lung lower lobe (D), multiple lesions with peripheral localization in the bilateral lung parenchyma (E), and bilateral millimetric lesions with faint contours in the lower lobes (F)  
 CT: Computed tomography, COVID-19: Coronavirus disease-2019



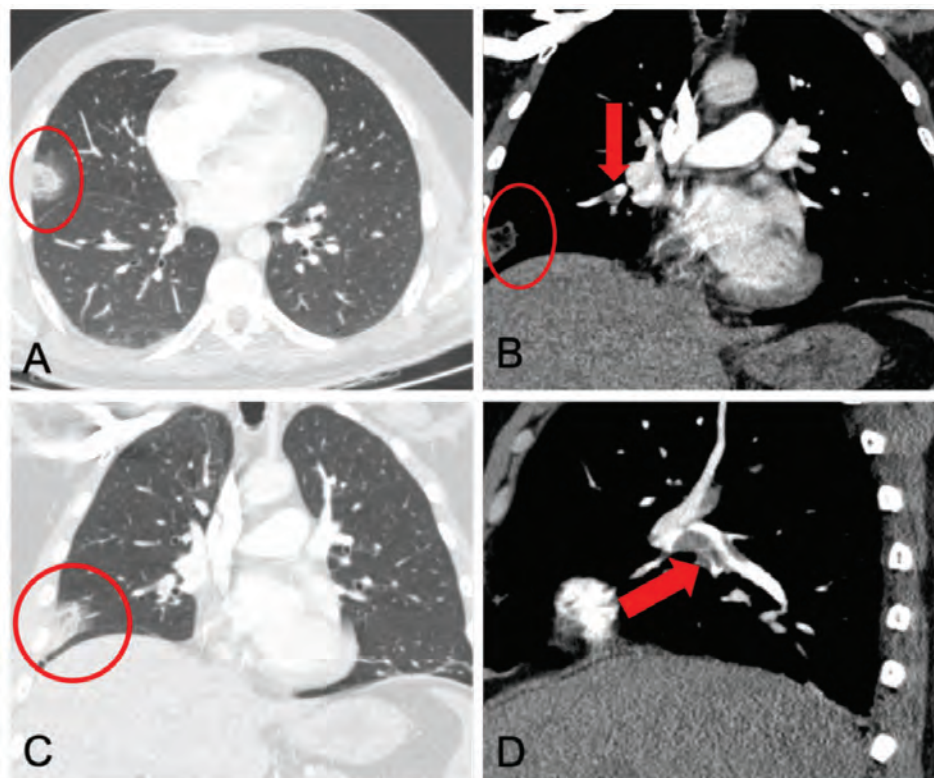
**Figure 2.** Axial (A) chest computed tomography in a patient with cryptogenic organized pneumonia shows a reversed halo sign in the posterior segment of the lower lobe of the right lung, with an adjacent irregularly contoured patchy area of consolidation, which is more clearly distinguished in the coronal (B) and sagittal (C) planes



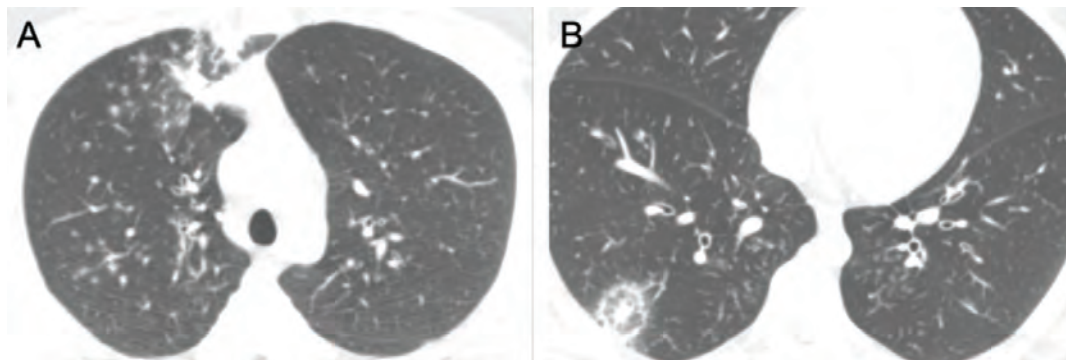
According to our findings, incomplete morphology was observed in the RHS of the home-treated group; in other words, the ground-glass component was dominant over the consolidated wall. In the hospitalized group, a more heterogeneous pattern was observed with complete and incomplete morphology seen together. The wall thickness of the reversed halo lesion was significantly higher in the hospitalized group than in the home-treated group. These findings may suggest that the RHS was seen in earlier stages of COVID-19 and the lesions progressed to

consolidations afterwards. Moreover, in our study, no additional disease was found in 26 (53%) patients with the RHS, mainly in the home-treated group. This may indicate the occurrence of the RHS in patients with less comorbidity.

The clinical course of COVID-19 pneumonia is quite variable; individuals may have no symptoms or have mild flu-like symptoms, and some may have an extremely poor prognosis. The inflammatory cascade triggered by COVID-19 infection, cytokine release, and activation of the coagulation cascade are



**Figure 3.** Axial (A) and coronal (C) chest CT sections revealed a pleural-based, triangular-shaped reversed halo sign (circled) in the lateral segment of the middle lobe of the right lung consistent with pulmonary infarction. Mediastinal window coronal (B) and sagittal (D) sections of pulmonary CT angiography show clot formation extending from the right descending interlobar artery to the middle lobe lateral segmentary branch (arrow)  
CT: Computed tomography



**Figure 4.** Axial chest computed tomography scans of a 38-year-old patient diagnosed with sarcoidosis reveal multiple millimetric nodules with faint contours, adjacent faint ground-glass opacities, and focal subpleural fibrotic changes in the right lung upper lobe (A) and reversed halo sign with nodularity on the wall and in the central region in the right lung lower lobe and millimetric centrilobular nodules on both lung lower lobes (B)

the mechanisms held responsible for a poor prognosis (12). In addition, the use of risk classifications based on comorbid factors and laboratory markers have been recommended to predict the clinical course of the disease (12-15). The levels of CRP, which indicate hyperinflammation in critically affected cases, procalcitonin, D-dimer, and ferritin are increased in some cases (16-18). In this study, a significant difference was found in the CRP level, D-dimer level, and monocyte count between the home-treated group and hospitalized group. Our findings also indicate a positive correlation between these laboratory markers and the lesion load characterized by the RHS. In this respect, the RHS detected in CT examination, which is frequently used in diagnosis, may contribute to the prediction of prognosis in these cases.

## CONCLUSION

The RHS plays an important role in the differential diagnosis of COVID-19 pneumonia from other diseases based on its characteristic distribution pattern and morphological features. In addition, studies with larger patient groups are needed to evaluate whether this rare radiological finding can be used as a prognostic factor.

## Ethics

**Ethics Committee Approval:** The study was approved by the Ethics Review Board of University of Health Sciences Turkey, Prof. Dr. Cemil Tascioglu City Hospital (approval no: 48670771-514.10).

**Informed Consent:** Written informed consent was obtained from all participants who were briefed about the study.

**Peer-review:** Externally peer-reviewed.

## Authorship Contributions

Concept: D.G., M.K.T., Design: D.G., M.K.T., Data Collection or Processing: D.G., M.K.T., H.Y., A.K., M.T.Y., H.Ö., Analysis or Interpretation: D.G., M.K.T., Literature Search: D.G., M.K.T., Writing: D.G., M.K.T., H.Y., A.K., M.T.Y., H.Ö.

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

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# Prediction of Clinical Results with the First Thoracic CT Findings in COVID-2019 Patients; Survey Study

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## Abstract

**Objective:** This study aimed to investigate the clinical and computed tomography (CT) features associated with severe and critical coronavirus disease-2019 (COVID-19) pneumonia.

**Methods:** A total of 50 patients with critical COVID-19 pneumonia, receiving mechanical ventilation support in the intensive care unit (ICU) due to moderate-severe acute respiratory distress syndrome (ARDS), were included in this retrospective study. Chest CT, laboratory results, and clinical conditions of patients were concurrently identified. Only the first chest CT findings of patients were reviewed by 50 physicians and they were asked about their opinions on the laboratory results and clinical conditions of patients. Data were then compared with the real-time data. The efficacy of the first chest CT findings in diagnosis and treatment guidance was analyzed.

**Results:** The simultaneous laboratory analyses of patients receiving mechanical ventilation support due to moderate-severe ARDS found a C-reactive protein of >40 mg/L in 72%, D-dimer was >1000 ng/mL and ferritin was >500 ng/mL in 57%, and lymphocyte count <800  $\mu$ L in 50% of patients. While 53% of participants proposed that patients would be treated in the ICU, 28.2% suggested the patients be treated in inpatient care. A total of 60.2% of participants stated that the patients suffered from moderate-severe ARDS based on CT findings.

**Conclusion:** A correlation was found between the clinical symptoms, laboratory analyses, and CT findings of patients presenting with severe COVID-19. The first chest CT alone may help a physician to determine the disease severity; however, additional laboratory data and clinical follow-up are needed to evaluate the prognosis and plan the treatment, as many factors are involved in determining the disease severity.

**Keywords:** COVID-19, SARS-CoV-2, ARDS, computed tomography

## INTRODUCTION

Coronavirus disease-2019 (COVID-19) infection, a highly contagious disease caused by the severe acute respiratory syndrome coronavirus-2 virus, was first reported in Wuhan, China, and the World Health Organization declared this increasingly spreading disease as a global public health emergency (pandemic) on January 30, 2020 (1). Chest computed tomography (CT) plays

an important role in the diagnosis and treatment of COVID-19. The common chest CT findings of COVID-19 are multiple ground-glass opacity, consolidation, and interlobular septal thickening in both lungs, which are mostly distributed under the pleura. A significant correlation between the severity of the pulmonary inflammation, basic clinical symptoms, and laboratory test results was reported (2,3). In addition, data on the efficacy of chest CT findings alone in predicting the clinical disease



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prognosis is limited (4). Thus, this study aimed to investigate the validity of the first CT findings in treatment guidance, beyond specific diagnosis, by the physicians involved in the diagnosis and treatment of patients with COVID-19.

## METHODS

The study was approved by the Scientific Research Platform of Directorate General for Health Services, the Ministry of Health of the Republic of Turkey, and the Ethics Committee of University of Health Sciences Turkey, Prof. Dr. Cemil Tascioglu City Hospital, (no: 48670771-514.10, 12.05.2020/158). A total of 50 out of 320 patients, admitted to the intensive care unit (ICU) due to COVID-19 [severe COVID-19-related acute respiratory distress syndrome (ARDS)] between March 20, 2020, and June 1, 2020, were included in the study through random selection.

The first chest CT scans of patients, taken before the admission to the ICU, were blindly evaluated by 50 physicians, without receiving information, including the names and recent clinical conditions of patients. Afterward, three questions were asked to all participants and the answers were noted. The actual data of 50 patients were compared to the given answers.

The three questions :

1. "Where should this patient be followed up and treated according to the examined thoracic tomography data?"
  - a. Quarantine at home
  - b. Treatment in the hospital clinic
  - c. In intensive care. No necessary treatment
2. "Are there signs of severe ARDS in the examined thoracic tomography?"
  - a. Yes, partial pressure of oxygen/fraction of inspired oxygen ( $\text{PaO}_2/\text{FiO}_2$ ) of  $<100$  mmHg, indication severe ARDS
  - b. Yes,  $\text{PaO}_2/\text{FiO}_2$  of 100-200 mmHg, indication moderate ARDS
  - c. Yes,  $\text{PaO}_2/\text{FiO}_2$  of 200-300 mmHg, indication mild ARDS
  - d. No,  $\text{PaO}_2/\text{FiO}_2$  of  $>300$
3. "What kind of treatment plan is suitable if the patient is followed up in the ICU according to the examined thoracic tomography data?"
  - a. Medical treatment + supportive treatment + invasive mechanical ventilation
  - b. Medical treatment + supportive treatment + non-invasive mechanical ventilation (HFNC)

## Statistical Analysis

Data were expressed as mean or median, and answers were calculated in percentage (%).

## Inclusion and Exclusion Criteria

Over 18 years old, with COVID-19- related severe ARDS diagnosis in the ICU ( $\text{PaO}_2/\text{FiO}_2$  of  $<100$  mmHg)

## RESULTS

All 50 physicians answered 7,500 questions in 2,500 surveys. Three CT scanners (Scanner-Toshiba-Alexion 16 slice, Scanner Philips-Brilliance 40 -slice, and Scanner Philips-Ingenuity Core 128-slice) were used for examinations. The simultaneous laboratory analysis found a C-reactive protein (CRP) of  $>40$  mg/L in 72% [minimum-maximum (min-max) (median) 3.24-513.78 (86.99)]; D-dimer was  $>1000$  ng/mL [min-max (median) 78-27.000 (1100)] and ferritin was  $>500$  ng/mL [min-max (median) 24.5-8378 (614.6)] in 57%; and lymphocyte count of  $<800$   $\mu\text{L}$  [min-max (median) 0.2-16.15 (0.92)] in 50% of patients (Table 1, Figure 1a-d).

To the question "Where should this patient be followed up and treated according to the examined thoracic tomography data?", 53% of participants responded as "in the ICU", 28.2% as "in the inpatient care", 17.4% as "in quarantine at home", and 1.4% stated that no treatment was required (Figure 2).

To the question "Are there signs of severe ARDS in the examined thoracic tomography?", 60.2% of participants responded as moderate-severe ARDS, 19.6% as mild ARDS, and 20.2% stated that the clinical presentation was not ARDS (Figure 3). All patients included were in the ICU due to severe ARDS.

To the question "What kind of treatment plan is suitable if the patient is followed up in the ICU according to the examined thoracic tomography data?", 58.2% of participants responded as medical treatment + supportive treatment + HFNC and

**Table 1. COVID-19-associated acute-phase reactants of patients**

CRP (mg/L)	Min-max	3.24-513.78
	(Median)	(86.99)
Ferritin (ng/mL)	Min-max	24.5-8378
	(Median)	(614.6)
D-dimer (ng/mL)	Min-max	78-27.000
	(Median)	(1100)
Lymphocyte ( $\mu\text{L}$ )	Min-max	0.2-16.15
	(Median)	(0.92)
COVID-19: Coronavirus disease-2019, Min: Minimum, max: Maximum, CRP: C-reactive protein		



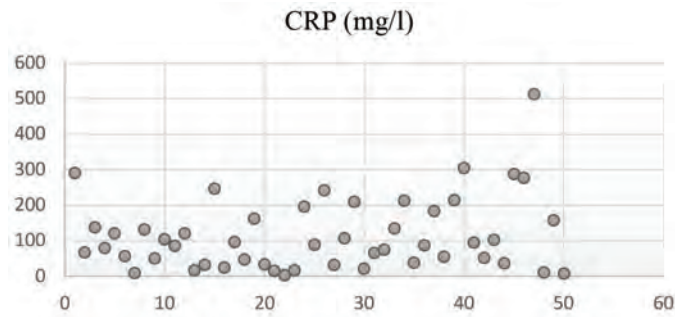
41.8% as medical treatment + supportive treatment + invasive mechanical ventilation (Figure 4).

### DISCUSSION

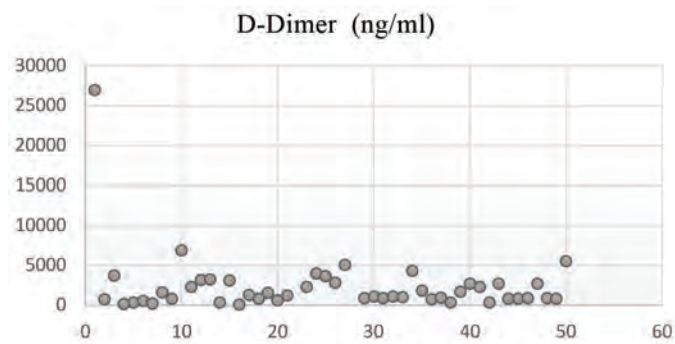
This study analyzed the chest CT findings of 50 patients treated for severe COVID-19-related ARDS in the ICU examined by 50

physicians without the real-time laboratory test results, as well as the clinical data and the validity of first CT findings alone in treatment guidance, beyond specific diagnosis.

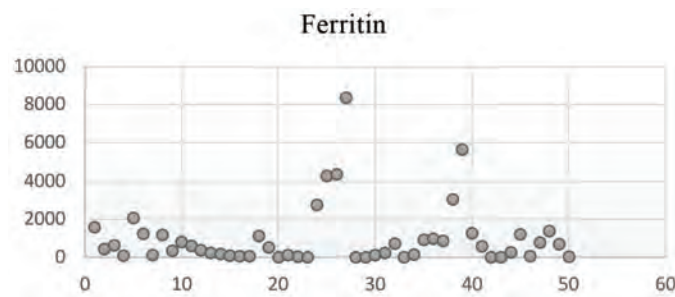
The meta-analyses of the high-risk group of patients with symptomatic COVID-19 primarily observed the ground-glass opacities (83.31%) and consolidation involving the bilateral lungs



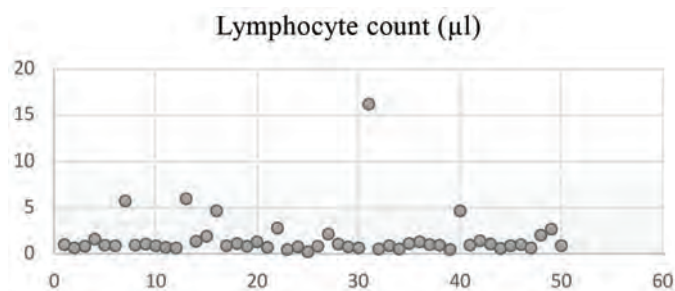
**Figure 1a.** CRP (mg/L) values of patients  
CRP: C-reactive protein



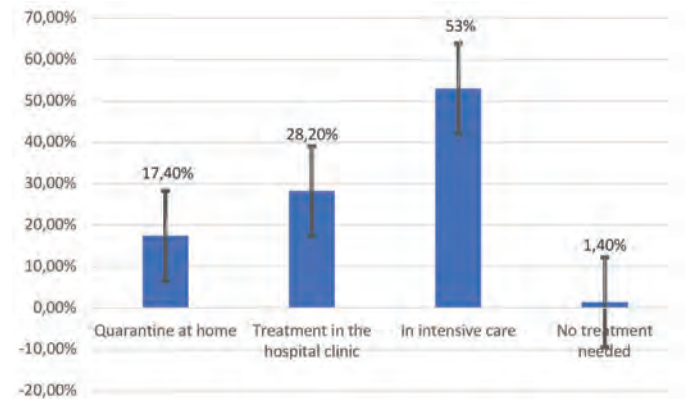
**Figure 1b.** D-dimer (ng/mL) values of patients



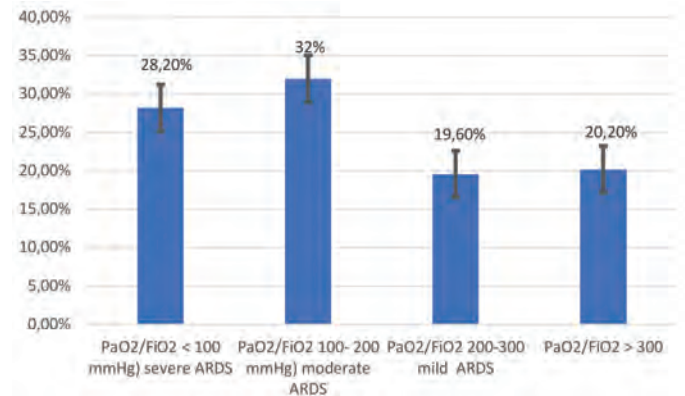
**Figure 1c.** Ferritin (ng/mL) values of patients



**Figure 1d.** Lymphocyte (µL) values of patients

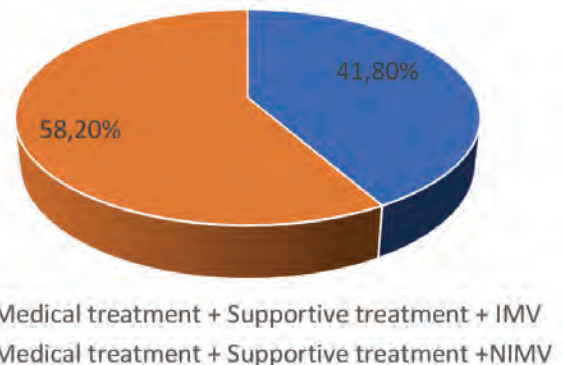


**Figure 2.** “Where should this patient be followed up and treated according to the examined thoracic tomography data?”



**Figure 3.** “Are there signs of severe ARDS in the examined thoracic tomography?”

ARDS: Severe acute respiratory distress syndrome



**Figure 4.** “What kind of treatment plan is suitable if the patient is followed up in the intensive care unit according to the examined thoracic tomography data?”

in a peripheral distribution (76.95%) in the chest CT. Compared to ordinary patients, characteristics specific to COVID-19 in the thoracic CT play an important role in guiding the treatment and evaluating the disease severity (5,6).

While one of every five physicians who participated in the study diagnosed COVID-19 based on the chest CT, they incorrectly predicted the clinical course and prognosis of the disease based on the first CT findings alone, without clinical findings and laboratory test results. Contrarily, 17.4% of them suggested quarantine at home.

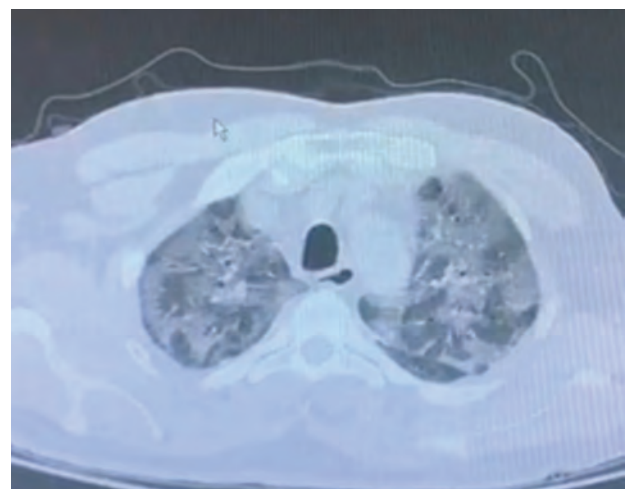
Advanced age, comorbidities, dyspnea, chest pain, cough, phlegm, decreased lymphocytes, and elevated inflammation indicators are risk factors for COVID-19 pneumonia (6). Significant differences were found between the ordinary patients and patients with severe/critical conditions in terms of clinical symptoms, laboratory examinations, and CT findings. Many factors related to the disease severity may help physicians identify the disease severity and evaluate the prognosis (4). Studies indicated a significant correlation between the severity of the pulmonary inflammation in the CT findings and main clinical symptoms (cough and high fever in 73% and 76% of patients, respectively) and laboratory test results in patients confirmed with coronavirus (7). No abnormality was observed in the thoracic CT scans of the early-stage (0-4 days). CT is a useful tool for evaluating the changes in the pulmonary abnormalities of patients in the acute and recovery period (7-9). Therefore, physicians need to evaluate the chest CT of patients in combination with the clinical course and laboratory findings.

Real-time polymerase chain reaction (RT-PCR) is accepted as a reference standard test in COVID-19 diagnosis. Chest CT findings may exist in the early stages before the onset of symptoms, and chest CT sensitivity is quite high, not only in the diagnosis but also in the follow-up of patients with COVID-19 having false-negative RT-PCR results (10). Our study observed a correlation between the initial CT findings, real-time laboratory test results, and clinical course. While 28.2% of physicians diagnosed severe ARDS based on the first chest CT scan, only 53% of them suggested a follow-up in the ICU and 28.2% suggested a follow-up in the inpatient care. Therefore, 20.2% of the participants declared that ARDS will not be developed. In reality, 50 patients were treated in the ICU due to respiratory distress with IMV. The arterial blood gas analysis identified a  $\text{PaO}_2/\text{FiO}_2$  of  $<100$  mmHg, indicating severe ARDS.

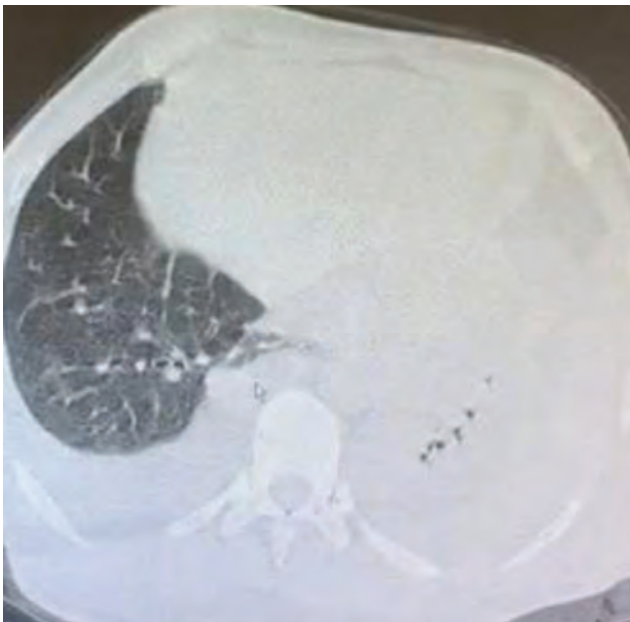
Hyperinflammation is observed in patients with critical COVID-19, and related biomarkers may be beneficial in risk classification. COVID-19 severity and poor prognosis were found

related to 96% serum CRP, 85% procalcitonin, 77% D-dimer, and 76% serum ferritin in the performed meta-analyses. The severity and the disease prognosis may be evaluated in a patient with positive PCR without CT findings by evaluating the acute-phase reactants in the first stage (11). Chest CT is guiding the clinical diagnosis and is effective in predicting the treatment and the prognosis. All 50 patients included in the study were PCR-positive. The examined acute-phase reactants were found proportionate to the CT findings and the severity of hypoxemia. CRP was especially the most elevated acute-phase reactant, with the disease severity, followed by ferritin and D-dimer.

While acute-phase reactants were concurrently found to be as lymphocyte count of  $680 \mu\text{L}$ , CRP of  $90.81 \text{ mg/L}$ , ferritin of  $637 \text{ ng/mL}$ , and D-dimer of  $3.720 \text{ ng/mL}$  (Figure 5) in a patient presenting with moderate to severe viral infection symptoms in the chest CT, another acute-phase reactant count was concurrently found to be normal in a patient with severe viral infection symptoms in the chest CT (lymphocyte count of  $156 \mu\text{L}$ , CRP of  $27.6 \text{ mg/L}$ , ferritin of  $121 \text{ ng/mL}$ , and D-dimer  $705 \text{ ng/mL}$ ) (Figure 6). Further studies on the correlation between the acute-phase reactants and chest CT findings are required. Treatment in the ICU has become increasingly difficult; therefore, early recognition of severe cases is necessary for a timely triaging of patients. Clinical conditions and concurrent comorbidities determine the necessity of treatment in the ICUs, whereas several laboratory parameters may help evaluate the disease severity. Physicians should also take the low lymphocyte count into account, as well as the CRP, D-dimers, ferritin, cardiac troponin, and interleukin-6 serum



**Figure 5.** Diffuse ground-glass infiltrations showing moderate to severe parenchymal involvement from the apex to the base, with a tendency to unite in the parenchyma of both lungs, fibrotic changes, and interlobular septal thickening, causing crazy-paving patterns. A pleural fluid of slightly over 1 cm in width was observed in the bilateral base. Diffuse infiltrates and accompanying pleural fluid suggested moderate to severe viral pneumonia



**Figure 6.** Pleural effusion was observed in the posterior base in both hemothorax. In the lung parenchyma, diffuse infiltration appearances, which were consolidated in the lower lobes of both lung parenchymas and caused the loss in total lung ventilation in the lower lobe of the left lung, were observed. The identified findings were evaluated in favor of severe specific viral infection. Concurrent acute-phase reactants: Lymphocyte count of 156  $\mu$ L, CRP of 27.6 mg/L, ferritin of 121 ng/mL, and D-dimer of 705 ng/mL  
CRP: C-reactive protein

levels, to determine severe and fatal COVID-19 in inpatient care. The disease course is likely to be negative when one or more of these parameters are altered (12).

## CONCLUSION

In conclusion, a correlation was found between the clinical symptoms, laboratory analyses, and CT findings of patients with severe to critical COVID-19. First chest CT alone may help physicians to determine the severity of the disease; however, additional laboratory data and clinical follow-up are needed to evaluate the prognosis and plan the treatment, as many factors are related to the severity of the disease.

## Ethics

**Ethics Committee Approval:** The study was approved by the Scientific Research Platform of Directorate General for Health Services, the Ministry of Health of the Republic of Turkey, and the Ethics Committee of University of Health Sciences Turkey, Prof. Dr. Cemil Tascioglu City Hospital, (no: 48670771-514.10, 12.05.2020/158).

**Informed Consent:** Survey study.

**Peer-review:** Internally peer-reviewed.

## Authorship Contributions

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

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# Evaluation of Obese Adolescents Using the Rosenberg Self-esteem Scale

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## Abstract

**Objective:** Obesity, is a global public health problem characterized by excessive body fat deposition in the body, it causes physical as well as mental problems but also such as anxiety, depression, and low self esteem. The aim of this study was to investigate the psychological problems associated to adolescent obesity.

**Methods:** Thirty-three obese volunteer patients of the pediatric outpatient clinic, and thirty non-obese routine volunteers were included in the study. Adolescents with a body mass index (BMI) of 95% and above with respect their gender and age were considered obese. In adolescents of the control group, BMI varied between the 5<sup>th</sup> and <85<sup>th</sup> percentile for their age and gender. All participants were evaluated using the Rosenberg self-esteem scale during direct interviews, with outcomes being of self-esteem, anxiety, depression, and isolation.

**Results:** The study included 63 adolescents, 33 (52.4%) females and 30 (47.6%) males, aged between 10 and 16 years. Self-esteem and anxiety were varied significantly between the groups ( $p < 0.05$ ). However, there was no statistically significant difference between the groups regarding depression and social isolation ( $p > 0.05$ ).

**Conclusion:** Although adolescent obesity prevention strategies are important, appropriate counseling should also be provided concerning mental health issues like anxiety and low self-esteem.

**Keywords:** Adolescent, obesity, psychopathology

## INTRODUCTION

Obesity is a metabolic disorder associated to physical and mental problems resulting from excessive body fat deposition. Obesity is a complex disorder resulting from an imbalance between calorie intake and consumption (1,2). Obesity, which can begin in childhood, is an important public health problem with social and economic scopes that significantly influence morbidity and mortality. The World Health Organization defined childhood obesity as one of the most important problems of the 21<sup>st</sup> century. It has been reported that 340 million children and adolescents aged between 5 and 19 years are affected by overweight and obesity (3).

One of the comorbid diseases accompanying obesity is psychosocial problems, anxiety, and depression. Some studies have delineated that childhood depression, anxiety, and obesity show a parallel course (4,5). The study aim was to evaluate obese adolescents using the Rosenberg self-esteem scale and to provide these patients with the necessary support through a multidisciplinary approach.

## METHODS

This study was conducted after ethical approval from the Clinical Research Ethics Committee of Okmeydani Training and Research Hospital's decision dated 08/01/2019 and numbered 1092 was



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issued. Inform consent was obtained from both participating adolescents and their families. Thirty-three obese volunteers of the pediatric outpatient clinic (study group); and thirty non-obese healthy routine volunteers with normal percentiles and without any chronic diseases (control group) according to the monitoring program of the Ministry of Health were included in the study. Obesity was determined according to body mass index (BMI) as a criterion. BMI was calculated as equal to the body weight (in kilograms) divided by the height in squared meters ( $\text{kg}/\text{m}^2$ ). Adolescents with a BMI of 95% and above with respect to their gender and age were defined as obese (6). In the control group, BMI was between the 5<sup>th</sup> and <85<sup>th</sup> percentile according to their gender and age.

Four outcomes of the Rosenberg Self-Esteem scale, translated into Turkish by Çuhadaroglu and consisted of 12 outcomes, were administered to all participants (7,8). These sub-headings, including self-esteem, depressive affect, psychosomatic symptoms, and psychosocial isolation, were applied through direct interviews using a questionnaire. Participants with any underlying chronic diseases and under treatment, presenting any genetic disorder, who refused to participate in the study, and who could not read and write Turkish were excluded from the study.

### Statistical Analysis

IBM SPSS Statistics 22 (IBM SPSS, Turkey) software was used for statistical analysis. During data analysis, the conformity of the parameters to the normal distribution was evaluated using the Shapiro-Wilks test; and the parameters did not follow normal distribution. Thus, the Mann-Whitney U test was used for the comparison of quantitative data and parameters between two groups as well as descriptive analysis (mean, standard deviation, frequency). Chi-square test, Fisher Freeman Halton test, and continuity (yates) correction were used for qualitative data analysis. The Significance level was set at the  $p < 0.05$  level.

## RESULTS

The study included 63 children, 33 (52.4%) girls and 30 (47.6%) boys, aged between 10 and 16 years. The mean and median ages were  $13.79 \pm 1.17$  years, and 14 years respectively. Children were evaluated under two groups as "Obese" ( $n=33$ ) and "Control" ( $n=30$ ). There was no statistically significant difference between the groups in terms of mean age and gender distribution ( $p > 0.05$ ).

The score comparison of both groups is illustrated in Table 1. Self-esteem and anxiety scores were significantly different

between groups ( $p < 0.05$ ). There was no statistical disparity in terms of social isolation and depression. Even though there was no significant difference with respect to depression, the depression level was higher in the obese group.

Both groups were compared for these scores with reference to gender in Table 2. There was no significant difference between the scores in both the obese and control groups as regards to gender.

As illustrated in Table 3, there was a significant difference in terms of self-esteem and anxiety levels when the groups were classified according to the scores.

## DISCUSSION

Despite the fact that there was no significant difference regarding the depression scores between the obese and control groups in our study, depression levels were found to be higher in the obese group. It has been revealed in some studies that obese children display more depression and anxiety related symptoms than their normal-weight peers (9,10). In a study by Lindberg et al. (11), the rate of depression was reported to be statistically significantly higher in obese children and adolescents. Consistent with these findings, Gibson et al. (12) conveyed that there was an association between increased (age- and gender-specific) BMI and higher depression levels in primary school-aged children. Mustillo et al. (13) found a relationship between obesity and depression in boys aged between 9 and 16 years. Anderson et al. (14) revealed a significant relationship between obesity and major depression in adolescent girls. In another meta-analysis, it was reported that obesity increases the risk of depression and that depression in return increases the probability of developing obesity. As a result, it would be beneficial to monitor overweight and obese patients for depression risk and as well evaluate patients with depression for obesity (15). In this study mentioned, despite the fact that there was no significant difference in terms of depression level, the depression score was found to be higher in the obese group. Due to the cross-sectional nature of our study,

**Table 1. Group evaluation in terms of self-esteem, depression, anxiety, and isolation scores**

	Obese (n=33)	Control (n=30)	p
	Mean $\pm$ SD (median)	Mean $\pm$ SD (median)	
Self-esteem score	1.83 $\pm$ 1.39 (1.83)	0.86 $\pm$ 0.94 (0.5)	0.000*
Depression score	2.36 $\pm$ 1.71 (2)	1.5 $\pm$ 1.33 (1)	0.024*
Anxiety score	5.18 $\pm$ 2.01 (5)	3.57 $\pm$ 2.37 (3)	0.002*
Isolation score	1.21 $\pm$ 0.82 (1)	0.77 $\pm$ 0.86 (0.5)	0.040*

\* $p < 0.05$ , Mann-Whitney U test, SD: Standard deviation

**Table 2. Group comparison with respect to self-esteem, depression, anxiety, and isolation scores regarding genders**

Groups	Gender	Self-esteem score	Depression score	Anxiety score	Isolation score
		Mean ± SD (median)	Mean ± SD (median)	Mean ± SD (median)	Mean ± SD (median)
Obese	Female	2.05±1.18 (2)	2.59±1.62 (2)	4.88±2.12 (5)	1.29±0.92 (2)
	Male	1.6±1.59 (0.7)	2.13±1.82 (1.5)	5.5±1.9 (5.5)	1.13±0.72 (1)
	p	<b>0.102</b>	<b>0.246</b>	<b>0.352</b>	<b>0.427</b>
Control	Female	1.04±1.2 (0.6)	1.5±1.55 (1)	4.06±2.29 (4)	0.88±0.89 (1)
	Male	0.67±0.47 (0.5)	1.5±1.09 (1)	3±2.42 (2.5)	0.64±0.84 (0)
	p	<b>0.350</b>	<b>0.663</b>	<b>0.101</b>	<b>0.455</b>

Mann-Whitney U test, SD: Standard deviation

**Table 3. Group evaluation in regards to self-esteem, depression, anxiety, and isolation levels according to the scores**

		Obese	Control	p
		n (%)	n (%)	
Self-esteem	High	15 (45.5%)	24 (80%)	*0.012*
	Medium	16 (48.5%)	5 (16.7%)	
	Low	2 (6.1%)	1 (3.3%)	
Depression	No depression	2 (6.1%)	6 (20%)	*0.087
	Mild	15 (45.5%)	18 (60%)	
	Moderate	10 (30.3%)	4 (13.3%)	
	Severe	6 (18.2%)	2 (6.7%)	
Anxiety	Mild	1 (3%)	10 (33.3%)	*0.001*
	Moderate	10 (30.3%)	12 (40%)	
	Severe	22 (66.7%)	8 (26.7%)	
Isolation	Mild	16 (48.5%)	21 (70%)	*0.140
	Severe	17 (51.5%)	9 (30%)	

<sup>1</sup>Fisher Freeman Halton test, <sup>2</sup>Chi-square test, <sup>3</sup>Continuity (yates) correction, \*p<0.05

other accompanying psychological disorders would be detected with longer follow-up periods and new interviews repeated.

In this study, the anxiety level was found to be significantly higher in obese adolescents. Consistent with the literature, it was revealed that obese children often frequently experience internal mental distress such as anxiety (16-19). If these patients do not receive support, they will probably continue to experience various forms of internal mental illnesses in the next stage. Contrary to our study, some studies suggest that the relationship between anxiety and obesity is unclear (20).

A meta-analysis of obese adolescents delineated that the overall prevalence of depression and anxiety symptoms among overweight/obese children and adolescents was 21.73% and 39.80%, respectively, and 17.96% and 13.99%, respectively, among non-overweight/non-obese children and adolescents (21). In a study by Topçu et al. (22) higher anxiety levels,

depression, and low self-esteem were diagnosed in obese adolescents. Notwithstanding that we found higher anxiety levels in our study in the obese group, similar to the literature, we did not find a significant difference between the groups in terms of depression rates. The fact that the scales we used were different and the numbers in the patient groups were not similar may have created the difference in terms of results.

Adolescents are very concerned about their physical appearance with the effect of hormones during the transition to adulthood. Since emotional relationships can also be experienced during this period, the desire to be liked/approved becomes prominent (23-25). Therefore, those who are overweight or obese have more self-esteem problems. Another important finding in our study was that the self-esteem of the obese group was significantly lower than in the control group. Similarly, in the study by Álvarez-García et al. (26) in a large adolescent group and the study by Çolpan et al. (27) on adolescents, it was reported that obese and overweight individuals had lower self-esteem and more conflict with their peers.

In our study, there was no difference between the two groups in terms of social isolation. However, we believe that obese adolescents will be more socially isolated in the following periods due to the higher anxiety and lower self-esteem levels. In some studies, it has been observed that low self-esteem is associated with social isolation (28,29).

### Study Limitations

The sample size of this study is relatively small. Moreover, since our study is a cross-sectional study, it does not reveal how the psychological effects of obesity will change over time. Whether patients with high anxiety rates will experience more depression over time or whether these patients will experience more social isolation can only be understood with follow-up. The design of future studies on this subject should be arranged with longer follow-up periods.

## CONCLUSION

In conclusion, obesity and its effects continue to manifest themselves as a public health concern. In practice, healthcare professionals must recognize that obese adolescents constitute a specific group. While struggling with obesity in adolescents, they should also be provided with the necessary psychological support.

### Ethics

**Ethics Committee Approval:** This study was conducted after ethical approval from the Clinical Research Ethics Committee of Okmeydani Training and Research Hospital's decision dated 08/01/2019 and numbered 1092 was issued.

**Informed Consent:** Inform consent was obtained from both participating adolescents and their families.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

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

**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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# Paracentral Acute Middle Maculopathy Associated with Different Clinical Entities: A Case Series

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## Abstract

Paracentral acute middle maculopathy (PAMM) implies the retinal lesions with hyperreflective inner nuclear layer (INL) changes in the spectral-domain optical coherence tomography (SD-OCT). PAMM occurs as a result of a flow deficit in the deep capillary plexus of the retina, with a prognosis depending on the associated retinal disease. This case series aimed to report the clinical findings of those diagnosed with PAMM and define the risk factors and associated pathologies. Medical records of patients diagnosed with PAMM between 2016 and 2019 in our hospital were reviewed. Detailed ophthalmologic examination and multimodal imaging were performed in all patients during the initial and follow-up visits. A total of 10 eyes from 9 patients were evaluated. The hyperreflective band-like lesion in the INL was observed in the SD-OCT imaging in all patients. The best-corrected visual acuities ranged between 20/20 and 20/1250. The idiopathic disorder was evaluated in 3 cases, 2 cases were secondary to central retinal artery occlusion, 1 case was secondary to retinal artery branch occlusion, 1 case was secondary to cilioretinal artery occlusion, 1 case was secondary to Susac syndrome, and 1 case was PAMM after pars plana vitrectomy. PAMM may be idiopathically seen without systemic diseases. Systemic research should be conducted for particularly systemic vascular risk factors when PAMM is detected. The prognosis of PAMM depends on the associated retinal pathology. Idiopathic cases generally have favorable visual outcomes, but severe vision loss occurs in other cases, such as PAMM secondary to retinal arterial pathologies.

**Keywords:** Multimodal imaging, paracentral acute middle maculopathy, retinal vascular disease, spectral-domain optical coherence tomography

## INTRODUCTION

Paracentral acute middle maculopathy (PAMM) is a clinical entity characterized by hyperreflective band-like lesions in the spectral-domain optical coherence tomography (SD-OCT) at the inner nuclear layer (INL) and outer-plexiform layer (OPL). The disease may either be idiopathic or usually associated with retinal vascular pathologies (1,2). With the advent of optic coherence tomography angiography (OCTA), PAMM occurs as a result of a flow deficit in the deep capillary plexus of the retina (1).

This case series aimed to report the cases diagnosed with PAMM and define the risk factors and associated pathologies.

## CASE PRESENTATIONS

Medical records of patients diagnosed with PAMM between 2016 and 2019 in a tertiary referral center were reviewed. Ten eyes from 9 patients diagnosed with PAMM were included in this case series (Table 1). All patients had a complete ophthalmologic examination, including the best-corrected visual acuity (BCVA) with a Snellen chart, slit-lamp biomicroscopy, and intraocular pressure (IOP) measurements using the Goldmann applanation tonometry and fundus examination after dilatation at baseline and follow-up visits. Patients underwent color fundus, fluorescein angiography (FA) imaging (Canon CX-1 digital retinal camera MYD/NM), SD-OCT, and near-infrared (NIF) imaging (Spectralis;



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No	Age/gender	Side	Systemic disease/risk factors	Complaint at presentation	Initial BCVA	Initial fundus finding	Initial SD-OCT	Initial FFA	Final BCVA
1	38/M	OS	10 years of smoking	Paracentral scotoma	20/20	The gray-white lesion with prominent borders in the superior fovea	Hyperreflective band-like lesion in the INL in the superior fovea	Arterial and usual vein filling	20/20
2	28/F	OS	-	Inferior altitudinal scotoma	20/20	The gray-white lesion with prominent borders extending from the superior fovea to the superior optic disc	Hyperreflective band-like lesion in the INL in the superior fovea	Arterial and usual vein filling	20/20
3	58/M	OS	-	Paracentral scotoma	20/20	A pale area in the superior papillomacular bundle	Hyperreflective band-like lesion in the INL in the superior macula	Arterial and usual vein filling	20/20
4	70/F	OS	CAD, carotid artery stenosis	Sudden vision loss	20/1250	Diffuse retinal whitening	A diffuse hyperreflective band-like lesion in the INL in the macula	Delay in central retinal artery filling and elongation in arteriovenous transit time	20/1250
5	53/F	OD	HT	Sudden vision loss	20/1250	Diffuse retinal whitening	A diffuse hyperreflective band-like lesion in the INL in the macula	Delay in central retinal artery filling	20/1250
6	40/F	OD	-	Misty vision	20/20	Edema in the nerve fiber layer extending from the papillomacular bundle to the inferior macula	Hyperreflective band-like lesion in the INL and OPL in the papillomacular bundle	Delay in the filling of the cilioretinal artery	20/20
7	61/M	OS	HT	Decreased vision and metamorphopsia	20/32	Edema in the nerve fiber layer extending from the superior temporal vein arch to the macula	Hyperreflective band-like lesion in the INL and OPL	Slight delay in left upper temporal artery branch filling	-
8	28/F	Bilateral	Hearing loss, headache, encephalopathy	Bilateral vision loss	OD: 20/50 OS: 20/100	OD: faint optic disc and whitening area with microangiopathic lesions in the fovea OS: microangiopathic lesions in the fovea and sub-ILM hemorrhage in the inferior fovea	OD: Hyperreflective band-like lesions in INL OS: Sub-ILM hemorrhage and hyperreflective band-like lesion in the INL around the sub-ILM hemorrhage	bilaterally small arteriolar obstructions and peripheral ischemic areas	OD: 4/50 OS: 20/63
9	76/M	OS	DM, CAD	Paracentral scotoma	20/1250	Gray-white lesion located deep in the paracentral fovea	Hyperreflective band-like lesion in the INL in the paracentral fovea		20/1250

F: Female, M: Male, BCVA: Best-corrected visual acuity, SD-OCT: Spectral-domain optical coherence tomography, FFA: Fundus fluorescein angiography, OD: Oculus dexter, OS: Oculus sinister, INL: Inner nuclear layer, CAD: Coronary artery disease, OPL: Outer-plexiform layer, DM: Diabetes mellitus, HT: Hypertension, sub-ILM: Sub-internal limiting membrane

Heidelberg Engineering), and three patients had OCTA imaging with Cirrus 5000 HD OCT with AngioPlex OCT Angiography device.

### Cases 1-3

The systemic workup was negative in 3 cases (cases 1, 2, and 3), without signs of retinal vascular diseases. Therefore, participants were classified as idiopathic PAMM. The only risk factor for vascular diseases was smoking for 10 years in case 3. At presentation, paracentral scotoma was the common finding among these cases, with a BCVA of 20/20 in the affected eyes. Fundus evaluation revealed a gray-white lesion with prominent borders, and the SD-OCT demonstrated a typical hyperreflective band-like lesion in the INL. The FA was unremarkable in 3 patients, and the OCTA showed reduced deep capillary flow in case 2. At the end of the follow-up, the BCVA was stable with middle retinal layer thinning on the SD-OCT (Figure 1).

### Cases 4 and 5

Cases 4 and 5 presented to our clinic with a sudden vision loss in one eye and both with a BCVA of 20/1250. Case 4 had a history of coronary artery bypass graft surgery 2 weeks ago and case 5 had hypertension (HT) that was controlled with medications.

Fundus examination and FA imaging demonstrated a central retinal artery occlusion (CRAO) in both patients, whereas a diffuse hyperreflective band-like lesion in the INL was observed in the SD-OCT. Further systemic evaluation of case 4 revealed severe carotid stenosis (80-90%). At month 6, the BCVA of both patients was stable with diffuse macular thinning in the SD-OCT (Figure 2).

### Case 6

A 40-year-old female complained of blurred vision in her right eye. Her past medical history was unremarkable, and the BCVA was 20/20 bilaterally. The fundus examination revealed a retinal thickening from the papillomacular bundle to the inferior macular region in her right eye. The NIF imaging revealed a dark-gray lesion at the corresponding area of the lesion. The FA showed a delay in filling of the right cilioretinal artery. The SD-OCT showed a hyperreflective band-like lesion in the INL and OPL in the region consistent with the lesion. The patient was referred to internal medicine for systemic workup, and her hypercoagulability tests were positive for factor V Leiden mutation.



**Figure 1.** Case 2: (A) Initial SD-OCT shows a hyperreflective band-like lesion in the INL. (B) Initial FA shows a normal filling in 15 min. (C) Initial FA shows a normal filling in 30 min. (D) Initial OCTA shows a normal superficial capillary plexus flow. (E) Initial OCTA shows a decreased flow of the deep capillary plexus. (F) SD-OCT at 6 months shows a middle retinal layer thinning

SD-OCT: Spectral-domain optical coherence tomography, INL: Inner nuclear layer, FA: Fluorescein angiography, OCTA: Optic coherence tomography angiography

### Case 7

A 61-year-old male presented with decreased vision and metamorphopsia in his left eye for 1 week. His past medical history was unremarkable, except for the HT that was controlled with medication. His BCVA was 20/32 in his left eye. The fundus examination of the left eye showed a retinal nerve fiber layer swelling, extending throughout the superior temporal vein arch, surrounding the macula. The NIF demonstrated dark-gray lesions and the FA showed a slight delay in the left upper temporal artery branch filling. A hyperreflective band-like lesion was observed in the INL and OPL in the region corresponding to the lesion in the SD-OCT. The patient was diagnosed with PAMM secondary to retinal artery branch occlusion.

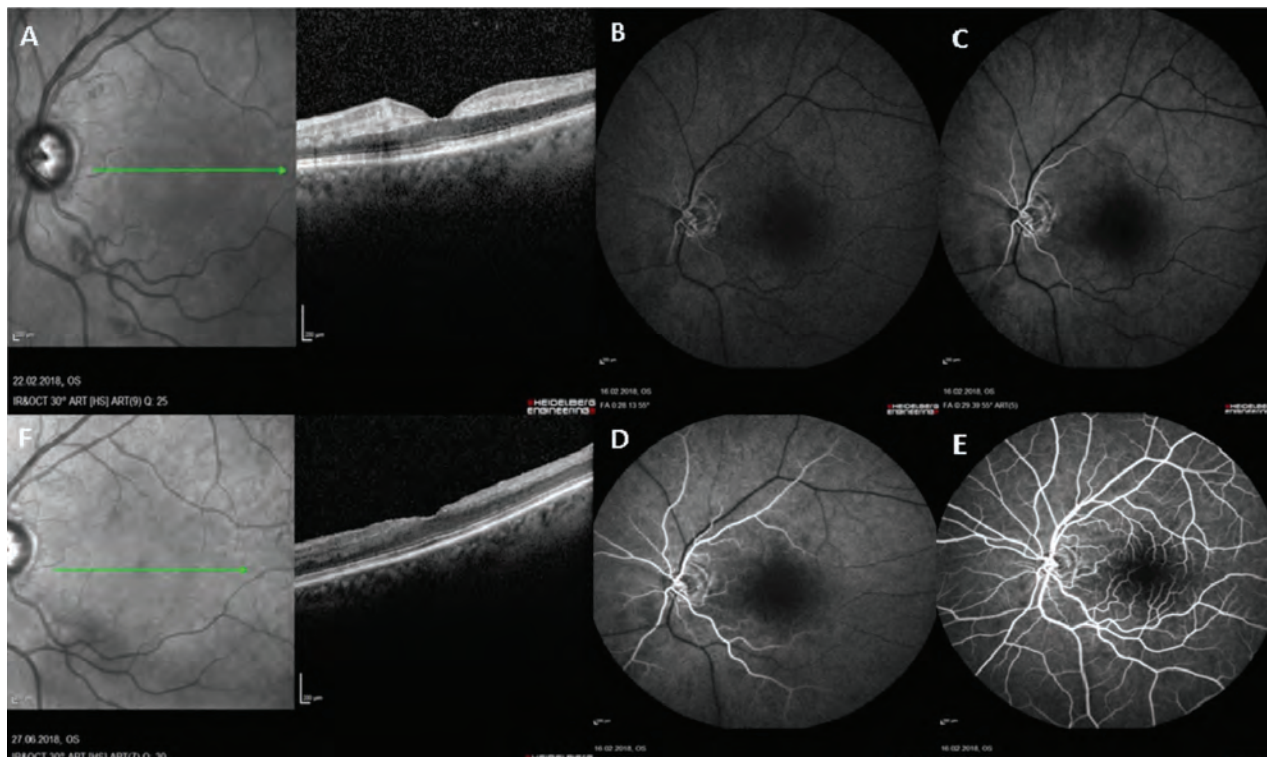
### Case 8

A 28-year-old female patient presented with decreased vision in both eyes. The patient suffered from hearing loss and severe headaches for 2 years. Her ophthalmologic evaluation revealed a BCVA of 20/50 in her right eye and 20/100 in the left. Fundus examination of the right eye revealed a pallor optic disk, with white microangiopathic lesions around the fovea. Perifoveal microangiopathic lesions and macular sub-internal limiting

membrane (sub-ILM) hemorrhage were also detected in her left eye. The NIF imaging revealed a grayish lesion in the inferior perifoveal region bilaterally. The FA showed small arteriolar obstructions and peripheral ischemic areas in both eyes. The SD-OCT revealed bilateral hyperreflective band-like lesions in the INL, with accompanying sub-ILM hemorrhage in her left eye. She was referred to neurology and diagnosed with Susac syndrome. She was treated with intravenous corticosteroid and methotrexate by the neurologists. After 6 months, her BCVA was 20/50 and 20/63, in her right and left eyes, respectively. The SD-OCT revealed a bilateral thinning of the affected layers in the corresponding region to the lesions and retinal pigment epithelial (RPE) atrophy in the left eye (Figure 3).

### Case 9

A 76-year-old male patient presented with visual disturbances and metamorphopsia in his left eye. His medical history was positive for coronary artery disease (CAD) and diabetes mellitus (DM). He had a coronary artery bypass graft surgery 6 years ago. The BCVA was 20/200 on his left eye. Fundus examination revealed an epiretinal membrane (ERM) and posterior vitreous detachment in his left eye. The SD-OCT imaging showed vitreomacular traction concurring with an ERM. He had pars



**Figure 2.** Case 4: (A) Initial SD-OCT shows a diffuse hyperreflective band-like lesion in the INL. (B) Initial FA shows delayed perfusion of CRA in 28 s. (C) Initial FA shows delayed perfusion of the CRA in 30 s. (D) Initial FA shows a delayed filling of the CRA in 34 s. (E) Initial FFA in 1 min. (F) SD-OCT in 6 months shows a diffused macular thinning

SD-OCT: Spectral-domain optical coherence tomography, INL: Inner nuclear layer, FA: Fluorescein angiography, CRA: Central retinal artery, FFA: Fundus fluorescein angiography



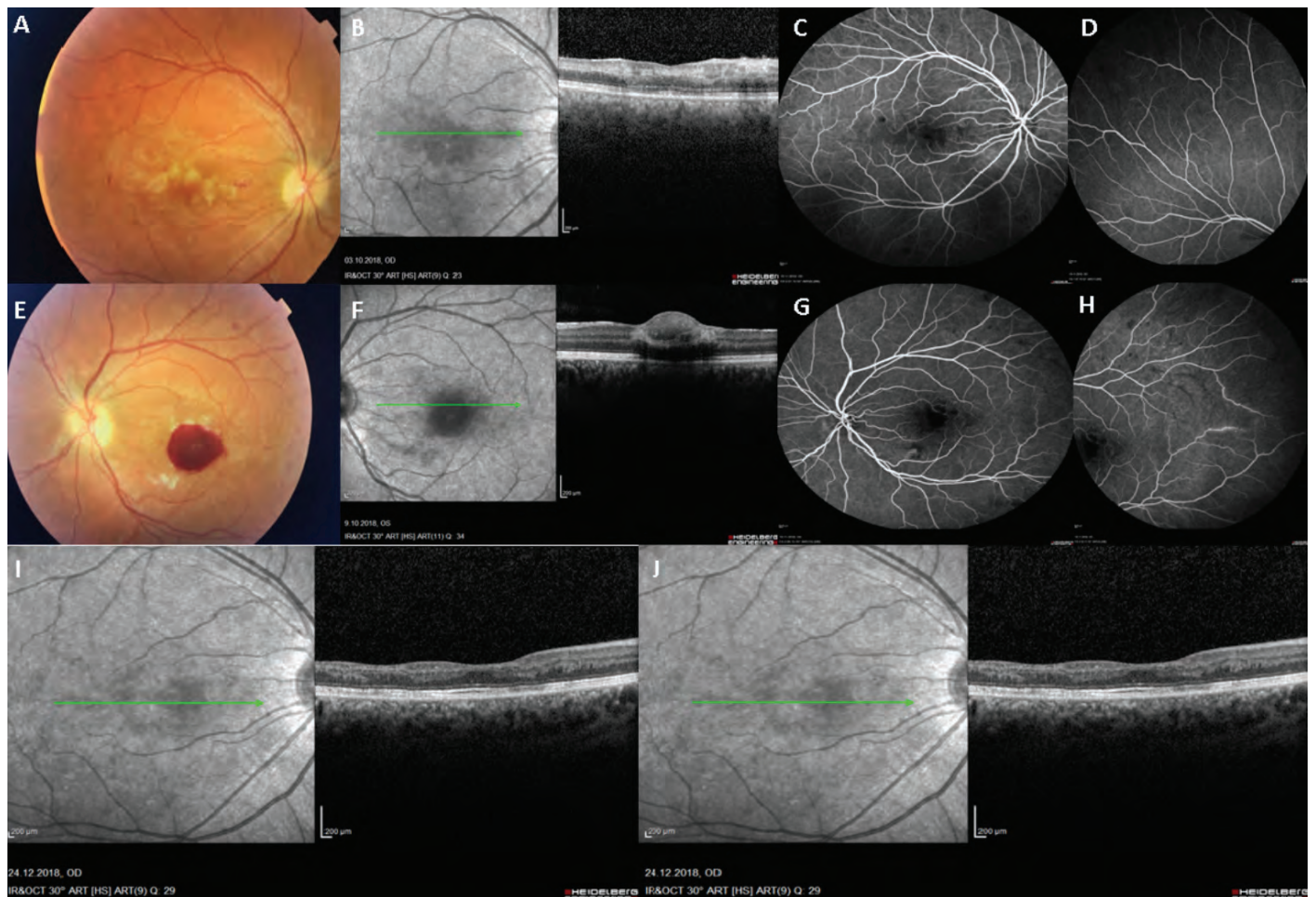
plana vitrectomy (PPV) surgery, with ERM and ILM peeling and air tamponade in his left eye.

The patient described a paracentral scotoma in the left eye 1 week postoperatively, with a BCVA of 20/800. The fundus examination revealed a grayish-white lesion located deeply in the paracentral fovea of the left eye. The NIF imaging revealed a gray-white lesion corresponding to the region of the lesion. A hyperreflective band-like lesion in the INL was observed on the SD-OCT. The patient was considered as PAMM development following PPV. At 6 months postoperatively, the BCVA in his left eye was improved to 20/50. The middle retinal layers of the corresponding region showed marked thinning in the macular SD-OCT (Figure 4).

## DISCUSSION

PAMM is characterized by hyperreflective band-like lesions in the INL in the SD-OCT and a hyporeflective lesion in the NIF in the acute phase. In the chronic phase, a middle retinal layer thinning is observed in the corresponding region to the lesion (3). Rahimy et al. (1) described PAMM as a clinical entity rather than a disease. Currently, no treatment modality has been defined for PAMM. A complete systemic workup for risk factors is recommended during diagnosis.

PAMM is a clinical finding that occurs with the occlusion of the intermediate capillary plexus and deep capillary plexus (3). Consider imaging techniques when PAMM is suspected is essential, since PAMM may often be missed during clinical evaluation. SD-OCT and NIF are the most useful imaging methods in PAMM



**Figure 3.** Case 8: (A) Initial right eye fundus photo shows a pallor optic disk, with white microangiopathic lesions around the fovea. (B) Initial right eye SD-OCT shows hyperreflective band-like lesions. (C) Right eye FA shows central arteriolar occlusion. (D) Right eye FA shows peripheral ischemic areas. (E) Initial left eye fundus photo shows perifoveal microangiopathic lesions and macular sub-ILM hemorrhage. (F) Initial left eye SD-OCT shows hyperreflective band-like lesions in INL and sub-ILM with hemorrhage in these lesions. (G) Left eye FA shows central arteriolar occlusion. (H) Left eye FA shows peripheral ischemic areas. (I) Right eye SD-OCT at 8 months shows thinning of the affected layers in the corresponding region of the lesions. (J) Left eye SD-OCT at 8 months shows thinning of the affected layers in the corresponding region of the lesions and RPE atrophy  
SD-OCT: Spectral-domain optical coherence tomography, FA: Fluorescein angiography, sub-ILM: Sub-internal limiting membrane, INL: Inner nuclear layer, RPE: Retinal pigment epithelial

diagnosis. Moreover, OCTA is another novel imaging method that visualizes the retinal vascular structures, thus detecting retinal pathologies (1). The FA is insufficient in PAMM diagnosis but is important for differential diagnosis. The association between the retinal vascular disorders and PAMM, as well as idiopathic cases, was reported in the literature (3). In addition, cases with PAMM secondary to systemic vasoconstrictive conditions were previously reported (2,4,5).



**Figure 4.** Case 9: Preoperative SD-OCT demonstrating an epiretinal membrane extending to the inner retinal layers and vitreomacular traction (A). SD-OCT at postoperative 1 week (B). A clear parafoveal hyperreflective band with distinct margins in the inner nuclear layer. SD-OCT at postoperative 6 months (C). Retinal atrophy involves the inner layers in the temporal region of the macula  
SD-OCT: Spectral-domain optical coherence tomography

PAMM can be idiopathically observed, even in young cases, without systemic and ocular risk factors (1,6,7). Several cases were reported as idiopathic PAMM in previous literature. The age range of idiopathic cases in the literature varies between 16 and 65 years (8). In idiopathic cases, the typical finding is a paracentral scotoma, which may also be accompanied by decreased vision. In most idiopathic PAMM cases, visual acuity is usually preserved, whereas paracentral scotoma becomes permanent during follow-ups (8). In our series, cases 1, 2, and 3 were considered as idiopathic due to insufficient systemic and vascular risk factors or ocular pathology coexistence. All idiopathic cases were relatively younger than other cases, and visual acuity was better both at presentation and during follow-ups. However, the paracentral scotoma became permanent in these patients. Possible causes of idiopathic PAMM include factors that cause small blood vessel constriction and coagulation disorders, such as HT, sympathetic excitement, hyperlipidemia, DM, pregnancy, arteritis, and systemic lupus erythematosus (1,8). Any risk factors for systemic inquiry in idiopathic patients were not defined, except for a positive history of smoking, in one case.

PAMM related to CRAO in cases 4 and 5 were reported. CRAO should be considered in patients with diffuse PAMM, even with normal clinical and angiographic findings (1). Yu et al. (9) reported cases with isolated diffuse PAMM due to CRAO. The absence of filling defect in the FA that was observed in some of these cases may be due to rapid recanalization in the CRA. These cases had severe vision loss consistent with CRAO. Similar to previous reports, our cases had a BCVA of 20/1250 at presentation. Both cases had diffuse PAMM in the SD-OCT and a filling defect in CRA in the FA.

Rahimy et al. (1) reported that detailed clinical evaluation with multimodal imaging is essential in the differential diagnosis of branch retinal artery occlusion (BRAO) and CRAO, even without evidence for arterial occlusion in the fundus examination of PAMM cases. The FA revealed a delay in filling of the cilioretinal artery in case 6 and BRA in case 7. Decreased BCVA was not severe in these cases; however, PAMM lesions covered a relatively large area in the NIF and SD-OCT.

Susac syndrome is an occlusive arteriolar disease and is thought of as an autoimmune reaction to an unknown antigen. The disease causes vasoocclusion in the vessels of the brain, ear, and retina (10,11). Patients are usually diagnosed in the 3<sup>rd</sup>-4<sup>th</sup> decade with female preponderance. Brain involvement, such as encephalopathy, focal neurological deficits and headaches, hearing loss, and retinal arterial occlusions is the pathognomonic triad. Retinal involvement includes focal segmental staining in the arterial wall in the FA and sectoral damage in the internal



retinal layers from the retinal nerve fiber layer to the OPL in the SD-OCT (11). In our PAMM case diagnosed with Susac syndrome, the FA showed focal arteriolar occlusion areas and peripheral retinal ischemia.

Case 9, a patient with CAD and DM, was diagnosed with PAMM after PPV. Increased IOP and use of subtenon, peribulbar, or retrobulbar anesthesia during an ocular surgery may alter the ocular perfusion, thus causing vascular occlusion (12). Systemic diseases, such as DM, HT, CAD, and hyperlipidemia, are also risk factors for vascular occlusion. The development of BRAO and CRAO was reported in the literature after cataract surgery, PPV, scleral buckle surgery, intravitreal anti-vascular endothelial growth factor injections, and glaucoma valve implantation (12-14). This case is the first PAMM case in the literature described after vitrectomy since the middle retinal layers are more vulnerable to ischemia (2). The presence of risk factors, such as increased IOP, local retinal layer damages, and capillary plexuses in these layers during a retinal surgery might explain the PAMM development in our case.

## CONCLUSION

Retinal imaging is essential in patients with visual disturbances that cannot be diagnosed with clinical examination alone. Patients suspected of PAMM should be investigated using SD-OCT imaging, even without FA findings. PAMM should be considered as idiopathic, even in young adults without systemic diseases. When PAMM is detected, systemic research should be conducted for systemic vascular risk factors. The PAMM prognosis depends on the associated conditions. Idiopathic cases usually have favorable outcomes and other PAMM cases may suffer severe vision loss. The hyperreflective bands on the SD-OCT are replaced with INL atrophy over time; however, the paracentral scotoma usually becomes permanent.

## Ethics

**Informed Consent:** Written informed consent was obtained from all patients for publication of this case report and accompanying images.

**Peer-review:** Externally peer-reviewed.

## Authorship Contributions

Surgical and Medical Practices: G.G., Ş.Ö., C.A., Ö.A., Concept: Ş.Ö., N.A., B.T.A., Design: N.A., B.T.A., Data Collection or Processing: G.G., B.T.A., C.A., Ö.A., Analysis or Interpretation: G.G., Literature Search: G.G., Writing: G.G., Ş.Ö., N.A.

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# An Unusual Presentation of Orbital Lymphoma with a Temporal Mass

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## Abstract

Orbital lymphomas (OLs) account for 2% of all lymphomas and only 1% of all non-Hodgkin's lymphoma (NHL). However, in patients >60 years of age, lymphomas are the most common primary orbital tumor. The majority of cases are primary, low-grade, B-cell, NHL. The most common sub-type is extranodal marginal-zone B-cell lymphomas of mucosa-associated lymphoid tissue (MALT) type lymphomas. OLs other than MALT lymphoma have different histologies, with diffuse, large, B-cell lymphoma being relatively common. The presentation of OL is variable based on the involved part of the orbit. Accurate differentiation of OL from benign lymphoproliferative disorders is crucial due to the differences in management. Imaging characteristics and the clinical findings should be carefully evaluated, and lymphomas should be considered in the differential diagnosis of slowly growing periorbital/orbital region masses in adults. We report an unusual presentation of a primary OL with a rubbery temporal region mass in a 59-year-old woman.

**Keywords:** Orbital lymphoma, temporal mass, benign lympho-proliferative disorders

## INTRODUCTION

Lymphoproliferative diseases of the orbit is a spectrum of disorders that includes lymphoid hyperplasia, atypical hyperplasia, and lymphoma. Orbital lymphoma (OL) may be a manifestation of systemic lymphoma or may occur primarily in the orbit. OLs account for 2% of all lymphomas and only 1% of all non-Hodgkin's lymphomas (NHLs) (1). However, in patients >60 years of age, lymphomas are the most common primary orbital tumor (2). The majority of cases are primary, low-grade, B-cell, NHL. The most common sub-type is extranodal marginal-zone B-cell lymphomas of mucosa-associated lymphoid tissue (MALT) type lymphomas (3,4). Although it is unclear whether MALT exists normally in the ocular adnexa, including the conjunctiva, lacrimal gland, orbital fat, eyelid, and lacrimal sac, the orbit is otherwise believed to be devoid of lymphatic tissue or lymphatic drainage. Therefore, this lymphoid tissue is thought to be acquired as a result of chronic inflammation or autoimmune disorders like systemic lupus erythematosus (3,5). One of the recently described possible associations of ocular adnexial MALT

lymphoma (OAML) is *Chlamydia psittaci* infection, which has lead to an antibiotic therapy being used to reduce the size of the tumor, and in some cases to remission (3,6,7). On the other hand, OLs other than OAML tumors have different histologies with diffuse, large, B-cell lymphoma being relatively common (8). The presentation of OL is variable based on the involved part of the orbit. We aimed to report a non-OAML primary OL presenting with a rubbery temporal region mass in a 59-year-old woman.

## CASE PRESENTATION

A 59-year-old woman presented to our hospital with a left frontotemporal swelling involving the outer periorbital area which had become more obvious in the last 1 month but was present for about 6 months. Physical examinations including neurological evaluations did not reveal any pathological findings. Globe movements were normal in all directions. Magnetic resonance imaging (MRI) was performed and revealed a 90x33x250 mm sized left temporal region mass with a large



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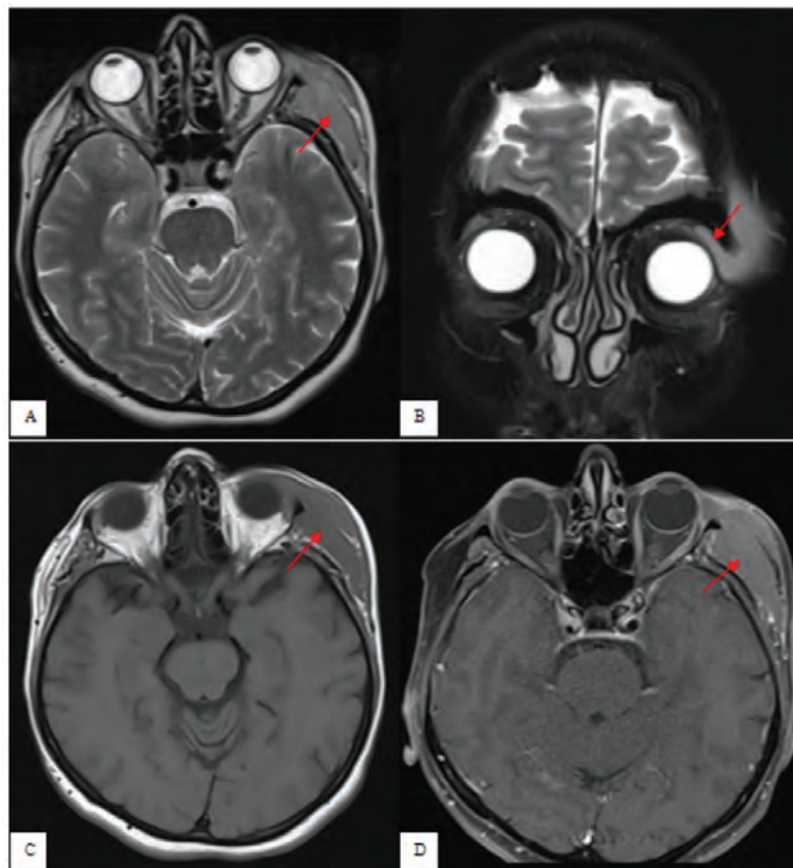
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extracranial temporal component covering the suprazygomatic temporal muscle, which ended inferiorly by obliterating the retroantral (buccal) fat. A small, intraorbital, extraconal extension of the mass at the region of the lacrimal gland in the left superolateral orbital quadrant was revealed without an intraconal component. The mass was isointense to extraocular muscles on T1w images and hyperintense on T2w images. It was involving the lacrimal gland and the lateral rectus muscle. Mild proptosis was noted. After gadolinium, moderate homogenous enhancement was present. The globe, retrobulbar fat, and the optic nerve appeared to be normal (Figure 1). On non-enhanced CT (NECT), the mass was homogenous and slightly hyperdense to the extraocular muscles with no adjacent bony destruction (Figure 2). She had no relevant medical history of chronic inflammatory or autoimmune diseases. Fine needle aspiration biopsy was performed, and histological examination proved non-OAML OL (Figure 3) which was revealed to be a primary by systemic evaluation.

## DISCUSSION

OLs may be seen as smooth, circumscribed, unifocal lesions affecting any orbital structure or may emerge as diffuse, infiltrative masses. However, different from the other aggressive intraorbital malign lesions, they have a tendency to slowly mold the adjacent orbital structures without infiltration or destruction. In these cases, the adjacent intraorbital structures are usually separately identifiable from the tumor as not being the origin. Although close contact may occur, since direct infiltration of the globe and optic nerve is rare, vision is preserved in the majority of cases (3,9). There may be bony remodeling without erosion or hyperostosis. The majority of OLs are unilateral and are typically located in the superior quadrants, particularly at the lateral part in close proximity to the lacrimal gland, which is involved in nearly 40% of cases (2). Patients usually present with a palpable, firm, soft tissue mass with possible proptosis, exophthalmos, diplopia, or restricted ocular motions depending on the involved orbital structures (3,4). In patients with conjunctival involvement, which accounts for 25% of the cases, a salmon-red patch of a

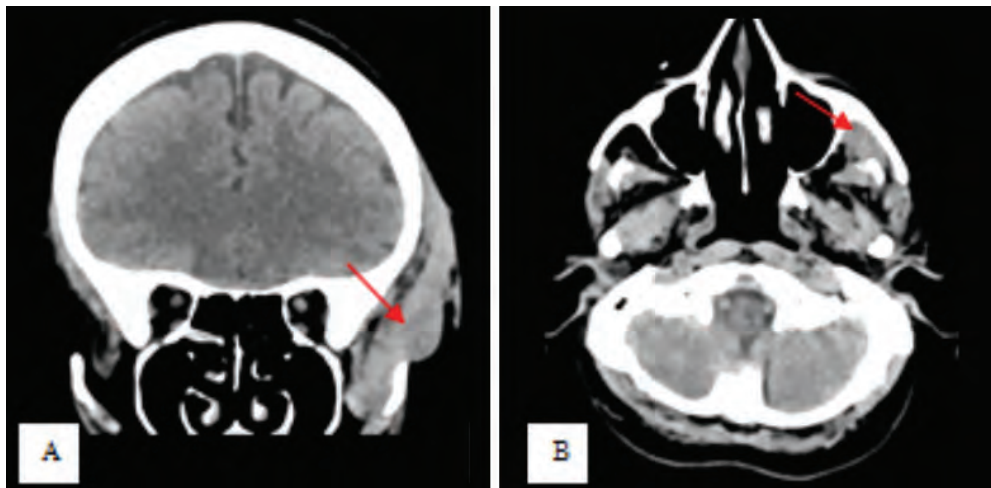


**Figure 1.** MRI of the brain and the orbit showing the left temporal region mass on axial T2w image (A, arrow). Intraorbital extension of the mass near the lacrimal gland in the left superolateral orbital quadrant is shown on coronal T2w image (B, arrow). The mass is hyperintense to extraocular muscles on T2w images (A, B) and isointense on T1w image (C). On postcontrast T1w image, homogenous moderate enhancement of the mass is seen (D, arrow)

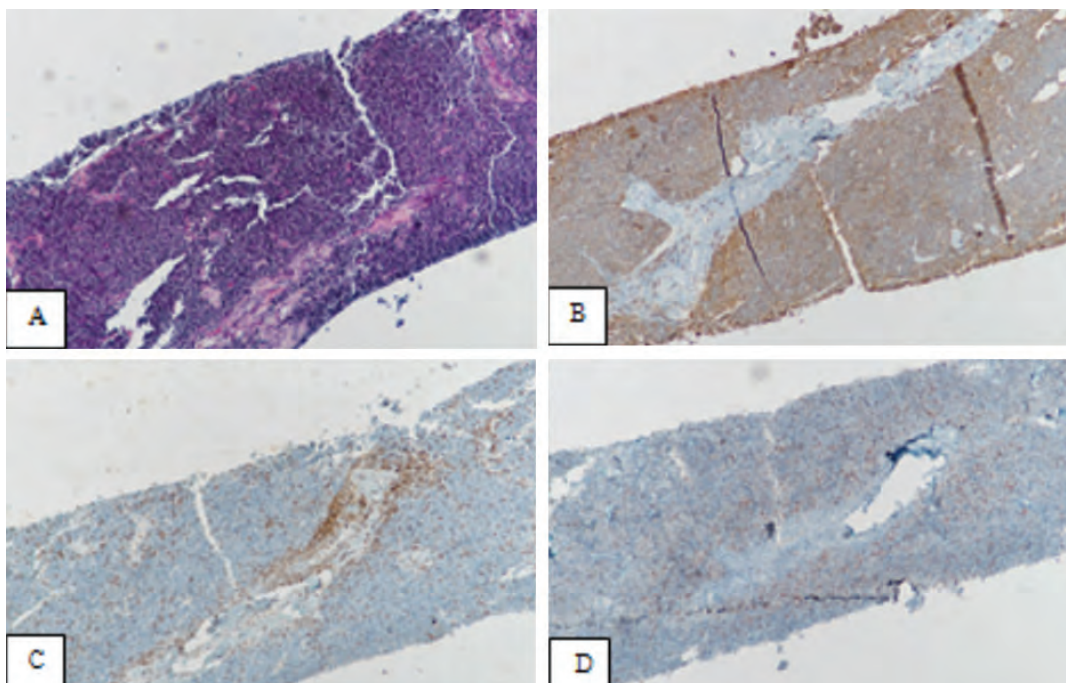
MRI: Magnetic resonance imaging

swollen conjunctiva may be the presenting manifestation, which is usually seen in cases of OAML (3). Although pain is uncommon as a general feature of lymphoproliferative lesions, it may occur in a small subset of patients with inflammatory changes like periorbital edema (3). Most of them are extraconal with a possible intraconal extension for large sized tumors, but intraconal occupation is predominantly seen in cases of orbital lymphoid hyperplasia and is not expected from OL (9,10). On NECT, the mass is usually homogeneous in attenuation, isodense, or slightly hyperdense compared to the extraocular muscles. On

MRI, the mass is iso- to hypointense to the extraocular muscles on T1w images and iso- to hyperintense to muscles on T2w images. Following administration of contrast on either CT or MRI, homogeneous moderate enhancement is demonstrated, similar again to extraocular muscles and the lacrimal gland (3,10,11). In the differential diagnosis in our patient, due to the homogenous and non-destructive nature of the lesion, aggressive orbital and lacrimal tumors or metastasis have not been considered. The densely cellular nature of OL with a high nucleus-to-cytoplasm ratio results in relatively specific imaging manifestations including



**Figure 2.** CT of the head showing the isodense left temporal region mass on coronal image (A, arrow). On axial images (A, B), the inferior extension of the mass obliterating the retroantral (buccal) fat at the left infratemporal fossa is seen (B, arrow). Small intraorbital part of the mass is shown (C, arrow)  
CT: Computed tomography



**Figure 3.** Histologic (A) and immunophenotypic (B-D) features of the lesion. The neoplastic cells are small in size, monomorphic in appearance, and are characterized by a slightly irregular nuclei, inconspicuous nucleoli, and narrow cytoplasm (A, 400). The neoplastic cells are positive with CD-20 with occasional Bcl-6 and CD-5 positivity (B-D, 400)

higher attenuation values on NECT and restricted diffusion on MRI (3,11,12). However, it is still challenging to differentiate it from some inflammatory conditions sharing similar features on imaging. The most challenging imaging differential of OL is idiopathic inflammatory orbital pseudotumor (IIO) which is a non-granulomatous inflammatory disease responding well to steroids. Among its five forms including anterior, apical, diffuse and sclerosing, myositic, and lacrimal types, the most common is the myositic form characterized by uniform enlargement of one or more extraocular muscles and their tendons. Since our patient did not have extraocular muscle enlargement, this was not considered in the differential diagnosis, like thyroid ophthalmopathy. The rare lacrimal sub-type was considered; however, orbital pseudotumor is characterized by a relatively acute onset of pain, which was not present in our patient. Although DWI was not included in the MRI of our patient, the presence of restricted diffusion if demonstrated, is a feature that differentiates OL from pseudotumor. *IgG4*-related orbital disease is a diffuse or mass forming fibroinflammatory reaction rich in *IgG4*-positive plasma cells which may also involve the orbit and may not be differentiated from IIO on imaging. It is characterized by an elevated serum titer of *IgG4* (13). Moreover, sarcoidosis and Wegener granulomatosis may also cause diffuse infiltration of orbital structures without any specific imaging features; however, there were no other associated signs of these diseases in our patient. The presentation of our patient with a frontotemporal region mass in which intraorbital extension was detected by imaging studies was quite unusual, and biopsy was required for the exact diagnosis which was shown as a non-OAML primary OL by immunohistochemical examination. In the treatment of non-MALT-lymphoma, as also in OAML a combination of two or more of surgical resection, radiotherapy, and chemotherapy are used. However, prognosis is less favorable than that of OAML.

## CONCLUSION

Lymphomas are the most common primary orbital tumors in patients >60 years of age. Accurate differentiation of OL from benign lymphoproliferative disorders is crucial due to differences in their management. Imaging characteristics and clinical findings should be carefully evaluated in the differential diagnosis, and OL should be considered in cases of a slowly growing periorbital/orbital region mass in adults.

## Ethics

**Informed Consent:** Informed consent was taken from the patient.

**Peer-review:** Externally and internally peer-reviewed.

## Authorship Contributions

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

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

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# Intracranial Tumor in a Patient with Eclampsia: The Importance of Differential Diagnosis

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## Abstract

Preeclampsia is a condition that usually occurs after the 20<sup>th</sup> week of pregnancy and is often accompanied by hypertension and proteinuria. Eclampsia is accompanied by convulsions. Presented herein is a case of a 32-year-old, 32-week pregnant woman, who presented with generalized tonic-clonic seizures and developed respiratory arrest, thus an emergency cesarean section was performed. The seizures did not stop in the postoperative period, and a brain tumor was diagnosed with magnetic resonance imaging. Therefore, every pregnant patient with convulsion, as in our case, should not only be considered as eclampsia but with other possible causes in the differential diagnosis.

**Keywords:** Pregnant, seizure, differential diagnosis

## INTRODUCTION

Preeclampsia is defined as hypertension (HT) with accompanying proteinuria or end-organ damage in a normotensive female after the 20<sup>th</sup> week of pregnancy (1). According to this definition, proteinuria is not excluded from the definition but is not an essential criterion. Pregnancy-related hypertensive diseases are the second most common cause of maternal death after thromboembolic diseases (2).

Preeclampsia is defined as the development of HT together with proteinuria after the 20<sup>th</sup> gestational week (3,4), and is seen in 2-3% of all pregnancies (5-7% of nulliparity pregnancies), wherein eclampsia develops in 2% (5). Generally, death occurs as a result of cerebral hemorrhage due to uncontrolled HT (systolic blood pressure of  $\geq 160$  mmHg). Cases of pre-eclampsia in the 2<sup>nd</sup> trimester have a worse prognosis than those after the 34<sup>th</sup> week. Symptoms usually recover within 48 hours after delivery (6). Eclampsia is the occurrence of generalized tonic-clonic convulsions, which cannot be explained by any other reason in a patient with preeclampsia. Generally, spontaneous recovery is achieved within 60 s and occasionally lasts for 3-4 min (7). The

definitive and only treatment for eclampsia is the delivery of the infant (8).

Presented herein is a case of a patient diagnosed with eclampsia, with convulsions continuing after cesarean section delivery, who was then determined with a frontal intracranial mass on the magnetic resonance imaging (MRI). This presentation aimed to emphasize the importance of differential diagnosis.

## CASE PRESENTATION

A 32-year-old female patient in the 32<sup>nd</sup> week of pregnancy, without a known history of chronic disease, presented at the emergency department having a generalized tonic-clonic seizure. An infusion of 5 gr IV magnesium sulfate ( $MgSO_4$ ) over 20 mins was started. However, with the development of respiratory arrest, orotracheal intubation was performed under emergency conditions. The blood gas values were observed as pH of 6.95, partial pressure of oxygen ( $PaO_2$ ) of 64 mmHg, partial pressure of carbon dioxide ( $PaCO_2$ ) of 90 mmHg, and bicarbonate ( $HCO_3$ ) of 19 mmol/L. The obstetric examination revealed fetal distress, thus an emergency cesarean section was performed with the



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diagnosis of eclampsia. The blood test results were normal: Aspartate aminotransferase: 20 U/L, alanine aminotransferase: 10 U/L, hemoglobin: 12.6 g/dL, and platelet: 235.000  $\mu$ L. Blood gas values during the procedure were: pH 6.87, PaCO<sub>2</sub> 81.1 mmHg, PaO<sub>2</sub> 48.7 mmHg, and HCO<sub>3</sub> 14.5 mmol/L and after 10 mins were: pH 7.4, PaCO<sub>2</sub> 36 mmHg, PaO<sub>2</sub> 405.8 mmHg, and HCO<sub>3</sub> 21.6 mmol/L. A healthy infant was delivered and the patient was extubated on the operating table, then transferred to the intensive care unit for advanced follow-up.

At postoperative 2 hours, despite normal blood tests and oxygen therapy using a mask, the orientation and cooperation were weak and the general condition was moderate. The patient was referred to the neurology department, which recommended administering 1 ampoule (10 mg) of diazepam in 150 cc mediflex and 3 ampoules (total 750 mg) of phenytoin in 500 cc of 0.9% NaCl in 45 mins. After the treatment initiation, the patient's level of consciousness started to recover, but she experienced another seizure during the treatment. The respiration worsened and the SpO<sub>2</sub> dropped, thus orotracheal intubation was applied and the patient was again referred to the neurology department. Cranial MRI and electroencephalography were recommended by the neurologist. On the same day, the patient recovered with full consciousness and was co-operative, thus extubated. A 2x1 tb of levetiracetam (Keppra® 500 mg) was started upon the recommendation of the neurologist. The patient was conscious, co-operative, oriented, and was followed up with TA: 113/65 mmHg, pulse: 87/min, SpO<sub>2</sub>: 99%, and clear diuresis. The postoperative 5<sup>th</sup>-hour urine test revealed trace amounts of protein and ketone, blood ++, erythrocytes were 17, and leukocytes were 0. On the following day, the patient no longer required intensive care and was transferred to the obstetrics postnatal ward.

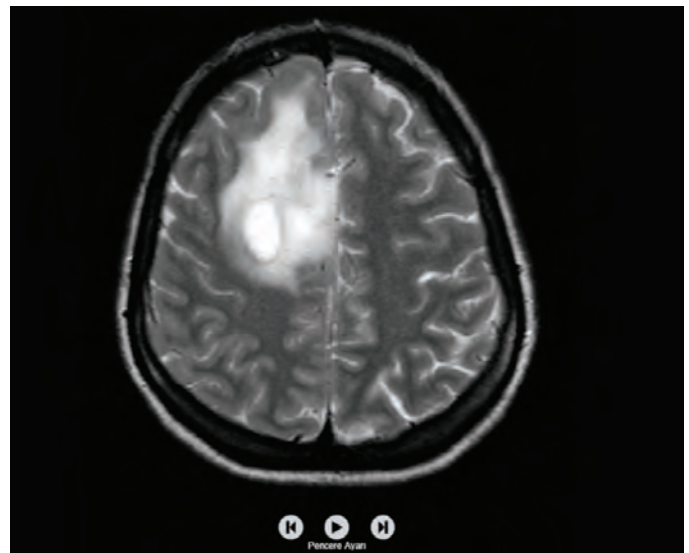
The cranial MRI evaluation revealed a mass lesion in the right frontal lobe parenchyma, within an area of parenchymal edema with margins that could not be differentiated from the edema (Figure 1, 2). The patient was evaluated as a frontal glial tumor and referred for brain surgery. The patient was operated on under elective conditions, was discharged without any sequelae, and was followed up by the brain surgeon.

## DISCUSSION

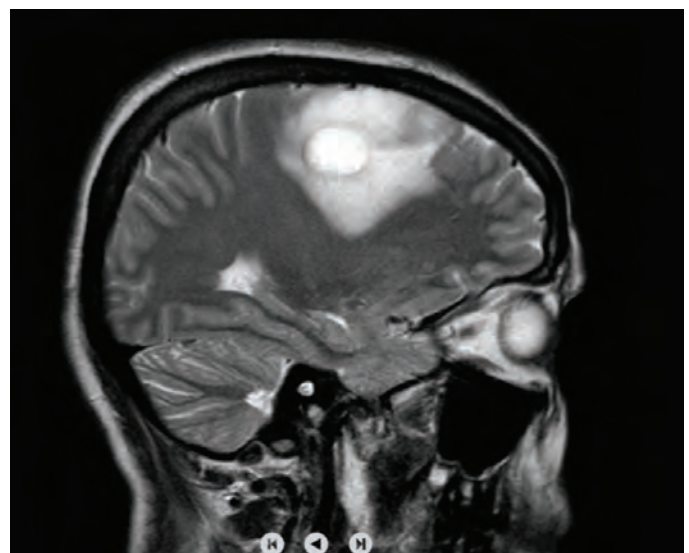
The patient was diagnosed with eclampsia, and as convulsions continued after the cesarean section delivery, an MRI was performed, which determined a frontal intracranial mass. This case report aimed to emphasize the importance of differential diagnosis.

In cases of eclampsia, without crisis and coma condition recovery, delivery of the infant is initiated as an intervention when the patient is hemodynamically stable. During the crisis and coma, findings of fetal distress are observed but are usually temporary.

The only treatment for uncontrolled preeclampsia is to terminate the pregnancy irrespective of the gestational week (9). Other causes of convulsions must be considered in the differential diagnosis (Table 1) (10). In the current case, an emergency cesarean section was performed as the fetal heart sounds decreased, fetal distress was observed, the mother developed respiratory arrest, and the definitive treatment for eclampsia is delivery of the infant (8).



**Figure 1.** Horizontal section brain MRI  
MRI: Magnetic resonance imaging



**Figure 2.** Sagittal section brain MRI  
MRI: Magnetic resonance imaging

**Table 1. Causes of seizures**

A. Primary (idiopathic)
B. Secondary (symptomatic)
1. Trauma
2. Tumors
3. Vascular events
a) Subarachnoid and intraparenchymal hemorrhage
b) Subdural and epidural hematoma
c) Stroke
d) Vasculitis
4. Infections
a) Meningitis
b) Encephalitis
c) Brain abscess
5. Metabolic
a) Hypoglycemia
b) Hyponatremia and hypocalcemia
c) Hypomagnesemia
d) Hepatic failure and uremia
6. Toxic
a) Cocaine and sympathomimetics
b) Tricyclic antidepressants
c) Anticholinergic drugs
d) Isoniazid
7. Eclampsia
8. Hypertensive encephalopathy

Brain MRI should be applied in patients who have undergone trauma, MgSO<sub>4</sub> treatment-resistant, and crisis development after the 24<sup>th</sup>-hour postpartum. The differential diagnosis is important. Seizures in patients with eclampsia are generally self-limiting in 60 s and occasionally last 3-4 mins. This period was longer in the current patient in the emergency department, and the development of respiratory arrest suggested a differential diagnosis. In the postoperative imaging of the current patient, an intracranial mass was determined, explaining the convulsions.

Due to the urgency and rapid deterioration of the general condition of the current patient, she was admitted immediately for surgery, but in cases that are not this severe, other reasons for convulsions should be determined. For treatable reasons, time should be allowed for better fetal development.

## CONCLUSION

The first was diagnosed as eclampsia for this pregnant patient with seizures; however, the nature of this case demonstrates the need to consider other reasons that may cause convulsions.

### Ethics

**Informed Consent:** Informed consent was obtained from the patient that it would be a case report.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

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

**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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