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VOLUME 34 • ISSUE 2 • MAY • 2021

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VOLUME 34 • ISSUE 2 • MAY • 2021

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State why the investigation was carried out, note any relevant published work, and delineate the objective of the investigation.

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ii. Walker M, Hull A. Preterm labor and birth. In: Taeusch HW, Ballard RA, eds. Avery's Diseases of the Newborn. Philadelphia: WB Saunders, 1998: 144,153.

iii. Hagström H, Nasr P, Ekstedt M, et al. Fibrosis stage but not NASH predicts mortality and time to development of severe liver disease in biopsy-proven NAFLD. J Hepatol 2017; 67: 1265-73. doi: 10.1016/j.jhep.2017.07.027.

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VOLUME 34 • ISSUE 2 • MAY • 2021

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Marmara Med J

MARMARA
MEDICAL JOURNAL

VOLUME 34 • ISSUE 2 • MAY • 2021

Contents

Review

Original Articles

VOLUME 34 • ISSUE 2 • MAY • 2021

MARMARA
MEDICAL JOURNAL

Review Article

https://dergipark.org.tr/tr/pub/marumj

General characteristics of clinical trials for biosimilar drugs

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ABSTRACT

Biosimilar is a highly similar product to biological reference medicinal product. The development, licensing and clinical use of these products differ from the implementations of conventional drugs, which were shaped on the concept of equivalence, in various aspects. Negative attitudes towards generic drugs, many of which are thought to be based on lack of knowledge, are still substantial. There is concern that the problem may reach more critical levels in the use of biosimilars, which are known to be more complex compared to generics. Knowing the prominent critical aspects of the development process of the biosimilars may contribute to the solution of this problem that causes significant difficulties in practice.

In all conventional and biological products, the innovative drug research consist of the preclinical phase followed by the successive phases I-IV. The first three phases are carried out before the licensing. The clinical trials required for licensing of generics are limited to bioequivalence studies. However, in biosimilars, this process is more complex due to the nature of biological products. Adequate quality, clinical efficacy and safety data are needed on the basis of comparability of the biosimilar with the reference product. Phase I and III are generally required for biosimilarity, although it may vary per product. Although, these phases are perceived as classical phase studies, they differ considerably from those in the development process of reference drug in terms of design, purpose, content and flexibility. Approaches that do not pay attention to these details sufficiently might cause many problems such as the advantages of biosimilars being limited, ineffective implementation of risk management, loss of trust, delay in product supply, unfair competition, etc. The general characteristics of clinical trials and the details of the subject specifically for biosimilars are mentioned in this review article.

Keywords: Biosimilarity, Biological drug, Generic, Clinical trials

1. INTRODUCTION

Various professional individuals and organizations, primarily pharmaceutical industry and academic institutions, strive to discover newer and more convenient drugs, introduce them into clinical practice, and form alternative options for treatment, during drug research and development process. All medicinal products for human use, whether being isolated from natural resources or synthesized from chemical or biological materials, are subject to drug research and development processes, including preclinical and clinical trials. Screening and toxicity tests, pharmacodynamic and pharmacokinetic studies in laboratory animals, and other processes such as formulation and stability studies are referred as preclinical research. Candidate medicinal products which successfully completed these processes with sufficient data reach the stage to be tested in humans. Drug development studies conducted on humans within the framework of certain protocols are called **clinical trials**. A more comprehensive definition, which is also often used by health authorities and other related institutions, is "the studies conducted on humans to reveal or confirm clinical, pharmacological and other pharmacodynamic effects of investigational product(s), define their adverse events/reactions, detect absorption, distribution, metabolism and excretion parameters, and investigate their safety and efficacy" [1]. Although, its history is associated with various cases experienced Before Christ, it can be said that modern drug development processes started from the beginning of the 1900s. Since then, clinical trials have been rapidly shaped through some important medical events, developments, and the regulations introduced

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as a result of those. Nowadays, it continues to evolve in line with emerging needs and demands. Main characteristics of clinical trials were shaped in the light of past experiences and regulations, and those are valid in universal standards for all drugs. Research on critical products, such as biological drugs (biologics) and their biosimilars, has to include some additional characteristics [2-4]. Although, biologics and their biosimilars are increasingly used in medicine, there seems to be a serious confusion about these products, and their distinguishing features from conventional drugs are not well understood. Regarding choice of generic drugs, a widespread audience among healthcare professionals and patients have negative knowledge, attitudes and behaviours, which are mostly inappropriate [5-7]. Considering this is the case even for the more simply understood conventional drugs, it is concerning that the problem may be even greater for "similars" of biologics, which are known to be more complex [6,8,9]. Therefore, lack of knowledge, misinterpretations, and comments about the development process of biosimilars have negative effects not only on the researchers and the parties responsible for the approval/authorization processes of these products, but also on the approach of the various addressees of drug use [5,6]. Knowing the critical issues that emerge during development of these products might contribute to solve the problems encountered in practice. In this article, which is mainly focused on the details of clinical research on biosimilar drugs, the main characteristics of clinical trials of drugs are discussed first, in order to facilitate understanding of the subject and to better emphasize its different aspects. Afterwards, the details of the main topic were presented within the framework of the concepts, requirements and regulations specific to biosimilar clinical trials.

Main Characteristics of Clinical Trials

Drug development around the world is carried out with unprecedentedly high levels of harmonization and strict regulations regarding research and development. At every step of these process, local integration is of particular importance. The intensive intertwined process requires multinational collaborations subject to follow-up and control, and it is tried to be carried out rigorously. Clinical trials can be conducted with the approval of independent scientific ethics committees and with the permission of health authorities. All these stages require sufficient workforce, infrastructure facilities, a long period of time, and large amounts of economic resources. The clinical trial process for a newly innovated drug takes approximately 10 years until approval. Factors such as the new facilities offered by science, technology, and informatics, or the time pressure caused by extraordinary conditions for urgent product needs, such as in the COVID-19 pandemic, provide the basis for the shortening of the aforementioned time period as much as possible. Although the financial burden of research varies depending on the characteristics of the products, generally it is far beyond the easily affordable figures. In other areas of research involving biotechnology and advanced technology, this amount is suggested to reach much higher than that of small-molecule (conventional) drugs, even to the range of one to two billion US dollars [2-4]. Pharmaceutical clinical trials, in which the lucky one among tens of thousands of candidates is determined, are conducted according to strict scientific, technical, administrative and ethical rules, and consists of four successive clinical phases (Figure 1).

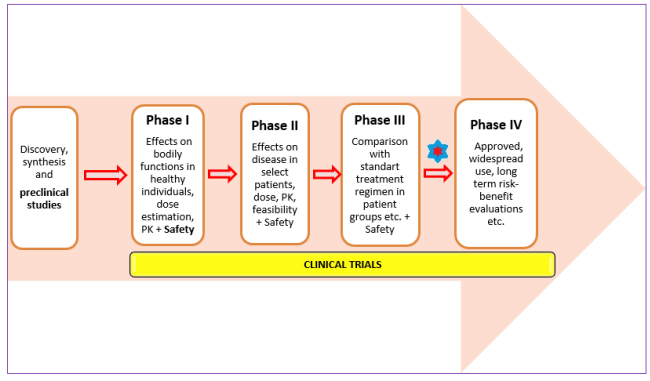

Figure 1. *Main characteristics of clinical trial phases*

Each of the clinical trial phases, which are carried out for different purposes, proceeds on the results of the previous one within the main framework. Most of the clinical trials are preferably designed as randomized and controlled, depending on the related phase. The first clinical trial phase following preclinical trials is **Phase I**. Considering the risks potentially involved, it is conducted in specific conditions and mostly in healthy volunteers (except for some cases that would be inappropriate for healthy individuals, which involve patients instead). Phase I aims to determine the preliminary pharmacokinetic properties in humans, pharmacological effects on systems, acute adverse effects, and the resistance of volunteer to the product. Generally, Phase I is carried out in small groups not exceeding 100 people, in specialized units unique to clinical trials, which are equipped for emergency intervention and approved by the related authorities. This stage is followed by **Phase II** studies, which is conducted on a limited number of patient volunteers (approximately 100-500 subjects) and could be regarded as some kind of feasibility studies. Therapeutic dose range, clinical efficacy, safety, pharmacokinetic properties in disease state, and clinical toxicity in that condition are the parameters investigated. After the drug candidate successfully completes Phase II, it goes into **Phase III**, that is conducted on a large number of patient volunteers (often in the thousands of patients), and mostly in multi-national and multi-center fashion, involving broad participation. In the light of the findings obtained from Phase III trials, the new drug license application for the drug candidate, which successfully completed the aforementioned critical stages, is submitted to the drug authority of the relevant country where the drug is planned to be marketed (e.g., European Medicines Agency [EMA] in Europe, Food and Drug Administration [FDA] in the United States of America [USA], Turkish Medicines and Medical Devices Agency [TMMDA] in Turkey). The common technical

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Marmara Med J 2021;34(2): 89-94

document (CTD) is used when presenting the information and documents containing preclinical and clinical trial data, along with comprehensive assessment of those. This document needs to be used upon applying to many of the drug authorities, such as that of Turkey, Europe, USA, and Japan. CTD is an internationally agreed format for the standardized submission of applications. This allows reviewing and evaluation to be more systematic [10]. The drug candidate whose application is approved by the authority becomes an "original drug". This new drug is also named as **reference drug**, as it is a medicinal product that has been licensed with complete dossier. After successfully completing this crucial stage and related other certification and authorization procedures, the product starts to be marketed on a shelf of a pharmacy as a proprietary medicine. Hence, this new drug is allowed to be marketed for the approved indication(s) and posology for the targeted patient audience. However, the licensing of the drug/being on the market does not end the clinical trial process, on the contrary, the research continues with new studies under the name of **Phase IV** clinical trials. Phase IV trials are vital in many aspects through the dynamic process of drugs. This phase provides access to many crucial information that could not be obtained in previous preclinical and clinical stages. Therefore, these post-marketing clinical trials play decisive roles in the maturation of the drug, its evolution, and its continued presence in the market. Phase IV trials and **observational drug research (pharmacoepidemiological studies)** which constitute a specific branch of those, in a way question and solidify the reasons for the existence of the drug in the market. Since, the time pressure which was present before licensing is over, the answers to the questions about the drug that could not be prioritized before are planned to be obtained via Phase IV clinical research data in various designs. In this way, important additional information based on evidence is presented to the parties concerned in usage and prescribing of the drug. Except for Phase IV, insurance is mandatory for every clinical trial phase, as well as bioavailability/bioequivalence studies [1-4]. Generics of conventional reference drugs begin to appear when their patent expires. It is assumed that the clinically important risks emerging from potential differences of generics from the reference might mainly originate from the production of the drug, the excipient added to the active substance, and the bioavailability of the product on the basis of the formulation. Owing to this approach, though not suitable for biologics, generics of conventional drugs have the chance to be marketed easily. For a generic drug application, some preclinical baseline data and bioequivalence studies (comparative bioavailability study) is sufficient to be presented to the health authority. If the application is approved, the product starts to be marketed rapidly, as a "generic drug". Standards on bioequivalence were started to be determined in the world around the 1990s, and concrete administrative regulations were quickly implemented. Turkey has necessitated conducting a bioequivalence study for these medicinal products in 1999. Bioequivalence means that "two pharmaceutically equivalent preparations are similar enough to ensure that their bioavailability and hence, their effects are essentially the same in both efficacy and safety after administration at the same molar dose" [1-4]. Both bioavailability/bioequivalence studies and Phase I clinical trials are conducted in healthcare institutions approved by the regulatory authority, with facilities suitable for emergency intervention and able to meet required standards for each type of study. As in Phase I, bioavailability/bioequivalence studies are carried out in a small number of healthy volunteers. The advantages such as inclusion of limited number of people, shorter duration (as long as the half-life of the drug allows), and well-known and modest designs, shorten the process of generic drugs entering into the market and significantly reduce the costs. This situation may present significant opportunities to reimbursement institutions, pharmaceutical industry, authorities, healthcare professionals, patients, and other parties in terms of competition between a reference drug and its generics [1,3,4].

Main Characteristics of Clinical Trials of Biosimilars

Biological medicinal product is a product which consists of a biological active substance. In more detail, it can be defined as "medicinal product whose active substance(s) are produced/purified from a biological source, and whose quality, production process and controls were demonstrated via physicochemical and biological tests" [11]. Clinical research and development process of these drugs are conducted similar to that of conventional drugs. With the patent expiration of a reference biological product, similars of those are developed, which are approved to be marketed only after presenting the obligatory trial data to the health authorities. **Biosimilar drug** is "a product which is shown to be similar to an approved reference biological product, in terms of physicochemical, in vitro and in vivo biological properties, as well as efficacy, safety and immunogenicity as shown in clinical trials". A more commonly used definition is "a product highly similar to an approved biological medicinal product" [11,12]. Biosimilars are not treated the same as conventional generic drugs, due to the large and complex structures of biological products, sensitive multi-step production phases, and their immunogenicity potential. Therefore, it is needed to put forth the similarities with the reference biological product in terms of quality, safety, and efficacy via comparability studies. In this way, satisfactory answers are sought for any uncertainty about residual differences between the reference drug and the biosimilar. Since bioequivalence studies are not sufficient to sort out these uncertainties, Phase I and – in select cases – Phase III trials are needed during development of biosimilars, differently from the conventional generics. Even though the primary structures of the reference biological product and the biosimilar are the same, distinct approaches through the production processes of separate manufacturers might lead to any differentiation of the secondary, tertiary and quaternary structures of the products. These potential differences and any related issues are the main reasons for the need for additional clinical trials. The trials need to be sufficiently sensitive in terms of design, method, endpoint and/or volunteer population, in order to detect potential differences between the products. The number and diversity of biotechnological drugs and their biosimilars, and consequently their utilization rates compared to conventional drugs, are consistently rising every year [11-19].

The clinical trial phases that biosimilars are subjected, and the clinical data obtained from them are of vital importance to answer questions on development in these drugs, competition between them, whether they provide benefits in terms of cost etc., their possible risks, and their place in clinical use.

The process leading to the registration of the reference biological drug and its biosimilar starts with the pharmaceutical quality studies of both products. In the reference biological drug, this is followed by preclinical studies, Phase I, II and III clinical trials, including analyses of "efficacy and safety, pharmacokinetics and pharmacodynamics, immunogenicity", and a risk management plan. In biosimilar drugs, the steps are Phase I and III clinical trials and risk management plan, respectively. The absence of the need for Phase II and the presence of comprehensive "comparative quality studies" are the main characteristics that distinguish the biosimilar research from the reference [1,4,9-11]. On the other hand, despite sharing the same name, Phase I and III clinical trials of biosimilars differ from the clinical trials of the reference in some aspects, especially in terms of the content. Clinical trials of biosimilar drugs aim to produce data that will contribute to the elimination of residual uncertainties between the reference and its biosimilar. Therefore, expectations from the clinical trial phases of these two products are not the same. Reference biological product trials focus on the production of unique clinical data for a novel product, whereas in biosimilar trials, the partial data production on potential microheterogeneity-related differences from reference drug is of concern [11,13]. Without sufficient attention to this critical detail of the content of the research, various demands that diverge from the true aim may be encountered in the process of biosimilar development. The burden of biosimilar clinical trials may increase unnecessarily and introducing these drugs to the market can become difficult.

Comparability data of biosimilars should be obtained using a product that has reached the point of clinical use and has passed the final production process. Pharmacokinetic studies form the basis of clinical comparisons between biosimilar and reference biological medicinal products [11-16]. Phase I clinical trials of biosimilars, unlike that of the reference drug, are not "regular dose estimation studies in which the active substance has been tested in humans for the first time". They generate pharmacokinetic and pharmacodynamic data comparable to the reference. These investigations are conducted by observing the appropriate sample size to meet the requirements of the pharmacokinetic and pharmacodynamic endpoints. These studies, which are generally designed as cross-over or parallel, are preferably carried out in healthy volunteers. In cases where there are risks that are difficult to tolerate in healthy volunteers, studies are carried out in patient volunteers. Another reason for patient volunteer preference is that the biosimilar product is, in some cases, a component of a standard combined treatment regimen. Phase I does not focus directly on efficacy. When the information and evidence on the mechanism of action are sufficiently clear and comprehensible, it can be concluded that a high level of similarity has been reached from a clinical point of view if these two conditions are met: (i) the pharmacokinetic and pharmacodynamic data of the biosimilar in question substantially support the clinical efficacy of the product and (ii) the immunogenicity profiles of the test product and the reference biologic are shown to be similar. In this context, assuming that residual uncertainties in biosimilarity are eliminated, Phase I clinical trials can be deemed sufficient, without requiring further Phase III trials [13-18].

Phase III clinical trials for biosimilars mainly provide efficacy and safety data. These trials are usually conducted as equivalence or non-inferiority studies. These types of studies are not interchangeable, and their results are interpreted quite differently from each other. Choosing the appropriate study type ensures that the hypothesis about the efficacy and safety of the drug is tested correctly and the clinical relevance of the results is accurately evaluated. After the applicant, who will conduct a clinical trial for a biosimilar, submits the planned clinical trial design to the health authority, taking appropriate action according to the consensus to be reached is highly decisive in the rational execution of the process. In the analyses done specifically for the endpoints in an **"equivalence trial"**, H0 hypothesis expresses that biosimilar candidate is "not similar", whereas the H1 hypothesis means that it is only **"similar"** (without presenting the argument whether the test product is better or worse than the reference regarding some features in common). While interpreting analyses of a **"non-inferiority trial"**, H0 hypothesis expresses that the tested product "is inferior/does not perform sufficiently", whereas the H1 hypothesis means that it is only **"not inferior and is sufficient to prove non-inferiority"** (but that does not provide any evidence concerning the superiority of test product to the reference drug). If there is valid scientific evidence and prediction that the test product will not be more effective than the reference biological product, non-inferiority studies may be preferred primarily in biosimilar clinical trials, considering the sampling advantage and similar aspects. However, interpretation of the results of these studies is difficult, and should be done carefully, taking any potential confounding into account. Apart from the equivalence and non-inferiority trials, there are also "superiority" studies, which are not used in trials of biosimilarity. As the name implies, it can be preferred in the examination of "biosuperior" products with superior efficacy and safety claims than the reference biological drug [11-19].

In phase III clinical trials, it is very important to accurately determine the primary and secondary endpoints. Conducting the trial within a sample large enough and in a suitable population in a randomized controlled manner by choosing the most appropriate study designs mentioned above is also of utmost importance. In this regard, biosimilar clinical trials, which provide comparable efficacy and safety data, are the main elements that guide and help solve problems such as the interchangeability of products, extrapolation, immunogenicity, pharmacovigilance applications and risk management accordingly. By conducting clinical trials within the framework of accurate predictions, the confidence in biosimilars increases and thus, the market entry process of these drugs becomes easier and their place in the market is solidified. For example, safety data obtained from pre-approval clinical trials are one of those

important details. Especially based on the signs of rare adverse effects, the clinical safety of biosimilar medicinal products, including the ongoing benefit-risk assessment, can be closely monitored following approval. Also, the existing concerns can be addressed or the risks in question can be managed correctly [5-7,11-15].

As with all medicinal products, it is not mandatory to conduct Phase IV clinical trials after registration for biosimilar drugs. Phase IV studies are planned and carried out in the normal course of life, taking the needs of the market into account. In some cases, the parties might plan new study designs earlier, which can be conducted following approval on specific issues that need further clarification (e.g., effects of the product in a large number of patients, or with some alternative treatment options) and make commitments/requests accordingly. Moreover, it might be planned to initiate new pharmacoepidemiological studies on some critical issues, especially those focused on safety. In addition, if pharmacoepidemiological studies are currently being conducted for the reference biological medicinal product, it might be encouraged to include biosimilar(s) in them [3,11,13].

The experience and knowledge gained in a quarter of a century about biological medicinal products, mostly in the last decade, has expanded the range of steps to be taken on biosimilars. In this respect, various flexible approaches and consensus between the parties can emerge more easily in the presence of sufficient scientific evidence on the clinical trial phase preference, design details and similar issues. These approaches, which in essence encourage opening the way for biosimilars, sometimes lead to different steps to be taken by the health authorities in different countries for the same drug. The situation of the medicinal product market, economic or infrastructural factors, other national requirements, different interpretation of the evidence etc. may play a role in that. In order to justify such differences in an indisputable manner, to make them universally consistent and valid, and to minimize confusion and problems that may arise, countries should have functional legislation, healthy communication environments and competent workforce on biosimilars. In addition, the close cooperation of the parties such as the authorities and manufacturers during the clinical research process is of key importance in solving the problems that may arise regarding biosimilars and paving the way for these products. In evaluations related to biosimilars, instead of focusing on a single clinical trial phase, a holistic understanding of the entire process and the related evidence is needed [5-7,12-16]. Moreover, it is necessary to avoid unfair, non-standard, non-transparent and shallow approaches, as those concern all stages of biosimilar clinical research and have the risks of adversely affecting both the national and international biosimilar market. In addition, problems of immunogenicity and pharmacovigilance should be made functional in a way that allows for discussion and improvement on scientific grounds, without turning them into a tool of unfair competition. It should be approached cautiously to avoid overstatements and making inferences without the support of appropriate evidence rooting from clinical trial data.

In Turkey, the "Guide on Biosimilar Medicinal Products" could still be regarded as a draft, despite the efforts to update the document in 2017 [11]. Rapidly eliminating this defect is of primary importance for the acceleration of clinical trials of biosimilar drugs and the success of the approval process of these products. In terms of market share, biosimilars follow a parallel trend to reference biologics in recent years, which make up almost one third of the total pharmaceutical market in the world [12,13,18]. In order to benefit as much as possible from the advantages offered by using biosimilars in health practice, Turkey is expected to improve their efforts, such as speeding up legal regulation changes, informing parties adequately and extending cooperation options.

Conclusion

In conclusion, biosimilar drugs will be more commonly encountered in clinical practice. The knowledge and experience gained so far on these drugs, mostly originated from clinical research, is significant. This experience allows further trials regarding new biosimilar drug candidates to be conducted in a flexible way through the context of universal acceptability criteria, rather than being limited by strict rules. It is necessary to adopt a rational approach at all stages of the biosimilar clinical research process, including planning, execution, and data evaluation. Therefore, countries are expected to constitute up-to-date and functional legislation, form transparent and strong communication between the parties such as the authorities and the industry, and proceed in the light of versatile and rigorous evaluations by actual experts. The reasons for conducting clinical trials with a product providing sufficient quality assurance should be determined correctly and the data should be obtained accordingly. The reasons for carrying out clinical trials to be conducted with the product providing sufficient quality assurance should be determined correctly, and the data should be obtained accordingly. To demonstrate the quality, efficacy, and safety of these drugs, it is necessary to stick with research and designs that will produce scientific data that will be at universally acceptable levels. In such matters, the parties are expected to convince each other before starting clinical trials. Clinical trials which produce data that do not meet even reasonable minimum expectations should be avoided. Likewise, approaches that would adversely affect the access to biosimilars should be avoided, including over-diversifying research with a defensive medicine approach, demanding convoluted designs, and excessive volunteer participation. In particular, pharmacoeconomic toxicity caused by irrational clinical research demands should be avoided. Approaches that consider these details could prevent unfair competition and loss of trust, provide effective risk management, bring biosimilars with patients in a timely manner, and enable the benefits of these drugs to be properly utilized.

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Revisiting the former approach: Low-dose dopamine in kidney transplant recipients

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ABSTRACT

Objective: We aim to evaluate the effects of low-dose dopamine (LDD) infusion (0.5 – 2.5 g/kg/min) on hemodynamic status and short-term graft function in kidney transplant recipients.

Materials and Methods: Patients who underwent kidney transplantation surgery between January 2007 and December 2016 were included in the study. Demographic and laboratory data, presence of delayed graft function, and the rates of rejection, graft loss, and mortality were recorded. The data were compared between patients with and without LDD treatment.

Results: A total of 126 patients were included in the study (M/F:50.8%/49.2%; mean age, 38.94 ± 11.8 years). Ninety-four patients (74.6%) received living-donor transplants. Fifty-seven patients underwent LDD infusion in the postoperative period (LDD group), while 69 patients did not receive LDD infusion. Demographic and laboratory data of the patients did not significantly differ between groups. Nineteen patients in the LDD group experienced delayed graft function (p=0.039). However, these patients tended to be older, have a longer dialysis period prior to transplantation, deceased and hypertensive donors. There was no significant difference in renal function at 6 months after transplantation between groups.

Conclusion: Although, LDD infusion increases kidney blood flow, we observed no significant effects on short-term graft function or patient survival between the LDD and non-LDD groups.

1. INTRODUCTION

Restoration of optimal blood flow is essential for achievement of proper graft function following appropriate surgical interventions and induction treatment. Although, intravenous hydration in the post-transplant period is regarded as the gold standard, the search continues for other methods or medications to increase renal blood flow in transplant recipients.

Dopamine is an endogenous catecholamine that exerts its effects through dopaminergic receptors. It affects the kidney via the dopamine agonist (DA1) receptor on the vascular smooth muscle of the kidney and the DA2 receptor in the presynaptic region. Activation of these receptors causes vasodilation, resulting in elevations in renal blood flow and glomerular filtration rate (GFR) [1]. The DA1 and DA2 receptors are also located on the proximal tubule, the thick ascending limb of the loop of Henle, and the collecting canal; dopamine inhibits Na/K-ATPase activity in these locations and contributes to the regulation of natriuresis and diuresis [2]. Furthermore, dopamine causes elevations in blood pressure, heart rate, and cardiac contractility through its actions on adrenergic receptors. The effects of dopamine are dose-dependent. Low-dose dopamine (LDD) is defined as treatment at a dose of 0.5 – 2.5 μg/kg/min; at this dose, the drug only affects dopaminergic (renal) receptors. Therefore, it is not expected to affect other receptors and cause systemic side effects. Because of the status of dopamine as a positive inotropic agent, treatment with LDD has been suggested to increase renal blood flow, while improving GFR and urine output.

Low-dose dopamine has been used in the treatment of acute kidney injury and for renoprotection during cardiovascular surgery in the past but the evidence failed to support this effect. Its well-known side effects like increase in blood pressure,

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heart rate, and cardiac contractility and lack of evidence for renoprotection, resulted in its widely abandonment [3, 4]. Furthermore, the use of dopamine has also been abandoned following renal transplantation mainly due to projecting evidence from cardiovascular surgery. Despite its proven ability to cause increased blood flow in the native kidney, there have been few studies regarding the effects of dopamine on denervated transplanted kidneys [3,5,6].

Low-dose dopamine treatment was used with an aim to increase renal blood flow early after renal transplantation at our institution until February 2013, but its use was abandoned due to accumulating evidence of lack of benefit for other indications mentioned above. The patients have been followed only with intravenous hydration applied as dictated by their volume status.

The present study was undertaken to retrospectively compare the historic cohort when LDD was used in the early postoperative period following kidney transplantation with the more recent cohort which only received intravenous hydration in the early postoperative period from early hemodynamic status and renal function perspective.

2. MATERIALS and METHODS

All patients older than 18 years of age who underwent renal transplantation between January 2007 and December 2016 were included in this study. Patients with primary non-functioning grafts and patients under 18 years of age were excluded. This study was approved by the institutional review board of Marmara University School of Medicine (approval number 09.2017.266).

Immunosuppressive drug regimens

In patients undergoing living donor kidney transplantation, calcineurin inhibitors and antimetabolites were initiated 2 days before surgery; patients with low immunological risk received basiliximab whereas anti-thymocyte globulin was used in patients undergoing deceased donor kidney transplantation and/or patients with high immunological risk for induction treatment. Calcineurin inhibitors and antimetabolites were initiated postoperatively in deceased donor kidney transplant recipients. All patients received 1 g of methylprednisolone at the time of anastomosis. Corticosteroid doses were tapered within 3 months postoperatively, and all patients were maintained on low-dose prednisolone.

Peri – and post-transplantation follow-up

A dedicated team performed all kidney transplantation procedures, using the standard anesthesia protocol. In the postoperative follow-up period, all patients received intravenous saline and 5% dextrose for hydration. We included consecutive patients who underwent kidney transplantation between 2007 and 2013 in the LDD group. Dopamine was started intravenously at a rate of 2 μg/kg/min during the operation and continued for the following 72 hours. Patients who underwent kidney transplantation between 2013 and 2016 did not receive LDD infusion, due to a change in protocol. The latter was the non-LDD group. All patients received intravenous hydration as described above. Demographics and clinical data were obtained retrospectively from the patients' files. Data regarding heart rate, blood pressure, plasma creatinine (Cr), blood urea nitrogen, hemoglobin, and diuresis were retrospectively collected for the study during the first week after transplantation for all patients. Any intraoperative inotropic agent administration was recorded. The presence of delayed graft function was recorded. Graft function was determined using GFR, as calculated by the Modification of Diet in Renal Disease formula ($175 \times (\text{Serum Cr})^{-1.154} \times (\text{Age})^{-0.203}$ ($\times 0.742$ if female) [7]; graft function and rejection rates were evaluated at 1, 3, and 6 months after transplantation. Mortality rate and graft loss data were also recorded. We compared the presence of delayed graft function, overall graft function, mortality, and graft loss between the LDD and non-LDD groups. Delayed graft function was defined as the need for one or more hemodialysis sessions after kidney transplantation [8] with < 70% reduction in the Cr level on post-transplant day 7, compared to the pretransplant level [9].

Statistical analysis

All data were analyzed using SPSS (version 22.0; IBM Corp., Armonk, NY, USA). Continuous descriptive variables are shown as means ± standard deviations for those that exhibited a normal distribution and as medians (minimums – maximums) for those that did not exhibit a normal distribution. The *t* test or Mann–Whitney U test was used for comparisons of continuous variables between the groups. The χ^2 test was used for comparisons of categorical variables. In all analyses, $p< 0.05$ was considered to indicate statistical significance. Use of dopamine and other risk factors for the study endpoints (i.e., delayed graft function, graft loss at 6 months, mortality, and GFR values at 6 months) were analyzed by Cox regression analysis.

3. RESULTS

The study population consisted of 126 renal transplant patients (64 men [50.8%] and 62 women [49.2%]) with a mean age of 38.94 ± 11.8 (range, 18 – 67) years. The most common primary renal disease was glomerulonephritis (32 patients, 25.4%) while primary renal disease was unknown in 36 (28.6%) patients. Twelve patients (9.5%) had undergone preemptive transplantation, 91 patients (72.2%) had received hemodialysis, and 23 patients (18.3%) had received peritoneal dialysis treatment prior to transplantation. The mean duration of renal replacement therapy was 40.91 ± 48.32 (range, 1 – 216) months. Ninety-four patients (74.6%) underwent living donor transplantation; 32 patients (25.4%) underwent deceased donor transplantation. The mean age of the donors was 44.24 ± 11.67 (range, 7 – 65) years. Sixty-five donors (57.5%) were women. Nine donors had a history of hypertension.

In total, 31 (24.6%) patients had delayed renal function. Two patients had graft loss; one patient with a functioning graft died due to sepsis 5 months after transplantation. Fifty-seven patients (45.2%) received LDD infusion for 72 hours postoperatively. Sixty-nine patients received only intravenous hydration without LDD after surgery. Of the twenty-three patients (18.3%) who required intraoperative vasopressors, one was (1.7%) in the

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LDD group (noradrenaline) while the remaining 22 patients (31.8%) were in the non-LDD group.

There were no significant differences in sex, age, or etiology between the patient groups. Demographic and clinical data of patients in both groups are summarized in Table I. A summary of the laboratory and clinical findings of the patients during the postoperative follow-up period is shown in Table II. While there were no significant differences in changes in Cr level between the two patient groups, urine output was significantly higher in the non-LDD group on the first day postoperatively. The urine output levels at 6 months were found to be correlated in both groups with Cr levels at 1 day, 1 week, 1 month, and 3 months postoperatively ($r = 0.322$, $p < 0.001$; $r = 0.776$, $p < 0.001$; $r = 0.868$, $p < 0.001$, respectively).

Table I. *Comparison of demographic data of patients with and without LDD*

	LDD patients (n= 57)	non-LDD patients (n=69)	p value
Sex (M/F)	27/30	37/32	0.59
Age (years)	40.82 + 12.3	37.38 + 11.3	0.106
Primary diseases			0.054
Unknown	16 (28.1%)	20 (29%)	
GN	12 (21.1%)	20 (29%)	
HT	13 (22.8%)	8 (11.6%)	
Polycystic Kidney Disease	4 (7%)	5 (7.3%)	
DM	2 (3.5%)	7 (10.2%)	
VUR	6 (10.5%)	5 (7.3%)	
Amyloidosis	2 (3.5%)	3 (4.3%)	
Pyelonephritis	2 (3.5%)	4 (5.7%)	
Chronic Interstitial Nephritis	0	2 (2.8%)	
Renal Replacement Therapy			0.31
Hemodialysis	37 (65%)	54 (78.3%)	
Peritoneum Dialysis	16 (28%)	7 (10.2%)	
Preemptive	4 (7%)	8 (11.5%)	
Duration of Renal Replacement Therapy (month)	50.91 + 42.7	32.23 + 51.3	0.36
Transplant Type			
Living	36 (63.2%)	58 (84%)	0.013
Deceased	21 (36.8%)	11 (16%)	
Donor Age (year)	42.69	45.03	0.33
Donor Sex (M/F)*	21/23	27/42	0.43
Donor HT	1 (1.7%)	8 (11.5%)	0.15

LDD: Low Dose Dopamine, GN: Glomerulonephritis, HT: Hypertension, DM: Diabetes Mellitus, VUR: Vesicoureteral Reflux.

Delayed renal function was observed in 19 (33.3%) patients in the LDD group and 12 patients (17.3%) in the non-LDD group ($p = 0.039$). Long-term renal replacement therapy, recipient age, deceased donor transplantation, and donor hypertension values were significantly different between patients with and without delayed graft function (Table III). Regression analysis showed that LDD infusion did not influence factors associated with delayed graft function.

While 36 patients (63.1%) in the LDD group had GFR > 60 ml/min at 6 months postoperatively, 38 patients (55.1%) in the non-LDD group had GFR > 60 ml/min at 6 months postoperatively ($p = 0.37$). There was no significant difference between the two groups in terms of renal function at 6 months (Table II).

Table II. *Comparison of laboratory and clinical follow-up data of patients with and without LDD*

	LDD patients (n= 57)	non-LDD patients (n=69)	p value
Preop Hgb (g/L)	11.34 + 1.60	11.24 + 1.66	0.74
Preop Alb (g/L)	4.15 + 0.57	4.12 + 0.61	0.74
1st day Cr (mg/dL)	5.97 + 2.77	4.89 + 2.1	0.22
1st week Cr (mg/dL)	2.59 + 2.46	1.84 + 1.5	0.35
1st month Cr (mg/dL)	1.43 + 1.6	1.31 + 0.56	0.55
3rd month Cr (mg/dL)	1.18 + 0.7	1.27 + 0.43	0.34
6th month Cr (mg/dL)	1.23 + 0.6	1.3 + 0.7	0.54
Postop 1st day input fluid (mL)	3798 + 1735	3932 + 1315	0.73
Postop 1st day output fluid (mL)	2465 + 1603	3779 + 1794	0.006
1st day mean SBP (mmHg)	141.31 + 14.3	133.45 + 19.5	0.12
1st day mean DBP (mmHg)	81.84 + 8.8	81.94 + 11.8	0.97
1st day mean pulse (minute)	91.43 + 15.7	88.95 + 11.6	0.47
Postop 7th day input fluid (mL)	3420 + 1463	3700 + 1240	0,43
Postop 7th day output fluid (mL)	3147 + 1787	3861 + 1385	0.81
7th day mean SBP (mmHg)	145.66 + 12.4	141.92 + 15.5	0.38
7th day mean DBP (mmHg)	87.82 + 8.9	88.08 + 10.1	0.93
7th day mean pulse (minute)	88.92 + 8.6	92.87 + 11.5	0.21
Weight (kg)	64.67 + 13.6	67.01 + 14.5	0.42
Surgical Complications	7 (12.2%)	5 (7.2%)	0.47
Rejection	3 (5.2%)	11 (16%)	0.86
Delayed Renal Function	19 (33.3%)	12 (17.3%)	0.039
6th month GFR >60 ml/min	36 (63.1%)	38 (55.1 %)	0.37

LDD: Low Dose Dopamine, Hgb: Hemoglobin, Alb: Albumin, Cr: Creatinine, SBP: Systolic Blood Pressure, DBP: Diastolic Bloood Pressure, GFR: Glomerular Filtration Rate

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Table III. *Factors affecting delayed graft function*

	Delayed Graft Function (n=31)	Non-Delayed Graft Function (n=95)	p value
Receiving LDD	19 (61.2%)	38(40%)	0.06
Living/deceased transplantation	15/16	79/16	<0.001
Age (year)	44.8 + 10.9	37.01 + 11.6	<0.001
Sex (M/F)	17/14	47/48	0.681
DM (n)	3 (33.3%)	6 (66.7)	0.688
Donor HT (n)	6 (66.7%)	3 (33.3%)	<0.001
Donor age (year)	48.6 + 15.7	43.2 + 10.4	0.06
Donor sex (M/F)	10/10	38/55	0.466
Renal replacement treatment duration (month)	58.2 + 52.4	34.7 + 45.3	0.022

LDD: Low Dose Dopamine, DM: Diabetes Mellitus, HT: Hypertension,

4. DISCUSSION

Postoperative LDD infusion therapy was frequently used in patients undergoing renal transplantation at the beginning of the last decade. The initial aim of this treatment was to increase renal blood flow by vasodilation and improve GFR. In this study, we found that LDD was associated with the presence of delayed graft function, overall graft function, mortality, and graft loss. Indeed, Doppler ultrasonography studies of renal vasculature showed administration of 2.5 mg/kg/min of dopamine resulted in increased peak systolic velocity in the arcuate arterioles and reduced the resistive index [10,11]. Calculation of renal blood flow was useful for determining these effects of dopamine on the kidney. However, there have been no parameters to measure the effects of LDD in denervated tissue, such as transplanted kidneys. Thus far, few studies have investigated the effects of dopamine on the blood flow of transplanted kidneys. Dalton et al., evaluated renal blood flow in 20 transplant patients and found no significant differences between patients receiving 3 µg/kg/min LDD and the non-LDD group (importantly, renal blood flow calculation was based on para-aminohippuric acid clearance) [5]. In another study, Spicer et al., used Doppler ultrasound to evaluate renal blood flow in patients who received 2.5 µg/kg/min LDD infusion; renal blood flow was found to be similar in patients with and without LDD treatment [6]. Thus far, no clinical studies have shown positive efficacy of LDD in improving renal function [3, 5, 12-14]. In the present study, in accordance with the findings of previous investigations, there was no significant difference in GFR at 6 months postoperatively (based on Cr values) between patients in the LDD and non-LDD groups in the kidney transplant population.

A significant clinical indicator of improvement in renal blood flow and Cr clearance of LDD is elevated urine output. One study showed that patients who received LDD for 4 days had higher urine output, compared to patients who did not receive LDD [14]. Flancbaum et al., also reported a significant increase in urine output in patients who received LDD, but found no difference in urinary sodium excretion between the two groups [15]. Hosseinzadeh et al., reported the time to initiate diuresis earlier in the LDD group in unrelated renal transplant patients [16]. In these studies, administration of LDD led to elevated urine output, but did not affect Cr clearance. In the present study, there were no significant differences between the LDD and non-LDD groups in urine output and Cr levels during the 7-day postoperative period. In the total patient population, patients with lower Cr levels at 6 months postoperatively had higher urine output in the immediate postoperative period. This may be a result of good hydration in the postoperative period, rather than an effect of LDD.

Delayed graft function, whether transplantation is performed from a living or deceased donor, is an important condition that increases short and long-term morbidity and mortality as well as decreasing graft survival [17]. Risk factors for delayed graft function are deceased donor, donor characteristics (e.g., donor hypertension, elderly donor, marginal donor, and high donor Cr), long cold ischemia time, and body mass index [18]. Delayed graft function constitutes acute kidney injury due to ischemia of the kidney, independent of the risk factor. LDD directly affects kidney hemodynamics [19]. LDD has been presumed to protect patients from ischemia by exploiting its vasodilating effects in the kidney. Therefore, LDD administration was expected to reduce the risk of delayed graft function development. However, in the present study, the rate of delayed graft function was greater in the LDD group than in the non-LDD group. However, patient age, number of patients with a deceased donor, the presence of hypertension in the donor, and the durations of renal replacement treatment were significantly different between the groups. Therefore, LDD may not be the direct cause of delayed graft function. The difference in rates of delayed graft function between the LDD and non-LDD groups can be explained by the higher rate of deceased donor transplantation in the LDD group. Further studies in larger cohorts are required to confirm this finding.

Another factor that affects graft survival in renal transplant patients is the frequency of acute rejection. Several studies have been conducted to investigate the association of peri-transplant dopamine administration with rejection; notably, factors impairing renal blood flow (e.g., deceased donor transplantation and prolonged ischemia time) were associated with acute rejection. Grundmann et al., reported that the number of patients who developed rejection within 1 week was significantly higher in the LDD group, whereas the number of patients who experienced rejection within 3 weeks was similar between LDD and non-LDD groups [14]. In another study, the rejection rates at 28 days post-transplantation were similar between patients with and without LDD [3]. Dönmez et al., reported no difference in rejection attacks between patients with and without LDD [13]. In the present study, consistent with previously reported findings, the rejection rates were similar in the LDD and non-LDD groups.

The side effects of postoperative vasopressor use in patients include tachycardia, arrhythmia, increased cardiac backload, increased myocardial oxygen demand, intestinal ischemia, electrolyte disturbance, and vasoconstriction of the extremities

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[19]. With respect to the side effect profile of dopamine use, one study showed a greater incidence of tachycardia (pulse > 100) in the group receiving LDD [14]; no significant differences in blood pressure or pulse values related to LDD use were observed in other studies [5,6,16]. In the present study, there were no significant differences in 7-day postoperative blood pressure and pulse follow-up between the LDD and non-LDD groups. Therefore, we concluded that early post-transplant vasopressor use did not cause any serious side effects in our study.

Although, the present study included a sufficient number of patients to demonstrate the positive or negative effects of LDD, it also had some limitations. The most important limitation was its retrospective design. In addition, because of the risk of infection, central venous catheters were not placed in all patients, and fluid balances were monitored by measurements of the amounts of fluid that each patient received and excreted. Some invasive or noninvasive tests (e.g., renal Doppler ultrasound, central venous catheterization, arterial pressure monitoring, urine Na excretion, and/or Cr clearance) are necessary to accurately determine the volume assessment and renal blood flow of kidney transplant recipients. However, it is more appropriate to evaluate the parameters used in daily practice, to ensure that the results reflect clinical practice. Additional limitations included lack of data regarding cold ischemia time and HLA mismatch number.

The abandonment of LDD in renal transplantation has been largely based on evidence from studies on its effect in acute kidney injury. In our study, we demonstrated that the routine administration of LDD did not provide any additional benefit with regard to increasing graft survival in kidney transplant recipients compared to those not receiving LDD. In our clinic, the use of LDD was discontinued in early 2013. Consistent with the findings of previous studies, our results confirmed that perioperative LDD infusion did not provide additional benefit in patients who underwent kidney transplantation. Nevertheless, dopamine remains a promising agent, because its administration in kidney donors has recently been reported to improve graft function [20]. Perhaps, based on the findings of future studies, giving dopamine infusion to the donor kidneys to improve graft function before transplant may become a routine procedure.

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Compliance with Ethical Standards

Ethical Approval: This study was approved by the Institutional Review Board of Marmara University, School of Medicine (approval number 09.2017.266). All patients provided written informed consent.

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Reliability and construct validity of the Turkish adaptation of the Assessment of Life Habits for children and adolescents with cerebral palsy

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ABSTRACT

Objectives: The Assessment of Life Habits (LIFE-H) is a well-known questionnaire used to evaluate participation. The aim of this study was to determine the reliability and validity of the Turkish version of the LIFE-H in children with Cerebral Palsy (CP).

Patients and Methods: The study included 450 children with CP between the ages of 2-18 years old. The internal consistency and test-retest reliability of the LIFE-H were calculated. The construct validity of the LIFE-H was determined with the Pediatric Evaluation of Disability Inventory (PEDI) domains and Pediatric Outcome Data Collection Instrument (PODCI) subscales.

Results: The mean age of the children was 8.37±5.13 years (42.4% female, 57.6% male). The internal consistency of the LIFE-H was determined to be acceptable for all categories (Cronbach alpha:0.794-0.999). The test-retest reliability values were found to be of good to excellent reliability (ICC:0.804-0.999). The correlation between the LIFE-H total scores, PODCI subscales and PEDI domains was determined as acceptable (rho between 0.538-0.894) except for the Pain/Comfort, Happiness subscales of the PODCI (rho:0.240 – 0.479).

Conclusions: It was determined that the Turkish LIFE-H had acceptable internal consistency, good test-retest reliability and satisfactory construct validity. Turkish LIFE-H is an appropriate tool to assess the participation of children and adolescents with CP.

Keywords: Cerebral palsy, Children, Participation, Reliability, Validity

1. INTRODUCTION

Participation is a multidimensional structure and means to be a part of life [1]. The International Classification of Functioning, Disability and Health-Children and Youth (ICF-CY), suggests a multidimensional assessment that includes body functions, activity, participation, personal and environmental factors for children up to 18 years of age [2].The participation in daily life of children involves going to the playground, playing with friends and sharing with friends and other people. By doing so children learn new skills, improve their abilities and develop their sense of personal identity [3, 4]. Preschool children frequently play both indoors and outdoors, while school-age children and adolescents communicate with their peers at school and social settings [3].

Cerebral palsy (CP) is a chronic picture that creates impairment and activity restriction in body structures and functions such as muscle tone disorder, joint contracture and cognitive and emotional changes [5]. In general, children with CP demonstrate lower participation levels compared their typically developing peers [6]. Over the past two decades, participation in daily life has begun to attract more and more attention as an outcome of rehabilitation of children with CP [7]. Considering the ICF framework, the main purpose of therapeutic intervention in children with CP is meaningful participation in daily life [8].

According to the Turkish Statistical Institute, in 2019 the number of live-born infants in Turkey was 1 million 183 thousand 652 [9]. Accordingly, the prevalence of CP in Turkey is 0.4%,

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with approximately 4,700 babies considered to be at risk of CP every year [10]. Despite the large population of children with CP there is no scale in the Turkish language that evaluates the participation of such children.

As explained above participation is a complex phenomenon, thus, it is important to better understand how personal, environmental and family factors affect the participation of children in daily activities [11]. Within this context, participation in daily life must be evaluated accurately and in detail. The Assessment of Life Habits (LIFE-H) is a valid and reliable questionnaire that has been widely used in the literature to evaluate participation in daily life [12]. It was created according to the Disability Creation Process model, the intention of which is to predict the risk of personal and environmental factors affecting participation in life or handicap experience [12]. The LIFE-H was originally created in English and French, and studies for the translation of the questionnaire into different languages continue today [12]. The present study primary aimed to examine the reliability and validity of the Turkish version of the LIFE-H children and adolescents of three different age groups (0-4 years, 5-13 years and general) with CP and secondary was to encourage to use it and focus on participation profile for Turkish children and adolescents with CP.

2. PATIENTS and METHODS

The required permits and approvals were obtained from the Ankara Provincial Directorate of National Education and the Non-Interventional Clinical Research Ethics Committee of Hacettepe University for the study (Permit No: GO 14/451-11). The study was registered in the Clinical Trials.gov system under the number NCT03195335. The families who accepted to participate were informed about the study and their written consent was obtained. The data were collected between September 2017 and January 2019.

In this methodological study, 450 children with CP and their parents residing in Ankara city and its districts participated. The participants were determined with the convenience sampling method. Evaluations were carried out on the children who applied to the Hacettepe University, Cerebral Palsy and Pediatric Rehabilitation Unit and those in the special education and rehabilitation centers in Ankara City.

The inclusion criteria of this study were as follows: (1) being diagnosed with CP, (2) being between the ages of 2-18 years old, (3) having parents capable of reading and writing in the Turkish language and (4) voluntarily consenting to participate in the study. Information regarding the age and sex of the children and adolescents with CP were recorded. The individuals with missing data in the evaluation form were excluded from the study.

The Gross Motor Function Classification System (GMFCS) [13, 14] was used to classify the gross motor function levels of the children, the Manual Ability Classification System (MACS) [15, 16] for the manual abilities, the Communication Function Classification System (CFCS) [17] for the communication abilities and the Eating and Drinking Ability Classification System (EDACS) [18] for the eating and drinking abilities. All these functional classifications were used for description of cases and sustained from family report.

LIFE-H

The LIFE-H has three different forms for different age groups: 0-4 years, 5-13 years and general (teenagers, adults and seniors). In this study all three forms were used. The general form was used for the children aged between 14-18 years old. The LIFE-H consists of 12 categories, namely nutrition, fitness, personal care, communication, housing, mobility, responsibilities, interpersonal relationships, community life, education, employment and recreation. The number of questions related to the categories varies according to the form of each age group. Detailed information is given in Appendix I. The questions are scored on a 9-point Likert scale. Scoring is performed by considering both the difficulty level of the skill (no difficulty/some difficulty) and the type of support (no assistance/with technical aid or adaptation/with human assistance) [19, 20]. The weighted scores are calculated for the LIFE-H scores. The highest score that can be obtained in total LIFE-H score or from each category is 10, while the lowest score is zero (0). Higher scores mean better participation in daily life. Detailed information on the scoring of the LIFE-H questions is provided in Appendix II. LIFE-H can be used as a patient report in patients with sufficient cognitive function. As well, it can be used as a parent report. In our study, parents of the children with CP completed the questionnaire. The scale was applied to face-to-face interview to the parents by physiotherapists.

Scores can be calculated for each category of LIFE-H. In addition, the Activities of Regular Living Total Score, which is the average of the first six categories; the Social Roles Total Score, which is the average of the last six categories and the LIFE-H Total Score, which is the average of all categories, can also be calculated [20-23].

In this study, the LIFE-H was translated into Turkish. To do so, the necessary permission was obtained from the International Network on the Disability Creation Process. Two translations were carried out from English into Turkish by two physiotherapists experienced in pediatric rehabilitation. After completion, the two translations were compared and combined. The obtained Turkish questionnaire was examined by an expert in Turkish language. It was then translated back into English by a translator who was not familiar with the subject of study. The back translated questionnaire was compared with the original [24]. For cultural adaptation, the questionnaire was presented to the families of the children with CP. Any item of the scale has not been changed. The questionnaire was evaluated in terms of grammar and its suitability to the Turkish culture by five physiotherapists and a pediatric neurologist specializing in CP for social acceptance. In order to define the reliability of the LIFE-H, a re-test was carried out 15 days after the initial evaluation.

The Pediatric Outcome Data Collection Instrument (PODCI) and Pediatric Evaluation of Disability Inventory (PEDI) were used to determine the construct validity of the LIFE-H.

Pediatric Outcome Data Collection Instrument

Pediatric Outcome Data Collection Instrument is used to determine the functional health status and health-related quality of life of children and adolescents. In this study, the Turkish version of PODCI, the validity and reliability of which have been proven, was applied to the children with CP [25, 26]. PODCI is comprised of five subscales: Upper Extremity and Physical Function, Transfer and Basic Mobility, Pain/Comfort, Happiness, Sports and Physical Functioning, and Global Functioning. The scores of PODCI are calculated separately for each subscale and range from 0-100 points. Higher scores represent better health [25].

Pediatric Evaluation of Disability Inventory

Pediatric Evaluation of Disability Inventory is a comprehensive clinical assessment tool that evaluates the functional ability and performance of children with disabilities. In this study, the Turkish version of PEDI, the validity and reliability of which have been proven, was applied to the children with CP [27, 28]. PEDI has three main subscales, namely functional skills, caregivers' assistance and modification. In this study, functional skills and caregivers assistance subscales were used due to the fact that the LIFE-H has similar content. The functional skills subscale measures the functional abilities of the children and consists of 197 items comprised of self-care (73 items), mobility (59 items) and social function (65 items) domains. In functional skills subscale children are scored as unable (0) or capable (1). Higher scores mean better functional ability and performance. The caregivers' assistance subscale measures the disability of the children according to the amount of help they require to perform functional activities and is comprised of self-care (8 items), mobility (7 items) and social functions (5 items) domains. The caregivers' assistance subscale is scored between '0 = totally dependent' to '5 = independent'. High scores mean that activities can be carried out independently.

Figure 1 presents the activity-participation and life habits covered by LIFE-H, PEDI and PODCI.

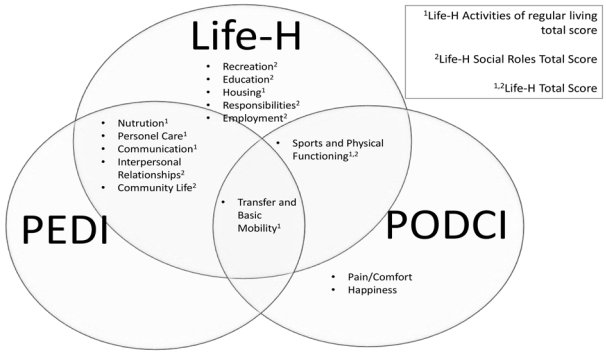

***Figure 1**. Areas covered by LIFE-H, PEDI and PODCI scales.*

Statistical Analysis

SPSS (IBM SPSS Statistics for Windows, Version 23.0. IBM Corp. Armonk, NY, USA) package program was applied for the data analysis. Mean and standard deviation were used as the descriptive statistics for the quantitative data. A p value of less than 0.05 was considered to indicate a statistically significant difference.

The internal consistency of the LIFE-H was calculated by using Cronbach's alpha, which was considered acceptable at ≥ 0.70 [29, 30].The intraclass correlation coefficient (ICC) was applied to examine the test-retest reliability. ICC values less than 0.5 were interpreted as weak reliability, those between 0.5-0.75 as moderate reliability, those between 0.75-0.9 as good reliability, greater than 0.90 as excellent reliability [31].

The construct validity was determined with the relation between the LIFE-H total scores and the PODCI subscales and PEDI dimensions using the Spearman's rho correlation coefficient. In addition, the correlations between LIFE-H total scores and functional classification systems were examined. Spearman rho values between 0.10 and 0.29 were interpreted as weak correlation, those between 0.30–0.49 as moderate correlation, those greater than 0.50 as high correlation [32].

3. RESULTS

A total of 450 children (42.4% girls, 57.6% boys) with CP and their parents participated in this study. The average age of the children was 8.37±5.13 years. The flow diagram of the participants is given in Figure 2. Information concerning the clinical type, extremity distribution, and function classification levels are presented in Table I.

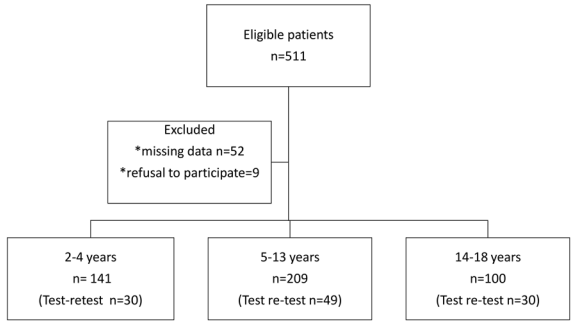

***Figure 2.** Flow Diagram*

Reliability

The internal consistency of the LIFE-H form for all the age groups was determined to be acceptable for all categories (Cronbach alpha: 0.794-0.999). The test-retest reliability of the LIFE-H according to the ICC values was found to be good for the fitness (ICC=0.879), communication (ICC=0.858), mobility (ICC=0.804), responsibility (ICC=0.883) and interpersonal relationships (IC=0.872) categories and excellent for the other categories (ICC=0.904-0.999) for 0-4 age form. ICC values were

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Marmara Med J 2021;34(2): 101-111

determined to be good for the interpersonal relations (ICC=0.817) category and excellent for the other categories (ICC=0.912-0.894) for 5-13 ages form. It was determined that all categories in general form showed excellent reliability (ICC=0.911-0.998).The internal consistency coefficients for the LIFE-H categories are presented in Table II and the test-retest reliability of the LIFE-H categories and total scores are given in Table III.

Construct validity

For 0-4 ages form a medium to high correlation (r=0.791-0.369) was observed between the LIFE-H total scores and PODCI subscales. The best relationship was observed between the LIFE-H Activities of Regular Living total score and the PODCI Transfer and Basic Mobility (r= 0.791). A high correlation (r=0.838-0.674) was determined between the LIFE-H total scores and PEDI domains. The best relationship was observed between the PEDI caregiver's assistance Mobility and LIFE-H Activities of Regular Living total score (r= 0.838).

Significant correlations for 5-13 age group form, varying from high to moderate, were discovered between the LIFE-H total scores and PODCI subscales (r= 0.894-0.374). When the relationships between the LIFE-H total scores and PEDI domains were analyzed it was determined that there was a high relationship between all domains (r=0.863-0.739). The most substantial relationship was observed between the caregiver assistance-mobility domain of the PEDI and the LIFE-H total score (r= 0.863).

General form a high-low correlation (r= 0.240-0.850) was observed between the LIFE-H total scores and PODCI subscales. The highest relationship was observed between the LIFE-H Activities of Regular Living total score and the transfer and basic mobility subscale of PODCI (r= 0.850). When the relationship between the LIFE-H total scores and PEDI domains were analyzed it was determined that there was a high correlation (r= 0.871-0.683). The construct validity of the LIFE-H with the PODCI subscales and PEDI domains are presented in Table IV.

There were high negative correlations of the LIFE-H total scores with the functional classification systems. All of the LIFE-H total scores showed the highest correlations with GMFCS level. As the GMFCS level worsens, participation in daily life decreases for all age groups. That was similar for the other classification systems. Correlations between the LIFE-H total scores with the functional classification systems are presented in Table V.

Table I. *Socio-demographic information and functional classification levels of participants*

Characteristics			Age Groups					
			0-4 years form		5-13 years form		General form	
			Number	%	Number	%	Number	%
Gender	Female		50	35.46	95	45.45	46	54.00
	Male		91	65.53	114	54.54	54	46.00
Clinical Type	Spastic	Hemiparesis	33	23.40	40	19.13	29	29.00
		Diparesis	30	21.27	64	30.62	18	18.00
		Quadriparesis	31	21.98	55	26.31	31	31.00
	Dyskinetic		25	17.73	29	13.87	13	13.00
	Ataxic		3	2.12	8	3.82	9	9.00
	Hypotonic		17	12.05	3	1.43	-	-
GMFCS	Level I		28	19.85	45	21.53	17	17.00
	Level II		31	21.98	42	20.09	31	31.00
	Level III		24	17.02	43	20.57	13	13.00
	Level IV		29	20.56	44	21.05	30	30.00
	Level V		29	20.56	35	16.74	9	9.00
MACS	Level I		40	28.36	65	31.10	23	23.00
	Level II		40	28.36	59	28.22	31	31.00
	Level III		21	14.89	36	17.22	24	24.00
	Level IV		15	10.63	16	7.65	15	15.00
	Level V		25	17.73	33	15.78	7	7.00
CFCS	Level I		61	43.26	118	56.45	62	62.00
	Level II		26	18.43	23	11.00	11	11.00
	Level III		19	13.47	21	10.04	18	18.00
	Level IV		17	12.05	26	12.44	6	6.00
	Level V		18	12.76	21	10.04	3	3.00
EDACS	Level I		92	65.24	141	67.46	78	78.00
	Level II		7	4.96	22	10.52	12	12.00
	Level III		25	17.73	24	11.48	6	6.00
	Level IV		8	5.67	7	3.34	2	2.00
	Level V		9	6.38	15	7.17	2	2.00

GMFCS: Gross Motor Function Classification System, MACS: Manual Ability Classification System, CFCS: Communication Function Classification System EDACS: Eating and Drinking Ability Classification System

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Marmara Med J 2021;34(2): 101-111

Table II. *Internal Consistency (Cronbach's alpha) coefficients for LIFE-H categories*

LIFE-H categories and total scores	Cronbach alpha		
	0-4 years form	5-13 years form	General form
Activities of Regular Living Total	0-990	0.986	0.992
Nutrition	0.969	0.924	0.911
Fitness	0.794	0.888	0.917
Personal Care	0.972	0.975	0.991
Communication	0.967	0.981	0.985
Housing	0.977	0.975	0.970
Mobility	0.873	0.957	0.960
Social Roles Total	0.973	0.985	0.987
Responsibility	0.894	0.933	0.944
Interpersonal Relationships	0.932	0.958	0.882
Community Life	NA	0.911	0.988
Education	0.999	0.972	0.993
Employment	NA	NA	0.952
Recreation	0.975	0.989	0.992
LIFE-H Total	0.992	0.993	0.994

NA: Values are not calculated because there is one question in Community Life category in the 0-4 age form, there are no questions in Employment category in the 0-4 age form, there are one question in Employment category in the 5-13 age form.

Table III. *Test-retest reliability of LIFE-H categories and total scores*

LIFE-H categories and total scores	0-4 years form		5-13 years form		General Form	
	ICC	95%CI	ICC	95%CI	ICC	95%CI
Activities of regular living total score	0.962	0.919-0.982	0.983	0.969-0.990	0.989	0.977-0.995
Nutrition	0.917	0.825-0.960	0.984	0.971-0.991	0.970	0.936-0.986
Fitness	0.879	0.746-0.942	0.970	0.946-0.983	0.947	0.888-0.975
Personal Care	0.939	0.871-0.972	0.962	0.931-0.979	0.978	0.953-0.989
Communication	0.858	0.689-0.935	0.947	0.902-0.971	0.976	0.950-0.989
Housing	0.947	0.888-0.975	0.953	0.915-0.974	0.998	0.995-0.999
Mobility	0.804	0.576-0.909	0.946	0.901-0.971	0.919	0.828-0.962
Social Roles Total Score	0.935	0.864-0.969	0.928	0.872-0.960	0.969	0.935-0.985
Responsibility	0.883	0.748-0.946	0.933	0.864-0.967	0.976	0.946-0.989
Interpersonal Relationships	0.872	0.732-0.939	0.817	0.670-0.899	0.974	0.945-0.988
Community Life	0.999	0.994-1.000	0.912	0.809-0.959	0.965	0.915-0.985
Education	0.961	0.866-0.989	0.916	0.825-0.959	0.940	0.845-0.977
Employment	NA	NA	NA	NA	0.984	0.957-0.994
Recreation	0.904	0.792-0.955	0.960	0.919-0.980	0.911	0.797-0.961
LIFE-H Total Score	0.953	0.901-0.978	0.970	0.947-0.983	0.988	0.976-0.995

ICC: Intraclass correlation coefficient, CI: confidence intervals, NA: Values are not calculated because there is one question in Community Life category in the 0-4 age form, there are no questions in Employment category in the 0-4 age form, there is one question in Employment category in the 5-13 age form.

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Table IV. *Construct validity of LIFE-H with PODCI subscales and PEDI domains*

Age groups			PODCI						PEDI					
									Functional Skills			Caregivers Assistance		
	LIFE-H total scores		Upper Extremity and Physical Function	Transfer and Basic Mobility	Pain/ Comfort	Happiness	Sports and Physical Functioning	Global Functioning	Self-Care	Mobility	Social Function	Self-Care	Mobility	Social Function
0-4 years form	Activities of regular living total score	Spearman rho	0.750	0.791	0.429	0.456	0.757	0.769	0.807	0.799	0.675	0.688	0.838	0.739
		p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	Social Roles Total Score	Spearman rho	0.672	0.648	0.369	0.538	0.676	0.646	0.765	0.715	0.674	0.691	0.754	0.742
		p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	LIFE-H Total Score	Spearman rho	0.724	0.743	0.409	0.479	0.737	0.736	0.807	0.778	0.688	0.702	0.812	0.749
		p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
5-13 years form	Activities of regular living total score	Spearman rho	0.845	0.894	0.405	0.417	0.823	0.866	0.853	0.826	0.841	0.835	0.862	0.791
		p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	Social Roles Total Score	Spearman rho	0.772	0.801	0.374	0.391	0.743	0.791	0.770	0.755	0.773	0.756	0.811	0.739
		p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	LIFE-H Total Score	Spearman rho	0.841	0.874	0.411	0.412	0.809	0.859	0.845	0.822	0.837	0.826	0.863	0.792
		p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
General Form	Activities of regular living total score	Spearman rho	0.797	0.850	0.240	0.352	0.833	0.839	0.729	0.831	0.818	0.831	0.871	0.791
		p	<0.001	<0.001	0.017	0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	Social Roles Total Score	Spearman rho	0.761	0.798	0.259	0.317	0.820	0.799	0.683	0.743	0.758	0.741	0.773	0.744
		p	<0.001	<0.001	0.010	0.002	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	LIFE-H Total Score	Spearman rho	0.799	0.840	0.250	0.330	0.842	0.834	0.728	0.806	0.809	0.812	0.840	0.786
		p	<0.001	<0.001	0.013	0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

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Table V. *Correlation between LIFE-H total scores and functional classification systems*

		0-4 years form				5-13 years form				General Form			
LIFE-H scores		GMFCS	MACS	CFCS	EDACS	GMFCS	MACS	CFCS	EDACS	GMFCS	MACS	CFCS	EDACS
Activities of regular living total score	r	-0.778	-0.775	-0.735	-0.715	-0.810	-0.689	-0.706	-0.654	-0.828	-0.700	-0.603	-0.582
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Social Roles Total Score	r	-0.734	-0.729	-0.712	-0.652	-0.696	-0.583	-0.624	-0.567	-0.768	-0.678	-0.555	-0.506
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
LIFE-H Total Score	r	-0.763	-0.756	-0.741	-0.698	-0.786	-0.668	-0.703	-0.560	-0.818	-0.705	-0.595	-0.558
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

GMFCS: Gross Motor Function Classification System, MACS: Manual Ability Classification System, CFCS: Communication Function Classification System EDACS: Eating and Drinking Ability Classification System

Spearman Correlation Analysis

4. DISCUSSION

The evaluation of the participation in daily life of children with CP is an essential concern as doing so may make it achievable to prevent the restriction of their participation in life habits. The LIFE-H is a vital questionnaire formed under the roof of the ICF and evaluates children in different life conditions from infancy to adulthood. In the present study it was determined that the questionnaire had good internal consistency and test-retest reliability and was valid at the acceptable level. This study is the first to display the validity and reliability of the LIFE-H in a large sample group by involving children of all age groups with CP.

According to the results of the study, the internal consistency of the 0-4 years, 5-13 years and general forms of the LIFE-H was determined to be acceptable for all categories. The highest values for internal consistency were observed for the general form. In their study conducted with 24 children and 25 adults, Noreau et al. [20] reported that the internal consistency for the LIFE-H was high (Cronbach $\alpha \geq 0.82$). This finding corresponds with the result obtained in the present study. The test-retest reliability of the LIFE-H was determined to be of high-very high reliability for all categories apart from the medium reliability observed for the mobility category for the 0-4 years ages form. In addition, test-retest reliability was determined to be high-very high reliability for the 5-13 years ages form and general form of the LIFE-H. The highest values for the test-retest reliability were taken for the general form. The test-retest results for the reliability of the LIFE-H revealed that the questionnaire was reliable. In their study conducted with children aged between 5-13 years with physical disabilities, Noreau et al. [23] determined that the intra-rater reliability was good-excellent for 11 categories of the LIFE-H. They reported that the lowest ICC value (0.58) was taken for the interpersonal relationship category and stated that this low score may have been caused by the lack of variability in the data. In the present study, the lowest ICC value for the 5-13 years ages form was obtained in the interpersonal relationships category. In a study conducted with 24 children and 25 adults it was reported that the test-retest reliability was lower in the children (ICC = 0.67) compared to the adults (ICC = 0.83) in terms of the total score [20]. In another study conducted with children with CP aged between 5-13 years old, it was determined that the Persian version of LIFE-H held good test-retest reliability as the ICC values for all categories were higher than 0.60 and 0.78 in terms of the total score [33].

In the present study, the relation of the LIFE-H for construct validity with two different surveys was examined. However, it is limiting to discuss the findings of this study with those of the literature as there are very few studies concerning the sample group included in this study. In general, the studies in the literature have been conducted with adults, thus, in these studies the general form was applied. PODCI and PEDI were used to demonstrate the validity of the LIFE-H. For all three forms of the LIFE-H better relationships were observed in the dimensions close to each other such as the LIFE-H Activities of Regular Living total score and LIFE-H total score and PODCI upper extremity and physical function, transfers and basic mobility, sports and physical function, global function subscales. Weak correlations were observed between distant dimensions such as the LIFE-H scores and PODCI Pain/Comfort and Happiness subscale.

A high and moderate relationship was observed between the LIFE-H total scores and the PEDI domains for all three forms. The best relationships for all forms were observed between the LIFE-H total scores and the PEDI caregivers' assistance-mobility domain. This may be due to the fact that there are many questions concerning mobility on both scales and that the LIFE-H not only considers the level of participation that is performed independently, but also the participation with human assistance. For this reason, a higher relationship may have been found between LIFE-H scores and the part in PEDI that questions how much caregiver assistance is needed for mobility. In a study carried out on children between the ages of 5-13 with CP the reliability of LIFE-H in terms of its relationship with PEDI was evaluated and it was reported that the dimensions that measured similar structures on these two scales presented higher correlations and the dimensions that measured different

structures gave lower correlations [23]. In that study, they determined that the self-care and mobility domain of PEDI and the personal care and housing categories of the LIFE-H (0.79 <r <0.88) were closely related, in addition to the Social Function domain of PEDI and the communication and responsibility categories of LIFE-H (r = 0.80-0.81) [23]. In the present study, it was observed that the relationships were relevant among the dimensions with similar structures. Mortavazi et al. [33] applied the 5-13 years form of the LIFE-H to children with CP and investigated the construct validity of the Persian version with Lawshe's method. As a result, they found that the questionnaire had good validity and was suitable for both research purposes and clinical use.

In our study, it has been shown that participation in daily life is broadly related to children's functional ability which is classified with four different functional classification systems. A negative relationship was found between all classification systems used and LIFE-H total scores. In a study evaluating participation in children with CP using the Child Engagement in Daily Life Measure; it is reported that children with better gross motor, manual ability, and communication functions had higher frequency and pleasure of participation [34]. In another study that assessed the participation of the children by semi-structured interviews with parents; it has been stated that the participation of children are closely related to communication and mobility [35]. Since the aim of our study was to determine the reliability and validity of LIFE-H, this subject was not focused on. However, in further studies, it is important to investigate the relationship between functional classifications (especially for EDACS) and participation in daily life should be examined in more detail and interventions that will encourage participation for children with different functional levels.

The study has some substantial aspects. A total of 450 children with CP and adolescents were involved in this study. In the literature, in the studies analyzing the validity and reliability of the LIFE-H mostly the general form was used and individuals over 60 years old with disabilities or with healthy young adults were involved. In that studies sample size is generally range between 75-100 individuals. In this regard, the present study is the first to have such a high sample size that involves children and adolescents with CP.

Limitations

As there are no other Turkish scales evaluating the participation in daily life of this age group, the construct validity of the LIFE-H was compared with PEDI and PODCI, which comprise various areas of ICF such as activity, participation, environmental and personal factors. In future studies, it would be beneficial to translate the different scales evaluating the participation in daily life of the related age group into Turkish and compare the strong and weak aspects of these scales in terms of clinical use and research purposes.

Conclusion

The LIFE-H is a worthy questionnaire showing functional independence, participation in daily life, education and leisure activities. The present study is significant as this much high sample size was comprised of children and adolescents with CP for the first time in the literature. In the study, the reliability and validity of the LIFE-H were presented for three different age forms and the Turkish LIFE-H was appended to the literature as a reliable and valid questionnaire to evaluate the participation in daily life of children and adolescents with CP. Admitting that the number of Turkish scales, which that directly evaluate participation are wholly insufficient, it is considered that the LIFE-H questionnaire for children with CP will have significant contributions both in clinical and research purposes. In addition, it is thought that the adaptation of the LIFE-H scale into Turkish will provide a useful resource for practitioners not only in Turkey and Turkish-speaking countries but also provide a useful resource for practitioners in many countries, where Turkish immigrants reside.

Compliance with Ethical Standards

Ethics approval: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of Non-interventional Clinical Research of Hacettepe University (Number: GO 14/451-11). Written informed consent was obtained from the parents of the children who participated in this study.

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Appendix I. Number of questions for LIFE-H categories according to different age group forms.

LIFE-H Categories	Question numbers in different age forms		
	0-4 years form	5-13 years form	General form
Activities of Regular Living Total Score	36	34	37
Nutrition	7	4	4
Fitness	3	4	4
Personal Care	8	8	8
Communication	9	8	8
Housing	6	6	8
Mobility	3	4	5
Social Roles Total Score	25	30	40
Responsibility	5	7	8
Interpersonal Relationships	5	6	7
Community Life	1	2	8
Education	4	6	2
Employment	-	1	8
Recreation	10	8	7

Appendix II. Scoring of LIFE-H

Life Habits Accomplishing Scale		
9	Without difficulty	Without assistance
8	Without difficulty	Assistive device (or adaptation)
7	With difficulty	Without assistance
6	With difficulty	Assistive device (or adaptation)
5	Without difficulty	Assistance of a person
4	Without difficulty	Assistive device (or adaptation), additional assistance of a person
3	With difficulty	Assistance of a person
2	With difficulty	Assistive device (or adaptation), assistance of a person
1	Accomplished by another one	
0	Not accomplished	
N/A	Not applicable	

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Impact of tocilizumab on clinical outcomes in severe COVID-19 patients and risk of secondary infection: A case-control study

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ABSTRACT

Objective: This study aimed to identify the effect of tocilizumab (TCZ) on clinical outcomes in severe COVID-19 patients.

Material and Methods: We included hospitalized COVID-19 patients with an initial WHO scale ≥4. We matched the patients with baseline characteristics by using propensity scores. Then, we selected patients with C-reactive protein levels above 30 and showing an upward trend. We assessed the effect of TCZ in patients on clinical outcomes by using Mann – Whitney U and Chi-square tests.

Results: Of 200 patients who had an initial WHO scale ≥ 4, 42 (21%) were given TCZ in addition to standard of care (SOC). Twenty-five patients (50%) needed mechanical ventilation (MV) in the TCZ group, compared with 35 (21%) of 158 patients with SOC (p<0.01). Nineteen (45%) and 37 (23%) patients died in 30 days in these groups, respectively (p <0.01). The secondary infection rate was significantly higher in the TCZ group (p=0.004). However, no difference was observed in all these parameters in the propensity score-matched cohort (14 patients in TCZ and 14 in the SOC group) (p=0.45, 0.45, 1.0 respectively).

Conclusions: Tocilizumab does not provide a beneficial effect on MV requirement and mortality in severe COVID-19, and it does not increase the risk of secondary bacterial infection.

Keywords: COVID-19, IL-6, SARS-CoV-2, Tocilizumab

1. INTRODUCTION

Since the end of December 2019, the infection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused the death of more than 1.7 million people all around the world [1]. Although, many potential drugs and vaccines are under clinical evaluation, an effective treatment of the disease has not been found so far. Many severe patients developed cytokine release syndrome (CRS), which played a crucial role in the pathogenesis of the coronavirus disease 2019 (COVID-19) [2, 3]. The elevated production of pro-inflammatory cytokines including interleukin 6 (IL-6) is considered to be the main factor in the development of CRS and respiratory failure [4, 5]. Furthermore, increasing plasma IL-6 levels have been observed in the intensive care unit (ICU) patients with COVID-19 and this has been associated with high mortality [4, 6]. Although, there is no proven treatment for COVID-19, inhibition of this inflammation at the right time suggests that the clinical outcome may be improved [7]. Tocilizumab (TCZ), a humanized anti-IL-6 receptor monoclonal antibody, blocks the IL-6-mediated pro-inflammatory cytokines and has been approved for the treatment of rheumatoid arthritis and systemic juvenile arthritis [8-10].

Following the COVID-19 outbreak, several studies have described the use of TCZ in COVID-19 pneumoniae [5, 11-14]. However, most of these studies are not randomized controlled

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trials (RCT) and have a small number of patients [11, 12]. The impact of TCZ on clinical outcomes in severe COVID-19 patients was found to be different in previous studies. While some studies have demonstrated that TCZ is associated with better overall survival [15-17], others have shown no additional benefit [18, 19].

Besides its life-saving effect, inhibition of IL-6 may have undesirable consequences. One of the most important complications of anti-IL-6 agents is secondary infections. In many safety studies, it was shown that TCZ increases secondary infection rates in patients with COVID-19 [15, 16, 20].

The Republic of Turkey Ministry of Health has allowed for compassionate use of tocilizumab in the event of cytokine storm or macrophage activation syndrome in patients with severe COVID-19 since the beginning of the pandemic. In this study, we aimed to evaluate the impact of TCZ on mortality and the need for mechanical ventilation (MV), in hospitalized severe COVID-19 patients using propensity score matching in two centers. Secondly, we evaluated the infection rates in matched patients.

2. MATERIAL and METHODS

This retrospective two-center case-control study was performed between March 22 and June 5, 2020 (the last follow up was on July 25) at Marmara University, Pendik Training and Research Hospital and Umraniye Training and Research Hospital. The participants of the matched case-control study were selected from a hospitalized COVID-19 real-time polymerase chain reaction (RT-PCR) positive patient population pool. We analyzed the data of patients who were World Health Organization (WHO) scale 4 and above [21].

We obtained the following data from computer-based patient records: gender; age; comorbidities (hypertension, diabetes mellitus, chronic obstructive pulmonary disease (COPD), asthma, immunosuppression, cardiovascular system disease, chronic renal and liver disease); serum inflammatory markers (Lymphocyte count and percent, C-reactive protein (CRP), ferritin, d-dimer); symptom onset dates; baseline clinical status (SpO_2/FiO2 ratio, need for O_2); length of hospital stay; requiring ICU; clinical outcomes (requiring MV and 30 days mortality) and secondary infections.

Severe cases were defined as saturation of oxygen <94% on room at sea level, a ratio of arterial PaO_2/FiO_2 <300 mm Hg, respiratory frequency >30 breaths/min, or lung infiltrates >50% according to National Institutes of Health (NIH) classification at the same time [22].

Tocilizumab was initiated in patients with worsening respiratory parameters and/or suspected cytokine storm, despite standard therapy, according to the evaluation of the attending physicians. TCZ dose was 8 mg/kg (up to a maximum 800 mg) infused over 60 min intravenously; in some patients, a second dose was applied after 24 hours in case of persistence of respiratory distress and high inflammatory markers. The choice and indication of TCZ treatment depended on attending physicians.

Propensity score matching

After analyzing data of patients with WHO scale ≥ 4, a propensity score matching was performed [23]. Propensity scores with a caliper width of 0.1 were calculated by using the variables of age, gender, and the number of comorbidities with an allocation ratio target of 1 to 3. According to the duration from the onset of symptoms to the initiation of TCZ treatment (in days), the patients were divided into 3 strata, namely 7 to 10 days, 11 to 13 days and more than 14 days. The control patients and three measurements or each ferritin, CRP, procalcitonin, lymphocyte count, SpO2/FiO2 ratio values. Among three measurments in distinct time periods, the measurement temporarily matched to the first day of TCZ treatment of respective case patient was selected for each control patient. For the selection of temporarily matched measurement, the aforementioned strata were used. Afterwards, two additional criteria two additional criteria or CRP value were used for matching, including: an increase in CRP value relative to CRP level at admission and a CRP value above 30 mg/L during the first day of TCZ treatment for cases and during the corresponding stratum for controls.

This study was approved by the Institutional Review Board of Marmara University, School of Medicine (approval number 092020.718). The necessary permission was obtained from the Republic of Turkey Ministry of Health.

Statistical Analysis

The normality assumption of numerical variables was tested with histogram, skewness kurtosis and Shapiro-Wilk tests [24]. The numeric variables without normal distribution were presented with median, interquartile range, minimum and maximum values. The categorical variables were presented with frequencies and percentages. The distributions of numerical variables among two independent groups (namely case and control groups) were tested with Mann-Whitney U test. The categorical variables were analyzed with Chi-squared test and Fisher's exact test. A p-value less than 0.05 was considered statistically significant. Microsoft Excel 2007 and Stata 15.1 software were used for data analysis.

3. RESULTS

Overall, 407 consecutive hospitalized adult patients (≥18 years) whose RT-PCR was positive for COVID-19 were enrolled in the study. Of 407 patients, 200 patients with WHO scale 4 and above at admission were analyzed. Of 200 patients, 158 (79%) received standard of care (SOC) (hydroxychloroquine (HQ) and/or favipiravir and/or azithromycin) and 42 (21%) received TCZ in addition to SOC. Baseline characteristics of both groups were summarized in Table I. The median age was similar, and the majority of the patients were male in both groups (78.6% in TCZ and 58.9% in SOC group, p= 0.02). Total 40 cases matched to 120 controls were selected with propensity score matching method. Of the matched cases and controls, 6 cases and corresponding 18 control patients were excluded, since their tocilizumab treatment started before day 7. After

using CRP criteria, 14 cases and 14 controls were included in this study (Figure 1).

When we analyzed a data of 200 patients, ferritin and procalcitonin were higher, and lymphocyte count and SpO_2/FiO_2 ratio were lower at admission in the TCZ+SOC group compared to the SOC group (Table I). All repurposed antivirals except HQ and steroid were used statistically more frequently in the TCZ group (Table I). Length of hospital stay (TCZ+SOC group 15.5 (18%) vs SOC group 12 (11%) days), mechanic ventilation requirement (n=25 (59.5%) vs n=35 (22.2%) cases), and 30-day mortality (7 (45.2%) vs 5 (23.4%) days) were found significantly higher in the TCZ+SOC group ($p < 0.01$ for all).

The secondary infection rates were higher in the TCZ group than in the SOC group (n=12 (28.5%), n=17 (10.7%) respectively, p=0.004). The most common infection was pneumonia in both groups: 9 of 12 patients in the TCZ group and 11 of 17 patients in the SOC group. *Acinetobacter baumanii* and other multiple drug resistant gram-negative bacteria were cultured in 15 tracheal aspirates. Bacteremia was detected in 7 patients in each group. Candidemia was detected only in two patients in the SOC group.

Propensity-score matched case-control

A total of 28 patients were matched; 14 patients were in the TCZ + SOC group, and 14 in the SOC group. The median age, sex, number and types of comorbidities, laboratory parameters, and concomitant use of antivirals and steroids were similar in each group (Table I). Compared with the SOC group, TCZ group had higher ferritin levels (p= 0.01).

Seven of 14 patients (50%) in TCZ group and 5 of 14 patients (35.7%) in SOC group died after intubation and there was no statistical difference (p=0.45). The secondary bacterial infections were detected in 4 patients in the TCZ group and 3 in the SOC group. Similarly, there was no significant difference in this parameter. The most common infection was pneumonia in both groups.

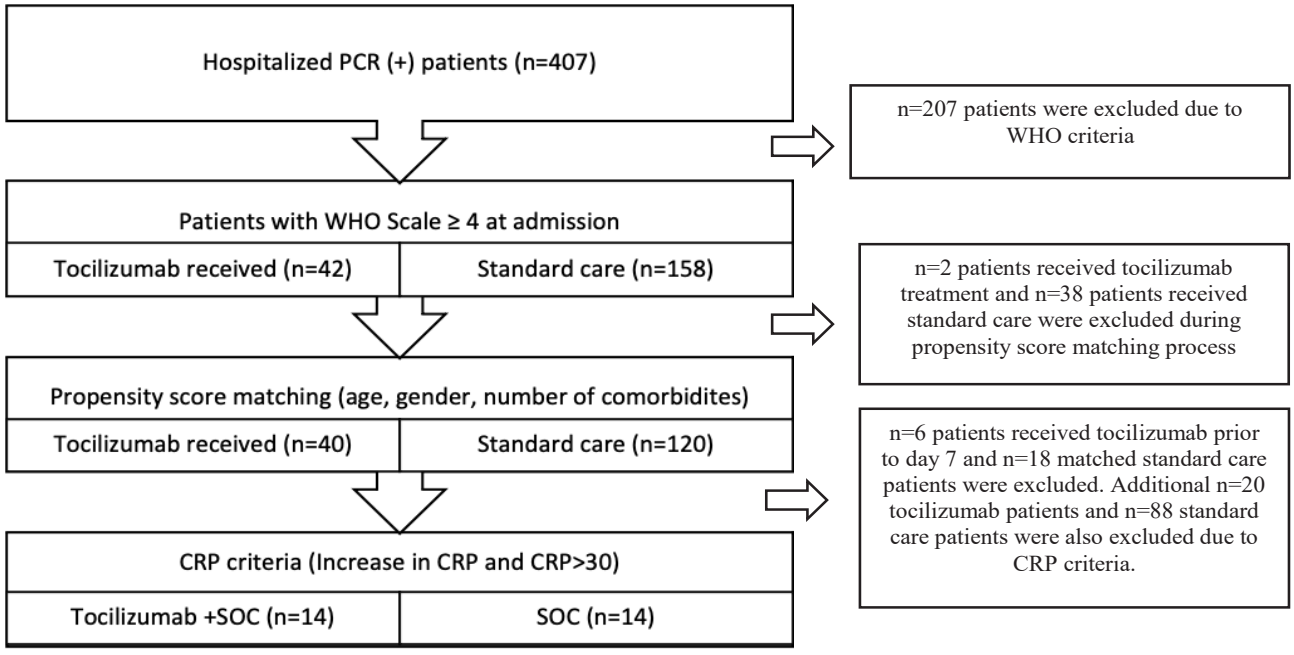

Figure 1. *Flowchart for patient selection*

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Table I. *Characteristics of patients receiving TCZ + SOC or only SOC, before and after propensity score matching*

		Total			Match		
Variable	**Statistics**	**TCZ + SOC**	**SOC**	**p**	**TCZ + SOC**	**SOC**	**p**
Observation	*n (%)*	42 (21.0)	158 (79.0)	n/a	14 (50.0)	14 (50.0)	n/a
Patient characteristics							
Age	*Median (IQR)*	61 (16.9)	60.8 (25)	0.63	61 (17)	59 (25)	0.43
	Min-Max	30-81	20-95		30-81	44-80	
Gender							
Male	*n (%)*	33 (78.6)	93 (58.9)	**0.02**	11 (78.6)	11 (78.6)	1.00
Female	*n (%)*	9 (21.4)	65 (41.1)		3 (21.4)	3 (21.4)	
Number of comorbidities	*Median (IQR)*	2(2)	1(3)	0.80	1 (2)	1 (2)	0.76
	Min-Max	0-6	0-5		0-4	0-3	
Comorbidity							
Hypertension	*n (%)*	22(52.4)	81 (51.3)	0.90	7 (50.0)	6 (42.9)	0.71
Diabetes	*n (%)*	14 (33.3)	58 (36.7)	0.69	2 (14.3)	2 (14.3)	1.00
COPD/Asthma	*n (%)*	8 (19.1)	33 (20.9)	0.79	3 (21.4)	3 (21.4)	1.00
Coronary artery disease	*n (%)*	10 (23.8)	46 (29.1)	0.50	5 (35.7)	4 (28.6)	1.00
Immuno-suppression	*n (%)*	4 (9.5)	16 (10.1)	1.00	1 (7.1)	1 (7.1)	1.00
Chronic kidney disease	*n (%)*	4 (9.5)	14 (8.9)	1.00	1 (7.1)	1 (7.1)	1.00
Chronic liver disease	*n (%)*	2 (4.8)	0 (0.0)	**<0.01**	0 (0.0)	0(0.0)	n/a
Laboratory							
Ferritin on admission	*Median (IQR)*	734.3 (823.7)	318.6 (450.9)	**<0.01**	751.6 (716.86)	278.05 (507.1)	0.09
	Min-Max	43.6 – 2939.2	5.2 – 9427		43.6 – 2676.11	13 – 3000	
Ferritin matched	*Median (IQR)*	n/a	n/a	n/a	1075 (1097)	564 (553)	**0.01**
	Min-Max	n/a	n/a		245-3295	50-1411	
CRP on admission	*Median (IQR)*	61.1 (130.8)	37.5 (82.3)	0.08	19.1 (67.7)	63.9 (78.1)	0.06
	Min-Max	0.2-412.4	0-391		0.2-255	18.5-250	
CRP matched	*Median (IQR)*	n/a	n/a	n/a	195 (108)	155 (236)	0.78
	Min-Max	n/a	n/a		40-274	56-381	
Procalcitonin on admission	*Median (IQR)*	0.27 (1.05)	0.1 (0.16)	**<0.01**	0.165 (0.9)	0.135 (0.17)	0.55
	Min-Max	0.03-22.57	0.03 – 100		0.05-13.42	0.04 – 3.43	
Procalcitonin (maximum, matched)	*Median (IQR)*	n/a	n/a	n/a	0.53 (0.73)	0.11 (1.25)	0.41
	Min-Max	n/a	n/a		0.05-3.8	0.04 – 15.02	

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Marmara Med J 2021;34(2): 112-119

Lymphocyte count	*Median (IQR)*	710 (700)	1000 (740)	**<0.01**	935 (970)	1000 (300)	0.82
	Min-Max	100 – 9600	0 – 7200		100-9600	500-2100	
Lymphocyte count matched	*Median (IQR)*	n/a	n/a	n/a	680 (360)	850 (800)	0.66
	Min-Max	n/a	n/a		100 – 9600	100 – 1700	
SpO_2/FO_2 ratio on admission	*Median (IQR)*	233.5 (186)	404 (184)	**<0.01**	243 (138)	333.5 (226)	0.12
	Min-Max	90-471	92-476		98-466	111-476	
SpO_2/FiO_2 ratio matched	*Median (IQR)*	n/a	n/a	n/a	161.5 (162)	281 (110)	0.054
	Min-Max	n/a	n/a		80-457	100-476	
Treatment							
Favipiravir	*n (%)*	38 (90.5)	105 (66.5)	**<0.01**	12 (85.7)	11 (78.6)	0.62
	Days of treatment						
	Median (IQR)	5(0)	5(0)	0.19	5(0)	5(0)	0.35
	Min-Max	0-6	0-9		0-6	5-5	
Hydroxychloroquine	*n (%)*	39 (92.9)	155 (98.1)	0.08	14 (100.0)	14 (100.0)	n/a
	Days of treatment						
	Median (IQR)	10(2)	9(5)	0.11	10(2)	10(2)	0.83
	Min-Max	0-10	0-10		5 – 10	5-10	
Macrolide	*n (%)*	35 (83.3)	100 (63.3)	**0.01**	13 (92.9)	8 (57.1)	0.08
	Median (IQR)	5(0)	5(1)	0.54	5(0)	5(0)	0.63
	Min-Max	0-6	0-7		3-6	5-5	
Steroid	*n (%)*	22 (52.4)	34 (21.5)	**<0.01**	10 (71.4)	5 (35.7)	0.06
ICU admission	*n (%)*	34 (80.95)	53 (33.5)	**<0.01**	10 (71.4)	6 (42.9)	0.13
Outcome							
Length of hospital stay	*Median (IQR)*	15.5 (18)	12 (11)	**0.01**	16 (18)	13 (14)	0.49
	Min-Max	2-67	3-69		2-53	3-31	
Secondary infection	*n (%)*	12 (28.57)	16 (10.13)	**0.002**	4 (28.57)	3 (21.43)	1.00
Requiring MV	*n (%)*	25 (59.52)	35 (22.15)	**<0.01**	7 (50.00)	5 (35.7)	0.45
30-day mortality	*n (%)*	19 (45.2)	37 (23.4)	**<0.01**	7 (50.0)	5 (35.7)	0.45
Discharge	*n (%)*	23 (54.8)	121 (76.6)		7 (50.0)	9 (64.3)	

Abbreviations: COPD: Chronic obstructive pulmonary disease, CRP: C-reactive protein, ICU: Intensive care unit, IQR: Interquartile Range, MV: Mechanical ventilation, SOC: Standard of care, TCZ: Tocilizumab

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4. DISCUSSION

In the present study, we found that TCZ did not improve the clinical outcome (need for MV or 30-day mortality) in severe COVID-19 patients. Also, TCZ did not increase secondary bacterial infections in severe COVID-19 patients. According to our early institutional policy, HQ was started for all patients except for some contraindications, and other antivirals and steroids were added in the absence of clinical improvement. Given the higher use of favipiravir, macrolide, and steroid in the TCZ group, this indicates that TCZ was given to patients with more severe conditions. As a result of this, ICU admission, length of hospitalization, requiring MV, mortality, and secondary infection rate were found significant in this group. Similarly, previous studies demonstrated that elevated serum IL-6, CRP, ferritin, and procalcitonin levels are correlated to poor outcomes and the development of secondary bacterial infection as prognostic factors [25, 26]. The lymphocyte count, another important prognostic factor in COVID-19, decreases depending on damage to the cytoplasmic component of lymphocyte, and this was also found associated with severe COVID-19 [27-29].

The RCTs relating to the impact of TCZ on clinical outcomes were limited and results are variable [11, 12]. In a recent study, Stone et al. showed that TCZ has no impact on preventing intubation and death [30]. Some case-control studies demonstrated that TCZ reduces the need for MV and mortality in severe patients with COVID-19 [13, 16, 31]. However, Campochiaro et al. showed that there is no difference in clinical improvement and mortality between TCZ and SOC [32]. In another study, it was demonstrated that severe to critical COVID-19 patients treated with TCZ have lower mortality, but it is not statistically significant [33]. In our study, after propensity score matching with baseline characteristics, we matched the patients by using CRP (above 30 mg/L and increasing trend), a covariate that most likely affects treatment assignment, to allow an appropriate matching. The severity of both groups may be considered quite similar to each other at treatment assignment period. However, ferritin levels were found higher in the TCZ group. This may reflect a greater hyperinflammation.

The higher WHO scale category is independently associated with the development of critical disease [34]. We included patients who needed oxygen (WHO scale 4 and higher) at admission to the study and found the SpO_2/FiO_2 ratio of the patients taking TCZ was lower in both overall and matched groups. Although, it was not statistically significant in the matched group, lower levels of SpO2/FiO2 ratio were observed in TCZ group. Previous studies showed that steroid treatment improves clinical outcomes in severe patients requiring supplemental oxygen, with or without the need for MV [35, 36]. In our study, although not statistically significant, steroid use was higher in the TCZ group correlated with oxygen need. At least we did not show worse outcomes in this group. However, we were unable to demonstrate any benefit of using TCZ in severe COVID-19 patients.

Some studies demonstrated that a combination of TCZ and steroids have better outcomes [37]. However, some studies support an association between steroid or TCZ use and the development of secondary infections [20]. Hill et al., also demonstrated that TCZ has no impact on outcomes and increases infection rates in hospitalized COVID-19 patients [18].

In a recent meta-analysis, it was demonstrated that the bacterial infection rate ranged from 5.9% to 8.1% in critically ill patients with COVID-19 [38]. In our study, the overall secondary bacterial infection rate was significantly higher in the TCZ group. Although, overall initial procalcitonin values were also found higher in this group, only 3 of 28 infections were observed within 48 hours after admission (2 cases in SOC, 1 in TCZ group). Other 25 of 28 infections developed after 48 hours. When cases were matched, despite the higher steroid use in the TCZ group, there was no difference in secondary infection between both groups. The procalcitonin values were already similar.

Limitations

There are some limitations to our study. First, the number of propensity score-matched cases were very limited. Second, we matched only CRP as a laboratory parameter at the treatment assignment period. We could not measure IL-6 levels, one of the most important pro-inflammatory cytokines, because it was unavailable at that time in our centers. Third, coinfection with other viral respiratory pathogens could not be demonstrated. This study was conducted in two centers, there may be a center effect in our results.

Conclusion

The present study showed that TCZ has no beneficial effect on the need for MV and 30-day mortality in patients with severe COVID-19. Besides, no significant association of TCZ on secondary bacterial infections has been demonstrated. Detailed randomized studies are needed in terms of TCZ's efficacy in the treatment of COVID-19 and its contribution to the development of superinfections.

Compliance with Ethical Standards

Ethical approval: This study was approved by the Institutional Review Board of Marmara University, School of Medicine (approval number 092020.718). The necessary permission was obtained from the Republic of Turkey Ministry of Health.

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Conflict of interest: The authors have no potential conflicts to declare.

Authors' contributions

Conception and design of the study, drafting the article: BES, Data collection and writing: SO, LNA and FG, Analysis and interpretation of data: CI and US, Data collection and drafting the article: FTT, Data collection and interpretation of data: FK, Revising: MA, Revising the article critically for intellectual content: IC and ZO, Conception and design of the study, revising

the article critically for intellectual content: VK. All authors read and approved the final version of the article.

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Does methylprednisolone affect time to recovery in COVID–19 pneumonia?

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ABSTRACT

Objective: Current literature has conflicting results on the role of steroids in the treatment of coronavirus disease 2019 (COVID-19) pneumonia. This study aims to evaluate the effects of steroids on clinical recovery, duration of hospitalization, and time needed for the cessation of oxygen treatment.

Patients and Methods: We retrospectively analyzed the medical records of patients hospitalized for COVID-19 between March and May 2020. Patient age, laboratory parameters, clinical stages, radiologic scores, length of hospital stay, and time needed for the cessation of oxygen supplementation were compared.

Results: Thirteen patients were treated with steroids, and 12 controls were included in the analysis. Regarding the laboratory parameters, the groups were similar except for lymphocyte percentage (9.8 ± 3.2, 7.0 ± 2.9; p=0.033), which was higher, and D-dimer levels (0.75 (0.60-1.43), 1.57 (0.91-2.29); p=0.047), which were lower in the steroid group on admission. Steroid treatment provided a tendency of decrease in time to cessation of oxygen supplementation (6.23 ± 3.4 vs 7.67 ± 2.1, p=0.217).

Conclusion: Although, systemic steroids, started in the subacute period, did not affect the length of hospital stay, they provided a tendency of decrease in the time until the cessation of oxygen supplementation in the subacute period.

Keywords: COVID-19, Steroids, Length of stay

1. INTRODUCTION

The new type of coronavirus, which appeared in Wuhan, the capital of China's Hubei region in December 2019, spread in a short time and caused a worldwide pandemic [1, 2]. The new type of coronavirus, named as severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2), and the disease it causes, coronavirus disease-19 (COVID-19), mainly targets the lower respiratory tract [2]. Although, the infection is mild in 81% of cases, it may result in respiratory failure, septic shock, and multi-organ failure in 5%. The fatality rate of the disease has been reported as 2.1% [3].

In the course of disease in advanced stages, distal airway involvement may result in alveolar destruction. It has been demonstrated that this lung damage is associated both with the virus and an uncontrolled immune response and an alveolar injury similar to acute respiratory distress syndrome (ARDS) [4]. On the other hand, the fact that lung compliance is preserved in some cases with hypoxemic respiratory failure suggests that there are other possible mechanisms in the development of hypoxemia other than alveolar damage [5]. In particular, it has been suggested that uncontrolled excessive inflammation tends to increase coagulation and can cause both arterial and venous thromboembolic disease. Also, the detection of pulmonary microthrombi in autopsy series supports the view of another possible cause for hypoxemia in these cases [1, 6]. The presence of hypoxemia in patients or prolonged hypoxemia is associated with prolonged hospitalization.

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Although, the use of anti-malarial agents in combination with anti-viral and macrolide antibiotics is recommended in the early treatment of the disease, the use of biologic agents may be an option in the event of an excessive inflammatory response in patients whose viral replication phase is over [7]. Corticosteroids are widely used in severe community-acquired pneumonia, especially in suppressing excessive and dysfunctional systemic inflammation [8]. Although, there are contradictory results about the use of systemic steroids in non-COVID viral infections in general, the idea that pulse-dose therapy and long-term high-dose steroid use is associated with more harm than benefit due to increased viral replication and the adverse effects of steroids [9-11]. However, it has been shown that corticosteroid therapies (usually 200-300 mg/day hydrocortisone, for 5-7 days) given at the correct dose and time in selected patient groups may have some clinical benefits and prevent pathologic deterioration [12, 13]. At the beginning of the pandemic, the use of steroids is very limited in SARS-CoV-2 infection. Wei et al. reported clinical improvement in patients who received an average of 400 mg/day hydrocortisone equivalent steroid treatment for an average of 9.5 days [14]. In July 2020, the preliminary data of the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial showed that especially patients with respiratory failure have decreased 28-day mortality in the dexamethasone treatment [15].

Hence, we retrospectively analyzed the medical records of 13 patients treated with steroids because of ongoing oxygen need and 12 control patients with a similar clinical picture to evaluate the effect of steroid treatment on clinical recovery, duration of hospitalization, and the time to the disappearance of oxygen need in patients with COVID-19.

2. PATIENTS and METHODS

Patients

The study was conducted at Marmara University, School of Medicine Pulmonary and Critical Care Medicine Clinic. The permission was obtained from the Ministry of Health of the Republic of Turkey on May 10th, 2020, and ethical approval was obtained from the Marmara University, School of Medicine Clinical Research Ethics Committee (approval number: 09.2020.561).

The data of patients who were hospitalized with COVID-19 pneumonia between March 13th, 2020, and May 25th, 2020, with severe acute respiratory infection (SARI) criteria (fever, cough, and dyspnea, tachypnea, hypoxemia, hypotension, widespread radiologic findings, and confusion) and found to have positive polymerase chain reaction (PCR) test results in oropharyngeal – nasopharyngeal swab samples were retrospectively examined. Among them, patients who still require oxygen supplementation despite standard medical treatment (anti-malarial, anti-viral, and macrolide antibiotics as single or combination regimen), in which other causes of secondary hypoxemia were clinically excluded, were analyzed. None of the patients were on long-term oxygen treatment before COVID-19 pneumonia for a known chronic respiratory illness. Thirteen patients treated with steroids and 12 patients with similar clinical pictures but who were not treated with steroids were included in the final analysis (Figure 1).

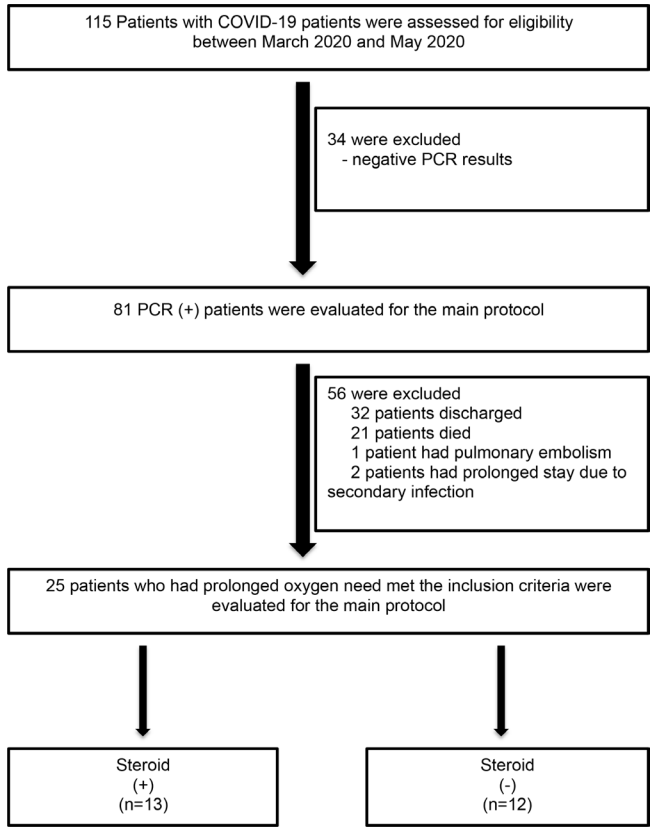

Figure 1. *Flow diagram of the study*

Demographics and comorbidities

All patients' gender, age, comorbid diseases (hypertension, diabetes mellitus, hyperlipidemia, chronic lung disease, coronary artery disease, congestive heart failure, thyroid dysfunction, chronic liver disease), smoking status, positive case contact history, the time between the onset of the first symptom, and the hospital admission were recorded.

Standard treatment

The treatments that patients received during their hospital stay were evaluated daily by three experts (pulmonary and critical care physicians) and treatment modifications were made according to the daily physical examinations and laboratory findings. Treatment planning for COVID-19 was implemented following the guideline prepared by the Republic of Turkey, Ministry of Health [16].

The recommended treatment scheme in this guide is hydroxychloroquine 200 mg bid maintenance after 400 mg bid loading for a total of 7-10 days [in patients with normal QT distance in electrocardiography (ECG) taken at the time of hospitalization] +/ – azithromycin 250 mg/day after 500 mg/day loading for 5 days (optimal), and additional favipiravir 600

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Marmara Med J 2021;34(2): 120-126

mg bid after 1600 mg bid loading in patients with high oxygen demand and respiratory distress for a total of 5 days. All patients were treated with low-molecular-weight heparin (LMWH) according to D-dimer levels at the time of hospitalization (D-dimer levels <3 mg/L were treated with 0.01 mg/kg/day once daily, D-dimer levels ≥3 mg/L were treated with 0.02mg/kg/day bid).

Laboratory parameters

In all cases, complete blood count (lymphocyte %, lymphocyte count x10^3/μL) D-dimer (mg/L), NT-proBNP (N terminal-proBrain Natriuretic Peptide) (ng/L), C-reactive protein (CRP) (mg/L), procalcitonin (μg/L), ferritin (μg/L), fibrinogen (mg/dL), lactate dehydrogenase (LDH) (U/L) results at admission and during hospital stay were recorded. In addition to the laboratory values on admission; the lowest values for lymphocyte percent, lymphocyte count, and fibrinogen level; the highest values for CRP, D-dimer, NT-proBNP, procalcitonin, ferritin, and LDH during hospitalization were included in the statistical analysis.

Severity of disease

Clinical staging for all patients during hospitalization was calculated based on the values on admission and worst clinical picture, according to the World Health Organization (WHO) progression scale [17] and the clinical-therapeutic staging suggested by Siddiqi et al. [18]. On the 7th-10th days, due to the continuation of the need for oxygen, re-staging was performed. Radiologic severity was assessed using computed tomography (CT) visual quantitative evaluation from 0-20 [19]. Each lung lobe was assessed for the percentage of lobar involvement and classified as none (0%), minimal (1-25%), mild (26-50%), moderate (51-75%), or severe (76-100%), with a corresponded score as 0, 1, 2, 3, or 4. The total severity score was reached by summing the five lobe scores.

Steroid treatment

The patients who still needed oxygen therapy on days 7-10 were evaluated for other possible causes of hypoxemia. H-scores were calculated for patients who were not considered as having clinical hypervolemia or pulmonary embolism or secondary bacterial infection [20] because of the risk of macrophage activation syndrome (MAS). In patients with H-scores <169, according to the opinion of the pulmonary medicine specialist in the clinic, single-dose intravenous methylprednisolone 0.5-1 mg/kg/day was started and tapered according to the need for oxygen in 7-10 days.

Statistical Analysis

Data are shown as mean ± standard deviation (SD), median and interquartile range (IQR), 95% confidence interval (CI), and categorical variables as numbers and percentages. For comparisons between groups, the independent sample Student t-test, or when appropriate, Mann-Whitney U test was used. The Chi-square test or when appropriate, Fisher's exact test was used for the comparison of categorical variables. All statistical tests were two-sided, and a *p*-value <0.05 was considered significant. Statistical analysis was performed using the Statistical Package for the Social Sciences, version 22.0 for Windows® system (SPSS® Inc., Chicago, Illinois, USA).

3. RESULTS

Study population and characteristics

As illustrated in Figure 1, patients hospitalized for COVID-19 pneumonia were retrospectively evaluated and a total of 25 patients (13 in the steroid group and 12 in the control group) were included in the final analysis.

The mean age of the participants was significantly higher in the steroid group (p=0.005); however, there was no significant difference between the groups in terms of comorbidities, smoking habits, and COVID contact (Table I).

Laboratory findings and disease severity scores

Baseline (on admission) laboratory findings regarding the lymphocyte count and percentage, D-dimer, NT-proBNP, CRP, procalcitonin, ferritin, fibrinogen, and LDH were compared between the groups (Table II). There were significant differences at baseline in lymphocyte percentage (9.8 ± 3.2, 7.0 ± 2.9; p=0.033) and D-dimer values (0.75 (0.60-1.43), 1.57 (0.91-2.29); p=0.047).

As shown in Table III, the lymphocyte percentage was higher in the steroid group when compared with the controls (9.8 ± 3.2, 7.1 ± 2.8; p=0.033). There was no significant difference between the groups for the remaining laboratory parameters that were evaluated in the study protocol regarding the worst results during the hospitalization period.

Table I. *Demographics and characteristics of participants (n=25)*

	Steroid (+)	Steroid (-)	*p value*
Demographics			
Age, years	**64.8 ± 13.9**	**48.3 ± 12.8**	**0.005**
Male gender, %	61.5	83.3	0.225
Current smoker, %	15.4	41.7	0.144
COVID-19 (+) contact, %	46.2	41.7	0.821
Comorbidities			
Hypertension, %	30.8	41.7	0.571
Diabetes Mellitus, %	23.1	16.7	0.689
Hyperlipidemia, %	7.7	0.0	0.327
Thyroid function disorder, %	7.7	8.3	0.953
Pulmonary disease, %	15.4	25.0	0.548
Hepatic disease, %	7.7	0.0	0.327
Cardiac disease, %	0.0	16.7	0.125
Cancer, %	7.7	0.0	0.327
Chronic inflammatory disease, %	15.4	0.0	0.157

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Marmara Med J 2021;34(2): 120-126

Table II. *Baseline laboratory findings, radiological and clinical scores of the study population (n=25)*

	Steroid (+)	Steroid (-)	*p value*
Laboratory			
Lymphocyte count, x10³ /µL	1200 ± 584.5	1116.7 ± 687.9	0.747
Lymphocyte, %	**20.4 ± 10.6**	**12.4 ± 6.9**	**0.038**
D-dimer, mg/L (IQR)	**0.75 (0.60 – 1.43)**	**1.57 (0.91 – 2.29)**	**0.047**
NT-proBNP, ng/L (IQR)	204.4 (118.01 – 512.50)	510.0 (204.0 – 2353.0)	0.159
CRP, mg/L	88.4 ± 61.63	126.8 ± 72.3	0.173
Procalcitonin, µg/ml (IQR)	0.11 (0.08 – 0.16)	0.18 (0.11 – 0.36)	0.056
Ferritin, µg/L	757.4 ± 241.5	555.4 ± 334.5	0.459
Fibrinogen, mg/dL	537.9 ± 213.0	627.2 ± 213.0	0.242
LDH, U/L	505.2 ± 400.3	544.0 ± 211.5	0.767
Radiological and Clinical Staging			
CT scores	12.5 ± 3.9	10.3 ± 4.7	0.199
WHO progression Scale	5.8 ± 1.3	5.8 ±1.2	0.990

NT: N terminal, BNP: brain natriuretic peptide, CRP: C-reactive protein, LDH: Lactate dehydrogenase, CT: computed tomography, WHO: World Health Organization

Table III. *The worst laboratory findings during hospitalization, lengths of hospital stay and time needed for cessation of oxygen requirement (n=25)*

	Steroid (+)	Steroid (-)	*p value*
Laboratory			
Lymphocyte count, x10³ /µL	807.7 ± 213.9	691.7 ± 314.7	0.289
Lymphocyte, %	**9.8 ± 3.2**	**7.0 ± 2.9**	**0.033**
D-dimer, mg/L (IQR)	1.78 (1.26 – 3.49)	1.56 (0.85 – 4.93)	0.538
NT-proBNP, ng/L (IQR)	155 (0 – 373)	375 (155-1204)	0.057
CRP, mg/L	144.2 ± 61.6	182.8 ± 56.5	0.118
Procalcitonin, µg /ml	0.24 (0.14 – 7.66)	0.29 (0.13 – 0.56)	0.807
Ferritin, µg/L	925.1 ± 881.1	839.9 ± 398.0	0.762
Fibrinogen, µg /dl	443.2 ± 243.1	415.4 ± 155.3	0.732
LDH, U/L	583.5 ± 374.1	681.3 ± 220.9	0.425
Clinical staging and length of hospital stay			
H-index (max)	45.4 ± 33.9	41.5 ± 19.3	0.727
WHO progression scale (max)	5.9 ± 1.8	6.1 ± 0.9	0.689
Time needed for cessation of oxygen need	6.23 ± 3.4	7.67 ± 2.1	0.217
Total length of hospital stay	18.5 ± 7.8	16.3 ± 4.7	0.406

NT: N terminal, BNP: brain natriuretic peptide, CRP: C-reactive protein, LDH: Lactate dehydrogenase, CT: computed tomography, WHO: World Health Organization

Also, there was no significant difference between the groups regarding the disease severity indices such as the WHO progression scale and H-index scores both at baseline and also considering the worst results during the hospitalization period. Most of the participants were in stage 2B in both the steroid and non-steroid groups regarding the pneumonia indices upon admission (Figure 2).

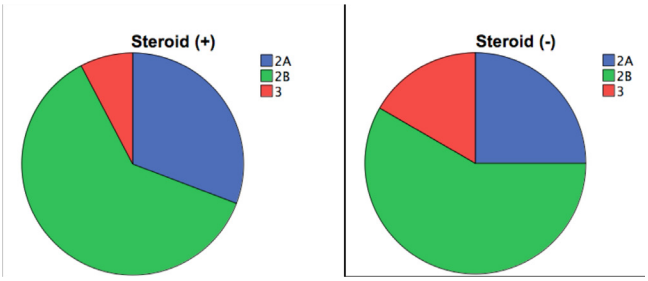

Figure 2: *Pneumonia indices of patients on admission*
2A: Pulmonary involvement without hypoxia
2B: Pulmonary involvement with hypoxia
3: Systemic hyperinflammation

Treatment

There were four different treatment modalities given to the participants. The hydroxychloroquine + azithromycin + favipiravir combination was preferred for 40% of the participants. Thirty-six percent were treated with hydroxychloroquine + azithromycin, 20% received hydroxychloroquine + favipiravir, and only one patient had hydroxychloroquine alone.

Steroid treatment

Methylprednisolone was started as a mean dose of 40-80 mg/day and the mean total steroid dose was 306 ± 119.8 mg, while mean steroid treatment period was 6.38 ± 3.6 days.

When cut-off points were determined for both the steroid and non-steroid groups (while patients were considered as recovered from the acute period of disease but had oxygen requirement in the 7-10th days of infection) regarding the duration till the cessation of oxygen support, it was observed that it took less time for the steroid group (6.23 ± 3.4 vs. 7.67 ± 2.1 days, p=0.217), but it was not statistically significant. Also, steroid treatment did not affect total length of hospital stay.

4. DISCUSSION

In this study, systemic steroid treatment initiated in the subacute period because of persisting oxygen requirement, despite

http://doi.org/10.5472/marumj.942800
Marmara Med J 2021;34(2): 120-126

standard COVID-19 treatment provided a tendency of decrease in time to cessation of oxygen supplementation.

Studies conducted to date about the use of systemic steroids in viral pneumonia (e.g. influenza, SARS) have shown that systemic steroids, particularly when used in the early period, have negative consequences on viral replication [21] and increase mortality [11, 22]. However, a retrospective study in patients with SARS showed that steroids were initiated either as acute or rescue treatments reduced mortality and length of hospital stay [23].

It has been stated that in non-COVID-19 viral pneumonia that progresss to ARDS, systemic steroids have little or no effect on the length of stay in intensive care, but they may have positive effects on the need for mechanical ventilation and length of hospital stay, albeit with a low level of evidence. However, it was also emphasized that severe hyperglycemia due to steroids could be observed [24]. Considering all these data, the general belief prevents the use of systemic steroids as a standard treatment in the early period of viral pneumonia.

There are few studies on the use of systemic steroids in the treatment of COVID-19, and the results are confusing. In a study evaluating the risk factors of ARDS and mortality in patients with COVID-19, it was stated that the use of methylprednisolone in patients with ARDS might reduce the risk of death [25]. A meta-analysis reported a decrease in 28-day mortality for critically ill patients with COVID-19 who received steroids [26].

Unlike these studies, our patients had no ARDS and were administered steroids due to their ongoing requirement of oxygen supplementation despite the regression of COVID-19 pneumonia. A study conducted in Spain showed that pulse methylprednisolone treatment given to the patients with worsening respiratory function and increasing inflammatory markers in the second week of the disease had improved the prognosis [27]. Contrary to the study [28] showing that low-dose steroid therapy provides early clinical recovery, reduced length of stay in intensive care, and improvement in oxygenation, the WHO does not recommend routine use of steroids in the treatment of COVID-19 and only recommends its use in critically ill patients [29]. The basis of this approach was derived from reviews and meta-analyses that indicated increased mortality or ineffective results on mortality and length of hospital stay after steroid treatment [30-32]. A recent trial in Brazil also could not show the mortality benefit of methylprednisolone in hospitalized patients [33]. The patients included in our study comprised those who were passed the early period of infection. Considering the pathologic extent of the disease, a study evaluating post-mortem biopsies of patients who died of COVID-19 pneumonia found that acute fibrinous and organizing pneumonia findings were prominent, especially in the subacute period of the disease. This damage was seen to occur from an organizing pneumonia pattern characterized by intense intraalvelolar fibrin deposition and fibrinous acute injury in alveolar ducts and bronchioles, and fibroblasts surrounding intraalveolar fibrin were noted in almost all patients. The authors noted that the use of corticosteroids might be beneficial in treatment with these findings [34]. In another paper, a perspective, authors have taken into attention that, due to organizing pneumonia patterns in COVID-19, prolonged duration of corticosteroid treatment; and careful and monitored tapering should be kept in mind [35]. In our study, patients who had left the acute period marked by ongoing viral replication but had ongoing oxygen demand, there was a tendency of decreased duration until the need for oxygen disappeared in the steroid treatment group when compared with the controls. This may have been due to the limited number of patients enrolled in the study. The cause of the increased total length of stay of patients who were treated with steroids could be attributed to the time before steroid treatment. Furthermore, the development of hyperglycemia, muscle weakness, gastrointestinal bleeding, or secondary bacterial infection due to steroid use was not observed and steroid therapy was administered safely.

Limitations

The most important limitation of our study is its retrospective character and a low number of patients. However, we aimed to share the short-term results of patients treated with corticosteroids as the experience in the first period of the pandemic.

Conclusion

As a result, in patients whose viral replication phase was over but still had persisting chronic inflammation and oxygen requirement, the addition of systemic steroids to the standard treatment affects the time to discontinuation of oxygen supplementation in a positive way. It was also observed that, in terms of adverse effects, low-medium dose steroid treatment was safe for these patients who are mostly old with comorbid medical conditions. To determine the role of steroids in the treatment protocols, randomized controlled studies with a large number of patients are needed.

Compliance with Ethical Standards

Ethical approval: The permission for the study was obtained from the Ministry of Health of the Republic of Turkey on May 10th, 2020, and the ethical approval was obtained from the Marmara University, School of Medicine Clinical Research Ethics Committee (approval number: 09.2020.561).

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Conflict of Interest: The authors have no conflicts of interest to declare.

Authors' Contributions: Conception-design, data collection, writing and critical revision: DK, Conception-design, writing and critical revision: SOY, Conception-design, data analysis, writing: BB, Conception-design, critical revision: EE, Conception-design, critical revision

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Determination of fosfomycin susceptibility in carbapenemase-producing *K. pneumoniae* strains isolated prior to clinical use of the intravenous formulation in Turkey

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ABSTRACT

Objectives: The incidence of infections caused by carbapenem-resistant *Enterobacteriaceae* has increased worldwide. Limitations in the development of new antimicrobial agents have led clinicians to reconsider the clinical efficiency of old antibiotics, such as intravenous formulation of fosfomycin, in the treatment of multidrug-resistant Gram-negative bacterial infections. We investigated the fosfomycin susceptibility of carbapenemase-producing *Klebsiella pneumoniae* strains isolated prior to the clinical use of the intravenous formulation of fosfomycin in Turkey.

Materials and Methods: A total of the 155 *K. pneumoniae* isolates which previously characterized at the molecular level for their carbapenemase were included in this study. The minimum inhibitory concentration of fosfomycin was determined by the agar dilution method.

Results: Overall, 65.1% of the isolates were susceptible to fosfomycin. The MIC50 and MIC90 values were 32 and 256 mg/L, respectively. According to our results, at least two-third of carbapenemase-positive *K. pneumoniae* are susceptible to fosfomycin.

Conclusions: Although, the susceptibility of fosfomycin, which has just been put into the clinical use of intravenous formulation in Turkey, is not very high, it can be considered as an alternative adjunct antimicrobial for the treatment of systemic infections caused by carbapenemase-positive *K. pneumoniae* isolates.

Keywords: Fosfomycin susceptibility, Carbapenemase-producing *Klebsiella pneumoniae*

1.INTRODUCTION

The emergence and spread of carbapenem-resistant *Enterobacteriaceae* (CRE) have become a global health problem during the last decade. Generally, CRE isolates are multi-drug-resistant, and the most prevalent mechanisms of carbapenem resistance in *Enterobacteriaceae* have been associated with the production of carbapenem-hydrolyzing enzymes. Different types of class A (e.g. KPC, GES), class B (e.g. NDM, IMP, VIM) and class D (e.g. OXA-48-like) enzymes have been identified in *Enterobacteriaceae* [1-3]. Treatment options of infections caused by CRE are challenging due to limited antimicrobials available. Therefore, it is very important to develop new and effective therapeutic strategies [4].

The limitations in the development of new antimicrobial agents have led physicians to reassess the clinical efficacy of old antibiotics, such as fosfomycin, in the treatment of multidrug-resistant Gram-negative bacterial infections. Fosfomycin is an old broad-spectrum antibiotic and active against both Gram-positive and Gram-negative bacteria [5]. Oral fosfomycin is commonly used for the treatment of uncomplicated urinary tract infections. The intravenous formulation has been available in many European countries (United Kingdom, Spain, France, Germany, Austria, Greece, etc.) and some Asian countries (Japan) for the treatment of systemic infections for several years [6]. In some European studies, the use of IV fosfomycin

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had a good effect on clinical and microbiological outcome in patients infected with various carbapenem-resistant *Klebsiella pneumoniae* strains. Fosfomycin seems to be an alternative agent for the treatment of such difficult to treat infections [7]. However, one of the main problems with this drug is the potential emergence of resistance during monotherapy. Therefore, it is recommended to use fosfomycin in combination with other antimicrobial agents (such as carbapenems, aminoglycosides, colistin, and tigecycline) in serious infections. Although, various combination regimens are used for the treatment of CRE infections, the clinical evidence is mainly based on case reports and retrospective studies. Therefore, more studies are needed to determine fosfomycin efficiency in the treatment of systemic infections [4, 6].

The intravenous formulation of fosfomycin was introduced in December 2018 for the treatment of systemic infections in Turkey. In this study, we investigated the fosfomycin susceptibility of carbapenemase-producing *K. pneumoniae* strains isolated prior to the commercial availability of the intravenous formulation of fosfomycin.

2. MATERIALS and METHODS

Study isolates

The *Klebsiella pneumoniae* isolates used in this study were collected from various clinical samples (bronchoalveolar lavage, deep tracheal aspirate, sputum, blood, urine, wound) of infected patients between January 2015 and December 2017 from hospitalized patients at Marmara University Hospital, Istanbul, Turkey. All of the non-duplicate isolates were identified by matrix-assisted laser desorption ionization-time of flight mass spectrometry (VITEK-MS, bioMerieux, Marcy l'Etoile, France). Carbapenem susceptibility was initially determined using an automated antimicrobial susceptibility test system (VITEK2, bioMerieux, Marcy-l'E´toile, France). Minimal inhibitory concentrations (MICs) of imipenem, meropenem, and ertapenem were determined by the gradient diffusion strip test (Etest®, bioMérieux, Marcy l'Etoile, France) and interpreted according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines [8]. Molecular detection of the different carbapenemase genes was carried out by in-house polymerase chain reaction (PCR) using the specific primers for genes encoding bla_{VIM}, bla_{IMP}, bla_{NDM}, bla_{KPC}, and bla_{OXA-48} [9-12]. A total of 155 carbapenemase-positive *K. pneumoniae* isolates confirmed by polymerase chain reaction (PCR) method were selected for fosfomycin susceptibility testing. We excluded isolates carrying more than one type of carbapenemases.

Fosfomycin susceptibility testing

Fosfomycin trometamol was obtained from Drogsan (Istanbul, Turkey) and glucose-6-phosphate (G6P) from Sigma Aldrich ((St. Louis, MO, USA). The agar dilution method was used to determine the susceptibility of fosfomycin on Mueller Hinton agar (MHA) ((Becton Dickinson, New Jersey, USA) supplemented with 25 mg/L G6P, according to the EUCAST guidelines. The MHA plates containing fosfomycin in concentrations from 0.06 to 256 mg/L were prepared, surface-inoculated with 10^4 CFU/mL and allowed to dry. The plates were incubated for 16 to 20 h at ambient air at 35°C. Results of antibiotic susceptibility testing were interpreted using the EUCAST criteria, where ≤ 32 mg/L is considered as susceptible and > 32 mg/L as resistant [8]. *Escherichia coli* ATCC 25922 was used as the quality control strain.

Statistical Analysis

The differences in fosfomycin susceptibility between the groups were compared using the Fisher's exact test. The differences between the groups were considered significant if the p-values were smaller than 0.05.

3. RESULTS

Carbapenemase-positive isolates expressed OXA-48 (n = 82), NDM (n = 50), IMP (n = 11), KPC (n = 7), and VIM (n = 5) carbapenemase. The isolates were resistant at least one of the carbapenems (ertapenem, imipenem, and meropenem) according to the EUCAST guidelines.

The fosfomycin MIC range was determined between 2 mg/L and > 256 mg/L using agar dilution method. According to the EUCAST criteria, 65.1% of the isolates were susceptible to fosfomycin. While the highest fosfomycin susceptibility was detected in KPC-positive isolates, the lowest susceptibility was found in IMP-positive isolates (Table I). The MIC_{50} and MIC_{90} values were 32 and 256 mg/L, respectively. Among the various carbapenemase types, KPC-positive isolates had the lowest MIC_{50} and MIC_{90} values (Table I).

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Table I. *Fosfomycin susceptibility in various types of carbapenemase producing K. pneumoniae*

Carbapenemase type	Susceptible (n)					Resistant (n)			MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC Range (mg/L)	Fosfomycin susceptibility (%)	p
	2*	4*	8*	16*	32*	64*	128*	256*					
OXA-48-like (n = 82)	1		13	14	26	12	3	13	32	256	2->256	**65.8**	1
NDM (n = 50)		1	2	14	16	6	5	6	32	256	4->256	**66**	1
IMP (n = 11)		1	1	1	3	2	2	1	32	128	4->256	**54.5**	1
KPC (n = 7)	1		2	1	1	1		1	8	64	2-256	**71.4**	0,52
VIM (n = 5)			3				1	1	8	128	8-256	**60**	1
TOTAL (n = 155)	**2**	**2**	**21**	**30**	**46**	**21**	**11**	**22**	**32**	**256**	**2->256**	**65.1**	

MIC: Minimal inhibitory concentration(mg/L)

** The MICs given in the table are the susceptibility breakpoint for fosfomycin recommended by EUCAST.*

4. DISCUSSION

Antimicrobial resistance in Gram-negative microorganisms is a global problem. In particular, carbapenem-resistant *K. pneumoniae* has spread all over the world in the last decade and represents one of the most critical challenges to the antimicrobial therapy of such infections. Because of the shortage of new antimicrobials, clinicians have begun to re-evaluate already existing antibiotics such as fosfomycin.

Fosfomycin is a small, hydrophilic agent with almost negligible serum protein binding. It is a broad-spectrum agent that is active against multidrug-resistant bacterial pathogens (MRSA, VRE, ESBL, CRE) and is excreted unchanged in the urine, reaching high urinary concentrations after administration of the 3-g single dose [13]. Therefore, the oral formulation is generally safe in uncomplicated urinary tract infections. Rapid penetration and distribution of fosfomycin into tissues such as soft tissue, lungs, bone, and cerebrospinal fluid is an important feature for preference in the treatment of serious infections caused by MDR-pathogens [7]. While intravenous fosfomycin has been prescribed for a wide variety of infections in many countries for more than 40 years, this formulation has been introduced into Turkey in late 2018. Therefore, clinical and *in-vitro* susceptibility studies are limited in this country [14, 15]. Fosfomycin susceptibility among CRE ranges between 42 and 98%, according to results of studies conducted in different countries [16-25]. We found a 65.1% susceptibility rate of fosfomycin against 155 carbapenemase-positive *Klebsiella pneumoniae* isolates in our study. Fosfomycin susceptibility rate found in our study was lower when compared to previous studies, mainly because most of these studies were performed only on KPC-producing strains and were evaluated according to EUCAST criteria (susceptible ≤ 64 mg/L) before 2011. Susceptibility data of CRE carrying other carbapenemases is also limited. Our study results will contribute to the literature in account of having the results for the most frequently observed five carbapenemase types (OXA-48, NDM, KPC, IMP, VIM) and evaluating them according to the current EUCAST fosfomycin breakpoint.

After intravenous administration of fosfomycin, mean peak serum concentrations commonly range from 200 to 600 mg/L, according to several studies [13]. These values are well above the clinical breakpoints determined by EUCAST for *Enterobacteriaceae* (susceptible ≤ 32 mg/L). Also, fosfomycin MICs of 85.8% of our study isolates had ≤ 128 mg /L and were below the achievable serum concentration values.

The correlations of PD parameters (concentration and/or time-dependent activity) with antibacterial activity of fosfomycin have not yet been clarified. Although it is known that even high doses (20-24 g/day) are well-tolerated, no definitive treatment protocol has been established yet. However, it should be remembered that resistance may develop during the use of fosfomycin monotherapy, and resistance development has been reported in approximately 3.4% during the treatment in some studies [6, 25]. Therefore, in serious infections, it is recommended to use it in combination with other antimicrobial agents such as carbapenems, aminoglycosides, colistin or

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Marmara Med J 2021;34(2): 127-131

tigecycline [26, 27]. In some studies, treatment success rates of > 80% have been achieved with the combined use of fosfomycin with other antimicrobial agents in the treatment of serious infections [6, 28-31].

The limitation of this study is that excluded isolates carrying more than one type of carbapenemases. Those isolates may have a different susceptibility pattern.

In the light of these findings, intravenous fosfomycin administration may be a valuable option in the treatment of CRE infections. For this reason, the determination of fosfomycin susceptibility in CRE strains has become a crucial issue in clinical microbiology laboratories, since the EUCAST recommends the agar dilution method for *Enterobacteriaceae*, which is not suitable for use in routine laboratory [8].

According to our study results, at least two-third of carbapenemase-positive *K. pneumoniae* in our center were susceptible to fosfomycin before the availability of the intravenous formulation, and it seems to be used as an alternative adjunct antimicrobial for the treatment of systemic infections caused by carbapenemase-positive *K. pneumoniae* isolates. It, therefore, seems adequate that laboratories should routinely perform fosfomycin susceptibility testing with reference methods to guide clinicians appropriately.

Compliance with Ethical Standards

Ethical approval: The study protocol was approved by the Marmara University, School of Medicine Ethics Committee (approval number: 09.2018.831).

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Effects of nutrition, depression symptoms and demographic characteristics on dementia in the elderly population

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ABSTRACT

Objective: Due to the increase in the elderly population, there is an increase in chronic diseases, infections, depression , and nutritional problems as well as a decrease in cognitive abilities. This study aimed to investigate the effects of nutritional status, depression symptoms and demographic characteristics on dementia in the elderly population.

Materials and Methods: This study is a cross-sectional analytic study which took place between first day of April to first day of June in 2018 in three family health centers selected by simple random sampling from random numbers table in Konya, Turkey. Mini Nutritional Assessment normal (MNA) and short form (MNA-SF), Geriatric Depression Scale-30 (GDS-30) and the Standardized Mini-Mental Test (SMMT) was applied to 298 elderly people.

Results: Mild dementia was found in 11.4% (n=34) and, depression symptoms were detected in 5.7% (n=17) of total. MNA-SF showed that 15.8% were under the risk of malnutrition while 2.3% had malnutrition. MNA-SF total score (p=0.004) was significantly higher in males than in females showing that there was more cognitive impairment in women than men. There was a significant relationship between the presence of dementia and gender (p=0.048), age groups (p=0.006), education (p<0.001), MNA-SF (p=0.012) and MNA (p=0.002).

Conclusion: The frequency of dementia was higher in women, in low educated, depressive and aged ones and in those with malnutrition. Regarding dementia, depression and malnutrition in the elderly in primary care; it is important to use well designed specific scales to these conditions for early diagnosis.

Keywords: Nutrition, Depression symptoms, Standard Mini-Mental Test, Elderly

1. INTRODUCTION

Aging is an inevitable and irreversible process that is easily identifiable and associated with structural and functional changes in the individual organism. Ageing is the primary risk factor for most neurodegenerative diseases, including Alzheimer's disease (AD) and Parkinson's disease (PD). One in ten individuals aged ≥65 years has AD and its prevalence increases with increasing age [1]. The ageing-related neurodegenerative diseases are associated with large socioeconomic and personal costs. Being elder is defined as 65 years of age by the World Health Organization (WHO) [2]. Although, elderly population was 4.2% in 1985, it increased to 7.7% in 2013 and to 8.5% in 2017, in Turkey [3].

The incidence of chronic diseases and cancers increases with old age and cognitive abilities frequently decrease. During this period, psychological problems, care problems resulting in skipping meals and poor diet are common and all these factors cause malnutrition. Malnutrition, on the other hand, increases mortality risk via deterioration in normal physiological functions, decrease in bone mass, impairment in immune system, delays in post-operative recovery and prolonged hospital stay [4].

The term 'dementia', called senility in daily life, is a word derived from 'mens' which means mind in Latin in origin and it means the loss of the established, existing, acquired mind with the negative suffix [5]. Dementia is a neurodegenerative disorder in which psychiatric and behavioral symptoms are seen together and characterized by a progressive deterioration in memory and other cognitive functions, a loss in acquired social and intellectual skills which influence daily life [2,5]. Elderly depression is accepted as an increasing public health problem worldwide. The importance of depression lies in the acceptance of depressive symptoms and cognitive loss as a normal ageing process, and the elderly generally declare the signs as an expected outcome of ageing. So, specific attention while taking patient history, and specific questions to identify depression are needed [6,7].

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It is difficult to diagnose dementia at an early stage because by getting older, forgetfulness is accepted as a normal process of ageing. The most commonly used clinical test for the evaluation of dementia is Standardized Mini Mental Test (SMMT). By reason of mimicking cognitive impairment, screening for depression is important. In addition to SMMT, Geriatric Depression Scale (GDS) should be performed to make a differential diagnosis for depression [1,2,8].

This study aimed to investigate the effects of nutritional status, depression and demographic characteristics on dementia in individuals aged 65 years and older who applied to family health centers (FHC) in Konya.

2. MATERIALS and METHODS

The type, place and population of the study

This study is a cross-sectional analytic study which took place between first day of April to first day of June in 2018 in three family health centers selected by simple random sampling from random numbers table in Konya. During this period, 298 individuals aged 65 years and over who applied to the family health center for general check-up and accepted to participate were included in the study.

In a previous study, the prevalence of dementia in individuals over the age of 65 in our country was found to be 8.4% [6]. Since, the number of individuals in the universe was unknown in our study, the number of subjects required to be included in the study was calculated using the formula "$n=t^2.p.q/d^2$." Accordingly, the study was completed with 298 individuals.

Exclusion criteria

Those who refused to participate, who were not able to answer the questions, those who had been diagnosed with dementia before and had been diagnosed with severe psychiatric disease and those whose native language was not Turkish were not included in the study.

Ethical authorization of the study

Ethics committee approval was received before starting the study (Approval number: 2017/1054 Date:03.11.2017). The participants were informed about the study and their written and verbal consent was obtained according to the principles of Helsinki Declaration.

Collecting the data

Sociodemographic variables of the participants were recorded The questionnaires used had three main parts: 1-Standardized Mini-Mental Test (SMMT), 2-Normal and short form of Mini Nutritional Assessment (MNA) test, 3-Geriatric Depression Scale-30 (GDS-30).

Sociodemographic Variables

The sociodemographic questionnaire included age, gender, marital status, occupation, education, place of residence, family structure, and economic status. Smoking, alcohol use and the existence of chronic diseases were also questioned. The researcher filled in the questionnaire using face to face interview method.

Standardized Mini Mental Test (SMMT)

Standardized Mini Mental Test, which provides assessment of cognitive status, was developed by Folstein et al. in 1975 and it is the most common and easy test for dementia screening [8]. The validity and reliability study of the test in the diagnosis of mild dementia for the Turkish population was performed by Güngen et al [9].

Standardized Mini-Mental Test was grouped under five headings: orientation (10 points), record memory (3 points), attention and calculation (5 points), recall (3 points) and language (9 points). The total score of the scale is 30 points and it has two different types for the educated and uneducated. Generally, the scores between 24 and 30 are accepted as normal. A score below 24 indicates cognitive impairment, a score between 18-23 shows mild dementia, a score between 12-17 means moderate dementia and a score below 12 is noted as severe dementia [9].

In the present study, the minimum SMMT score was 19 points, and there was no participant with moderate or severe dementia. Therefore, those with SMMT total score between 24 and 30 were considered as the normal group and under 24 points as the cognitively impaired (dementia group). Two different MMSE forms for educated and uneducated individuals were applied.

Mini Nutritional Assessment (MNA)

Recently, MNA has been widely used in the assessment of nutritional status. It was developed in 1994 in collaboration with the University of Toulouse, Medical Faculty of New Mexico and Nestle Research Center of Switzerland [10]. Following MNA, MNA-SF was developed and validated in 2001 by Rubenstein et al [11]. The validity study of MNA and MNA-SF forms in geriatric patients in Turkey was studied by Sarikaya [12].

Mini Nutritional Assessment starts with six screening questions (questions A-F1/F2), which are a maximum of fourteen-point MNA-Short form (MNA-SF). If eleven or less points are obtained as a result of this questioning, it is recommended to continue the other questions (questions G-S). This will the final MNA score: Under 17 points means malnutrition, 17-23.5 points means there is a risk of malnutrition and >23.5 points indicates adequate nutrition [13].

Geriatric Depression Scale (GDS)

This scale was developed by Yesavage, et al., in 1983 for screening depression in elderly patients based on self-report [14]. The reliability and validity study of the scale was performed by Ertan, Eker and Sar in 1997 [15]. It has 30 'yes or no.' questions which the elderly can easily answer. While scoring the scale, 1 point is given for each response in favor of depression and 0 points is given for the other response, and as a result, it is accepted as total depression score. The scoring of the scale was arranged as 0-10 points no depression, 11-13 points possible depression, 14 and above points definite depression. The scores obtained from the scale are minimum:0, maximum:30 [15].

Anthropometric Measurements

Height measurements required for the calculation of body mass index (BMI) were performed without shoes with a tape measure attached to the wall while looking ahead in the most upright position possible. Body weight was determined with a digital scale sensitive to 100 grams while looking ahead in the upright position without shoes. BMI was calculated by dividing body weight (in kilograms) by the square of the height (in meters). For the measurement of mid upper arm circumference, the arm was bent to 90° and the point between the acromial protrusion on the shoulder and olecranon protrusion on the elbow was marked and the circumference of the arm from this point was measured and recorded as centimeters. For calf circumference measurement, while the person was lying on his back, the leg was bent to 90° from the knee, the largest calf circumference was measured and the obtained value was recorded in centimeters.

Skin Fold Thickness

It provides a rough measurement of subcutaneous adipose tissue, hence fat storage and lean muscle mass. In this study, skin fold thicknesses of triceps and abdominal region were measured. Measurement of the abdominal region was performed vertically on the two cm right side of the umbilicus. Triceps measurements were performed vertically from the midpoint of the distance between the acromion and olecranon with the arm released near the body. While the measurements were made, the caliper was placed just above the skin fold, held with two fingers and the skin fold continued to be held with the fingers during the measurement. All measurements were performed by the same person with the same skin fold caliper.

Statistical Analysis

The data of the study were analyzed by Statistical Package for Social Sciences (SPSS) for Windows 20.0. Before comparing the educational status and dementia status of the participants, the educational status was divided into two groups as 'illiterate' and 'primary and higher education' taking into account the number in each group. Before comparing the nutritional status of the participants according to MNA, MNA-SF and dementia status, taking into account the numbers in each group again, the nutritional status according to MNA and MNA-SF was divided into two groups as 'malnutrition and risk of malnutrition' and 'normal nutritional status'. Before statistical evaluation, the economic status and dementia of the participants, taking into account the numbers in each group, the economic status was divided into two groups as 'less income than expenses' and 'equal or more income than expenses'. Descriptive statistics of continuous variables were summarized in terms of mean and standard deviation, and descriptive statistics of categorical data were summarized in terms of frequency and percentage in tabular form. In the comparison of quantitative data, independent t-test was used in paired groups that met the normal distribution assumption, and One-Way ANOVA test and Post Hoc test were used for three or more groups. Chi-square test was used to compare categorical data. Results were evaluated at 95 percent confidence interval and significance was at $p<0.05$ level. Pearson correlation analysis was used for correlations between parameters. Correlation coefficient (r) was evaluated as weak between 0.00-0.24, moderate between 0.25–0.49, strong between 0.50–0.74, very strong between 0.75–1.0.

3. RESULTS

A total of 298 data of the participants who met the inclusion criteria were analyzed. The mean age of the study group was 72.1±5.7 years and most of them (71.5%; n=213) were 64-74 years of age. The 52.7% (n=157) were male, 74.5% (n=222) were married, 67.4% (n=201) had nuclear families and 55.7% (n=166) were graduated from primary school.

According to the results of the SMMT; 88.6 %(n=264) of the elderly were at normal level and 11.4 % (n=34) had cognitive impairment (dementia). GDS scores of participants showed that the prevalence of depression was 5.7% (n=17). The median score of SMMT was 27.0 (min=19.9, max=30.0). The median score of GDS was 2.0 (min=0.0, max=21.0). The risk of malnutrition was 15.8% (n=47) and 2.3% (n=7) had malnutrition according to MNA-SF. MNA long form was applied to 54 people with 11 points and below in MNA-SF. This time 14.4% (n=43) were at risk of malnutrition and 1.0% (n=3) had malnutrition according to MNA.

Body mass index values of the participants showed that 45% (n=134) of them were overweight and 37.9% (n=113) were obese. Multidimensional geriatric assessment tests and the distribution of BMI were shown in Table I.

The participants were compared in respect to gender, age, educational and economic status and dementia scores. A significant relationship was found between dementia and gender (p=0.048), age groups (p=0.006), educational status (p<0.001). The prevalence of dementia was higher in the 75-year-old group, the illiterate ones and in female gender. The incidence of dementia was lower in educated ones. When the relationship between gender and dementia of the participants was examined, there was no relationship between dementia and education in male gender (p=0.277), whereas dementia was less common in educated women (p=0.005). The comparison of sociodemographic characteristics and SMMT scores of the participants is shown in Table II.

A significant relationship was found between the dementia scores of the participants and GDS-30 (p<0.001), MNA-SF (p=0.012), MNA (p=0.002) and those with dementia according to SMMT, but no relationship was found between BMI (p=0.820) and dementia (Table III). The dementia percentage was higher in those with malnutrition and at risk of malnutrition according to MNA-SF and MNA, than in those in normal nutritional status.

While 47.1% (n=8) of the participants with depression according to GDS-30 had dementia, 9.3% (n=26) of those without depression had dementia. The prevalence of dementia was higher in patients with depression according to GDS-30 than those without depression. The comparison of the dementia status of the participants to GDS-30, MNA-SF, MNA and BMI is shown in Table III.

Marmara Medical Journal
Original Article

Table I. *Multidimensional geriatric assessment tests and distribution of BMI*

Parameters	n	%
SMMT		
Normal (Between 24 – 30 points)	264	88.6
Mild dementia (Between18-23 points)	34	11.4
GDS-30		
No depression (Between 0-10 points)	281	94.3
Depression (Between 11-30 points)	17	5.7
MNA-SF		
Malnutrition between 0-7 points	7	2.3
At the risk of Malnutrition between 8-11 points	47	15.8
Normal nutrition between12-14 points	244	81.9
MNA		
Malnutrition below17 points	3	1.0
Risk of malnutrition between 17-23.5 points	43	14.4
Normal nutrition between 24-30 points	252	84.6
BMI		
BMI weak (below 18.5 kg/m^2)	2	0.7
BMI normal weight between18,5-24,99 kg/m^2	49	16.4
BMI overweight between 25-29,99 kg/m^2	134	45.0
BMI obese 30 kg/m^2 and over	113	37.9
Total	298	100.0

SMMT: Standardized Mini-Mental Test, GDS-30: Geriatric Depression Scale Long Form, MNA: Mini Nutritional Assessment, MNA-SF: Mini Nutritional Assessment Short Form, BMI: Body Mass Index

Table II. *Comparison of sociodemographic characteristics and SMMT results*

Parameters	SMMT					
	Dementia		No dementia			
	n	%	n	%	χ^2	p*
Gender						
Male	12	7.6	145	92.4	3.902	**0.048**
Female	22	15.6	119	84.4		
Age groups						
Between 65-74 years of age	17	8.0	196	92.0	7.534	**0.006**
≥75 years of age	17	20.0	68	80.0		
Educational Status						
Illiterate	19	24.1	60	75.9	15.336	**<0.001**
Primary and higher education	15	6.8	204	93.2		
Education in males (n=12)						
Illiterate	2	16.7	10	83.3	1.180	0.277
Primary and higher education	10	6.9	135	93.1		
Education in females (n=22)						
Illiterate	17	25.4	50	74.6	7.895	**0.005**
Primary and higher education	5	6.8	69	93.2		
Economical situation						
Less income than expenses	9	18.8	39	81.2	2.246	0.134
Equal or more income than expenses	25	10.0	225	90.0		
Total	34	100.0	264	100.0		

*SMMT: Standardized Mini-Mental Test. * Chi-square test was used for analysis*

Table III. *Comparison of SMMT with GDS-30, MNA-SF, MNA and BMI*

	SMMT					
	Dementia		No dementia			
	n	%	n	%	χ^2	p*
GDS-30						
Depression	8	47.1	9	52.9	14.776	**<0.001**
No depression	26	9.3	255	90.7		
MNA-SF						
Malnutrition / malnutrition risk	12	22.2	42	77.8	6.378	**0.012**
Normal nutrition	22	9.0	222	91.0		
MNA						
Malnutrition / malnutrition risk	12	26.1	34	73.9	9.940	**0.002**
Normal nutrition	22	8.7	230	91.3		
BMI						
Obese	14	12.4	99	87.6	0.052	0.820
Non-obese	20	10.8	165	89.2		
Total	34	100.0	264	100.0		

*SMMT: Standardized Mini Mental Test, GDS-30: Geriatric Depression Scale Long Form, MNA-SF: Mini-Nutritional Assessment Short Form, MNA: Mini-Nutritional Assessment, BMI: Body mass ndex. * Chi-square test was used for analysis*

When the SMMT subcomponents were compared according to the gender of the participants, a significant relationship was found between the orientations (p<0.001), language (p<0.001) and the genders. The mean scores of orientation and language were higher in men than the mean scores of orientation and language in women. When the SMMT subcomponents of the participants were compared according to age groups, the mean scores of attention-calculation (p=0.041) and recall and language (p<0.001) were higher in individuals below 75 years of age compared to individuals older than 75 years (Table IV).

Table IV. *Comparison of SMMT subcomponents in terms of gender and age*

SMMT subcomponents	Male	Female	t	p*
	Mean±SD	Mean±SD		
Orientation	9.8±0.6	8.9±1.1	8.109	**<0.001**
Record memory	2.9±1.1	2.9±1.2	0.482	0.630
Attention-calculation	4.4±1.2	4.5±1.1	-0.501	0.617
Recall	1.1±1.3	1.1±1.0	-0.023	0.982
Language	8.6±0.5	8.4±0.6	4.014	**<0.001**
SMMT total score	26.8±2.0	25.8±2.2	3.975	**<0.001**
SMMT Subcomponents	**65-74 years of age** Mean±SD	**≥75 years of age** Mean±SD	**t**	**p***
Orientation	9.3±0.9	9.2±0.9	1.187	0.236
Record memory	2.9±0.1	2.9±0.2	1.325	0.186
Attention-calculation	4.5±0.9	4.2±1.3	2.057	**0.041**
Recall	1.2±1.2	0.7±0.9	3.472	**<0.001**
Language	8.6±0.5	8.2±0.6	4.631	**<0.001**
SMMT total score	26.7±1.9	25.5±2.3	4.463	**<0.001**

*SMMT: Standardized Mini Mental Test. * Independent samples t-test was used for analysis*

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When multidimensional geriatric assessment tests compared gender, the total score of SMMT in male (p<0.001) was significantly higher than in the female gender. The total score of GDS-30 (p<0.001) was significantly lower in males than in females. MNA-SF total score (p=0.004) was significantly higher in males than in females. There was no significant relationship between MNA total score (p=0.299) and gender.

The mean of weight, height, arm and calf circumference, BMI and abdominal skin thickness was significantly higher in normal nutritional level than in those with malnutrition and those at risk of malnutrition (p<0.05), according to MNA-SF, except the thickness of the triceps skin (p=0.332). The comparison of nutritional level and anthropometric measurements according to MNA-SF is shown in Table V.

Table V. *Comparison of nutritional status and anthropometric measurements according to MNA-SF*

Parameters	Malnutrition (a)	Risk of Malnutrition (b)	Normal nutrition (c)		
	Mean±SD	Mean±SD	Mean±SD	F	p*
Weight (kg)	63.2±15.1	69.1±15.4	78.8±12.9	13.951	**0.027**[ab] **0.001**[ac]
Height (cm)	161.1±9.5	157.2±9.1	163.2±9.9	7.421	**0.001**[bc]
Arm circumference (cm)	22.8±2.8	25.3±3.2	27.2±2.9	14.279	**<0.001**[bc] **0.001**[ac]
Calf circumference (cm)	30.3±3.8	32.8±4.3	34.5±3.8	6.880	**0.017**[ac] **0.023**[bc]
Triceps skin thickness (mm)	14.4±6.9	18.9±8.7	18.5±7.3	1.108	0.332
Abdominal skin thickness (mm)	16.8±10.4	24.3±7.8	26.7±6.8	8.243	**0.027**[ab] **0.001**[ac]
BMI (kg/m^2)	24.4±5.7	28.0±6.2	29.6±4.8	5.287	**0.020**[ac]

** BMI: Body mass index. p*= One-Way ANOVA test and Post Hoc tests were used*

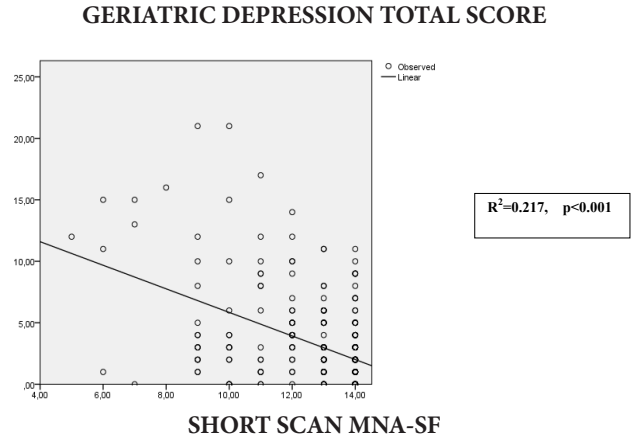
There was a moderate strong relationship in negative direction, between MNA-SF and GDS-30 (r=-0.465, **p<0.001** and in positive direction, moderate strong relationship between MNA and SMMT (r=0.415, p=0.002). Also a moderate negative relationship was found between MNA and GDS-30 (r=-0.393, p=0.003) and a high positive correlation between MNA and MNA-SF was noted (r=0.809, **p<0.001**). The correlation of age and geriatric assessment tests of the participants is shown in Table VI.

According to linear regression 21.7% of the decrease in MNA-SF total score was attributed to the total score of GDS-30 (R^2=0.217, p<0.001). The linear regression analysis between the GDS-30 total score and MNA-SF is shown in Figure 1.

Table VI. *Correlation of age and geriatric assessment tests of the participants*

Parameters		Age	SMMT	GDS-30	MNA-SF	MNA
Age	r	1				
	p					
SMMT	r	-0.285*	1			
	p	0.000				
GDS-30	r	0.018	-0.277*	1		
	p	0.758	0.000			
MNA-SF	r	-0.219*	0.283*	-0.465*	1	
	p	0.000	0.000	0.000		
MNA	r	-0.128	0.415*	-0.393*	0.809*	1
	p	0.356	0.002	0.003	0.000	

*SMMT: Standardized Mini Mental Test, GDS – 30: Geriatric Depression Scale Long Form, MNA: Mini-Nutritional Assessment Test, MNA-SF: Mini-Nutritional Assessment Short Form. * Correlation is significant at 0.01 level*



R^2= Regression coefficient of determination

Figure 1. *Linear regression analysis between GDS-30 total score and MNA-SF*
GDS-30: Geriatric Depression Scale (Long Form)
MNA-SF: Mini-Nutritional Assessment (Short Form)

4. DISCUSSION

Due to the increase in the elderly population in Turkey and in the world, there is a significant increase in the prevalence of chronic diseases and malignancies besides a decrease in cognitive abilities. In this study, the prevalence of dementia was found as 11.4%. In a study conducted by Ertekin et al., the prevalence of dementia was found to be 6.4% [16]. Another study conducted in Elazıg noted the prevalence of dementia as 5.9% in males, 9% in females and 7.3% on average [17]. Scazufca et al., reported the prevalence of dementia as 5.1% in those over 65 years of age in the 2072 study group. In the same study, the prevalence of dementia was found to be 21.4% in participants over 85 years of age [18]. We think that this difference is due to different sociodemographic characteristics such as education, sociocultural level and living standards.

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The prevalence of depression was 5.7% in this study. Cankurtaran et al., found the prevalence of depression as 21.8% in 1255 elderly consisting of 789 women and 466 men [19]. Hustey and Smith studied 267 people over 70 years of age in the USA and the prevalence of depression was 16.5 %in their study [20]. Sahin and Yalcın reported the prevalence of depression as 37.2 % for those living in their own homes and 48.1 % for those living in nursing homes in individuals aged 65 and over in Edirne [21]. Comparing to the literature, the depression risk seems to be lower in the study we reported. This difference may be due to the cultural effect like family structure and partly may be due to the higher number of men in this study.

Malnutrition risk was 15.8%, and 2.3% of the study group had malnutrition. In the study performed on elderly patients admitted to the internal medicine geriatrics outpatient clinic of Hacettepe University, 32.2% of the 236 patients were at risk of malnutrition and 19.5% had malnutrition [12]. In another study, it was found that 26.5% of males over 65 years were at risk of malnutrition and 0.9% had malnutrition [22]. The risk of malnutrition was lower in this study and this may be attributed to the research area. In the primary health care centers it was supposed to be lower than in a university hospital.

One step further MNA showed that 14.4% of the participants were at risk of malnutrition and one percent of them had malnutrition. In the study conducted at Istanbul University, the prevalence of malnutrition risk was 31% and malnutrition was 13% in patients who applied to the geriatrics outpatient clinic; malnutrition risk was 39% and malnutrition was 25% in patients who stayed in hospital [23]. The prevalence of malnutrition was found to be 12.2 % in Iranian elderly over 60 years of age with MNA test and this rate was 21.6% in elderly in nursing homes [24]. In the assessments performed by MNA test in Taiwan in individuals aged 65 and over, the prevalence of malnutrition was 1.7% for males, 2.4% for females and the prevalence malnutrition risk was 13.1% [25]. Again this study became different, with a lower prevalence of malnutrition and primary health care and university specific units in geriatrics may be the reason for this difference.

This study showed that there was more cognitive impairment in women than in men. Similarly, in a study conducted in China, the prevalence of cognitive impairment was found to be higher in women than in men [26]. Kutlu et al., noted similar results also [27]. Although, there was no relationship between dementia and education in male gender, dementia was less common in educated women according to the study we reported. Due to the high level of education in men, it was thought that the difference in cognitive function in women may be related to education level.

The presence of dementia was found to be more in those aged 75 years and over as expected because advanced age was a risk factor for cognitive impairment. In another study, the prevalence of dementia also increased in correlation with age, while it was found as 3% between the ages of 65-74 and it was found as 50% in people aged 85 and over [28]. As in previous studies, according to the increase in the prevalence of dementia according to age groups in this study, it may be claimed again that age is a risk factor for dementia.

A significant relationship was found between the decrease in education level and SMMT deterioration. According to education level, 24.1% of illiterate people had dementia, but for primary school and upper educational level, this rate was 6.8%. In a metaanalysis authors noted that 51 studies (58%) reported significant effects of low education on dementia risk, while 37 studies (42%) reported no significant relationship [29]. It can be considered that education level is a reflection of socioeconomic level and higher education reduces the risk of dementia due to better living conditions and less environmental factors.

The prevalence of dementia was higher in participants with malnutrition and in those at risk of malnutrition than in those with normal nutrition. Consistent with the literature, SMMT scores were also lower in patients who had low scores according to MNA and MNA-SF [23]. People with cognitive decline are known to have various eating and swallowing problems. Behavioral and psychological symptoms of dementia, as well as eating and swallowing problems, can strongly influence nutritional status.

Dementia was found in nearly half of the patients with depression, while it was found to be lower in patients without depression. The literature also says that depression is an important risk factor for dementia [19]. The mean score of SMMT was higher in men than women. Similar results have been reported in two studies [30]. The higher total SMMT score in males may be due to the higher level of education in them as mentioned above.

Limitations

Although, the subject of our study was extensive and important, we had to keep our working group small because of the economic factors. The fact that this study was not planned in larger groups as a multi-center study shows our limitation. Although, the results of the study cannot be reflected in the general public, we believe that it will be a study that contributes to the literature and can contribute to future studies with its important results about the role of family physicians in primary care.

Conclusion

In this study, the prevalence of dementia, depression, malnutrition and malnutrition risk was 11.4%, 5.7%, 1%, and 14.4%, respectively. The presented study showed a higher prevalence of dementia specifically in lower educated women, in more depressive women, in women who had malnutrition and in individuals aged 75 years over. Priority should be given to the training of physicians providing primary health care services so that they can recognize the symptoms of dementia, depression and malnutrition. They should be taught how to make a differential diagnosis and when to make a consultation and when to make a referral to specific health care. Regarding dementia, depression and malnutrition in the elderly in primary care; it is important to use well – designed specific scales for these conditions for early diagnosis. It will affect the quality of life of the elderly and their care givers.

Compliance with Ethical Standards

Ethical approval: Ethics committee approval was received before starting the study (Number: 2017/1054 Date:03.11.2017). The participants were informed about the study and their written and verbal consent was obtained according to the principles of Helsinki Declaration.

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Conflict of interest: The authors have no potential conflicts to declare.

Authors' contributions: Study conception: ST and RK, Design: RK, ST, Supervision: RK and NK, Data collection: ST, Formal analysis and investigation: RK and NK, Resources: ST, Writing-review and editing: RK, ST and NK. All authors approved the final version of the article.

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Comparison of endotracheal tube cuff pressures inflated with saline or air in gynecological laparoscopic surgery

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ABSTRACT

Objective: We compared the air or saline insufflated endotracheal tube (ETT) cuff pressures and their effects on postoperative respiratory complications in gynecological laparoscopic surgeries in the Trendelenburg position (TP).

Patients and Methods: This prospective study was carried out on a total of 60 patients, whose ages ranged from 18 to 65 years and who were classified by the American Society of Anesthesiologists (ASA) as I-III. They were scheduled for gynecological laparoscopic surgery in TP. Patients included in the study were randomly divided into two groups as the saline (Group S, n=30) and air (Group A, n=30) groups. ETT cuff pressures and peak airway pressures were recorded immediately after intubation and at 10-minute intervals during the intraoperative period.

Results: The cuff pressure and maximum cuff pressure values in the saline group were significantly lower than in the air group in the 50-minute ($p<0.05$). The sore throat and analgesic consumption were significantly lower in Group S in postoperative 24 hours ($p<0.001$, for all).

Conclusion: The intraoperative cuff pressures, postoperative sore throat, and analgesic consumption were lower in the saline-insufflated group than in the air-insufflated group in gynecological laparoscopic surgery in TP.

Keywords: Laparoscopic surgery, Trendelenburg position, Sore throat, Cuff pressure.

1. INTRODUCTION

Endotracheal intubation (EI) is the process of tube placement in the trachea to maintain the respiratory tract open and regulate breathing. The environmental pollution that may result from aspiration of gastric contents into the airway, gas leakage, and release of medical gases to the external environment is prevented by the cuffed endotracheal tubes (ETT) used during EI monitoring [1].

Close monitoring of the ETT cuff pressures insufflated immediately after EI and during the intraoperative period, with a cuff manometer is essential during general anesthesia. Although, cuff pressures are closely monitored after tracheal intubation, cuff pressures can also be affected by various factors such as patient position, temperature, and degree of neuromuscular blockade [2-4]. Besides, used medical gases such as oxygen, nitrous oxide, volatile inhalation agents can also have an effect on cuff pressures.

More severe complications such as transient hoarseness, sore throat, tracheal mucosal ulcer, nerve palsy, tracheal rupture, or fistula and subglottic stenosis can be observed due to the increase in high volume-low pressure ETT cuff pressures that are frequently used during general anesthesia [5-8]. Tracheal ulcers are more common in intubated intensive care patients after long-term intubation. Most complications occur due to high ETT cuff pressures, especially ischemia of the mucosa in the anterolateral surface of the trachea [9]. These complications can be prevented by keeping tracheal cuff pressures within the 20-30 cm H_2O

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range, which is regarded as safe. These cuff pressure values are considered to be below the values that impair the perfusion of the tracheal mucosa and above the values preventing possible tracheal aspiration [10-14].

Laparoscopic surgery technique is frequently preferred to open surgery in recent years due to its less invasiveness, less post-operative pain, and providing faster recovery [15]. The endotracheal cuff pressure is known to increase in operations performed in the Trendelenburg position (TP) in the laparoscopic surgery technique [16].

As a result of the insufflation of the stomach with CO_2 during the laparoscopy, intrathoracic pressure increases and lung compliance decreases in the TP. This causes an increase in cuff pressure and related complications [15]. Many drugs and methods have been used to prevent postoperative complications due to tracheal mucosa damage that occurs after the excessive swelling of cuff pressures [17-19].

The primary aim of the present study was to compare the ETT cuff pressures insufflated with air or saline during the laparoscopic gynecological operations performed in the TP and to assess sore throat complications in the postoperative period. The secondary aim is to investigate the correlation of post-operative period duration with surgical position, peak airway pressures and changes in cuff pressures.

2. PATIENTS and METHODS

Our study was conducted as a prospective clinical study in Anesthesiology and Reanimation Department between August 2017 and March 2018. The study protocol was approved by the Institutional Ethics Committee of Karadeniz Technical University, School of Medicine (approval number: 09.2013. 0262). All patients provided written informed consent.

Sixty-two patients who were scheduled to have laparoscopic gynecological surgery in the TP were included in the study. The patients were between 18-65 years old, and in the American Society of Anesthesiologists (ASA) I-III risk group. The expected operation time was 60-180 minutes. Two patients were excluded from the study, as one patient's cuff pressure was deformed which caused unreliable values, and one patient's operation time was less than 60 minutes.

Patients with neurological and psychiatric disorders, serious cardiovascular and respiratory diseases, an upper respiratory infection in the last ten days and had treatment,

a history of smoking, who was morbidly obese, who had a known allergy to anesthetic agents, alcohol or drug addiction, a history of bronchospasm, anticipation of difficult intubation, estimated duration of surgery below 60 minutes or more than 180 minutes, with a history of malignant hyperthermia, unexpected difficult intubation, who could not be intubated with first-time insertion success and whose cuff pressures were above 40 mmHg during follow-up periods were excluded from the study. Besides, patients with tracheostomy and severely disordered pulmonary compliance including airway anomaly and chronic obstructive pulmonary disease were excluded from the study.

The patients in both groups were administered 0.015 mg/kg midazolam as premedication 15 minutes before anesthesia induction in the operating room. Patients were given preoperative 30-min infusion of 10 ml/kg/h 0.9% sodium chloride. After patients were taken to the operating table, electrocardiography (ECG), heart rate (HR), non-invasive mean arterial pressure (MAP), peripheral oxygen saturation (SpO_2), end-tidal CO_2 ($EtCO_2$), (Spacelabs Healthcare, Snoqualmie, WA, USA) and bispectral index (BIS) (Aspect Medical Systems, Norwood, MA, USA) were applied in standard monitoring.

Patients included in the study were divided into two groups after their ETT cuffs were randomly insufflated with saline (Group S, n=30) or air (Group A, n=30) to a pressure of 25 cm H_2O with the help of a cuff pressure manometer (VBM, Medizintechnic GmbH, Germany) after EI. Randomization was performed before group assignment using computer-assisted random numbers from www.randomization. Cuff pressure follow-ups were performed with a cuff pressure manometer.

After pre-oxygenation with 100% oxygen for three min., 1µg/kg fentanyl, 1 mg/kg lidocaine, 2-3 mg/kg propofol, and 0.6 mg/kg rocuronium were administered for the induction of anesthesia. After sufficient time for muscle relaxation, EI was performed after the BIS values decreased below 60 (Macintosh blade 3 or 4). Before the EI procedure, cuff leakage control was done, and straight tubes with an inner diameter of 7 to 7.5 mm were used. Intubation was performed by anesthesiologists who had 3 to 4 years of experience. Following a successful EI, patients were ventilated with tidal volumes of 6-8 ml/kg, frequencies of 10-12/min. and 32-35 mmHg $EtCO_2$. O_2/air (1: 1) and 2-3% sevoflurane gas mixture was used and 0.05-2 mcg/kg/min remifentanil infusion was administered for the maintenance of anesthesia in both groups. The required depth of anesthesia was adjusted to be between BIS 40-60. Sevoflurane concentration was titrated to a maximum of 3% with 1% increase in cases without tachycardia and hypertension, whose BIS values were above 60. Muscle relaxants, hypnotics, and analgesics were administered when necessary. Heart rates, oxygen saturation, mean arterial pressure (MAP), BIS values, cuff pressure values, highest cuff pressure values, $EtCO_2$, inspired oxygen values, internal positive end expirium pressure (PEEP), and peak airway pressure values of all patients were recorded before induction, after intubation, in 10 – min intervals after induction and just before extubation. Besides, the highest values of airway and cuff pressures of the patients in the TP were also recorded.

At the end of the operation, when all patients had train-of-four (TOF) value above 25%, the non-depolarizing muscle relaxant was antagonized with 0.04 mg/kg neostigmine + 0.01 mg/kg atropine. When they all had an adequate respiratory depth and rate and had stable cardiovascular findings, the patients were extubated after oropharyngeal secretions were removed. The patients were taken from the operating room to the post-anesthesia care unit (PACU) when sufficient muscle strength (the ability to lift the head and move the extremities according to the commands) was observed, and airway stability was adequate. Patients with an Aldrete score of ≥ 9 were sent to the service from PACU [21]. Besides, sore throat in both groups

was evaluated in the postoperative period with the numeric rating scale (NRS) scoring system (NRS 0 was described as painlessness and NRS 10 was described as the worst pain ever experienced) when they were swallowing and not swallowing, and the patients with an NRS score of > 3 were administered iv. 50 mg. tramadol in PACU and in wards. In the postoperative period, the NRS scores at the 2nd and 24th hours, and the amount of analgesic used during the first 24 hours were evaluated and recorded.

Statistical Analysis

The sample size was calculated based on the cuff pressure parameter. After setting the alpha error level at 0.05, beta error level at 0.20, effect size at 0.7, the required sample size was determined as 26 for each group (By considering the potential data loss 10%), we averaged the total sample size as 60 (30 patients for each group).

The data were evaluated with IBM SPSS Statistics 25.0 (IBM Corp., Armonk, New York, USA) statistical package software. In the complete data, the number of units, denoted by (n), percentage, denoted by (%), mean ± standard deviation, denoted by (mean ± sd), median, denoted by (M) and quartile values, denoted by (Q_1-Q_3) were used as descriptive statistics. The Shapiro-Wilk Normality Test was used for the normality distribution of the numerical variables and Q1-Q3 graphics were used for evaluation. The Independent Samples t-Test was used for the comparisons between saline and air group for normally distributed variables, and the Mann-Whitney U test was used for non-normally distributed variables.

Since, there were missing observations in repetitive measurements, the comparison of the groups over time was made with mixed effect models. The estimation of missing observations was made according to the restricted maximum likelihood method. The Bonferroni test was used for multiple comparisons. The descriptive statistics were given as the predictive values of the mean and standard error (mean ± sd) in the comparisons with missing observations in the findings. Spearman Correlation Analysis was used to examine the relationships between measurements. p <0.05 was considered statistically significant.

3. RESULTS

Demographic and clinical characteristic data are shown in Table I. The cuff pressures of patients in Group S in TP and in supine position maximum cuff pressure values were significantly lower than in Group A, and peak airway pressure values in the supine position were found to be significantly high (p <0.05).

There was no significant difference between the groups during follow-up periods in terms of heart rate, mean arterial pressure, $EtCO_2$, internal PEEP, and IAP values (p> 0.05).

Cuff pressure values at 10th, 20th, 30th, 40th, and 50th minutes were found to be significantly lower in Group S than in Group A (p <0.05) (Table II).

When the airway pressure change of the groups was compared, the airway pressure values were found to be significantly higher in Group S than in Group A regarding the measurements immediately after intubation and at the 10th minute (p <0.001, for all) (Table III).

Group S had significantly lower NRS values than Group A at the postoperative 2nd and 24th hours, when groups were compared for sore throat without swallowing and swallowing (p <0.001, for all) (Table IV).

Total tramadol consumption of the groups in the postoperative 24-hour period was significantly lower in Group S compared to in Group A (p = 0.002) (Figure 1).

A moderate correlation was found between the duration of pneumoperitoneum and TP airway pressure (r = 0.596, p <0.001), and a weak positive correlation was found between supine peak airway pressure and TP cuff pressure change for all patient groups (r = 0.281, p = 0.015; r = 0.257, p = 0.027, respectively) (Table V).

Table I. *Demographic and clinical characteristic.*

	Group S (n=30)	Group A (n=30)	p
Demographic data			
Age (year)	39.9±13.8	37.9±12.5	0.517
BMI (kg.m-2)	27.1±6.7	26.9±5.7	0.955
ASA (I/II/III)	14/12/4	13/14/3	0.511
Intraoperative data			
Anesthesia time (min)	80 (64-125)	85 (65-125)	0.905
Operation time (min)	75 (60-118)	80 (60-120)	0.641
Pneumoperitoneum time (min)	45 (30-81.3)	45 (24.5-91.3)	0.854
Trendelenburg position time (min)	50 (35-87.5)	47,5 (25-95)	0.516
Supine position time (min)	30 (20.5-40)	35 (25-40)	0.192
Intraoperative pressures			
Supine peak airway pressure (cm H_2O)	24,5 (18.3-27)	18,5 (16-21,3)	0,001
Supine cuff pressure (cm H_2O)	26,5 (25-28)	28 (26-30)	0,040
Trendelenburg position peak airway pressure (cm H_2O)	27 (22-29.8)	27 (21-32)	0,991
Trendelenburg position cuff pressure (cm H_2O)	28 (28-30)	32(30-35)	<0,001
Maximum cuff pressure (cmH_2O)	28 (28-30)	32 (30-35)	<0,001

Group S: saline, Group A: air, ASA: American Society of Anesthesiologists Classification, BMI: body mass index. Data presented as mean ± SD or median.

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Table II. *Changes in endotracheal tube cuff pressure during surgery in groups*

Group	Immediately after intubation	10 min after intubation	20 min after intubation	30 min after intubation	40 min after intubation	50 min after intubation	60 min after intubation	70 min after intubation	80 min after intubation	90 min after intubation	100 min after intubation	110 min after intubation	120 min after intubation
Group S	25.0±00	25.5±0.2	26.7±0.5	27.4±0.7	27.9±0.6	28.6±0.6	28.5±0.6	28.4±0.7	28.5±0.7	28.1±0.8	26.7±0.9	27.5±0.9	27.4±0.9
Group A	25.0±00	26.8±0.2	30.5±0.5	31.1±0.7	31.2±0.6	30.3±0.6	30.1±0.6	29.6±0.6	28.6±0.6	28.2±0.8	27.2±0.9	27.1±0.8	26.6±0.9
P value	–	<0.001	<0.001	<0.001	<0.001	0.046	0.081	0.189	0.864	0.898	0.881	0.782	0.589

Group S: saline, Grup A: air. Data presented as mean ± SD, n=30 in groups, cm H2O)

Table III. *Changes in peak airway pressure during surgery in groups*

Group	Immediately after intubation	10 min after intubation	20 min after intubation	30 min after intubation	40 min after intubation	50 min after intubation	60 min after intubation	70 min after intubation	80 min after intubation	90 min after intubation	100 min after intubation	110 min after intubation	120 min after intubation
Group S	22.2±09	23.5±1.0	24.8±1.2	24.5±1.1	23.9±1.1	23.8±1.1	22.4±1.3	21.9±1.2	21.1±1.4	19.9±1.8	19.8±2.1	24.2±1.6	33.8±3.4
Group A	16.4±09	17.9±0.9	22.3±1.1	24.7±1.0	24.2±1.1	23.2±1.1	22.0±1.2	22.0±1.2	20.4±1.4	19.5±1.7	17.9±2.0	22.4±1.5	33.7±3.2
P value	<0.001	<0.001	0.133	0.916	0.857	0.682	0.823	0.953	0.730	0.875	0.525	0.433	0.996

Group S: saline, Grup A: air. Data presented as mean ± SD, n=30 in groups, cm H_2O).

Table IV. *Sore throat scores with and without swallowing in the postoperative period*

	Group S (n=30)	Group A (n=30)	p
Sore throat with swallowing at the 2nd hours postoperatively	0 (0-1)	3 (1-4)	**<0.001**
Sore throat without swallowing at the 2nd hours postoperatively	0 (0-0)	2 (0-3)	**<0.001**
Sore throat with swallowing at the 24nd hours postoperatively	0 (0-0)	2 (0-3)	**<0.001**
Sore throat without swallowing at the 24nd hours postoperatively	0 (0-0)	1 (0-2)	**<0.001**

Group S: saline, Group A: air

Table V. *Correlations between pneumoperitoneum time and peak airway-cuff pressures change*

	Pneumoperitoneum time
	All Groups (n=60)
Trendelenburg position peak airway pressure change	
rho	0.596
p	<0.001
Supine position peak airway pressure change	
rho	0.281
p	0.015
Trendelenburg cuff pressure change	
rho	0.257
p	0.027
Supine position cuff pressure change	
rho	0.126
p	0.287

rho: correlation coefficient

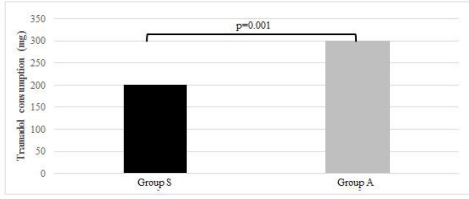

Figure 1. *Total tramadol consumption of the groups in the postoperative 24 hour period (mg).*
Group S, saline ; Group A , air.

4. DISCUSSION

In our study, lower cuff pressures, less sore throat, and fewer analgesic requirements were reported in the patients whose ETT cuffs were insufflated with saline compared to the air-insufflated group in the operations performed with the gynecological laparoscopic method in the TP.

Endotracheal intubation is a frequently used method to ensure airway safety. However, due to the increase in cuff pressures of the cuffed ETTs, frequently used during EI, laryngotracheal morbidity can occur due to damage to the tracheal mucosa which contacts with the cuff [21]. Increased cuff pressure can cause tracheal complications in short-term surgeries as well as long-term surgeries [22]. In vivo studies have shown that tracheal capillary perfusion pressure ranges from 30 to 44 mmHg [14]. Thus, as a general approach, the intraoperative cuff pressure is recommended to be 20 cm H_2O [23]. High cuff pressures in the intraoperative period may cause sore throat and hoarseness during the postoperative period [24]. In our study Group S had significantly lower NRS values than Group A at the postoperative 2nd and 24th hours.

Laparoscopic surgery is common, and it has many advantages [25]. In laparoscopic surgeries, CO_2 is commonly used to provide intra-abdominal distention to improve the surgical field of view [26]. After the TP with pneumoperitoneum (PP), the diaphragm increases, even more, lung expansion is restricted and lung compliance decreases due to the increase in airway pressures [25]. The pressure applied to the trachea wall also increases due to the increase in cuff pressures caused by the increase in airway pressures depending on CO_2 PP. Due to this pressure increase, it can cause ischemic damage and tracheal necrosis as a result of the disruption of perfusion in the tracheal mucosa [22]. As a result of all these, sore throat and hoarseness are common during the postoperative period.

In a study by Yıldırım Z et al., it was reported that the effect of PP on cuff pressure in patients undergoing laparoscopic cholecystectomy and open abdominal surgery, the cuff pressures were found to be higher in the laparoscopic group during all follow-up periods. Besides, the cuff pressure was found to exceed 30 cm H_2O after the first 5th minute of PP. In the clinical image of this pressure increase, sore throat was found to be higher in the laparoscopic group at the 12th hour after the surgery [26]. While laparoscopic cholecystectomy operations are often performed in the reverse TP position, we performed our gynecological operations in the TP position.

The position of the patient is as important as the insufflation of the abdomen to provide a good surgical view in the operations performed with the laparoscopic method. This can increase the risk of airway complications in the postoperative period [27]. A frequently used position in gynecological laparoscopic operations, TP was found to increase cuff pressure significantly and the frequency of postoperative sore throat compared to laparotomy patients [15]. In a study conducted by Geng G et al., cuff and airway pressures and postoperative sore throat of patients undergoing open and laparoscopic gynecological surgery were compared. A significant increase was observed in airway and EI cuff pressures in the TP after PP in the laparoscopic group compared to the open surgery group. Besides, sore throat at the 2nd and 24th hours after surgery was found to be significantly higher in the laparoscopic group compared to the open surgery group [15].

In a study of Wu CY et al., the effects of PP and surgical position on the cuff and airway pressures in laparoscopic surgery were investigated, no significant change in the cuff and airway pressures were observed during 15 minutes before PP, while a significant increase in the mean airway and cuff pressures was detected in patients in the TP. Although, there was a strong correlation between airway pressure change and cuff pressures caused by abdominal insufflation, there was no correlation between position [16].

Kwon Y et al. investigated the relationship between ETT cuff pressure change and body mass index (BMI), pneumoperitoneum period, and cuff pressure in patients undergoing laparoscopic cholecystectomy. N_2O was used for analgesic purposes during surgery. There was no difference between airway pressures and cuff pressures throughout the operation between groups with different BMIs. In the same study, there was a weak positive correlation between pneumoperitoneum duration and cuff pressure change. The change in cuff pressure was not affected by BMI, but pneumoperitoneum duration caused a change in cuff pressure [28]. In our study, there was no significant difference in BMI between groups. In addition, we found a weak correlation between pneumoperitoneum duration and cuff pressure change in the TP.

In the study conducted by Rosero EB et al., in patients with BMI≥30 kg/m², who underwent laparoscopic gynecological surgery without using nitrous oxide, the mean cuff pressure, and peak airway pressures were found to be significantly higher in PP period than the period from intubation to insufflation of the abdomen. Besides, the increase in peak airway pressure and cuff pressure was reported to be related to each other, and every 1 cm H_2O increase in peak airway pressure was found to cause a 0.25 cm H_2O increase in EI cuff pressure [9]. In our study, we investigated the relationship between pneumoperitoneum periods and peak airway pressures in the TP. A moderate correlation was reported between PP time and peak airway pressure change in the TP. Therefore, we believe that increase in peak airway pressures in the TP would cause an increase in cuff pressure.

The frequency of postoperative sore throat induced by EI ranges from 60 to 90% [29]. Depending on the swelling of the cuff and damage to the pharyngeal mucosa and recurrent laryngeal nerve, it can lead to many complications such as hoarseness, aphonia, stridor and respiratory distress. Postoperative sore throat is also affected from the factors such as age, gender, intubation conditions the diameter of the ETT, the shape of the cuff, the movement of the EI in the trachea, the medical gases used and the increased cuff pressure [30].

In the literature, the fluid mechanics was used to explain the basis of the studies carried out with saline-insufflated ETT cuff to prevent postoperative sore throat after EI. According to the Pascal principle, given the mechanics of fluids, the pressure, applied externally to a system, is transmitted equally by the liquid to all points of the liquid and every point of the inner surfaces of the container regardless of the volume of the container [31]. In accordance with the same principle, during positive pressure ventilation, the trachea and the ETT cuff are considered as part of the same closed pneumatic system [9]. In the light of this information, we determined the hypothesis of our study as the insufflation of the cuffs of the EI tubes with saline to prevent the increase of EI cuff pressure in gynecological laparoscopic operations performed in TP and to prevent postoperative sore throat.

Ahmad NL et al., found that the cuff pressures were lower in the saline-insufflated ETT cuff group than the air-insufflated group in patients undergoing elective abdominal and limb surgery under general anesthesia with N_2O [32]. In our study, cuff pressures were reported to be lower in the group whose cuffs were insufflated with saline to prevent postoperative complications due to possible high cuff pressures in the TP, while remifentanil was used instead of nitrous oxide when maintaining the patients' heads and necks in the neutral position. As a result, less sore

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throat was observed in the postoperative period due to low cuff pressures in the saline-insufflated group.

In a study by Besir A et al., the ETT cuffs were insufflated with saline and air in patients under low flow general anesthesia using N_2O. The ETT cuff pressures were found to be lower in the saline-insufflated group with the prevention of the diffusion of N_2O into the cuff, and the sore throat was significantly lower in the saline-insufflated group during the postoperative period [33].

In a study by Shroff PP et al., in which the ETT cuffs were insufflated with air, saline, and 2% lignocaine, cuff pressure, postoperative sore throat, and hoarseness in the saline group were the same as the group insufflated with 2% lignocaine and were significantly lower than air-insufflated group [34].

In the laparoscopic gynecological operations performed in the TP, insufflation of ETT cuffs in the prevention of postoperative sore throat due to the increase in cuff pressures are not common in the literature. In our study, we concluded that sore throat can be prevented by preventing the increase of intraoperative cuff pressure with the insufflation of ETT cuff with saline.

Limitations

There are some limitations of our study. **First,** we could not directly evaluate the tracheal mucosal damage, which could reveal the symptoms of hoarseness and sore throat that may occur in the trachea after EI and develop in the postoperative period. **Second,** the patients were followed up for 24 hours in the postoperative period. Although, the frequency and severity of sore throat tend to decrease in the postoperative 24-hour period, there is a need for longer periods of follow-up for the evaluation of postoperative sore throat and hoarseness in the long term. **Third,** we used the ETTs of a single type from the same manufacturer. Therefore, our findings may not apply to different types of ETTs produced by different manufacturers. **Fourth,** although, nitrous oxide was not used as an analgesic in the maintenance of anesthesia in our study, we did not measure the concentrations of other medical gases (e.g. CO2 or O2) that would cause pressure changes in the ETT cuffs and therefore we could not evaluate their effects on ETT cuff pressure changes. **Finally,** anatomical structures such as the upper part and inner diameter of the trachea differ according to the geographical regions. Since, our study is a single-center study, the results are limited to a specific region. There is a need to carry out further multi-center studies.

Conclusion

We believe that the method of the insufflation of the ETT cuff with saline, an easily applicable method, can reduce the postoperative sore throat that occurs due to the increase in ETT cuff pressure and the need for analgesic consumption that occurs accordingly in the TP in gynecological laparoscopic surgery.

Compliance with Ethical Standards

Ethical Approval: The study protocol was approved by the Institutional Ethics Committee of Karadeniz Technical University, School of Medicine (approval number: 09.2013. 0262). All patients provided written informed consent.

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Conflict of Interest: The authors have no conflicts of interest to declare.

Authors' Contributions: Literature search: SS and AB, Study design: SS and AB, Legislative applications: SS and AB, Data collection: SS, AA and ET, Supervision and quality control: SS, AA and ET, Statistical advice: SS and AB, Statistical data analysis:SS, AB,SS and AA, Data interpretation: SS, SS, ET and AB, Drafting the manuscript: SS, AB, ET and SS. All authors approved the final version of the article.

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Clinicopathological features of trichoblastomas and malignant variant: trichoblastic carcinoma

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ABSTRACT

Objective: Trichoblastomas are rare benign tumors of the skin appendages with epithelial and mesenchymal components that exhibit differentiation to the follicular germinative epithelium and particularly to the follicular stroma of the skin. Our aim was to contribute to already limited literature data in order to gain more insights into the treatment and follow-up of patients with this condition.

Methods and Materials: A total of 9 patients with trichoblastoma and 1 patient with malignant trichoblastoma were surgically treated between 2016 and 2020 at the Department of Plastic, Reconstructive and Aesthetic Surgery, School of Medicine, Marmara University.

Results: Of the 10 patients with trichoblastoma, 5 were female and 5 were male, with a median age of 49 years. The smallest and largest lesion lenghts were 0.4 and 2 cm, respectively. Seven lesions had developed in the head and neck region, while 2 were in the trunk. One of our cases was a 45-year old female patient with a malignant trichoblastoma presented with a lesion in the right side of the lower lip.

Conclusion: Trichoblastomas are rare tumors that affect both sexes equally and are seen most commonly in the head and neck region. Recurrence rates were found to be low when they were treated with negative surgical margins.

Keywords: Skin Neoplasms, Plastic Surgery, Histopathology

1. INTRODUCTION

Trichoblastomas are rare benign tumors of the skin appendages with epithelial and mesenchymal components that exhibit differentiation to the follicular germinative epithelium and particularly to the follicular stroma of the skin [1]. Although they may develop at any site harboring hair follicles, the most common site of involvement is the head and neck region [2-5]. Generally, they form plaques, nodules, or papilla. Although, most patients have sporadic lesions, multiple lesions may occur generally in conjunction with Brooke-Spiegler Syndrome or its phenotypic variant, i.e. "multiple familial trichoepithelioma" [6]. The malignant form is even more uncommon, with two morphological types reported: trichoblastic carcinoma and trichoblastic carcinosarcoma.

Histopathologically, trichoblastomas are symmetric lesions with well-defined boundaries that are localized in the dermis. The tumor consists of basaloid cell islets with occasional areas of palisading cells surrounded by intense follicular fibrotic stroma. It has several subtypes depending on the growth pattern: large nodular, small nodular, cribriform (trichoepithelioma), racemiform, retiform, and columnar (desmoplastic trichoblastoma). It is important to be aware of the presence of these subtypes for successful differential diagnosis. Furthermore, other pathological features may be observed including sebaceous and ductal differentiation, hyaline transformation, and melanocytic hyperplasia. Basal cell carcinoma (BCC), microcystic adnexal carcinoma, and syringoma may be associated with challenges in differential diagnosis, particularly in smaller biopsy samples. BCC, the most common malignant skin tumor, lacks specific follicular stroma. Palisading alignment around the cell islets is more prominent

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and retraction artifacts are present. Immunohistochemical staining showing androgen receptor positivity and lack of Merkel cells which can be detected with cytokeratin 20, favor a diagnosis of BCC, while the opposite favors a diagnosis of trichoblastoma [7].

Our aim was to contribute to already limited literature data in order to gain more insights into the treatment and follow-up of patients with this condition.

2. MATERIALS and METHODS

A total of 9 patients with trichoblastoma and 1 patient with malignant trichoblastoma, surgically treated between 2016 and 2020 at the Plastic, Reconstructive and Aesthetic Surgery Department, School of Medicine Marmara University were included in the study. Information such as the site of involvement, therapeutic modalities administered, recurrence rate, and presence of concomitant skin tumors was retrieved from patients' records and pathology reports. All patients underwent excisional biopsy with total tissue sampling. Following routine tissue preparation, the cross-sections were stained with Hematoxylin and Eosin. If required, additional cross-sections were prepared and immunohistochemical studies were performed to aid in the differential diagnosis.

Excisional biopsy was performed in all lesions. Due to narrow surgical margins, two patients underwent re-excision. Since, trichoblastoma is a rare tumor of the skin appendage, its treatment is relatively obscure. The mean duration of follow-up in our patients was 33 months. Absence of recurrences, including the three patients with longest follow up (53, 55, and 62 months, respectively), suggests that excision with negative surgical margins may suffice for treatment.

The study was conducted in accordance with the principles of the Declaration of Helsinki. This study was approved by the Marmara University, School of Medicine, Ethics Committee (Approval number: 08.05.2020; 09.2020.530).

Statistical Analysis

Statistical analysis was performed using the SPSS version for Windows 15.0 software (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed in mean ± standard deviation (SD), median (min-max), while categorical variables were expressed in number and percentage. The unpaired *t*-test was used to compare continuous random variables between the time periods, while the chi-square test was used to compare discrete random variables. A p value of <0.05 was considered statistically significant.

3. RESULTS

Of the 10 cases with trichoblastoma, 5 were female and 5 were male, with a median age of 49 years. Seven patients were less than 60 years of age, while 2 were ≥ 60 years of age. The smallest and largest lesion lenghts were 0.4 and 2 cm, respectively. Seven lesions had developed in the head and neck region, while 2 were in the trunk. In one case, trichoblastoma in association with concomitant syringocystadenoma papilliferum had developed on the background of a sebaceous nevus. Also, three patients had concomitant BCC, poroma, and seborrheic keratosis, one in each respectively. A negative surgical margin was considered to indicate adequate treatment. However, resection was done in 2 patients, due to deep or lateral continuation, one each respectively. The mean duration of follow up was 33.44 ± 15.48 months. The clinical characteristics of the patients are shown in Table I. Histopathologically 8 lesions were localized in the superficial dermis, had well-defined margins, and contained basaloid cell groups and specific follicular stroma in their surroundings (Figure 1). With regard to growth pattern, the most common subtype was the nodular subtype, with 5 patients having double or triple patterns such as small nodular, cribriform, racemiform and retiform types. It was interesting to note the presence of melanin pigment in two patients. No patients had recurrence.

One of our cases differed slightly from the others. This case was a 45-year old female patient with a history of malignant trichoblastoma who presented with a lesion in the right side of the lower lip that had existed for a one-year period with accelerated growth within the past 3 months. The lesion was 1 cm in length and had a nodular appearance (Figure 2). A pre-diagnosis of BCC was made and the patient underwent excisional biopsy with a 2-mm surgical margin. Due to a pathological diagnosis of malignant trichoblastoma, re-excision with wedge excision was carried out with a surgical margin of 1 cm. Cervical computed tomography did not show any lymph node metastases. In histopathological examination, the tumor consisted of small nodules with significant follicular differentiation that infiltrated into the subcutaneous tissue and superficial muscles. The perineural invasion observed in one field facilitated the diagnosis of malignancy (Figure 3). The patient was followed up for 36 months and no recurrence was detected.

4. DISCUSSION

In the current study, the largest lesion was 2 cm. However, patients with lesions of up to 6 cm have also been reported [8]. Trichoblastomas are papule or nodule like lesions that are generally less than 2 cm in diameter. The lesions are generally the same color as the skin. Less frequently, brown-black colored pigmented forms that can be clinically mistaken for malignant melanoma or pigmented BCC have also been reported [5, 9]. In our patient series, although, two patients had focal melanin pigment microscopically, no cases had clinical pigmentation. Lesions the same color as the skin were more likely to be confused with BCC.

It has been reported that both trichoblastoma and malignant trichoblastoma may develop on the background of sebaceous nevus, and such lesions are generally larger and more heavily pigmented [10,11]. One of our patients also had a lesion that developed on the background of sebaceous nevus, although, with no pigmentation. This lesion was accompanied by

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syringocystadenoma papilliferum that also developed on the background of sebaceous nevus. Syringocystadenoma papilliferum is a benign tumor of the skin appendage that frequently develops on sebaceous nevi. Total excision and primary repair were performed for these sebaceous nevi with negative surgical margins.

Although published literature suggests that trichoblastomas mostly occur in subjects over 60 years of age, an 11 year old pediatric patient has also been reported [12]. In our study, the median age was 49 years, with only two patients being older than 60 years of age, and the youngest patient was 16 years old. With regard to gender distribution, there were 5 male and 5 female patients. Again, in line with the published data, 7 of the lesions (77.77%) were in the head and neck region [13]. Although, more frequent occurrence in this region suggests that UV light may play an etiological role, definitive evidence for this hypothesis is lacking.

Malignant trichoblastoma has only been described in case reports in the literature. Pigmented forms such as trichoblastomas and giant forms have also been reported [14,15]. As in our patients, these lesions mostly affect the head and neck region [16] and the elderly, although, other locations such as the abdomen [17] and the paraspinal area [18] may also be involved.

The histopathology of malignant trichoblastoma consists of an epithelial component that is surrounded by special follicular stroma, as in the benign form, although, it has also moderate or marked atypia. On the other hand, in trichoblastic carcinosarcoma, both components are of malignant nature. Our patient had well – differentiated trichoblastic carcinoma that displayed pronounced follicular differentiation. Although predisposing factors have not been fully elucidated, lesions developing on the background of trichoblastoma have been reported [19], with a more aggressive clinical course. Our patient lacked the benign trichoblastoma component. Also, other 9 patients with trichoblastoma did not have malignant transformation.

As this tumor is very rare, no treatment principles have been established. The therapeutic option may be determined on the basis of the tumor stage. A screening for metastatic lesions is recommended, as patients with lymphatic or hematogenous spread have been reported [20]. The primary form of treatment reported in the literature involves surgical excision. There is no clear-cut consensus regarding the surgical margins, with some studies reporting excisions ranging between 0.5 cm and 1.5 cm [13-15]. In our patient, excision was performed to achieve a surgical margin of 1 cm, with primary repair. Since, the screening for metastatic lesions was negative, no additional treatments were administered. However, some authors opted for radiotherapy even in non-metastatic patients [21]. Our patient was followed up every 3 months in the first year, and by bi-yearly exams thereafter, as the lesion was small, pathological stage was low (pT1), and surgical margins were extended. No recurrence or lymphatic/hematogenous metastases were detected at the end of 36 months' of follow-up.

Trichoblastomas are rare tumors originating from hair follicles and their malignant forms have been reported even less frequently. In this study, our aim was to contribute to already limited literature data in order to gain more insights into the treatment and follow-up of patients with this condition. Recurrence rates were found to be low when they were treated with negative surgical margins.

Table I. *Demographic features of patients*

No	Sex	Age	Localization	Size (cm)	Accompanying tumor	Follow-up (month)
1	Female	32	Left medial canthus	0,5	BCC	16
2	Male	41	Left upper eyelid	0,4	-	16
3	Male	78	Left deltoid	0,6	Poroma	23
4	Male	49	Nasal dorsum	0,6	Seborrheic keratosis	28
5	Female	49	Left nasolabial fold	0,5		29
6	Male	51	Trunk	2		55
7	Male	34	Right nasolabial fold	0,6		53
8	Female	64	Left temporal	1,3	Syringocyst-adenomapapilliferum	62
9	Female	16	Nasal dorsum	0,5		19
10	Female	45	Lower lip	1		36

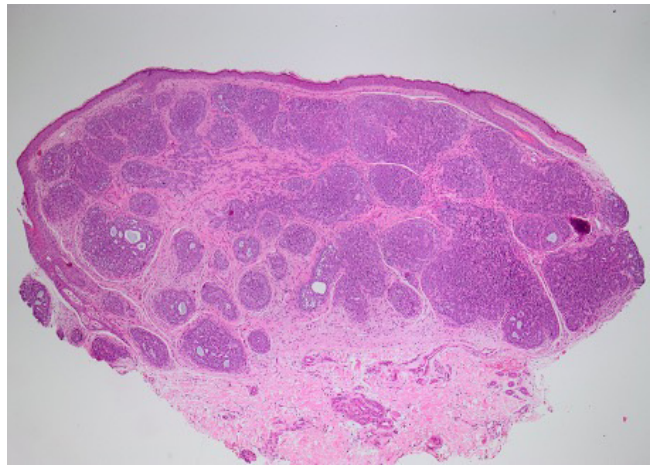

Figure 1. *Well – circumscribed basaloid cell groups and the surrounding fibrotic stroma in the dermis. Large nodular and cribriform growth pattern are seen. H&Ex40*

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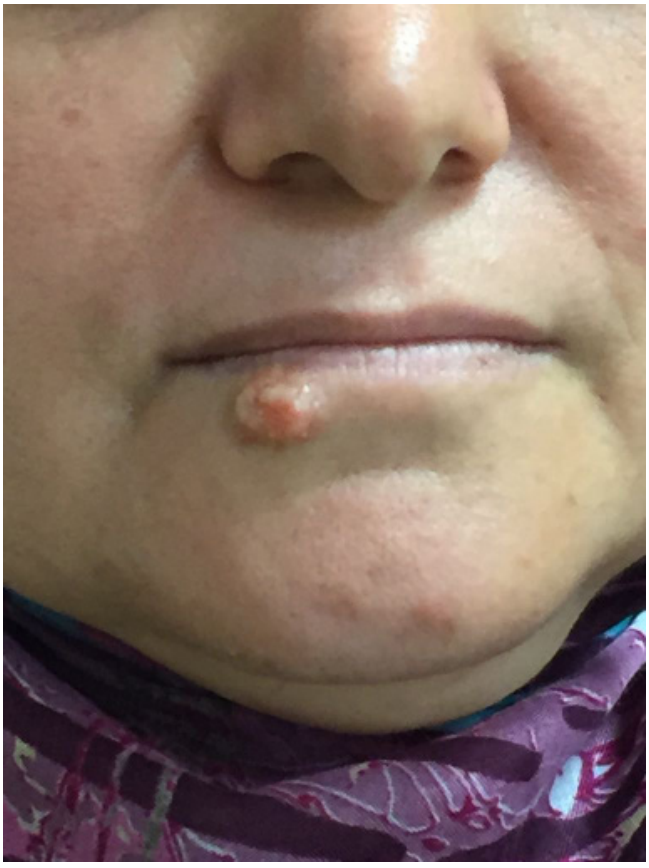

Figure 2. *Nodular lesion at the right of the lower lip diagnosed as malign trichoblastoma.*

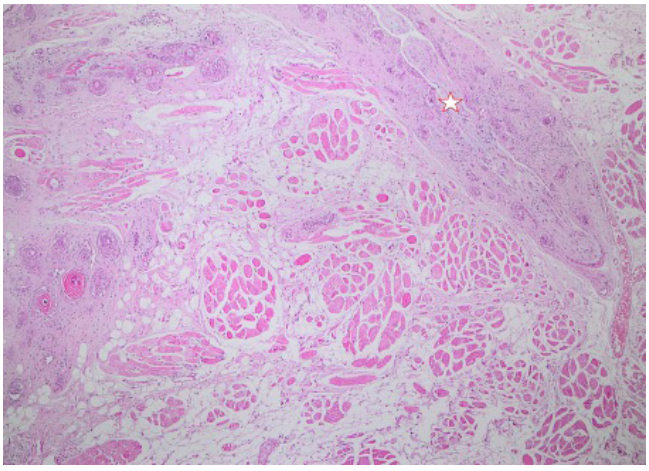

Figure 3. *Subcutaneous fat tissue and perineural invasion of malign trichoblastoma (Shown with star). H&Ex40*

Compliance with Ethical Standards

Ethical approval: The study was conducted in accordance with the principles of the Declaration of Helsinki. This study was approved by the Marmara University, School of Medicine, Ethics Committee (Approval number: 08.05.2020; 09.2020.530).

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Conflict of interest: The authors have no potential conflicts to declare.

Authors' contributions

Conception and design of the study, data collection and writing: MCO and ZLC, Analysis and interpreation of data: MCO, Editing: ZLC. Both authors read and approved the final version of the article.

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Original Article

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Ultrasound guided steroid injection of subacromial bursa: morphologic and clinical effects on patients with supraspinatus tendon calcifications

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ABSTRACT

Objective: Subacromial injection (SAI), due to its ease of application and increased patient tolerability, is one of the preferred invasive therapies. In this study, we aimed to evaluate effectiveness of ultrasound-guided SAI in patients with supraspinatus calcific tendinitis by assessment of roentgenograms and clinical appraisal.

Patients and Methods: Thirty-five patients with supraspinatus tendon calcifications as revealed by the roentgenography underwent ultrasound-guided SAI. Pre-treatment the Disabilities of the Arm, Shoulder and Hand questionnaire (QuickDASH) scores and Gartner's Classification of calcific tendinitis were obtained. Clinical follow-up was scheduled at 1st, 3rd and 6th months post-treatment along with a single roentgenogram planned at 6th month.

Results: A total of 53 SAIs were performed on 36 shoulders, 21 female and 14 male patients. Mean size of calcifications were 12.3 and 7.1 mm, pre-treatment and at 6th month, respectively. Pre and post-injection calcification mean sizes in the group with clinical improvement were 13.6 and 5.7 mm; whereas, in group without diminished symptoms, they were 11.8 and 9.4 mm demonstrating a statistically significant intergroup difference ($p<0.05$). Pre-injection QuickDASH mean score was 52.2; this showed improvement at 1st, 3rd and 6th months post-treatment; 20.7, 22.2 and 19.5, respectively.

Conclusion: Subacromial injection is a well-tolerated, easily applicable, safe and effective treatment for pain alleviation in supraspinatus calcific tendinitis.

Keywords: Calcific tendinitis, Shoulder joint, Subacromial bursa, Sonography guided injection, Steroid injection

1. INTRODUCTION

Calcific tendinitis occurs due to accumulation of calcium hydroxyappatite crystals in tendons close to insertion points. It is most commonly observed in shoulder and hip joints and is a major cause of joint pain. It has been reported to be the culprit in about 7 to 50% of shoulder artralgia cases [1, 2]. Approximately, 20% of patients with rotator cuff calcific tendinits are asymptomatic despite tendon calcifications [3]. Condition progresses through 3 phases initially from formative (precalcific) phase to resting (calcific) phase, and finally to resorptive (post-calcific) phase with gradually worsening symptoms. Most common symptoms are pain, typically in deltoid region, and decreased range of motion especially worsening after exertion or during night. Most painful period is when fragmentation of calcification develops and fragments migrate into adjacent bursae causing bursitis [1] .

Noninvasive palliation through physical therapy and use of non-stereoidal anti-inflammatory drugs are valid treatment options for this usually self-limiting condition. First-line treatment is deemed unsuccessful if clinical improvement cannot be achieved despite minimum total of 3 months of treatment within a 6 months period [4]. In cases where pain could not be alleviated leading to a lesser quality of life, more invasive treatment options should be considered including minimally invasive surgery, extracorporeal shockwave lithotropsy (ESWL), ultrasound

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or fluoroscopy guided needling and lavage (barbotage) and isolated subacromial injection (SAI) [5, 6]. Among these treatment methods, although there is no consensus which one should be prefered for these patients, SAI is preferred frequently because it can easily be performed and it is also well tolerated by patients [7], but effect of SAI on tendinic calcification levels and clinical outcomes has been controversial. In this study, we aimed to evaluate effectiveness of ultrasound-guided SAI in patients with supraspinatus calcific tendinitis by assessment of the roentgenograms and clinical appraisal.

2. PATIENTS and METHODS

This study was approved by the Marmara University School of Medicine ethics committee (approval number: 09.2020.703) and was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amndments or comparable ethical standards.

A total of 208 patients who referred to interventional radiology due to chronic shoulder pain between 2017 and 2019, who did not respond to conservative treatment and received ultrasound-guided SAI treatment were reviewed, retrospectively. Among them 35 patients with supraspinatus tendon calcification detected on roentgenographs were included in the study. Case files of 35 patients pertaining to procedure reports, shoulder antero-posterior (AP) roentgenograms, clinical and radiologic outcomes were assessed. The Disabilities of the Arm, Shoulder and Hand Score (QuickDASH) questionnaire was completed by the patients prior to treatment [8]. Gartner's classification was used for the evaluation of tendon calcifications [9]. Number of calcifications and affected tendons, and calcification dimensions were also recorded. In cases with multiple calcifications in the supraspinatus tendon, statistical evaluation of effect of SAI on calcifications was based on interval measurements of the largest calcification prior to intervention. A 4-point Likert scale (completely reduced, significantly reduced, unchanged and worsened) was used for patients to assess their perceptions of pain. While patients with completely and significantly reduced pain were classified as clinically improved, the others were identified as clinically non-improved.

The QuickDASH is a 11-item questionnaire that evaluates symptoms as well as the ability to perform certain activities in patients with any musculoskeletal disorders of the upper limb. It is a 5 point Likert scale (1 being no difficulty, 5 being unable). It has also two optional 4-item additional modules: sport/music and work modules. The completed responses are summed and averaged. This value is then transformed to a score out of 100 by subtracting one and multiplying by 25. Higher scores indicate a greater level of disability and severity [8] .

Gartner's classification is a radiological classification of calcifying tendinitis [9]. It has three types;

Type I: clearly circumscribed, dense calcification, formative

Type II: clearly circumscribed, translucent calcification or dense calcification without a clear outline

Type III: translucent appearance without a clear outline, resorptive

Injections were guided using a Logic E9 sonography device (GE Healthcare, Milwaukee, USA) and a 6-15 MHz linear probe. After appropriate skin preparation and draping, subacromial bursa was entered using a dental needle attached to the tip of a 5 ml disposable syringe and a total of 5 ml sterile mixture of 4 ml Prilocaine (Citanest) and 1 ml Betamethasone (Diprospan) was injected. Local infiltration anesthesia of the skin and subcutaneous tissues was not performed. Needle entry into tendon calcifications and barbotage were consciously avoided. All patients routinely received oral non-steroidal anti-inflammatory drugs for 3 days post-procedure and use of pain medications was extended up to 15 days when pain did not subside within early post-intervention period. Movement restrictions were not suggested. Patients were called for follow-up at the first, third and sixth months post-injection. The SAI was repeated in patients who did not clinically improve during follow-up. Control roentgenograms were performed at the sixth-month follow-up to record changes in tendon calcifications.

Statistical Analyis

Data analysis was performed using SPSS Statistics software (Version 23, IBM Corp. Armonk, NY). The normality of the parameters was assessed with Shapiro-Wilk test. Descriptive statistical analyses were done for patient age, gender, treatment response, Gartner classification distribution of calcifications and Quick DASH scores. Dependent samples t-test was used to evaluate effect of SAI on tendon calcification dimensions. Relationship between clinical response to treatment and decrease in tendon calcification dimensions after SAI was assessed by independent sample t-test.

3. RESULTS

A total of 35 patients, 21 female and 14 male, with a mean age of 50.6 (22-71) years had undergone SAI. Mean ages in male and female patient groups were 46.2 (22-68) and 52.7 (29-71) years, respectively. Demographic and clinical data of patients are presented in Table I. Four patients received bilateral shoulder injection; only one of those had tendon calcifications bilaterally. In total, 35 patients and 36 shoulders were included in the study. There were 13 right shoulder and 23 left shoulder involvements. Excluding one patient with bilateral supraspinatus tendon calcifications, 19 patients had involvement of dominant hand side and 15 had calcification of the non-dominant hand side. Average time between onset of shoulder pain and SAI procedure was 5 (range 2-8) months. Technical success was achieved in all patients. There were no early or delayed procedure related complications. A total of 53 SAI were performed on 36 shoulders. Multiple injections were performed on 12 shoulders in different sessions; 7 shoulders received 2 injections while 5 shoulders received 3 injections each due to unremitting pain. During first and third month control visits repeat SAI were performed on a total of 8 and 9 shoulders, respectively. Treatment findings and follow-up results are summarized in Table II.

Table I. *Clinical and demographic data of patients*

Age $_{(years)}$ (mean ± SD) (min-max)	50.6 ± 13.7 (22-71)
Male	46.2 ± 11.6 (22-68)
Female	52.7 ± 15.4 (29-71)
Gender (Female/Male)	14/21
Affected side (Right/Left)	13/23
Affected side (Dominant/non – dominant)	20/16
Symptom duration before SAI $_{(months)}$ (min – max)	5.2 (2-8)
Gartner's Classification (Type I / type II/ type III)	9/12/15
Number of SAI	
1 injection	24 Shoulder
2 injections	7 patients
3 injections	5 patients
Re-injections	
1st month	8 patients
3rd month	9 patients
QuickDASH score before SAI (mean ± SD)	52.17 ± 16.33
Calcification diameter before SAI $_{(mm)}$ (mean ± SD) (min-max)	12.3 ± 4.9 (3.6-24.9)

SAI: Subacromial injection, DASH: Disabilities of Arm, Shoulder and Hand

Table II*. Treatment and follow-up results*

	1st month	3rd month	6th month	P value
Patients (n)	28	32	33	
Pain response				
Completely reduced	18	20	22	
Significantly reduced	2	3	4	
Unchanged	5	8	7	
Worsened	3	1	0	
QuickDASH scores				
Before SAI/1st month	49.9/20.7	52/22.2	51.9/19.5	**<0.0001**
Before SAI/3rd month				**<0.0001**
Before SAI/6th month				**<0.0001**
Calcification Diameter $_{(mm)}$				
Clincally improved patients			13.6/5.7	**<0.0001**
Before SAI/ 6th month			11.8/9.4	0.24
Clinically non-improved patients				
Before SAI/ 6th month				

SAI: Subacromial injection, p:

Calcifications were of Gartner type I in 9, type II in 12 and type III in 15 shoulders. Mean calcification dimension, measured in longest axis, was 12.3 mm (3.6 – 24.9 mm) preintervention. Quick DASH mean score was 52.17 prior to procedure. Patient compliances to follow-up were as follows: 28 shoulders at 1st month; 32 at 3rd month; and 33 at 6th month-visits. Three patients had undergone arthroscopic surgery prior to 6th month visit, hence provided no 6th month control roentgenograms. 18 shoulders were painless and 2 had reduced pain at 1st month control with an average Quick DASH score of 11.02 which was 48 preintervention. At the 3rd month visit 20 shoulders were completely pain-free and 3 were with significantly reduced pain with a mean Quick DASH score of 9.88 which was 49.45 preintervention. At the 6th month visit 22 shoulders were painless and 4 had significantly reduced pain; mean Quick DASH score was 10.05 (preintervention Quick DASH score 48.99).

Arhroscopic surgery was performed in 4 patients due to increased pain after SAI, one of those was after the 6th month-visit. Mean interval between surgery and onset of pain and first SAI were 9.3 and 3.7 months, respectively. Three patients had a single repeat SAI whereas, 1 had two repeat SAI before resorting to surgery.

Calcification types had been altered in 27 of 33 shoulders on the 6th month control roentgenograms. Fourteen Gartner type II calcifications had evolved to type III; whereas type I to type II and type I to type III evolutions were observed in 7 and 6 shoulders, respectively. All shoulders had smaller calcifications in control roentgenograms with a reduced mean longest dimension of 7.1 mm which was 12.3 mm prior to SAI. Comparison of interval change of calcification sizes among clinically improved and non-improved patients was statistically significant ($p<0.05$). Clinically improved group had preintervention and control calcification dimensions of 13.6 and 5.7 mm with 58% postintervention reduction. On the other hand, clinically non-improved group had only 20% reduction, from 11.8 to 9.4 mm. All patients with >50% reduction in calcification dimensions had either complete or significant remission of shoulder pain.

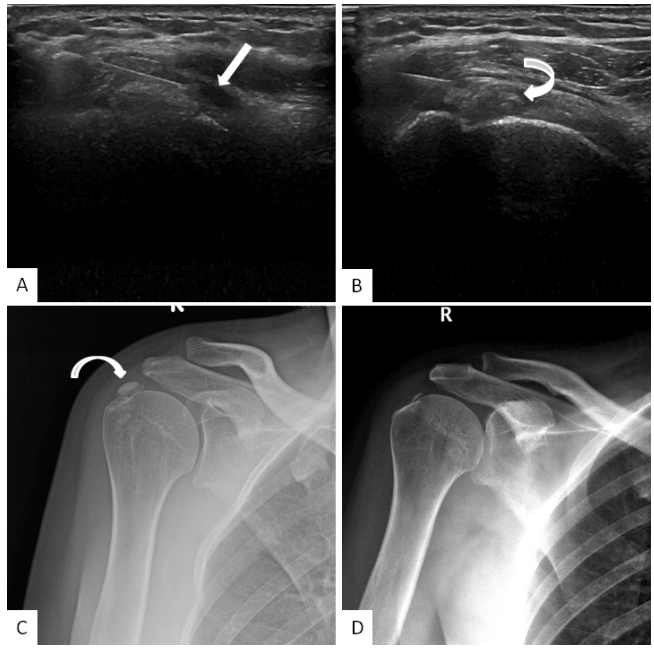

Figure 1. *A 53-year-old, female patient. A. Coronal US examination. Tip of needle is seen within subacromial bursa (white arrows). B. Coronal US examination. Calcification is seen at supraspinatus tendon (curved arrow). C. Right shoulder, A-P roentgenogram. Supraspinatu stendon calcification prior to SAI (curved arrow). D. Right shoulder, A-P roentgenogram, sixth month control. Near-total regression of calcification*

4. DISCUSSION

The results of this study demonstrated that SAI improves the clinical and radiological findings of patients with calcific tendinitis of supraspinatus. SAI is a widely available treatment method in paitents with rotator cuff tendinitis . Although, clinical outcomes of subacromial steroid injections were found to be favorable for treatment of rotator cuff tendinitis in several studies [10] there is limited data assessing the effectivenes of this treatment in patients with calcific tendinitis.

Sonography guided treatment methods for calcific tendinitis of rotator cuff has become increasingly popular because they are less expensive, more readily accessible and feasible, and can be performed under local anesthesia in an outpatient setting [11]. Two main sonography guided treatment options are barbotage, i.e. needling and aspiration of calcifications, and SAI. SAI generally has the easier application, lower cost and lower complication rate compared to barbotage, and is better tolerated by patients. Barbotage is more invasive and thus more painful and time consuming; it also requires special equipment which in turn necessitates special training and experience. In a randomized controlled study, Witte et al., compared treatment outcomes in two groups with similar baseline Gartner class and Constant shoulder score; one undergoing both barbotage and SAI, and the other treated with SAI alone. Although, barbotage group had better improvement of clinical and radiographic outcomes compared to SAI only group, there was improvement in both treatment groups at 6 months and 1 year follow-up. Total regression of calcifications was observed both barbotage (57%) and SAI-only (26%) groups. There were no complications or long-term sequelae post-intervention in both groups. Though, in barbotage group 2 patients developed frozen shoulder which gradually regressed spontaneously [12]. On the other hand, the authors reported the 5-year outcomes of this trial in another study and revealed that no more significant differences were found in the clinical and radiological outcomes between groups. [5]

In our study, 72% of shoulders (26 out of 36) had either total or marked regression of pain symptoms by six months post-intervention. In a previous study, similar to our results 72% of patients showed clinically significant improvement with conservative treatments of calcific tendinitis [13]. Varying results have been reported regarding the radiologic changes of calcifications depending on treatment methods. Elimination rates of calcific deposits with barbotage have been shown 72.2 % in a recent study [14]. In patients treated with ESWT, the rate of totally removed calcifications was reported as 86.6% [15]. With conservative tratments, 62% of the calcific deposits presented complete resolution (12%) or decrease (50%) in the size of calfication [13]. There was no complete resolution in our study however, reduction of calcifation size was present in all patients.

Although, initial radiologic type and size were not found to be related with clinical results in a previous study [13], we found that reduction of calcification size was 58% in responsive group, whereas it was 20% in non-responsive group. In a non-inferiority study, the authors hypothesised that steroid injections are not necessary after the barbottage and saline solution was non-inferior to steroids. However, non-inferiority of saline could not be proven and the results showed that although steroids have no significant effect on calcification resorption they are beneficial for decreasing pain and disability in the short term when compared to saline [16].

The results of all these studies suggested that good radiologic outcomes may be expected with all conservative treatment methods and SAI may have additional effects on pain and functional improvement in patients with calcific tendinitis of the supraspinatus tendon.

The study has also some limitations. First of all, a control group, treated with other conservative treatment methods could not be included in this study due to its retrospective design. Effectiveness of SAI in calcific tendinitis treatment needs to be verified and compared to other treatment options in larger prospective randomized controlled settings.

In conclusion; SAI treatment is a feasible, safe and well tolerated treatment option in alleviating shoulder pain of calcific tendinitis of the supraspinatus tendon.

Compliance with Ethical Standards

Ethical approval: This study was approved by the Marmara University School of Medicine Ethics Committee (approval number: 09.2020.703) and was performed in accordance with the ethical standards as laid down in the Declaration of Helsinki and its later amendments or comparable ethical standards.

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Authors' contributions: Conceptualization: NAB and MD, Data collection: NAB and MD,

Data analysis: NAB, ES and CST, Investigation: NAB, ES, CST and MD, Supervision: NAB and MD, Writing original draft: NAB, ES and MD, Writing – Review and editing: NAB and CST

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Evaluation of the effects of emotional intelligence status on the communication skills of the faculty of medicine students

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ABSTRACT

Objective: In this study, we aimed to evaluate the emotional intelligence levels of the faculty of medicine students and to determine the effects of emotional intelligence levels on communication skills, and the effect of sociodemographic factors on emotional intelligence and communication skills.

Materials and Methods: The faculty of medicine students constituted the sample of this descriptive study. The research was completed with a total of 225 students selected by the haphazard sampling method from each year of a six – year medical school. The data were collected using a questionnaire consisting of sociodemographic characteristics, the Emotional Intelligence Assessment Scale (EIAS), and the Communication Skills Evaluation Scale (CSES).

Results: In our study, 44.4% (n = 100) of the participants were male , 55.6% (n = 125) were female. Approximately, 46.7% (n = 105) had low, 44.4% (100) had normal and 8.9% (n = 20) had high emotional intelligence. The communication skills mean score was found to be statistically significantly higher in female than in male. There was a moderate level of a positive correlation between emotional intelligence and communication skills.

Conclusion: In conclusion, participants with a high level of emotional intelligence have better communication skills. In training programs, more emphasis can be given to emotion management, emotional intelligence, and communication skills.

Keywords: Emotional intelligence, Communication, Medicine, Students, Empathy

1. INTRODUCTION

Emotional intelligence is defined as "the individual's ability to mobilize himself, to continue his path despite setbacks, to control impulses, to postpone satisfaction, to regulate moods, to empathize, to hope and to not allow problems to prevent thinking" [1]. Its adaptive abilities include the ability to evaluate and express emotions, the regulation of emotions and the positive use of emotions for the solution of problems encountered in life. In addition, emotional intelligence includes the ability to accurately perceive, evaluate and express emotions, the ability to create emotions that facilitate the perception of emotions, the ability to effectively use the knowledge acquired with these emotions and the ability to organize emotions for intellectual development and good mood [2]. Generally, it is the ability to be aware of and understand the feelings of others, to understand them correctly and to use the information resulting from these perceptions in a way that will add value to life [3]. Emotions according to Mayer and Salovey; are adaptive organized responses involving physiological, cognitive, motivational and experimental psychological systems, and act as internal events coordinating many psychological sub-systems such as one's physiological responses, cognition, consciousness, and awareness [4]. Emotional intelligence is basically emphasized on two dimensions. These are personal abilities (personal awareness and personal management) and social abilities (social awareness and relationship management). It includes emotional awareness (understanding the impact of emotions in decision making), self-evaluation (knowing and accepting personal weaknesses and advantages) and self-confidence (self-esteem and abilities) within personal awareness. Another important dimension includes important skills such as managing social relations, being effective in conflict management and managing team work [5].

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In his book Emotional Intelligence, Goleman emphasizes that emotional intelligence is more important than cognitive intelligence, and states that emotional intelligence deprivation can have very bad results in many areas, from family life to professional success and from social relationships to health [6]. In professional life, a person should not only have professional knowledge and skills, but should also know how they can relate to other people and get along with them [7]. In their research on university students, Schutte et al. found that students with high social skills levels had higher levels of emotional intelligence. Also, they displayed more cooperative behaviors and were more successful in close emotional and social relationships [8].

Communication skills can be defined as sensitivity to verbal and non-verbal messages, listening effectively and reacting effectively. In addition to those who think that communication skills are natural and intuitive, in many studies, most elements of communication techniques show that they have learnable and teachable features [9]. According to Omololu, communication skills include; listening, speaking comprehensively, establishing eye contact, promoting speech, praising, using nonverbal behavior appropriately [10]. Effective communication skills can be facilitative in all kinds of human relationships and in all kinds of professional areas [11]. Communication, which forms the basis of interpersonal interaction, has an important place in each individual's life. Professionals' success also depends on their communication skills [12,13].

A certain level of communication skills is required in all professional groups. Communication skills are found to be more important in some professions because the performances of these professions are mostly based on human relations [14]. Communication skills are of great importance in professions where human relations are prominent [15]. In cases where communication is not healthy, people may find themselves alone, excluded or unsuccessful in their professional life. If interpersonal skills are not learned, productivity and satisfaction, which are important for the relationship will be lost [16].

Patient-physician communication is the basis of clinical medicine. Communication is required to cooperate with the patient and ensure his participation in the treatment. There are studies emphasizing the importance of communication at patient care to draw attention to this situation [17]. Physicians' high emotional intelligence and communication skills are important in terms of understanding patients, evaluating their diseases and establishing a patient-physician relationship, which increases treatment compliance [18,19] and patient satisfaction [20,21]. In this sense, it is very important that students starting their medical profession, develop their communication skills before stepping into the profession. It is thought that emotional intelligence is the basis of competencies such as patient care, empathy and communication skills in medical education, and skills related to emotional intelligence play a key role in physician-patient and teamwork relationships.[22]. In this context, it is reported that emotional intelligence is predictive in terms of communication skills and interpersonal competence [23]. Therefore,it was aimed to evaluate the emotional intelligence levels of Marmara University School of Medicine students, to determine the effects of emotional intelligence levels on communication skills and to determine the effect of sociodemographic factors on emotional intelligence and communication skills.

2. MATERIALS and METHODS

Ethics committee approval and research permit were obtained from the Ethics Committee of Marmara University, School of Medicine (approval number: 09.2020.14). The people who constituted the sample size of the research were asked to participate in the study after being informed about the research and permits. This study was performed in line with the principles of the Declaration of Helsinki. This descriptive study was conducted in January-February 2020. The sample size of the research consisted of 1538 students studying at the Marmara University, School of Medicine in the academic year 2019-2020. The study was completed with a total of 225 students who were willing to participate. Medical education at Marmara Medical School consists of six academic years. The students from each year were selected by haphazard sampling method.

The data were collected with a questionnaire consisting of sociodemographic features filled out by the participants under observation, the Emotional Intelligence Assessment Scale (EIAS) and the Communication Skills Evaluation Scale (CSES). EIAS was developed by Hall in 1999 to measure emotional intelligence [24]. The Turkish validity and reliability study was carried out by Ergin with university students in the same year [25]. The scale consists of five sub-groups. These are ; awareness of emotions (6 items), controlling emotions (6 items), self-motivation (6 items), empathy (6 items) and social skills (6 items). Using a Likert type scale consisting of 30 items, it is scored as 1: I totally disagree, 2: I partially disagree, 3: I disagree very little, 4: I agree very little, 5: I partially agree, 6: I totally agree. There is no reversed statement in the assessment. Scores of sub-groups; the scores of the responses given to the items that constitute the sub-group are calculated by adding up the scores. When each sub-group score and emotional intelligence total score increases, it means the emotional intelligence level increases. Emotional intelligence total score shows the level of emotional intelligence in general, regardless of sub-groups. This value ranges from 0 to 180. It is the score obtained as a result of the sum of the points obtained from 30 items. Emotional intelligence is categorized as low emotional intelligence if it is 129 and below, and high emotional intelligence when it is 155 and above.

A Communication Skills Evaluation Scale was developed by Korkut in 2016 to understand how individuals evaluate their communication skills [26]. Using a Likert type scale consisting of 25 items, it is scored as 5: Always, 4: Often, 3: Sometimes, 2: Rarely and 1: Never. There is no reversed statement in the assessment. The highest score that can be obtained from the scale is 125 and the lowest score is 25. The scale does not have a cut-off point and the increase in the scale score means that the individual's communication skills is assessed positively.

Variables examined as descriptive in the research were gender, class, place mostly lived in as a child, perceived income level, educational status of parents and families, family type, upbringing, number of people they lived with, number of siblings, thoughts on empathy, if they were able to express themselves or not, willing to communicate and to think, and whether they could listen effectively.

Statistical Analysis

Descriptive data in the study were presented with means-standard deviation values and frequency tables. For the statistical analysis of the data, the Chi-Square test was used to compare the classified data, and the Mann-Whitney U test and Kruskal Wallis variance analysis were used to compare continuous variables that did not fit the normal distribution. The suitability of variables to normal distribution was examined using visual (histogram) and analytical methods (Kolmogorov-Smirnov / Shapiro-Wilk). Correlation coefficients and statistical significance were calculated with the Spearman test for relationships between variables, at least one of which did not fit the normal distribution or ordinal. In this study, $p < 0.05$ was considered statistically significant.

3. RESULTS

Sociodemographic characteristics of the participants are presented in Table I. Fifty-five point 6 percent (n = 125) of the participants are male and 44.4% (n = 100) are female. Participants who were in the 1st, 2nd and 3rd years were classified as preclinical, and those who were in the 4th, 5th and 6th years were classified as clinical. Fifty point seven percent (n = 114) of the participants were preclinical students and 31.6% (n = 71) thought their income was more than their expenses. Seventy-seven point three percent of the participants (n = 174) stated that they mostly lived in the metropolis / city when they were children. While the education level of the father of 64.4% (n = 145) of the participants was university and above, the education level of 45.8% (n = 103) of the mother of the participants was university and above. Ninety point seven percent (n = 204) of the participants reported that they had a nuclear family structure and 26.2% (n = 59) reported that they lived alone.

In Table II, 61.3% (n = 138) of the participants defined their child rearing style as supportive, 12% (n = 27) as overprotective and 6.7% (n = 15) as oppressive.

Four percent (n = 9) of the participants in the research did not think that they were unable to empathize, 14.2% (n = 32) could not listen effectively, 25.3% (n= 57) had difficulties in interpersonal communication, 17.3% (n = 39) reported that they could not express themselves and 30.7% (n = 69) reported that they were not willing to communicate (Table III).

Table I. *Sociodemographic characteristics of the participants*

		Number(s)	Percentage(%)
Gender	Female	125	55.6
	Male	100	44.4
Class	Preclinic	114	50.7
	Clinic	111	49.3
Perceived income level	Expense more than income	71	31.6
	Expense equal to income	140	62.2
	Expense less than income	14	6.2
Place mostly lived as a child	Metropolitan / City	174	77.3
	District / Village	51	22.7
Mother's education level	No education / has not finished primary school	11	4.8
	Primary school	31	13.8
	Middle school	17	7.6
	High school	63	28.0
	University and above	103	45.8
Father's education level	No education / has not finished primary school	5	2.3
	Primary school	16	7.1
	Middle school	14	6.2
	High school	45	20
	University and above	145	64.4
Living alone or with other people	With family	78	34.7
	With roommate	88	39.1
	Alone	59	26.2
Family type	Nuclear family	204	90.7
	Extended family	21	9.3

Table II. *Parent child rearing style through the eyes of the participants*

		Number(s)	Percentage(%)
Child rearing style	**Indifferent**	**3**	**1.3**
	Inconsistent	**7**	**3.1**
	Excessively free	**7**	**3.1**
	Not aware of their feelings	**11**	**4.9**
	Oppressive	**15**	**6.7**
	Democratic	**17**	**7.6**
	Overprotective	**27**	**12.0**
	Supportive	**138**	**61.3**
	Total	**225**	**100.0**

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Marmara Med J 2021;34(2): 157-166

Table III. *Participants' opinions about the following items*

		Number(s)	Percentage(%)
To establish empathy	Yes	216	96.0
	No	9	4.0
Difficulty in interpersonal relationship	Yes	57	25.3
	No	168	74.7
Being able to express yourself	Yes	186	82.7
	No	39	17.3
Being willing to communicate	Yes	156	69.3
	No	69	30.7
Listening effectively	Yes	193	85.8
	No	32	14.2
	Total	225	100.0

In Table IV, when the averages of the CSES and EIAS scores of the participants were compared according to their sociodemographic characteristics; the average communication skill scores of the females (102.90 ± 9.64) were found to be statistically significantly higher than in the males (97.92 ± 11.65) (p = 0.001). When the participants were compared in terms of class, perceived income level, place where they lived mostly as a child, mother education level, father education level, living alone or together and family type, there was no statistically significant difference (p> 0.05). When the EIAS scores were compared according to their sociodemographic characteristics, the mean scores of the emotional intelligence scale scores of the students in the clinic (133.35 ± 19.44) were found to be statistically significantly higher than the preclinical students (128.96 ± 17.17) (p = 0.026). When the participants were compared in terms of gender, perceived income level, place where they mostly lived as a child, mother's education level, father's education level, living alone or together, and family type with EIAS scores, no statistically significant difference was observed (p> 0.05). While there was no statistically significant correlation between age and CSES score (p> 0.005), there was a noteworthy weak (Spearman rho = 0.170) significant correlation with EIAS score (p = 0.011).

When the emotional intelligence sub-groups were examined according to the sociodemographic characteristics of the participants, it was found that in the sub-dimensions of an awareness of emotion and being able to empathize sub-groups, the females scored significantly higher than the males, in the sub-dimensions of controlling the feelings and self-motivation sub-groups, the males scored significantly higher than the females (respectively; p = 0.040, p = 0.002, p = 0.070, p = 0.077). It was determined that the students in the clinic received higher scores in the empathy and social skills sub-groups than the students in the preclinic (respectively; p = 0.006, p = 0.010). There was no statistically significant difference between the perceived income level of the participants, the place where they lived as a child, the level of mother education, the level of father education, living alone or together, the number of siblings and family type and emotional intelligence sub-groups (p> 0.05). There was a significant positive correlation between age and emotional intelligence sub-groups, self-motivation, empathy and social skills scale scores (respectively; Spearman rho = 0.147, rho = 0.178, rho = 0.213) (p=0.027, p=0.007, p=0.001).

Table IV. *Communication skill scores and emotional intelligence scores according to the sociodemographic characteristics of the participants*

		Communication skills Score		p	Emotional Intelligence Score		p
		Mean	Standard deviation		Mean	Standard deviation	
Gender	Female	102.90	9.64	0.001	130.58	19.14	0.559
	Male	97.92	11.65		131.81	17.53	
Class	Pre-clinic	100.38	10.13	0.442	128.96	17.17	0.026
	Clinic	101.00	11.57		133.35	19.44	
Perceived income level	Expense more than income	101.32	10.30	0.883	130.42	13.70	0.654
	Expense equal to income	100.40	11.29		130.45	18.64	
	Expense less than income	100.35	9.39		132.60	18.90	
Place mostly lived in as a child	Metropolitan / city	101.08	10.79	0.431	130.85	18.42	0.671
	District/ village	99.33	11.03		132.07	18.55	
Mother's education level	No education / has not finished primary school	101.09	8.89	0.691	133.00	17.96	0.507
	Primary school	98.87	10.27		130.00	16.73	
	Middle school	97.58	16.14		133.88	22.86	
	High school	101.39	10.49		128.60	18.21	
	University and above	101.27	10.41		132.35	18.43	
Father's education level	No education / has not finished primary school	101.60	4.33	0.768	140.20	8.34	0.223
	Primary school	103.62	8.76		135.87	16.19	
	Middle school	98.85	16.33		132.07	21.40	
	High school	99.80	9.79		125.42	21.31	
	University and above	100.78	10.93		131.97	17.37	
Living alone or with other people	With family	100.91	9.77	0.295	130.50	17.10	0.501
	With roommate	99.56	11.93		130.59	19.08	
	Alone	102.06	10.50		132.76	19.27	
Family type	Nuclear family	100.96	10.85	0.300	131.07	18.14	0.955
	Extended family	98.04	10.70		131.66	21.38	

Communication Skills Evaluation Scale scores and EIA scores are given in Table V according to the opinions of the participants about themselves. When examined in terms of communication skills; comparing those who did not think that they had difficulty in communicating (102.42 ± 10.42) with those who thought that they had difficulty (95.57 ±

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10.53), those who did not think they had difficulty expressing themselves (101.90 ± 10.66) compared to those who thought they had difficulties (94.89 ± 9.89), those who were willing to communicate (102.65 ± 10.37) compared to those who were not willing to communicate (96.24 ± 10.65) and communication skill scores of those who thought they could listen effectively (101.39 ± 10.56) were found to be statistically significantly higher than those who did not think they listened effectively (96.40 ± 11.73) (p <0.05). However, there was no significant statistical difference in terms of CSES scores between those who thought they could empathize (100.91 ± 10.77) and those who thought they could not empathize (95.33 ± 12.00) (p> 0.05).

When the participants were examined in terms of emotional intelligence; comparing those who thought that had no difficulty in communicating amongst people (133.97 ± 17.28) with those who thought that they had difficulty (122.75 ± 19.23), those who did not think they had difficulty expressing themselves (133.10 ± 17.42) compared with those who thought they had difficulty (121.69 ± 20.29), those who were willing to communicate (134.27 ± 17.35) compared with those who were not willing (124.01 ± 18.90) and the scores of those who thought they could listen effectively (132.24 ± 18.20) compared with those who did not think they could listen effectively (124.37 ± 18.52) were found to be statistically significant (p <0.05). However, no statistically significant difference was found in terms of communication skills scores between those who thought they could empathize (131.19 ± 18.43) and those who thought they could not (129.55 ± 19.09) (p> 0.05).

Table V. *Communication skill scores and emotional intelligence scores according to the participants' opinions*

		Communication skills Score		p	Emotional Intelligence Score		p
		Mean	Standard deviation		Mean	Standard deviation	
To establish empathy	Yes	100.91	10.77	0.195	131.19	18.43	0.788
	No	95.33	12.00		129.55	19.09	
Difficulty in interpersonal relationship	Yes	95.57	10.53	<0.001	122.75	19.23	<0.001
	No	102.42	10.42		133.97	17.28	
Being able to express yourself	Yes	101.90	10.66	<0.001	133.10	17.42	0.001
	No	94.89	9.89		121.69	20.29	
Being willing to communicate	Yes	102.65	10.37	<0.001	134.27	17.35	<0.001
	No	96.24	10.65		124.01	18.90	
Listening effectively	Yes	101.39	10.56	0.027	132.24	18.20	0.030
	No	96.40	11.73		124.37	18.52	

When the sub-scales of emotional intelligence were examined according to the opinions of the participants about themselves; participants who stated that they were willing to communicate were found to have significant higher scores in the sub-groups of being aware of their emotions, controlling their emotions, self-motivation and social skills than those who stated that they were not willing to communicate (p = 0.004, p = 0.001, p = 0.005, p = 0.002). It was found that those who did not think that they had difficulty in expressing themselves had a significantly higher score in the sub-scales of awareness of their feelings, controlling their feelings, self-motivation and social skills (respectively; p = 0.030, p <0.001, p = 0.002, p = 0.084). When comparing those who thought that they could listen actively with those who did not think they could, a higher statistical significance was found in terms of empathy and social skills sub-groups (respectively; p = 0.007, p <0.037). It was found that when comparing those who thought that they did not have difficulty in communicating with those who thought they did, a higher statistical significance was found in terms of the sub-groups of being aware of their emotions, controlling their emotions, self-motivation and social skills (respectively; p = 0.047, p <0.001, p <0.001, p = 0.005). There was no statistically significant difference between the participants who thought they could empathize and those who thought they could not (p> 0.05).

When the communication skill scores of the participants according to the emotional intelligence sub-groups were examined, it was concluded that as the score obtained from the scale increases in all sub-groups, the communication skill score increases, and those in the high score category for all sub-groups receive a statistically significantly higher communication skill score than those in the low score category (p <0.001) (Table VI).

Table VI. *Communication skill scores of the participants according to emotional ıntelligence sub-groups*

	LOW		MODERATE		HIGH		
	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation	p
Awareness of emotions	93.96	10.87	101.39	9.54	105.13	10.49	<0.001
Controlling their feelings	98.13	10.74	104.87	7.79	105.33	14.91	<0.001
Self-motivation	96.98	10.95	103.08	8.17	107.02	11.59	<0.001
Being able to empathize	95.40	10.19	100.94	8.77	108.23	10.19	<0.001
Social skill	93.83	10.36	103.31	8.00	107.18	9.87	<0.001
General emotional intelligence	95.60	10.28	103.75	8.05	112.10	11.89	<0.001

In our study, no statistically significant difference was found when comparing the number of siblings and their parenting style with communication skill score, general emotional intelligence scores and emotional intelligence subscale scores (p> 0.05).

According to the analysis results of the research data, there was a moderately positive correlation (Spearman rho = 0.534) between the CSES scores and the EIES scores (p <0.001). In addition, when the sub-groups of emotional intelligence; awareness of emotions, controlling emotions, self-motivation, empathy and social skills scores were compared with the CSES scores, a positive statistically

significant (respectively; Spearman rho = 0.361, 0.296, 0.399, 0.476, 0.544) correlation was detected (p <0.001).

4. DISCUSSION

In our study, it was found that the average communication skill scores of the females were statistically significantly higher than those of the males. Similarly, in a study by Durukan et al. conducted on 140 Turkish teachers based on their communication skills in 2010, it was found that there was a significant difference between gender and communication skills scores but it was in favor of the female teachers [27]. In a study done by Tepeköylü et al. among students of physical education and sports school in 2009, a statistically significant difference was found between gender and communication score, and the communication skills scale score of the female students was found to be significantly higher [28]. Unlike these results, in two studies conducted by Dilekman et al. in 2008 and Kutlu et al. in 2007 on the students of the faculty of education, the communication skills of the education faculty students were examined and there was no significant difference between the communication skills of the students and gender [14, 29].

In this study, no significant difference was found between emotional intelligence level and gender. Similar to our study, in the study of Yeniceri et al. conducted with medical faculty students in 2015, no significant difference was found between emotional intelligence level and gender [30]. When examining the studies investigating the relationship between emotional intelligence and gender, different results were found. In a study on university students in Iran, it was shown that there was no difference between emotional intelligence and communication skills in terms of gender [31]. While it was reported that there was no relationship between emotional intelligence scores and gender in the studies conducted by Shuttle et al. in 2001, Kutlu et al. in 2007 and Füsun's in 2002 [8, 32, 33], in many other studies, emotional intelligence scores were found to be higher in females. For example, in a study by Austin et al. conducted on first year medical students, emotional intelligence levels of females were found to be significantly higher compared to males [20]. Similarly, another study by Aslan et al. on health workers, it was found that females had higher levels of emotional intelligence than males [34]. Additionally, in a study conducted on students studying dentistry, it was determined that females' emotional intelligence levels were higher than males' [35].

In a study examining the relationship between interpersonal relationships and emotional intelligence by Schutte et al., social skills, communication and cooperation increased as emotional intelligence scores increased; it was reported that there was no relationship between empathy and awareness of emotions with emotional intelligence scores [8]. In our study, those who thought that they had no difficulty in communicating with people and in expressing themselves, those who were willing to communicate, and those who thought they could listen effectively got significantly higher score than the others from the EIAS.

Effective communication is being able to express, explain and understand oneself. One of the biggest obstacles in effective communication is not being able to explain and express oneself [36]. In this study, the participants who thought that they could express themselves were expected to have higher emotional intelligence and communication skills scores, thus it was concluded that there was a positive relationship in this direction. The communication skill scores of those who did not think they had difficulty in expressing themselves (101.90 ± 10.66) and those who thought that they did (94.89 ± 9.89) were found to be statistically significantly higher.

Effective communication depends on listening skills. Therefore, the language skill that human beings learn first is the basis of communication [37]. In this study, it was thought that those who thought they could listen effectively would have higher communication skills scores and this expectation was confirmed. Also, the communication skill scores of those who thought they could listen effectively were found to be statistically significantly higher than those who did not think they could.

In our study, a moderately positive correlation was found between CSES scores and EIES scores. In addition, a statistically significant positive correlation was found between the emotional intelligence sub-groups; awareness of emotions, controlling emotions, self-motivation, empathy and social skills scores and CSES scores. Participants with high emotional intelligence were found to have better communication skills. Similarly, in a study conducted by Kuzu in 2010 with nursing students, it was determined that as the emotional intelligence score averages of the students participating in the study increased, the communication skills mean scores increased, and all emotional intelligence sub-dimensions had a strong positive relationship with each other [38]. In a study conducted by Çetinkaya et al. in 2011 on university students to evaluate the communication skills and emotional intelligence, it was found that there was a positive correlation between the sub-groups of emotional intelligence and the sub-groups of communication skill [7]. In a different study conducted in 2011 by Erginsoy on university students in different departments, the relationship between emotional intelligence and communication skills scale scores was observed and it was reported that a positive relationship between emotional intelligence and communication skills scale sub-groups was found [39]. Accordingly, as emotional intelligence scores increase, communication skills scores also increase. In a study by Schutte et al., as emotional intelligence scores increased, social skills, communication and collaboration also increased. It was reported that there was no relationship between empathy and awareness of emotions with emotional intelligence scores [8].

In a study by Mayer, he found that students in the age group of 18-21 received higher scores in terms of emotional intelligence than students in the age group of 13-16 and he stated that emotional intelligence increases with age at least until the beginning of the young adult years [4]. Also, in a study conducted by Ergin et al., on high school adolescents in 1999, 15-year-olds were found to have lower emotional intelligence than 16 and 17-year-old students, thus concluded that emotional intelligence increases with age [25]. In the study by Harrod and Scheer in 2005 in terms of age and emotional intelligence, it was observed that

emotional intelligence can develop at any age, and emotional intelligence increases as the age gets older [40]. Furthermore, other studies on this issue also show that emotional intelligence increases with age [41,42]. In accordance with the literature, in our study, when the general emotional intelligence level and emotional intelligence sub-groups were examined, it was found that the level of emotional intelligence increased as the age increased. However, in a study conducted with medical faculty students in Mugla, Turkey in 2015, no significant difference was found between age and emotional intelligence and sub-scales of emotional intelligence [30].

In our study, the mean score of emotional intelligence scale scores of the students in the clinic were found to be statistically significantly higher than the preclinical students. On the other hand, in the studies of Yeniceri et al. conducted with medical students, no significant difference was found between class and emotional intelligence [30]. In our study, there was no significant relationship in terms of communication skills between the clinical and preclinical students. Similarly, in the studies of Erigüç and Eriş in 2013 and Dilekman et al. in 2008, there was no significant difference between the communication skills levels of the students according to their class levels [14, 43]. However, unlike the results of the aforementioned studies, in a study conducted in 2002 on nursing students' communication skills, it was found that the relationship between the class level and communication skills level was statistically significant and that the average score of CSES scored increased as the grade level increased from the first grade to the third grade [44].

According to the results of our study, it was found that the communication skills levels and emotional intelligence levels of the participants did not change according to the education level of the mother. Similarly, in a research conducted by Çetinkaya in 2011 on Turkish teachers, it was concluded that there was no significant difference between the emotional intelligence levels of the teachers and their mothers' educational status [45]. Unlike these results, in the study conducted by Kuzu, there was a statistically significant relationship between emotional intelligence level and mothers' and fathers' educational level [38]. Similar findings were observed in the study of Ismen in 2004 and also in the studies of Harrod and Scheer [40, 46].

According to the results of this research, it was seen that there was no significant difference in terms of emotional intelligence and communication skills levels according to the students' lodgings. Similar results have been obtained from other studies [40, 47, 48]. This finding supports the results of similar studies in the literature.

According to Goleman, it has been reported that attitudes such as ignoring emotions, not respecting emotions, and excessively releasing them are the most common among emotionally inadequate parental attitudes [49]. The results of the research by Ciarrochi et al. on observing the relationship between family attitudes and emotional intelligence are similar [50]. When the relevant literature is analyzed, it is seen that the contribution of parents' child-rearing attitudes to the communication skills of the child is emphasized [51-53]. However, in our study, no statistically significant difference was found between the parents' parenting attitude and communication skill score with general emotional intelligence scores and emotional intelligence sub-group scores. Similar to our study, in the study of Yeniceri et al.with medical faculty students in 2015, no significant difference was found between parents' child-rearing attitudes and emotional intelligence and emotional intelligence subscales [30].

In this study, the family type with emotional intelligence and communication skills score was examined, but no meaningful result was obtained. Similarly, in a study conducted by Karakuş et al. in 2010, emotional intelligence levels of nurses working in a training hospital were examined and no statistically significant difference was found between family type and emotional intelligence [54].

In a study by Bingöl et al. 2011, in Amasya, no statistical relationship was found between family structure, number of siblings, father and mother's education level, mother's level of work with students' communication skills assessment scale scores [55]. When the results of our study were analyzed, no statistically significant difference was found between the number of siblings and the education level of mother and father with the communication skill score, general emotional intelligence scores and emotional intelligence sub-group scores. Similarly, in a study conducted with medical students, no statistically significant difference was found between parents' education level and general emotional intelligence scores and emotional intelligence subscale scores [30]. In the study conducted by Köker et al. in 2005, it was stated that the socioeconomic level did not affect the communication skill level [56]. Similarly, in the research of Tepeköylü et al., It was found that there was no significant relationship between the student's communication skill level and the family's monthly income level [28]. In the studies of Yeniceri et al., no significant difference was found between perceived income level and emotional intelligence and sub-scales of emotional intelligence [30]. In our study, in accordance with the literature, no significant difference was found between the socio-economic status of students with the emotional intelligence and communication skills. However, unlike these results, in the research carried out by Kutlu et al. on the students of education faculty, a difference was found between the socio-economic levels in terms of emotional intelligence and communication skills scores [29]. Harrod and Scheer, in their study with young people aged 16-19, reported that as the family income increased, the emotional intelligence scores of the youth increased [40].

Limitations

Since, our study was a descriptive study, those who agreed to participate in the study may be people with high emotional intelligence and communication skills. This situation may have caused us to determine higher emotional intelligence and communication scale mean scores of the students. Also, this study only covered the students of a single university. A similar study can be done on a wider sample size, so that factors associated with emotional intelligence and communication

skills of medical students in general in Turkey can be examined on a more comprehensive level.

Conclusion

In our study, the mean scores of the EIAS of the students in the clinic were found to be statistically significantly higher than those of the preclinical students. A weak positive correlation was found between age and emotional intelligence scale score. Those who thought that they had no difficulty in communicating between people and in expressing themselves, those who were willing to communicate, and those who thought they could listen effectively got significantly higher scores than the others from the EIAS scores. A statistically significant positive and moderate level correlation was found between the CSAS scores and the EIAS scores.

As a result, communication skills and emotional intelligence levels of medical students participating in this study differed from each other. Proper use of communication skills and emotional skills in the practice of the medical profession increases the quality of professional practice. Programs should be developed to improve students' qualifications in this direction. In a case control study conducted on medical students in the United Kingdom, communication skills of the experimental group, which were given 7 months of training to develop communication skills, showed a significant difference when compared to the control group [57]. Since, the communication skills of those with high emotional intelligence are high in our study, the trainings to be developed for developing emotional intelligence will affect their communication skills positively. From the beginning of the training to the development of the emotional intelligence, a training program that improves social relations and motivates people can be created. Educational programs may include emotional management, emotional intelligence and communication skills. In addition, guidance / counseling hours can be included to support personal development.

Compliance with Ethical Standards

Ethical Approval: Ethics committee approval and research permit were obtained from the Ethics Committee of Marmara University, School of Medicine (approval number: 09.2020.14).

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Conflict of Interest: The authors have no potential conflicts to declare.

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Mature cystic ovarian teratomas: Relationship between histopathological contents and clinical features

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ABSTRACT

Objectives: Mature cystic teratomas (MCT) originate from three germ layers: ectoderm, mesoderm and endoderm. The predictive significance of tumor markers in mature cystic teratomas is still unclear. In this study, we aimed to evaluate the predictive value of tumor markers in ovarian MCTs and histopathological contents of tumor.

Materials and Methods: The data of 106 patients who were operated for ovarian MCT between 2015 and 2020 were retrospectively analysed. In addition, slides in the pathology archive were re-examined under a microscope to evaluate their histopathological contents.

Results: The average age of the patients was 35.7; 26.7 in the cystectomy group and 42.1 in the oophorectomy group (p = 0.000). The ratio of tumor markers exceeding the cut off value for carbohydrate antigen (CA 19-9), lactate dehydrogenase (LDH), cancer antigen (CA 125), carcinoma antigen (CA 15-3), carcinoembryonic antigen (CEA) were 45.2%; 47.7%; 8.15%; 12.3%; 6.9%, respectively. Histopathological examination of MCTs revealed 99.1% ectoderm, 45.3% mesodermal, 39.6% endodermal origin.

Conclusion: Mature cystic teratoma is a benign tumor of the reproductive age that contains three germ layers in various proportions. LDH and CA 19-9 can be a helpful tool in predicting mature cystic teratomas.

Keywords: Mature cystic teratoma, Germ layers, Tumor markers

1. INTRODUCTION

Ovarian germ cell tumors (OGCT) are neoplasms in which malignant cells form in the germ cells of the ovary. OGCTs are subdivided into categories as teratomas (benign cystic mature teratomas, immature teratomas), dysgerminomas, yolk sac tumors, mixed germ cell tumors (yolk sac, dysgerminoma, and/or embryonal carcinoma) and rare ones (pure embryonal carcinomas, nongestational choriocarcinomas, and pure polyembryoma). Dysgerminoma, immature teratoma, yolk sac tumors, and mixed germ cell tumors account for 90 percent of malignant OGCTs cases [1]. OGCTs arise primarily in young women between 10 and 30 years of age and represent 70 percent of ovarian neoplasms in this age group [2].

A teratoma is a tumor made up of several different types of tissues, such as hair, muscle, teeth, or bone. Teratoma is a word introduced by Virchow in 1863. The term comes from the Greek words for "monster" and "tumor" [3]. Ovarian teratomas include mature cystic teratomas (MCTs), immature teratomas, and monodermal teratomas (e.g., struma ovarii, carcinoid tumors, and neural tumors) [4].

Mature cystic teratoma originates from primordial germ cells and histologically includes at least two of the three germ layers (ectoderm, endoderm and mesoderm) [5,6]. It is the most common tumor (60%) among benign tumors [5]. Since, MCTs tend to arise at an early age, it is undoubtedly also encountered during pregnancy [7]. Dermoid cyst means a MCT comprising specially hair and other structures characteristic of normal skin and other tissues derived from the ectoderm [8]. One of the most common locations is the ovary. MCT is liable for 20% of all ovarian neoplasms [7,9]. Although, dermoid cysts are commonly unilateral, 10-12% are bilateral. While all ovarian

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cysts can range in size from very small to quite large, dermoid cysts are not classified as functional cysts.

Alternative treatments should be considered before making the surgery decision. In many cases, the expectant approach may be appropriate for patients, as it will take years before the cyst can reach large sizes. Complications exist, such as torsion, rupture, and infection, although their incidence is rare. Dermoid ovarian cysts which are larger present complications which might require removal by either laparoscopy or laparotomy [10].

It is impossible not to benefit from radiological imaging while establishing the initial diagnosis. Magnetic resonance imaging (MRI), computed tomography (CT) and ultrasonography (USG) are used to define the location and prominent features of MCT. It is easy to apply the USG as first step in clinic. However, MRI and CT are more useful in identifying MCT. Whereby the recording of images such as MRI or CT, it is easier to compare the natures of the cyst with past examinations in patients with an expectant approach.

Several serum tumor markers may increase in MCTs. These specific serum tumor markers are cancer antigen 125 (CA-125), carcinoma antigen 15-3 (CA 15-3), carbohydrate antigen 19-9 (CA 19-9), carcinoembryonic antigen (CEA), and lactate dehydrogenase (LDH) [11-15]. However, these are not specific tumor markers. In addition, there is no study stating to what extent these markers are affected by MCT content. We present to reveal the relationship between histopathological contents and serum tumor markers of MCTs. In this study we also aimed to investigate to surgical information and clinical findings.

2. MATERIALS and METHODS

Ovarian tumors reported as mature cystic teratoma between January 2015 – January 2020 at Pamukkale University Pathology Department, were included in this retrospective study. Before conducting the study, approval was obtained from the Pamukkale University, Shool of Medicine Clinical Research Ethics Committee (19.11.2019-20). Patient information was accessed from the hospital record-archive system. 106 mature cystic teratoma patients were included in the study. While investigating patients with ovarian teratoma, 3 patients with immature teratoma were detected. Immature teratoma patients were not included in the analysis. Patients were imaged with at least one of MRI, CT and USG before their diagnosis was confirmed by pathology. Characteristic features, diameter and laterality of the tumors were noted. Age, pregnancy, menopause status, ovarian torsion, intraabdominal fluid and frozen section evaluation status, incision, surgical method, pathological findings and laboratory values were analyzed. Each patient's medical records were reviewed retrospectively. Preoperative serum analysis were evaluated for tumor markers when available, CA-125 (n = 76); CA 15-3 (n = 73); CA 19-9 (n = 73); CEA (n = 72) and LDH (n = 44). Cut off values of these tumor markers were 35 U/mL; 25 U/mL; 27 U/mL; 4.7 ng/mL and 214 U/L, respectively. Hematoxylin-eosin (H-E) stained slides of teratoma tissues were re-examined, thus, endodermal, mesodermal or ectodermal origin of tissues were analyzed. The slides examined were evaluated by at least two researchers, one being a pathologist, with a Nikon eclipse e200 microscope.

Statistical Analysis

The IBM SPSS Statistics (Version 21.0, SPSS Inc.) program was used for the statistical analyses. When the study data were evaluated, the relationships between descriptive statistical methods for mean ± standard deviation (SD), median, minumum (Min) – maximum (Max) were used. Categorical variables were calculated as rate (%) and the Chi-square test was performed. Due to the failure of the normality test (Kolmogorov Smirnov), comparisons between groups were made using the Mann Whitney U non-parametric test. p-value < 0.05 was considered statistically significant.

3. RESULTS

A total of 106 cases of MCT were studied. Table I presents demographic, clinical and surgical data of the patients. The mean age of the cases was 35.7 and the median age was 32.5 (9-84) years. Nine of all patients were pregnant, 24 were postmenopausal and 11 were children. Five of the pregnant women were in term and four was in the second trimester (Figure 1A). While only one patient had ruptured cyst, five patients had torsion. Approximately half of the MCTs were located on the right side, while nine of MCTs were bilateral. The mean diameter of the cysts was 6.7 cm with preoperative radiological imaging. The average tumor volume obtained by examining the pathology reports was 206 cm^3. During surgery, abdominal fluid sample was obtained from 36 cases for cytological examination, and 41 cases were evaluated with a rapid pathological examination, frozen section. The initial diagnoses revealed by imaging, anamnesis and physical examination were as follows; adnexal mass 17%, Cesarean section (C/S) 4.7%, endometrioma 0.9%, dysgerminoma 0.9%, mature cystic teratoma (MCT – dermoid cyst) (Figure 1B) 74.5%, acute abdomen 1.9%. In one patient with acute abdomen, appendicitis (Figure 1C) was present concurrently with MCT. Laparotomy was the preferred approach for the 80.2% cases while laparoscopy was performed for 18.9% of the cases. There was only one vaginal operation. The most preferred method in laparotomy cases was pfannestiel incision.

Due to the retrospective nature of our study, preoperative tumor marker values could not be achieved in all patients (Table II). Average values for CA 19-9 (n = 73), LDH (n = 44), CA 125 (n = 76), CA 15-3 (n = 73), CEA (n = 72) were 43.9, 216.1, 22.2, 16.6, 2.1, respectively. The percentage of those who exceeded the cut off value in the same order were 45.2%, 47.7%, 15.8%, 12.3%, 6.9%. CA 19-9 was statistically significantly higher in 33 patients who exceeded the cut off value than lower mean group (83.1 U/mL vs 11.5 U/mL) (p=0.03). CA 19-9 was statistically lower in tumors containing all three germ layers than others (23.9 U/mL vs 51.9 U/mL) (p=0.007). High CA 19-9 values had no effect on other parameters.

The macroscopic view of a tumour is presented in figure 2A. Microscopic examination of the most of the mature teratomas revealed squamous epithelium, adnexal structures and adipose tissue. A total of 42 cases (39.6%) out of 106 cases showed

endoderm (Figure 2), 48 cases (45.3%) mesoderm (Figure 3) and 105 cases (99.1%) ectoderm (Figure 4) derived components (Table III). There were 29 (27.3%) cases including all three germ layers. Nine cases were bilateral. Ovarian squamous epithelium and skin adnexal structures was seen in total 94.3%. There were serous epithelium, serous papillary cyst and mucinous epithelium in total 22, 5 and 19 of the cases, respectively. Adipose tissue was detected in 24, glial tissue in 22 and chondroid tissue in 36 cases. In addition, psammoma body, choroid plexus, bronchial epithelium, thyroid tissues, teeth, salivary gland, bones, bone marrow, melanin pigment, ganglion, peripheral nerve tissue, lymph node were observed. Statistically significant mesodermal component predominance was observed in younger ages (32.3 ± 17.28 vs 38.5 ± 15.9) (p = 0.025).

Comparisons in accordance with the surgical method options showed the comparable distribution of patient age, tumor diameter and volume among groups by Mann-Whitney U-test (Table IV). The mean age of 44 patients who underwent cystectomy was 26.7, while the mean age of 62 patients who underwent oophorectomy was 42.1 (p=0.000). The preoperative diameters of teratomas were smaller in the cystectomy group than those in the oophorectomy group (5.8 cm vs 7.3 cm, p=0.023). When the volumes calculated in histopathological examinations were compared, the cystectomy group had smaller sizes (80.1 cm^3 vs 296.4 cm^3, p=0.000). The majority of those examined in the frozen section consisted of those undergoing oophorectomy. Tumors examined in frozen section were found to have a larger diameter (mean 7.8 vs 6.1 cm, p=0.01)

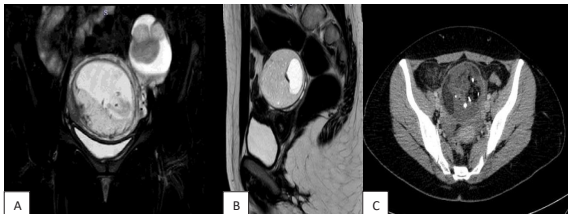

***Figure 1**. (A) View of pregnant uterus in the pelvis and a mass with cystic-solid content in the left ovary on MRI. (B) Sagittal view on MRI of the MCT case, which has a cystic structure in its centre with adipose component about 5 cm in diameter, which pushes the ovarian parenchyma into the periphery. (C) Axial view of the pelvis by CT imaging shows a large cystic mass containing fat and calcification in the case of perforated appendicitis.*

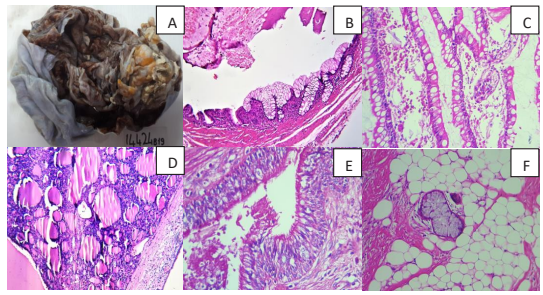

***Figure 2.** Endodermal components and macroscopic view of MCT. (A) Multi-cystic structure, thickening on the wall, adipose tissue and sebaceous contents are observed in several areas. (B) Cystic area covered with mucinous epithelium, H-E, x100. (C) Intestinal metaplasia area, H-E, x 200. (D) Thyroid follicle structures containing colloid, H-E, x200. (E) Ciliated pseudo-sturative respiratory epithelium, H-E, X400. (F) Mucinous gland in adipose tissue, H-E, x400.*

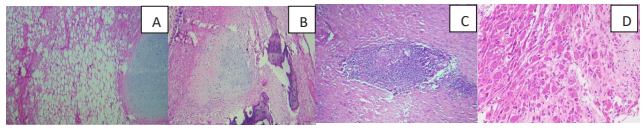

***Figure 3.** Mesoderm components. (A) Areas containing adipose and chondroid tissue, H-E, x100. (B) Chondroid tissue and osseous metaplasia, H-E, X 40. (C) Lymphoid follicle, H-E, X100. (D) Degenerate myocytes, H-E, x200.*

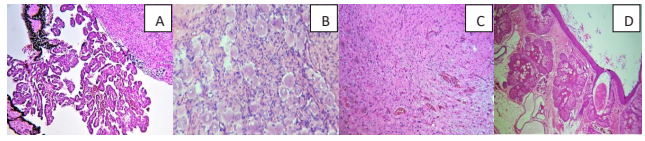

***Figure 4.** Ectodermal components. (A) Choroid plexus papilloma and melanin pigmented areas, H-E, x100. (B) Ganglion cells, H-E, x400. (C) Glial tissue, H-E, x100. (D) Skin and skin adnexal, H-E, x40*

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Marmara Med J 2021;34(2): 167-174

Table I. *Demographic, clinical and surgical data*

Age (years, mean±SD)	35.7 ± 16.7
Min-Max	9-84
Pregnancy (%)	9 (8.5%)
Post-menopause	24 (22.6%)
Children	11 (10.3%)
Lateralization	
Unilateral left	43 (40.6%)
Unilateral right	54 (50.9%)
Bilateral	9 (8.5%)
Radiologic diameter (cm, mean±SD)	6.76±3.39
Min-Max	1.5-24
Histopathological tumor volume (cm3, mean±SD)	206.9 ± 530.9
Min-Max	1.6-3494
Torsion	5 (4.7%)
Frozen section	41 (38.7%)
Intraabdominal fluid examination	36 (34.0%)
Initial diagnosis	
Adnexal mass	18 (17%)
Cesarean section (C/S)	5 (4.7%)
Endometrioma	1 (0.9%)
Dysgerminoma	1 (0.9%)
Mature cystic teratoma (MCT- dermoid cyst)	79 (74.5%)
Acute abdomen	2 (1,9%)
Surgical method	
Laparotomy	85 (80.2%)
Laparoscopy	20 (18.9%)
Vaginal	1 (0.9%)
Type of incision in laparotomy	
Pfannenstiel	69 (81.2%)
Infraumbilical median incision (IMI)	12 (14.1%)
IMI + Supraumblical median incision	4 (4.7%)

Table II. *Preoperative serum levels of tumor markers*

Tumor markers	Cut-off value	Mean ± SD	Median	Min-Max	Cut-off exceeding rate (%)
CA 19-9 N=73	27 U/mL	43.9 ± 67.9	23.5	0.6-494.0	33/73 (45.2%)
LDH N=44	214 U/L	216.1 ± 70.9	206.5	99.0-408.0	21/44 (47.7%)
CA 125 N=76	35 U/mL	22.2 ± 18.5	15.7	5.3-132.0	12/76 (15.8%)
CA 15-3 N=73	25 U/mL	16.6 ± 7.2	16.5	3.7-34.1	9/73 (12.3%)
CEA N=72	4.7 ng/mL	2.1 ± 1.6	1.7	0.2-9.2	5/72 (6.9%)

Table III. *Classification according to the germ layers and the components content (N=106)*

Contains all three germ layers n=29 percentage 27.3%		
Component/Quantity (%)	Component/Quantity (%)	Component/Quantity (%)
Ectoderm 105 (99.1%)	Mesoderm 48 (45.3%)	Endoderm 42 (39.6%)
Skin 104 (98.1%)	Chondroid tissue 36 (34.0%)	Mucinous epithelium 19 (17.9%)
Skin attachment 100 (94.3%)	Adipose tissue 24 (22.6%)	Thyroid tissue 8 (7.5%)
Glial tissue 22 (20.8%)	Serous epithelium 22 (20.8%)	Intestinal epithelium 4 (3.8%)
Choroid plexus 4 (3.8%)	Osteoid tissue 7 (6.6%)	Lymphatic gland 1 (0.9%)
Ganglion 4 (3.8%)	Dental tissue 6 (5.7%)	Salivary gland 1 (0.9%)
Sebaceous gland 2 (1.9%)	Serous papillary cyst 5 (4.7%)	Bronchial epithelium 1 (0.9%)
Peripheral nerve 1 (0.9%)	Muscle tissue 5 (4.7%)	
Melanin pigment 1 (0.9%)	Bone marrow 1 (0.9%)	
Psammoma body 1 (0.9%)		

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Table IV. Comparison of patients undergoing cystectomy and oophorectomy

Parameters	Cystectomy (N=44)	Oophorectomy (N=62)	p value[b]
Age (years, mean ± SD)	26.7 ± 7.1	42.1 ± 18.6	0.000
Radiologic diameter (cm, mean ± SD)	5.8 ± 2.5	7.3 ± 3.7	0.023
Histopathological tumor volume (cm3 , mean ± SD)	80.1 ± 136.8	296.4 ± 672.4	0.016
Frozen section (N)[a]	7/44	34/62	0.02

[a] p=0.02 by Chi-square test, [b] p value < 0.05 was considered statistically significant

4. DISCUSSION

Mature cystic teratomas are benign tumors of the reproductive age that contains three germ layers in various proportions. Our findings show that simultaneous elevation of CA 19-9 and LDH may be a helpful tool in predicting MCTs.

Mature cystic teratomas, commonly referred to as dermoid cysts, which corresponds to 95% of ovarian teratomas, is one the leading causes of benign tumors in premenopausal women [16]. While these cysts are seen in adults at the rate of 20%, they make up half of the pediatric ovarian tumors [2,7]. Accordingly, the average age was found to be 35.7 ± 16.7 in the current study. Sushma et al. reported that third and fourth decade patients accounted for two thirds of all patients [17]. In this current study, less than half of all MCTs were seen in this age group. Comerci et al. (517 cases), Ayhan et al. (501 cases) and Kikkawa et al. (92 cases) reported a mean tumor diameter of the cyst as 6.4, 7.0 and 8.8 cm, respectively [6,16,18]. We found that the radiological diameter was similar to the literature with 6.76 ± 3.39 cm. In accordance with the study of Sushma et al., the unilaterality with dominance of right ovary with 50.9% was detected in our study [17]. Bilaterality was observed in 8.5% of our cases while in previous studies, approximately 10-14% of cases were bilateral [16,18-19]. The mean volume calculated in histopathological examinations was 206.90 ± 530.90 cm^3 in the present study. In the study of Eskicioglu et al. , while the average tumor volume is 128.2 cm3, we obtained that the high rate in our study using the same calculation formula (volume calculation of the ellipsoid shape ovary= longitudinal * transverse * antero-posterior diameter * 0.52) [20]. Five cases in our data had torsion in conformity with the study of Ayhan et al. [16]. In our study three of the five patients with torsion underwent oophorectomy and two had cystectomy. Initial diagnosis was in compliance with pathologic diagnosis in three quarters of the patients.

Mature cystic teratoma is both the most common germ cell neoplasm and the most common removable ovarian neoplasm [21]. More than 90% of germ cell neoplasm evolve in gonads (ovaries and testicles). Partlow and Taybi also suggested that the most common teratoma site was ovary [22]. The remaining extragonadal part can appear in other parts of the body such as mediastenium, central nervous system, retroperitoneum and sacracoccygeal teratoma [23]. Most MCTs are nonviolent, such that abdominal pain or other nonspecific symptoms come out in a little group with MCT. Thus, the tumor is commonly noticeable in routine physical examination or radiological evaluation for different reasons and detected incidentally during abdominal surgery [24]. Some authors suggest non-surgical treatment of small (<6 cm) tumors due to the fact that MCTs expand into an average rate of 1.8 mm per year. This expectant therapy is currently a topic in debate [25]. Our study shows that the tumor sizes of the operated patients are distributed between 1.5 to 24 cm.

Mature cystic teratoma has own characteristic cystic structure. Since, the cyst may originate from any three germ layers, it contains many tissues. The characteristic morphological appearance of MCTs are the multi-cystic strict mass (Rokitansky nodule) with hair, teeth, and sebaceous material which is sticky and sniffy [6,26]. Teratomas dominated by ectodermal tissues are specially called dermoid cysts. In the study of Caruso et al., ectodermal, mesoderml and endodermal origin were found be 100%, 73% and 30% of the cases, respectively [27]. In our study, ectodermal, mesoderml and endodermal origin were 99.1%, 45.3% and 39.6%, respectively. In addition, mesodermal content was present more frequently at a younger age. Endoderm and ectoderm contents did not differ by age. The percentage of those containing all three germ layers was 27.3%. Varma et al., studied on 72 teratomes, analyzed the cyst contents at the microscopic appearance and reported that respiratory epithelium in 3 cases, glial tissue in 2 cases, cerebellar tissue in 1 case, choroid plexus in 1 case, teeth in 5 cases, bone and cartilage tissue in 13 cases [28]. In our study, similar to this study, there were 6 teeth and 1 bronchial epithelium. However, unlike this study, we detected 36 cartilage tissues, 22 glial tissues, 4 choroid tissues. In the study of Shin et al., 13 cases were examined histopathologically, 8 of them had glial tissue and 3 of them had thyroid tissue [29]. The most common tissues found in our study are; skin 98.1% and skin adnexal structures 94.3% followed by chondroid tissue 34.0%, adipose tissue 22.6%, serous epithelium 20.8%, glial tissue 20.8%, mucinous epithelium 17.9%.

Ustunyurt et al. reported elevated percentage for CA 19-9 (39.6%) and CA 125 (23.3%) [11]. According to our data obtained from 73 patients, CA 19-9 was statistically significantly higher in 33 patients who exceeded the cut off value. Ito reported that the mean value for CA 19-9 was 32.9 U/ml in the belove cut-off group and 83.8 U/ml in the above cut-off group [12]. In our study, it was 83.1 U / mL for the above cut-off group. However, the values for belove cut-off group of our study (11.5 U / mL) was lower than that study. We observed that CA 19-9 was statistically lower in tumors containing all three germ layers than others. In studies involving the larger patient groups, attention should be paid to how histopathological content affects tumor markers. Mikuni et al. reported the ratio of CA 19-9, CA 125, CEA and LDH who exceeded the threshold value, as 45.5%, 12.7%, 1.6%, 0.6%, respectively [13]. In our study, the percentage of those who were high compared to the cut off value for LDH, CA19-9, CA125, CA15-3, CEA was 47.2%, 45.2%, 15.8%, 12.3%, 6.9% respectively. CA 19-9 and CA 15-3 were higher proportionally in our study compared to the published study of Var et al. [14]. LDH enzyme are very sensitive indicators of the cellular metabolic state, aerobic or anaerobic direction of glycolysis,

activation status and malignant transformation. Few published reports investigated the relationship between LDH and MCTs. Therefore, the data about this subject are limited. Mikuni et al. reported LDH level was no significant in mature cystic teratomas [13]. Contrary, Konishi et al. declared that LDH is useful tumor marker for specific histological type of dysgerminoma and other ovarian solid germ cell tumors [15]. Our data support that LDH levels significantly high in MCTs. Further studies are needed to clarify this issue.

The frozen section is a pathological laboratory procedure to perform rapid microscopic analysis of a specimen. Although there are no frozen section studies of ovarian MCTs in the literature, it is a useful pathological examination method in masses suggesting malignancy [30]. In our study, the pathological material of 41 (38.7%) patients was studied with frozen section. Malignancy was not observed in frozen section examination of MCTs. This high frozen rate of study obtained from our study shows that MCTs in benign nature are not morphologically innocent for the surgeon. In our study, cytological examination of intraabdominal fluid was performed in 36 (34.0%) cases, althoug they were negative in terms of malignancy.

The malignant teratoma account for 3-4% of ovarian carcinomas. The squamous epithelium covers the wall of the cyst and and hyalinized ovarian stroma often covers the outer surface [19]. MCT shows malignant transformation in 1-2% of the cases, squamous cell carcinoma being the commonest [31,32]. Teratomas commonly are classified using the Gonzalez-Crussi grading system: 0 or mature (benign); 1 or immature, probably benign; 2 or immature, possibly malignant (cancerous); and 3 or frankly malignant [8]. The ratio of immature teratomas to total ovarian teratomas is between 1-3% in the literature. In our study this ratio is 2.75% [16,33]. All cases were benign in our study.

Which surgical method should we prefer in the treatment of mature cystic teratomas, laparotomic or laparoscopic? Actually factors influencing the choice of suitable management depend on patient's age, reproductive plans, pre-operative findings, the size of the mass and the surgeon's experience. The benefits of laparoscopic surgery are less postoperative pain with better wound healing, mini scarring, short hospital stay and early return to routine daily work compared to laparotomy [34]. Usually, laparotomy is preferred in large tumors, presence of previous surgical operations and pelvic adhesion. In our study, 18.9% of the cases were performed with laparoscopy, while 80.2% were with laparotomy. In addition, one (0.9%) of the cases underwent vaginal hysterectomy and bilateral salpingooferectomy. The common incision type in laparotomy was pfannestiel incision. The tumor's diameter of the laparoscopy group in our study was significantly smaller than laparotomy (5.4 ± 1.4 vs 7.1 ± 3.6.6) cm (p=0.001). However, we observed no significant difference in age between laparoscopy (31.5 ± 18.6.6) and laparotomy (36.4 ± 16.1.1) group.

The tumor diameter (cm) of the laparoscopy group in our study was significantly smaller than laparotomy (5.4±1.4 vs 7.1±3.6 cm) (p=0.001). However, there was no difference between the laparoscopy (n=20, 31.5±18.6) and laparotomy (n=85, 36.4±16.1) as the surgical method according to age (p=0.232). An oophorectomy should be performed for all peri – or post-menopausal patients, independently of the aspect of the cyst. In younger patients, ovarian cystectomy can be considered. There was a significant difference in the decision of cystectomy versus oophorectomy in terms of age (26.7±7.1 vs 42.1±18.6, p<0.001), radiological diameter (cm) (5.88±2.5 vs 7.38±3.7, p=0.023), tumor volume (cm^3) (80.1±136.8 vs 296.4±672.4, p=0.016). As these data were small in the cystectomy group, frozen section examination rate was also lower (17.1% vs 83.9%, p=0.02). Ayhan et al. reported the cyst diameter (7.0 vs 7.0) were similar in both groups, as the mean age of the cystectomy group lower than the oophorectomy group (27.9 vs 31.2) [16]. In the study of Uysal et al., cystectomy cases had a mean diameter of 6.7 cm while the mean diameter for ooferectomy cases was 9.1 cm [35]. Although laparoscopic surgery has been more preferred in recent years, laparotomy should be unconsidered as a defeat, but as a safe alternative for prominent cases. The surgeon must keep in mind the risk of a laparoscopic rupture and spillage of a malignant tumour, and must weigh the risks of laparoscopy versus laparotomy. There was only one ruptured MCT case where we could access information from patient files. Laparotomy was performed in 90.1% of the cases in a study of Sahraoui et al [33].

Mature cystic teratoma is one of the most common benign ovarian neoplasms encountered during pregnancy (24-40%) [6]. Sahraoui et al. reported 19.8% of MCTs as pregnant [33]. In this article, the pregnancy rate was found to be less than previous studies. The pregnancy rate is 8.5%. While five of the pregnant cases were performed simultaneous cesarean section, the other four cases (15-18 weeks) were still in the second trimester.

Based on the literature and supported by our findings we suggest that simultaneous elevation of CA 19-9 and LDH may be predictive for ovarian MCTs [11-13,15,36]. However, since MCTs can contain many different tissue types, we think that studies with larger sample size are needed to understand the specific responses of which tumor markers are elevated when different tissue types are included. In addition to the anatomical region of the teratoma and the age of the patient, it is important to recognize tissues in MCT and rule out the immaturity in teratomas. Therefore, pathologists have a very important role in histopathological evaluation and reliable prognostic profile.

In our study, these features could not be evaluated since we could not reach some data such as admission symptoms and laboratory examination results in all cases. Its retrospective nature is the limitation of our study in this respect.

Conclusion

Mature cystic teratomas are unilaterally located masses with low tendency for malignant transformation, which are frequently encountered in reproductive women. While, USG is the first-line imaging modality, more detailed information about the mass can be obtained through MRI or CT. Although, very successful results are obtained with laparoscopic surgery, laparotomy is safer in selected cases.

Compliance with Ethical Standards

Ethical Committee Approval

The study was approved by the Pamukkale University, School of Medicine Clinical Research Ethics Committee (approval date and number 19.11.2019-20).

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Conflicts of interest: The authors declare no conflict of interest.

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The effect of patient's age on the outcomes of Salter pelvic osteotomy

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ABSTRACT

Objective: We hypothesized that as the patient's age increases, the outcomes of Salter pelvic osteotomy (SPO) get worse. This study aims to compare the results of surgery in developmental dysplasia of the hip (DDH) with at which age SPO is performed.

Patients and Materials: Forthy six hips of 36 patients with at least 1 year of regular radiological and clinical follow-up were included in this study. The patients were retrospectively divided into three groups, group I for ages between 18 months and 4 years, group II for ages between 4 and 6 years, and group III for ages over 6 years. The clinical and radiological results of the patients were compared between groups.

Results: At the time of surgery, the mean age of patients was 4.51 years (18 months-11 years). After a mean follow-up of 72.7 months; although there was no statistically significant difference between groups according to Severin's radiological criteria, it was observed that the success of the clinical outcome decreased and the avascular necrosis (AVN) rates increased in children who were operated after the age of 6 years.

Conclusions: Although, SPO was an effective treatment option for patients with DDH after the age of walking, it might cause a decrease in the success of clinical outcomes and an increase in AVN after 6 years of age.

Keywords: Developmental hip dysplasia, Surgical treatment, Avascular necrosis, Patient age, Salter pelvic osteotomy

1. INTRODUCTION

The ideal time for diagnosis and treatment of developmental dysplasia of the hip (DDH) is the neonatal period. Early diagnosis is very important for the success of treatment [1]. Guidelines for detection and improved screening techniques have aided in early diagnosis, significantly reducing the number of patients requiring closed or open procedures [2,3].

While open or closed reduction may be sufficient in the early period of DDH treatment, pelvic and/or femoral osteotomies may be necessary for addition to the reduction in the treatment of DDH after the age of walking. Salter pelvic osteotomy (SPO) is an effective surgical treatment option in patients with DDH after the age of walking and although it is recommended to be performed between 18 months and 6 years [4], there is no definite upper age limit [5].

In this study, we evaluated the effect of age, which the patients had been operated on, with the radiological and clinical results in the treatment of DDH. These patients were surgically treated with SPO with or without femoral shortening. This study aims to compare the results of surgery in DDH with the age at which SPO was performed.

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2. PATIENTS and METHOD

This study was approved by the Istanbul, Kartal Dr.Lutfi Kirdar Training and Research Hospital Ethics Committee (approval number: 2020/514/173/3).

In this retrospective study, we analyzed 46 hips of 36 patients who had undergone SPO surgery (with or without femoral shortening). Patients were followed up for at least 1 year. The patients comprised 33 (91.7%) girls and 3 (8.3%) boys with a mean age of 4.51 years (range, 18 months-11 years) at the time of surgery. Bilateral DDH was present in 10 (27.8%) patients, left hip involvement was present in 11 (30.6%) and right hip involvement was present in 15 (41.6%). The demographic data of the patients are given in table I.

Table I. *Demographic data of the patients.*

Patient demographics	n (number of patients)
Right DDH	15
Left DDH	11
Bilateral DDH	10
Female/ Male	33 / 3
Group I (18 months-4 years)	19
Group II (4-6 years)	11
Group III (6-11 years)	10

DDH: developmental dysplasia of the hip

The surgery was performed with single-stage surgery for all the patients. No preoperative traction was applied to any patient. Patients with a definite diagnosis of the disease and no prior operation were included in the study. Considering exclusion criteria, cases with other comorbidities such as cerebral palsy, arthrogryposis, myelomeningocele were excluded from the study. Type of surgery for each patient, patient's age at the time of diagnosis, gender, level of pain, limping degree, and decreased range of motion of the hip joint were recorded on a data sheet. Patients were invited for follow-up physical examination and control radiographs of pelvic were obtained. Open reduction was performed through the anterior Smith Peterson approach in all hips [6,7]. The SPO decision for hips where open reduction could not be applied was determined by the Acetabular Index (AI) [8].

To investigate the effect of surgical age on clinical and radiological outcomes, the cases were retrospectively divided into three age groups. Nineteen (41.3%) cases between 18 months and 4 years were studied in group I (Figure 1), 16 (34.8%) cases between 4-6 years in group II (Figure 2), and 11 (23.9%) cases over 6 years in group III (Figure 3).

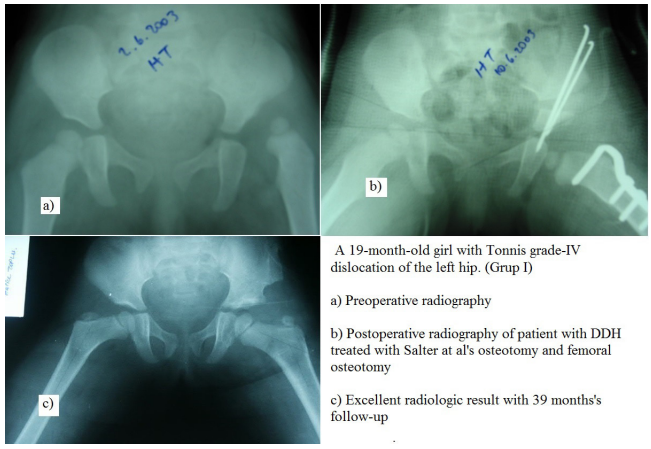

Figure 1. *Radiological evolution of an 19 month-old girl patient with DDH treated with Salter osteotomy and femoral osteotomy. (Grup I)*

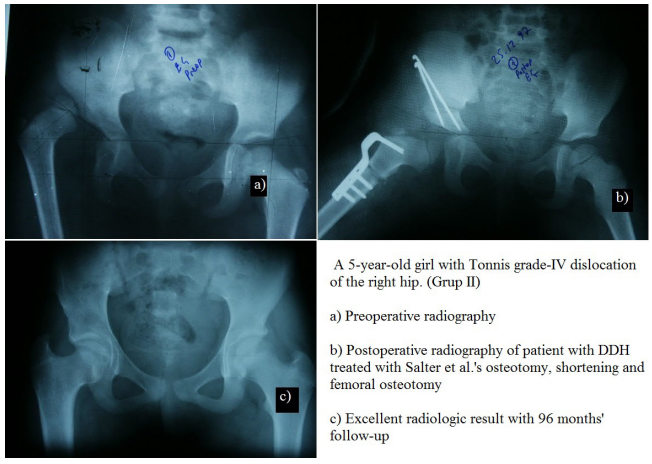

Figure 2*. Radiological evolution of a 5-year-old girl patient with DDH treated with Salter osteotomy, shortening and femoral osteotomy. (Grup II)*

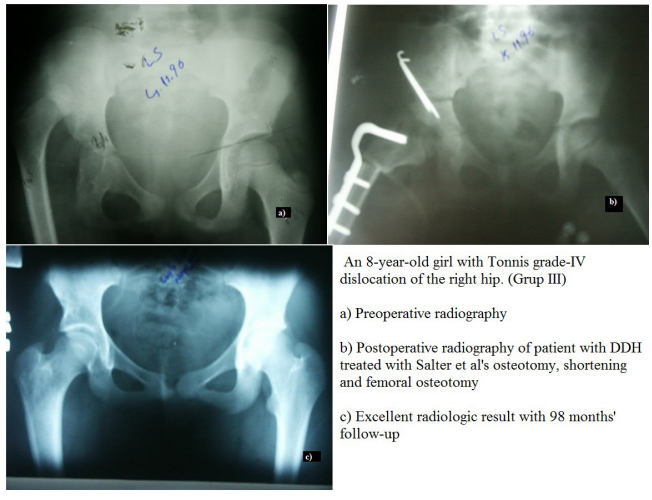

Figure 3*. Radiological evolution of a 8-year-old girl patient with DDH treated with Salter osteotomy, shortening and femoral osteotomy. (Grup III)*

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The pelvipedal plaster applied during surgery was removed after 4 weeks and active hip movements were recommended without weight-bearing on the operated hip for the first 20 days. The preoperative and postoperative pelvis radiographs were examined and the AI and centre-edge angle (CEA) which were the signs of lateral coverage and showing the long-term success of the surgery were measured. Postoperative radiological evaluation was made according to the Severin criteria [9] (Table II) and the clinical evaluation was performed according to the modified McKay criteria [10] (Table III).

Table II. *Severin's radiological evaluation criteria [9].*

CLASS	RESULTS
I (Very good)	Normal hip
A	CEA>19º (6-13 years) CE>25º (>14 years)
B	CE 15º-19º (6-13 years) CE 20º-25º (>14 years)
II (Good)	The head, neck or acetabulum has a mild deformity, but hip joint is concentrically reducted. CE values are the same as Class Ia and Ib.
III (Moderate)	Dysplastic hip (no subluxation) CE<20º (>14 years) CE<15º (6-13 years)
IV (Bad)	Subluxated hip
A	Moderate subluxation CE>0º
B	Severe subluxation CE<0º
V (Very bad)	The head is articulated with the secondary acetabulum at the top of the original acetabulum
VI (Redislocated)	Redislocated hip

CEA: center-edge angel

Table III. *Modified McKay clinical evaluation criteria [10]*

Modified McKay clinical evaluation criteria group	STABILITY-PAIN-LIMPING-TRANDELENBURG-RANGE OF MOTION-DISLOCATION
Group 1 (Excellent)	A stable and painless hip. No limping. Trandelenburg test (-). Full range of joint motion.
Group 2 (Good)	A stable and painless hip. Normal walking or slight limping. Trandelenburg test (-). There is a slight limitation in the range of motion of the joint.
Group 3 (Moderate)	A stable and painless hip. There's limping. Trandelenburg test (+). There is a moderate restriction of the range of motion of the joint
Group 4 (Bad)	An unstable, painful hip. There's limping. Trandelenburg test (+). There is no dislocation even though the range of motion of the joint is very limited.
Group 5 (Unsuccessful)	An unstable, painful or painless hip. There's limping. Trandelenburg test (+). There is dislocation.

Postoperative avascular necrosis (AVN) was diagnosed according to Salter criteria [11]. Within one year after the reduction, absence of an ossification nucleus, non-growth of an existing ossification nucleus, increase in its density and fragmentation, metaphyseal enlargement and decrease in bone density of the femoral neck, and the development of deformity in the femoral head and neck were evaluated as AVN findings [11]. The radiological findings of the hips where AVN developed were identified and classified according to the Kalamchi-MacEwan classification [12] (Table IV).

Table IV. *Kalamchi-Mac Ewen AVN classification [12].*

GROUP	FINDING
1	Changes in the center of ossification
2	Group 1+ Lateral physis injury
3	Group 2+Central physis injury
4	Group 3+Whole physis injury

Statistical Analysis

For the statistical analysis, IBM SPSS 25.0 (Armonk, NY: IBM Corp.) and MedCalc 15.8 (MedCalc Software Ltd, Acacialaan Ostend Belgium) was used. The definitive statistical analysis was used for ages and the characteristics of the groups, the clinical and radiological findings obtained for the groups, and developing complications were statistically analyzed by using the Mann-Whitney, Paired Samples t-test, and Student's t-test. The values of $p<0.05$ were considered statistically significant.

3. RESULTS

There were no significant differences in terms of gender distribution, disease type of patients (patients with high hip dislocation, subluxation, acetabular dysplasia, or both), type of surgery, and additional operations ($p>0.05$). The patients were followed up for a mean of 72.7 months (range, 12-160 months).

As a result of radiological evaluation in all groups, the mean values of AI were measured as 31.6° preoperatively and 16.6° at the late postoperative period. When the AI values were measured preoperatively and at the final follow-up examination were compared, it was determined that mean AI was improved 15° in all groups and this was statistically significant ($p<0.05$). Mean values of femoral neck-shaft angle were 139.6° preoperatively and 130.7° at the final follow-up examination. A significant decrease as 9° was observed at the final controls in all groups ($p<0.05$) (Table V).

In the clinical evaluation according to modified McKay criteria, excellent and good results were obtained in 16 of 19 hips (84.2%) in group I, in 13 of 16 hips (81.3%) in group II and 6 of 11 hips (54.5%) in group III. According to age groups, more successful results were obtained at (Group I) younger ages (Table VI).

According to Severin's radiological criteria, excellent and good results were obtained in 79.1% of group I, 81.3% of group II,

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and 81.8% of group III. There was no statistically significant difference between the groups (p>0.05) [9] (Table VI).

According to the Kalamchi-McEwan AVN classification, AVN was observed in 5 of 19 hips (26.3%) in group I, in 5 of 16 hips (31.2%) in group II and 10 of 11 hips (90.1%) in group III. A statistically significantly higher rate of AVN was determined in group III (p<0.05) [12] (Table VII).

Table V. *Preoperative and final control mean AI and femur neck-body angle values of all patients.*

Mean AI		Mean femoral neck-shaft angle	
Preoperative	**Final control**	**Preoperative**	**Final control**
31.6°	16.6°	139.6°	130.7°
15° correction		9° correction	
Significant improvement (p<0.05)		Significant decrease (p<0.05)	

Table VI. *Clinical and radiological evaluation according to groups*

	Group I (18 months-4 years)	Group II (4-6 years)	Group III (>6years)	Statistical comments
Modified McKay criteria (Excellent and good results)	84.2%	81.3%	54.5%	More successful results at younger ages
Sever's radiological criteria (Very good and good results)	79.1%	81.3%	81.8%	No statistically significant difference

Table VII. *Kalamchi-McEwen classification of AVN seen in groups*

	Group I	Group II	Group III	Comment
Kalamchi-McEwen (AVN rate)	5\19 (26.3%)	5\16 (31.2%)	10\11 (90.1%)	AVN increases as surgical age increases

4. DISCUSSION

This study revealed that the majority of patients with DDH who underwent SPO surgery had satisfactory results according to Severin's radiological criteria. However, this study also showed that functional outcomes and AVN rates were worse in children operated after the age of 6 when compared to younger age groups.

In this study, we found radiologically satisfactory results (excellent and good results) The success rate was 79.1% in group I, 81.3% in group II, 81.8% in group III. There was no statistically significant difference between the groups (p>0.05) as observed by other studies [13,14,15,].

Barrett et al., did not specify an upper age limit for SPO, but reports revealed that successful outcomes were mostly between 1.5 and 4 years of age [16]. Gulman et al.,

reported that when cases were divided into three groups as 18 months-4 years of age, 4-6 years, and over 6 years, the most successful results with SPO were obtained in the patients between 18 months-4 years age group [17]. We, clinically achieved satisfactory (excellent and good results) results in group I (84.2%), group II (81.3%), and group III (54.5%). Although, groups I and II had similar satisfactory results, group III had statistically significantly poor results. Thus, we found that the clinical results were significantly poorer in group III, which included patients older than six years as observed by other studies [5,13,16,17].

It is a general belief that the age of the patient is an effective factor in the surgical outcomes and that this success is decreasing with the increased age [5]. Although, there is a consensus about the lower limit of age for SPO, there is serious debate about the upper limit [5,6]. According to Salter, the upper limit of age is 6 years [11].

Avascular necrosis seen after SPO was reported mostly at rates between 1.2% and 63.4% [5,6,16,17]. In this study, we found the rate of AVN as 26.3% in group I, 31.1% in group II and 90.1% in group III according to age groups. We found that the ratio of AVN increased in the patients (10/11) who were older than 6 years of age. The rate of AVN reported by Gulman et al., was 63.3% which was extremely high compared to other studies and was attributed to inadequate surgical techniques and enforced indications [17].

In this study, the average correction of the CEA (9 degrees) and the AI (5 degrees) obtained by the Salter innominate osteotomy (SIO) were within the range of correction reported in most studies [8,13,17-19].

In conclusion, early diagnosis and treatment are very important in DDH. Although, SPO is an effective treatment option for patients with DDH after the age of walking, it might cause a decrease in the success of clinical outcomes and an increase in AVN after 6 years of age.

Compliance with Ethical Standards

Ethical approval: This study was approved by the Istanbul Kartal Dr.Lutfi Kırdar Training and Research Hospital Ethics Committee (approval number: 2020/514/173/3).

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Conflict of Interest: The authors have no conflicts of interest to declare.

Authors' Contributions: Concept: FI and GB, Design: FI, GB and SG, Supervision: FI, GB and SG, Data Collection and/or Processing: FI, GB Literature review: FI and GB, Writing the article: FI, GB and SG, Critical review – FI, GB and SG. All authors read and approved the final virson of the article.

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The efficacy and clinical outcomes of transarterial embolization in acute massive upper gastrointestinal bleeding: a single-center experience

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ABSTRACT

Objective: To evaluate the efficacy of transarterial embolization (TAE) in the treatment of acute upper gastrointestinal bleeding (UGIB) and identify potential factors affecting the treatment outcome.

Patients and Methods: Eighteen patients with UGIB treated with TAE were included in the study. The demographic data, causes of bleeding, angiography findings, treatments applied, and clinical outcomes were retrospectively analyzed.

Results: Thirteen (72.2%) patients were male, five (27.8%) were female, and the mean age was 55 years (range: 33-68 years). A pseudoaneurysm (n = 7; 38.9%) was the most common finding, followed by tumor staining (n = 4; 22.2%). The most common pathology causing bleeding was peptic ulcer disease (n = 9; 50%). The most commonly embolized artery was the gastroduodenal artery (n = 11; 61.1%). There were three (16.7%) patients with hemobilia due to iatrogenic hepatic artery pseudoaneurysm. In most cases (n = 9; 50%), coils and polyvinyl alcohol particles were used in combination. Technical success was achieved in all patients. The clinical success rate was 78.5% (11/14 patients) after the exclusion of patients who died for non-UGIB causes (n = 4; 22.2%).

Conclusion: Transarterial embolization is an effective method used with high technical and clinical success rates in the treatment of endoscopy-refractory acute UGIB.

Keywords: Interventional imaging, Nonvariceal upper gastrointestinal bleeding, Endoscopy, Angiography, Embolization

1. INTRODUCTION

Acute upper gastrointestinal bleeding (UGIB) is an emergency that can lead to morbidity and mortality if proper treatment is not undertaken promptly [1]. Anatomically, UGIB refers to bleeding originating from the distal esophagus, stomach and duodenum, proximal to the ligament of Treitz. It is a common pathology with an incidence of 50-100 per 100,000 population and a mean disease age of 60-70 years [2]. Peptic ulcer disease (PUD) is the most common cause of non-varicose UGIB, and it less frequently occurs due to arteriovenous malformations, such as benign and malignant tumors, gastritis, ischemia, Dieulafoy's lesions, Mallory-Weiss syndrome, trauma, and iatrogenic causes [3]. A rapid and accurate diagnosis (localization and etiology) should be made in order to effectively treat acute massive UGIB. Following patient stabilization, endoscopy is usually performed to detect active bleeding and achieve hemostasis, but this primary hemostatic procedure fails in 10-30% of patients. If bleeding (1 ml/min) still continues after endoscopy or primary hemostasis fails despite endoscopic techniques, a more aggressive treatment with transarterial embolization (TAE) or surgical intervention is required. TAE has replaced the surgical procedure in recent years and has been shown to be effective in controlling bleeding and reducing mortality [3, 4]. The current study aimed to evaluate the safety and efficacy of TAE in the treatment of acute UGIB due to non-varicose causes and to identify potential factors affecting the treatment outcome.

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2. PATIENTS and METHODS

Patient population

For this study, the clinical records of 37 patients treated for acute massive UGIB between March 2018 and October 2019 at our center were retrospectively examined. Patients treated with medical (n = 6), surgical (n = 5) and endoscopic (n = 8) methods were excluded. As a result, a total of 18 patients treated in the interventional radiology unit with endovascular methods were included in the study. Ethics committee approval was obtained for this single-center retrospective study (approval number: 2020/ 8-12).

During the angiography procedure, all patients had active massive UGIB that did not respond to medical and endoscopic treatment. The study group consisted of 13 men and five women, and the mean age was 55 years (range: 33-68 years).

Clinical data and definitions

The demographic characteristics, laboratory findings, co-morbidities, bleeding pathology, rebleeding, clinical findings, and mortality rates were obtained from the electronic medical records of the patients. The shock index (heart rate/systolic blood pressure) indicating the hemodynamic instability of each patient was recorded. A shock index of >0.9 was defined as hypovolemic shock [5]. The hemoglobin concentration at the time of presentation and the number of blood units transfused before embolization were measured. The presence of hemodynamic instability and the need for at least four units of blood within 24 hours was evaluated as acute massive UGIB [3]. The presence of one or more of the following criteria was considered to indicate coagulopathy: International normalized ratio (INR) > 1.6, partial thromboplastin time > 45 sec, or prothrombin time > 13.5 seconds. The patients with a platelet count of <50,000/mm^3 were diagnosed with thrombocytopenia [3]. A pre-angiographic investigation was accepted as endoscopy or computed tomography angiography (CTA) performed after the onset of acute UGIB and seven days before the TAE intervention. All patients underwent endoscopy and CTA before angiography.

Angiography and TAE

Selective angiographies were performed in the interventional radiology unit by an interventional radiologist (IR) with a minimum of five years of experience in endovascular procedures. All patients signed an informed consent form prior to interventional treatment. After the patients were placed on the operation table for interventional treatment, their blood pressure, oxygen saturation, and heart and respiratory rates were monitored. The right inguinal area was disinfected, and the procedure was started by covering the location with a surgical towel. With the patient under local anesthesia, the common femoral artery was punctured with a retrograde technique using an 18-gauge single-wall needle under ultrasound guidance. Using the Seldinger technique, a 5-French (Fr) vascular sheath was placed over a 0.035-inch guide-wire. A long femoral guiding sheath (6 Fr – 45 cm Destination® Terumo, Tokyo, Japan) was used in cases where catheterization was difficult due to tortuous arteries. Depending on the bleeding site identified on CTA images, the celiac truncus and the superior mesenteric artery (SMA) were selectively catheterized using 4-Fr or 5-Fr angiographic catheters (Simmon-1 or Cobra-2; Cordis, Miami Lakes, FL, USA). Angiography was performed to confirm bleeding, localize the source (active contrast extravasation, contrast blushing, or tumor bleeding), or to detect pseudoaneurysms. Then, the target artery was superselectively catheterized using a microcatheter (1.7–2.1 Fr Echelon, Medtronic, USA; 2.7 Fr Progreat®, Terumo, Tokyo, Japan). The appropriate embolic agent was selected depending on the patient and administered by the IR to the patient through the microcatheter. The materials used for embolization were 0.018-inch platinum microcoils (Boston Scientific, Ireland) or polyvinyl alcohol (PVA) particles (Contour TM; Boston Scientific), or a combination thereof. The sizes of the PVA particles used were 355—500, 500—710 and 710—1,000 microns. In addition, in the treatment of pseudoaneurysms, a covered stent-graft was placed using a 60 cm 8 Fr vascular sheath (Arrow, Arrow International, USA) and a 0.014 inch guide-wire (Jostent, Graftmaster, Coronary stent graft, Germany).

Finally, a post-embolization angiography was performed to confirm the technical success of the procedure and reevaluate the presence of other possible bleeding. The angiographic data were obtained by examining the Picture Archiving and Communication System of the hospital. The bleeding focus associated with the artery feeding the bleeding area and positive angiographic findings were recorded for each patient.

Technical and clinical endpoints

Based on angiographic findings, technical success was defined as the disappearance of contrast extravasation immediately after embolization, loss of flow in the arteries or their branches feeding the bleeding focus, and disappearance of the filling of the pseudoaneurysm causing bleeding, and technical failure as the spontaneous cessation of bleeding as a result of arterial spasm during catheter advancement or the bleeding artery not being selectively catheterized and embolized. Clinical success was defined as the improvement of the signs and symptoms of bleeding, including hemoglobin level and blood pressure within 30 days following TAE, and clinical failure as persistent or recurrent active bleeding that occurred within 30 days following the procedure, requiring surgical intervention and/or resulting in mortality [1, 6].

Short-term follow-up

In the short-term follow-up of the patients, post-procedural persistent bleeding, early recurrent bleeding within the first three days, and 30-day mortality rates were recorded. It was also determined whether a second intervention, such as surgery or TAE was performed after the procedure.

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Original Article

Statistical Analysis

All analyses were performed using SPSS software v. 22.0 (IBM SPSS Statistics Version 22.0. Armonk, NY: IBM Corp.). The variables were divided into two groups as categorical and continuous. Categorical variables were expressed as numbers and percentages, and continuous variables as mean and range values. Technical success, clinical success, technical failure, and clinical failure were calculated as percentages. Categorical variables were compared with Fisher's exact test. The statistical significance level was accepted as $p < 0.05$.

3. RESULTS

Pre-angiographic investigations and cause of bleeding

During the investigations performed before angiography, the presence of active bleeding and/or a bleeding focus were detected in all 18 (100%) patients by endoscopy in 13 cases (72.2%) and CTA in 10 (55.5%). The most common pathology causing bleeding was PUD (n = 9; 50%). Other causes of UGIB, pre-procedural investigations, and demographic data of the patients are detailed in Table I.

Table I. *Demographic data and clinical parameters of 18 patients with acute upper gastrointestinal bleeding treated by transarterial embolization*

Variable	n (%)
Sex	
Male	13 (72.2)
Female	5 (27.8)
Age (years) (range: 33-68)	
≤60	12 (66.7)
>60	6 (33.3)
Units of blood transfusion 24 hours before angiography (range: 2-5)	
<4	4 (22.2)
≥ 4	14 (77.8)
Comorbidity	
Cardiovascular disease (IHD, HT)	12 (66.7)
Malignity	5 (27.8)
Metabolic disease (DM and DLP)	11 (61.1)
Unknown	4 (22.2)
Serum Hb level on the day of bleeding (g/dL) (range: 6-11)	
<8	13 (72.2)
≥8	5 (27.8)
Coagulation	
Normal	14 (77.8)
Coagulopathy (prolonged PT, PTT, or INR)	2 (11.7)
Thrombocytopenia (platelet count < 50,000/mm^3)	2 (11.7)
Hemodynamic instability	
No	2 (11.1)
Yes	16 (88.9)
Investigation before TAE within seven days	
Not performed	-
Negative CTA	7 (38.9)
Negative endoscopy	4 (22.2)
Positive CTA	10 (55.5)
Positive endoscopy	13 (72.2)
Etiology of bleeding	
Peptic ulcer disease	9 (50)
Tumor bleeding	5 (27.8)
Traumatic or iatrogenic	4 (22.2)

DM: diabetes mellitus, DLP: dyslipidemia, IHD: ischemic heart disease, HT: hypertension, Hb: hemoglobin, PT: prothrombin time, PTT: partial thromboplastin time, INR: international normalized ratio, TAE: transarterial

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Marmara Med J 2021;34(2): 180-188

Angiography and embolization

Positive angiography findings were present in 13 (72.2%) of patients with acute UGIB. In order of frequency, these findings were pseudoaneurysms in seven patients (38.9%), tumor staining in four (22.2%), tumor staining and a pseudoaneurysm in one (5.5%), and contrast extravasation in one (5.5%). In the remaining five (27.8%) patients, no positive findings were detected on angiography. The focus of UGIB most frequently had a gastric origin fed by the celiac artery (n = 13; 72.2%). The most commonly embolized artery was the gastroduodenal artery (GDA) (n = 11; 61.1%). Pathologies causing bleeding, embolized arteries, and embolization methods used are detailed in Table II.

Table II. *Angiography findings, treatments applied, and clinical outcomes of 18 patients with acute gastrointestinal bleeding*

Patient Number	Age / sex	Etiology	Angiography findings	Endovascular treatment	Clinical outcome	Follow-up (30-day) mortality
1	58/F	PUD	-	Blind embolization of GDA (PVA and coil)	BS and NFB	-
2	60/F	Gastric lymphoma	Tumor staining	Blind embolization of GDA (PVA and coil)	BS and NFB	Died on day, due to AMI
3	63/M	PUD	Superior pancreaticoduodenal artery pseudoaneurysm	Coil embolization of the aneurysm	BS and NFB	-
4	57/M	Periampullary tumor	Tumor staining	Blind embolization of GDA (PVA and coil)	BS and NFB	Died on day 3 due to underlying malignancy
5	60/F	Periampullary tumor	Tumor staining and microaneurysms in the branches of GDA	Coil embolization of GDA and PVA embolization of the tumor	BS and NFB	Died on day 4 due to multiorgan failure
6	60/M	PUD	GDA pseudoaneurysm	Coil embolization	BS and NFB	-
7	65/M	PUD	-	Blind embolization of GDA (PVA and coil)	BS and NFB	-
8	68/M	Gastric tumor	Tumor staining	PVA embolization of the left gastric artery	BS and NFB	Died on day 10 due to underlying malignancy
9	56/M	PUD	-	Blind embolization of GDA (PVA and coil)	BS and NFB	-
10	58/M	Gastric tumor	Tumor staining	PVA embolization of the right gastric artery	BS and NFB	-
11	48/F	PUD	-	Blind embolization of GDA (PVA and coil)	Recurrent bleeding 16 hours later; underwent surgical revision	Died on day 2 due to uncontrolled bleeding
12	46/M	PUD	GDA pseudoaneurysm	Coil embolization	Recurrent bleeding 24 hours later; underwent surgical revision	Died on day 10 due to abdominal sepsis
13	44/M	Following PTBD (iatrogenic)	Left hepatic artery pseudoaneurysm	Coil embolization	BS and NFB	-
14	50/M	PUD	GDA pseudoaneurysm	Coil embolization	BS and NFB	-
15	55/M	PUD	-	Blind embolization of GDA (PVA and coil)	BS and NFB	-
16	33/M	Trauma	Contrast extravasation from the left gastro-epiploic artery	PVA and coil embolization	BS and NFB	-
17	54/M	Following PAD (iatrogenic)	Left hepatic artery pseudoaneurysm	Coil embolization	Recurrent bleeding 12 h later; underwent covered stent-graft placement	-
18	55/F	Following cholecystectomy (iatrogenic)	Right hepatic artery aneurysms	(covered stent-graft placement)	BS and NFB	-

GDA: gastroduodenal artery, PAD: percutaneous abscess drainage, PTBD: percutaneous transhepatic biliary drainage, PVA: polyvinyl alcohol particles, AMI: acute myocardial infarction, PUD: peptic ulcer disease, BS and NFB: Bleeding stopped and no further bleeding. The sizes of the PVA particles used were 355—500, 500—710 and 710—1,000 microns

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Marmara Med J 2021;34(2): 180-188

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Due to hepatic artery pseudoaneurysms (HAPs), three (16.7%) patients developed hemobilia and UGIB after liver transplantation, cholecystectomy, and percutaneous transhepatic biliary drainage (PTBD) catheterization, respectively. Although, the patient that developed HAP after the liver transplant underwent embolization of the aneurysm sac by coil, rebleeding occurred after 12 hours. During the second angiography, a covered stent-graft was placed while preserving the hepatic artery. No mortality or complications developed during the 30-day follow-up. In the second patient, the 5x9.6 cm narrow-necked giant aneurysm that developed after cholecystectomy was treated with a stent-graft (Figure 1). The third patient developed HAP due to the PTBD catheter placed in the left lobe in another hospital, but a diagnosis could not be made there despite the massive bleeding from the catheter site and upper gastrointestinal tract. This patient was referred to our center with hemodynamic instability, and the bleeding focus could not be determined on endoscopy or the first CTA examination. Thereupon, the catheter in the left lobe was removed, and the repeat CTA revealed a pseudoaneurysms in the left hepatic artery; thus, the patient was immediately taken to the interventional radiology unit. Embolization was performed with microcoils upon the detection of the left HAP in the selective hepatic arteriogram. The patient was discharged after observing no bleeding or complication during the follow-up (Figure 2).

In five (27.8%) patients with peptic ulcers, the finding that caused bleeding (extravasation or pseudoaneurysm) could not be detected by angiography. Following the administration of PVA particles through GDA to these patients, blind embolization was performed with the sandwich method using a coil. No retrograde filling was detected in the control angiography performed from SMA after embolization. Surgical revision was performed in one of these patients due to rebleeding that occurred after 16 hours. However, on the second day, mortality developed due to uncontrollable bleeding. No signs of bleeding or ischemia developed in the follow-up of the remaining four patients with peptic ulcers.

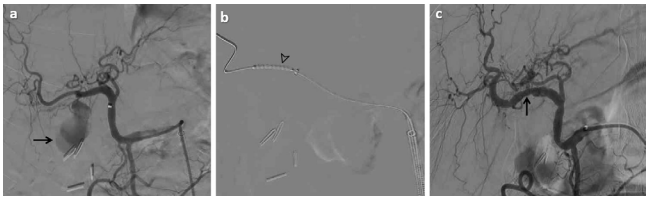

Figure 1. *Digital subtraction angiography images of a 55-year-old patient that developed a hepatic artery pseudoaneurysm following cholecystectomy. a Angiography before the procedure reveals a 5 x 9.6 cm-sized pseudoaneurysm sac (arrow) with a short neck originating from the right hepatic artery. b Angiography showing the placement of a covered stent-graft (arrow head). c disappearance of the aneurysm and continuation of blood flow through the covered stent-grafts (arrow) placed by preserving the hepatic artery.*

For the pseudoaneurysms originating from GDA (n = 3; 16.7%) and the superior pancreatic-duodenal artery (n = 1; 5.5%) due to peptic ulcers, embolization was performed by coil (Figure 3). One of these patients required surgery due to rebleeding after 24 hours. Mortality caused by sepsis occurred on the 10th day in the follow-up of this patient.

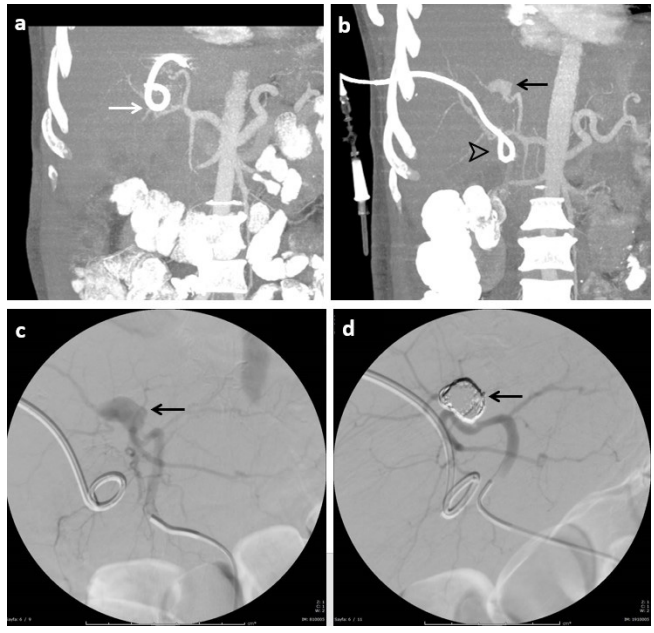

Figure 2. *Images of an iatrogenic hepatic artery pseudoaneurysm that developed after PTBD performed due to distal common bile cancer. a The maximum intensity projection image shows no hepatic artery aneurysm when the PTBD catheter (white arrow) is in the biliary duct in the left lobe. b Following the removal of the catheter and placement of a different catheter (arrow head) from the right side, a 2.4 x 1.3 cm pseudoaneurysm sac originating from the left hepatic artery (black arrow) appears. c Pre-procedural hepatic arteriography shows the left hepatic artery pseudoaneurysm (arrow). d Post-embolization angiography shows the coil-packed and embolized pseudoaneurysm (arrow).*

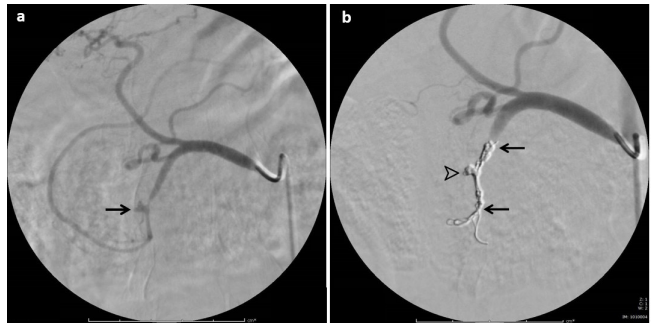

Figure 3. *Upper gastrointestinal bleeding in a 50-year-old male with bleeding peptic ulcer and unsuccessful endoscopic hemostasis. a Digital subtraction angiography images reveal the pseudoaneurysm in the gastroduodenal artery (arrow). b The images also show that the pseudoaneurysm in the gastroduodenal artery, which was the source of bleeding, has been embolized by coil (arrow head). It is also shown that the proximal and distal of the artery have been embolized by microcoil using the sandwich technique to prevent rebleeding (arrows).*

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Marmara Med J 2021;34(2): 180-188

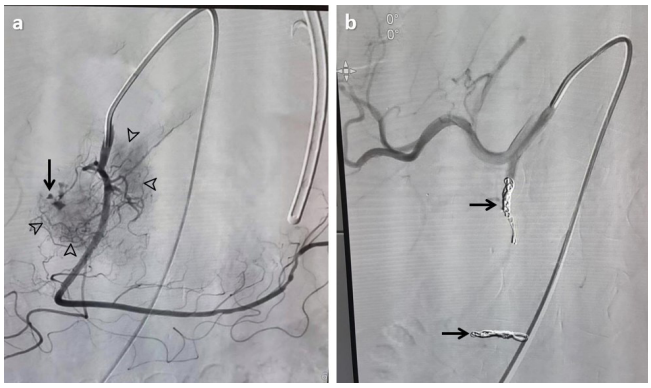

Figure 4. *Digital subtraction angiography (DSA) images of a 60-year-old woman with a periampullary tumor. a Pre-embolization selective DSA image shows tumor staining (arrowheads) and microaneurysms (arrow) originating from the gastroduodenal artery. b Post-embolization control DSA image shows that the proximal and distal of the artery have been embolized by coil using the sandwich technique to prevent antegrade and retrograde filling (arrows). Polyvinyl alcohol particles were given before coil embolization.*

Various embolizing agents were used to occlude the artery feeding the bleeding tissue. In most cases (n = 9; 50%), coils and PVA particles were used in combination. This was followed by the use of coils alone (n = 6; 33.3%). Tumor staining and microaneurysm were detected in one of the five (27.8%) patients with tumorous bleeding, and embolization was performed in this patient using the coil and PVA particles combination (Figure 4).

Technical success was achieved in all 18 (100%) patients during the TAE procedure. Catheterization was not possible with a standard femoral introducer in two (11.1%) patients due to arterial tortuosity but the procedure was successfully performed using long femoral guiding sheaths in these cases.

After excluding the four patients (22.2%), who died due to non-UGIB causes (multiorgan failure, underlying malignancy, and acute myocardial infarction) within 30 days of hospitalization (based on the definition of clinical success as the presence of no rebleeding for at least 30 days following TAE), the clinical success rate was calculated as 78.5% (11/14 patients). As shown in the flow diagram in Figure 5, of the three (16.7%) patients with clinical failure that developed recurrent bleeding within the first 24 hours, two diagnosed with PUD (11.1%) required surgical intervention and one diagnosed with HAP (5.5%) underwent a second angiography.

Table III shows the comparison of clinical success rates according to the causes of bleeding and the types of endovascular treatment performed.

The 30-day mortality rate for all causes was 6/18 (33.3%). Minor complications (non-flow-limiting arterial dissection at the puncture site) occurred in two (11.1%) patients due to the procedure. No major complications occurred in any of the patients.

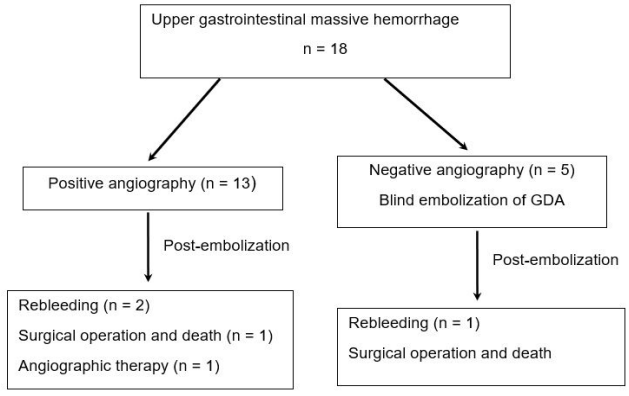

Figure 5. *Flow diagram of the patients included in the study*

Table III. *Comparison of clinical success rates according to the causes of bleeding and endovascular treatment types*

Etiology of bleeding	Total, n (%)	Clinical success, n (%)	p value
Peptic ulcer disease	9 (50)	7 (77.8)	0.505
Tumor bleeding	5 (27.8)	5 (100)	
Traumatic or iatrogenic	4 (22.2)	3 (75)	
Type of embolization			
PVA and coil embolization	9 (50)	8 (78.9)	0.485
Coil embolization	6 (33.3)	4 (66.7)	
PVA embolization	2 (11.1)	2 (100)	
Covered stent-graft placement	1 (5.5)	1 (100)	

p value <0.05 at 95% confidence interval is significant

4. DISCUSSION

In this study, the technical and clinical success rates of TAE performed following acute UGIB were 100% and 78.5%, respectively. There were no cases in which TAE technically failed. This is in agreement with previous studies reporting the technical success rate of TAE to be over 90% [7-9]. These high success rates can be attributed to the development of endovascular devices with the advancements in technology, growing experience of IRs, and the combined use of embolic agents [10]. Researchers stated that technical failure occurred most frequently due to difficult vascular anatomies, arterial dissection, vasospasm, false negatively read angiogram, multiple

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Marmara Med J 2021;34(2): 180-188

bleedings, and tumorous bleeding [9, 11, 12]. In our study, this problem was resolved using a long femoral guiding sheath only in two (11.1%) cases for which selective catheterization was not possible due to arterial tortuosity.

With transarterial embolization, 89-98% of initial bleeding can be taken under control. The clinical success rate of TAE was found to be different in previous research (52-98%) while most showing success rates of 70 to 80% [7-9]. In all patients in the current study, bleeding was successfully controlled at the first stage using the TAE method. Similar to previous studies, a high clinical success rate of 78.5% was achieved. Among the cases of clinical failure, two diagnosed with PUD experienced rebleeding shortly after the procedure, and thus underwent surgical revision; however, mortality developed in both due to uncontrolled bleeding and abdominal sepsis. The third case of clinical failure presented with the rebleeding of the aneurysm that had been caused by HAP and embolized by coil after liver transplantation. HAP usually occurs as a result of surgical and interventional procedures applied to the biliary tract or develops secondary to trauma. Today, parallel to the increase in percutaneous interventions for the biliary tract, there is an increase in the incidence of pseudoaneurysms observed [13]. Tessier et al., reported that among 153 patients with HAPs, the causes of these pseudoaneurysms in order of frequency were PTBD (31%), laparoscopic cholecystectomy (28%), open cholecystectomy (13%), and percutaneous liver biopsy (7%) [14]. In addition, if hemobilia, a rare cause of UGIB that occurs due to HAP rupture is not treated immediately, it may result in mortality [9]. All HAP cases in the current study had iatrogenic causes and presented to the clinic with hemobilia. As in the patient that was referred to our center with a delayed diagnosis in a hemodynamically unstable condition, a PTBD catheter can hide existing pseudoaneurysms in some cases and cause delay in treatment. In such cases, investigations performed after the removal of the catheter can be diagnostic. In light of all this information, patients who have undergone liver interventions and developed UGIB should be promptly taken to the angiography unit even if their endoscopy findings are negative. Thus, serious complications, such as HAP, which can result in massive bleeding and mortality, can be treated quickly and safely by TAE.

In this study, PUD (50%) was the most common cause of bleeding, which is consistent with the literature [9]. This was followed by tumorous bleeding and iatrogenic causes. The majority of patients with positive angiography findings had pseudoaneurysms. Tétreau et al., reported that 17% of gastrointestinal bleeding occurred due to pseudoaneurysms, and 91% of these cases were successfully treated by TAE [15]. In the current study, pseudoaneurysms were detected at a rate of 38.9% on angiography, and embolization was performed. Despite technical success in all patients, mortality related to rebleeding occurred in one case. Nevertheless, previous authors also emphasized that TAE could be successfully applied in patients who develop massive bleeding as a result of splanchnic artery pseudoaneurysms [16].

Angiographic findings of bleeding (contrast extravasation, vascular blush, pseudoaneurysms, or arterial spasm) may not always be evident in massive UGIB. In such cases, blind embolization can be performed on the arteries feeding the bleeding focus. Although blind embolization is controversial, most researchers argue that this procedure should be performed based on endoscopic findings [9, 10]. Aina et al., [17], Loffroy et al., [18], and Padia et al. [19] performed blind embolization of GDA using coils in those with and without positive angiography findings in their case series. Although, the negative extravasation group had a higher incidence of comorbidities, such as respiratory distress, none of these researchers found any difference between the two groups in terms of the treatment success rate and short-term outcome (30-day mortality). However, the sandwich technique, in which the proximal and distal of GDA are filled during the blind embolization procedure, is reported to prevent retrograde filling that may result from SMA [9, 17-19]. In our study, UGIB was taken under control, and hemostasis was achieved in the first stage in all five (27.8%) patients, in whom we performed blind embolization with the sandwich technique. Only one patient had rebleeding. Based on this information and the results of our study, it is possible to state that blind embolization is an effective treatment for hemostasis control when performed with the appropriate technique.

Various embolic agents, such as gelatin sponges, metallic coils, PVA, glue, N-butyl cyanoacrylate, and autologous blood clots can be used in the TAE procedure [3, 9, 10]. In this study, the combination of coil and PVA particles was most commonly used for embolization. During the procedure, attention was paid to placing the coils close to the bleeding artery as possible, which was supplemented by PVA to embolize collaterals with bleeding potential. Recurrent bleeding being seen in only one patient shows that the combined use of PVA with a coil results in a successful procedure. Although, there are a few researchers who applied coils alone in the embolization of GDA and pancreaticoduodenal arteries, it is generally recommended to use coils together with gelatin sponge or PVA to successfully achieve distal levels of hemostasis. Despite the low cost and easy availability of gelatin sponge, due to its resorbable nature, it leads to higher recurrent bleeding rates compared to non-resorbable PVA. Furthermore, studies have shown that the success rate of using gelatin sponge alone is very low (62%), and therefore it should be avoided to achieve long-term hemostasis [9]. Aina et al., [17] and Loffroy et al., [18] showed a relationship between the use of coils alone and incidence of recurrent bleeding, especially in patients with coagulopathy, and emphasized the advantages of using it in combination with PVA or gelatin sponge could not be overlooked. In the current study, coils were used alone only in the treatment of six patients with pseudoaneurysms (33.3%), and clinical success was achieved in all but two patients. In the patients with a liver transplant that developed bleeding, embolization of the parent artery was avoided due to the risk of liver failure, and a stent-graft was placed. Mortality and morbidity did not develop during the short-term follow-up (30 days). In such cases, specific endovascular treatments, such as filling the pseudoaneurysm sac with a coil or placing a covered

stent can provide favorable results in maintaining the patency of the parent artery [9]. To date, only a few cases of endovascular covered stent-graft repair have been described during acute bleeding in liver transplant patients. The use of a covered stent with a stiff structure is a technically difficult method due to the tortuosity of the transplanted hepatic artery [20]. Given the success rates observed in other reports and in our own experience, we believe that the proper and safe endovascular placement of a covered stent-graft may be a good alternative to open surgery because this approach can simultaneously control active bleeding and reconstruct HAP after liver transplantation. Therefore, it should be considered as a less morbid approach in high-risk patients.

In this study, the total 30-day mortality rate was 33.3%, which is similar to previous studies (20-46%) [9, 17-19]. Following TAE performed with technical success, most in-hospital mortality (4/6) occurred for non-UGIB causes, but it was as a result of the deterioration of patients' comorbidities. This is in agreement with the reports in the literature [9]. The variability of the mortality rates among the studies in the literature further emphasizes the importance of individual expertise and center experience. In addition, although mortality rates seem to be high, patients undergoing TAE generally consist of an older age population with a high incidence of comorbidities, who are often unable to bear the surgical burden. Therefore, providing bleeding control with TAE seems to reduce the incidence of laparotomy, and thus indirectly decrease morbidity and mortality in patients.

Limitations

This study had certain limitations, such as its retrospective design and absence of randomization. The current study reveals that different embolization methods and bleeding etiology have no effect on clinical success. However, the small number of patients between the groups may not give reliable results for comparison. This is among the limitations of our study. Therefore, large population-based, prospective, and, if possible, multicenter studies are needed to better explain the best initial management in patients with active UGIB and to elucidate the variables that may affect the treatment outcome.

Conclusions

TAE is a safe and effective treatment method with high technical and clinical success rates in the treatment of life-threatening acute non-varicose UGIB. It is concluded that in cases with endoscopy-refractory acute massive UGIB, TAE should be promptly performed by experienced IRs, and a multidisciplinary team is required for the pre – and post-procedural management of patients.

Compliance with Ethical Standards

Ethical approval: All procedures performed in this study were in accordance with the ethical standards of institutional and/or national research committees and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The research project was approved by Harran University, Faculty of Medicine Institutional Review Board (approval number: 20/08/12, 27.04.2020). Informed consent was obtained from all individual participant included in the study.

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Authors' Contrubitions: Concept and Design: MT and MK, Resources: MT and MK, Materials: MK, Data Collection and processing: MK, Analysis and interpretation: MT and MK, Literature search: MT and MK, Writing the article article: MT and MK, Critical Review: MT and MK. Both authors read and approved the final version of this article.

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Determination of the effect of COVID-19 pandemic on the anxiety levels and life quality of healthcare workers

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ABSTRACT

Objective: This study was conducted to determine the effects of the interventions made to prevent the COVID-19 pandemic on the anxiety level and life quality of healthcare workers.

Materials and Methods: The study is a descriptive one, and the data were collected online using the Google Forms application. The Information Form including 15 questions, the Beck Anxiety Scale, and Short Form-36 (SF-36) Life Quality Scale were used to collect data. Five hundred and eight healthcare workers participated in the study. Statistical significance was set as $p<0.05$. The findings showing statistically significant differences were evaluated using the Games-Howel Post-hoc test.

Results: The study revealed that 81.3% of the healthcare workers are worried about their own health during the COVID-19 pandemic. It has been found that 38% of the healthcare workers have been experiencing a shortage of protective equipment in the hospital where they work. As far as worrying about one's own health during the pandemic is concerned, it was found that there was a statistically significant difference between the Beck Anxiety Scale mean scores and the SF-36 Life Quality Scale mean scores.

Conclusion: Our study revealed that the anxiety levels of healthcare workers were low during the pandemic and their quality of life was high. It should be foreseen that pandemics such as COVID-19 may also occur in the future, and the psychological effects on healthcare workers should be monitored during pandemics.

Keywords: COVID-19, Healthcare worker, Anxiety, Life quality

1. INTRODUCTION

The World Health Organization (WHO) reported on 30 January 2020 that the new corona virus was a public health problem of international concern with more than one million cases [1]. This health problem was named as corona virus disease 2019 (COVID-19) by the WHO [1,2]. COVID-19, or SARS-CoV-2, infection emerged in China [3]. Since this new virus is of very small size, it is spread mainly by respiratory droplets and close contact [4-6]. In addition, the disease is spread when the surfaces and items that patients touch are touched by others and when individuals touch their face and eyes or handshake etc. with their infected hands. Spread occurs in contacts [6]. As the disease progresses, a series of complications and multiple organ failures are observed. The transmission and spreading rate of infection is faster than in other viral infections [7]. The COVID-19 pandemic affects all health systems around the world. No specific treatment method has been established for COVID-19 yet; only supportive treatment is provided. The number of people affected by COVID-19 has increased day by day and countries have started to report new cases, and this disease has aroused concern in people [7,8]. The first case was seen in our country in March 2020 and the importance of health services has increased. The healthcare workers risk their own health while providing care to patients with COVID-19, as in other epidemics such as measles, HIV/AIDS, and Ebola virus disease [9]. Healthcare workers are exposed to the infected cases for a long time. Therefore, they are expected to be at high risk of infection [10].

Epidemics and pandemics may have psychological and behavioral effects [8]. They may lead to a variety of psychological problems in individuals such as insomnia, anxiety, fear, concern, anger,

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and depression, and these psychological effects may persist even after the threat is lifted [2,11]. Epidemics and pandemics have caused people to change their life routines. They also lead to concerns in healthcare workers regarding constant exposure to the infectious agent, becoming infected and spreading the infection to their environment. Healthcare workers who treat infected patients and meet their needs fear spreading the infection and feel guilty about the health of their relatives [8]. Even when healthcare workers manage to avoid infection, psychological distress associated with the pandemic and the fear of passing the virus to their families continue to raise serious concerns [9]. The most basic step in managing the psychological distress of healthcare workers is giving them training and providing them with adequate personal protective equipment before they interact with infected or suspicious patients [9-13]. This study was conducted to determine the impact of the COVID-19 pandemic on healthcare workers' anxiety level and quality of life.

2. MATERIALS and METHOD

Research type, setting and time

The study is a descriptive study seeking relationships. No setting or location was determined for the study since it was carried out online. The aim was to reach as many people as possible working in the field of health in Turkey. The literature review of the study started in April 2020, and the data collection process took 14 days.

Population, sample and research group

The healthcare workers in Turkey constitute the research population. Since, it is impossible to reach the whole population, the lowest number of people to be included in the study and the ideal sample size were calculated by taking the p and q values in Çelebi and Sunal's study titled "Quality of Life of Nurses Working in Surgical Services and Determination of the Effective Variables" as a reference [12]. When population is unknown, n=t2pq/d2 is used to calculate the sample. The confidence level was accepted as 95% and the deviation was taken as d=0.05 in the formula. The sample size of the study was found to be 200 [14]. The sample of our study consisted of 508 healthcare workers.

Data Collection Tools

Information Form: The form was developed by the researcher in line with the literature (Çelebi and Sunal, 2016;Yıldırım and Hacıhasanoğlu, 2012; Zengin and Gümüş, 2018). It includes 15 questions aimed at obtaining information about the socio-demographic and occupational characteristics of the participants [12,13,15].

Beck Anxiety Scale (BAS): The scale was developed by Beck et al., The Cronbach's alpha of the scale was determined as 0.86 [16]. The Turkish validity and reliability study of the scale was conducted by Ulusoy et al. and the Cronbach's alpha was found to be 0.80. The scale consists of 21 items, which are ranked from 0 to 3 according to the severity of depression. The main purpose of the scale is to evaluate the degree of depression symptoms objectively and quantitatively. Higher scores obtained from the scale indicate higher levels of anxiety. A score between 0-9 points to minimal depressive symptoms, while scores between 10-16, 17-29, and 30-63 refer to mild, moderate, and severe depressive symptoms, respectively [17]. In our study, the Cronbach's alpha was found to be .93.

Short Form 36 (SF-36) Life Quality Scale: It is an individual assessment scale developed by Ware et al., in 1987 to examine the general population in the monitoring of health policies in clinical practices and research [18]. The Turkish validity study of the scale was conducted in 2018 by Bilir and İçağasıoğlu [19]. The scale consists of eight sub-scales which are physical functioning, physical role limitations, emotional role limitations, vitality (life energy), social functioning, bodily pain, mental health and general perception of health. Each scale is scored separately. The SF-36 evaluates the positive as well as the negative aspects of the state of health. The scale gives separate total points for each subscale. Sub-scale scores range from 0-100. Increasing scores indicate good quality of life [19]. In our study, the Cronbach's alpha value was found to be .81.

This study was approved by the Lokman Hekim University Non-Interventional Clinical Research Ethics Committee (approval number: 2020/029). For this study, permission was obtained from the Republic of Turkey, Ministry of Health, Scientific Research Studies on COVID-19. The study was conducted in accordance with the Helsinki Declaration. The Informed Consent Form was read and approved by the healthcare professionals who participated in the study.

Statistical Analysis

The statistical analysis of the data was conducted using the SPSS Statistics 25.0 package program, number, percentage, mean, standard deviation and significance analyses were performed. The Kolmogorov-Simirnov test was used to determine the normal distribution of the data. T-test and ANOVA tests were performed according to the distribution of the variables. The level of significance in relationships between independent variables and scale scores was accepted as $p<0.05$. The findings showing statistically significant differences were evaluated according to the Games-Howel Post-hoc test.

3. RESULTS

A total of 508 healthcare workers participated in the study. Seventy-two percentof the participants are women and 70.1% are university graduates. The majority live in Konya province. Sixty-six point one percent of them are nurses or midwives. Forty-nine point one percent of them work in a state hospital. Eighty-one point three of the healthcare workers in our study reported that they are concerned about their own health during the COVID-19 pandemic. It was revealed that 38% of the healthcare workers had a shortage of protective equipment in the hospital they work in (Table I).

Table I. Socio-demographic characteristics of healthcare workers and their emotional states during COVID-19 (n=508).

Characteristics	n	%
Gender		
Female	366	72.0
Male	142	28.0
Age		
18-25	145	28.5
26-33	203	40.0
34-41	109	21.5
42-49	47	9.3
50 and over	4	0.8
Marital Status		
Married	247	48.6
Single	261	51.4
Education		
High School	73	14.4
University	356	70.1
Masters	54	10.6
PhD	25	4.9
Number of children		
0	284	55.9
1	85	16.7
2	103	20.3
3 and more	36	7.1
City of residence		
Ankara	47	9.3
Istanbul	40	7.9
Konya	268	52.8
Izmir	33	6.5
Antalya	8	1.6
Other	112	22.0
Occupation		
Nurse-Midwife	336	66.1
Doctor-Dentist	45	8.9
Paramedic-Emergency Medical Technician	21	4.2
Other (Patient Care Staff etc.)	106	20.8
The Institution/Hospital		
State	251	49.4
Private	55	10.8
University	202	39.8
Who do you live with?		
Alone	105	20.7
With friends	45	8.9
With wife/husband	49	9.6
With spouse and children	179	35.2
With extended family	130	25.6
Are you worried about your health during the COVID-19 pandemic?		
Yes	413	81.3
No	95	18.7
Is there a shortage of protective equipment in the hospital you work at?		
Yes	193	38.0
No	315	62.0

The total BAS mean score of the individuals participating in the study was found to be 12.26 and the standard deviation was 11.26. The mean of the SF-36 total score of the participants was found to be 90.53 ± 11.23 (Table II).

Table II. Beck Anxiety Scale and SF-36 Life Quality Scale Mean Scores

	N	Mean	SD	Min	Max
BAS	508	12.26	11.258	0	60
SF-36	508	90.53	11.226	39	115

The BAS scale mean scores of the female and male participants were found to be 14.17±11.594 and 7.35±8.602, respectively. The SF-36 scale mean scores of the female and male participants were found to be 90.98±9.927 and 89.39±14.007, respectively. It is seen that there is a statistically significant difference between the BAS scale mean scores according to gender (p=0.000), while there is no statistically significant difference between the SF-36 scale mean scores according to gender (p=0.217).

The BAS scale mean score of the participants who are worried about their health during the pandemic is 13.38 ± 11.275 and the BAS scale mean score of the participants who are not anxious about their health is 7.41 ± 9.855. The SF-36 scale mean score of the participants who are worried about their health during the pandemic was found to be 89.80 ± 11.031, while the SF-36 scale mean score of the participants who were not anxious was found to be 93.73 ± 11.562. It was seen that there is a statistically significant difference between the BAS scale mean scores according to the state of being worried about one's own health during the pandemic (p=0.000). It was also seen that there is a statistically significant difference between the SF-36 scale mean scores according to the state of being worried about one's own health during the pandemic (p=0.002).

It was further revealed that there is a statistically significant difference between the BAS scale mean scores in terms of shortage

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Marmara Med J 2021;34(2): 189-194

of equipment in the hospital participants work at (p=0.002). It was observed that there is no statistically significant difference between the SF-36 scale mean scores in terms of shortage of equipment in the hospital participants work at (p=0.732). It is seen that there is a statistically significant difference between the BAS scale mean scores according to the hospital participants work at (p=0.004). It has been observed that there is no statistically significant difference between the SF-36 scale mean scores according to the hospital participants work in (p=0.806). The BAS, which showed a statistically significant difference, was evaluated according to the Games-Howel post-hoc test. It was observed that the mean scale scores of the participants working in private hospitals and those working in state and university hospitals differ (p=0.035, p=0.025) (Table III).

Table III. *Evaluation of Beck Anxiety Scale and SF-36 Life Quality Scale of the healthcare workers according to some variables (n=508).*

		Beck Anxiety Scale		*SF-36 Life Quality Scale*	
Characteristics	**n**	**Mean±SD**	**Test Value**	**Mean±SD**	**Test Value**
Gender					
Female	366	14.17±11.594	***t=16.111***	90.98±9.927	***t=26.299***
Male	142	7.35±8.602	***p=.000***	89.39±14.007	***p=.217***
Are you worried about your health during the COVID-19 pandemic?					
Yes	413	13.38±11.275	***t=7.743***	89.80±11.031	***t=3.3731***
No	95	7.41±9.855	***p=.000***	93.73±11.562	***p=.002***
Is there a shortage of protective equipment in the hospital you work at?					
Yes	193	14.29±11.762	***t=5.152***	90.75±10.857	***t=4.570***
No	315	11.02±10.769	***p=.0024***	90.40±11.460	***p=.732***
The Institution/ Hospital					
State	251	12.00±11.085		90.36±10.563	
Private	55	16.95±14.703	***F=5.649***	90.17±12.075	***F=7.164***
University	202	11.32±10.089	***p=.004***	90.53±11.226	***p=.806***

SD:standard deviation t= T-test F= ANOVA tests

4. DISCUSSION

The total BAS mean score of the participants was found to be 12.26±11.26 and the SF-36 total mean score was found to be 90.53±11.23. The BAS mean scores of the female and male participants were 14.17±11.594 and 7.35±8.602, respectively. Since the highest point that can be obtained from the scale is 60 points, it is seen that the BAS scores of the healthcare workers are low. The mild level of anxiety of healthcare workers may be due to the rapid spread of the COVID-19 pandemic and its fatal effects. The SF-36 scale mean scores were found to be 90.98±9.927 in female participants and 89.39±14.007 in male participants. As the highest score that can be obtained from the scale is 115, it is seen that the mean score of healthcare workers is at a high level [19]. This may be attributed to the fact that protective measures are taken in the hospital, trainings about the COVID-19 pandemic are given, and accommodation needs of healthcare workers are met free of charge in some provinces.

It was found that socio-demographic characteristics of healthcare workers such as age, marital status, educational status, number of children, place of residence, other people living with them, occupation and the institution they work at did not affect the BAS and SF-36 scores. Unlike our research findings, Huang et al., reported that the COVID-19 pandemic have led to more depressive symptoms in people under 35 years of age [20,21]. Anxiety symptoms are more likely to develop in people younger than 35 and those who spend a lot of time focusing on the pandemic. Su et al., conducted a study in Taiwan during the SARS pandemic and they reported high anxiety symptoms in the young [22]. In addition, it is seen that there is a statistically significant difference between the BAS mean scores of female and male participants (p=0.000). However, no statistically significant difference was observed between the SF-36 scale mean scores of female and male participants (p=0.217). In their study conducted with healthcare workers, Zhang et al., revealed no significant difference in the anxiety and depression levels of men and women during the COVID-19 pandemic [23]. Ekiz et al., concluded in their study that women's health anxiety levels were higher than men [24]. Another study reported that the prevalence of anxiety and depression has been higher in female healthcare workers and nurses during the COVID-19 pandemic [25]. Women's anxiety levels were also found to be high in the worldwide Swine Flu (H1N1) epidemic experienced earlier [26]. In their study conducted in Wuhan, Lai et al., reported that there was more psychological burden on female nurses [27]. In our study, anxiety levels of women were also found to be higher than men, and there are studies supporting this finding in the literature [27,28]. It is thought that this is because women are more sensitive and they are more prone to mental health problems. In addition, contrary to our findings, some studies conducted with nurses revealed that male nurses had higher anxiety levels compared to female nurses [29-31]. There are also studies in the literature arguing that gender does not affect anxiety levels [32,33].

Eighty-one point three percent of the participants in our study were found to be worried about their own health due to the COVID-19 pandemic. The BAS mean scores of these participants was found to be 13.38±11.275, while the BAS mean score of those who are not worried about their health was found as 7.41±9.855. The SF-36 scale mean score of the participants who are worried about their own health due to the pandemic

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Marmara Med J 2021;34(2): 189-194

was found to be 89.80±11.031, while the SF-36 scale mean score of those who are not worried about their health was found as 93.73±11.562. It is seen that there is a statistically significant difference between the BAS mean scores of those who are worried and not worried about their own health during the pandemic (p=0.000). On the other hand, it was observed that there is a statistically significant difference between the SF-36 scale mean scores of those who are worried and not worried about their own health during the pandemic (p=0.002). In their study with administrative staff and healthcare professionals, Lu et al., found the anxiety levels of healthcare workers to be at a moderate level during the pandemic [34]. Lai et al., examined the anxiety levels of healthcare professionals at some hospitals in China. The study was conducted with 1257 healthcare workers and 44.6% of the participants stated that they have experienced anxiety during the pandemic. It has been further reported that psychological symptoms are more severe in doctors and nurses [27]. The majority of healthcare workers reported anxiety in Xiao et al.'s study [35]. It is seen that our findings coincide with the findings of some studies in the literature.

Thirty-eight percent of the healthcare professionals stated that they had a shortage of protective equipment in the hospital they work at. It is seen that there is a statistically significant difference between the BAS mean scores in terms of having equipment problems or not (p=0.002). It was observed that the presence or lack of equipment at the hospitals did not affect the SF-36 scale mean scores (p=0.732). Xiao et al., found that the majority of healthcare workers (60.8%) had insufficient access to protective materials (masks, bonnets, gowns, glasses and visors) [35]. They found a significant link between preventive measures and anxiety. Our study revealed that the lack of protective equipment affects the level of anxiety, but not the quality of life.

Limitations

One limitation of our study is that the study was conducted when COVID-19 pandemic first started. Another limitation is that the data was collected over the Internet.

Conclusion

Epidemics and pandemics which affect the whole world and cause deaths have social, economic, and emotional consequences and they specifically affect the psychology of healthcare professionals. In our study, the anxiety levels of healthcare workers were found to be low and their quality of life was found to be high during the pandemic. Although, it is seen in the literature that the anxiety levels are high and the quality of life is low under normal conditions, the findings in our study differed and positive results were obtained contrary to expectations. Pandemics such as COVID-19 may also occur in the future, and the psychological conditions of healthcare professionals should be monitored during this process. The coping skills of healthcare professionals should be developed, and approaches that protect and support their mental health should be routine practices. Various strategies can be developed and used during a pandemic. For example, it should be ensured that healthcare workers have easy access to protective equipment support; psychological support groups should be established to increase their psychological resilience and to help reduce pressure; psychological training on coping skills, stress management, anxiety therapies etc. should be provided; and finally, promotions and financial incentives may be given to encourage healthcare workers during epidemics and pandemics.

Compliance with Ethical Standards

Ethical approval: This study was approved by the Lokman Hekim University Non-Interventional Clinical Research Ethics Committee (approval number: 2020/029). For this study, permission was obtained from the Republic of Turkey, Ministry of Health, Scientific Research Studies on COVID-19.

The study was conducted in accordance with the Helsinki Declaration. The Informed Consent Form was read and approved by the healthcare workers who participated in the study.

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Authors' contributions: Literature search: MAC, GT and YT, Study design: MAC and GT, Legislative applications: GT and YT, Data collection: MAC and GT, Supervision and quality control: ET, Statical advice: ET, Statical data analysis: ET and GT, Data interpretation: ET and GT, Drafting the manuscript: MAC. All authors read and approved the final version of the article.

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Mid-term functional and radiological results of endoprosthetic reconstruction of proximal humeral bone tumors

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ABSTRACT

Objective: Functional and radiological mid-term results and survival of endoprosthetic reconstructions following proximal humeral resections were evaluated.

Patients and Methods: Between 2006 and 2013, 29 patients (14M/15F) who underwent resection and endoprosthetic reconstruction for primary or metastatic tumors of the proximal humerus were retrospectively reviewed. Average age during surgery was 45 years (18-70 years) and the patients were followed-up for 20 months (6-57 months) on average. Patients with giant cell tumor of bone (2), chondrosarcoma (7), osteosarcoma (2), Ewing's sarcoma (1), multiple myeloma (5) and metastatic carcinoma (12) underwent surgery. Functional parameters and proximal migration of the endoprosthesis were evaluated. Complications, revision rate and implant survival were investigated. Oncological follow-up was recorded.

Results: The average Musculoskeletal Tumor Society (MSTS) score was 81% (50-93%), and average active/passive abduction and flexion of the shoulder was measured as 40°/90° and 50°/90° respectively. Follow-up radiographs demonstrated proximal migration of the endoprosthesis in 8 (27.5%) patients. None of the patients had infection, wound problem, aseptic loosening or implant failure. Except for one revision (3,5%) due to mechanical loosening, all reconstructions survived with the patients until the end of study.

Conclusion: Endoprosthetic reconstruction following resection of primary or metastatic tumors of proximal humerus is a satisfactory treatment method with good functional results and low complication and high implant survival rates.

Keywords: Proximal humerus, Bone tumor, Endoprosthesis

1. INTRODUCTION

Proximal humerus is one of the most common location for primary benign and malignant bone tumors and also metastases [1,2]. The bone defects following desections in this region can be reconstructed by using osteoarticular allografts, allograft – or autograft-prosthesis composits, clavicula pro humero procedure, vascularized or non-vascularized bone transfers, arthrodesis or by using simple endoprosthetic implants [3,4]. Considering the fact that metastatic patients have a shorter survival time, endoprosthetic reconstructions are preferred in order to get a faster symptomatic relief and functional recovery [5-7].

Endoprosthetic reconstruction of the proximal humerus is an optimal surgical procedure with a relatively low complication rate, good functional outcome and a long implant survival time [8,9]. Many authors advocate that endoprosthetic replacement following proximal humerus resection merely functions as a spacer that maintains the stability of the extremity and this method is functionally not superior to other reconstruction techniques [10-13]. On the other hand, the main objective of inserting a tumor prosthesis is to gain a stable shoulder joint, though with a limited motion capacity and an independent functioning hand and elbow.

The aim of this study is to present mid-term functional and radiological results of patients, who underwent a proximal humerus endoprosthetic replacement operation after resection of a primary or metastatic bone tumor. We also determined the general complications following this surgery, the implant survival rate and the requirement for a revision surgery.

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2. PATIENTS and METHODS

The study protocol was approved by the local ethics committee of Marmara University School of Medicine (approval number 09.2020.1211). The study was conducted in accordance with the principles of the Declaration of Helsinki.

In this study 31 patients were evaluated who underwent proximal humerus resection and endoprosthetic reconstruction due to primary or metastatic bone tumor in our clinic between the years 2006 and 2013. Two patients who did not come to follow-up controls or could not be reached, were excluded from the study group. The mean age of the 14 male and 15 female patients at the time of surgery was 45 (18-70 years). The data used were obtained from orthopedic oncology files including clinical and radiological evaluations during the first admission and follow-up visits, operation and pathology reports, and perioperative pictures. Musculoskeletal Tumor Society (MSTS) function score [14,15], range of motion of the active and passive shoulder motion and migration of the prosthesis were evaluated. Surgical complications and the need for additional interventions were investigated. Together with complications such as endoprosthesis-related aseptic loosening or mechanical failure, implant survival and the need for revision were examined.

Except for previously diagnosed 3 patients with multiple myeloma and 7 patients with metastatic carcinoma, the diagnosis was made by a preoperative biopsy procedure performed in operating room conditions. Pathological diagnoses for primary lesions include giant cell tumor of bone (2), chondrosarcoma (7) conventional osteosarcoma (2), Ewing sarcoma (1), and multiple myeloma (5), while 12 patients had carcinoma metastasis (lung (6), breast (2), colon (2), stomach (1), rectum (1)) (Table I). According to the Enneking staging system, the giant cell tumor cases were staged as Stage 3 (aggressive) benign bone tumor, and the primary sarcoma cases as Stage IIB (8), IIA (1) and IA (1) malignant bone tumor [15].

Table I. *Demographic data, surgical and adjuvant treatments and oncological follow-ups of the patients.*

Patient	Age/ Gender	Diagnosis	Adjuvant Treatment		Surgery (Resection type)	Follow-up (months)	Oncological follow-up
			Preop.	Postop.			
1	37, M	Giant cell tumor	-	-	Type1B	18	Alive w/o disease
2	46, F	Breast ca metastasis	CT+RT	CT	Type1B	16	Alive w disease
3	45, F	Breast ca metastasis	CT	CT+RT	Type1B	12	Alive w disease
4	51, F	Multiple myeloma	-	CT+RT	Type1B	28	Alive w disease
5	18, M	Ewing sarcoma	CT	CT	Type1B	38	Alive w/o disease
6	31, F	Chondrosarcoma (H-G)	-	-	Type1B	26	Alive w/o disease
7	47, M	Colon ca metastasis	CT	CT+RT	Type1B	19	Alive w disease
8	25, M	Chondrosarcoma (H-G)	-	-	Type1A	24	Metastasectomy - Alive w/o disease
9	70, F	Lung ca metastasis	-	CT+RT	Type1A	8	Exitus
10	24, F	Osteosarcoma	CT	CT	Type1B	15	Alive w/o disease
11	59, M	Lung ca metastasis	CT	CT+RT	Type1B	18	Exitus
12	48, M	Lung ca metastasis	CT	CT+RT	Type1B	11	Exitus
13	40, F	Chondrosarcoma (H-G)	-	-	Type1B	12	Alive w/o disease
14	34, M	Chondrosarcoma (L-G)	-	-	Type1A	36	Alive w/o disease
15	63, M	Multiple myeloma	-	CT+RT	Type1B	24	Alive w disease
16	65, F	Lung ca metastasis	-	CT+RT	Type1A	15	Alive w disease
17	40, F	Gastric ca metastasis	-	CT+RT	Type1B	6	Exitus
18	70, M	Lung ca metastasis	-	CT+RT	Type1A	13	Exitus
19	24, F	Chondrosarcoma (H-G)	-	-	Type1A	20	Alive w/o disease
20	63, M	Multiple myeloma	CT	CT+RT	Type1B	18	Exitus
21	54, F	Multiple myeloma	CT+RT	CT	Type1A	30	Exitus
22	40, M	Chondrosarcoma (H-G)	-	-	Type1B	57	Alive w/o disease
23	60, F	Lung ca metastasis	CT	CT+RT	Type1B	11	Alive w disease
24	58, F	Multiple myeloma	CT+RT	CT	Type1A	17	Alive w disease
25	61, M	Rectal ca metastasis	-	CT+RT	Type1A	18	Exitus
26	27, F	Chondrosarcoma (H-G)	-	-	Type1B	29	Alive w/o disease
27	22, F	Osteosarcoma	CT	CT	Type1B	10	Alive w/o disease
28	48, M	Colon ca metastasis	CT+RT	CT	Type1B	11	Alive w disease
29	32, M	Giant cell tumor	-	-	Type1B	24	Alive w/o disease

Ca: Cancer, CT: Chemotherapy, RT: Radiotherapy, H-G: High grade, L-G: Low grade, w: with, w/o: without

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Marmara Med J 2021;34(2): 195-201

Surgical resection and reconstruction was performed immediately after diagnosis of cases with giant cell tumor and chondrosarcoma. Surgery was performed after neoadjuvant chemotherapy in patients with osteosarcoma and Ewing sarcoma. No preoperative or postoperative radiotherapy was applied to any of these patients who received adjuvant chemotherapy after surgical resection. Two recently diagnosed multiple myeloma patients had severe pain and bone lesions causing inability to use the arm. These lesions that caused severe destruction in the proximal diaphysis together with the humeral head were accompanied by pathological fractures and deformities. Surgical treatment was applied first, followed by systemic chemotherapy and radiotherapy in these patients. Endoprosthetic replacement was preferred, as the severe involvement did not allow any internal fixation method to be an option. For two of the remaining 3 patients with multiple myeloma who were under chemotherapy treatment, radiation therapy was applied for the known proximal humeral involvement, however lesions that were resistant to radiotherapy progressed. The other patient had a lesion that appeared in a short time and progressed rapidly both clinically and radiologically and surgical treatment was decided for this patient without radiotherapy. While patients with multiple myeloma continued their chemotherapy after surgery, the whole humerus was irradiated postoperatively in those who did not receive neoadjuvant radiotherapy.

All of the previously diagnosed seven metastatic carcinoma patients received chemotherapy before surgery. Besides, in two patients, the lesion was irradiated, however the lesions progressed despite radiotherapy. For the other five patients, direct surgical treatment was applied as their lesions showed rapid progression and accompanied by pathological fractures. All of the recently diagnosed patients who underwent immediate resection and endoprosthetic replacement had severe involvement leading to a pathological fracture. While all the metastatic patients continued their chemotherapy after surgery, the entire humerus of those who did not receive neoadjuvant radiotherapy was irradiated postoperatively. Table 1 summarizes the interventions and preoperative and postoperative adjuvant treatments for patients.

None of the patients in the series had any previous surgical procedure for proximal humerus involvement. Achieving wide surgical margins was the benchmark for all resections, regardless of pathological diagnosis. In one patient with metastatic carcinoma that was extending to the distal humerus, tumor continuity was present at the osteotomy line; in this patient, an additional distal osteotomy was performed at a level that allowed intramedullary placement of the prosthetic stem. On the other hand, it was reported that the tumor continued in the soft tissue in 2 patients with metastastasis which was accompanied by displaced pathological fracture and diffuse extra-compartmental spread. Wide surgical margins were obtained in all the remaining cases.

Intra-articular proximal humerus resection (Type IA or B) was performed in all patients (Figure1).

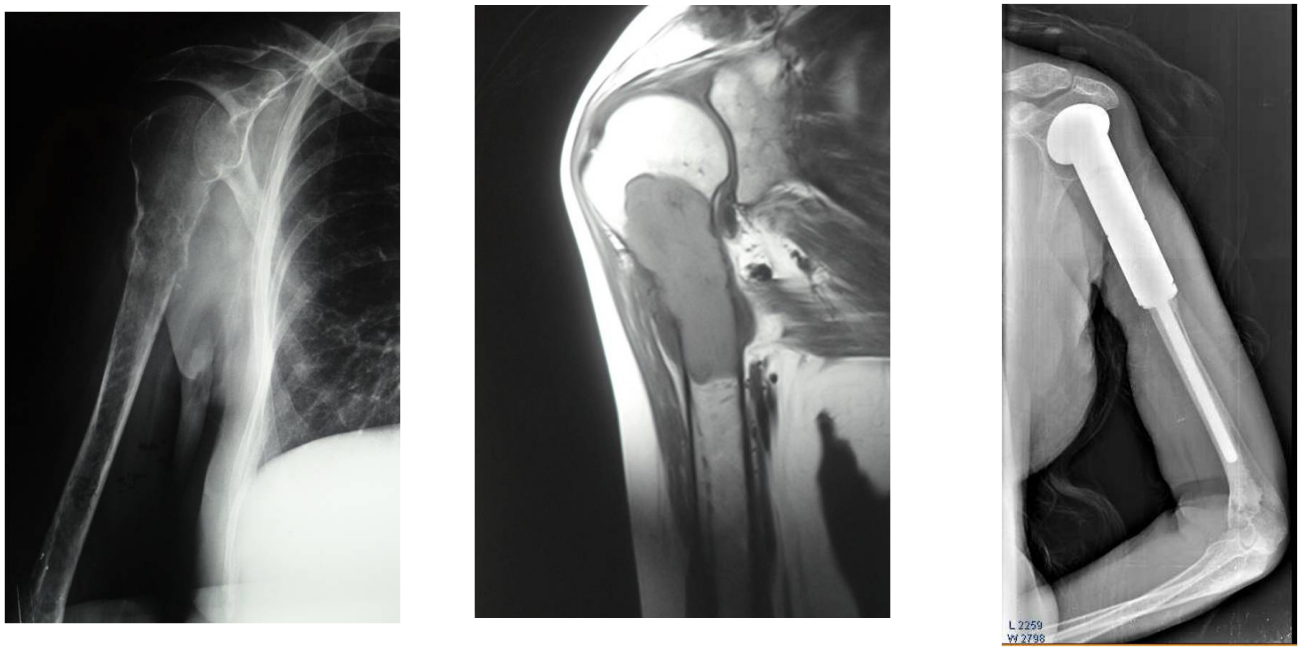

Figure 1a-c. *Pathological fracture accompanied by a minimal deformity located in the proximal humerus of a 58-year-old female patient diagnosed with multiple myeloma (a,b). Control x-ray of the third postoperative year following wide resection and endoprosthetic replacement operation (c).*

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Marmara Med J 2021;34(2): 195-201

Intraosseous and soft tissue spread of the lesions were determined according to last preoperative MR imaging. All cases in the series had humeral head and / or proximal metaphysodiaphyseal involvement. In some patients, the spread extended to the mid-part or even distal part of the diaphysis. The osteotomy was performed 2 cm distal passing the medullary spread of the tumor according to MR imaging. The average resection length was measured as 13 cm (8-20 cm). While the involvement was found to extend to the extraosseous area in most of the cases, the tumor was confined within the compartment in some patients. Type IB resection was performed by sacrificing the abductor mechanism (anterior, middle and sometimes posterior part of the deltoid muscle fibers) and axillary nerve in 20 cases where the tumor had spread out of the bony compartment. Eight cases in which the involvement was completely limited to the bone, including the patient with Stage IIA chondrosarcoma, and one patient with stage IIB chondrosarcoma, which did not form a distinct soft tissue component despite penetrating the cortex, a type IA resection was performed and these structures were preserved. In one patient, a bony fissure occurred in the distal humerus while inserting the prosthesis, and an osteosynthesis was added using a cerclage wire. Apart from this, no perioperative complications occurred. For endoprosthetic reconstructions, two different types of prosthesis made of titanium (TiA16V4 composition, MUTARS, Implantcast, Buxtehude, Germany) for 20 cases and cobalt-chromium (CoCrMo composition Hipokrat Medikal, Izmir, Turkey) for 9 cases were used. Titanium prostheses were fixed with cement in 3 cases, and without cement in the remaining patients with a press-fit technique. The method of fixation of the intramedullary stem was determined according to the technical properties of the implant (handle geometry, surface features) rather than patient-related factors such as diagnosis or adjuvant therapies. A 'Trivera tube' containing polyethylene terephthalate ('attachment tube', MUTARS, Implantcast, Buxtehude, Germany) was used in all patients in order to create shoulder joint stability between the prosthesis and the opposite glenoid, and to create a surface where the remaining part of the joint capsule and the preserved muscle tissues could be attached. Non-absorbable sutures (5 or 2 Ethibond) passed through the glenoid were sutured all around the tube surrounding the prosthesis. The preserved muscle tissues were sutured to the tube and each other to cover the implant and create a suppressor effect on the endoprosthesis.

A velpau bandage was applied to all patients for six weeks for postoperative soft tissue healing. In the postoperative period, passive elbow, active wrist and finger movements were initiated within the first week, as much as the patient could tolerate pain [16]. Active elbow movements were generally allowed at the end of the 4th week. Passive shoulder movements were delayed until the end of the 6th week and gradually increased. Active movements were allowed at the end of the third month.

Modified MSTS scoring system was used to evaluate postoperative functional results; so pain, function, emotional state, hand position, hand skill and weight lifting properties were evaluated. Scores between 0 and 5 were given for each parameter, and the results obtained were converted into a percentage over the total score of 30. Postoperative 6th, 12th and 24th month MSTS scores were calculated according to the follow-up period of the patients. For the patients who were lost during follow-up, the last follow-up score was taken as basis. For patients who were still alive, the scores for the last month were used for those with a follow-up less than 24 months, and for those with a longer follow-up, the scores for the 24th month were evaluated.

In addition, active and passive range of motion of the shoulder joint was presented as a separate functional parameter. Proximal migration of the endoprosthesis was evaluated with plain radiographs.

Surgical procedure-related complications such as infection, hematoma formation, and wound problems were recorded. Using the Kaplan – Meier survival method, endoprosthesis survival was calculated for each patient [17]. For endoprosthesis survival time, the starting point was determined as the time of implantation and the end point was determined as the time of revision due to reasons such as infection, mechanical failure or loosening or patient's death.

Theoncologicalfollow-upofthepatientswasalsorecorded(TableI); While local recurrence and distant metastasis were followed for primary lesions, local and systemic progression of the disease was evaluated for multiple myeloma and metastatic carcinoma cases. For local recurrence, patients with giant cell tumor and primary bone sarcoma were seen at 6-month intervals for the first 2 years, followed by annual clinical follow-up and MR imaging (including the entire surgical site). Rare pulmonary metastases in cases with giant cell tumors were monitored by annual CT. Follow-up for distant metastasis in primary sarcomas was performed by observing lung CT every 3 months and whole body bone scintigraphy every 6 months for the first 2 years. After the second year, lung CT and whole body bone scintigraphy were continued to be performed every 6 months. MR imaging, CT, scintigraphy and positron emission tomography (PET-CT) were used for local and systemic follow-up of multiple myeloma and metastatic carcinoma cases.

Statistical Analysis

For statistical analysis, the relationship between functional results and proximal migration of the prosthesis and the type of resection (Type IA or B) and the amount of resection were examined. Variables in the study were expressed in terms of frequency, percentage and mean. SPSS 18 for Windows 7 was used for statistical analysis. The survival time of the prosthesis was determined by Kaplan – Meier survival method. The comparison of gender and survival distributions of the groups were evaluated with the Chi-Square Test, the comparison of the mean age was evaluated with the independent samples t-test, and the mean follow-up time and MSTS score averages were evaluated with the Mann-Whitney U-test. Results with a p value less than 0.05 were considered as significant.

3. RESULTS

Of the 29 patients participating in the study, 21 were still alive at the time of the study and the average follow-up period was

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Marmara Med J 2021;34(2): 195-201

calculated as 20 months (6-57 months). No local recurrence or pulmonary metastasis did develop in the postoperative period in 2 patients with giant cell tumor of bone. In one patient with high-grade chondrosarcoma, a two-stage metastasectomy procedure was required for multiple pulmonary metastatic lesions detected in both lungs at the 18th postoperative month controls. In the second follow-up year, no local recurrence or any new metastasis was observed. All of the remaining primary sarcoma patients had disease-free survival. Two patients with multiple myeloma died at 18th and 30th month follow-up, respectively. Of the metastatic carcinoma cases, one patient died in the 6th month, 2 patients were lost between the 6th and 12th months and 3 patients were lost between the 12th and 24th months after the operation due to disease-related complications. Clinical and radiological evaluations of the patients who were lost during follow-up were made according to the last follow-up results.

Twenty patients had excellent (80%, no pain), eight patients had good (60%, limitation of strenuous activities such as sports), and one patient had a poor (50%) MSTS score. Mean MSTS score was determined as 81% (50-93%). Active and passive abduction and flexion movements of the shoulder were also included in the functional evaluation. The mean active abduction was measured as 40 degrees (20-90 degrees), while passive shoulder abduction was measured as 90 degrees (50-160 degrees). Mean active and passive shoulder flexion was measured as 50 degrees (20-90 degrees) and 90 degrees (60-160 degrees), respectively.

Following Type IA resections, due to preservation of the abductor mechanism, relatively better MSTS scores and shoulder range of motion were obtained compared to Type IB resections. However, the difference between functional results obtained following Type IA and B resections was not statistically significant ($p = 0.205$). There was also no significant correlation between functional scores and amount of resection ($p = 0.410$) either. Proximal migration of prosthesis was found in eight patients (27.5%). Radiographic examinations revealed,that there was direct contact between the prostheses of these patients and the acromion. The statistical relationship between proximal migration and resection type and amount of resection was also not significant ($p = 0.798$, $p = 0.687$). Except for a revision surgery in one patient, no failure developed in the remaining 28 endoprostheses until the patient died or the study was completed. Therefore, endoprosthesis survival was determined as 96.5% (Figure 2). The endoprosthesis was revised in one patient (3.5%) due to symptoms like posterior dislocation, pain and limitation of movement. This implant was removed at the 38th month postoperatively and replaced with a reverse type resection prosthesis (humerus inverse, MUTARS, Implantcast, Buxtehude, Germany). No surgical complications such as deep or superficial infections, wound problems or hematoma formation did occur in any patient.

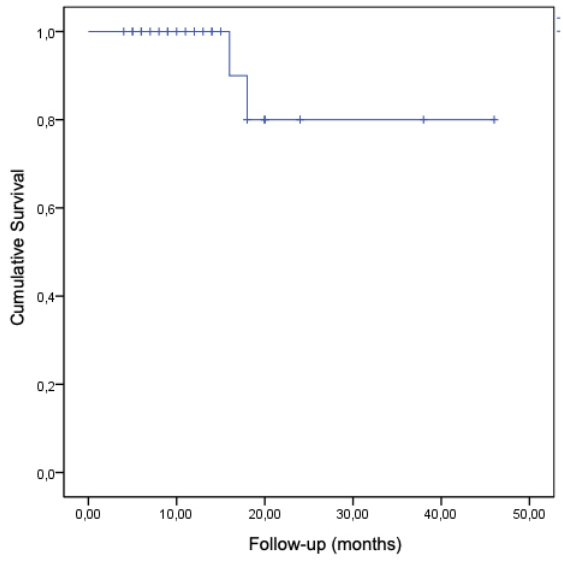

Figure 2. *The Kaplan –Meier curve demonstrates the implant survival*

4. DISCUSSION

In this study, favorable functional and radiological results have been achieved in patients who underwent proximal humerus resection and endoprosthetic reconstruction.

There are various surgical reconstruction techniques applied for large proximal humerus defects following tumor resection at this region [18]. Each procedure has its own advantage and disadvantages [19].

Osteoarticular allografts and allograft-prosthesis composits provide attachment for periarticular tendons and muscles around the shoulder, so their functional and satisfactory outcomes in the early postoperative period is good. These tecniques are mainly applied for young patients undergoing primary tumor resection surgery. Isolated utilization of osteoarticular allografts is limited by increased infection rate, nonunion and fractures and also functional disintegrity in the late term [3,4]. Allograft-prosthesis composits are more readily preferred for patients having primary bone cancer because of their relatively lower complication rates and better functional outcomes [20].

For the defects where non-vascularized autografts are used, a high incidence of graft fracture, delayed union and non-union has been reported [21]. For the pediatric population and young adults, osteoarticular autografts can be preferred, where fibula is transferred with it's accompanying epiphysis. The disadvantage of vascularized bone graft is the requirement of microsurgical techniques and the long duration of time spent during surgery. However, the limited capacity of the fibular head to remodel might result in continiuing incongruent joint with the glenoid in the long term. It has been reported, that, osteoarticular grafts applied at this region do not have better outcomes compared to other techniques [15].

http://doi.org/10.5472/marumj.944260
Marmara Med J 2021;34(2): 195-201

So endoprosthetic replacement with tumor type prostheses after resection is the preferred reconstruction method for the proximal humerus defects because of its' low complication rate [14,16,22]. On the other hand, it should be kept in mind that the restriction of shoulder motion is inevitable after proximal humerus resection, and regaining this function is almost impossible after endoprosthetic replacement. However by stabilizing the proximal part of the upper extremity, the function of the elbow, wrist and fingers of the hand are maintained, which provides a certain satisfaction to the patient. The functional evaluation of endoprosthetic reconstruction is usually performed by MSTS system. The mean MSTS value reached in this study was 81%, which was correlating with the values (75-85%) mentioned in the literature following resection and endoprosthetic replacement [11-14].

Metastatic lesions located at the proximal humerus frequently exhibit progression and might result in pathological fractures. The purpose of management of these destructive lesions is to gain a painfree extremity with adequate funtion and provide these patients a more comfortable time during the rest of their life. The time spent for healing of pathological fractures is longer, besides radiation therapy applied to palliate pain delayes this healing further. Considering the fact that proximal humerus is exposed to various shearing and rotational forces and its' thin cortical structure at this region and also short life expectancy of these metastatic cases, lead the surgeons to prefer endoprosthetic replacement instead of performing biological reconstructions [23]. In the current study we performed endoprosthetic replacement for 12 patients, who had metastatic lesions exhibiting rapid progression and patients were resistant to radiation therapy. We observed a functional and painfree upper extremity in these patients at the postoperative period.

There is no muscular barrier in the upper extremity, that prevents extension of tumoral mass to the neurovascular structures. Due to the limited mobility of the brachial plexus and direct contact of the axillary nerve to the bone, it's almost impossible to achieve a successful resection of a primary malignant tumor without sacrificing the axillary nerve. There is a strong correlation between the amount of bone resection, preservation of deltoid muscle fibers and axillary nerve and positive functional outcomes after tumor resection and endoprosthetic replacement operation [11]. In our series, preservation of the deltoid muscle and axillary nerve was possible after short segmental resection in a limited number of cases, although it was statistically not significant, we also observed better functional results, which supports this correlation. However, even when the deltoid and axillary nerve was protected, patients could not reach 40-50 degrees of shoulder abduction [12]. While, the mean active abduction range of the study group was 40 degrees (20-90 degrees), it was observed as 80-90 degrees for three young patients, where preservation of abductor system became possible.

The most common complication following proximal humerus reconstruction has been reported as migration of humerus to the proximal site [10-12]. Studies suggest, that with the increased time spent for follow-up, the frequency of this complication is encountered more frequently. Although, frequently seen, the proximal migration of the endoprosthetic implant does not cause too many clinical symptoms, and indications for revision surgery are very rare. We observed this complication in eight patients (27.5%), however, it was totally asymptomatic and no patient required an endoprosthetic revision procedure for this complication.

The complication rate of endoprosthetic replacement following tumor resection surgery in the upper extremity is extremely low. While, aseptic loosening and implant failure are observed very infrequently, the rate of infection is between 0-5 % [8,11-13,18]. On the other hand, the implant survival of a proximal humerus endoprosthesis after 20 years of follow-up has been reported as high as 85% [11]. Infrequent revision requirements due to the low complication rate and long implant survival time led the orthopaedic surgeons to prefer more often endoprosthesis for the reconstruction of proximal humerus. In our study, only one patient required revision due to mechanical failure; there was no other problem with the remaning endoprostheses that survived until the patients were lost or the study was completed, a fact that supports the classical literature knowledge [19].

Limitations

There are some limitations of the current study; it is retrospective and contains a heterogenous group of patients, besides the mean follow-up period is relatively short. However, it should be considered, that the number of cases requiring segnental tumor resection in the proximal humerus is also low. The indication for endoprosthetic replacement surgery is limited due to the fact that the incidence of primary malignant sarcomas in this region is low and primary benign lesions if ever they require surgery are managed by procedures other than resection. On the other hand metastatic lesions and multiple myeloma are radiosensitive tumors which also limit the utilization of endoprosthesis. In addition, there are studies concerning heterogenous group of patients having either primary proximal humerus sarcoma or metastasis which analyze clinical outcomes,survival and complications of these endoprostheses [10-13,18].

Conclusion

In conclusion, endoprosthetic replacement following proximal humerus resection is a preferrable method in the treatment of primary and metastatic tumors because of its low complication rate, good functional results and emotionally high acceptability. While restoring the stability of the extremity, this method allows early motion and provides a painless and functional arm. Infrequent need for revision and long implant survival time are other benefits of this region's endoprostheses.

Compliance with Ethical Standards

Ethical approval: The study was conducted in accordance with the principles of the Declaration of Helsinki. This study was approved by the Marmara University, School of Medicine, Ethics Committee (approval number: 9.2020.1211).

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Authors' contributions: Study design, data collection, data anlysis and writing the article: OMT and ES. Both authors read and approved the final version of the article.

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The effect of patient characteristics to the acute procedural success and long term outcome of atrial tachycardia and atrial flutter cases undergoing catheter ablation

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ABSTRACT

Objective: In the present study we aimed to demonstrate clinical characteristics, predictors of procedural success and long term recurrence of atrial tachyarrhythmia patients undergoing catheter ablation (CA).

Patients and Methods: Consecutive patients who had undergone CA due to an atrial tachyarrhythmia in a single centre arrhythmia unit between 2012 – 2020 were screened. Predictors of procedural success and recurrence were analysed by logistic regression.

Results: Study population consisted of 299 consecutive patients (95 [31.8 %] atrial tachycardia, 204 [68.2 %] atrial flutter cases);163 (54.5 %) were male; median age was 54 (IQR; 42-64). Median follow up was 330 (IQR; 90 – 810) days. Atrial flutter patients were older and had more co-morbidities. Acute procedural success rate was 82.1 % vs. 77.0 % (p= 0.313) and recurrence was 9.3 % vs. 21.6 % (p=0.022) in atrial tachycardia (AT) and atrial flutter (AFL) cases respectively. History of valvular or congenital heart disease surgery, left atrium diameter and age were found to be independent predictors of failed ablation, recurrence and post-procedural atrial fibrillation.

Conclusion: Age, left atrium diameter, valvular or congenital heart disease surgery are independent predictors for acute procedural success, recurrence and post-procedural atrial fibrillation in AT and AFL patients who undergo catheter ablation.

Keywords: Atrial arrhythmia, Atrial tachycardia, Atrial flutter, Catheter ablation

1. INTRODUCTION

Atrial arrhythmias including frequent atrial extrasystoles, atrial tachycardia (AT) and atrial flutter (AFL) are seen less commonly in the clinical practice compared to other types of supraventricular tachyarrhythmias. However, in some cases, these arrhythmias may cause tachycardiomyopathy and severe symptoms. In addition, AT and AFL may precipitate atrial fibrillation. Focal automaticity, triggered activity, micro or macro re-entry may be underlying mechanism of ATs, whereas macro re-entry is the only mechanism of atrial flutter [1-5]. Liu et al., showed that unresponsiveness of focal AT to adenosine is a sign of micro re-entry mechanism rather than automaticity or triggered activity [6]. Although, focal ATs are mostly observed in patients with structurally normal heart, those may also be seen in patients with structural heart disease. Fibrosis in the atria causes slow conduction areas and focal conduction block. These areas with conduction disturbance constitute the underlying mechanism of micro or macro-re-entry. Aging, heart failure, hypertension, diabetes mellitus, coronary and valvular heart disease can cause fibrosis in the atria by using different pathways [7,8]. Atriotomy scar in patients with prior open-heart surgery is also a common source of re-entrant atrial arrhythmias [9,10]. Antiarrhythmic drugs may fail to control heart rate in most AT and AFL cases. Catheter ablation (CA) of those arrhythmias can effectively be performed, and satisfactory results have been reported in the current literature [1-4]. There is a wide range of variation with respect to clinical characteristics in patients with AT and/or AFL. Patients with AT who have micro or

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macro re-entry as underlying mechanism may display similar clinical characteristics and CA outcomes, when compared to patients with AFL. There is limited data in the current literature regarding the comparison of clinical characteristics and CA outcomes of patient population with AT and AFL.

In the present study, we aimed to comparatively investigate the clinical characteristics of patients with AT and AFL by retrospectively evaluating the data of patients who had undergone CA for these arrhythmias in a single centre. We also aimed to investigate the potential variables that might have predictive values for the outcomes of CA and long-term recurrence in these patients.

2. PATIENTS and METHODS

Study design, patient population and data collection

This study was designed to be conducted in a retrospective observational manner. Patients who had undergone CA because of AT and AFL between December 2012 and September 2020 in a single centre arrhythmia unit were screened. Electronic archive files were used to obtain patients' data. Demographic characteristics of patients, history of prior cardiac surgery, history of coronary artery disease, hypertension and diabetes mellitus were noted. Left atrium (LA) diameter and left ventricle ejection fraction data were extracted from pre-procedural echocardiography reports. Follow – up echocardiography parameters of patients with low pre-procedural ejection fraction were also recorded to evaluate the recovery of left ventricular function after the ablation. Patients whose data could not be achieved were excluded from the study. The study protocol was approved by the Kartal Kosuyolu Training and Research Hospital Ethics Committee (approval number: 2019.7/15-231).

Catheter ablation procedure and follow-up

Catheter ablation was performed in accordance with the standard protocols. All of the antiarrhythmic drugs were stopped at least five half-live times before the procedure. Tachycardia was induced with programmed electrical stimulation and/or isoproterenol infusion in patients with sinus rhythm. Ablation was not performed if the tachycardia could not be induced except for the cases who had surface electrocardiogram (ECG) tracing of the tachycardia suggestive of typical AFL. After the tachycardia was induced, the diagnosis of AT was confirmed with diagnostic maneuvers. Atrial flutter was diagnosed if the isoelectric line was displaced by flutter waves on surface ECG. However, in some cases, the definitive distinction of AFL and AT could only be made by electro-anatomical mapping. Conventional radiofrequency (RF) ablation or electro-anatomic mapping system was employed depending on complexity of the case or eligibility of equipment. Electro-anatomic mapping system was used in most of AT and atypical AFL cases. Ablation was performed during sinus rhythm in some patients whose arrhythmia was assumed to be cavotricuspid isthmus (CTI) dependent AFL. In remaining AFL and AT cases, ablation was performed during tachycardia. Activation mapping and entrainment maneuvers were used to detect critical isthmus of tachycardia in AFL cases. All the left sided ablations were performed via transseptal approach. Non-coronary aortic cusp was mapped initially in case of right sided parahisian localisation. Non inducibility with aggressive programmed electrical stimulation or burst pacing for AFL and AT cases was accepted as procedural success after ablation. In addition, isoproterenol infusion was used to check inducibility of arrhythmia for AT patients. Post – procedural follow – up data were obtained from polyclinic visits or emergency admission records. Recurrence was diagnosed if the patient had presented with the same tachycardia that was confirmed by 12-derivation surface ECG. Recurrence was also accepted to be present in patients with tachycardia episodes on 24-hour rhythm Holter monitoring during follow-up and in whom pre-ablation tachycardia was induced during electrophysiological study. Patients who had presented with atrial fibrillation (AF) after the procedure were also noted.

Statistical Analysis

All statistical analyses were performed by using SPPS version 21.0 (SPSS Inc., Chicago, IL, USA). Data distribution was evaluated by using Kolmogorov-Smirnov test and histogram. Categorical variables were expressed with percentages, continuous variables were expressed as mean or median depended on distribution of the data. Two-sided t-test or Mann-Whitney U test was used to compare continuous variables and Chi-square was used for categorical data. Binary logistic regression analysis was performed to estimate predictors of study outcome (composite of failed ablation, recurrence, post ablation AF). Predictors that were found to be statistically significant in uni-variable analysis and those with potential that may predict study outcome based on reported data in previous studies were included in the multivariable model. Statistical power of logistic regression was estimated to be 0.90 for an Odds ratio of 1.5 for a sample size of 283 patients. Kaplan-Meier analysis with Log-rank test was used to compare event-free survival between AT and AFL patients. A p value < 0.05 was accepted as statistically significant.

3. RESULTS

A total of 339 consecutive patients were evaluated. Of those; 32 patients were excluded due to inadequate data, 8 patients were excluded because ablation was not performed and procedure remained as a diagnostic EP study. Final study population consisted of 299 patients (95 [31.8 %] AT, 204 [68.2 %] AFL cases); 163 (54.5 %) were male and median age was 54 (IQR; 42-64). Median follow up was 330 (IQR;90-180) days (range between 30-2543 days). Characteristics of study patients grouped as AT and AFL are displayed on Table I. None of the patients had a prior history of AF ablation procedure. Atrial tachycardia originated from the left atria (LA) in 13 patients including 4 patients from pulmonary veins. In the remaining 82 patients AT originated from the right atrium. Atrial flutter cases were older, had more co-morbidities and more frequently had history of open heart surgery. In addition, there were more

male patients in AFL group. Patients in AFL group had larger LA diameter and lower left ventricle ejection fraction values compared with patients in AT group. Acute procedural success rate was 82.1 % in AT group while it was 77.0 % in AFL group (p = 0.313). Recurrence rate was 9.3 % and 21.6 % in AT and AFL patients respectively (p= 0.022). Among patients with failed ablation or recurrence, 2 patients in AT and 22 patients in AFL group presented with paroxysmal or persistent AF during follow–up. There were 16 patients who displayed improvement in left ventricle ejection fraction after CA (4 patients in AT group, 12 patients in AFL group). Multivariable logistic regression analyses showed ; age (OR 1.023 [1.004-1.041] p= 0.015), history of valvular or congenital heart disease (CHD) surgery (OR 2.020 [0.987-4.136] p= 0.05) and LA diameter (OR 2.549 [1.487-4.368] p=0.001) had emerged as independent predictors of failed ablation, recurrence and AF occurrence in patients with AT and AFL (Table II). Age, history of valvular or CHD surgery and LA diameter also independently predicted composite endpoint including failed ablation, recurrence and AF occurrence in patients with AFL (Table III). Multivariate analysis could not be performed for AT patients separately due to low number of patients who exhibited study outcome. Kaplan Meier analysis with Log-rank test demonstrated that there was a non-significant trend for higher event-free survival in AT patients compared to AFL patients (Log-rank p= 0.115) (Figure 1).

Table I. *Characteristics of study patients with comparison of atrial tachycardia and atrial flutter cases*

	Atrial tachycardia (n= 95)	Atrial flutter (n= 204)	P value
* Age (years)	51 (29-59)	57 (45-66)	<0.001
Female (n%)	62 (65.3)	74 (36.3)	<0.001
HT (n%)	22 (23.2)	69 (33.8)	0.06
DM (n%)	4 (4.2)	17 (8.3)	0.194
CAD (n%)	5 (5.3)	37 (18.1)	<0.001
Cardiac Surgery (n/%)	7 (7.2)	52 (25.5)	<0.001
CABG (n/%)	1 (1.1)	13 (6.4)	
Valve replacement (n/%)	1(1.1)	26 (12.7)	
Congenital (n%)	5 (5.3)	13(6.4)	
Echocardiography	61.1 (± 7.6)	56.5 (± 10.7)	< 0.001
LV Ejection Fraction (%)	3.5 (± 0.44)	4.1 (± 0.53)	< 0.001
LA diameter (mm)			
Tachycardiomyopathy (n,%)	4 (4.2)	12 (5.9)	0.783
Acute procedural success (n/%)	78 (82.1)	157 (77)	0,313
** Recurrence (n%)	7/75 (9.3)	33/153 (21.6)	0.022

**Age was expressed as median and 25-75 interquartile range, remaining continuous data were expressed as mean ± standard deviation. HT: Hypertension; DM: Diabetes mellitus; HT: Hypertension; CAD: Coronary artery disease; CABG: Coronary artery by-pass graft; LV: Left ventricle; LA: Left atrium. **Patients with failed ablation and lost to follow-up were extracted.*

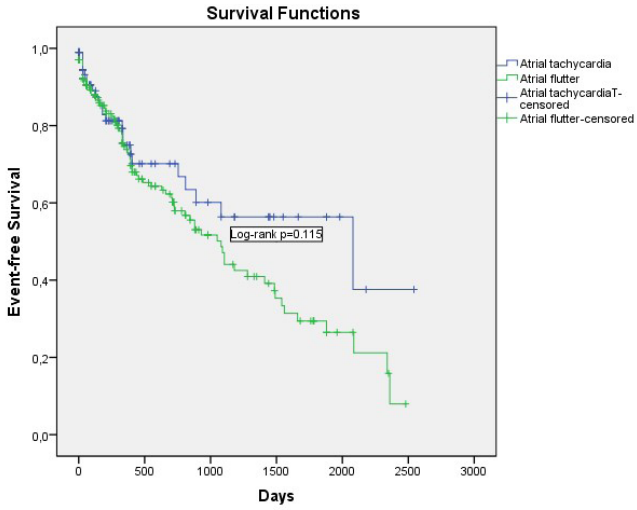

Figure 1. *Kaplan-Meier curve showing the event free survival after catheter ablation*

Table II. *Univariable and multivariable regression analysis of study patients for composite endpoint (failed ablation, recurrence and post-procedural AF)*

	Univariable OR (%95 CI)	P value	Multivariable OR (% 95 CI)	P value
Female gender	0.982 (0.689-1.584)	0.941		
Age	1.028(1.011-1.044)	0.001	1.023(1.004-1.041)	0.015
DM	1.445 (0.588-3.550)	0.423		
HT	1.024 (0.611-1.717)	0.927		
CAD	1.672 (0.863-3.237)	0.128		
CABG	1.938 (0.661-5.684)	0.228		
Heart valve or Congenital heart disease surgery	2.486 (1.307-4.727)	0.005	2.020(0.987-4.136)	0.05
Atrial flutter vs AT	1.909 (1.111-3.280)	0.019	0.935 (0.500-1.750)	0.834
LV Ejection fraction	0.995 (0.972-1.019)	0.706		
LA diameter	3.226 (2.017-5.161)	<0.001	2.549 (1.487-4.368)	0.001

DM: Diabetes mellitus; HT: Hypertension; CAD: Coronary artery disease; CABG: Coronary artery by-pass graft; LV: Left ventricle; LA: Left atrium

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Table III. *Predictors of failed ablation,recurrence and post-procedural AF in atrial flutter patients*

	Univariable OR (95 % CI)	P value	Multivariable OR (95%CI)	P value
Age	1.017(0.997-1.038)	0.092	1.025(1.006-1.043)	0.009
Female Gender	1.552(0.868-2.777)	0.138		
DM	1.838(0.678-4.982)	0.232		
HT	0.907(0,500-1.647)	0.748		
CAD	1.672(0.863-3.237)	0.128		
CABG operation	1.886(0.610-5.831)	0.271		
Heart valve or CHD operation	2.734(1.333-5.563)	0.006	1.534(0.716-3.290)	0.049
LA diameter	3.226 (2.017-5.161)	<0.001	2.489(1.501-4.127)	<0.001
LV EF	0.995(0.972-1.019)	0.706		
Atypical AFL vs CTI dependent AFL	3.339(1.337-8.343)	0.01	1.534(0.716-3.290)	0.271

DM: Diabetes mellitus; HT: Hypertension; CAD: Coronary artery disease; CABG: Coronary artery bypass graft; CHD: Congenital heart disease; LA: Left atrium; LV EF: Left ventricle ejection fraction; AFL: Atrial flutter; CTI: Cavo-tricuspid isthmus

4. DISCUSSION

Main findings of the present study are; (i) patients who had AT and had undergone CA were younger, mostly female and had less frequent co-morbidities compared to patients who had undergone CA due to AFL (ii) older age, history of valvular or CHD surgery and LA diameter were independent predictors of failed ablation, recurrence of index arrhythmia and occurrence of AF (iii) same variables predicted same outcomes when AFL patients were analysed separately. We have observed significant differences regarding some clinical characteristics and recurrence rates between patients with AT and AFL who had undergone CA in this single centre study. Although, focal automaticity has been suggested to be underlying mechanism for majority of ATs, macro re-entry has also been demonstrated as underlying mechanism in a growing number of AT patients undergoing CA. Fibrosis in the atria causes electrical heterogeneity and focal conduction alterations. Degeneration in the atria causes fibrosis and scar formation. Aging, coronary artery disease, hypertension are all contributing factors for development and progression of atrial fibrosis. Atriotomy scar, sutures, prosthetic valves, patches and baffles can serve as a ground for both AT and AFL. In addition, CA itself can create functional block and slow conduction areas in the atria. Currently, as the number of atrial fibrillation ablation procedures increase, electrophysiologists face with left sided AT and AFL more frequently [11,12]. On the other hand, the mechanism of AT may have automaticity; triggered activity or micro-re-entry in a restricted area of atrium and those patients generally have healthy myocardium in the remaining atria. Young age is a predictor for automaticity mechanism of focal AT [6]. In some type of focal ATs, the mechanism of tachycardia is micro re-entry. For instance, confined slow conduction area and micro re-entry have been demonstrated to have an underlying pathology in crista terminalis ATs [12]. In accordance to that finding, patients with crista terminalis AT are older than the other focal AT patients. Our findings showed that the older age and larger LA diameter are both emerging factors for failed ablation, recurrence, and post – procedural AF in atrial tachyarrhythmia patients. In most studies, it has been shown that larger LA diameter is related with recurrence after CA of AF. [13]. Voight et al., demonstrated that LA diameter is an independent predictor for new onset AF after CTI dependent AFL ablation [14]. In our study, 2 patients in AT group and 22 patients in AFL group presented with AF. Among the study population with post procedural AF; CA had been unsuccessful in 10 patients and recurrence of index arrhythmia had been detected before the AF in 6 patients. Remaining 8 patients presented with AF following the successful ablation. Larger LA diameter is related with advanced fibrosis, scar formation and inflammation in both atrial myocardial tissues. Therefore, LA diameter may predict CA results not only for left sided arrhythmias but also for the tachyarrhythmias that is confined to the right atrium. In addition, it is also relevant to say that altered electrical activity due to unhealthy atrial substrate can precipitate both AFL and AF. Kaneshiro et al,, demonstrated that pulmonary vein firing may initiate AFL in patients with prior AF diagnosis [15]. Hence, it is common to observe AF following atrial tachyarrhythmia ablation or vice versa particularly in cases with diseased atrial substrate. Patients with more complex electrical characteristics in atria including functional blocks, slow conduction areas and low amplitude fractioned local electrograms comprise more difficulties for mapping and ablation [16]. In addition, due to progressive nature of fibrosis, arrhythmia recurrence and incidence of post ablation AF are both more common in those patients.

Older age has emerged as an independent predictor of our study outcome. In a study by Brunch et al., it was reported that older age is related with AFL/AF recurrence and increased mortality after AF ablation [17]. In contrast, patients older than 70 years of age had lower recurrence rates after AFL ablation in another study which focused on relationship between age and AFL ablation outcomes [18]. However, patients older than 70 years of age had higher incidence of AF after CA of AFL in the same study. In a study by Huo et al., it was suggested that presence of low voltage zone in LA was related with older age in AF patients who had undergone CA [19]. Hence, poor outcome of elderly patients in our study might be explained with increased atrial fibrosis.

Early diagnosis and technical improvements in the surgical procedures have led to increased survival through older ages for patients with CHD and valvular heart disease. However, atrial arrhythmias are commonly seen in those patients. It has been shown that CA ablation procedures for CHD patients that present with ATs and AFL are more challenging with high recurrence rates [20,21]. Occurrence of more than one tachycardia mechanism (biatrial re-entry, AFL, AF, focal micro re-entry), complexity of cardiac abnormality, dilatation in heart chambers, complexity of corrective surgery, prosthetic heart valves, conduits and patches are all contributing factors of failed ablation and arrhythmia recurrence. In accordance with prior data, prior history of CHD and heart valve operation emerged as an independent predictor of failed ablation and arrhythmia recurrence in our study population.

Limitations

This study has several limitations: (i) Our study was a retrospective study, and we could not obtain rhythm Holter recordings after ablation for evaluation of recurrence in each patient. Given the fact that Holter monitoring had been performed only in symptomatic patients, recurrence of index arrhythmia or asymptomatic AF attacks might have been undiagnosed in some patients. (ii) Pooled analyses of patients that exhibit large variety of clinical conditions (iii) Cumulative study outcome including failed ablation, recurrence of index arrhythmia and post-procedural AF. We used pooled patient analysis by combining AT and AFL population because we think that it would define the characteristics of these patients more precisely as both may have similar arrhythmia mechanisms. We preferred to evaluate cumulative outcome, because statistical power of analysis would have been reduced if the outcomes had been evaluated separately.

Conclusion

Atrial tachycardia patients were younger and more frequently female compared to AFL patients in our study. Recurrence was more common in AFL patients compared to AT after CA. Age, LA diameter, history of CHD or heart valve operation were independent predictors of failed ablation, recurrence and post-procedural AF in both pooled patient population and AFL patients.

Compliance with Ethical Standards

Ethical approval: The study protocol was approved by the Kartal Kosuyolu Training and Research Hospital Ethics Committee (approval number: 2019.7/15-231).

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Conflict of interest: The authors have no potential conflicts to declare.

Authors' contributions: Literature search: MC and AK, Study design: KG, AK and SD, Legislative applications: KG and SD, Data collection: KG, AU, GBK and TA, Supervision and quality control: AK, Statistical advice: AK, Statistical data analysis: AK and KG, Data interpretation: SA and TA, Drafting the manuscript: KG. All authors read and approved the final version of the article.

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Clinical and biochemical characteristics of Sjögren's syndrome and its differences from keratoconjunctivitis sicca

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ABSTRACT

Objective: In this study we aimed to compare the clinical and biochemical characteristics of primary Sjögren's syndrome patients with that of keratoconjunctivitis sicca, secondary Sjögren syndrome and undifferentiated disease.

Patients and Methods: Patients with Sjögren's syndrome and keratoconjunctivitis sicca who applied between August 2009 and January 2010 were included in this study. Demographic data, laboratory characteristics, Schirmer's test and salivary gland biopsies of the patients were recorded.

Results: Average diagnosis age for 87 primary Sjögren's syndrome, 25 secondary Sjögren's syndrome, 27 keratoconjunctivitis sicca and 44 undifferentiated group patients were 45±13, 43±14, 44±11 ve 45±11 years ($p>0.05$), accordingly. Critical and severe mouth dryness rate was 45% in primary Sjögren's syndrome group and 7% in keratoconjunctivitis sicca group, critical and severe eye dryness was 43% in primary Sjögren's syndrome group and 78% in keratoconjunctivitis sicca group ($p<0.001$). Grade 3≥ positivity in salivary gland biopsy was found as 71.2% in primary Sjögren's syndrome group and 27.2% in the undifferentiated group ($p<0.001$).

Conclusions: More dense lymphocyte infiltration was detected in primary Sjögren's syndrome in salivary gland biopsies. As 27.2% of undifferentiated group patients had positive salivary gland biopsies, they might need follow-ups in terms of having increased risk of developing primary Sjögren's syndrome.

Keywords: Keratoconjuctivitis sicca, Schirmer's test, Sjögren's syndrome

1. INTRODUCTION

Sjögren's syndrome (SS) is a chronic autoimmune disease of unknown cause, mainly involving the salivary gland and lacrimal gland. Primary Sjögren's syndrome (PSS) is one of the three most common autoimmune disorders in the population, having an average incidence of 0.5-1.0%. The disorder may be confined only to the salivary and lacrimal glands, or in one-third of the cases, it may be associated with various organ/system involvements such as musculoskeletal, gastrointestinal, nervous systems and skin, kidneys, lungs, and lymph nodes. Symptoms such as fatigue and arthralgia, which severely affect patients' quality of life, are frequently identified beside the objective signs. SS can occur alone or with rheumatological diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). Such a situation is named secondary Sjögren's syndrome (SSS) [1, 2].

Keratoconjunctivitis sicca (dry eye) is a disease in which eye complaints are observed with an increased frequency with advanced age. In this case, biochemical and serologic markers are negative. Even though common in the population, it is, unfortunately, a neglected disease group because patients do not perceive its symptoms adequately and physicians do not recognize its systemic findings well [3].

The presence of systemic involvement and some other serological and biochemical markers are important indicators for the disease progression. For this reason, patients' clinical and

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biochemical characteristics at first admission have some clues about how the disease will progress in the early period.

Our study aimed to determine the demographic, clinical, and laboratory features of patients followed up for SS. Its other aim was to determine the SS group's differences from the keratoconjunctivitis sicca and undifferentiated groups.

2. PATIENTS and METHODS

The study's patient group comprised the patients followed up with the diagnoses of Sjögren's syndrome (primary and secondary) and keratoconjunctivitis sicca (dry eye) in the Rheumatology Department of a university hospital between August 2009 and January 2010. In this context, the newly diagnosed patients and the previously diagnosed patients who presented for a control examination were included in the study. Patients who did not consent and those who did not accept to undergo salivary gland biopsy were excluded from the study. The patient age and gender, ages at diagnosis and the onset of symptoms, initial symptoms, smoking status, physical examination findings such as blood pressure, articular features (arthritis/arthralgia), Raynaud phenomenon, lymphadenopathy, and laboratory parameters such as complete blood count, liver and renal function tests, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), complement 3-4 (C3-C4), urinalysis, thyroid tests – thyroid autoantibodies, antinuclear antibody (ANA), anti-Ro, anti-La, anti double stranded DNA (anti-ds DNA) ,lupus anticoagulant, antiphospholipid and anticardiolipin antibodies, hepatitis markers, and the gammaglobulin ratio in serum protein electrophoresis were recorded. The evaluation of salivary gland biopsy was performed according to the Chisolm-Mason criteria [4]. Biopsy results revealing Grade 3 and over were considered as diagnostic for SS. (Lymphocytes per 4 mm2/ salivary tissue. Grade 0: absent, grade 1: slight infiltration, grade 2: moderate infiltration or less than one focus, grade 3: one focus, grade 4: more than one focus. Focus: aggregate of ≥ 50 lymphocytes and histiocytes). When present, the patients' parotid scintigraphy results were recorded.

The patients were queried thoroughly regarding dry mouth and eye, the primary symptoms of SS. Dry mouth and dry eye were assessed as present/absent. The symptoms were classified as mild, moderate, severe, and highly severe in patients with dry mouth/eye. While classifying the symptoms of dry mouth and eyes of the patients, the patients were asked and scored from 1 to 10 according to the severity of the complaints. (1-4 points: mild, 5-6 points: moderate, 7-8 points: severe, 9-10 points: highly severe). The dry mouth/eye symptoms were recorded as between 0-100 mm using the Visual Analog Scale (VAS), and the symptom durations were also recorded. Fatigue, a significant SS symptom, was recorded as present/absent, like dry mouth/eye. Then, VAS was used to record its severity between 0-100 mm.

Schirmer's test was performed at the Outpatient Ophthalmology Clinic, and test results under 5 mm were considered positive [5].

The imaging methods (computed tomography, magnetic resonance imaging) guided the investigations, especially regarding the lung and the central nervous system involvements and serologic markers for hepatic involvement.

The diagnosis of vasculitis was verified by discovering palpable purpura on physical examination and identifying leukocytoclastic vasculitis in skin biopsies.

The patients' medications, such as hydroxychloroquine, corticosteroids, methotrexate, sulphasalazine, and acetylsalicylic acid, and their dosages were recorded.

The accompanying rheumatologic diseases, such as RA, SLE, and scleroderma, were recorded. Besides, other disorders that might have been associated, such as autoimmune thyroiditis, autoimmune hepatitis, and primary biliary cirrhosis, were recorded.

In this study, patients were divided into 4 different groups. The patients with four of the SS criteria were defined as 'primary' SS, whereas, those with positive for three criteria or less as 'undifferentiated' group. Patients who fulfilled the diagnostic criteria for SS and had additional rheumatologic disease were defined as SSS. Only patients with dry eye complaints and negative biochemical/serological markers were evaluated as keratoconjunctivitis sicca (dry eye).

The diagnosis of SS was made according to the criteria defined in 2002 [6].

This study was approved by the Ethics Committee of a university hospital where the study was conducted (approval number: HEC 09/91-227).

Statistical Analysis

Statistical analysis was performed by the "Statistical Package for Social Sciences (SPSS) v. 15.0" software. Data were presented as mean and standard deviation. The Student's t-test was used for continuous variables and the Chi-square test for categorical variables. A "p" value under 0.05 was considered statistically significant.

3. RESULTS

This study evaluated a total of 183 patients. Eighty-seven patients fulfilled the criteria for PSS diagnosis, whereas 25 patients met the criteria for diagnosing SSS. When patients with SSS were analyzed regarding rheumatologic disorders, it was found that 11 patients (44%) had RA, 13 (52%) SLE, and one (4%) patient had spondyloarthropathy. In 27 patients, only dry eye findings were present. In 44 patients, the diagnostic criteria of SS were not fulfilled; however, they were defined as the "undifferentiated group" because of their symptom/antibody positivity or a positive result in salivary gland biopsy.

All patients' demographic data and clinical features/organ involvement were presented in Table I. In all four groups, more than 85% of the patients were females. In all groups, the mean patient age was within the 4th decade. No significant differences were present among the four groups regarding the present age and the age at the onset of symptoms (p>0.05).

Table I: *Demographic and clinical characteristics of the patients in the study*

	Primary SS (n=87)	SSS (n=25)	Dry eye (n=27)	Undifferentiated (n=44)
Age (years±SD)	48±13	49±14	45±12	47±11
Gender n(%)				
Female	83 (95)	22 (88)	23 (85)	40 (91)
Male	4 (5)	3 (12)	4 (15)	4 (9)
Disease duration (years)	1 (0-20)[2]	3 (0-26)[2]	1 (0-10)[2]	2 (0-15)[2]
Severity of dry mouth n (%)				
Absent	3 (3.4)	1 (4)	14 (51.8)	19 (43.2)
Mild	17 (19.5)	4 (16)	4 (14.8)	7 (15.9)
Moderate	28 (32.2)	11 (44)	7 (26.0)	10 (22.7)
Severe	37 (42.5)	7 (28)	2 (7.4)	7 (15.9)
Highly severe	2 (2.3)	2 (8)	0 (0)	1 (2.3)
Mouth VAS mm	53±22[1]	54±21[1]	0 (0-80)[2]	25 (0-90)[2]
Severity of dry eye n (%)				
Absent	1 (1.1)	3 (12)	1 (3.7)	17 (38.6)
Mild	19 (21.8)	3 (12)	1 (3.7)	6 (13.6)
Moderate	30 (34.5)	4 (16)	4 (14.8)	15 (34.1)
Severe	34 (39.1)	13 (52)	16 (59.3)	6 (13.6)
Highly severe	3 (3.4)	2 (8)	5 (18.5)	0 (0)
Eye VAS mm	53±21[1]	49±30[1]	67±18[1]	28±27[1]
Schirmer's test mm	4 (1-35)[2]	5 (1-35)[2]	3.2±1.9[1]	13.4±9.1[1]
Fatigue n (%)	70 (80.5)	22 (88)	19 (70.4)	34 (77.3)
Fatigue VAS mm	50±27[1]	53±22[1]	42±30[1]	45±28[1]
Arthralgia n (%)	63 (74.1)	24 (96.0)	18 (66.7)	32 (72.7)
Arthritis n (%)	11 (12.9)	17 (68.0)	2 (7.4)	5 (11.4)
Raynaud phenomenon n (%)	12 (14.1)	3 (12.0)	0 (0)	6 (13.6)
Vasculitis n (%)	1 (1.2)	2 (8)	0 (0)	2 (4.5)
Neurologic involvement n (%)	2 (2.4)	2 (8.0)	2 (7.4)	3 (6.8)
Transverse myelitis	1	0	0	0
Optic neuritis + T. Myelitis	1	0	0	0
Optic atrophy	0	1	0	0
Peripheral neuropathy	0	0	0	1
Myasthenia Gravis	0	1	0	0
Demyelinating Disease	0	0	2	0
Ischemic Changes	0	0	0	2
Lung Involvement n (%)	6 (7.2)	3 (12)	0 (0)	0 (0)
Interstitial	1	0	0	0
Ground glass	2	2	0	0
Pulmonary nodule	2	0	0	0
Honeycomb + ground glass	1	0	0	0
Ground glass + pulmonary nodule	0	1	0	0
Liver n (%)	4 (4.6)	0 (0)	0 (0)	1 (2.3)
Autoimmune hepatitis	3	0	0	1
PBS	1	0	0	0
Autoimmune thyroiditis n (%)	10 (11.4)	3 (12)	3 (11)	3 (6.8)

Data were presented as mean ± SD or median (min-max).
The average value was shown in the table as [1] and the median value as [2].
PBS: Primary biliary cirrhosis

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In PSS patients with severe and highly severe mouth dryness, biopsy results revealing Grades 3 and 4 were more common in the minor salivary gland biopsies (p=0.003) (Table II).

Table II. *The grades of minor salivary gland biopsy according to the severity of dry mouth in PSS patients*

	≥ Severe dry mouth (n=39)	≤ Moderate dry mouth (n=48)
Grade 0 n (%)	4 (10.2)	3 (6.2)
Grade 1 n (%)	2 (5.1)	8 (16.7)
Grade 2 n (%)	1 (2.6)	7 (14.6)
Grade 3 n (%)	17 (43.5)	26 (54.2)
Grade 4 n (%)	15 (38.6)	4 (8.3)

Positive results in salivary gland biopsies were less frequent in patients with severe and highly severe dry eyes (56.8%) when compared to those with mild and moderate dry eyes (82.0%) (p=0.01) (Table III).

Table III. *The grades of minor salivary gland biopsy according to the severity of dry eye in PSS patients*

	≥ Severe dry eye (n=37)	≤ Moderate dry eye (n=50)
Grade 0 n (%)	3 (8.1)	4 (8.0)
Grade 1 n (%)	7 (18.9)	3 (6.0)
Grade 2 n (%)	6 (16.2)	2 (4.0)
Grade 3 n (%)	11 (29.8)	32 (64.0)
Grade 4 n (%)	10 (27.0)	9 (18.0)

The results of laboratory parameters were presented in Table IV.

There was a history of cardiac pacemaker implantation in two patients with PSS because of a heart block due to anti-Ro antibodies. A similar situation was determined in a patient with the undifferentiated disease.

Non-Hodgkin lymphoma (NHL) was diagnosed in two patients with PSS. The pathological typing was large cell B-cell lymphoma in both patients, and one of them was CD20(+). Both patients had pathological-sized lymphadenopathies. One of the patients was diagnosed with leukocytoclastic vasculitis accompanying SS. NHL developed ten years after the patient had been diagnosed with SS. The other patient was also diagnosed with NHL accompanying SS. This patient had leukopenia and hepatosplenomegaly at admission.

In 70 (80.4%) of PSS patients, 21 (84%) of SSS patients, and 25 (56.8%) of patients with the undifferentiated disease, the salivary gland biopsy revealed the severity as Grade 2 and above. No patient had a salivary gland biopsy result of Grade 2 and above in the dry eye group (Table V). A Grade 3 and over salivary gland biopsy result was present in 62 of 87 PSS patients. Severe and highly severe dry mouth was present in 32 (51.6%) of these 62 patients, whereas in 7 (28.0%) of 25 patients with a grade between 0 and 2 (p=0.01) (Table II).

When the PSS patients were compared to the patients with a dry eye only, significant differences were determined regarding clinical findings (mouth-eye dryness severity and VAS scores, Raynaud phenomenon), laboratory parameters (ESR, globulin, RF, ANA, anti-Ro, anti-La), and minor salivary gland biopsy results. While the severity of mouth dryness and laboratory investigations indicated PSS, the severity of eye dryness and Schirmer's test's frequency and severity were more significantly determined in the group with a dry eye only (Table VI).

Table IV. *Laboratory results of the patients*

	Primary SS (n=87)	SSS (n=25)	Dry eye (n=27)	Undifferentiated (n=44)
ANA n (%)				
Absent	8 (9.2)	3 (12.0)	21 (77.8)	7 (15.9)
1/80	16 (18.4)	4 (16.0)	4 (14.8)	5 (11.4)
1/160	42 (48.3)	8 (32.0)	2 (7.4)	16 (36.4)
1/320	19 (21.8)	7 (28.0)	0 (0)	14 (31.8)
1/640	2 (2.3)	3 (12.0)	0 (0)	2 (4.5)
RF n (%)	43 (54.0)[3]	14 (56.0)	6 (22.3)	14 (31.8)
Anti-Ro n (%)	55 (62.5)	15 (60.0)	0 (0)	27 (63.6)
Anti-La n (%)	30 (34.1)	8 (32.0)	0 (0)	14 (31.8)
Anti-TPO n (%)	8 (9.1)	2 (8.0)	3 (11)	2 (4.5)
Anti-thyroglobulin n (%)	9 (10.2)	1 (4.0)	3 (11)	2 (4.5)
Hemoglobin gr/dl	12.8±1.4[1]	12.8±1.6[1]	13.7±1.6[1]	13.1±1.4[1]
Leukocyte mm^3 x 10^3	6.2±2.4[1]	6.5±2.1[1]	7.6±2.3[1]	6.1±2.6[1]
Thrombocyte mm^3 x 10^3	268±73[1]	269±98[1]	234±40[1]	258±61.7[1]
ESR mm/hour	27±21[1]	42±30[1]	10±7	25±20
CRP mg/dl	0.3 (0.1–21)[2]	0.8 (0.1–9,2)[2]	0.30 (0.1–1.6)[2]	0.27 (0.1–11)[2]
Hyperglobulinemia n (%)	10 (12.6)	2 (8)	0 (0)	2 (4.6)

Data were presented as mean ± SD or median (min-max).
The average value was shown in the table as [1] and the median value as [2].
[3] RF was evaluated with 80 patients. ANA: antinuclear antibody, RF: rheumatoid factor, Anti-TPO: anti thyroid peroxidase antibody, ESR: erythrocyte sedimentation rate, CRP: C reactive protein

Contrary to the dry eye patients, fewer differences were determined between the PSS and undifferentiated groups. When the PSS patients were compared to the patients with the undifferentiated disease, while significant differences were determined regarding clinical findings (mouth-eye dryness severity and VAS scores) and minor salivary gland biopsy results, the laboratory tests of the two groups revealed similar results (Table VII).

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Marmara Med J 2021;34(2): 208-214

The patients' treatment characteristics were presented in Table VIII.

Table V. *Salivary gland biopsy results of the patients*

	Primary SS n (%)	SSS n (%)	Dry eye n (%)	Undifferentiated n (%)
Grade 0	7 (8.1)	2 (8)	19 (70.4)	10 (22.7)
Grade 1	10 (11.5)	2 (8)	8 (29.6)	9 (20.5)
Grade 2	8 (9.2)	5 (20)	0 (0)	13 (29.5)
Grade 3	43 (49.4)	10 (40)	0 (0)	10 (22.7)
Grade 4	19 (21.8)	6 (24)	0 (0)	2 (4.5)

Table VI. *The differences between primary SS and dry eye*

	Primary SS	Dry Eye	p
Severe/highly severe dry mouth n (%)	39 (45)	2 (7)	0.001
Dry mouth VAS (mm) mean±SD	53±22	21±25	<0.001
Schirmer (mm) mean±SD	8.7±8.6	3.3±1.9	0.002
Schirmer positivity n (%)	61 (70)	27 (100)	0.002
Dry eye VAS (mm) mean±SD	53±21	67±17	0.001
ESR (mm/hour) mean±SD	27±21	10±7	<0.001
Globulin (units) mean±SD	3.69±0.63	2.94±0.35	<0.001
Severe/highly severe dry eye n (%)	37 (43)	21 (78)	<0.001
RF > 40 IU n (%)	43 (54)	3 (11)	<0.001
ANA ≥ 1/160 titration positivity n (%)	63 (72)	2 (7)	<0.001
Anti-Ro n (%)	55 (62)	0 (0)	<0.001
Anti-La n (%)	30 (34)	0 (0)	<0.001
Raynaud Phenomenon n (%)	12 (14)	0 (0)	0.028
Salivary gland biopsy ≥ grade 3 n (%)	62 (71)	0 (0)	<0.001

VAS: visual analog scale, ESR: erythrocyte sedimentation rate, RF: rheumatoid factor, ANA: antinuclear antibody

Table VII. *The differences between primary SS and undifferentiated groups*

	Primary SS (n=87)	Undifferentiated (n=44)	p
Severe/highly severe dry mouth n (%)	39 (45)	8 (18)	0.003
Dry mouth VAS (mm)	53±21	28±29	<0.001
Schirmer positivity n (%)	61 (70)	11 (25)	<0.001
Dry eye VAS (mm)	53±20	28±27	0.001
Severe/highly severe dry eye n (%)	37 (43)	6 (14)	0.001
Salivary gland biopsy (+) n (%)	62 (71)	12 (27)	<0.001

Table VIII. *Treatment features of all patients included in the study*

	Primary SS (n=87)	SSS (n=25)	Dry eye (n=27)	Undifferentiated (n=44)
Hydroxychloroquine n (%)				
200 mg	27 (30.7)	6 (24.0)	0 (0)	9 (20.5)
400 mg	54 (61.4)	18 (72.0)	0 (0)	32 (72.7)
Corticosteroid mg	5.5 (2–1000)[1]	6.75 (1–40)[1]	0 (0)	3.25 (2–1000)[1]
Methotrexate n (%)				
7,5 mg/week	0 (0)	2 (8)	0 (0)	0 (0)
10 mg/ week	3 (3.4)	2 (8)	0 (0)	2 (4.5)
15 mg/ week	0 (0)	5 (20)	0 (0)	1 (2.3)
Azathioprine n (%)				
50 mg	2 (2.3)	2 (8)	0 (0)	1 (2.3)
100 mg	13 (14.8)	5 (20)	0 (0)	4 (9.1)
150 mg	2 (2.3)	0 (0)	0 (0)	0 (0)
Sulfasalazine n (%)	0 (0)	9 (36)	0 (0)	2 (4.5)
Cyclosporin n (%)	1 (1.1)	0 (0)	0 (0)	1 (2.2)

4. DISCUSSION

In our study, a total of 183 patients were evaluated, involving 87 PSS, 25 SSS, 27 keratoconjunctivitis sicca patients, and 44 patients with the undifferentiated disease. No significant differences were present regarding age and gender among these groups. The onset of the disease was in the 4th decade in all groups.

Evaluating the dry mouth and dry eye using a Likert scale is not a frequently performed practice in SS. These symptoms have generally been defined as present or absent. In fact, dry mouth and dry eye symptoms were defined as present/absent during diagnostic criteria constitution. However, they were classified as absent, mild, moderate, severe, and highly severe in our study. We think that such a classification reflects the patient symptomatology better. Actually, the salivary gland biopsies of the patients with severe and highly severe dry mouth symptoms revealed positive results more commonly.

In daily practice, the number of patients with dry mouth and/or eye, a positive/negative result in Schirmer's test, and a positive result for any antibody is not small. It is not uncommon to identify lymphocytic infiltration of Grade 2 and over in biopsies of the minor salivary glands in these patients (undifferentiated group). In this patient group, 29.5% of patients had Grade 2 lymphocytic infiltration, whereas, in 27.2% of patients, it was Grade 3 and over. For this reason, even though these patients could not fulfill the diagnostic criteria of PSS, they had many subjective and objective findings. We defined this group as the group "not entirely differentiated to PSS." The undifferentiated group was similar to the PSS group regarding age and gender.

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While there was no dry mouth symptom in more than 40% of this group, severe and highly severe dry mouth was present in only 18% of the group. Like the dry mouth symptom, dry eye was not identified in 38% of the patients, and only 14% had highly severe dry eye symptoms. In this group, 77% of the patients had fatigue as one of the primary symptoms. There were no differences between the PSS and undifferentiated groups regarding arthralgia, Raynaud phenomenon, arthritis, neurological involvement, autoimmune thyroiditis, vasculitis, and autoimmune hepatic involvement. Fatigue is one of the major complaints in rheumatological diseases. A study investigating the quality of life in PSS determined that patients had encountered a 5-65% reduction in quality of life [7-8]. We used a 100 mm VAS, commonly used in the literature, as a practical and straightforward measurement method. Even though it might reveal false-positive and false-negative results according to patients' socioeconomic levels, it is a test commonly used today. In our study, 80% of PSS patients had fatigue, and this ratio was a little higher than those in the literature.

Auto-antibodies are among the most significant objective criteria in diagnosing SS. Various studies have reported auto-antibody positivities in PSS as follows: RF: 6-60%, ANA: around 90%, anti-Ro: 23-60%, anti-La: 5-50% [9]. In our study, ANA≥1/160 titration was present in 72.4% of PSS patients, whereas 18.4% of the patients had an ANA positivity at the titration of 1/80. RF was present in 54%, anti-Ro in 62%, and anti-La antibody in 34% of the patients. These results were consistent with those in the literature. The autoantibodies were absent in the dry eye patients. Intriguingly, there was no difference between the PSS and undifferentiated groups regarding autoantibody commonness. The high auto-antibody positivity in the undifferentiated group might have been evidence of the close relationship of this group with the PSS group.

PSS is 10-fold more common in patients with autoimmune thyroiditis. Similarly, autoimmune thyroiditis is 9-fold more frequently met in PSS patients. In a study conducted in 1998 by Gaches et al. on 218 patients with autoimmune thyroiditis [10], the most common autoimmune disorders were reported as SLE and SS. In another recent study, the close coexistence of the two conditions was reported [11]. In our patients, autoimmune thyroid disease was determined with a frequency of 11.4% in PSS. However, autoimmune thyroid disease had a high ratio in the SSS, dry eye, and undifferentiated groups. In our SSS patients, such a high ratio is not surprising because RA and SLE disorders have been well-known to lead to autoimmune thyroiditis.

On the other hand, the rate of 6.8% for autoimmune thyroiditis in the undifferentiated group might support the fact that the undifferentiated group was a sub-group of PSS. In our study, 3 of 27 dry eye patients had autoimmune thyroiditis. The relationship between autoimmune thyroid diseases and dry eye is a subject that necessitates further research.

Raynaud's phenomenon is a vascular disorder characterized by episodes of reversible digital ischemia in response to cold or stress. Raynaud's phenomenon is generally classified as primary (in the absence of any associated process) or secondary if an associated disease (most frequently an autoimmune disease) or an environmental condition is present. Raynaud phenomenon has been reported with a frequency between 13-38% in previous studies [12]. In our study, the incidence of the Raynaud's phenomenon was 14.1% in PSS patients, similar to those in the literature.

In our study, in two (2.3%) PSS patients and in one patient in the undifferentiated group, congenital heart block due to blocking antibodies (anti-Ro/anti-La) was determined, and this result was similar to the literature [13-14].

Various studies have reported that the lymphoma risk was increased in PSS patients [15, 16]. In our study, two (2.3%) PSS patients had lymphoma. One patient had persistent hepatosplenomegaly leukopenia and lymphadenopathy, whereas another patient had cutaneous vasculitis and lymphadenopathy in our study.

The dry eye symptom is mostly at the forefront among the causes for admission of PSS patients to Rheumatology Clinics. There is a significant patient population with only dry eyes followed up at ophthalmology clinics. The differential diagnosis of PSS with dry eye is crucial. In our study, the clinical and laboratory results suggesting PSS were determined as the severity of mouth dryness, Raynaud phenomenon, high ESR, elevated globulin level, and positivity of RF, ANA, anti-Ro, and anti-La antibodies. The frequency of positive results in Schirmer's test and more severe eye dryness were determined as the characteristics of the dry eye group. It is not always possible to differentiate the two conditions clinically and by laboratory methods. In such conditions, salivary gland biopsy is a beneficial method. No biopsy result of Grade 2 and over was encountered in patients with dry eyes.

In this study, the most common treatment that the PSS patients received was hydroxychloroquine. Besides this treatment, low-dose glucocorticoids were administered. Azathioprine, cyclophosphamide, and methotrexate were used in the patients with extraglandular involvement. The patients in the PSS and undifferentiated groups received similar treatments. Because our study was not designed as a follow-up study, we could not further interpret the treatment's efficacy.

The evaluation of symptoms, Schirmer's tests, auto-antibody investigations, and salivary gland biopsies were performed in all patients. On the other hand, the parotid scintigraphy was not evaluated in every patient, which was our study's most significant limitation. The patients positive for four of the SS criteria were defined as "definite" SS, whereas those positive for three criteria or less as "undifferentiated" group. One of these six criteria was identifying the parotid gland involvement by an objective test. The most commonly used method for this purpose is parotid gland scintigraphy in daily practice. However, we performed the scintigraphic investigation in only 8.7% of our patients. The cause of such a low rate for scintigraphic evaluation was that the salivary gland biopsy was an easily applicable investigation that could be performed in outpatient clinics.

Conclusion

The severity of mouth and eye dryness was more significant, and more dense lymphocytic infiltration was identified in biopsies in PSS patients than patients in the undifferentiated group. Severe ocular symptoms were present in dry eye patients when compared to PSS patients. Because the salivary gland biopsy revealed positive results in 27.2% of patients in the undifferentiated group, follow-up of these patients would be required regarding PSS development.

Compliance with Ethical Standards

Ethics approval: This study was approved by the Ethics Committee of a university hospital where the study was conducted (approval number: HEC 09/91-227).

Funding: The authors have no relevant financial information to disclose.

Conflict of Interest: The authors declare no conflict of interest.

Authors' Contributions: Literature search: IT, Study design: IT and UK, Legislative applications: IT, Data collection: IT, Supervision and quality control: SK and UK, Statistical advice: UK, Statistical data analysis: UK, Data interpretation: IT, UK and SK, Drafting the manuscript: IT. All authors read and approved the final version of the article.

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Brachial plexus paralysis associated with traumatic asphyxia

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ABSTRACT

Traumatic injuries are the most common cause of brachial plexus lesions in children and adults. There are many causes of brachial plexus injuries such as accidents, falls and prolonged pressure. Traumatic asphyxia (TA) is a rare but serious clinical syndrome. Rarely, brachial plexus lesion may develop after TA and it is extremely rare in children. The cause of brachial plexus injury in patients without posttraumatic nerve root avulsion has not yet been fully explained. In this case report, we present the case of a child with neurological damage following TA which is very rare in the literature.

Keywords: Asphyxia, Brachial Plexus, Children, Trauma

1. INTRODUCTION

Traumatic asphyxia (TA) or *Perthes syndrome* is a very rare clinical syndrome that develops after a person is caught between two objects or trapped under heavy furniture. Almost all patients have facial edema, cervicofacial cyanosis, petechiae, subconjunctival hemorrhage and, respiratory distress [1].

The incidence of reported TA in adults is 1 case per 18.500 accidents. However, it is very rare in children and its true incidence is not well known in pediatric population [2].

Rarely, brachial plexus lesions may develop after TA and it is extremely rare in children. In this case report, we present a case of neurological damage following TA in a child.

2. CASE REPORT

A 12-year-old male patient, who was followed up for attention deficit hyperactivity syndrome, was brought to the Pediatric Emergency Department after being trapped by an automatic door. It was learned from his history that he played with the automatic door and tried to pass when it was about to close, he was stuck under the door for up to two minutes. The patient reported pain in the right side of his neck and difficulty in moving his right arm. On admission, he was alert and awake. Initial vital signs were stable. Physical examination revealed an excessive number of petechial rashes on the face and upper trunk, subconjunctival hemorrhage (Figure 1) and pain with palpation in the right side of the neck. In the neurological examination, motor deficits in the right shoulder, elbow and wrist in addition to paresthesia of the right forearm were observed. Biceps reflex in the right arm was absent and the triceps reflex was hypoactive. The range of motion of the right shoulder was limited because of pain.

A bedside postero-anterior chest radiography showed a suspicious fracture line in the right clavicle (Figure 2). Cervical radiography (Figure 3), extended focused assessment with sonography for trauma (eFAST) and craniocervical tomography findings were normal. Craniocervical magnetic resonance imaging (MRI) showed edema between the subcutaneous and muscle planes in the right side of the neck and edema in the supraclavicular segment of the C_6 nerve root originating from the C_5-C_6 intervertebral disc, and no avulsion was detected (Figure 4).

He was evaluated by orthopedics and physical medicine and rehabilitation therapy departments and surgical intervention was not considered. His arm was immobilized. Brachial plexus paralysis secondary to trauma was considered in the patient.

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Surgical treatment was not considered due to the absence of avulsion, edema between subcutaneous structures and muscle tissues, and edema in the supraclavicular segment of the C_6 nerve root in the MRI examination. He was discharged with antiinflammatory treatment. Two weeks later, no change was detected in the control examination and EMG was planned. Since, EMG was not recommended in cases without avulsion, for our patient we planned EMG before the first month after the trauma. EMG was performed approximately one month after the event and a partial lesion of the upper trunk of the brachial plexus was detected İn the right side.

He was followed-up with these findings and physiotherapy was started. There was no significant improvement in his clinical condition at the end of three months follow-up. Surgical intervention was not considered in our patient because no avulsion was detected. The patient left our follow-up after three months of follow-up, so long-term follow-up could not be done.

Written consent was obtained from the patient's family.

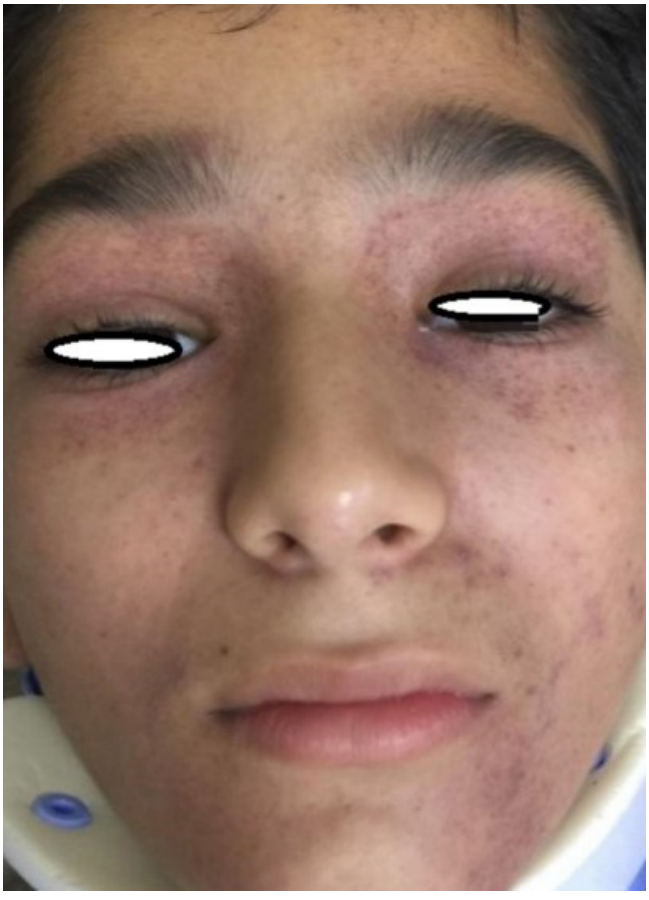

Figure 1. *The appearance of the patient's face. A lot of petechiae on his face.*

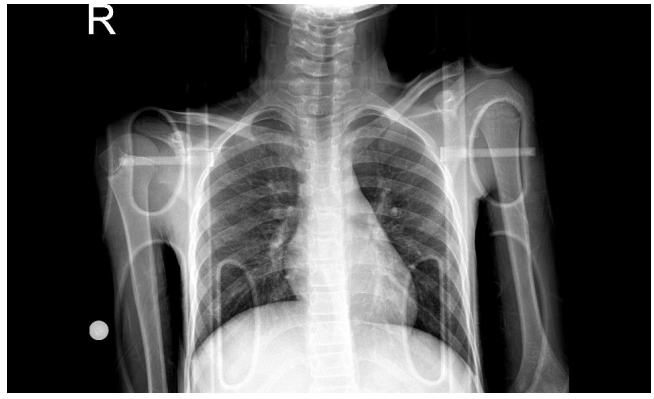

Figure 2. *Bedside antero-posterior lung radiography of the patient. Irregularity of cortical bone in the lateral 1/3 of the right clavicle.*

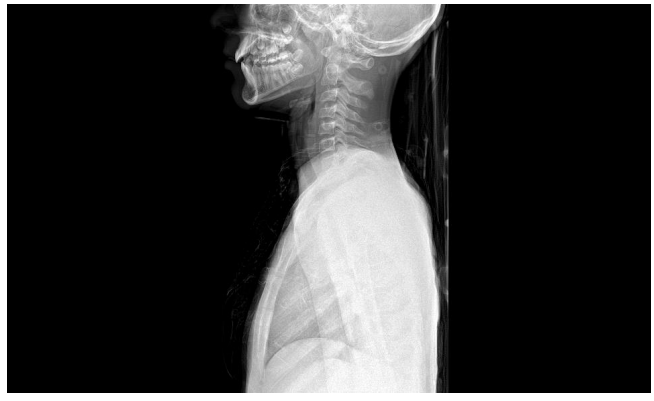

Figure 3. *Lateral cervical radiography*

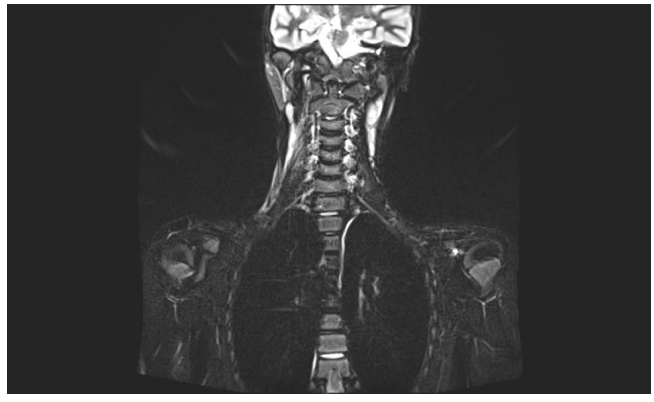

Figure 4. *Cervical magnetic resonance imaging of the patient. Edema between the subcutaneous muscle plans on the right side of the neck and the root of the C_6 nerve.*

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3. DISCUSSION

Traumatic injuries are the most common cause of brachial plexus paralysis (BPP) in children and adults [3]. Motor vehicle accidents, industrial accidents, objects falling on a shoulder, sports injuries, falls and prolonged pressure on the plexus during deep sleep are among the many causes of brachial plexus injuries [3,4]. Rarely, BPP may develop after TA [5,6].

The main pathophysiological mechanism in TA is the increase in the pressure in the thorax due to a sudden and severe force on the chest and upper abdomen resulting in the rapid passage of blood in the right atrium to the valveless jugular and innominate veins in the head and neck region and the occurrence of small bleeding in the vein bed [7]. It is emphasized in the literature that the most likely cause of injury to the brachial plexus may be hypoxia in the injured area due to trauma to the upper body and shoulder, but the effect of hypoxia has not been clearly demonstrated [2,3].

BPP develops according to the underlying causes of compression, transection, ischemia, inflammation, metabolic abnormalities, neoplasia, and radiation therapy in this region. Since, this region is protected under the bone structure, nerve compression rarely occurs by direct compression of this region. Excess transaction of the nerve is also often seen in major trauma due to high-energy traction. The mechanism of trauma causes nerve roots to rupture, leading to the emergence of a clinical condition. Ischemia is a condition caused by obstruction of small intraneural vessels and is a common pathophysiological condition for inflammatory, metabolic and radiation-induced plexopathies. Ischemia causes localized axon damage and denervates muscle and skin receptors [8,9]. In our opinion, as in ischemia-related brachial plexus injuries, intramural vessel occlusion due to the sudden increase in intravenous pressure in TA cases may cause the development of brachial plexus lesions. Also, cytotoxic edema due to hypoxia caused by asphyxia may result in compression of nerve roots. In cases with plexus injury on physical examination, if the mechanism of trauma is appropriate, root avulsions should be considered and excised with imaging methods. Cytotoxic edema caused by hypoxia may be the most important pathophysiologic mechanism in cases where avulsion cannot be detected.

Agitation, loss of consciousness, confusion, or seizures have been reported after TA. It has been reported that this clinical situation develops due to indirect injury after anoxic damage, ischemia or increased vascular pressure and cerebral edema secondary to venous obstruction [10-12].

Traumatic asphyxia has almost good prognosis, if the compression is brief [2,13]. In cases without accompanying injuries death may occur due to prolonged compression, hypoxia and apnea. It heals spontaneously within weeks except the neurological and ocular signs [1,14,15]. There is no clear information about the follow-up period of these cases in the literature. Because the course of the disease depends on the severity of the trauma and accompanying additional injuries, it is appropriate to determine the follow-up period for each patient [1,16].

The number of BPP patients with TA is very few and most of them are adult cases. Neurological abnormalities were reported in 85% (29 patient) of 34 patients with neurological sequelae (loss of consciousness, brachial plexopathy, visual disturbances, paralysis, confusion, seizures) who were evaluated as TA; BPP in seven cases (21%). Three patients had mild residual muscle weakness, while others recovered completely [5]. In this study, no information was given about the follow-up period of these patients. However, it is reported in the literature that mild neurological findings usually regress within 24-48 hours [10-12].

In a study in which 14 TA cases were evaluated, it was reported that a 42-year-old patient developed post-traumatic consciousness, blindness, confusion and BPP and neurological improvement was 15 months later. In this case series, no pediatric cases with BPP after TA were reported. Follow-up was established for all 14 patients from 6 to 117 months (mean, 41 monts). There was no long-term disability related to TA and there were no late sequelae releated to neurologic abnormalities. [5]. Since, our case was out of follow-up after three months of follow-up, its long-term effects could not be followed.

In our case, BPP was developed after TA which was not reported before in a pediatric case in the literature according to our knowledge. Brachial plexus injury is a condition that can occur with many different mechanisms. Brachial plexus injuries are of four types: avulsion, rupture, axonogenesis, and neuropraxia [17]. While lesions such as axonogenesis and neuropraxia heal spontaneously, avulsion injuries cannot heal spontaneously [18]. These injuries should be differentiated before treatment. Generally, surgical treatment is required if no improvement is noted within 2-3 months. Since, primary repair of avulsion injury is not possible, the option of nerve reconstruction should be considered [19].

As a conclusion, cytotoxic edema caused by asphyxia without avulsion of nerve roots after trauma can cause BPP. We made the diagnosis of BPP that developed after trauma in our patient with the results of EEG and MRI examinations after clinical evaluation. In our case, no avulsion was detected with the MR results. Surgical intervention was not considered in our patient because no avulsion was detected. Follow-up was taken with the physical therapy and rehabilitation plan. However, the family left the hospital follow-up after three months of follow-up. However, the absence of avulsion should be demonstrated by radiological methods and the patient should be monitored for long-term sequelae. The period of monitoring should be decided according to the patient's clinical status.

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Informed consent: Written informed consent was obtained from patient's father for anonymized patient information to be published in this article.

Human rights: All procedures were performed in **accordance** with basic ethical principles.

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Bilateral variations of the great saphenous vein

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ABSTRACT

The great saphenous vein is the longest in the human body and has been one of the most preferred autologous tissue in bypass surgery. It is affected by the life conditions causing pathological dilatations called varices. We observed bilaterally duplicated great saphenous vein in both lower limbs of an elderly male human cadaver during our routine dissection for undergraduate anatomy education. After a detailed inspection of the veins at both sides, we measured and illustrated the variant branches. In this case report, we presented bilaterally duplicated great saphenous veins, accompanied by an accessory saphenous vein. To the best of our knowledge, there are no such variations reported in the literature so far. We think that recognizing this and such variations before surgery will increase success.
Keywords: Great saphenous vein, Bilateral variation, Cadaver

1. INTRODUCTION

The great saphenous vein (GSV) starts from the medial marginal vein of the dorsal venous arch of the foot and ascends to the lower extremity's medial side. It drains into the common femoral vein below the inguinal ligament [1]. GSV is the longest superficial vein in the human body used as an autologous tissue in coronary artery bypass surgery due to its structure rich in elastic and muscular fibers [2]. Conversely, the GSV and its branches are prone to venous insufficiency resulting in varicose veins, a condition treated with high ligation, stripping, or radiofrequency thermoablation. Thus, knowledge of the morphological features and concomitant structures (especially saphenous nerve) of the GSV is crucial.

In our department, routine dissections performed in a 60-year-old male human cadaver revealed GSV variations in both lower extremities.

2. CASE REPORT

Herein, we report GSV variations in both lower extremities of a 60-year-old male human cadaver during routine dissection for the medical undergraduate students. In the right lower extremity, at 145 mm above the medial malleolus, a 540-mm-long GSV was divided into a thin medial (with a diameter of 1 mm in the leg and 2 mm in the thigh) and a thick lateral (with a diameter of 3 mm in the leg and 6 mm in the thigh) branches, reunited and drained into a common femoral vein (15.2 cm long and 7 mm thick). An accessory saphenous vein (ASV) was observed in the thigh region (Fig 1). In the left lower extremity, at 140 mm above the medial malleolus, a 112-mm-long GSV was divided into a thick medial (with a diameter of 3 mm) and a thin lateral (with a diameter of 2 mm) branch. These adjacent branches ascended proximally along 88 mm and at 485 mm in length, were divided into thick medial (with a diameter of 3.5 mm) and thin lateral (with a diameter of 3 mm) branches, similar to the leg region, and finally drained into the femoral vein separately (Fig 2).

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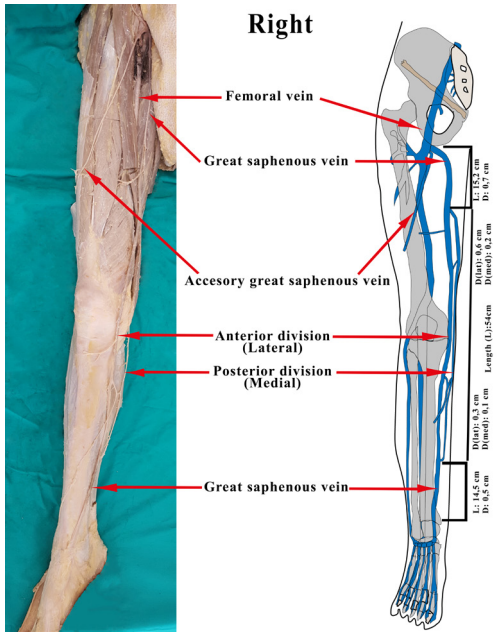

***Figure 1**. A photograph and an illustration of the variation of the right great saphenous vein and the accessory saphenous vein on the right thigh. D, diameter; D (lat), diameter of the lateral division; D(med), diameter of the medial division; L, length.*

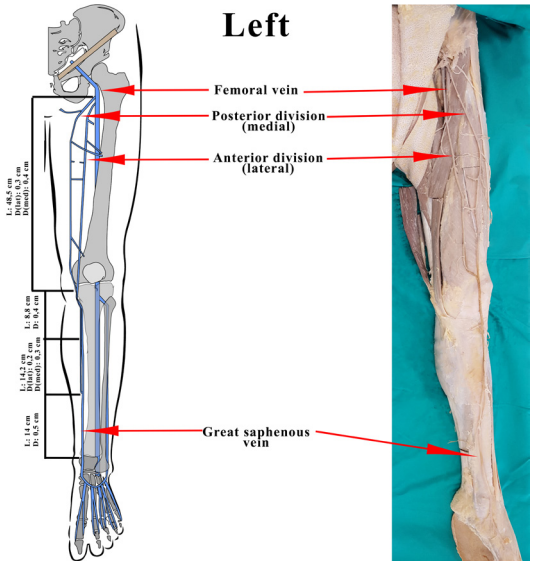

***Figure 2.** A photograph and an illustration of the variation of the left great saphenous vein. D, diameter; D(lat), diameter of the lateral division; D (med), diameter of the medial division; L, length.*

3. DISCUSSION

The frequency of variations observed in venous anatomy causes difficulties in nomenclature and teaching. GSV duplication has been reported unilaterally [3], complete [4], or segmental [5]. However, as far as we know, bilateral duplication has not been reported in the literature yet [6]. They are also unique in that they differ from each other according to how they drain into the common femoral vein.

On the other hand, to the best of our knowledge, ASV variation in the right lower extremity has not been reported so far. In a recent study, it has been reported that accessory veins in the lower extremity negatively affect superficial venous thrombus treatments [7]. For this reason, defining this variation seen in our case may be useful in thrombophlebitis treatment.

Variations in this structure are important in clinical conditions such as harvesting as a graft for coronary bypass surgery [8]. The larger the graft's diameter, the more successful the surgical procedure [9]; accordingly, variations with a bifurcation of narrow vessels have been associated with poor outcome of surgery [10]. Besides, duplicated GSV cases have been reported to cause recurrent varicosities [11].

In conclusion, awareness of this variation in surgical and medical treatment processes will reduce its potential negative effects.

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