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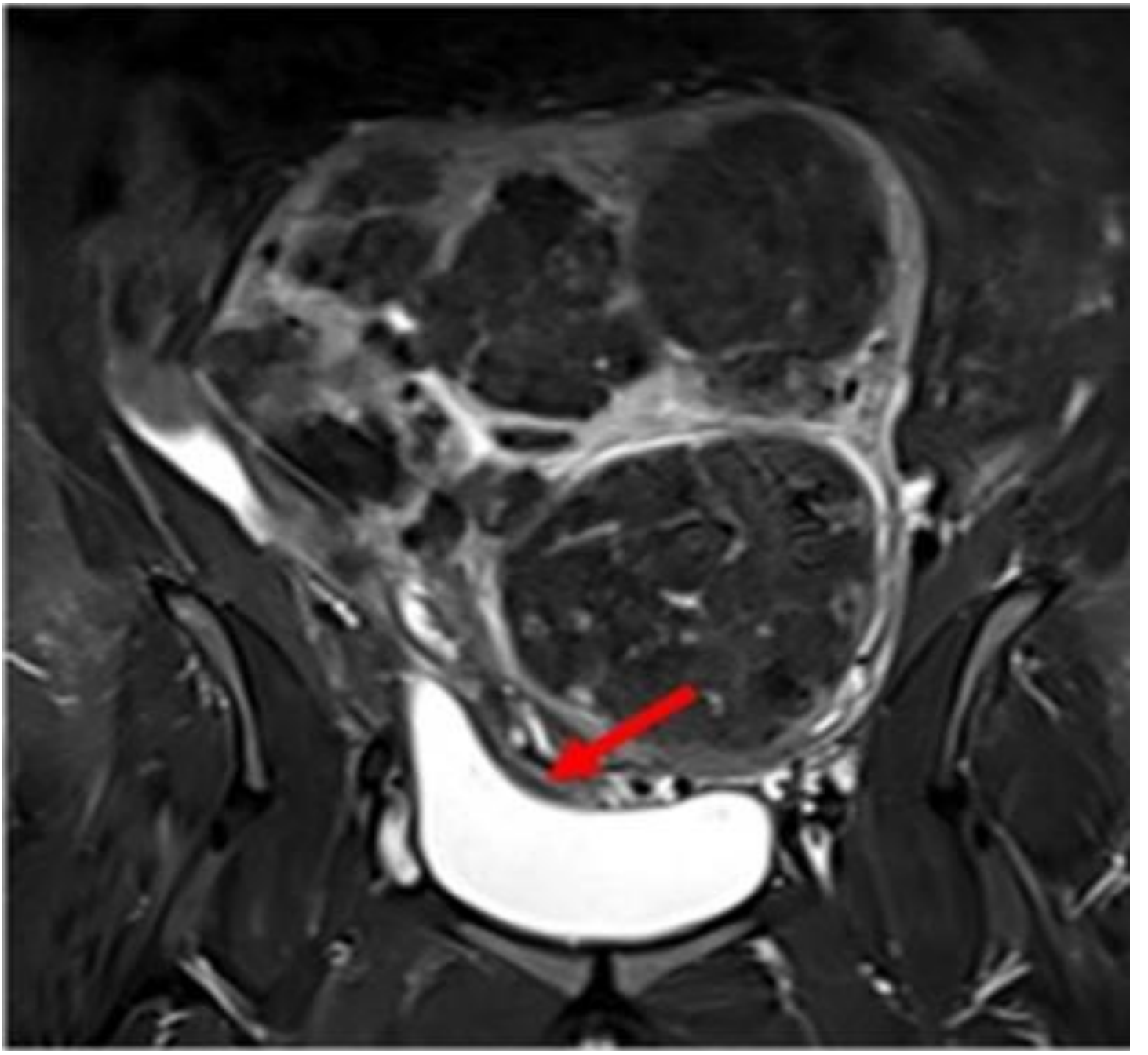

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Criteria for choosing anticoagulant therapy in COVID 19 patients

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ABSTRACT

Objective: While COVID-19 continues to circulate around the world, there are still many uncertainties on how to treat patients infected with the potentially deadly virus and, more importantly, for how long!

COVID-19 causes many different symptoms, among which coagulopathy seems to play an essential role in the survival prognosis of patients. While WHO recommends thromboprophylaxis in all admitted covid patients, it is still not routinely used in many medical centers worldwide. It is also worth mentioning that there is no animosity on the anticoagulant agents' choice or the duration they should be prescribed. Recent data suggest that it is wise to prescribe a prophylactic dose of anticoagulant for a minimum of 3 months post-discharge to minimize the risk of thrombosis in COVID-19 patients.

Keywords: COVID-19, Thrombosis, Coronavirus, SARS-cov-2, coagulopathy, anticoagulants, DVT

INTRODUCTION

While COVID-19 continues to circulate around the world, there are still many uncertainties on how to treat patients infected with the potentially deadly virus and, more importantly, for how long!

COVID-19 causes many different symptoms, among which coagulopathy seems to play an essential role in the survival prognosis of patients.

MATERIALS and METHODS

A search was conducted through PubMed and Google Scholars using the keywords COVID-19, coagulopathy, thromboprophylaxis, thrombosis, and deep vein thrombosis.

While WHO recommends thromboprophylaxis in all admitted Covid patients (1), it is still not routinely used in many medical centers worldwide. It is also worth mentioning that there is no animosity on the anticoagulant agents' choice or the duration they should be prescribed. Recent data suggest that it is wise to prescribe a prophylactic dose of anticoagulant for a minimum of 3 months post-discharge to minimize the risk of thrombosis in COVID-19 patients (2, 3).

What is the Most suitable pharmacotherapy agent for COVID-19?

COVID-19 Hypercoagulable state has a specific inflammatory character which in some cases leads to thrombosis even in case of full-dose anticoagulant(4) therapy in hospitalized patients(4).

SO we need to define Criteria for an Ideal anticoagulant Agent for preventing COVID-19 induced Thrombosis.

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Preventing Thromboembolic Events

Any agent used for thromboprophylaxis should effectively prevent clot formation and thrombosis. Low Molecular weight Heparins (LMWs) are currently the mainstay of preventing thromboembolic events in COVID-19 patients. In some cases, such as severe kidney dysfunction, as well as in the case of severely ill patients, Unfractionated heparin is used.

On the other hand, Direct Oral Anticoagulants such as Aparoxaban are getting more popular, especially for Post-hospital prevention of thromboembolic events.

However, emerging information suggests that hospitalized patients with SARS-COV-2 infection can still develop thromboembolic events despite the therapeutic dose of anticoagulant therapy with current agents (5).

Wide therapeutic Window

Practically all currently used anticoagulant agents have relatively a narrow therapeutic window; this is especially of great concern in COVID-19 patients, who are more prone to bleeding due to the COVID-induced coagulopathy (6).

Well tolerable and appropriate for long-term use

Heparin is one of the oldest biological medicines and has an established place in preventing and treating venous thrombosis (7). Its long-term use may lead to severe side effects such as thrombocytopenia and Osteoporosis. LMWHs also may cause Osteoporosis, and as they are excreted through kidneys, LMWHs are contraindicated in patients with severe kidney dysfunction. Furthermore, both aforementioned classes need to be administered parentally, making them difficult to use for the post-discharge period. On the other hand, although the use of direct oral anticoagulants as a prophylactic measure seems to a good choice in terms of compliance and ease of intake, it is associated with a relatively high risk of bleeding(8).

Have an antidote in case reversal is needed

An ideal agent should have an effective antidote, as COVID-19 induced coagulopathy may need a reversal of anticoagulant agents. While protamine sulfate may completely reverse the heparin effect, its reversal impact on LMWs is only partial at best. In terms of DOCS, there are currently two reversal agents available, Idarucizumab for the reversal of Dabigatran and Andexanet alfa for the reversal of Rivaroxaban and apixaban. So in severe cases, patients may require prothrombin complex concentrates (9).

Anti-inflammatory effects

Cumulative evidence points to the inflammatory nature of the COVID-19 induce hypercoagulable state (10,11). Hence, it is essential that the pharmacotherapeutic agents used to prevent COVID-19 related thrombotic events have strong anti-inflammatory properties.

Heparin, LMWS, and DOACS all have shown noticeable but not sufficient anti-inflammatory properties to tackle the viral-related thrombo-inflammation (12–14).

DISCUSSION

While the current treatment protocols fail to fully prevent thrombosis in COVID-19 hospitalized patients, changing the administration route could help potentiate the anticoagulatory effect of the medications while reducing the possible complications. A good example is the case of nebulized heparin, where the medications are delivered directly into the lung and can prevent and even resolve the microhrombotic events in the lungs (15,16).

Another interesting agent that has been used off-label among other indications for treating reperfusion injury and diabetic microvascular complications is Sulodoxide (17), which has, among other properties, Antiogulant, antiaggregant and anti-inflammatory properties (18). It can be injected or taken by mouth as heparin sulfate, a member of the short heparin family, can readily pass through the enterocytes and get into circulation.

CONCLUSION

To conclude, while there has been good progress in identifying and treating the thromboembolic complications of COVID-19, there is currently no clear pharmacologic agent that could completely address the hypercoagulable state induced by SARS-COV2 infection. Hence more research is required in order to identify and address the mechanisms through which the thrombo-inflamation could be adequately managed. Furthermore, guidelines need to include a post-discharge thromboprophylactic regimen to prevent late-onset thrombosis.

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Author Contributions: HMSP, DY, SV: Study design, Literature review, Data collection and processing, **HSMP:** Writing, Revisions

Ethical approval: All procedures performed in studies involving human participants were in accordance with the institutional and/or national research committee's ethical standards and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Changes in glycocalyx related biochemical parameters during lung resection in non-small cell carcinoma cases: A pilot study

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ABSTRACT

Objective: Non-small cell lung cancer (NSCLC) is one of the most common neoplasms with high mortality rates, and new studies are needed to understand its characteristics better. This study aimed to determine the changes in the glycocalyx structure related to surgery regarding histopathologic subtypes and to evaluate the correlation of these changes on the development of metastasis and mortality.

Material and methods: Serum levels of hyaluronan, VEGF-A, FGF-10, BMP-2, and BMP-4 were measured before and after surgery in 42 patients with NSCLC. The alterations in serum levels of studied markers were evaluated as related to metastasis status and mortality in post-operative 18-24 months.

Results: Our study included 15 adenocarcinoma and 27 squamous cell carcinoma cases. Pre- and post-operative values of serum hyaluronan, VEGF-A, FGF-10, and BMP-2 showed significant differences for the whole group (p=0.006, p=0.001, p=0.002, and p=0.004, respectively). Post-operative BMP-2 values also correlated with hyaluronan and VEGF-A values. Post-operative values of hyaluronan and VEGF-A values found incorrelation with metastasis and mortality, while BMP-2 with metastasis and FGF-10 with mortality. Serum values of hyaluronan, VEGF-A, FGF-10 and BMP-2 differed significantly in-between the pre- and post-operative measurements in adenocarcinoma cases (p=0.020, p=0.009, p=0.003, and p=0.011, respectively) , but not that of squamous cell carcinoma.

Conclusion: Pre- and post-operative changes in serum hyaluronan, VEGF-A, FGF-10 and BMP-2 values may be associated with metastasis and/or mortality in NSCLC. These findings were also more prominent in adenocarcinoma cases, though further extended studies are needed for a better conclusion.

Keywords: Non-small cell lung cancer, Surgery, Glycocalyx, Hyaluronan, VEGF-A, FGF-10, BMP-2, BMP-4

INTRODUCTION

Lung cancer is one of the most common and fatal neoplasms in the World. Unfortunately, most of the lung cancer patients are still diagnosed in advanced stages. The 5-year survival rate of patients with stage I non-small cell lung cancer (NSCLC) is 54.8%, while that of patients with stage IV is 4.2% 1. Due to the high mortality rates in lung cancer despite advanced treatment modalities, new scientific strategies are being developed to determine the prognosis (1, 2) .

Glycocalyx is a gel-like layer that covers the luminal surface of vascular endothelial cells, and maintains the homeostasis of the blood in the vascular system interacting with mechanotransduction, signaling, and blood cell–vessel wall interactions. Glycocalyx also composed of glycoproteins and proteoglycans in structure, and glycosaminoglycans (heparan sulfate, chondroitin sulfate, hyaluronan) are also closely related to this structure (3). Interestingly, hyaluronan, fibroblast growth factor (FGF) and VEGF (vascular endothelial growth factor), which are included in the functional structure of the glycocalyx, are among the biochemical markers studied in prognosis of lung cancer (4-6). Bone morphogenetic proteins (BMPs) play a role not only in embryonic and postnatal development, but also in tumor development and spread. Several experimental and clinical studies have also demonstrated the correlation between serum levels of BMP-2 or BMP-4 with poor prognosis or metastasis in NSCLC (7).

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Some studies have shown that glycocalyx damage may occur during the operations in patients with acute care surgeries as well as pulmonary resections (8, 9). In our literature review, we could not find out a prospective study on the possible relationship in-between the glycocalyx injury and the metastasis and mortality of cancer, in patients with NSCLC undergoing pulmonary resection.

The aim of this study is to determine the changes in serum markers (hyaluronan, VEGF-A, FGF-10) and molecular prognostic factors (BMP-2, BMP-4) of endothelial glycocalyx damage during surgery in NSCLC. In addition, we aimed to examine the relationship between the studied markers and post-operative mortality and metastasis.

MATERIAL and METHODs

This prospective cohort study was conducted in the Thoracic Surgery Department of Aydın Adnan Menderes University Medical Faculty Hospital between 2018-2021 after the approval of the ethics committee (2018/1444). Patients with NSCLC and scheduled for elective segmentectomy, lobectomy or pneumonectomy were included in the study after obtaining the informed consent. The exclusion criteria were; patients with primary lung cancers other than NSCLC, metastatic cancers, body mass index > 35 kg/m2, heart failure (>New York Heart Association class II), pulmonary hypertension, clinically severe obstructive or restrictive lung diseases or existence of coagulation disorders.

Pre-operative Evaluations, Anesthesia and Surgical Technique

In all cases, pulmonary function tests, blood gas analysis, and if necessary, V/Q (ventilation/perfusion) scan were performed to evaluate respiratory physiology in the pre-operative period. A 6-minute walk test was performed for cardiac evaluation, and in high-risk patients, a cardiology consultation with additional examinations was performed. All patients underwent thoracic computed tomography (CT scan) and positron emission tomography (PET) scanning to evaluate their AJCC designated staging by TNM (tumor, node, metastasis) classification to define NSCLC and the resectability of pulmonary malignancies before surgery (10) . For histopathological diagnosis flexible bronchoscopy was performed in all cases and also transthoracic needle aspiration biopsy under radiological guidance was achieved in appropriate cases.

All patients received 0.02 mg/kg midazolam for premedication. For general anesthesia induction, 1.5-2.5 mg/kg propofol, 1 µg/kg fentanyl and 0.8 mg/kg rocuronium were used. Tracheal intubation was performed with a double-lumen endotracheal tube, and the correct position of the tube was confirmed by fiberoptic bronchoscopy. Maintenance of anesthesia was provided by 0.1-0.4 µg/kg/min infusion of remifentanil and 0.5-2% sevoflurane. The patients were placed in the lateral decubitus position, and single lung ventilation (OLV) was started. After the resection was completed, double lung ventilation was started again. During the operation all fluid and blood treatments, hemodynamic data, vasoactive drug usage, and urine quantities of the patients were recorded.

Open thoracotomy was performed in our patients with a standard muscle-sparing posterolateral approach. During surgery, pulmonary resection (segmentectomy, lobectomy or pneumonectomy) with radical mediastinal lymph node dissection was performed in all cases after the malignancy was confirmed by examination of the frozen sections.

Biochemical Analysis of Specific Serum Proteins

All blood samples were obtained from the central vein catheter; first 15 minutes after anesthesia induction, just before the operation and then in the first hour after the operation and serum levels of hyaluronan, VEGF-A, FGF-10, BMP-2 and BMP-4 were measured. The correlation between pre- and post-operative changes in serum levels of these markers and the development of metastasis and mortality were evaluated.

An enzyme-linked immunosorbent assay (ELISA) was used to detect hyaluronan, VEGF-A, FGF-10, BMP-2 and, BMP4 levels in the collected blood serum samples. After centrifugation at 3500 rpm for 5 min at room temperature, the serum samples were stored at -80˚C until the tests were studied. All samples were thawed only once before use.

Serum hyaluronan levels were analyzed by using Human Hyaluronic Acid (HA) ELISA Kit-Sunred Catalogue NO: 201-12-1375 with inter-assay CV:<12%, and intra-assay CV:<10%, respectively. The mean detectable dose (MDD) of human HA was 2.113 ng/mL.

Serum VEGF-A levels were analyzed by using Human Vascular Endothelial Cell Growth Factor A (VEGF-A) ELISA Kit-Sunred Catalogue NO: 201-12-0051 with inter-assay CV: <12% and intra-assay CV: <10%, respectively. The MDD of human VEGF-A was 2.677 pg/mL.

Serum FGF-10 levels were analyzed by using Human Fibroblast Growth Factor 10 (FGF-10) ELISA Kit-Sunred Catalogue NO: SRB-T-81339 with inter-assay CV: <12% and intra-assay CV: <10%, respectively. The MDD of human FGF-10 was 4.451 ng/mL.

Serum BMP-2 levels were analyzed by using Human Bone Morphogenetic Protein 2 (BMP-2) ELISA Kit-Sunred Catalogue NO: 201-12-1990 with inter-assay CV: <12% and intra-assay CV: <10%, respectively. The MDD of human BMP-2 was 1.233 ng/L.

Serum BMP4 levels were analyzed by using Human Bone Morphogenetic Protein 4 (BMP4) ELISA Kit-Sunred Catalogue NO: 201-12-1991 with inter-assay CV:<11%, and intra-assay CV:<8%, respectively. The MDD of human BMP was 0.927 ng/L.

Clinical Follow-up & Detection of Metastases

Before and after surgical resections, all patients' physical examinations and follow-ups were performed by both the thoracic surgeon and a clinical oncologist. The patients were followed up with clinical examinations as well as radiological evaluations (chest x-ray, CT scans, PET) in the post-operative third month and then by three to four months intervals in the first two years. Only the results of the first post-operative two years of follow-up periods were evaluated in this study. If suspected lesions were detected, further evaluations and histopathological confirmation were performed as necessary.

Statistical Analysis

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The Kolmogorov-Smirnov test was used to assess the normality of numeric variables. For variables that weren't normally distributed, Wilcoxon T or Mann–Whitney U tests made comparisons between paired or independent two groups. Descriptive statistics are presented as mean ± standard deviation, median (25-75 percentiles) and frequency. Spearman correlation test was used to determine the relationship between biochemical markers and long-term metastasis and mortality. The p values below 0.05 were considered as statistically significant.

RESULTS

Our study included 15 adenocarcinoma and 27 squamous cell carcinoma cases. The demographical and clinical characteristics of the patients are summarized in Table 1. During the post-operative 18-24 months of follow-up, distant organ metastases (in the brain, liver, bones and opposite lung) were observed in 9 (21.4%) patients and death was observed in 7 (16.7%). The gender and age of the patients, histopathologic subtype, and stage of the cancer were not associated with the development of metastasis or mortality in the first two years of the post-operative follow-up (p>0.05 for all). Also the type of operation, operation time and the length of stay in the ICU in the post-operative period were not associated with the development of metastasis or mortality (p>0.05 for all).

Pre- and postoperative serum hyaluronan, VEGF-A, BMP-2, and FGF-10 values had differed significantly (p=0.006, p=0.001, p=0.004, and p=0.002, respectively) (Table 2). These differences between the measured values were not found to be related with either the gender or ages of the patients and the stage of the cancer (p>0.05). Also, the type of operation, operation time and length of stay in the ICU were not associated with these measurements significantly (p>0.05). According to the pre-operative values hyaluronan, VEGF-A, FGF-10, and BMP-2 values changed significantly in post-operative measurements in adenocarcinoma cases (p=0.020, p=0.009, p=0.003, and p=0.011, respectively), while there was no difference in squamous cell carcinoma (Table 3).

A significant difference was found between metastasis development and post-operative hyaluronan, VEGF-A and BMP-2 values (p= 0.001, p=0.002, and p=0.009, respectively) (Fig. 1A, B and C). Mortality was also found to be associated with post-operative hyaluronan, VEGF-A and FGF-10 values (p=0.001, p=0.001, and p=0.049, respectively) (Fig. 2A, B, and C). After the operation, VEGF-A values were correlated with hyaluronan and BMP-2 values (p=0.0001, r= 0.687 and p=0.0001, r=0.528, respectively), while hyaluronan values were also correlated with BMP-2 values (p=0.0001, r= 0.543).

Table 1. Demographical and Clinical Characteristics of Patients

Cancer Histopathology (n / %)	**SCC*** 27/62.8	**AC**** 15/37.2	**All** 42/100	**P value**
Age; (Mean±SD) (years)	64.18±7.24	65.46±8.5	64.64±7.6	0.503
Gender (n/%)				
Female	4/14.8	1/6.7	5/11.9	0.425
Male	23/85.2	14/93.3	37/88.1	
Stage[Ψ] (n/%)				
Ia	13/ 30.1	5/ 11.9	18/ 42	
Ib	2/ 4.7	1/ 2.3	3/ 7	
IIa	3/ 7.2	2/ 4.7	5/ 11.9	0.355
IIb	3/ 7.2	2/ 4.7	5/ 11.9	
IIIa	5/ 11.9	5/ 11.9	10/ 23.8	
IIIb	1/ 2.3	0/ 0	1/ 2.3	
Operation type (n/%)				
Segmentectomy	2/ 4.7	1/ 2.3	3/ 7	0.09
Lobectomy	18/ 42.8	14/ 33.3	32/ 77.1	
Pneomonectomy	7/ 16.6	0/ 0	7/ 16.6	
Mortality (n/%)	5/ 11.9	2/ 4.7	7/ 16.6	0.669
Metastasis (n/%)	6/ 14.2	3/ 7.1	9/ 21.3	0.868
Duration of Operation (Mean± SD) (minutes)	294±12.6	298±18.82	295.83±17.53	0.094
Duration of ICU[Ω] **stay**				
Median (Min-Max) (days)	2.5 (0-114)	2.2 (2-103)	2.3 (0-114)	0.124
Per centile 25-75	2-3	2-3	2-3	

* Squamous Cell Carcinoma, ** Adenocarcinoma, [Ψ] The AJCC, TNM (tumor, node, metastasis) classification to define NSCLC (10), [Ω] Intensive Care Unit, n=number, %= percentage of cases of the same histopathology

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Table 2. Pre- and Post-Operative Marker Levels of All Patients

Marker	Pre-operative	Post-operative	P values
Hyaluronan (ng/mL)			
Median	65.21	77.71	0.006
Min-Max	38.59-188.14	44.30-432.87	
Percentile	59.03	61.20	
25 75	91.82	168.99	
VEGF-A (pg/mL)			
Median	45.91	52.56	0.001
Min-Max	8.99 – 98.58	22.83 - 625.72	
Percentile	29.90	95.02	
25 75	52.96	170.59	
BMP-2 (pg/mL)			
Median	60.02	69.51	0.004
Min-Max	28,22- 199.97	27.50-420.20	
Percentile	45.72	49.31	
25 75	67.57	147.81	
BMP-4 (pg/mL)			
Median	76.76	72.20	0.069
Min-Max	14.07-292.67	18.75-273.37	
Percentile	64.81	65.38	
25 75	103.38	84.74	
FGF-10 (pg/mL)			
Median	445.74	324.49	0.002
Min-Max	103.75-1351.86	70.68-991.44	
Percentile	217.01	163.56	
25 75	602.28	539.91	

Table 3. Pre- and Post-Operative Marker Levels and Histopathologic Subtypes

	Pre-operative Median (percentile 25%-75%)	**Post-operative** Median (percentile 25%-75%)	P values
	Adenocarcinoma		
Hyaluronan (ng/mL)	67,71 (59,19-93,55)	75,19 (62,67-171,89)	**0,020**
VEGFA (pg/mL)	42,59 (17,85-57,07)	61,89 (22,83-135,50)	**0,009**
BMP2 (pg/mL)	59,63 (46,7-67,52)	72,36 (50,68-148,31)	**0,011**
BMP4 (pg/mL)	76,22 (68,09-103,17)	73,12 (66,13-91,04)	0,061
FGF10 (pg/mL)	465,59 (313,4-607,45)	335,2 (220,39-542,48)	**0,003**
	Squamous Cell Carcinoma		
Hyaluronan (pg/mL)	62,65 (58,57-91,25)	80,24 (59,19-168,54)	0,156
VEGFA (pg/mL)	48,35 (11,78-74,99)	75,31 (16,68-99,53)	0,069
BMP2(pg/mL)	61,41 (42,69-67,72)	67,31 (45,99-143,2)	0,112
BMP (pg/mL)	80,92 (63,29-104,02)	71,74 (59,9-82,66)	0,609
FGF10 (pg/mL)	322,05 (157,11-557,98)	244,45 (132,22-477,29)	0,256

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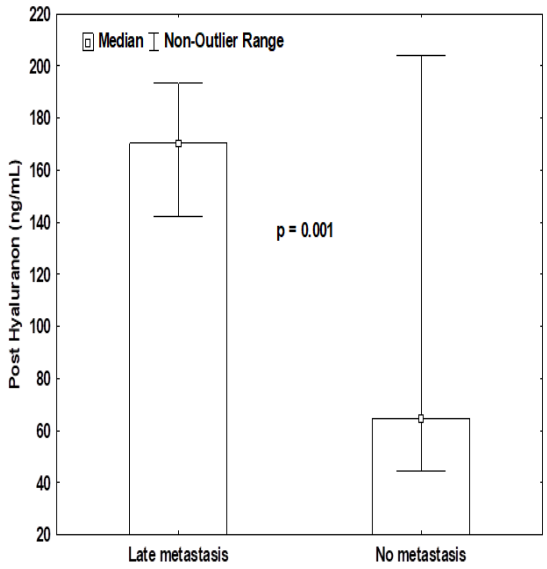

Figure 1A. Postoperative Hyaluronan Levels and Metastasis

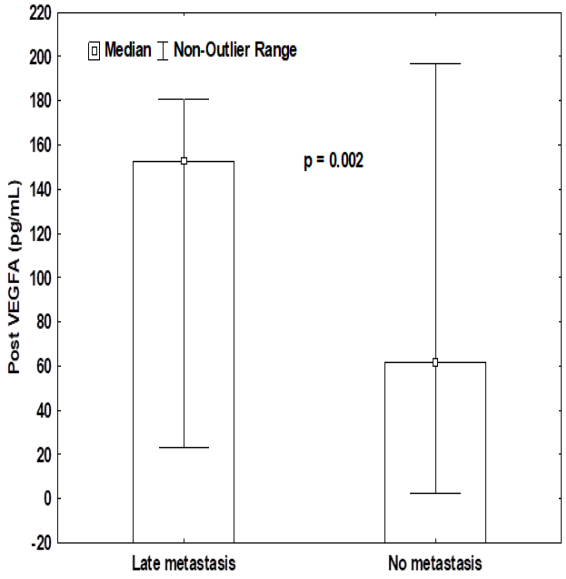

Figure 1B. Postoperative VEGF-A Levels and Metastasis

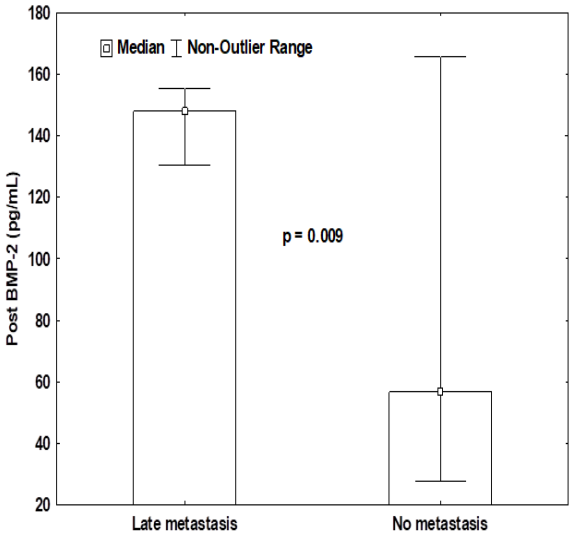

Figure 1C. Postoperative BMP-2 Levels and Metastasis

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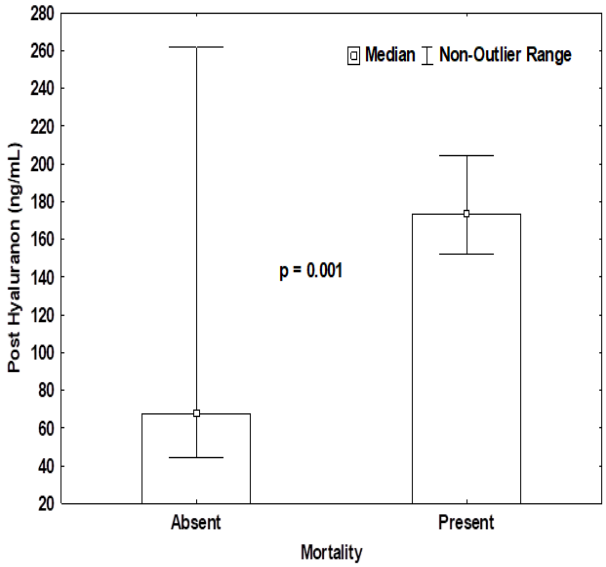

Figure 2A. Post-operative Hyaluronan Levels and Mortality

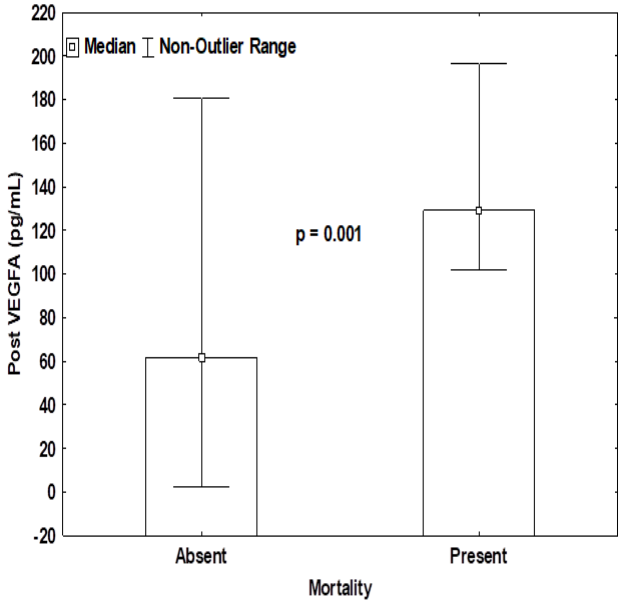

Figure 2B. Postoperative VEGF-A Levels and Mortality

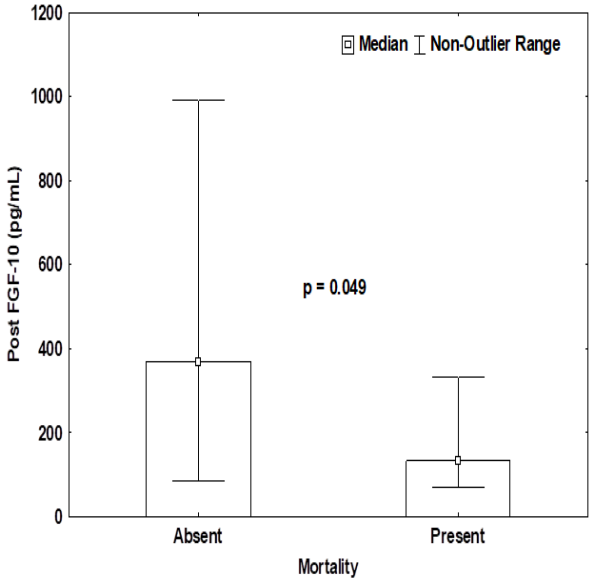

Figure 2C. Postoperative FGF-10 Levels and Mortality

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DISCUSSION

In this study, significant changes were observed in serum levels of glycocalyx products (hyaluronan, VEGF-A and FGF-10) and molecular prognostic factors (BMP-2) during pulmonary resection operations in NSCLC patients. The differences were more prominent in adenocarcinoma cases, but not in squamous cell carcinoma. Another important finding was found in relationship between the studied biochemical parameters and metastasis development (hyaluronan, VEGF-A and BMP-2) as well as the mortality (hyaluronan, VEGF and FGF-10).

The endothelial glycocalyx plays an important role in homeostasis by regulating vascular permeability and reducing inflammation and coagulation. The endothelial glycocalyx structure includes membrane-bound (proteoglycan-fixed) sulfated glycosaminoglycans such as heparan sulfate and chondroitin sulfate, and non-sulfated (non-proteoglycan-bound) glycosaminoglycan hyaluronan (3) . In some vascular diseases such as atherosclerosis, stroke, hypertension, kidney diseases and sepsis, the glycocalyx is damaged and this causes increased level of glycocalyx components in the blood circulation (11) . Acute care surgery may also result with glycocalyx damage during the operation (8,9) . Inflammatory reactions caused by ischemia-reperfusion injury, hypoxia-reoxygenation and tissue trauma during the single lung ventilation for pulmonary resection surgeries may cause damage of the alveolocapillary glycocalyx (9,12) . Similarly, in this study, an increase was observed in the hyaluronan serum levels as an endothelial glycocalyx breakdown biomarker in the post-operative period. While hyaluronan has beneficial effects during normal tissue and wound healing, some forms can lead to an increase in metastasis and poor prognosis as a result of the changes in both production and disintegration processes in the presence of tumor cells (13). Several studies have shown the importance of hyaluronan in the progression of various human cancers such as breast, ovarian, colorectal, and lung cancers (4,14-16).

Increased hyaluronan levels in the stroma of NSCLC cases; especially in adenocarcinomas were shown to have significant prognostic value (17). In accordance with the literature, hyaluronan levels increased in all cases in the post-operative period in our study. Furthermore, the increase in serum hyaluronan level in the post-operative period was found to be associated with metastasis and mortality in our study. Similarly, Gong et al. (18) demonstrated that tumor hyaluronan level could be used as a novel biomarker for survival and metastasis in NSCLC in their cohort study involving 174 patients. In this study, the increase in serum VEGF-A level in the post-operative period was found to be associated with metastasis and mortality. Platelets and macrophages secrete VEGF-A in response to tissue damage in early wound healing. While VEGF promotes the growth, development and permeability of endothelial cells under normal conditions, it also increases the repair of the vascular wall in hypoxic and ischemic conditions (19). VEGF, one of the proangiogenic factors secreted by tumor cells, enables the formation of new blood vessels that feed the tumor and performs angiogenesis, a prerequisite for metastasis (20). Hyaluronan and VEGF-A are important biomarkers for the development of angiogenesis in malignancy cases (14). In our study, we found a positive correlation between hyaluronan and VEGF-A serum levels in accordance with the literature. Zhan et.al. (21) also concluded that VEGF overexpression indicates a poor prognosis for patients with NSCLC and small cell lung cancer (SCLC). In our study, we found a significant relationship in-between the rising serum VEGF levels in the post-operative period and mortality. The increment in the levels of angiogenic factors such as VEGF following oncological surgeries is important in residual tumor cell growth and metastasis. VEGF also plays a key role in wound healing, and so the increase in post-operative serum VEGF levels may reflect the extent of surgical trauma (21, 22).

Similarly, Ng et al. (22) investigated the influence of open and video-assisted thoracic surgery (VATS) lung resections for early stage NSCLC on post-operative circulating VEGF (as a circulating angiogenic factor) in their prospective study. The authors concluded that VATS might attenuate the angiogenic response by leading to lower circulating VEGF release compared to open surgery (22). However, they did not investigate the post-operative late metastasis development in NSCLC cases in their study. In our study, open surgery was performed, and a significant relationship was found between VEGF-A increments and late metastasis. In recent years, novel anticancer drugs related to hyaluronan and VEGF-A get promising results in clinical studies, though more randomized controlled studies are needed (18, 21) .

Fibroblast growth factors (FGFs) regulate many cellular functions, including migration, proliferation, differentiation, and survival. Malfunction of the FGF / FGF receptor (FGFR) signal axis can cause many diseases in the lung system, such as chronic obstructive pulmonary diseases, respiratory distress syndrome (RDS) and malignity (23). Twenty-two FGF ligands have been identified for the FGF family in humans. Of these, FGF10 can improve the lung repair and increase the epithelial survival after injury or reduce the inflammatory response after acute lung injury (ALI). It also has roles in alveolar repair and resolution in ALI or acute RDS (23, 24). In our study, serum FGF10 levels were significantly decreased in the post-operative period compared to pre-operative values, and this was also found to be associated with mortality. As in the literature mentioned above, the decrease in serum level of FGF10 during the operation may cause a decrease in its protective effect on the lung, and this may cause a risk in terms of cancer mortality.

In our study, serum BMP-2 levels increased in the post-operative period and were found to be associated with metastasis. However, no significant change was observed in BMP-4 level. BMP2 and BMP4 have been described to mediate pro-angiogenic effects and also promote tumor (ovarian, stomach, lung, colon, breast) angiogenesis through different mechanisms (24). Bieniasz et al. (7) suggested that two angiogenic factors such as VEGF and BMP-2 are interrelated and that they are important for metastasis in lung malignancy.

Our study also found a positive correlation between BMP-2 and VEGF serum levels. The weaknesses of our study can be summarized in four headings. Firstly, biochemical values could not be analyzed simultaneously in both blood samples and tumor tissues. Secondly, cases of open thoracic surgery were included in our study, and no comparison was made with video-assisted thoracoscopic surgery (VATS) cases.

CONCLUSION

In conclusion, pre-and post-operative changes in serum hyaluronan, VEGF-A, FGF-10, and BMP-2 values may be associated with metastasis and/or mortality in NSCLC. These findings were also more prominent in adenocarcinoma cases. Further extended studies are needed for a better conclusion.

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Author Contributions: SC, SS, IKO, AK, SS, SS: Study design, Literature review, Data collection and processing, **SC:** Writing, Revisions

Ethical approval: All procedures performed in studies involving human participants were in accordance with the institutional and/or national research committee's ethical standards and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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The Effect of Neuropathic Pain on Sleep Quality in Patients with Axial Spondyloarthritis

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ABSTRACT

Objective: This study aims to determine whether neuropathic pain (NP) presence affects sleep quality in patients with axial spondyloarthritis (AxSpA).

Materials and Methods: Demographic data of the patients were documented. The patient's NP was evaluated with painDETECT questionnaire. Pittsburgh Sleep Quality Index (PSQI), Ankylosing Spondylitis Quality of Life (AsQoL), Ankylosing Spondylitis Disease Activity Score (ASDAS-CRP), and visual analog scale (VAS) were used to evaluate sleep quality, quality of life (QoL), pain severity and disease activity, respectively.

Results: Among the 108 patients who participated in the researh, 51 were female and 57 were male. NP was found in 41.7% of them. 65.7% Of all patients had a sleep disorder. AxSpA patients with NP had a statistically significant higher VAS-activity, VAS-night, and VAS-rest scores ($p<0.001$, $p<0.001$, $p=0.002$, respectively). They also had higher ASQoL scores and higher disease activity. ($p=0.008$, $p=0.012$, respectively).

Although impaired sleep was detected in 71.1% of AxSpA patients with NP, it was present in 61.9% of AxSpA patients without NP, and we didn't find a statistically significant difference ($p=0.32$). Total painDETECT scores were correlated with PSQI ASQoL, and VAS scores ($p< 0.001$). But there was no correlation with ASDAS-CRP scores ($p=0.57$).

Conclusion: A large majority of AxSpA patients have a sleep problem, independent of the presence of NP. Not only targeting the inflammatory pain but also targeting NP and sleep disorder together in the follow-up of patients with AxSpA will improve QoL.

Keywords: Axial Spondyloarthritis, Neuropathic Pain, Sleep Quality, Visual Analog Scale, Quality of Life

INTRODUCTION

Axial spondyloarthritis (AxSpA) is one of the chronic rheumatic diseases. Inflammatory back pain is characteristic for AxSpA and usually has an insidious onset. At first, it is intermittent over time it turns into a permanent pain. Patients often feel pain in the lower back and buttocks (1,2). Also, some patients have reported persistent pain while in clinical remission. This condition suggests that pain in AxSpA includes neuropathic and nociceptive components in addition to inflammatory components (3–5).

Neuropathic pain (NP) was explained as ‘’pain that arises as a direct consequence of a lesion or diseases affecting the somatosensory system” (6). It consists of abnormal sensations and unpleasant symptoms (throbbing, stinging or burning, shooting pain, allodynia or hyperalgesia, numbness) (6). In the general population, the prevalance of NP was found to be 6.9% to 10% (7). This rate is increased in chronic inflammatory rheumatic diseases, and NP was reported in 26.7% in spa patients (3).

Sleep disorder was observed in AxSpA patients, at ratings varying between 35.4-50 (8,9). Stiffness and pain and in the axial spine impact sleep. Moreover, poor sleep and decreased QoL have frequently encountered problems in patients with NP (10,11).

We sought to analyze the existence of NP in AxSpA patients and the association between NP and sleep quality, quality of life (QoL), and disease activity. According to our knowledge, the current study is the first to examine how NP presence affects sleep quality in AxSpA.

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MATERIAL and METHODs

Study Design and Participants: This cross-sectional study was established between May 2020 and November 2020. Patients with AxSpA who met the ASAS AxSpA criteria were enrolled in the research (12). The local ethics committee (NO: 2020/76) gave its approval to the study protocol. All patients who participated in this study gave written, informed consent in accordance with the principles of the Declaration of Helsinki. Patients under the age of 18 and above the age of 65 were not allowed to participate in the trial. Other exclusion standards included past or present neurological, psychiatric or other chronic inflammatory diseases, acute post-acute infectious diseases, pregnancy or current breastfeeding, malignancy, and substance abuse. Patients who took part in the study underwent an interview and completed the questionnaires in the same session. Age, gender, body mass index (BMI), education level, smoking status, and treatments were among the demographic information. The patients' sleep quality, disease activity, pain severity and QoL at the outpatient admission were questioned. Two groups of patients were formed based on the existence of NP as detected by painDETECT. Accordingly, Group 1 (n = 45) was classified as those with NP (painDETECT score > 13), and Group 2 (n = 63) as without NP. The groups' quality of life, disease activity, sleep quality, and pain intensity were compared.

Materials: PainDETECT: NP symptoms were assessed by the painDETECT questionnaire. It evaluates pain qualities, pain radiation, and course of pain. Score between 0 and 12 are thought to be unlikely NP, the score between 13 and 18 is considered as possible NP, and those between 19 and 38 to be likely NP (13).

Pittsburgh Sleep Quality Index (PSQI): The index distinguishes “poor” sleep from “good” sleep. A “poor” sleeper is one with a total score of 5 or higher (14).

Ankylosing Spondylitis Quality of Life (ASQoL): It evaluates the effect of ankylosing spondylitis (AS) on patient-reported health-related QoL. A high score indicates a decreased quality of life (15).

Ankylosing Spondylitis Disease Activity Score (ASDAS): Both the subjective and objective components of disease activity are assessed by the ASDAS. It includes acute-phase reactants and patient-reported metrics (16).

Visual Analog Scale (VAS): Patients rate their level of discomfort on a scale from 0 (no pain) to 10 (the most intense pain possible) (17).

Statistical Analysis: The Statistical Package for the Social Sciences, version 25.0, for Windows (SPSS Inc; Chicago, IL, USA) was used for statistical analysis. The data were reported as mean ± standard deviation for continuous variables, and for categorical variables, as number (n) and percentage (%). The normal distribution was analyzed using the Shapiro-Wilk and Kolmogorov-Smirnov tests, however the data were not normally distributed. For intergroup analysis, Mann-Whitney U tests were used. Comparing qualitative data was done using the chi-square test. According to the data distribution, Spearman correlation analysis was used to assess the correlation between the variables. Statistical significance was defined as p 0.05.

RESULTS

A total of 108 patients—51 female and 57 male—were evaluated. **Table 1** displays the clinical data of individuals with AxSpA. In 41.7% of the patients, NP was found (23,1% had possible NP components, and 18.5% had likely NP components). 65.7% of the patients had a sleep issue. The VAS activity, VAS night, and VAS rest, scores were all statistically significantly higher in AxSpA patients with NP (p<0.001, p<0.001 and p=0.002, respectively). They also had higher ASQoL scores and higher disease activity. (p=0.008, p=0.012, respectively)

Table 1. Patient characteristics

		n (%) // median (min-max) / mean±sd
Gender	female	51 (47.2%)
	male	57 (52.8%)
Age		40 (23-65) / 41.6±10
BMI		26.3 (18-39) / 26.8±4.6
Smoking status	smoker	52 (48.1%)
	nonsmoker	56 (51.9%)
Education	primary	71 (65.7%)
	secondary	25 (23.1%)
	university	12 (11.1%)
Disease duration		48 (4-384) / 74.10±72.7
	<10years	81 (75%)
	>10years	27 (25%)
B-DMARD	none	5 (4.6%)
	adalimumab	39 (36.1%)
	etanercept	22 (20.4%)
	golimumab	14 (13%)
	sekukinumab	17 (15.7%)
	sertolizumab	11 (10.2%)
ASDAScrp		3.1 (0.4-6.0) / 3.1±1.1
	<2.1	37 (34.3%)
	>2.1	88 (81.5%)
PainDETECT		11 (0-35) / 11.4±7.8
Neuropathic pain	None (<13)	63 (58.3%)
	Likely (13-18)	25 (23.1%)
	Probable (>18)	20 (18.5%)
PSQI		6 (0-20) / 7.1±4.3
Sleep disorder	Present(PSQI≥5	71 (65.7%)
	Not present PSQI<5	37 (34.3%)
VASr		6 (0-10) / 5.5±2.7
VASa		5 (0-10) / 5.3±2.8
VASn		5 (0-10) / 5.5±2.8

BMI: body mass index; B-DMARD: biological disease-modifying antirheumatic drugs; ASDAS-crp: Ankylosing Spondylitis Disease Activity Score-crp; PSQI: the Pittsburgh Sleep Quality Index; VAS: visual analog scale (r:rest, a: activity, n: night)

The comparison of AxSpA patients according to NP presence is shown in **Table 2**. Although impaired sleep was detected in 71.1% of AxSpA+ NP patients, it was present in 61.9% of AxSpA patients without NP, which wasn’t statistically significant (p=0.32). Total painDETECT scores correlated moderately with ASQoL scores (r = 0.360, p< 0.001), VAS rest scores (r = 0.313, p<0.001), VAS activity (r = 0.437, p < 0.001), VAS night scores (r = 0.355, p<0.001) and PSQI scores (r=0.283, p<0.001). There was no correlation between painDETECT scores and ASDAS-CRP scores (r=0.183, p=0.57) (**Table 3**).

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Table 2: Comparison of groups according to neuropathic pain presence. (a) median (minimum–maximum), (b) number (percentage)

		NP (+) 45 (41.7%)	NP (-) 63 (58.3%)	p
Age[a]		42.0 (23-65)	40.0 (26-58)	0.345
Gender	Male[b]	25 (55.6%)	32 (50.8%)	0.625
	Female[b]	20 (44.4%)	31 (49.2%)	0.625
BMI [a]		26.6 (19-39)	26.2 (18-39)	0.876
Disease duration[a]		60 (6-360)	42 (4-384)	0.171
	<10years[b]	32 (77.8%)	49 (71.1%)	0.430
	>10years[b]	13 (22.2%)	14 (28.9%)	0.430
Smoking	Present[b]	22 (48.9%)	30 (47.6%)	0.896
	Not present[b]	23 (51.1%)	33 (52.4%)	0.896
ASDAScrp[a]		3.2 (1.3-6.0)	2.8 (0.4-5.0)	**0.012**
ASQOL[a]		7.0 (0-12)	5.0 (0-12)	**0.008**
VASr[a]		7.0 (0-10)	5.0 (0-10)	**0.002**
VASa[a]		8.0 (0-10)	4.0 (0-10)	**<0.001**
VASn[a]		8.0 (0-10)	6.0 (0-10)	**<0.001**
PSQI [a]		7.0 (0-20)	6.0 (0-19)	0.177
Sleep disorder	Present[b] PSQI≥5	32 (71.1%)	39 (61.9%)	0.320
	Not present[b] PSQI<5	13 (28.9%)	24 (38.1%)	

NP: neuropathic pain; BMI: body mass index; ASDAS-crp: Ankylosing Spondylitis Disease Activity Score-crp; ASQoL: Ankylosing Spondylitis Quality of Life; VAS: visual analog scale (r:rest, a: activity, n: night) PSQI: the Pittsburgh Sleep Quality Index

Table 3: Correlation between outcome parameters

		ASQOL	ASDAS crp	PSQI	PAINDETECT
yaş	rho	0,068	-0,036	,222*	0,012
	p	0,486	0,709	0,021	0,901
BMI	rho	-0,077	-0,040	0,017	-0,002
	p	0,425	0,678	0,861	0,982
disease duration	rho	0,037	0,105	0,096	0,057
	p	0,701	0,278	0,320	0,555
ASQOL	rho	1,000	,381**	,483**	,360**
	p		0,000	0,000	0,000
ASDAScrp	rho	,381**	1,000	0,120	0,183
	p	0,000		0,216	0,057
PSQI	rho	,483**	0,120	1,000	,283**
	p	0,000	0,216		0,003
PinDETECT	rho	,360**	0,183	,283**	1,000
	p	0,000	0,057	0,003	
VASr	rho	,404**	,642**	0,156	,313**
	p	0,000	0,000	0,108	0,001
VASa	rho	,447**	,595**	,275**	,437**
	p	0,000	0,000	0,004	0,000
VASn	rho	,413**	,562**	,302**	,355**
	p	0,000	0,000	0,001	0,000

BMI: body mass index; ASDAS-crp: Ankylosing Spondylitis Disease Activity Score-crp; ASQoL: Ankylosing Spondylitis Quality of Life; VAS: visual analog scale (r:rest, a: activity, n: night) PSQI: the Pittsburgh Sleep Quality Index;

DISCUSSION

Chronic inflammatory back pain with nociceptive and neuropathic components is characteristic for AxSpA. We evaluated AxSpA patients with and without NP according to the PainDETECT scale regarding disease duration, pain intensity, QoL, and sleep disorder. In 108 AxSpA patients, 41.7% had NP, which was associated with significantly worse pain, more active disease, and poor QoL than those without NP. However PSQI scores, did not differ between the NP and non-NP groups.

Wu et al was the first who demonstrated NP in patients with AS using neuroimaging studies in addition to the painDETECT score (4). In previous studies that used painDETECT scores, NP rates were found to be 25%-37.9% in AxSpA patients (18–20). Compared to these results, our study showed a higher NP rate of 41.7%. We found that among AxSpA patients 23.1% had possible, 18.5% had likely NP components. Similar to our results Rifberg et al. found 21% of SpA patients had possible NP, and 24% had likely NP (21).

In inflammatory rheumatic disorders such as rheumatoid arthritis, ankylosing spondylitis (AS), osteoarthritis and others, it has been demonstrated that NP's existence is related to poor QoL (22). In addition to low QoL, patients with AxSpA who had NP also had high disease activity and high VAS scores (18,19,21). It was found that as PainDETECT scores increased, VAS scores also increased. VAS scores of patients with NP were twice as severe as patients without NP (23). And also higher BASDAI scores were obtained in patients with NP (20,21). In our study, pain intensity and disease activity were increased, and QoL was significantly impaired with NP presence.

Sleep disturbance has been reported in a range of 58-90% in AxSpA patients (24,25). We found 65.7% of the AxSpA patients had a sleep disorder. Poor sleep was associated with depression, anxiety, active disease, higher pain levels, and nocturnal pain within AxSpA patients (9,26–28). Pain impairs sleep quality independently of the others (8). There is a bidirectional association between pain and poor sleep (30). Chronic pain is thought to impair sleep quality while poor sleep quality worsens the pain (29). Poor sleepers have been shown to have more back pain during the night (26). We also found that poor sleep correlated with nocturnal pain and activity pain but no correlation with disease activity. Pain caused by inflammation and sleep disturbance in AS are related to each other, affecting the patient's functional status, disease activity and QoL (30).

Sleep disorders and decreased QoL have frequently encountered problems in patients with NP (7). NP alone causes poor sleep, and either NP or poor sleep significantly reduces the patient's QoL (31). In a study among the patients with NP 80% of them had poor sleep quality, while the rate was found to be 37% in healthy controls (10). In our study, 71.1% of AxSpA patients with NP had a poor sleep, while 61.9% of AxSpA without NP had a poor sleep. Despite the NP group having higher PSQI values, there was no statistically significant difference between the groups.

Previous studies found poor sleep quality and high disease activity to be positively correlated. (8,26,32). In contrast to these findings we found that poor sleep was not associated with disease activity. Sleep disturbance, mood, and generalized pain all had independent negative effects on QoL of patients with AxSpA in addition to high disease activity (33). Additionally, we observed that poor QoL was associated with worse sleep, severe pain, and high disease activity.

Study Limitations:

The current study has several limitations. First, other possible relationships between NP and sleep quality or QoL could not be established because of the cross-sectional design. Second, our results were based on patients' self-reported data. Also we could assess anxiety/depression with a disease specific questionnaire since these impact QoL and sleep quality negatively.

CONCLUSION

AxSpA Patients with NP had considerably worse QoL, more active disease, and more severe pain than those without NP. And also, a large majority of AxSpA patients have a sleep problem, independent of the presence of NP. Sleep disturbance and the presence of NP independently impair QoL.

In cases where the pain cannot be controlled despite the suppression of inflammation in patients with AxSpA, the presence of a neuropathic component should also be considered. Not only targeting the inflammatory pain but also targeting NP and sleep disorder together in the follow-up of patients with AxSpA will lead to an improvement in QoL.

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Ethical approval: All procedures performed in studies involving human participants were in accordance with the institutional and/or national research committee's ethical standards and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Are there fitness-related physiological changes following a series of Rebirthing sessions?

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ABSTRACT

Objective: The current study is only the second known empirical study of Rebirthing, a holistic self-improvement therapy. The study looked at fitness-related physiological outcomes following a series of rebirthing sessions.

Methods and materials: Ten healthy young women (mean age, weight, and height: 372.7 years, 54.16.4 kg, and 161.24.9 cm, respectively) underwent two identical resting pulmonary function tests (PFTs) and two two-stage all-out graded cardiopulmonary exercise tests (CPETs) before (pre) and after (post) a series of 10 weekly Rebirthing treatments. The rebirthing sessions were held at the Israeli Rebirthing Center in Tel Aviv. All rebirthing treatments were performed by a single qualified Rebirthing therapist and lasted approximately 40-50 minutes each.

Results: There were no significant changes ($p>0.05$) in resting lung functions (PFTpost) or peak values at maximal effort (CPETpost) after the rebirthing program (except for a decrease in HRpeak). Nonetheless, the results show a significant reduction ($p<0.05$) in several cardiopulmonary attributes measured during the submaximal phase of the second CPET (HRsub, VO_2sub, RERsub, VEsub, BRsub; Bfsub and an increase in Vd/Vtsub).

Conclusions: As the first study to investigate the effect of a series of rebirthing treatments on responses of selected fitness-related physiological measures at rest and during exercise, it is not surprising that no unambiguous answers to the research questions were found. Further studies are needed to provide reliable support and explanations for the study findings.

Keywords: Rebirthing therapy, voluntary hyperventilation, exercise, habituation, PFT, CPET, MRT

INTRODUCTION

Voluntary hyperventilation has recently been used in clinical psychology and psychiatry to induce panic for diagnostic purposes and as part of anxiety disorder desensitization therapies (1, 2). Rebirthing (also known as Breastwork, Conscious Breathing, Circular Breathing, and Connected Breathing), which reproduces over-breathing or hyperventilation, is a holistic self-improvement therapy that has received substantial interest and numerous clients since its development in 1975 by Leonard Orr (3, 4).

Millions of rebirthing advocates worldwide claim that rebirthing treatment helps overcome physical and mental difficulties and improves overall well-being. The primary rationale for these positive effects of rebirthing therapy is based on the claim that an intense breathing process (hyperventilation) can improve concentration and sleep quality, combat fatigue, and increase energy (5, 6, 7).

Although millions of people worldwide have been successfully Rebirthing (8), no controlled scientific research has empirically studied the reported effects. One major benefit of Rebirthing claimed by leaders in the field is that rebirthed people can use their positive thoughts and full breathing to eliminate unwanted emotional and physical symptoms. More specific claims include improving and curing mood, increasing lung capacity, improving physical fitness, curing various respiratory problems, increasing energy levels during the day, curing migraines and headaches, relieving and curing chronic pain in various parts of the body, improving concentration, and improving learning ability (5, 9, 3, 10, 11).

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Since, to the best of our knowledge, only one scientific/empirical study (12) has examined the validity of those largely subjective reports on healthy adults, the purpose of the current study was to investigate some of the aforementioned claims regarding pulmonary functions and physical fitness in an objective manner.

It is generally accepted that under healthy normal conditions, the respiratory system is not a limiting factor in aerobic capacity (VO_2max) or performance unless at very high-intensity levels (13, 14, 15).

Thus, even specific respiratory muscle training (RMT) that improves respiratory muscle strength and endurance at rest (16, 17) is not expected to increase aerobic or exercise capacity (18, 19). Therefore, even if we consider the rebirthing session series used in the present study to be a type of RMT, thereby significantly improving resting lung function, it is not expected to strengthen participants' aerobic capacity/performance noticeably.

When we proposed the overall Rebirthing project, we sought to answer the following key questions:

1. What physiological changes occur during a single rebirthing session (already published (12)?

2. Are there any physiological changes related to physical fitness after a series of rebirthing sessions?

3. Are there physical, emotional, or mental changes after a series of rebirthing sessions?

This report addresses only the second question of the project, i.e., "Are there any fitness-related physiological changes that occur after a series of rebirthing sessions?"

We hypothesized that a series of rebirthing sessions would result in a significant improvement in resting lung function. We also hypothesized that the sequence of rebirthing sessions would not significantly increase physical fitness attributes such as aerobic power and performance.

MATERIAL and METHODs

Participants: Participants were recruited from a pool of potential clients. Eleven healthy young women were selected from potential clients in central Israel. Their mean age, weight, and height were 37±2.7 years, 54.1±6.4 kg, and 161.2±4.9 cm, respectively.

All participants were medically examined (including resting and exercise ECG), found healthy, and did not take any medications (except birth control pills). Participants were instructed to eat a regular diet, not to consume caffeine or alcohol the day before testing, and not to engage in vigorous exercise for 24 hours before the experiment.

The Helsinki Committee for the Protection of Human Subjects (Institutional Review Board) at Kaplan Medical Center in Rehovot, Israel, approved all study protocols and procedures.

Participants were fully informed of the procedures, risks, and inconveniences of study participation, and all gave their signed informed consent to participate. Participants were informed that they might withdraw from the study at any time and for any reason.

Of the eleven "starters," only one participant withdrew from the study (because of early pregnancy).

Study design and procedures

Preliminary visit: The preliminary measurements for this study were performed at the Human Performance Laboratory at Washington Hill College in Israel.

At the initial visit, participants received a detailed explanation of the study objectives and procedures and signed an informed consent form. Participants provided information on their medical history and exercise habits. Weight and height were measured to the nearest 0.02 kg and 0.1 cm, respectively, using a model H151-8 Shekel scale (Shekel Scales Ltd., Beit Keshet, Israel), while participants were barefoot and wearing light athletic clothing.

Following the preliminary visit, two additional visits to the laboratory were made three months apart (before and after a ten rebirthing sessions), during which a resting pulmonary function test (PFT) and a cardiopulmonary exercise test (CPET) were performed.

The pulmonary function test (PFT): For this test, the subject was set upright in front of a spirometry machine [the K4b2 portable metabolic system (Cosmed, Rome, Italy)] attached to a plastic mouthpiece and wearing a nose clip. She was asked to take a deep breath in, then exhale as forcefully and quickly as possible until she emptied her lungs. She was then allowed to breathe normally before repeating the test twice.

The exercise tests: Two-stage incremental cardiopulmonary exercise tests to voluntary exhaustion (CPETs) were carried out, and measurements of some 14 physiological variables were obtained. The exercise tests (CPETs) were performed on a motorized treadmill (Ram 770CE, Germany). The exercise protocol began with the subject walking on the level at 3 km/h for 2 min. This was followed by work rate increments of 1 km/h each minute until the participant reached a work rate (speed) eliciting 70-75% of her age-predicted maximal HR. This work rate was kept constant for 5-6 min to secure steady-state conditions (verified by unchanged HR and VO_2 for at least two consecutive minutes). Immediately following this stable work-rate stage, work-rate increments of 2% inclination were imposed each minute (with speed being maintained) until the patient reached her tolerance limit (typical total CPET time was 13-17 min) (19, 20). An attempt was made to ensure that each participant gave maximal effort by providing continuous verbal encouragement and support based on age-predicted maximal HR, RER>1.15, and falling of $ETCO_2$ during the last 3 minutes of the test (by>3-4 mmHg). Continuous 12- lead ECG was monitored throughout the tests, with recordings made at baseline and the end of each minute of exercise, and during the recovery period (see Figure 1).

Gas exchange was measured continuously during the exercise tests, namely oxygen uptake (VO_2), carbon dioxide production (VCO_2), and minute ventilation (VE) using the $K4b_2$ portable metabolic system (Cosmed, Rome, Italy). The pneumotachograph and analyzers of the $K4b_2$ were calibrated before each test session according to the manufacturer's specifications.

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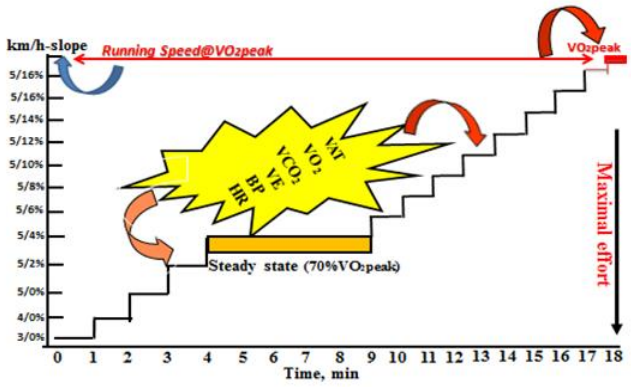

Figure 1: Schema of exercise protocol

Peak cardiopulmonary values were obtained as the highest 30-second average during the last minute of the test. Submaximal values were calculated by taking a one-minute average of the fifth minute of the constant workload (submaximal stage).

The second (post) PFT and CPET were performed under identical conditions (environmental and protocol) by all study participants shortly (2-3 days) after the last (10th) rebirthing session).

The Rebirthing sessions

Location: Rebirthing sessions took place at the Israeli Rebirthing Center in Tel Aviv. All treatments were conducted by a single qualified rebirthing therapist who has experienced thousands of rebirthing sessions over the past 15 years.

The sessions took place in a dark, quiet room and were conducted in a one-to-one situation (see picture) with the same trained therapist for all participants. Participants were asked to remove their shoes and coats and lie supine on a mattress with a blanket to warm and soothe them. The therapist instructed participants to begin connected breathing and increase it to a full, forceful, and steady rhythm, drawing high on the inhale and releasing freely on the exhale.

Image 1: The Rebirthing session's set-up

The sessions lasted about 50 minutes. When a participant showed signs of difficulty in breathing or drowsiness, the therapist recognized it and guided the participant accordingly. At the end of the rebirthing sessions, the therapist gently escorted the client back to the clinic waiting room.

Measurements taken during the rebirthing sessions

Selected physiological (cardiopulmonary) measurements were taken breath-by-breath using the same portable metabolic system (COSMED K4b$_2$, Rome, Italy) used during the CPETs and the rebirthing sessions.

RESULTS

The following tables compare the data of selected physiological parameters measured before (pre) and after (post) the rebirthing treatment series

Table 1 compares the results of lung functions at rest obtained before and after the ten weekly rebirthing sessions. The data show statistical equality ($p > 0.05$) in all spirometric indices between pre- and post-sessions. Thus, we conclude that the present rebirthing sessions did not affect the study participants' resting pulmonary functions (refuting the first study's assumption).

Table 1: Pulmonary function test's variables before and after the Rebirthing treatments.

	FVC, liter		FEV1, l/sec		FEV1/FVC, %		PEF, l/sec		MEF25- 75 %, l/sec	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Mean	3.65	3.62	3.07	3.06	84.3	84.7	7.05	7.25	3.53	3.65
SD	0.035	0.33	0.26	0.25	4,67	4.52	0.55	1.05	0.81	0.90
t	- 0.25		-0.12		0.14		0.69		0.40	
P	0.40		0.45		0.45		0.26		0.35	

FVC - Forced vital capacity; FEV1 – Forced expiratory volume in 1 second; FEV1/FVC,% - The ratio between FEV1 to FVC; PEF – Peak expiratory flow rate; MEF25- 75 % - Mid expiratory flow rate.

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The effect of rebirthing treatments on selected physiological responses during submaximal aerobic exercise.

Table 2 shows a significant decrease ($p<0.05$) of VO_2sub, RERsub, HRsub, VEsub, BRsub, Bfsub, VE/VCO_2sub, and an increased Vd/Vtsub. A decrease in the above attributes suggests more economical and less demanding cardiopulmonary responses to a similar mechano-metabolic load after the rebirthing treatment regimen. There were no significant differences in the remaining cardiopulmonary attributes between the pre and post-rebirthing regimen.

The effect of rebirthing treatments on selected physiological responses during maximal aerobic exercise.

Table 3 compares selected physiological data measured during a maximal graded aerobic effort before (Pre) and after the last rebirthing session (Post). A look at Table 3 shows that of the fourteen (14) cardiopulmonary variables measured during the maximal graded aerobic effort, only peak pulse rate (HR) was significantly affected (decreased) after the rebirthing treatments. All other thirteen peak cardiopulmonary attributes did not change following the rebirthing program (supporting our 2nd hypothesis). These findings suggest no improvement in the participants' aerobic capacity (peak VO_2) or aerobic performance (peak workload).

Table 2: compares responses of selected physiological attributes measured while performing a submaximal effort before and after a series of Rebirthing sessions.

Variable	Mean (±1SD)			
	Pre	Post	t	p
Work load$_{sub}$, kmh/%	5.7/8.1 (0.5/1.4)	5.7/8.1 (0.5/1.4	0.00	1.00
VO_{2sub}, ml/kg/min	20.6 (2.77)	19.17 (2.97)	4.10	**0.00**
RER$_{sub}$, L/L	0.97 (0.07)	0.92 (0.09)	1.92	**0.05**
HR$_{sub}$, b/min	140.15 (12.94)	131.5 (9.27)	1.91	**0.05**
O_2pulse$_{sub}$, ml/kg/beat x100	14.72 (1.82)	14.64 (2.1)	0.96	0.47
VE$_{sub}$, l/min	32.37 (5.65)	30.42 (5.42)	2.99	**0.01**
Vt$_{sub}$, L	1.17 (0.24)	1.19 (0.27)	-0.28	0.39
Bf$_{sub}$, b/min	28.42 (3.04)	26.55 (4.32)	2.13	**0.004**
BR$_{sub}$, %	27.55 (4.55)	26.32 (4.97)	1.97	**0.03**
VE/VO_{2sub}, L/L	28.13 (1.65)	28.11 (1.62)	0.05	0.48
VE/VCO_{2sub}, L/L	29.18 (1.54)	30.77 (1.56)	-2.28	**0.03**
$PETO_{2sub}$, mmHg	106.91 (2.55)	105.63 (2.74)	1.44	0.09
$PETCO_{2sub}$, mmHg	39.24 (2.35)	37.66 (2.06)	1.51	0.08
Vd/Vt$_{sub}$, %	33.73 (0.61)	35.02 (1.25)	-4.61	**0.00**

Workload$_{sub}$ – Mechanical power in treadmill's speed (km/hr) and slope (%); **VO_2/kg$_{sub}$** – Oxygen uptake per kg; **RER$_{sub}$** – Respiratory exchange ratio; **HR$_{sub}$** – Heart rate; **O_2pulse$_{sub}$** – Oxygen pulse; **VE$_{sub}$ –** Minute ventilation; **BR$_{sub}$ –** Breathing reserve [FEV1x37/VE (%)]; **Vt$_{sub}$ –** Tidal volume; **Bf$_{sub}$ –** Breathing frequency; **VE/VCO_{2sub} and VE/VO_{2sub} –** Ventilatory equivalents for CO_2 and O_2; **$PETO_{2sub}$** – End-tidal O_2; **$PETO_{2sub}$** – End-tidal O_2; **Vd/Vt$_{sub}$** – The ratio of Vd to Vt.

Table 3: Effects of ten (10) rebirthing sessions on selected cardiopulmonary indices measured during maximal effort.

variable	Mean (±1SD)			
	Pre	Post	t	p
Workload, kmh/%	5.7/11.3 (0.7/1.8)	5.7/11.6 (0.7/1.9)	0.98	0.51
VO_2, ml/kg/min	32.82 (3.91)	33.76 (4.72)	-0.34	0.37
RER, L/L	1.25. (0.04)	1.24 (0.04)	0.99	0.17
HR, b/min	185.33 (7.54)	181.75 (7.80)	**2.09**	**0.04**
O_2pulse, ml/kg/beat x100	17.8 (1.94)	18.4 (3.07)	0.98	0.35
VE, l/min	67.88 (8.43)	70.38 (10.94)	-0.85	0.21
Vt, L	1.66 (0.27)	1.60 (0.19)	0.71	0.25
Bf, b/min	41.63 (2.97)	45.25 (6.56)	-1.11	0.15
BR, %	60.5 (7.25)	62.3 (7.55)	-0.61	0.35
VE/VO_2, L/L	40.15 (3.78)	39.93 (4.30)	0.19	0.43
VE/VCO_2, L/L	29.98 (1.79)	31.03 (1.52)	-1.21	0.13
$PETO_2$, mmHg	120.38 (2.63)	118.63 (3.47)	1.49	0.09
$PETCO_2$, mmHg	36.63 (2.31)	35.00 (1.75)	1.60	0.08
Vd/Vt, %	32.63 (1.47)	33.13 (1.84)	-1.00	0.8

Workload$_{sub}$ – Mechanical power in treadmill's speed (km/hr) and slope (%); **VO_2/kg$_{sub}$** – Oxygen uptake per kg; **RER$_{sub}$** – Respiratory exchange ratio; **HR$_{sub}$** – Heart rate; **O_2pulse$_{sub}$** – Oxygen pulse; **VE$_{sub}$ –** Minute ventilation; **BR$_{sub}$ –** Breathing reserve [FEV1x37/VE (%)]; **Vt$_{sub}$ –** Tidal volume; **Bf$_{sub}$ –** Breathing frequency; **VE/VCO_{2sub} and VE/VO_{2sub} –** Ventilatory equivalents for CO_2 and O_2; **$PETO_{2sub}$** – End-tidal O_2; **$PETO_{2sub}$** – End-tidal O_2; **Vd/Vt$_{sub}$** – The ratio of Vd to Vt.

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DISCUSSION

This study aimed to see if there were any changes in the fitness-related physiological attributes after a series of rebirthing sessions.

There were no significant changes in either resting lung functions (PFTpost) (negating the first hypothesis) or peak values of the second maximal effort (CPETpost) after the rebirthing program (except for a decrease in peak HR) (supporting the second hypothesis). The lack of change in both the PFTpost and the maximal values of the second exercise challenge (CPETpost) suggests that rebirthing treatments do not improve either resting pulmonary functions or aerobic exercise capacity (as measured by peak VO_2) or aerobic performance (characterized by maximal workload). Nonetheless, the results show a significant reduction ($p<0.05$) in several cardiopulmonary attributes measured during the submaximal phase of the second (post) CPET (HRsub, VO2sub, RERsub, VEsub, BRsub; Bfsub, VE/VCO2sub and an increase in Vd/Vtsub). While physiological responses at maximal effort represent the strength and power of the respective bodily systems, physiological responses during submaximal effort express the degree of efficiency and physiological stress to which they are subjected (13) when a similar mechano-metabolic load is encountered, a decrease in the above parameters indicates a more economical and less demanding physiological load. In most cases, physiological improvement in the latter (reduced submaximal responses) should result in increased maximal exercise capacity (22, 23), but this was not the case in our study. So, what could explain the above changes, which were only observed during the second exercise test's submaximal phase but not during the second resting PFT (PFTpost) or at the height of the second CPET (CPETpeak post)? First, the physiological changes observed could be attributed to a possible ventilatory "training effect" induced by the rebirthing treatments, which included ten prolonged periods of heavy breathing. But then, why were changes observed only at the submaximal effort and not at resting PFT or maximal effort? Although some authors claim that respiratory muscle training improves whole-body exercise capacity (17, 18), many researchers contend that respiratory muscle power and capacity do not limit exercise performance or affect maximal oxygen uptake (VO_2max). (19, 20, 21). Therefore, even if the rebirthing series did improve the respiratory system of the study participants, this improvement might not have led to an increase in maximum exercise capacity (VO_2 peak and/or peak workload) (17, 24), as was the case in the current study (supporting the second study hypothesis).

One obvious argument against the rebirthing regimen's functional improvement of the respiratory system is the relatively long interval between each rebirthing session (one week). Such a "break" between training sessions was most likely too long to cause an appreciable respiratory training effect of the Rebirthing treatments. It should be noted that most RMT protocols necessitate at least one training session per day, if not three or more (16, 25, 26). Furthermore, an assumed functional improvement of the respiratory system should be reflected in the second resting PFT (an increase in the PFTpost), but this was not the case in the current study (rejecting our first hypothesis).

Therefore, it is reasonable to suspect that the changes observed during the second submaximal effort were caused by factors other than actual respiratory system strengthening. Another probable explanation for the study's findings could be the "habituation effect." "A decrease in response to repeated stimulation is called habituation." "It occurs in the nervous system and may impact the associated physiological responses to the applied stimulus." (27). Habituation is a popular explanation for a decrease in response intensity to a repeated stimulus or set of stimuli.

The term "habituation" is frequently used in the stress literature to describe a situation in which an individual has learned to perceive a repeated stressor as innocuous. (28, 29). The fact that study participants were unfamiliar with exercise testing procedures and were new to the laboratory environment at the first visit (pre) suggests that habituation played a vital role in both psychological and physiological responses at the second visit to the laboratory (post) (27, 30).

The relatively long-time interval (approximately three months) between the first (pre) and second (post) laboratory visits must be a major weakness of this argument, namely linking the improved physiological responses at a constant submaximal effort to the presumed habituation effect. A time interval of this length has the potential to "cancel out" suspected habituation.

Given that this is the first and only study to report the findings of a scientific investigation examining fitness-related physiological responses following a series of rebirthing treatments, it is not surprising that no satisfactory or conclusive explanations for the main study's findings were found. Nonetheless, it is tempting to "blame" the rebirthing sessions for the significant reduction in selected physiological responses during the second exercise challenge's submaximal phase. More research, however, is needed to provide reliable support for this claim. Therefore, we'd like to propose a few potential future lines of research to test our hypotheses further. First, a controlled study of Rebirthing with a large enough sample size representing a homogeneous healthy or clinical population is needed to determine whether rebirthing is a beneficial complementary or alternative treatment for the study population. Second, a placebo or wait-list control condition with random group assignment would significantly improve the results' interpretability. Third, more precise neuroimaging techniques, such as fMRI, should be used to pinpoint changes in brain activity during rebirthing treatment.

CONCLUSIONS

Unsurprisingly, the first study to investigate the impact of rebirthing treatments on responses of selected fitness-related physiological variables at rest and during exercise failed to provide clear answers to the research questions. More research is necessary to provide trustworthy support and explanations for the study's findings

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Does Chronic Immune Thrombocytopenia Lead to Hearing Loss?

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ABSTRACT

Objective: We aimed to investigate the incidence of hearing loss in patients followed up for Chronic Immune Thrombocytopenia Purpura (ITP).

Material and Methods: All patients over the age of 18 who referred to the hematology outpatient clinic between January and June 2020 and followed up with the diagnosis of Chronic ITP were included in the study. Hearing tests of patients diagnosed with Chronic ITP and received first-line treatment (IVIG and corticosteroid) for any reason other than ear diseases during their treatment were evaluated retrospectively. Patients with a history of hearing loss, perforation of the tympanic membrane or who had any squeal due to a previous chronic ear infection and patients who had a previous ear operation were excluded from the study. In addition, patients' age, gender, time of ITP diagnosis, platelet values at the time of diagnosis, platelet values during audiological evaluation, concomitant disease, history of splenectomy, additional drug use and ISTH-SSC Bleeding Evaluation Score data were also recorded.

Results: Of the 34 cases, 58.8% (n=20) were female and 41.2% (n=14) were male. The mean age was 49.06±18.26. Similarly, when compared, usage of IVIG/Methylprednisolone, IVIG/ Methylprednisolone /Eltrombopag, and IVIG/Methylprednisolone /Rituximab/Eltrombopag was not found to be a factor that would cause hearing loss ($p>0.05$). No statistical correlation was found between ISTH-SSC and time of diagnosis (months) and hearing loss ($p>0.05$).

Conclusion: Parameters such as various drugs used in the course of Chronic ITP disease, age, gender, time of diagnosis, and presence of concomitant disease do not cause hearing loss.

Keywords: Chronic ITP, hearing loss, inner ear hemorrhage, thrombosis

INTRODUCTION

Immune Thrombocytopenia Purpura (ITP) is an autoimmune disease characterized by increased peripheral immune-mediated platelet destruction and impaired platelet production in megakaryocytes. The newly diagnosed ITP is defined as ITP within first 3 months from diagnosis, Persistent ITP within 3-12 months from diagnosis without spontaneous remission, or for cases that cannot remain in remission when treatment is stopped (1). Chronic ITP is an autoimmune bleeding disorder that lasts more than 12 months with thrombocyte values <100,000 / mm3 and there is no additional disease to explain this condition (2). Although in some patients single episodes of ITP early remission are experienced, up to 70% of adults develop Chronic ITP (3). ITP occurs with an incidence rate of 1.6 to 3.9 per 100,000 patient-years, which increases with age and has a slight female preponderance worldwide (4). Similarly, ıt has an annual incidence of 2.92 / 100,000 and a prevalence of 35.1 / 100,000 in Turkey (5,6).

There is a wide spectrum of presentations from mild cases with petechiae and ecchymosis on the skin to severe mucocutaneous bleeding, even life-threatening bleeding (7). Although the risk of critical-serious bleeding such as intracerebral hemorrhage is quite low (about 1%) in ITP patients, a history of previous bleeding, platelet values <10,000 / microL, and being <60 years of age increase the risk of bleeding (8). The risk of venous thromboembolism in ITP patients is twice as high when compared to the general population (9).

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Hearing loss is a condition that can be caused by a wide variety of etiologies. Developmental losses, advanced age, infectious conditions, middle ear pathologies, trauma, otosclerosis, exposure to loud noise, Menieré, chronic diseases, autoimmune and central causes and some drugs (aminoglycosides, erythromycine, tetracycline etc.) are included in etiology [10]. In addition, bleeding or vascular occlusion can cause hearing loss [11]. For maintaining the ion and fluid balance of the inner ear, sufficient blood supply to the cochlea is necessary and essential for normal hearing function. If cochlear microcirculation (e.g., intralabyrinthine hemorrhage) is interrupted. It may result in dysfunction of hearing and balance [12]. Intralabyrinthine hemorrhage (ILH) is a rare complication in patients with haematological disease and / or under anti-coagulant therapy [11].

In our study, we aimed to investigate the incidence of hearing loss in Chronic ITP patients undergoing different treatment protocols and whether the loss is due to bleeding in the vascular structures of the inner ear or secondary to the development of treatment-related thrombosis.

To our knowledge, this is the first study about Chronic ITP's affect on hearing levels.

MATERIAL and METHODs

The available data of all patients over 18 years of age who were followed with a diagnosis of Chronic ITP in the hematology outpatient clinic were retrospectively analyzed. The ethical approval was taken from the local ethical committee (prot.no:2021/514/197/1). Thirty-four patients some received first step (IVIG and corticosteroid) treatment and some second step treatment (splenectomy, rituximab, immunomodulatory drugs) were included in the study. All of the patients were examined in the otolaryngology clinic by the same specialist. Patients with known chronic ear disease and known hearing loss, who had an abnormal appearance in the tympanic membrane, those who did not want to participate in the study voluntarily, and the ones with the diagnosis of secondary ITP were excluded from the study. Patients who had history of drug use with known ototoxic effects such as aminoglocosides, tetracycline, vancomycin or chemotheuropatic drugs as cisplatin, carboplatin, bleomycin or chloroquine, quinine and furosemide were excluded from the study.

None of the patients were under corticosteroid therapy at the time of pure tone audiometry tests. However, corticosteroid (methylprednisolone) was present in the past treatment history of all patients for which it is the most commonly used group of drugs in the first-line treatment of ITP.

Pure tone audiometry was performed to all patients regardless of the time of diagnosis and treatment. In addition, patients' age, gender, duration of diagnosis, diagnosis platelet values, accompanying disease (diabetes, coronary artery disease, hypertension, kidney and liver disorders, etc.), splenectomy, additional drug use, and ISTH-SSC Bleeding Assessment Score data were also recorded.

Statistical Analysis: The compatibility of the data to normal distribution was examined with the ShapiroWilk test. Comparison of normally distributed characteristics in two independent groups was performed using Student's t test One-way analysis of variance, and comparison of more than two independent groups were done using (ANOVA) and LSD multiple comparison tests. Mann Whitney u test was used for the comparison of non-normally distributed features in two independent groups, and Kruskal Wallis test and All pair wise multiple comparison tests were used in comparison of more than two independent groups. Relationships between numerical variables were tested with Spearman rank correlation coefficient. The relationship between two categorical variables was examined using the Exact Chisquare test. In addition, the relationship between hearing loss and independent variables was examined using the multivariate binary Logistic Regression (enter) model.

As descriptive statistics, mean ± standard deviation, median, min and max for numeric variables, number and % values for categorical variables were presented.

SPSS Windows version 23.0 package program was used for statistical analysis and $p < 0.05$ was considered statistically significant.

RESULTS

Of all patients, 20 (58.8%) were women, and 14 (41.2%) were men, with a mean age of 49.06 ± 18.26. In pure tone audiometry averages of air and bone conductions were; right air conduction (17.68 ± 13.84), left air conduction (17.61 ± 13.66), right bone conduction (10.84 ± 14.14), left bone conduction (11.19 ± 13.92). Mild to moderate sensorineural hearing loss was detected in 5 of the patients included in the study. Thrombocyte values at the time of audiometric test were observed as (174781.25 ± 91186.70). (Table 1)

There was statistically no significant difference in air and bone conduction results in both ears in women and men, patients with different drug history and patients with and without splenectomy ($p = 0.377$).

There was no significant difference between the mean age of those with hearing loss 51.80 ± 17.88 (56) and the mean age of those without hearing loss 48.11 ± 18.75 (53.50) ($p = 0.686$). Similarly, ISTH-SSC scores and time to diagnosis not significantly different in both groups ($p > 0.05$).

A statistically significant relationship was found between drug use and hearing loss ($p = 0.028$). It was observed that the use of IVIG/ methylprednisolone and IVIG/ methylprednisolone/Eltrombopag was high in patients with no hearing loss, while the use of IVIG/ methylprednisolone/Rituximab/Eltrombopag and others(methylprednisolone/IVIG+ immunosuppressant agents) was significantly more used in the group in patients with hearing loss (Table 2).

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Table 1. Demographic properties of patients and drugs used

Age mean±sd (M) (min-max)	49,06±18,26 (55) (23-85)	
Right air conduction mean±sd (M) (min-max)	17,68±13,84 (12) (5-58)	
Righ bone conduction mean±sd (M) (min-max)	10,84±14,14 (5) (0-53)	
Left air conduction mean±sd (M) (min-max)	17,61±13,66 (15) (5-55)	
Left bone conduction mean±sd (M) (min-max)	11,19±13,92 (7) (0-50)	
Gender $_{n(\%)}$		
Male	14 (41,2)	41,2
Female	20 (58,8)	58,8
Drugs used $_{n(\%)}$		
IVIG/Methylprednisolone	17 (50)	50,0
IVIG/Methylprednisolone/Eltrombopag	4 (11,8)	11,8
IVIG/Methylprednisolone / Rituksimab /Eltrombopag	4 (11,8)	11,8
Other (Prednol/IVIG+immunosuppressant agents)	9 (26,5)	26,5
Splenectomy $_{n(\%)}$		
Yes	7 (20,6)	20,6
No	27 (79,4)	79,4

Table 2. Relationship analysis of hearing loss between age, medication used, duration of diagnosis and ISTH-SSC score

	Hearing Loss		
	Positive (n=5) Mean±sd (M)	Negative (n=28) Mean±sd (M)	p
Age	51,80±17,88 (56)	48,11±18,75 (53,50)	0,686
ISTH-SSC	0±0 (0)	0,50±0,75 (0)	0,173
Drugs Used n(%)			
IVIG/Methylprednisolone	0 (0)	17 (60,7)	0,028
IVIG/Methylprednisolone/Eltrombopag	0 (0)	3 (10,7)	
IVIG/Methylprednisolone/Rituksimab/Eltrombopag	3 (60)	5 (17,9)	
Others(Methylprednisolone/IVIG+immunosuppressant agents)	2 (40)	3 (10,7)	
Duration of diagnosis (months)	46,41±26,01 (34,5)	93,28±85,20 (61,35)	0,509

DISCUSSION

Hearing loss is a condition that negatively affects people's quality of life and can be caused by a wide variety of drugs. Although hearing loss can occur due to many different etiologies, it can also be seen due to drug use or inner ear blood supply disorder.

In the case of ototoxicity, sensorineural hearing loss occurs as a result of damage to the cochlear cells in the inner ear, while balance disorders are observed if damage occurs in the vestibular system [13].

Chau et al. reported that sudden hearing loss may resulted by vascular causes, and these may be due to cardiovascular diseases, subdural hematoma, pontine hemorrhage, transient ischemic attacks, sickle cell anemia or hemodialysis coagulopathy[14]. Some authors believe that blood viscosity and plasma changes create perfusion disturbances [15].

As a result of the widespread use of Magnetic Resonance Imaging (MRI) acute sensorineural hearing loss (SNHL) due to hemorrhage in inner ear has been reported in the literature [16]. Also, especially in patients with underlying coagulation disorders, cases of SNHL as a result of ILH have been reported [17,18]. None of our patients developed a clinical thrombosis that could cause hearing loss, which suggests that the inner ear structures are not impaired due to thrombotic plugs in our patients. The thrombocyte count of the patients in our study was not at critical low values such as 10,000/micro L and with close follow-ups of thrombocyte counts that no serious bleeding side effects were observed. We thought this was the absence of hearing loss due to ILH.

In a long-term study about the incidence of thrombosis in ITP patients, in some patients thrombotic events (both arterial and venous) occurred, and the median platelet count at thrombotic events was found as 102 × 109/l. It was n that smoking, hypertension, male gender, history of thrombosis, and atrial fibrillation (AF) were significantly associated with thrombosis [19]. We think the reason why we did not detect hearing loss even with high platelet values in some patients, because our patients were mostly female, none of them smoke, only 1 had atrial fibrillation history, and none had a previous thrombosis history.

Mild to moderate sensorineural hearing loss was detected in 5 of the patients included in our study. All of these were losses that were found incidentally in our study, none of them was acute SNHL; it may be the result of oral steroids which all of the patients have at least once used. When the patients with hearing loss were evaluated, it was found that all of them had at least one additional disease. Hearing loss was seen significantly high in patients who got IVIG/ methylprednisolone /Rituximab/Eltrombopag and others (methylprednisolone/IVIG+ immunosuppressant) treatment. But in the literature there is no evidence of SNHL due to drugs used during ITP treatment such as Rituximab, Eltrombopag, Vincristine [20,21]. Since we had a very small group of patients we believe that to say these drugs cause hearing loss, a more detailed analysis of hearing levels during the use of these specific drugs will give more accurate answers. In these patients, no specific difference was found in terms of age, gender, platelet values, mean diagnosis, and treatment times, or that could cause hearing loss.

One thing to explain this can be that since these hearing losses were mild to moderate patients were not aware of it or it may be that they were aware but since it did not affect their daily life, they did not seek any medical help.

According to the ISTH-SSC bleeding risk score ISTH-SSC Bleeding Assessment Tool) one patient scored 3 and one patient 2 at the time of diagnosis and during follow-up [22]. No hearing loss was observed in these patients. When 5 patients with hearing loss were evaluated, it was found that they all had ISTH-SCC bleeding risk scores were 0. Due to the patients' low bleeding score, we did not evaluate this hearing loss as a bleeding complication. Since there was no evidence of bleeding or thrombosis in the inner ear it was thought that no hearing loss emerged. In addition, we think that the median age of our patients is 49.06 ± 18.26. and the thrombocyte count is not low at critical values such as 10,000 / microL, which reduces the risk of serious bleeding in the course of the disease and, thus, the risk of hearing loss due to bleeding. We have some limitations in our study. We worked with a small number of patients. Patients' hearing levels were evaluated once, and patients were at different time intervals of their treatment.

CONCLUSION

We can say that parameters such as age, gender, time of diagnosis or concomitant diseases do not cause hearing loss. If bleeding or thrombosis does not occur during treatment, it is less likely to see hearing loss.

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Author Contributions: MDE: conception, writer, critical review**; ETE:** data collection and reporting, literature review

Ethical approval: All procedures performed in studies involving human participants were in accordance with the institutional and/or national research committee's ethical standards and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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Surgeons' Preferences in Treating Acute Uncomplicated Appendicitis during COVID-19 Pandemic: Results of Online Survey among General Surgeons

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ABSTRACT

Objective: The pandemic has affected the entire world. Even though most elective surgeries have been canceled, emergency cases pose a significant concern when the hospital resources are used for patients with COVID. Notably, surgery is the standard treatment for acute appendicitis; however, some studies have analyzed the use of antibiotics in selected cases. Our study aimed to analyze a surgeon's preferences in treating acute appendicitis during the COVID-19 pandemic.

Material and Method: An online survey was conducted for surgeons via the social media platform. 102 surgeons participated in the survey.. The survey was designed for consultant general surgeons. The survey queried regarding the surgeons' work hospitals, pandemic status, and treatment strategy before and after the pandemic. Answers to the survey questions were analyzed using descriptive statistics.

Results: 31% of surgeons reported they had changed the treatment strategy for acute appendicitis during the pandemic. 7% of surgeons stated that patients who received antibiotics had to undergo surgery owing to unresponsiveness to the therapy. Two percent of surgeons stated that patients on antibiotherapy developed early complications. Moreover, 29% of surgeons stated that they might change the treatment strategy in selected cases after the COVID-19 pandemic, and only 13% of surgeons may continue to prescribe antibiotics for uncomplicated cases.

Conclusion: Most surgeons did not change the treatment strategy for acute uncomplicated appendicitis during the COVID-19 pandemic. Even though recent guidelines and studies have revealed promising results for antibiotherapy in uncomplicated appendicitis cases, surgery seems to be regarded as the primary treatment strategy.

Keywords: Appendicitis, COVID 19, antibiotherapy, appendectomy

INTRODUCTION

Acute appendicitis is one of the most common causes of acute abdominal pain necessitating emergency surgery. The diagnostic and therapeutic processes related to appendicitis still experience challenges with complications like perforation that still have an incidence as high as 16%–40%, besides the high morbidity and mortality associated with complicated appendicitis (1).

The COVID-19 disease that was declared a pandemic by the World Health Organization has massively burdened the healthcare systems since late 2019. Accordingly, elective surgeries were cancelled, and oncological priorities have been established per the surgical society recommendations. In addition, the COVID-19 pandemic has negatively impacted acute surgical treatments except those for absolute emergencies like trauma (2).

Although appendectomy has been widely accepted as the treatment for uncomplicated appendicitis, antibiotherapy has been used for 60 years, and its use has been analyzed by several randomized trials (3). Nevertheless, the use of antibiotherapy in selected patient groups has been reconsidered during the COVID-19 pandemic, which mandated the optimal use of healthcare resources (4).

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Moreover, with the persistent concern of viral spread amidst the restricted health resources, several studies have explored the nonoperative management of nontraumatic surgical emergencies, including acute appendicitis (5).

Therefore, this online survey was conducted to analyze a surgeon's preferences in treating acute uncomplicated appendicitis during the COVID-19 pandemic.

MATERIAL and METHODs

After obtaining approval from the local ethics committee, an online survey was conducted for general surgeons by invitation via a closed social media platform. Overall, 102 surgeons participated in the survey during the 6-month data collection period between March 2020 and September 2020. Informed consent was obtained from the participant during inclusion in the study. The language of the survey was Turkish, and the survey consisted of 16 questions.

The survey queried the surgeons' consultancy year, their hospital's academic attributes, their hospital's pandemic status, and their treatment strategy of uncomplicated acute appendicitis before and during the pandemic. In addition, the reasons for a surgeon's choice of treatment modality were analyzed. Moreover, surgeons' diagnostic orders for excluding the diagnosis of COVID-19 in patients with uncomplicated acute appendicitis, as well as the effect of patient's COVID-19 status on the choice of treatment strategy by surgeons, were questioned.

Furthermore, the survey queried the follow-up criteria for patients who received antibiotherapy. In addition, the survey queried regarding patients who had to undergo surgery after a month of antibiotherapy or those who had complicated appendicitis after this early nonoperative treatment period. Moreover, the survey queried the surgeons' treatment strategy for patients who failed nonoperative treatment. Finally, the survey queried if surgeons would change their treatment strategy after the COVID-19 pandemic.

Statistical Analysis: The study findings were descriptive, and which were statistically analyzed using the "Statistical Package for the Social Sciences", version 20.0 for Windows (SPSS Inc, Chicago, IL, USA) program. Notably, frequency tables, and pie and bar charts were used.

RESULTS

Table 1 presents the participant consultant surgeon's general surgery experience in years, the hospitals' academic attributes, and its COVID-19 pandemic status.

Notably, 47.6% of participating surgeons ordered a thoracic computed tomography (CT) before diagnosis, whereas 31.1% of surgeons ordered other additional diagnostic tests only in patients suspected of COVID-19 [**Table 2**].

Overall, 31.4% of the participating surgeons (n = 32) stated that they changed their treatment strategy of acute uncomplicated appendicitis during the COVID-19 pandemic. Furthermore 54.5% (n = 24) choosing a strategy per the scientific evidence and surgical society's recommendations [**Table 3**].

Moreover, only 40.2 % (n = 41) of the participant surgeons stated that they would not change their treatment strategy in a patient with acute uncomplicated appendicitis with a positive COVID-19 status while the remaining percentage of the surgeons would change their treatment algorithm partially, or totally.

Before the COVID-19 pandemic, 88.6% of surgeons performed surgery (laparoscopic or open) for uncomplicated appendicitis, but during the pandemic, the preference for surgery was low at 60% as the primary modality and at 25.46% based on the characteristics of the cases. The remaining percentage of surgeons considered antibiotherapy [**Table 4**].

Furthermore, when a surgeon's approach in case of complications was queried, 41.66% of surgeons chose the surgical approach (n = 35), 4.76% of surgeons (n = 4) managed with interventional radiological methods plus antibiotherapy, and only 1.19 of surgeons (n = 1) prescribed another antibiotic regimen.

Among the patients treated with antibiotherapy, 19.1% of patients (n = 18) were followed up with clinical examination, laboratory investigation, and abdominal ultrasonography (USG); 18.1% of patients (n = 17) were followed up with clinical examination, laboratory investigation, and CT; 16% of patients (n = 15) were followed up with clinical examination and laboratory investigation; and only 4.3% (n = 4) of patients were followed up with clinical examination. The remaining percentage of surgeons selected other methods.

Notably, 8.9% (n = 8) of patients who were prescribed antibiotics needed to undergo surgery early on during the 1-month follow-up period, per surgeons' survey answers.

Based on the surgeons' survey responses, 59% of patients (n = 49) who were prescribed antibiotics did not have any complications. However, 37.3% (n = 31) of surgeons were unaware if the patient had a complication early during the 1-month follow-up period. Notably, only 3.6% (n = 3) of patients had complications, such as abscess and perforation, early during the 1-month follow-up period [**Table 5**].

Furthermore, 52.2% of surgeons (n = 47) stated they would discontinue their treatment strategy after the COVID-19 pandemic, with 33.3% of surgeons (n = 30) stating that they would alter their treatment strategy to accommodate a case-based approach. In addition, only 14.4% (n = 13) of surgeons stated that they would continue to evolve their treatment strategy after the COVID-19 pandemic.

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Table 1: Descriptive data of participant surgeons and hospital properties

Variable	Categories	Number (n)	Percentage (%)
Participant surgeons experience at general surgery (Year)	0-5 Year	16	15,7
	6-10 Year	**34**	**33,3**
	11-15 Year	16	15,7
	16-20 Year	16	15,7
	20 and more year	20	19,6
Hospital properties of the participant surgeons	State Hospital	**36**	**35,3**
	State affliated research and education hospital	21	20,6
	Private clinic	2	2,0
	Private hospital	24	23,5
	Private university hospital	4	3,9
	State affliated university hospital	15	14,7
Hospital's pandemic status	Yes	**71**	**69,6**
	No	31	30,4

Table 2: Surgeons diagnostic workups for excluding COVID 19

Diagnostic Tools	Number	Percentage (%)
Ordering Thorax CT	**49**	**47,6**
PCR and other laboratory tests	12	11,7
Other investigations	10	9,7
Only for high suspicious cases for COVID 19	31	30,4

Table 3: The rationale behind the changing treatment strategy during COVID-19 pandemic

		Number (n) 70	Percentage (%)68,6
The rationale behind the changing treatment strategy during COVID-19 era	Possibility of Transmission of COVID-19 Virus to Patient or Myself	6	5,9
	Other	2	2,0
	Failure of the Patient to Have a COVID-19 Test	1	1,0
	Personal Experience	3	2,9
	Recommendations of surgical associations and scientific literature suggestions	**20**	**19,6**

Table 4: Surgeons treatment strategy for acute uncomplicated appendicitis before and during COVID 19 pandemic

Variable	Categories	Number (n)	Percentage (%)
Participant surgeons approach to uncomplicated appendicitis before COVID 19 pandemic	Surgery (Open,laparoscopic)	**94**	**88.6**
	Intravenous/oral antibiotherapy with hospitalization	11	10.3
	İntravenous/oral antibiotherapy without hospitalization	1	1.1
Participant surgeons approach to uncomplicated appendicitis during COVID 19 pandemic	Surgery (Open,laparoscopic)	**60**	**52,63**
	Intravenous/oral antibiotherapy with hospitalization	18	15,78
	İntravenous/oral antibiotherapy without hospitalization	5	4,38
	Referral to a suitable center	2	1,75
	Surgery or antibiotherapy according to the case properties	29	25,46

Table 5: Surgery needs and complication rates of cases treated with antibiotherapy according the participant surgeons

Surgery needs on early follow-up	**Cases underwent surgery**	**Cases did not underwent surgery**
	8,9 % (n :8)	*91,1 % (n:82)*
Complication rates on early follow-up*	**Cases with complication**	**Cases without complication**
	3,6 % (n:3)	59,9 % (n:49)

*37,3 % /n:31) of surgeons did not know as if the antibiotherapy fails

DISCUSSION

The COVID-19 pandemic has brought on a new normal era. The governors and health givers have set aside the limited healthcare resources primarily to treat patients with COVID-19. However, the "stay-at-home" strategy and precautions contained the pandemic's spread, and emergency hospital visits were reduced by 50%, according to the reports. Nevertheless, some acute-care patients did not visit the emergency care units because of the fear of contracting COVID-19 infection. However, a significant increase in patients with complicated appendicitis was observed compared with previous years. This situation led to additional healthcare costs and burdens when competing with a worldwide pandemic paradoxically (6).

Clinical evaluation of patients adopted new strategies to rule out COVID-19 infection by ordering more CT scans, focusing on the thoracic cavity. This strategy could be to avoid viral exposure in patients and surgeons. Romero et al. revealed that proportionally more appendicitis cases were diagnosed using the CT during the pandemic era than before. Moreover, appendicitis cases might be more complex during the COVID-19 pandemic owing to the patient's delayed referral (7).

Notably, the surgical institutions have been issued guidelines during the pandemic to prioritize and perform the most critical surgeries that cannot be delayed further. Therefore, when using the limited health resources, which were primarily set aside for patients with COVID-19, several surgical clinics chose to prescribe antibiotherapy as a nonoperative treatment for uncomplicated acute appendicitis. Ganeshe et al. reported that patients with no persistent peritoneal signs on physical examination and finally considered noncomplicated were the primary candidates for antibiotherapy (8). Recent meta-analyses have revealed the feasibility of an antibiotics-first approach in uncomplicated cases. Nevertheless, the most crucial factor is the identification of suitable patients for antibiotherapy who may not develop complications, such as perforation and abscess. Notably, appendicolith has been determined to be an independent risk factor for antibiotherapy failure. (1).

Our study results revealed that 69.6% of participant surgeons worked at hospitals dedicated to COVID-19 with limited surgical resources. Moreover, only 31.4% of surgeons changed their treatment strategy for acute uncomplicated appendicitis during the pandemic. In addition, the pandemic volume status of hospitals might differ in each region of Turkey, and hence, some surgeons would have had to change their treatment algorithm according to the hospital resources. In this online survey, the most proportional group of surgeons (19.6 %) stated that their treatment strategy mainly was based on scientific evidence and surgical society's recommendations. This finding indicates the significance of rapid dissemination of free scientific knowledge during the COVID-19 era.

Before the COVID-19 pandemic, 88.6% of surgeons performed surgery (laparoscopic or open) for uncomplicated appendicitis but this ratio was low at 60% for surgery as the primary modality and 25.46% based on the characteristics of the cases during the COVID-19 pandemic.

This result is concordant with the percentage of surgeons (31.4%) who stated that they changed their treatment strategy during the COVID-19 pandemic.

Most surgeons (48%) in our survey stated that they ordered COVID-19 tests, including thorax CT, for excluding COVID-19. This result is compatible with the literature findings (7). Moreover, our study revealed that only 40.2% of surgeons did not change their treatment strategy in case of confirmed COVID-19 positivity of patients with appendicitis. This result indicated the importance of COVID-19 pandemic status among surgeons. Notably, the latest Jerusalem guidelines state that selected cases might be appropriate for nonoperative management of uncomplicated acute appendicitis (1). Furthermore, our survey queried the participating surgeons regarding the follow-up strategies for patients who were administered antibiotics. Notably, 43.1% of surgeons did not prescribe any antibiotherapy, whereas the remaining percentage of surgeons followed up patients with some degree of physical examination and radiological tests. Nevertheless, the follow-up methods for patients treated using antibiotherapy might differ based on the surgeon's practice. Moreover, the literature evidences no consensus regarding the follow-up methods.

Another significant finding of our survey was that surgeons who primarily prescribed antibiotics for uncomplicated appendicitis cases had to operate on only seven patients after antibiotherapy failure early during the 1- month follow-up period. This result is compatible with recent studies (1, 3, 8). In addition, this survey revealed that only three patients had complications after antibiotherapy during the 1- month follow-up period. An earlier case report had indicated that even in patients with comorbidities, conservative treatment would provide successful results (9).

Although no study has analyzed the use of antibiotherapy for appendicitis in patients with COVID-19, antibiotic use in other pathologies have evidenced no additional harm related to the viral disease (2). The rationale for choosing nonoperative treatment modality with antibiotherapy for uncomplicated cases during the COVID-19 pandemic might be to reduce the risk of viral spread in operation room staff and the postoperative mortality of patients with COVID-19, which has been noted to be higher than expected recently (2).

Furthermore, the responses to our last question that interrogated the possibility of evolving the treatment strategy of surgeons for acute uncomplicated appendicitis revealed that only 14.4% of surgeons (n = 13) would continue to evolve their treatment strategy after the COVID-19 period. This result indicates that surgeons still believed that surgery is the mainstay of acute uncomplicated appendicitis treatment. Nevertheless, the pre-COVID-19 era studies and guidelines have analyzed the effectiveness of nonoperative antibiotherapy and determined that it is feasible in selected groups with considerable outcomes (1, 10, 11).

Limitations of the Study: Nonetheless, this online survey study had some limitations. Based on evidence-based medicine, survey studies have an underlying bias stemming from participants' sentiments and practices. Although this survey was organized for general surgeons through a closed social media hub, the free survey site would allow multiple attempts to answer the survey questions, leading to

misinformation. In addition, some logical issues could arise with inconsistent answers by some participants resulting in irrational proportions.

Although our survey was conducted among a group of surgeons from Turkey, it might not represent the general clinical assessment worldwide because surgeons seem to act according to the local resources and patient characteristics when treating acute uncomplicated appendicitis.

CONCLUSION

Our survey revealed that surgeons still believe that surgery is the primary treatment modality for uncomplicated appendicitis, even during the COVID-19 pandemic. Although the latest guidelines recommend nonoperative management in selected cases, more extensive pragmatic trials are warranted to ascertain the effectiveness and use of antibiotherapy.

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Author Contributions: Concept-**ACY, SZ**; Supervision-**FY, MCA**; Materials- ACY, MFE; Data Collection and/or Processing- **ACY,SZ,MFE**; Analysis and/ or Interpretation-**ACY, OA**; Writing **ACY, SZ**. Peer-review: Externally peer-reviewed

Ethical approval: All procedures performed in studies involving human participants were in accordance with the institutional and/or national research committee's ethical standards and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This research was related to COVID-19 so we firstly were applied to Turkish Ministry of Health Scientific Research Committee and get approval for his COVID research. In this research, ethical approval was obtained from the Kutahya University Local Ethical Committe (Date:04.06.2020, decision no:2020-09-16)

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Detection of Viral Respiratory Factors via Multiplex PCR in Newborn & Pediatric Patients and Their Distribution According to Seasons

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ABSTRACT

Objective: Respiratory viruses are a global public health problem, and viruses cause up to 80% of respiratory infections. This study aimed to elucidate the viral respiratory tract factors and the frequency of coinfections in the newborn and pediatric age groups determined by the molecular respiratory tract panel (MRTP) kit.

Materials & Method: The results of the respiratory tract panel test with the molecular multiplex method were applied to 1486 newborn and pediatric patients between 01.10.2020 and 30.04.2022 to determine the viral respiratory tract factors were analyzed retrospectively. The Multiplex RT – PCR test confirmed results were recorded from the hospital database under the supervision of a microbiologist, negative and positive controls were evaluated, and test was validated.

Results: Clinical virology laboratory test results were scanned and at least one respiratory tract virus was detected in nasopharyngeal swabs of 499 (33.6%) patients. A total of 634 viruses were detected in 499 NS-positive samples. The most commonly detected viral pathogens were parainfluenza – 3 (36.9%, n=184), respiratory syncytial virus (22.8%, n=114), human rhinovirus (19.2%, n=96), SARS-CoV-2 (12.6%, n=63), and human bocavirus (10.8%, n=54) respectively.

Conclusion: In this research, we tried to elaborate the accuracy of molecular multiplex method and the respiratory tract panel test to determine the respiratory factors in newborn and pediatric age group patients. The logic behind this lies beneath the fact that diagnosing with a kit that can detect both single and multiple factors causing coinfection can be performed simultaneously.

Keywords: viruses, multiplex RT – PCR, nasopharyngeal swab, respiratory tract infection, newborn, childhood

INTRODUCTION

Respiratory viruses are a global public health problem, and viruses cause up to 80% of respiratory infections. This incidence leads to significant morbidity and mortality worldwide (1, 2). Viral respiratory tract infections are common in newborns and children (3, 4). They constitute approximately half of pediatric community-acquired pneumonia cases and a quarter of adult pneumonia cases (5). Acute respiratory tract infections are considered to be one of the most important causes of death in children <5 years of age (4). Winter and spring are peak seasons for flu and other common respiratory infections (5, 6).

The use of rapid antigen tests with extremely high specificity and low sensitivity is reliable when respiratory viral infections are at a high prevalence. Serological tests are primarily used for epidemiological studies and their application in the diagnosis of viral respiratory tract infections is limited (7, 8). Technological advances in molecular diagnostic tests have started a revolution in the field of diagnostic virology. Molecular methods such as polymerase chain reaction (PCR) and real-time polymerase chain reaction (RT – PCR) are more widely performed than other methods for the laboratory diagnosis of viral respiratory tract infections and can be used in conventional methods such as cell culture. Because they show high sensitivity and specificity, obtain results in a short time, and identify viruses that are difficult to culture or slow to reproduce. Today, many multiplex RT – PCR tests have been developed to diagnose an increasing number of respiratory tract viruses, in which more than one virus can be detected simultaneously in a single test (9, 10).

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This study aimed to elucidate the viral respiratory tract factors and the frequency of coinfections in the newborn and pediatric age groups determined by the molecular respiratory tract panel (MRTP) kit and to investigate the seasonal distribution with demographic data such as age and gender.

MATERIAL and METHODs

The results of the respiratory tract panel test with the molecular multiplex method, which was applied to 1486 newborn and pediatric patients between 01.10.2020 and 30.04.2022 in order to determine the viral respiratory tract factors, were analyzed retrospectively. The ethics committee approval was granted on 29/04/2022 with protocol number: 4/87. The study complied with the Declaration of Helsinki, and informed consent was obtained from all participants.

Nasopharyngeal and throat nasopharyngeal swab samples, containing a viral nucleic acid extracting and protective liquid have been collected from from pediatric patients with respiratory symptoms. These materials were delivered to the microbiology laboratory with a transfer tube. After the nucleic acid was obtained, the RT – PCR result was gained by processing the protocol specified by the manufacturer. Negative and positive controls were carefully evaluated, and the test was validated.

Statistical Analysis: SPSS 25 (SPSS Inc, Chicago, IL, USA) package program was used for statistical evaluation of the data. Continuous data were given as the median. Categorical data were expressed as numbers and percentages. Visual features (histogram and probability plots) and Kolmogorov-Smirnov test were utilized for the normal distribution of the variables. Student's T test or Mann – Whitney U test was used for comparison. The Mann – Whitney U test was utilized to compare continuous variables. Qualitative variables were compared via Pearson Chi-Square or Fisher exact tests. A P value <0.05 was considered statistically significant.

RESULTS

RT – PCR results of the nasopharyngeal swab (NS) samples taken from 1486 children aged 0 – 18 years who were diagnosed with acute respiratory tract infection between October 2020 and April 2022 were included in this study. The gender distribution was 58.6% (n=871) of the children were male, and 41.4% (n=615) were female. The median age was 2 years (ranging between 0 – 18 years).

The most commonly detected viral pathogens were Parainfluenza – 3 (PIV3) (36.9%, n=184), RSV (22.8%, n=114), HRV (19.2%, n=96), SARS-CoV-2 (12.6%, n=63), and HBoV (10.8%, n=54) respectively. The frequency of respiratory viral pathogens detected by RT – PCR is presented in **Table 1**.

Single viral infections were detected in 442 (29.7%) of 1486 samples, and two or more viral infections were found in 57 samples (3.8%). The most common multiple infections were found to be HRV and PIV3 (12.3%, n=7) (**Table 2**).

Viral agents were detected in 499 of the 1486 patient samples with the diagnosis of respiratory tract infection, of which 292 (33.5%) were male, and 297 (33.7%) were female. No statistically significant difference was found when the gender distribution of single and multiple infections was evaluated. PIV3, RSV, HRV were the most common viral agents in both male and female patients. Distribution of viruses by gender in respiratory tract samples is presented in **Table 3**.

Viral respiratory pathogens were observed at the highest rate in the 0 – 1 year-old age group (37.9%, n=245). The other distribution was as follows: >1 – 5 years old (34.4%, n=185), >5 – 10 years old (26.1%, n=37) and >10 – 18 years old (20.1%, n=32). While RSV (15.3%) was the most common factor in the 0 – 1 age group ($p<0.001$), it was determined that PIV3 was the most frequent viral pathogen in other age groups. RSV (15.3%), PIV3 (14.2%) and HRV (8.3%) were the most common respiratory tract viruses at ≤1 year of age. Single infection was more in the 0 – 1 year age group (33.5%, n=217), while multiple infections were found in the >1 – 5 years age group (4.6%, n=25) ($p<0.001$) (**Table 4**).

During the study period, the respiratory test positivity rate was found to be the highest in spring (February – March – April) (61.4%, n=226) ($p<0.001$). At the same time, it was found that 215 (58.4%) of the patients were infected with a single virus in this season, and 11 (3.0%) were infected with at least two viruses.

When each virus's seasonal and monthly distribution was analyzed, it was observed that PIV3, RSV, HRV, and HBoV were detected in all four seasons. HRV (9.1%) was the most common cause in winter, and adenovirus (AV) in summer. The seasonal distribution of viral agents was elaborated in **Table 5**.

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Table 1. Demographic and laboratory characteristics of the patients

		%	n	p
Viral pathogen positive patient	Total	33.6	499/1486	
	Male	33.5	292/871	0.957
	Female	33.7	207/615	
Median Age (years)			2 (0-18)	
Single infection		29.7	442/1486	
Multipl infection		3.8	57/1486	
	AV, HBoV	1.8	1/57	
	AV, HRV	3.5	2/57	
	AV, HCoV HKU1	1.8	1/57	
	AV, PIV3	5.3	3/57	
	HCoV 229E, HRV	1.8	1/57	
	HCoV HKU1, EV	1.8	1/57	
	HCoV OC43, HCoV NL63	1.8	1/57	
	HCoV OC43, PIV3	1.8	1/57	
	HCoV OC43, RSV	5.3	3/57	
	HCoV OC43, HRV	1.8	1/57	
	HBoV, EV	1.8	1/57	
	HBoV, PIV3	1.8	1/57	
	HBoV, Sars CoV-2	1.8	1/57	
	INF-A, HBoV	1.8	1/57	
	INF-A, RSV	1.8	1/57	
	INF-A, Sars CoV-2	1.8	1/57	
	HpeV, PIV3	3.5	2/57	
	PIV2, PIV3	1.8	1/57	
	RSV, HBoV	5.3	3/57	
	RSV, PIV3	8.8	5/57	
	RSV, HRV	3.5	2/57	
	HRV, EV	1.8	2/57	
	HRV, HBoV	1.8	1/57	
	HRV, PIV3	12.3	7/57	
	HRV, Sars CoV-2	1.8	1/57	
	Sars CoV-2, EV	1.8	1/57	
	Sars CoV-2, PIV3	5.3	3/57	
	AV, HCoV 229E, HCoV OC43	1.8	1/57	
	HCoV OC43, HCoV HKU1, PIV3	1.8	1/57	
	HBoV, PIV1, PIV3	1.8	1/57	
	hMPV, HpeV, HRV	1.8	1/57	

HpeV: human parechovirus; HRV: human rhinovirus; INF-A: influenza A virus; hMPV: human metapneumovirus; HBoV: human bocavirus; HCoV: human coronavirus; PIV: parainfluenza virus AV: adenovirus; RSV: respiratory syncytial virus; EV: Enterovirus. Data are given as number (%).

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Table 2. Distribution of respiratory viral pathogen samples (n=499) detected by RT – PCR

Specific viral pathogen	N	%
Adenovirus	27	5.4
Bocavirus	54	10.8
Corona 229 E	9	1.8
Corona HKU1	8	1.6
Coronavirus NL63	3	0.6
Coronavirus OC43	18	3.6
Enterovirus	7	1.4
Human metapneumovirus A/B	11	2.2
Influenza A	26	5.2
Influenza B	0	0
Influenza A-H1	3	0.6
Parechovirus	6	1.2
Parainfluenza 1	1	0.2
Parainfluenza 2	4	0.8
Parainfluenza 3	184	36.9
Parainfluenza 4	0	0
RSV	114	22.8
Rhinovirus	96	19.2
Sars-CoV-2	63	12.6
Total	634	100

Table 3. Distribution of viruses by gender in respiratory tract samples

	Male (n=871)	Female (n=615)	Total (n=1486)	P value
Single infection	259 (29.7)	183 (29.8)	442 (29.7)	0.993
Multipl infection	33 (3.8)	24 (3.9)	57 (3.8)	
Positive Respiratory Test	292 (33.5)	297 (33.7)	499 (33.6)	0.957
Viral pathogen				
AV	22 (2.5)	5 (0.8)	27 (1.8)	0.015
HBoV	31 (3.6)	23 (3.7)	54 (3.6)	0.855
HCoV 229 E	4 (0.5)	5 (0.8)	9 (0.6)	0.502
HCoV HKU1	4 (0.5)	4 (0.7)	8 (0.5)	0.725
HCoV NL63	1 (0.1)	2 (0.3)	3 (0.2)	0.573
HCoV 0C43	10 (1.1)	8(1.3)	18 (1.2)	0.791
EV	2 (0.2)	5 (0.8)	7 (0.5)	0.106
hMPV	11 (1.3)	0 (0)	11 (0.7)	0.004
INF-A	9 (1.0)	17 (2.8)	26 (1.7)	0.012
INF-B	0 (0)	0(0)	0(0)	
INF-A-H1	2 (0.2)	1 (0.2)	3 (0.2)	0.777
HpeV	3 (0.3)	3 (0.5)	6 (0.4)	0.696
PIV1	0 (0)	1 (0.2)	1 (0.1)	0.414
PIV2	1 (0.1)	3 (0.5)	4 (0.3)	0.313
PIV3	108 (12.4)	76 (12.4)	184 (12.4)	0.981
PIV4	0	0	0	
RSV	68 (7.8)	46 (7.5)	114 (7.7)	0.815
HRV	65 (7.5)	31 (5)	96 (6.5)	0.061
SARS-CoV-2	34 (3.9)	29 (4.7)	63 (4.2)	0.444

HpeV: human parechovirus; HRV: human rhinovirus; INF-A: influenza A virus; hMPV: human metapneumovirus; HBoV: human bocavirus; HCoV: human coronavirus; PIV: parainfluenza virus AV: adenovirus; RSV: respiratory syncytial virus; EV: Enterovirus. Data are given as number (%).

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Tablo 4. Distribution of viruses by age groups in respiratory tract samples

Viral Pathogen	Age Groups 0-1 n = 647	>1-5 n = 538	>5-10 n = 142	>10-18 n = 159	Total n = 1486	P Value
ADV	5 (0.8)	20 (3.7)	1 (0.7)	1 (0.6)	27 (1.8)	0.001
HBoV	12 (1.9)	38 (7.1)	3 (2.1)	1 (0.6)	54 (3.6)	< 0.001
HCoV 229 E	7 (1.1)	2 (0.4)	0 (0.0)	0 (0.0)	9 (0.6)	0.320
HCoV HKU1	3 (0.5)	4 (0.7)	1 (0.7)	0 (0.0)	8 (0.5)	0.690
HCoV NL63	1 (0.2)	1 (0.2)	1 (0.7)	0 (0.0)	3 (0.2)	0.521
HCoV 0C43	8 (1.1)	9 (1.7)	1 (0.7)	0 (0.0)	18 (1.2)	0.430
EV	3 (0.5)	2 (0.4)	2 (1.4)	0 (0.0)	7 (0.5)	0.332
hMPV	8 (1.2)	2 (0.4)	0 (0.0)	1 (0.6)	11 (0.7)	0.303
INF-A	9 (1.4)	12 (2.2)	2 (1.4)	3 (1.9)	26 (1.7)	0.723
INF-B	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
INF-A-H1	0 (0.0)	2 (0.4)	1 (0.7)	0 (0.0)	3 (0.2)	0.144
HpeV	2 (0.3)	3 (0.6)	0 (0.0)	1 (0.6)	6 (0.4)	0.835
PIV1	0 (0.0)	1(0.2)	0 (0.0)	0 (0.0)	1 (0.1)	0.565
PIV2	2 (0.3)	2 (0.4)	0 (0.0)	0 (0.0)	4 (0.3)	0.622
PIV3	92 (14.2)	64 (11.9)	12 (8.5)	16 (10.1)	184 (12.4)	0.176
PIV4	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
RSV	99 (15.3)	14 (2.6)	1 (0.7)	0	114 (7.7)	< 0.001
HRV	54 (8.3)	35 (6.5)	5 (3.5)	2 (1.3)	96 (6.5)	0.005
SARS-CoV-2	33 (5.1)	12 (2.2)	8 (5.6)	10 (6.3)	63 (4.2)	0.031
Pathogen Number						
Single infection	217 (33.5)	160 (29.7)	36 (25.4)	29 (18.2)	442 (29.7)	< 0.001
Multipl infection	28 (4.3)	25 (4.6)	1 (0.7)	3 (1.9)	57 (3.8)	
Total	245 (37.9)	185 (34.4)	37 (26.1)	32 (20.1)	499 (33.6)	< 0.001

Table 5. Respiratory viruses and seasonal distribution

	Spring n= 368	Summer n= 148	Autumn n= 333	Winter n= 637	P Value
Single infection	215 (58.4)	60 (40.5)	73 (21.9)	94 (14.8)	<0.001
Multipl infection	11 (3.0)	17 (11.5)	20 (6.0)	9 (1.4)	
Viral pathogen					
ADV	0	26 (17.6)	1 (0.3)	0	<0.001
HBoV	29 (7.9)	20 (13.5)	2 (0.6)	3 (0.5)	<0.001
HCoV 229 E	0 (0)	9 (6.1)	0 (0)	0 (0)	<0.001
HCoV HKU1	3 (0.8)	5 (3.4)	0 (0)	0 (0)	<0.001
HCoV NL63	0 (0)	3 (2.0)	0 (0)	0 (0)	0.001
HCoV 0C43	0 (0)	18 (12.2)	0 (0)	0 (0)	<0.001
EV	1 (0.3)	3 (2.0)	3 (0.9)	0 (0)	0.003
hMPV	11(3.0)	0 (0)	0 (0)	0 (0)	<0.001
INF-A	26 (7.1)	0 (0)	0 (0)	0 (0)	<0.001
INF-B	0 (0)	0 (0)	0 (0)	0 (0)	
INF-A-H1	3 (0.8)	0 (0)	0 (0)	0 (0)	0.069
HpeV	6 (1.6)	0 (0)	0 (0)	0 (0)	0.001
PIV1	1 (0.3)	0 (0)	0 (0)	0 (0)	0.571
PIV2	4(1.1)	0 (0)	0 (0)	0 (0)	0.016
PIV3	151(41)	6(4.1)	11 (3.3)	16 (2.5)	<0.001
PIV4	0 (0)	0 (0)	0 (0)	0 (0)	
RSV	62(16.8)	3 (2.0)	3(0.9)	46 (7.2)	<0.001
HRV	1 (0.3)	4(2.7)	33 (9.9)	58 (9.1)	<0.001
SARS-CoV-2	2 (0.5)	0 (0)	61(18.3)	0 (0)	<0.001

DISCUSSION

Respiratory viruses play an important role in LRTI during infancy and childhood. Routine laboratory tests and radiological examinations cannot differentiate between viral and bacterial, and empirical antibiotic therapy is mostly given (10). Gonzalez – Carrasco et al. (11)emphasized that viral respiratory tract infections should also be considered in newborns with a runny nose, apnea, and high oxygen requirement, and suspected sepsis. In another study, it has been shown that viral tests can make a significant contribution to elucidating the etiology in infants under 3 months of age presenting with unfocused fever (12). Kidszun et al. (13) reported that in some of the newborns who showed clinical worsening and were thought to have late-onset sepsis in the ICU, no growth was found in the blood culture, and respiratory viruses were detected in the nasopharyngeal aspirate.

In previous literature, it has been reported that RSV was the most common cause of LRTI in infants (14 – 17). RSV was the most common factor with 80% of patients hospitalized in the neonatal ICU due to LRTI. This rate was found to be 80% in the study of Cho et al. (16) and 95% in the study of Bukhari et al. (17).

Designating a single factor can be considered an advantage in terms of precautions and preventive treatments. As it is known, RSV is transmitted mostly by direct contact and contaminated items, and to a lesser extent by droplets. Homaira et al. (18) isolated the ribonucleic acid molecule of RSV from visitors' clothes and frequently used surfaces in the ICU, and it was shown that this was important in contamination.

Due to its high sensitivity and specificity for the diagnosis of respiratory tract viruses, the multiplex RT – PCR test is the method of choice today (19). Lin et al. (2020) stated that RT – PCR had higher detection rates compared with traditional antigen tests and viral cultures (75.3% versus 48.3%). They have detected that RSV, RV, and PIV3 were the leading pathogens detected in pediatric RTI patients (19). In this study, single viral infections were detected in 29.7% of 1486 samples, two or more (multipl) viral infections were found in 3.8% of samples. The most common multiple infections were found to be HRV and PIV3 with a ratio of 12.3%.

Jansen et al. (20) aimed to investigate respiratory tract viruses with multiplex RT – PCR method, using nasopharyngeal aspirate samples from 133 pediatric patients admitted for acute respiratory infection during the winter of 2007 – 2008 in the Netherlands. With the Multiplex RT – PCR test, positive results for one or more viruses were obtained in 68% of samples. Single infection was detected in 50% of the samples, and dual infection in 17%. Rhinovirus was the most common pathogen detected with a rate of 27% followed by RSV 16.5%, adenovirus 10.5%, influenza A 6.7%, hMPV 6%, HBoV 3%, HCoV 2.2%, influenza B 2.2%.

In this study, we found at least one respiratory tract virus in 33.6% patients diagnosed with respiratory tract infection by RT – PCR method. A total of 634 viruses were detected in 499 NS-positive samples. The most commonly detected viral pathogens were parainfluenza–3 (PIV3) (36.9%), respiratory syncytial virus (RSV) (22.8%), human rhinovirus (HRV) (19.2%), SARS-CoV-2 (12.6%), and human bocavirus (HBoV) (10.8%4) respectively.

Özcan et al. (21) investigated the presence of viral respiratory pathogens using multiplex RT – PCR in 104 children aged 3–17 years who had asthma attacks. Respiratory viruses were detected in 53.8% of the nasopharyngeal and nasal swab samples. The most common viral agent was rhinovirus (35.6%). Although viral URTIs are the most common cause of asthma attacks, it has been stated that the severity of exacerbation was independent of the presence of respiratory virus.

Beka et al. (22) tested samples of 109 children with acute respiratory tract infections for RSV, rhinovirus, influenza virus, hMPV, adenovirus, PIV and HCoV by multiplex PCR test in their study in Istanbul. Respiratory viruses were detected in 39.4% of the cases (rhinovirus 14.7%, RSV B 7.3%, influenza A 6.4%, hMPV 3.6%, adenovirus 3.6%, HCoV 0.9%, PIV 3 0.9%, PIV 4% 0.9 and RSV A were found to be 0.9%). For the diagnosis of RSV infections, the sensitivity of PCR and DFA testing was 100% and 100%, and the specificity was 97% and 100%, respectively.

The main limitation of this research may be attributed to its retrospective nature. On the contrary, the high number of sample size, and segmentation of patients according to age and seasonal effects can be counted as the study's strengths.

CONCLUSION

In this research, we tried to elaborate the accuracy of molecular multiplex method and the respiratory tract panel test to determine the respiratory factors in newborn and pediatric age group patients. The logic behind this lies beneath the fact that diagnosing with a kit that can detect both single and multiple factors causing coinfection can be performed simultaneously.

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Ethical approval: All procedures performed in studies involving human participants were in accordance with the institutional and/or national research committee's ethical standards and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The ethics committee approval has been granted at 29/04/2022 with protocol number: 4/87. The study complied with the Declaration of Helsinki and informed consent has been obtained from all participants.

Abbreviations

AV : Adenovirus
DFA : Direct Fluorescent Antibody
EIA : Enzyme Immunoassay
HBoV : Human Bocavirus
HCoV : Human Coronavirus
HEV : Human Enterovirus
HPeV : Human Parechovirus
HRV : Human Rhino Virus
ICU : Intensive Care Unit
LRTI : Lower Respiratory Tract Infection
MPV : Metapneumovirus
MRTP : Molecular Respiratory Tract Panel
NS : Nasopharyngeal Swab
PIV : Parainfluenza virus
RSV : Respiratory Syncytial Virus
RT – PCR : Real Time- Polymerase Chain Reaction
SPSS : Statistics Package for Social Sciences

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Effect of clinical progress in antihypertensive medications among COVID-19 patients

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ABSTRACT

Objective: Many chronic diseases, such as hypertension, diabetes, and coronary heart disease, paving the way for the disease to progress unfavorably in Covid-19. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-2 receptor blockers (ARBs) can upregulate ACE2 receptors (which SARS-COV-2 uses to enter the host cell) or protect against infection by limiting the effects of Angiotensin 2. This study aimed to reveal the impact of antihypertensive drugs on the hospital staying, and mortality in Covid-19 patients followed in the hospital.

Methods and Results: One hundred patients were randomly selected with hypertension, diabetes mellitus and coronary artery disease hospitalized in Kayseri City Training and Research Hospital due to Covid-19 infection. Patients were grouped as taking ACEIs and ARBs group and not taking ACEIs and ARBs group. There were no differences among the groups in terms of the frequency of chronic disease and treatment modalities. The length of the hospital stays, bedding into the Intensive Care Unit (ICU), and mortality rates were higher in the group without ACEIs or ARBs. Mortality was significantly lower among patients who used ACEIs and ARBs (P=0.00, P=0.02, respectively) and incredibly high among beta-blocker users (P=0.00). It was found that the advanced age, male gender and use of beta-blockers were associated with mortality.

Conclusion: Although antihypertensive medications are allegedly associated with increased mortality rates, the risk of mortality has not been detected in people taking ACEIs and ARBs. Further studies involving a greater number of patients are needed.

Keywords: Angiotensin receptor blockers (ARBs); Angiotensin-converting enzyme inhibitors (ACEIs); Antihypertensive regimen; Beta-adrenergic blockers, mortality; prolonged hospitalization; Covid-19.

INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the virus responsible for Covid-19, a global pandemic that had devastating effects on the health system.and populations worldwide. In March 2020 declared a pandemic by the World Health Organization.

Many studies has been shown that the mortality increases in patients with hypertension due to Covid-19 infection (1). Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) inhibit the renin-angiotensin-aldosterone system (RAAS) and play an important role in the treatment of hypertension.

Researchers believe that the Angiotensin-converting enzyme 2 (ACE2) receptor on alveolar epithelial cell serves as a high-affinity receptor and co-transporter for SARS-CoV-2 to enter the lungs (2). It has been reported that ACE2 expression is down-regulated in Covid-19 infection and causes pneumonia progression due to RAAS over-activation (3). Therefore, ACEIs and ARBs can prevent lung injury via preventing RAAS activation by preventing down-regulation of ACE2. However, due to insufficient clinical evidence, it is unclear how the treatment approach will be in the presence of Covid-19 infection in hypertensive patients.

In this study, the effect of ACEIs/ARBs treatment on mortality rate in Covid-19 infected patients with hypertension has been searched.

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MATERIAL and METHODs

Study Design and Participants

This retrospective study was carried out in a tertiary hospital with a total of 1607 beds and also includes 253 intensive care beds. Between March 2020 and October 2020, patients with positive RT-PCR (Reverse Transcription Polymerase Chain Reaction) tests obtained from nasopharyngeal swab samples and taking antihypertensive were selected randomly. Patients who suspected SARS-COV2 but negative RT-PCR test were excluded from the study. Patient information was recorded electronically.

Statistical Analysis

The collected information was processed using Statistical Package for Social Sciences (SPSS) for Windows (version by 22.0). Categorical variables are expressed as numbers and percentages, and Chi-square or Fisher's Exact Test analysis was used for comparisons. Histogram analyzes were performed to determine whether continuous variables show normal distribution. Non-parametric data: median (min-max), while the significance between groups was determined using Mann Whitney U test. In all analyzes, $p<0.05$ was considered statistically significant.

RESULTS

A total of 102 patients were included in the study. The characteristics of the patients are shown in **Table 1**. The mean hospital stay of all patients was 13.5±6.7 SD (min-max: 2-44) days.

Patients' classifications according to the ongoing treatment: ACEIs (38 patients, 37.6%), ARBs (25 patients, 24%), beta-blockers (45 patients, 44%), calcium channel blockers (32 patients, 31%), diuretics (38 patients, 37%).

The mean age of the patients was 67.6 ±12.2 years. Fifty-four patients (52.9%) were male. Diabetes mellitus (40 patients, 39%) was the most common underlying disease. The most common symptom was cough (50 patients, 49%). According to the status of receiving oxygen support, 79% (81) of the patients received high-flow cannula O2 support, 5% (6) of the patients received CPAP (Continuous positive airway pressure), 20% (21) of the patients received invasive mechanical ventilation. The 37% (38) of the patients needed ICU (Intensive care unit) admissions, and 24% (25) of them died.

Table 1. Demographic characteristics of the Patient groups.

	ACEIs/ARBs group n=60 (%)	Non-ACEIs/ARBs group n=42 (%)	P-value
Age -Median (min-max)	66.3 (63.3-69.3)	69 (65.3-72.1)	0.46
Male	26 (43%)	28 (67%)	0.02*
Symptoms			
Fever	20 (33%)	21 (50%)	0.91
Cough	26 (43%)	24 (57%)	0.17
Dyspnea	22 (37%)	16 (38%)	0.88
Fatigue	19 (32%)	13 (31%)	0.93
Headache	10 (16%)	1 (2%)	0.02*
Diarrhea	2 (3%)	6 (14%)	0.04*
Vomiting	2 (3%)	1 (2%)	0.77
Comorbidities			
Diabetes Mellitus	25 (42%)	15 (35%)	0.54
Coronary artery disease	7 (11%)	10 (23%)	0.10
Chronic Obstructive Pulmonary Disease	9 (15%)	4 (10%)	0.41
Treatment			
Hydroxychloroquine	11 (18%)	3 (7%)	0.10
Corticosteroid	14 (23%)	13 (31%)	0.39
Favipiravir	44 (73%)	36 (86%)	0.13
Enoxaparin sodium	37 (61%)	33 (79%)	0.07
Coumadin	3 (5%)	1 (2%)	0.50
Antibiotics	53 (88%)	40 (95%)	0.22
Respiratory support			
High flow O2	47 (78%)	34 (81%)	0.74
Non-invasive Mechanical Ventilation	1 (2%)	5 (12%)	0.31
Invasive Mechanical Ventilation	3 (5%)	18 (43%)	0.00*
Prognosis			
Median day of hospitalization (min-max)	13 (11-14)	17 (13-20)	0.03*
Hospitalization in intensive care	12 (20%)	26 (62%)	0.00*
Mortality	4 (7%)	21 (50%)	0.00*

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Mortality risk factors

The death rate is 3.9 times higher among patients aged 65 and over than those under 65. Mortality rates for men are higher than those for women (p=0.02).

Mortality was significantly lower among patients using ACEIs and ARBs (P=0.00, P=0.02, respectively) and incredibly high among beta-blocker users (P=0.00). Beta-blocker use rate in patients with coronary artery diseaswas significantly higher than other antihypertensives (p=0.004). There was no effect of comorbidity on mortality.

While the white blood cell and neutrophil counts, BUN (blood urea nitrogen), creatinine and SGOT (for the first two weeks), lactate dehydrogenase, procalcitonin, c-reactive protein, D-dimer values were found to be higher in patients who died, but the lymphocyte levels were found to be considerably lower than in surviving patients.

Platelet levels were found significantly lower in patients who died 14th day after hospitalization, and there was no significant difference in creatinine and AST levels.

Monocyte, fibrinogen, ferritin, and ALT levels were similar to patients who died and survived.

The patients were divided into two groups, those who received ACEIs and ARBs and those who did not use (Non-ACEIs and ARBs). D-dimer, BUN, and LDH levels were significantly lower in patients who use at least one ACEIs and/or ARBs. Lymphocyte levels were found significantly higher in this group. CRP levels were substantially lower except for the seventh day in ACEIs and ARBs groups. No significant differences were observed between the two groups regarding monocytes count, fibrinogen, glucose creation, and ALT values. Like the dead patient, platelet count was significantly lower in patients' Non-ACEIs and ARBs on the fourteenth day (**Table 3**).

Table 2. Comparison of Overall Mortality Rates

	Cases of Death (n=25)	Cases of Surviving (n=77)	Multivariate Analysis OR (95% CI) P	*P-Value*
Age -Median (min-max) (65 years and older)	74 (70-79)	65 (62-67)	3.93 (1.23-12.56)	0.01**
Male gender	18 (72%)	36 (46%)	0.34 (1.09-7.81)	0.17**
Antihypertensives				
ACEIs	2 (4%)	36 (46%)	10.09 (2.25-45.83)	0.00**
ARBs	2 (4%)	24 (31%)	5.20 (1.13-23.88)	0.02**
Beta Blocker	20 (80%)	25 (32%)	0.12 (0.04-0.35)	0.00**
Calcium Channel Blocker	7 (28%)	25 (32%)	1.23 (0.45-3.34)	0.67
Diuretic	9 (36%)	29 (37%)	1.07 (0.42-2.74	0.88
Comorbidities				
Diabetes Mellitus	9 (36%)	31 (40%)	1.19 (0.47-3.05)	0.70
Coronary artery disease	3 (12%)	14 (18%)	1.91 (0.39-9.30)	0.41
Chronic Obstructive Pulmonary Disease	5 (20%)	8 (10 %)	0.46 (0.13-1.57)	0.21
Treatment				
Hydroxychloroquine	3 (12%)	11 (14%)	1.22 (0.31- 4.78)	0.77
Corticosteroid	10 (40 %)	17 (22%)	0.42 (0.16-1.11)	0.07
Favipiravir	23 (92%)	57 (74%)	0.24 (0.05-1.14)	0.05
Enoxaparin	20 (80 %)	50 (64 %)	0.46 (0.15- 1.37)	0.15
Coumadin	0	4 (5 %)	0.74 (0.66-0.83)	0.24
Antibiotic	24 (96%)	69 (89 %)	0.35 (0.04-3.02)	0.32
Respiratory support				
High flow O2	21	60	0.31 (0.01-5.24)	0.39
Non-invasive Mechanical Ventilation	4 (16%)	2 (2.6%)	0.19 (0.03-1.24)	0.05**
Invasive Mechanical Ventilation	21 (84%)	0 (0%)	0.23 (0.16-0.32)	0.01**

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Table 3: Laboratory findings of first, 7th, and 14th day of hospitalization in ACEIs/ARBs group and Non-ACEIs/ARB's group

	First day of hospitalization			7th day of hospitalization			14th day of hospitalization		
Laboratory measures-median (min-max)	**ACE/ARB Group n=60 (%)**	**Non-ACE/ARB Group n=42 (%)**	**P**	**ACE/ARB Group n=60 (%)**	**Non-ACE/ARB Group n=42 (%)**	**P**	**ACE/ARB group n=60 (%)**	**Non-ACE/ARB Group n=42 (%)**	**P**
White blood cell count, $\times 10^9$/	6735 (2700-18950)	7550 (3140-16360)	0.097	6670 (2560-19720)	7850 (3040-18950)	0.195	8430 (3430-18490)	8200 (1780-39090)	0.804
Lymphocyte count, $\times 10^9$/L	1565 (350-7390)	1270 (340-2890)	0.039*	1380 (430-5860)	960 (350-2180)	0.007*	1320 (440-7380)	725 (170-1890)	0.000*
Neutrophil	4055 (300-16500)	5450 (2210-14890)	0.010*	4650 (810-18770)	6340 (2410-17290)	0.053*	5820 (1890-16860)	6750 (840-37390)	0.131
Monocytes	600 (40-1780)	520 (50-1430)	0.629	500 (180-1140)	525 (100-8430)	0.942	625 (240-1420)	500 (80-1360)	0.082
Platelets	205 (116-399)	197 (119-1160)	0.994	236 (125-463)	244 (113- 520)	0.934	308 (145-495)	234 (105-468)	0.029*
Blood urea nitrogen (BUN)	18 (7-176)	26 (10-111)	0.003*	18 (2-97)	24 (8-95)	0.026*	18 (5-48)	27 (9-111)	0.026*
Creatinine	1 (0.54-2.89)	1.15(0.3-2.99)	0.192	0.83 (0.16-5.70)	1.01 (0.46-5.4)	0.183	0.81 (0.65-3.28)	0.95 (0.49-4.59)	0.423
Aspartate aminotransferase, U/L	23 (10-169	30 (12-333)	0.041*	28 (14-146)	32 (11-146)	0.167	22.5 (11-122)	26 (12-90)	0.300
Alanine aminotransferase, U/L	20 (6-200)	21(4-353)	0.422	23 (9-292)	25 (8-281)	0.978	29 (11-297)	27 (13-105)	0.933
Lactate dehydrogenase IU/L	274 (158-4022)	330 (137-880)	0.038*	294 (187-4462)	417 (125-747)	0.009*	306 (82-4443)	409 (174-645)	0.027*
Glucose mg/dL	144 (70-465)	125 (74-354)	0.375	124 (65-377)	133 (70-427)	0.996	134 (59-314)	127 (61-374)	0.293
Procalcitonin, ng/ml	0.08 (0.02-0.90)	0.22 (0.02-7.34)	0.000*	0.09 (0.02-4.61)	0.16 (0.02-6.63)	0.395	0.06 (0.03-0.33)	0.13 (0.02-1.48)	0.076
C-reactive protein, mg/dl	21.5 (0.50-278)	83 (1.8-330)	0.006*	38 (0.70-304)	53 (3.7-242)	0.250	16.9 (1.6-20)	37.8 (1.2-144)	0.014*
Ferritin, ng/ml	239 (6-1526)	440 (44-5560)	0.019*	487 (158-1687)	575 (43-8898)	0.666	433 (76-2204)	718 (246-5971)	0.261
D- dimer, ng/ml	550 (40-7670)	1070 (100-16260)	0.021*	675 (90-2750)	1245 (140-20000)	0.009*	630 (90-22660)	2035 (250-18020)	0.001*
Fibrinogen	4750 (209-8890)	5190 (208-10700)	0.217	5310 (2100-10880)	5665 (250-97602)	0.936	5050 (1910-8000)	4770 (250 -6820)	0.929

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DISCUSSION

In this study, we tried to evaluate the effects of antihypertensive drugs on survival and length of hospitalization for Covid-19 patients, retrospectively. A meta-analysis of 52 studies indicated no higher risks of multivariable-adjusted mortality associated with the receipt of ACEIs/ARBs, which is consistent with recommendations for the continuation of these medications among patients for whom they are prescribed for the treatment [4]. We observed that ACEIs and ARBs users reduced the length of hospital stay and mortality compared to non-users. These findings support some published studies to continue ACEIs/ARBs in patients with Covid-19 [5] [6] But there is limited information about reducing mortality rates and length of stay [7].

It has been argued that over-activation of the RAAS system may contribute to the progression of Covid-19-related lung injury by causing an inflammatory response and cytokine storm, stimulating the NADH/NADPH oxidase system and triggering cell contraction and vasoconstriction [5]. Angiotensin II (AT2) has proinflammatory, profibrotic, vasoconstrictor, and prothrombotic effects via the Angiotensin type 1 (AT1) receptor, which have mechanical complications associated with severe Covid-19 infection. Therefore, decreased AT2 levels or inhibition of the AT1 receptor may reduce these harmful effects [8]. However, evidence for the efficacy of ARBs or ACEIs is lacking outside of animal models and observational studies of SARS-CoV.

Beta-blockers have been used to treat cardiovascular conditions such as hypertension, arrhythmias, and myocardial infarction. Observational retrospective studies have established a link between beta-blocker therapy and increased survival in critically ill patients caused by different conditions, such as sepsis acute respiratory failure. The beneficial effects of β-blockers in Covid-19 in including improved oxygenation, reducing bronchial secretion, inhibiting the entry of SARS-CoV-2 through ACE2 and CD147, inhibiting the release of pro-inflammatory cytokines, reduce the development of pulmonary edema and ARDS, inhibiting the growth of endothelial dysfunction and coagulopathy, blocking proliferation of SARS-CoV-2, suppression of NLRP3 inflammasome and NF-κB signaling and prevention development of neural-cytokine loop in SARS-CoV-2 infection [9] [10]. Most of our patients were using metoprolol (39/45 patients). Clemente-Moragón et al. demonstrated that metoprolol was safe. It has effects on reduced exacerbated intravenous lung inflammation, and improved oxygenation in Covid-19–associated ARDS [11]. In this study, metoprolol was used during infection, unlike our study. Our patients were already taking metoprolol because of hypertension or coronary artery disease. Although using beta-blockers was associated with mortality in our study, this was attributed to the fact that beta-blockers are more frequently used in coronary artery disease.

Our study showed that advanced age and male gender were independent variables associated with mortality in Covid-19, consistent with the literature [12]. Pre-existing conditions such as cardiovascular disease, chronic kidney disease, chronic lung diseases (especially chronic obstructive airways disease), diabetes mellitus, hypertension, immunosuppression, and obesity may predispose patients to an adverse clinical course and an increased risk of intubation and death [13]. However, our study detected no significant relationship between comorbidity, mortality, and prolonged hospitalization.

In our study, the most important prognostic factors affecting mortality in the patients included advanced age, male gender and beta-blocker use, non-invasive and invasive mechanical ventilation. These data need to be confirmed by prospective cohort studies.

Although white blood cell levels were found to be useful in estimating mortality, no significant correlation was detected with the levels of white blood cells in ACEIs and ARBs groups. However, increased neutrophil levels and decreased lymphocyte levels were demonstrated in ACEIs and ARBs groups. Neutrophilic inflammation contributes to the higher mortality of Covid-19 in patients with underlying co-morbidities such as diabetes and cardiovascular diseases [14].

High D-dimer levels suggest extensive thrombin production and fibrinolysis. In our study, D-dimer levels were significantly lower in ACEIs and ARBs groups, while considerably higher during the first fourteen days in patients who died. Some researchers have suggested using D-dimer levels for patient triage [15].

Our limitations are patients' vital signs could not be accessed and small number of patients since it was a retrospective study. The disease could not be classified as mild-moderate or severe-critical concerning mortality, and evaluations were made outside of this information. Another limitation is the single-center nature of the study.

CONCLUSION

In our study, similar to the studies in the literature, it was thought that the use of ACEIs/ARBs in hypertensive patients would not worsen the disease. ICU admission, mechanical ventilation, and mortality are not associated with ACEIs/ARBs therapy. Evidence from this study triggers an idea for future prospective studies to confirm the potential role of β-blockers in the management of Covid-19.

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Biopsied breast masses in adolescents. Analysis of clinical features

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ABSTRACT

Objective: Breast lesions in childhood are mostly benign and self-limiting, and the biopsy indications are restricted in this period. The differentiation between fibroadenomas and phyllodes tumors is difficult with imaging because of their overlap in initial size and growth rate. Therefore, biopsy or excision may be required.

Material and Methods: We retrospectively reviewed data from 531 patients (404 females, 76.1%; 127 males, 23.9%) that were applied to our center between 2009 and 2019. Breast US was performed to all applicants with pain and swelling in the their breast. Patients with fibroadenoma with and without core biopsy were recorded.

Results: Thirty-one solid breast lesions were detected. Twenty-one lesions were performed biopsy (21/531, 3.9 %). The most common mass lesion was fibroadenoma (27/31, 87.1%) and the most frequently biopsied lesion was fibroadenoma (11/21; 52.3%). The 10 simple fibroadenomas, one juvenil fibroadenoma, one benign phyllodes tumors, and two invasive ductal carcinomas have been identified. A statistically significant difference ($p < 0.05$) was detected between the groups with or without core biopsy for the size of fibroadenomas, but there was no statistically significant difference between both groups for patients' age with fibroadenoma.

Conclusion: Malignancies in the breast and lesions such as fibroadenoma that requires a malignancy exclusion are observed in children and adolescents. Large size is a statistically significant parameter in the biopsy decision.

Keywords: child, adolescent, breast, biopsy, fibroadenoma

INTRODUCTION

Breast lesions in childhood are mostly benign and self-limiting (1). Biopsy indications are limited, as they have adverse effects on breast development (1,2). Therefore, radiological findings gain more importance. Those radiologists know normal breast development and pathologies, like clinicians do, can improve the correct management of the process.

Ultrasonography (US) is the primary and major imaging method in childhood (1,2). Mammography is not beneficial in this age group, and it has radiation. Magnetic resonance imaging (MRI), on the other hand, is useful in the evaluation of some malformations and rare breast malignancy (1,2). Not only that; the Breast Imaging Reporting and Data System (BI-RADS) classification, which is useful in breast lesions, is not preferred in children due to the extremely rare occurrence of malignant lesions (0.08/100000 in female younger than 20 years) (3).

Fibroadenoma is the most common pediatric breast mass (4). The various subtypes of fibroadenomas as juvenile and giant fibroadenoma occur in childhood. Fibroadenomas and phyllodes tumors are clinically and sonographically similar. Phyllodes tumors are usually benign but can be borderline and rarely malignant (5). Macrolobulations and microcystic components are suggestive to phylloides tumor on US (6). The phyllodes tumors have more likely than fibroadenomas to rapid growth and large initial size (7). Biopsy can be required for differential diagnosis.

In this study, we discussed factors affecting the breast biopsy decision in fibroadenomas and results of the biopsy in children and adolescents.

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MATERIAL and METHODs

The study was conducted in accordance with the principles of the Helsinki Declaration. As a routine procedure, written informed consent was obtained from each patient for all procedures and publication. Ethics committee approval was received for this study from the Clinical Trials Ethics Committee (2020 / GOKAE / 682).

We retrospectively analyzed the data of 531 patients aged 1-19 years who underwent breast imaging in our center between 2009 and 2019. We saw that all patients had been evaluated with US. Three patients had breast MRI (1.5 Tesla MRI device, General Electric Signa HDx, GE Medical Systems, USA) but none of them had mammography. We used adult breast disease criteria for BI-RADS 3-5 lesions. In cases where there is more than one lesion, we evaluated the largest lesion.

Sonographic assessment and US- guided biopsies

Ultrasonography was examined using a 13 MHz superficial probe and a Hitachi Ezu-MT28-S1 model (Hitachi Inc.Japan) device by an experienced breast radiologist. In US-guided core needle biopsy procedures, 16 gauge tru-cut automatic biopsy needles (Estacore® Geotek Healthcare Products, Turkey) were used. The same radiologist performed the biopsies.

Immunohistochemical analysis

Breast cancers were grouped by hormone receptors into four molecular subtypes. The status estrogen (ER) and progesterone receptors (PR), human epidermal growth factor 2 (HER 2), and Ki 67 index were evaluated.

Statistical analysis

Data were evaluated in the IBM SPSS Statistics 22.0 statistics package program. In addition to descriptive statistical values, we confirmed a normal distribution for age and lesion size between undergoing biopsy and without biopsy in patients with fibroadenoma by Kolmogorov–Smirnov test. Subsequently, independent samples t-test was applied, which is a parametric test. We considered it statistically significant if the P value was <0.05.

RESULTS

The mean age of all cases was 14 ±5.7. 196 (36.9%) of 531 cases who applied were evaluated as completely normal since neither developmental, nor physiological, nor pathological findings were detected. Benign physiological or developmental changes were detected in 191 cases (35.9%). Of these, 182 had early or normal development, 3 had asymmetry, and 6 had neonatal hypertrophy. Gynecomastia (n=82) and adipomastia (n=14) cases were added to this group. Two patients with axillary involvement were reported. Patients diagnosed with Burkitt lymphoma and cat-scratch disease were excluded from the study.

Forty eight mass lesions were detected in 48 patients (9.0 %), (**Table 1**) as BI-RADS 0. Additionally, one patient was reported as BI-RADS 4 and another as BI-RADS 5 (0.4%). Twenty-one patients (3.9%) underwent breast biopsy (**Table1**). FNAB was applied to 4 patients (19 %) in total. These were cases with a prediagnosis of cyst and mastitis (n=2), upon the request of the family and clinician, and two male cases with unilateral gynecomastia. A total of 17 people (80.1 %) underwent core biopsy (**Table 2**). Four (4/17; 23.5 %) masses showed greater than 20% interval growth before tissue diagnosis, with imaging intervals ranging from 6 months to 2 years, and one of these was a benign phyllodes tumor. Two patients had axillary lymphadenopathy (n=2), and the other two had a suspected malignant mass (n=2). All patients who underwent core biopsy were women.

Only 2 of 21 biopsies were performed on male patients. Fibroadenoma was the most common mass lesion (27/48, 56.25%) and the most frequently biopsied lesion (11/21; 52.4%) as well. The mean age of patients with fibroadenoma was 15.5 ± 3.4 (11–19). The mean age of patients who underwent core biopsy was (15.9 ± 2.2); the mean age of the others 15 was (15.4 ± 1.8) in patients with fibroadenoma. There was no statistically significant difference between both groups (p=0.556). The mean sizes of fibroadenomas with 11 core biopsies were 35.4 ± 10.9 (24-46) mm, while the mean size of fibroadenomas that did not undergo biopsy was 16.1 ± 4.2 (8-24) mm. There was a statistically significant difference between the groups (p<0.001).

Both of our primary breast cancer cases were ER positive. A 19-year-old patient with high Ki 67 index (40%) was HER2 positive, and her molecular subtype was luminal B. Tumor's size was 4 cm, and there were multiple lymph nodes with impaired hilus-cortex relations and compatible with metastasis. Two aunts of the patient had a history of breast cancer in the premenopausal period. Chemotherapy and radiotherapy were given to the patient who underwent breast conserving surgery and axillary dissection. The protective chemotherapeutic agent (transtuzumab) was continued in the following year. However, due to recurrence in the same breast at the end of one year, a mastectomy was performed.

The other 17-year-old patient with molecular subtype luminal A had a tumor size of 2 cm and a negative axilla. BRCA 1 and 2 were negative. Breast conserving surgery was performed. After chemotherapy and radiotherapy, prophylactic antiestrogen therapy was started. Clinical, radiological and laboratory findings were normal during the four-year follow-up period.

Table 1: Distribution of developmental anomalies, benign and malignant pathologies by gender.

	Female (n)	Male (n)
Neonatal hypertrophy	6	-
Early or normal development	182	-
Asimetry	3	-
Gynecomastia	-	82
Adipomastia	-	14
Fibroadenoma	27	-
Phyllodes tumor	1	-
Cyst	18	-
Mastitis	3	1
Malignancy	2	-
Other *	2	-

*: Burkitt lymphoma , Cat-Scratch disease

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Table 2: Gender and diagnosis distribution of patients that underwent fine needle aspiration and core biopsy.

	Female (n)	Male (n)
Fibroadenoma	11	-
Phyllodes tumor	1	-
Mastitis	2	-
Malignancy	2	-
Gynecomastia	-	2
Cyst	1	-
Other *	2	-

*: Burkitt lymphoma, Cat-Scratch disease

DISCUSSION

In childhood, lesions that most frequently require biopsy are fibroadenomas, which are also the most common lesions. However, even a little, biopsy is performed due to malignancy, granulomatous and lymphoproliferative diseases, too. We showed that patient's age does not affect the biopsy decision of fibroadenomas but large lesion size is a statistically significant parameter in this study.

It has been reported in various series that the most common pediatric breast mass is fibroadenoma (54% - 94%) (8-11). Because these masses are estrogen sensitive, they are not usually seen before puberty (12). The management of the pediatric breast masses has a wide spectrum. In this period, the management strategies show differences for BI-RADS 3 lesions from adult management (2,13,14). The frequency of sonographic follow-up is shorter, and the referral size of surgical resection is larger than adults. It is stated that a 20% increase in size in six months during the follow-up period cannot be accepted as in adults (10). It is argued that doubling of the lesion size in children should be an indication for biopsy. The size increase in our patients was between 20 and 50%. On the basis of the recommendations for surgical resection, size cutoffs of 4 cm or 5 cm (2,13,14). However the sensitivity is around 67% for the detection of phyllodes tumors.

While taking a biopsy decision, risk factors such as family history; are taken into consideration. The primary criteria in the biopsy decision are the presence of one or more of the features such as the first dimension being above 3 cm, inhomogeneous internal echo, increased size during follow-up, increased vascularization and lobulation, millimetric cystic components and microcalcification (15).

Fibroadenomas, which are often defined as oval, well-defined, homogeneous hypoechoic lesions parallel to the chest wall on US, are usually simple fibroadenomas (16,17). We included simple fibroadenomas under US follow-up for at least two years, once every six months in the first year. In these lesions, spontaneous regression can be observed at the level of 10% during the follow-up period (8). Juvenile fibroadenomas and phyllodes tumors cannot be distinguished sonographically, and complex fibroadenomas may be seen in childhood and may be associated with breast cancer (17).

In our study, all lesions except the diagnosis of simple fibroadenoma were surgically excised. There was no upgraded lesion. Upgrade can develop after excision in juvenile fibroadenomas, which is also defined as cellular fibroadenoma, or in some phyllodes tumors (2). Phyllodes tumors are rare, of which 9–35% are malignant (18-20). Additionally, phyllodes tumors may have a recurrence, less in benign ones (10% - 25%), therefore, continuous follow-up is required (21). In cases of fibroadenoma and phyllodes tumor differentiation, core biopsy should be performed, as FNAB will not be sufficient. The negative effects of core biopsy on normal breast development are negligible (13,22).

It has been reported that the most common primary breast cancer in children is cystosarcoma phyllodes, and the most common breast malignancy is metastatic masses originating from extra-breast neoplasms (23). The literature reports that the main breast carcinomas are secretory carcinomas with a good prognosis in the pediatric age group (3). However, as in our cases, invasive ductal carcinomas constitute the majority of cases and their prognosis is poor (24).

One of our two breast cancer cases was luminal A and the other was luminal B. In a large series of studies by Warner et al. the relationship of the molecular breast cancer subtypes in childhood and young adults with body size and body mass index was compared (25). This study reported that breast cancers belonging to four molecular subtypes were seen at similar rates compared to adults.

There is no consensus on treatment in the literature. Breast-conserving surgery is usually preferred (3). It has been reported that axillary metastasis is observed in 20% - 30% of cases (26).

Breast US examinations always include the axilla. Most of the breast lymphatic drainage (75% - 97%) goes to the axillary lymph nodes (27). Therefore, a pathology in the breast is expected to affect the axilla first. However, large axillary masses can cause edema in the breast through the obstruction. Two of our cases had complaints of swelling in the armpit and ipsilateral breast fullness and pain. No malignant lesions were observed in the breasts in sonographic examinations. In the unilateral axilla, multiple lymph nodes with a diameter of 3-5 cm with impaired hilus-cortex relations were observed. A case (17-year- old, female) had scratches on the ipsilateral hand and arm. Upon learning that a house cat had scratched her, "Cat-scratch disease" was considered, and core biopsy was performed from the axilla. Histopathological findings included granulomas, diffuse polymorphous core leukocytes, and focal necrosis areas consistent with the initial diagnosis (28). Findings regressed with short-term antibiotic therapy.

The axillary core biopsy diagnosis of the other case (16-year-old, female) was high-grade Burkitt lymphoma, which accounts for approximately 40% of childhood non-Hodgkin lymphomas. Survival rates in this disease have increased dramatically recently, an achievement attributed to the use of chemotherapy and immunotherapy (29). However, in this study, the disease progressed very rapidly, and the patient died within three months.

One of the limitations in our series is that our hospital is not a pediatric or oncology-specific hospital. However, our series still gives an idea about the frequency of pediatric patients who resort to hospitals in a general population. Other limitations are that our series is a retrospective and single-center study. Since our case number was small, we could only evaluate lesions with and without biopsy in terms of size and age. We could not evaluate them in terms of features such as

inhomogenity, increased size on follow-up, increased vascularization and lobulation, millimetric cystic components and microcalcification.

CONCLUSION

In childhood up to 19 years of age, there may be malignancies in the breast and lesions such as fibroadenoma that require malignancy exclusion.

Age is not decisive in the biopsy decision. Large size is a statistically significant parameter. Additionally, it should be kept in mind that lymphoproliferative diseases and granulomatous pathologies, which are more common in these ages, may cause secondary complaints in the breast.

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Administration of the Cook Cervical Ripening Balloon to Stop Cervical Bleeding in a Patient with Placenta Previa: A Case Report

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ABSTRACT

Objective: Placental implants in the cervical canal may occur result in patients with placenta previa that lead to bleeding after placental removal. Bleeding from the cervical canal can be stopped by inserting the Cook Ripening Balloon.

Case Presentation: A 31-week pregnant an was brought to the emergency clinic with a complaint of vaginal bleeding, and active vaginal bleeding was observed. Ultrasonography showed a fetus with fetal bradycardia and placenta previa. The patient underwent emergency Caesarean delivery. The placenta was easily removed without any complications. Bleeding from the cervical canal was observed by vaginal examination. The Cook Cervical Ripening Balloon was inserted into the cervical canal, and the bleeding stopped. The patient was discharged healthy.

Conclusion: Bleeding from the uterine cervix can be stopped by insertion of the Cook Cervical Ripening Balloon.

Keywords: Cervical Bleeding, Caesarean delivery, Cook Cervical Ripening Balloon, Placenta Previa.

INTRODUCTION

The placenta covering the opening of the cervical canal is defined as placenta previa; the worldwide incidence of placenta previa is 0.3–0.9% (1,2). The placenta previa rate has increased in recent years due to the increase in the number of Cesarean section deliveries and the application of assisted productive technology (1,3). Placenta previa may result in excess bleeding before, during, or after delivery, which could cause maternal and fetal morbidity and mortality (4,5). In the case of placenta previa, Cesarean delivery is required. After the removal of the placenta, there may be excessive bleeding in the placental bed, sometimes resulting in life-threatening blood loss (4,5). A Bakri balloon, two autonomous Zhukovsky balloon catheters (intravaginal and intrauterine), and a Foley balloon can be placed in the uterus in cases in which bleeding arises from the lower uterine segment (6). If these interventions do not stop the excess bleeding, an emergency Cesarean hysterectomy may be required to decrease maternal morbidity and even prevent mortality.

In some cases, placental implants placed in the cervical canal can lead to excessive bleeding after the removal of the placenta (6). Bleeding from the cervical canal cannot be observed through a Cesarean incision. Thus, in pregnant patients with placenta previa undergoing a Cesarean delivery, a vaginal examination should be performed to check if there is bleeding from the cervical canal. If bleeding is observed, the Cook Cervical Ripening Balloon can be implanted in the cervical canal to stop it. The Cook Cervical Ripening Balloon contains two balloons; it is inserted into the canal before labor in a prolonged pregnancy in which the cervix is unfavorable for induction (6,7).

In this case report, we aim to present how we stopped cervical canal bleeding in a patient with placenta previa after Cesarean delivery by placing the Cook Cervical Ripening Balloon in the cervical canal and how doing so prevented the need for a Cesarean hysterectomy. We also aim to draw attention on this subject.

Case Report Article

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CASE

A 23-year-old, 31-week pregnant woman was brought to the emergency clinic by ambulance with complaint of vaginal bleeding. She had a prior vaginal delivery, but had been diagnosed with placenta previa for her current pregnancy. Bleeding from the cervical canal was observed upon vaginal examination. The ultrasonographic evaluation revealed an intrauterine fetus compatible with a 32-week pregnancy. The fetus had deep bradycardia. The patient was transferred to the operating room for an emergency Cesarean delivery with a diagnosis of fetal bradycardia and placental decolman. Hypotension and tachycardia occurred in the patient at the beginning of the surgical procedure. A live male fetus weighing1880 grams with an Apgar score of 9 at the fifth minute was delivered by Pfannenstiel incision, and a low segment transverse uterine incision.

The placenta was completely removed without any complications. There was no sign of placental invasion anomalies. Bleeding from the lower uterine segment was within normal limits. The incision was closed within the anatomic folds. During surgery, 40 units of oxytocin and 0.25 mg methylergonovine were administered as uterotonic agents. During surgery, as soon as the patient's hemoglobin (Hgb) level was detected as 5.5 gr/dl, 2 units of red blood cells, two units of fresh frozen plasma, and 1 g fibrinogen were transfused intraoperatively. Moreover, 2 ampoules of calcium gluconate infusion were administered after the detection of low blood calcium levels during the procedure.

The operation was completed without any complications. Vaginal examination was performed at the end of the operation to evaluate if there was any excess bleeding. Abnormal bleeding from the cervix was observed. We observed that the bleeding stopped when we applied pressure on the cervix with a retractor. When the retractor was pulled back, bleeding started again (**Figure 1A, B**).

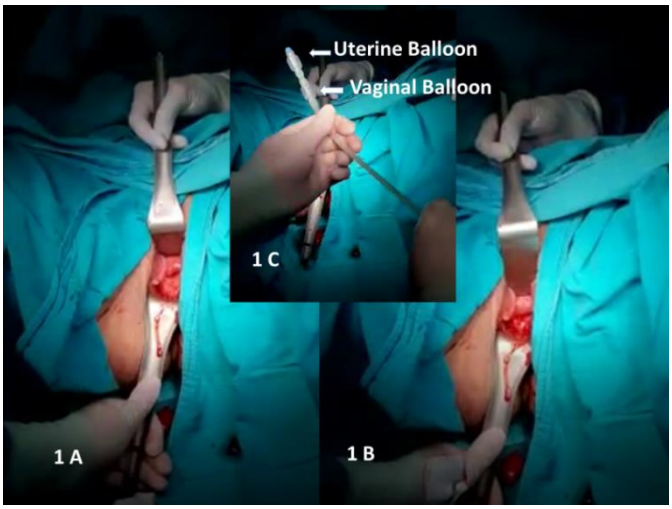

Figure 1. Vaginal bleeding. **A)** When the retractor was press on the cervix, the bleeding stopped. **B)** When the retractor was drawn back, the bleeding started from the cervix. **C)** The Cook Cervical Ripening Balloon.

Based on this finding, the origin of bleeding was thought to be the cervical canal, not the lower uterine segment. Thus, we thought that placing a Bakri balloon or urinary catheter in the lower uterine segment would be ineffective for stopping the bleeding. To achieve that aim, we decided to apply pressure to the cervical canal with the help of the Cook Cervical Ripening Balloon, which is used in a prolonged pregnancy to achieve cervical ripening before inducing labor. The Cook Cervical Ripening Balloon has two balloons; one is inserted into the uterine cavity, and the other is inserted into the vagina (Figure 1C). When the two balloons are inflated, such as with a saline infusion, the balloons are placed in the cervical canal and apply pressure on it. The Cook Cervical Ripening Balloon was placed into the patient's uterine cavity (**Figure 2A,B, Appendix 1**).

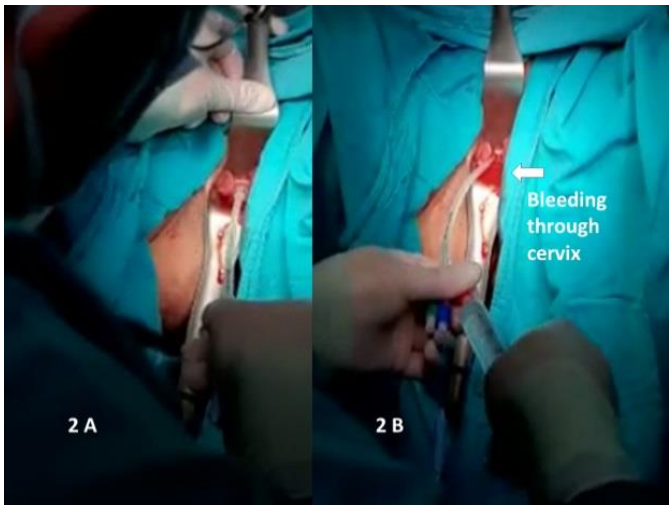

Figure 2. A) Administration of the Cook Cervical Ripening Balloon. **B)** Inflation of the Cook Cervical Ripening Balloon.

Appendix 1. Video showing vaginal bleeding and administration of the Cook Cervical Ripening Balloon.

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The uterine balloon was inflated with 80 cc of saline infusion, and then the cervical balloon was inflated with 60 cc of saline infusion.

After the procedure, the bleeding stopped, and the patient was transferred to the intensive care unit (ICU). In the ICU, the patient's hemoglobin level was detected as 7.8 gr/dl, and 2 units red blood cells and 2 units fresh frozen plasma were transfused. Twelve hours after the Cesarean section, 6000 units of enoxaparin were administered subcutaneously for prophylaxes of venous thromboembolism. In the follow-up in the ICU, the patient's vital signs were stable, so she was transferred to the clinic on the postoperative of first day. The saline solution used in the balloons of the Cook Cervical Ripening Balloon was drained step-by-step. During observation, no complications were seen, and the patient was discharged at the postoperative of the third day in a healthy condition.

DISCUSSION

Obstetric bleeding secondary to placenta previa can be life-threatening and is a frequent cause of postpartum hysterectomy. Bleeding originates from the lower uterine segment, where the contractile capacity of the thin myometrium is limited. Additionally, larger vessels are developed to supply the placental bed. Therefore, life-threatening bleeding may occur after placental removal, which can be a challenge for obstetricians (8).

Sometimes, an obstetrician must perform a hysterectomy to minimalized maternal morbidity, and even prevent mortality. The risk of undergoing a hysterectomy following a Cesarean delivery is 30-times higher for patients with placenta previa than those without placenta previa, requiring a longer hospital stay (9).

In some cases, bleeding can be stopped by applying pressure to the lower uterine segment by placing a Bakri balloon, two autonomous Zhukovsky balloon catheters, and a Foley balloon tamponade. However, these are not placed in the cervical canal and cannot stop bleeding from that canal. The effectiveness of the Cook Cervical Ripening Balloon for stopping cervical canal bleeding is supported in the literature (6).

In some cases of placenta previa, the placenta could reach the internal cervical os and the upper part of the cervical canal, leading to increased vascularization and adequate placental blood supply (6). Furthermore, Young et al. reported a case in which the placenta tissue protruded through the cervical os in a patient with placenta previa (10).

After placental removal, massive bleeding occurred due to a larger vascular bed at the internal cervical os and the upper part of the cervical canal, which was unrelated to the uterine cavity. In this case, the Cook Cervical Ripening Balloon seems to be an effective tool that can be implemented into the cervical canal to stop bleeding. Gu et al. evaluated the Cook Cervical Ripening Balloon's efficacy during surgery in a patient with placenta previa and placenta accreta spectrum disorder in which an abnormal invasive placenta reached the cervical internal ostium and the upper part of the cervical canal (6).

In the control group (n = 39), they placed an infrarenal abdominal aorta balloon occlusion and a longitudinal parallel compression suture to the lower uterine segment (6). In the study group (n = 35), the Cook Cervical Ripening Balloon was inserted into the cervical canal (6). Based on the results, they suggested that the Cook Cervical Ripening Balloon implantation is a simple and effective method for stopping bleeding from the cervical canal in some patients (6). Their suggestion supports the result of our case report.

CONCLUSION

The Cook Cervical Ripening Balloon can stop bleeding by exerting pressure on the blood vessel that originates at the cervical canal. In the case report presented here, we demonstrated the effectiveness of the Cook Cervical Ripening Balloon in stopping cervical canal bleeding in a patient with placenta previa who had undergone a Cesarean delivery. We recommend using the Cook Cervical Ripening Balloon to treat bleeding from the cervical canal based on previous reports of its efficacy in the literature and our experience. However, more research is needed to obtain further information about the effectiveness of the Cook Cervical Ripening Balloon for stopping cervical canal bleeding.

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Ethical approval: All procedures performed in studies involving human participants were in accordance with the institutional and/or national research committee's ethical standards and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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