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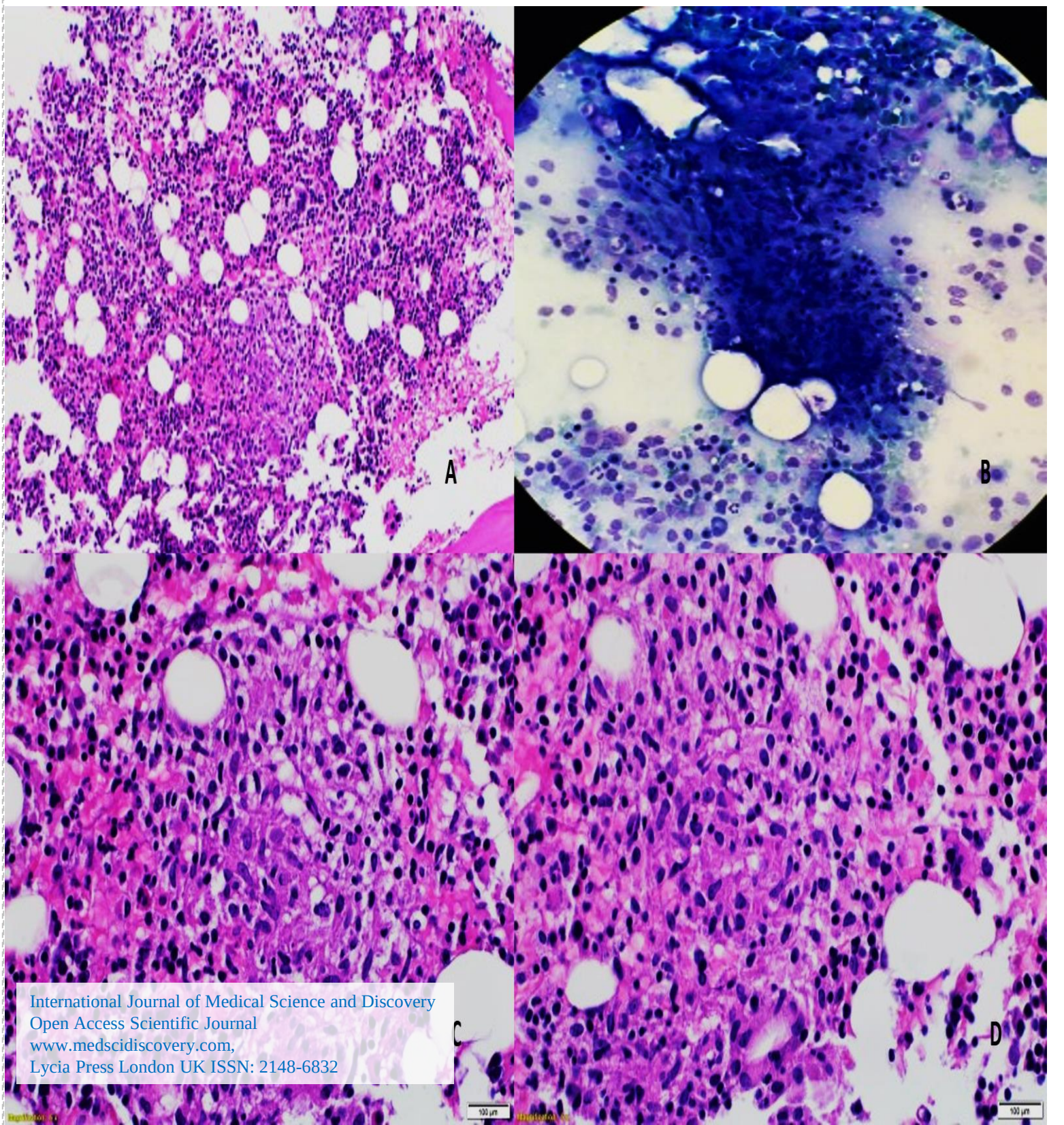

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Contents

Research Articles

Case Report Articles

Short Communication

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Palliative Split-Course pelvic radiotherapy for symptomatic cervical cancer

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ABSTRACT

Objective: Palliative pelvic RT effectively relieves significant health issues such as bleeding from the tumor, pain, discharge, or mass effect on the rectum genitourinary tract vessels and nerves in cervical cancer patients. There is no exact conclusion about an ideal palliative radiation treatment dose regimen. Thus we share the results of a commonly used split-course palliative pelvic RT regimen in our hospital.

Material and Methods: For a retrospective study, 9 patients records treated between 2015 and 2019 were reviewed. The dose of prescribed irradiation for the target was 20Gy in 5 daily fractions. An additional 20Gy in 5 fractions was delivered after a 2-week time for recovery. Symptomatic improvement and treatment-related toxicity during and after RT were assessed from handwritten clinician reports.

Results: Vast majority of patients enduring, and rapid symptomatic improvement was observed. Grade 3 to 5 treatment toxicity was not examined. Maximum acute toxicity was grade 1 GI or GU toxicity in 4 patients and G2 in two patients. Three patients had no acute side effects. All patients had complete symptom remission after treatment, one patient did not complete the second course of therapy due to deteriorating performance status, but local symptom relief was achieved.

Conclusion: Split course regimen effectively improved symptoms without significant toxicity. The integrated 2-week break allowed doctors to assess patients for increased dose palliative radiation and balanced therapeutic benefits with possible adverse effects. This regimen is a reasonable strategy for patients who do not tolerate definitive treatment.

Key words: cervical cancer, palliation, radiation, split course, 2-week break.

INTRODUCTION

Cancer of the cervix uteri (CC) is regarded as the 4th most common cancer type in women. In 2018, about 570000 newly diagnosed cases were registered, representing 66 percent of all gynecological cancers in females, about 90 percent of total cervical cancer CC related deaths occur in low- and middle-income countries (1). Diagnosing of CC at an early stage where access to successful care is available will dramatically increase the chances of survival. In many low economic counties, the disease is not diagnosed timely until cancer will reach an advanced stage or treatment is inaccessible; therefore, a high death rate induced by CC is observed. Multiple studies in developing countries clearly show that awareness is very low and the use of CC early detection screening programs as well (2-9). This lack of efficient screening programs also explains why more than 75 of women affected are at an advanced stage in developing countries while more than 75 of women affected are at an early stage in developed countries (10-12). Radical surgery with or without neoadjuvant chemotherapy or concomitant chemo-radiation will successfully treat early-stage cervical cancer (stage I to IIa). Chemo-radiotherapy or palliative chemotherapy with or without radiotherapy is mostly used to treat locally advanced CC (stages IIb to IVb) (13)

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The basic difficulty in the treatment of women with locally advanced cervical cancer (LACC) is the poor performance status of the patients. Because of poor tolerance for any type of therapy, treatment effects may be uncertain. In women with advanced or metastatic cervical cancer, symptoms such as vaginal bleeding or mass effects on the rectum, genitourinary tract, vessels, and nerves frequently require palliation. In the care of patients with pelvic symptoms who were unable to undergo intensive therapy, palliative RT is an important part of treatment and standard practice.

By the World Health Organization, palliative care is regarded as "an approach that improves the quality of life of patients and their families facing the problems associated with a life-threatening illness, through the prevention and relief of suffering employing early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual (14). For all stages of cancer treatment of a patient, this is correct; since the disease is not curable and life expectancy is limited, care priorities are based on symptom management and quality of life. In the palliative treatment of advanced CC, RT plays a crucial role, especially in hemostasis and pain control.

The main goal of palliative radiotherapy is to provide permanent and rapid improvement of symptoms while lessening acute or late side effects, resource use, and the frequency of cancer center visits (15). The other goals include tumor regression and a short period of rehabilitation. For palliative patients, a short course of radiotherapy delivering a high dose per fraction is preferred, as tumors do not need to be fully eradicated to achieve symptom improvement (16). Although palliative radiotherapy plays a very important role in the treatment of advanced cervical cancer, the optimum dose or fractionation schedule is not estimated.

For the gynecological malignancies palliation, several hypofractionated regimens have been recommended (17). Schemes vary from 30Gy/10 fractions to shorter 3.7Gy twice daily given in 4 fractions and a single 8Gy dose in one fraction. Many of these fractionation regimens can be repeated. Administration of palliative RT for gynecologic cancer may be delivered using the external beam approach and brachytherapy. The radiation fractionation regimen decision is based on many different factors, including tumor characteristics, radiological features, previous history of radiation therapy, and response to that intervention, patient's performance status, and estimated life expectancy. Ongoing or potential systemic therapy should be taken into consideration, as well. In decision making, physician choice and preparation often play an important role.

The most commonly used palliative pelvic RT scheme for cervical cancer has been the split course hypofractionated schedule at the EVEX Medical Corporation – Oncology Center. The idea is that in this challenging patient population, the first course of 20Gy delivered in five daily fractions offers a trial course to evaluate treatment tolerance. The first phase of treatment will be followed by a scheduled 2-week break, enabling patients to recover from acute adverse effects caused by the first phase of RT.

However, from either disease progression or intolerance to the first course of radiation during the break, a minority of patients would deteriorate. Patients who felt better could continue RT at the final total dose of 40Gy by completing the second phase of RT with 4Gy per fraction. This regimen thereby allows the identification of patients who may tolerate high-dose palliative RT after the initial dose. This approach has been well-tolerated in our practice. Most patients have benefited from the relief of pelvic symptoms while offering all patients an opportunity to receive the higher palliative radiotherapy trial course. In this study, we conducted a retrospective analysis to determine the overall efficacy of a split-course palliative radiotherapy protocol for symptom palliation.

MATERIAL and METHODS

Patient Population

Clinical reports were analyzed of all patients treated for cervical cancer with split course pelvic RT between May 2015 and May 2019. Nine patients were found in total with cervical cancer who underwent treatment with this regimen by checking the unit's disease-specific treatment reports built-in ARIA software. Histopathologically confirmed stage IVB cervical cancer had been diagnosed in all patients (Including squamous cell carcinoma, adenocarcinoma, or adenosquamous cell carcinoma).

Due to severe comorbidity, low-performance status, or metastatic illness, these patients were not suitable for radical treatment. History and physical examination included height, weight, body surface area, and The Eastern Cooperative Oncology Group Performance Status (ECOG) score. An initial examination was performed by a gyne-oncologist and radiation oncologist together. All patients had signed a treatment-specific informed consent before treatment.

Treatment

Chosen patients were treated with external beam RT using Clinic IX or True Beam (Varian Medical Systems) only. A megavoltage beam of 6 MV or greater, with a minimum source-axis distance of 100 cm and a minimum source-to-skin distance of 80 cm. Throughout the simulation and planning, methods were used to reduce small bowel irradiation, including full bladder or advanced physics planning for IMRT. The distal-most aspect of cervical-vaginal disease was marked using radio-opaque seeds. CT scan with or without MRI was used in treatment planning.

The tumor responsible for vaginal bleeding, mass effect, or pelvic pain identified by pelvic CT and/or MRI was outlined as the gross tumor volume (GTV). With a 1.0 margin, given the setup instability and organ movement, the planning target volume (PTV) was defined. The clinical target volume (CTV) was not defined due to care was given for palliative intent. Originally, it was planned that all patients would receive the full course of treatment with a maximum dose of 40Gy. All plans were generated in Eclipse (Varian Medical Systems): using a conformal 4-field technique with 16-MV photon beams or IMRT/VMAT technique with 6-MV photon beams.

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Daily image verification on the treatment unit was followed by prescribed treatment delivery. For the first course of RT, a dose of 20Gy in 5 fractions was approved.

All patients were treated once a day, five days a week, with a daily fraction size of 4Gy. Complete blood count analyses were performed weekly. Serum chemistry included creatinine and liver function tests. Transfusion was given if HGB <80 g/l. Patients were given a 2-week break after this first phase of palliative RT, during which patients and doctors jointly decided whether a patient should continue to the second course of palliative radiotherapy. Good performance status, the patient's ability to continue, stable cancer status of the treated tumor, and no distant progression were the indicators used to pick patients for the second phase of treatment, which included an extra 20Gy in 5 fractions.

Analyses

Symptom Palliation: Data regarding patient symptom improvement was obtained from clinician assessment reports performed during RT and clinic follow-up notes. All patients were followed-up via planned follow-up visits in the clinic if patients were able to come. If the patients' performance status had deteriorated and they could not come for follow-up checks, the clinic's administrative department started the interview process with a phone call to determine the vital status until the patient's death. The response to treatment, recurrence of disease, or survival is well beyond the context of this study.

Toxicity: At the monthly therapy reviews, at regular follow-up visits in two weeks and/or months following RT completion, toxicities were determined retrospectively from physician notes. The worst treatment-related toxicity observed during treatment or retrospectively analyzed was graded using the Common Terminology Criteria for Adverse Events v4.0 scale.

For the whole population of patients, only one clinician collected this data. A proportion of these charts was then evaluated by a group of physicians (resident a senior physician for each patient) to determine and validate the patients' toxicity score. Any discrepancy in scores was overcome by re-examining the patients' clinical charts, and the senior physician took the final decision.

RESULTS

Patient characteristics: Basic hallmarks of patients and diseases are outlined in Table 1. Patients were staged according to the 7th edition of the classification of the AJCC staging.

All the patients had stage IVB cervical cancer proven by pathology and radiological studies. None of the nine patients has ever undergone pelvis irradiation. The entire course of therapy was finished by eight patients, for a total of 40Gy. Because of low-performance status and severe comorbidities (acute hemorrhagic stroke during a 2-week break), only one patient was found not fit for the second phase of RT.

Symptom Palliation: Symptomatic improvement was measured in all cases with a cumulative follow-up of 12 months from the monthly treatment assessment clinical reports and from the follow-up charts to the final follow-up or until death. Table 2- shows that after finishing the complete course of palliative RT, patients had different symptomatic improvements. Bleeding and pain were palliated in most patients. 100% described symptom relief at the end of care in patients that had bleeding. In all patients, pelvic pain was relieved. All patients suffering from pelvic pain were prescribed non-steroidal anti-inflammatory medications or opioids during RT. These patients stopped or were able to decrease the pain drug dosage following completion of therapy. Palliation from vaginal discharge and mass effect was also reported in two weeks of treatment.

Toxicity: Table 3 - shows the treatment-induced acute and late toxicities. The majority of our patients well tolerated split course radiation. There was no grade 3, 4, or 5 RT side effects. Three patients showed no acute side effects at all. Diarrhea was the most frequent acute toxicity observed in 4 patients.

Table 1. Patient and Disease Characteristics

Demographics	Number (%), N = 9 (100%)
Age	
Median	66
Range	50-83
ECOG	
1	1 (12)
2	3 (33)
<2	5 (55)
Weight loss >5% of body weight	
Yes	4 (44)
No	1 (12)
Unknown	4 (44)
HGB	
>120 g/l	0
80 – 120 g/l	4 (44)
< 80 g/l	5 (56)
Histology	
Adenocarcinoma	2 (22)
Squamous cell carcinoma	6 (66)
Adeno-squamous carcinoma	1 (12)
Chemotherapy	
Prior	4 (44)
After	2 (22)
Prior to and after	2 (22)
No chemo	1 (12)
Prior Surgeries	
Yes	1 (12)
No	8 (88)

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Table 2. Palliation of Symptoms in Evaluable Patients

Symptom	Patients with Symptoms at Presentation Number (%),	Patients with Symptom Improvement in two weeks Number (%)	Patients with Symptom Improvement in 6 months Number (%)
Bleeding	8 (89)	8 (100)	8 (100)
Mass effect/obstruction	2 (22)	1 (50)	2 (100)
Vaginal discharge	8 (89)	3 (37)	5 (62)
Pelvic pain	5 (56)	4 (100)	5 (100)

Table 3. Treatment Toxicity by CTCAE v.4.0

	Grade 1	Grade 2	Grade 3,4 and 5
Acuity toxicity			0
Nausea/ Vomiting	2	1	
Diarrhea	2	2	
Anal mucositis	1	0	
Cystitis	2	0	
Vaginal mucositis	2	0	
Late toxicity			
Proctitis	2	0	0
Cystitis	1		
Vaginal stenosis	0		

DISCUSSION

The task frequently posed by radiation oncologists is to treat a patient with stage IVB or recurrent cervical carcinoma that has induced pelvic pain, mass effects, or bleeding. Conducted literature review confirms that numerous dose fractionation schedules have been tested (19, 22-30), but about RT dose and fraction size recommended for palliative pelvic RT, there is broad international heterogeneity (Table 4). Tumors respond quickly to radiation, and after a few days of treatment, bleeding stops. Several options can be useful if vaginal bleeding is the primary concern.

According to the Lonkhuijzen's descriptive analysis of eight papers reporting palliative care results, the evidence is not enough to prove the widespread presumption that better and durable palliation is accomplished with a higher dose administered in many smaller fractions. There is a strong need for a comparative study that will analyze various radiation fractionation schedules to determine an ideal palliative radiation regimen (18). Numerous regimens have been reported, with various fractionation schemes. Several studies have identified whole-pelvic palliative RT using single or multiple monthly doses of 10Gy. This treatment plan was generally well-tolerated, impacting vaginal bleeding and discharge after 2 or 3 fractions were reported (19-20). Late toxicity is poorly reported, and because of the large fraction size and wide irradiated area, the increased risk of late toxicities is a problem. In patients with different pelvic malignancies, RTOG 7905 research took this monthly fraction of 10Gy schedule concurrently with misonidazole (a hypoxic cell sensitizer).

A high incidence of late gastrointestinal (GI) complications (45 percent) were recorded, leading to the trial's premature termination (21).

The RTOG prospectively examined the use of a lower dose per fraction: 3.7Gy delivered twice a day to a total dose of 14.8Gy, repeated every month for up to three months. Spanos et al. reported on a phase II study of 142 patients with recurrent or metastatic disease in the pelvis using this fractionation and repeated at 3- to 6-week intervals for a total of three courses. The planned total tumor dose was 44.4Gy, and LDR intracavitary insertion (4,500 mg) was occasionally accompanied by 14.4 Gy EBRT dose with midline block. Twenty-seven patients lived for longer than one year. There were only two reported cases of grade 3 toxicity in the lower gastrointestinal tract. The research was extended to provide a phase III protocol randomizing 136 patients to rest for a short (2 weeks) or longer (4 weeks) time between split radiation courses. In patients with shorter rest intervals, there was a tendency towards increased acute toxicity (5 of 58 vs. 0 of 68; P = .07). In the two groups, late toxicity was not substantially distinct. The pelvic tumor response was 34 percent vs. 26 percent in both groups, reported as comparable. A 6 percent complication rate was reported by Spanos et al. in 290 patients treated under RTOG Protocol 8502. There was no late toxicity in any patient receiving <30Gy. No major variation in the occurrence of complications was observed for patients who had 2 or 4 weeks of rest (P = .47) (22-23). The weakness of this protocol is that the two days of treatment require at least a 6-hour interval between two daily fractions, which can be troublesome for the symptomatic patient.

It was impossible to compare the results from these studies, considering the patient sample variations (performance status spectrum, age, methods of symptom assessment, and measured outcomes). It appears that the highest control was achieved with bleeding. Pain palliation was correlated to the overall dose delivered. However, almost all these studies indicate that higher cumulative doses of RT could be considered in some patients to result in more effective palliation and potentially better overall survival. The latter is beyond the scope of our study. Therefore, in this population, which also has low-performance status or severe comorbidities, the proper selection of patients who may benefit more from a split course of RT is essential. In palliative care, balancing symptom improvement with RT side effects remains very important. We suggest that our treatment regimen prevents the overtreatment of very ill patients with the consequent toxicity and enables healing from the acute side effects of the first phase RT. This strategy allows the evaluation and identification of patients fit for escalated dose palliative RT after a trial dose of 20Gy. Further RT was continued only in patients who did not get worse after the 2-week break. Apparently, in most patients, split course RT offered symptom improvement. Treatment was well-tolerated, with mild and irregular events of toxicity over the planned 2-week break, both grade 1 or 2 GI and GU toxicity entirely resolved. Grade 3 or higher acute or late toxicity was not detected during radiation or within the six months after.

The scheduled break could provoke controversy as seen in patients undergoing curative-intent RT for other cancer forms the prolonged duration or delay of care can adversely affect local tumor control and disease-specific survival. Particularly because of short survival in patients treated with palliative intent, the goal of palliative RT regimens has centered on symptomatic improvement rather than local control of the tumor. Tumor local control or OS was not assessed in this study. Although understanding that symptom palliation can also be a feature of local tumor response. A significant portion of our patients has poor prognostic factors, including stage IVB disease, weight loss, and a higher ECOG score of performance status. The key reason for split course palliative RT is that the 2-week break allows the doctor to choose patients for the full dose palliative RT of 40 Gy. The retrospective nature of this clinical study did not allow us for precise measurement of the degree of improvement, new symptoms during RT, or span of palliation.

Indeed, findings from a retrospective analysis of clinical details, considering the possible subjectivity, patient selection, and bias implicit in this research design style, did not permit an objective comparison of efficiency. We retrieved data relating to whether the symptoms were improved during treatment and afterward. Symptom palliation and toxicity were analyzed mainly by doctors, and it is well known that physicians appear to overestimate or neglect the symptoms compared to patients. The analysis of the results could be influenced by the process by which these endpoints have been evaluated, as information was derived from clinical notes. For most studies oriented on palliative schedules, as this protocol, this issue of estimation is one of the main rationales. It should always be acknowledged that variables apart from the fraction size, including treatment volume and prior interventions, affect complication rates of radiation therapy.

CONCLUSION

We report that symptom palliation using this regimen is promising and posed minimal toxicities. There is clearly a need for well controlled studies with validated palliative and quality of life endpoints to determine the best fractionation schemes for palliative radiotherapy in cervical cancer. Therefore, we propose that these data may serve as the basis for the design of future prospective studies evaluating split-course palliative pelvic RT, with the incorporation of validated symptom inventory tools and a formal quality of life assessment.

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Asthma control and treatment steps in Turkish children with Asthma during the COVID-19 pandemic

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ABSTRACT

Objective: Since viral infections are one of the most important factors affecting asthma control, various precautions and recommendations for asthma patients came to the fore at the beginning of the COVID-19 pandemic. In our study, we aimed to evaluate the effects of the COVID-19 pandemic on asthma control and treatment steps of children with asthma.

Materials and Methods: The date of March 11, 2019, was accepted as the beginning of the pandemic. The application deadline to our outpatient clinic of patients within one year after the onset of the pandemic (AOP) was determined. After that, the period of the same season before the beginning of the pandemic (BOP) was determined. We recorded the asthma treatment steps, asthma control test (ACT) scores, and the number of applications to our outpatient clinic during the BOP and AOP periods of the patients.

Results: In our study, 384 patients, 64.8% of whom were male, with a median age of 11 years, were evaluated. SARS-CoV-2 PCR positivity was detected in 6 (1.6%) patients. BOP, patient treatment steps, and the number of outpatient clinic applications were higher ($p < 0.001$). AOP, there was no significant change in ACT scores ($p = 0.059$). Whereas asthma control was worse in patients susceptible to house dust mite ($p = 0.01$).

Conclusions: Although measures such as home quarantine and mask use have been reported to have positive effects on asthma control, increased exposure to house dust mites in susceptible patients may pose a risk of uncontrolled asthma.

Keywords: Asthma, pandemic, house dust mites, treatment, COVID-19, children

INTRODUCTION

COVID-19 (coronavirus disease-2019) caused by the new Coronavirus named SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2), which causes severe acute respiratory syndrome and death, was declared as a pandemic disease by the World Health Organization on March 11, 2020.

On that date, the first case was detected in Turkey (1-3). During the pandemic, various measures were taken worldwide, face-to-face education was discontinued, and curfews were imposed at intervals in our country. Asthma, one of childhood's most common chronic diseases, is most triggered by allergens, air pollution, and viral infections (4-7).

In asthma guidelines, it was recommended that patients' asthma control, treatment adherence, written asthma action plan, and spirometric measurements be evaluated every 3 to 6 months (5,7). Since the effect of Covid-19 on asthma is unknown, conflicting explanations regarding the relationship between asthma and COVID-19 in the early days of the pandemic have led to the emergence of numerous emergency precaution guidelines and new recommendations for allergy and immunology physicians (8-10).

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Although the pandemic process is discussed in many aspects in previous articles, studies investigating its effect on asthma control in children are limited. Therefore, in our study, we aimed to evaluate the effect of the COVID-19 pandemic on follow-up numbers, asthma control, and treatment steps of our pediatric patients with asthma by comparing it with the pre-pandemic period.

MATERIAL and METHODS

In this study, we included patients with asthma between the ages of 6 and 18 who were followed up in a tertiary hospital's pediatric allergy and immunology outpatient clinic between March 11, 2019, and March 11, 2021. The diagnosis and treatment steps of the patients with asthma were evaluated according to the Global Initiative for Asthma guidelines (5). Patients with additional morbidity other than allergic diseases who were followed up in an allergy center other than our clinic and whose data could not be accessed were excluded from the study.

Data collection: With reference to the pandemic start date, March 11, 2020, the 1-year period of the patients Before the Onset of the Pandemic (BOP) and After the Onset of the Pandemic (AOP) were compared.

The results of the treatment step and treatment adherence of their asthma and the Asthma Control Test (ACT) scores in their application deadline to our outpatient clinic during the period AOP were compared with the results of the same season during the year BOP. In addition, the number of applications to the allergy outpatient clinic of the patients within one year of BOP and AOP was recorded.

The most recent skin prick testing (SPT) results were recorded from the patient files. In the SPT in our department includes pollens (grasses, Artemisia vulgaris, Alnus glutinosa, Populus alba, Betula alba, Fagus sylvatica, Parietaria officinalis, Olea europaea); house dust mites (Dermatophagoides pteronyssinus, Dermatophagoides animal farinae); Felis domesticus, Canis familiaris, Blattella germanica (cockroach); molds (Alternaria alternata, Cladosporium herbarum, Aspergillus fumigatus) (Alk-Abello®, Hørsholm, Denmark). SPT was accepted as positive if the induration diameter of any allergen was 3 mm or more compared to the negative control. More than one allergen sensitivity was considered multiple sensitizations.

The cut-off for the total IgE level was determined as 100 IU/mL, and the patients were divided into two groups as normal and high (11). Absolute eosinophil counts (AEC) were recorded, and 450 cells/uL and above were considered eosinophilia (12).

The ACT is a questionnaire, and its Turkish reliability and validity have been confirmed according to age groups (4–11 years and ≥12 years) and the patients' asthma control levels were evaluated using this test (13,14). The patients with an ACT score of 20 or more points were considered to have controlled asthma.During the last three months, treatment adherence was evaluated based on self-reports and pharmacy records. The status of receiving ≥80% of the required controller medication was classified as ‘‘good adherence’’ while receiving <80% was classified as ‘‘poor adherence’’ (15).

The patients' information, such as upper respiratory tract infection (URTI) diagnosis, confirmed COVID-19 status, application to health institutions due to asthma attack, was accessed through the information registered in the hospital information system and/or through the National Health Information Bank (https://enabiz.gov.tr/) system and/or by inquiring over registered phone numbers.

Statistical analysis: Kolmogorov–Smirnov normality test was performed to select the statistical methods to be used. Pearson’s chi-square test or Fisher’s exact test was used to comparing the categorized data. Logistic regression analyses were also conducted to determine the risk factors for asthma control after the onset of the pandemic. The Wilcoxon signed-rank test, McNemar test, and ROC curve analysis were the other analysis used in the study. Statistical analysis of the study was performed using IBM SPSS Statistics for Windows, Version 25, and the statistical significance limit was determined as $p \leq 0.05$.

RESULTS

In our study, 384 patients were evaluated, 249 (64.8%) of whom were male. According to SPT, 273 (71.1%) were sensitized to at least one allergen (Table 1). The most common aeroallergens were pollens (44.3%) (**Figure 1**).

During the period BOP, the annual number of patients who applied to our outpatient clinic was 4 (min-max: 1–14), asthma treatment step was 2 (min-max: 1–5). There were 76 (19.8%) patients who applied to any healthcare facility due to an asthma attack. According to ACT scores, in 225 (58.6%) patients, asthma was under control.

During the period AOP, the annual number of patients who applied to our outpatient clinic was 2 (min-max: 1–8), asthma treatment step was 2 (min-max: AOP 1–5). There were 48 (12.5%) patients who applied to any healthcare facility due to an asthma attack. According to ACT scores, asthma was under control in 246 (64.1%) patients. 102 (26.6%) patients were diagnosed with URTI in a health institution.

When evaluated in general, there was no significant difference between the ACT scores of the patients in both periods. However, the number of applications of our patients to our clinic, their asthma treatment steps, and the number of applications to any healthcare facility due to asthma attack were significantly lower during the period AOP. Their treatment adherence increased significantly (**Table 2**).

According to AOP ACT, no significant differences were noted in asthma control and gender, presence of allergic rhinitis (AR), SPT positivity, URTI diagnosis, the presence of eosinophilia, high total IgE, admission to healthcare facilities due to asthma attack and changes in asthma treatment stepwise ($p = 0.094$, $p = 0.202$, $p = 0.106$, $p = 0.262$, $p = 0.594$, $p = 0.380$, $p = 0.809$, $p = 0.122$ respectively).

It was found that the treatment step did not change or decrease in 115 (83.3%) of 138 patients with uncontrolled asthma during the period AOP. The asthma treatment steps of these patients during the period AOP were lower than BOP ($p = 0.01$).

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During the period AOP, the patients with asthma control were older, had better treatment adherence, and had earlier admission to the outpatient clinic than patients with uncontrolled asthma (**Table 3**).

To ensure asthma control of patients, the cut-off value was determined as 4.5 months with 75.6% sensitivity and 37% specificity (95% CI 66%–76.7%) in the ROC analysis performed for the first outpatient clinic control time during the period AOP. Accordingly, in 232 (60.4%) patients who came for control earlier than 4.5 months during the period AOP, treatment adherence was better, asthma was more controlled, asthma treatment steps were higher, and the number of outpatient clinic applications was higher (p= 0.011, p< 0.001, p= 0.001, p< 0.001, respectively).

Asthma was uncontrolled in 64 (56.6%) of 113 mite-sensitive patients. Treatment adherence was good in 74 (65.4%) patients. Asthma treatment step of the patients increased in 25 (22.1%), decreased or unchanged in 88 (77.9%) patients. Asthma control was lower compared to the period BOP (p= 0.01). However, there was no difference between the periods AOP and BOP in asthma treatment steps and asthma treatment adherence (p= 1.000, p= 0.099, respectively).

The change during the period AOP in asthma control of aeroallergen-sensitive patients who had controlled asthma is summarized in Table 4. Of the 158 (41.1%) patients whose asthma treatment step decreased during the period AOP, 72.2% were receiving step 1 treatment. In these patients, asthma control was increased during the period AOP compared with BOP. (47.4% vs 64.5% p< 0.001).

During the period AOP, the asthma treatment step of 48 patients who were admitted to the health institution due to asthma attack was step 2 (min-max: 1–3). Asthma was uncontrolled in 18 (37.5%) patients. There was no relationship between the application to a health institution due to asthma attack and asthma control, gender, presence of AR, and asthma treatment step change (p= 0.80, p= 0.71, p= 0.90, p= 0.06, respectively).

In patients with aeroallergen sensitivity, there was no significant difference between applications to a healthcare facility due to asthma attack during the periods BOP and AOP (15.8% vs. 12.1%, p= 0.282). However, in patients who were not aeroallergen sensitive, the number of applications to a healthcare institution due to asthma attack during the period BOP was higher than AOP (29.7% vs. 13.5%, p= 0.003).

The median age of the patients with good treatment adherence (median, min-max: 12, 6–18 years) during the period AOP was significantly higher than those with poor adherence (median, min-max: 8, 6–18 years) (p < 0.001).

It was found that advanced age, pollen sensitivity, and good treatment adherence increased the possibility of having controlled asthma (p< 0.01). In mite-sensitive patients, the probability of having uncontrolled asthma increased by 2.747 times (p= 0.013). In addition, the 1-month increase in the first outpatient clinic check-up time AOP increased the risk of uncontrolled asthma 1.4 times (p = 0.001) (**Table 5**).

The SARS-CoV-2 polymerase chain reaction (PCR) test was positive in 6 (1.6%) patients. Mild symptoms developed in all patients, and hospitalization was not required. The asthma treatment step of the patients was 2 (min-max: 2–3). The asthma treatment adherence was good for 4 (66.6%) patients. All patients were male. However, there was no correlation between SARS-CoV-2 PCR positivity and sex (p = 0.06). The mean AEC of these patients was 350 ± 242.89 /mm^3. No significant relationship was found between SARS-CoV-2 PCR positivity and presence of eosinophilia and SPT positivity (p= 0.89, p= 0.80, respectively). Asthma was uncontrolled in 5 patients according to ACT. SARS-CoV-2 PCR positivity was less in patients with controlled asthma (p= 0.024).

Table 1: Demographic, clinical and laboratory findings of the patients by age

		6-11 years	12-18 years	p	Total
Sex (n,%)	**Male**	151 (39.3)	98 (25.5)	-	249 (64.8)
	Female	69 (18)	66 (17.2)		135 (35.2)
Age (years) median (min-max)		8 (6-11)	14 (12-18)	-	11 (6-18)
AR* presence (n. %)		133 (34.6)	104 (27.1)	0.555	237 (61.7)
SPT† positivity (n. %)		147 (38.3)	126 (32.8)	0.032	273 (71.1)
SPT† multi-sensitivity (n. %)		121 (31.6)	95 (24.7)	0.161	216 (56.3)
Total IgE (IU/mL) median (min-max)		157.5 (5.7-3297)	146.5 (1.8-3200)	0.683	153 (1.8-3297)
AEC‡ (cells/uL) median (min-max)		300 (0-2100)	300 (0-2600)	0.620	300 (0-2600)

*AR, allergic rhinitis; † SPT, skin prick test; ‡AEC, absolute eosinophil count

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Table 2: Comparison of clinical findings of before and after the onset of the pandemic

	BOP*	AOP†	p
Number of applications to our outpatient clinic median (min-max)	4 (2-14)	2 (1-8)	<0.001
The first application to our outpatient clinic. AOP (month) median (min-max)	-	4 (2-11)	-
Application deadline to our outpatient clinic, AOP (month) median (min-max)	-	6 (2-12)	-
Distribution of asthma treatment steps (n, %)			
Step 1	92 (24)	159 (41.4)	
Step 2	176 (45.8)	122 (31.8)	
Step 3	101 (26.3)	88 (22.9)	<0.001
Step 4	13 (3.4)	14 (3.6)	
Step 5	2 (0.5)	1 (0.3)	
Good treatment adherence (n. %)	261 (68.0)	301 (78.4)	0.001
Controlled asthma‡ (n, %)	225 (58.6)	246 (64.1)	0.060
Number of patients with asthma attack§ (n, %)	76 (19.8)	48 (12.5)	0.006

BOP, before the onset of the pandemic; †AOP, after the onset of the pandemic; ‡Controlled asthma according to ACT scores; §Number of patients admitted to the healthcare institution due to asthma attack

Table 3: Relationship between asthma control and the other factors

Other factors	Asthma Control*		P
	Good control	Poor control	
Age (years) median (min-max)	12.5 (6-18)	8.5 (6-18)	<0.001
Pollen sensitivity (n, %)			
yes	123 (32)	47 (12.3)	0.003
no	123 (32)	91 (23.7)	
House dust mite sensitivity (n, %)			
yes	49 (12.8)	64 (16.7)	<0.001
no	197 (51.2)	74 (19.3)	
Number of applications median (min-max)	2 (1-4)	1 (1-4)	0.132
First application to our outpatient clinic, AOP† (month) median (min-max)	3 (2-11)	6 (3-8)	<0.001
Application deadline to our outpatient clinic, AOP† (month) median (min-max)	5.5 (2-11)	6.5 (3-12)	0.060
Good treatment adherence (n, %)			
yes	233 (60.7)	68 (17.7)	<0.001
no	13(3.4)	70 (18.2)	

*Asthma control according to the asthma control test; †AOP, after the onset of the pandemic

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Table 4: Change in asthma control of patients after pandemic according to aeroallergen sensitivity

		Pollens‡	House dust mites§	Molds‖	Animal danders¶
Controlled asthma (n, %)	**BOP***	113 (66.5%)	64 (56.6%)	67 (68.4%)	80 (67.8%)
	AOP†	123 (72.4%)	49 (43.4%)	68 (69.4%)	85 (72%)
p		0,123	0,01	1,00	0,44

* Before the onset of the pandemic; †After the onset of the pandemic; ‡For the 170 pollen sensitive patients; §For the 113 patients with house dust mite susceptibility; ‖For the 98 mold susceptible patients; ¶For the 118 patients with animal danders susceptibility

Table 5: Logistic regression analysis of possible risk factors for asthma control after the onset of the pandemic

Risk factors	Odds ratios (95% CI: lower- upper bound)	p
Age	0.705 (0.643-0.774)	<0.001
House dust mite sensitivity	2.747 (1.234-6.115)	0.013
Pollen sensitivity	0.290 (0.135-0.626)	0.002
First application to our outpatient clinic, AOP*	1.415 (1.160-1.727)	0.001
Application deadline to our outpatient clinic, AOP*	0.949 (0.807-1.117)	0.530
Number of applications AOP*	1.214 (0.811-1.816)	0.346

*AOP, after the onset of the pandemic

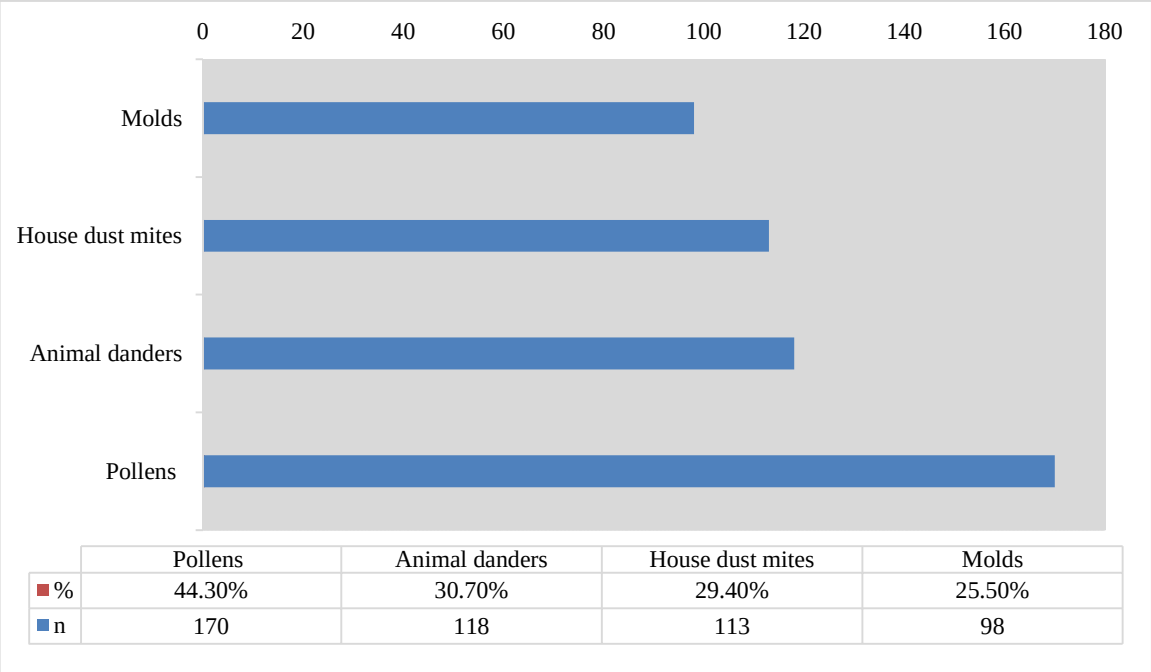

Figure 1: Distribution of aeroallergens according to skin prick test results

DISCUSSION

The COVID-19 pandemic has affected asthma control by causing changes in asthma follow-up and treatment plans due to the measures taken for the pandemic. Because of the important role of viral infections in triggering asthma attacks, it has been thought that patients with asthma may be more susceptible to SARS-CoV-2 infection, and asthma controls may be affected during infection (16,17).

COVID-19 is rare in children (16). In parallel with the prevalence of asthma in pediatric patients with COVID-19, there are few studies evaluating the prevalence of COVID-19 in children with asthma. The prevalence of asthma in 115 children with COVID-19 was 13%, and asthma was reported as the most common comorbidity (18). In a study evaluating 182 pediatric patients with COVID-19 who were hospitalized, asthma was reported in only one patient (19).

Another study reported that uncontrolled and severe asthma might pose a risk of COVID-19 mortality and morbidity (10).

In our past study conducted on the pediatric population, 45 (18.9%) of 237 patients were positive for SARS-CoV-2 PCR (20). In our current study, 6 (1.6%) of 384 children with asthma were found to be PCR positive, and asthma was uncontrolled in most of the patients. When comparing both of our studies, we found that the prevalence of COVID-19 in children with asthma was much lower than in the general pediatric population. SARS-CoV-2 PCR sampling was performed in both of our studies when patients were contacted or symptomatic. The lower SARS-CoV-2 PCR positivity in pediatric asthmatic patients may have a protective effect on families' stricter implementation of preventive measures and treatments given for asthma.

Some researchers have argued that eosinophilia in patients with asthma may be protective against COVID-19 infection and may lead to a mild course of the disease (21, 22). In one study, no significant effect of the presence of atopy on clinical symptoms and complications in COVID-19 was found (19). We did not find a relationship between SARS-CoV-2 PCR positivity and the presence of eosinophilia or atopy in our patients. None of our asthmatic COVID-19 patients had signs of severe illness.

During the pandemic, some measures have been taken, such as using masks, staying at home, and decreasing school days. As a result, it has been reported that risk factors for asthma attacks, such as viral infections, air pollution, and outdoor allergens have been avoided. Thus asthma control has improved (23). In our study, no significant increase was found in asthma control during the pandemic. We thought that patients not being able to manage their asthma treatment steps well, their poor treatment adherence, and their sensitivity to household allergens might be effective in this situation.

The AOP period treatment adherence of our patients was approximately 80%, it was increased compared to the BOP period, and asthma control was better in patients with good treatment adherence. Another factor that we thought could be effective was whether stepwise asthma treatment changes were made appropriately. Approximately 75% of our patients whose AOP step treatment decreased were receiving the first step asthma treatment, and their asthma controls were better than BOP. This made us think that our patients generally managed the decrease in the treatment steps correctly. However, the expected increase in asthma treatment steps was not found in patients with uncontrolled asthma and mite-sensitive patients with reduced asthma control. This suggests that according to their own perceptions, patients reduce their treatment when symptoms are mild but cannot increase treatment when symptoms increase.

In current guidelines, it has been recommended to increase telemedicine applications, reduce allergy clinic applications, continue asthma medications, and use written asthma action plans to increase treatment adherence and reduce contact (5, 24).

Our clinic is a tertiary hospital, and the rate of use of telemedicine applications in hospitals with similar conditions has been reported to be 13% (25). However, we do not know how many patients in our study could benefit from telemedicine services. Perhaps in line with the recommendations, or perhaps due to the fear of COVID-19, the outpatient clinic applications of the patients decreased significantly. We found that delaying AOP control is a risk factor for uncontrolled asthma. Although asthma control was worse in patients who applied late to the first outpatient clinic control during the pandemic, their asthma treatment steps were lower. This suggests that some patients may not have been managed the treatment properly on their own without medical assistance.

Studies during the pandemic reported that children with asthma were not adversely affected by the virus, and there was a 76% decrease in emergency room visits (26).

In our study, in general, applications to the health institution due to asthma attack decreased during the pandemic. This was evident in patients without aeroallergen sensitivity. Due to pandemic measures, the decrease in viral infections, which are the most important risk factors for asthma attack in non-atopic patients, may affect this situation.

The effects of allergens on asthma control and attack development have been discussed in studies. It has been reported in the studies conducted during the BOP period that measures to reduce mite exposure are insufficient in providing asthma control (27). During the pandemic, it has been reported that restrictions cause patients to be exposed to more domestic allergens, such as molds and mites, which may aggravate their asthma (28). A recent study from our country reported that despite domestic allergens, asthma control was better than before the pandemic (29). In our study, mite sensitivity was present in approximately 1/3 of our patients, and we found that asthma control of these patients decreased after the pandemic. Although there was no significant change in stepwise asthma treatments and treatment adherence was good, the decrease in ACT scores was significant. The presence of house dust mite sensitivity was the most important risk factor for uncontrolled asthma in our patients.

Our data consist of only a cluster of patients whom we follow. Therefore, it may fall short of demonstrating the ultimate effects of universal changes on childhood asthma. In addition, another limitation was that we evaluated the asthma controls of the patients only based on ACT scores and could not benefit from spirometric measurements or other parameters indicating inflammation.

CONCLUSION

As a result, this study is one of the rare studies evaluating the effects of the COVID-19 pandemic on the control, stepwise management, and exacerbation of asthma in children with asthma. Thanks to the measures taken during the pandemic, it is thought that the effect of viral infections on asthma attacks has lost its importance. Considering that restrictions may continue in this period, it would be beneficial to take domestic precautions in patients susceptible to house dust mites, which are found to pose a risk of uncontrolled asthma. Particular care should be taken to ensure adherence of young patients with treatment and change the treatment steps of uncontrolled asthma patients. Although asthma guidelines recommend minimizing face-to-face meetings, we think that it would be appropriate to evaluate more frequently uncontrolled asthma patients who have not been able to or who have been late to create asthma treatment plans during the pandemic process.

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Ethical approval: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by Local Ethical Committee. All procedures performed in studies with human participants met the ethical standards of the Institutional Research Commission and the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical standards. Ethics committee approval was received for this study from the Local Ethics Committee of Dokuz Eylül University, School of Medicine (Approval number: 2021/14-34)

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Evaluation of postpartum depression and maternal attachment scale in a low socioeconomic level region: How was it affected during the Covid-19 pandemic period?

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ABSTRACT

Objective: We aimed to investigate the frequency of Postpartum Depression (PPD) and maternal attachment status in a region with a low socioeconomic level during the Covid-19 pandemic.

Materials and Methods: Two hundred women who gave birth in our hospital were evaluated on postpartum 10th day with Edinburgh Postnatal Depression Scale (EPDS) and Maternal Attachment Inventory (MBI).

Results: The mean EPDS in the group with Normal Body Mass Index (BMI) was lower than in the other two groups. Average EPDS was higher in the group with sleep problems than those without sleep problems. Women who received support from their spouses had lower EPDS scores and higher MBI scores. EPDS scores were lower in the group with a good income. MBI scores were found to be lower in people within the increased length of hospital stay.

Conclusion: In the study, we conducted with a group with a low socioeconomic level during the pandemic. We determined that PPD rates increased considerably, and this situation

Keywords: Postpartum depression, maternal attachment, COVID-19, Edinburgh

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INTRODUCTION

Although pregnancy and childbirth are happy for women, this can negatively affect some women (1). Usually, patients show mild, self-limiting symptoms, but some of them may experience severe symptoms. Untreated postpartum depression (PPD) can have devastating consequences for maternal and infant health (2).

The Covid-19 pandemic has caused the development of many negative psychological effects on people. The pandemic process; has harmed people in two ways. First of all, the fear experienced due to the disease caused by the virus. Secondly, the negative psychological impact of the measures taken to reduce the effect and spread of the virus in humans can be counted (3). These effects are fear, stress, panic, paranoia, mental health disorders, anxiety, depression, impaired quality of life, sleep disorders, and insomnia (4,5).

The most common complication during pregnancy and postpartum is postpartum depression (6). Although it varies depending on the method used, it has been reported that it is generally seen in 10-15% of women who have just given birth (7). The American College of Obstetricians and Gynecologists (ACOG) recommends that obstetricians-gynecologists and other obstetric care providers screen all pregnant women at least once during pregnancy and the postpartum period using a standardized and approved tool (8).

Maternal attachment is the mother-infant harmony that begins immediately after birth and develops over time. In the postpartum period, the psychological and social status of the mother might affect the mother-infant relationship. Expectant mothers who develop negative mood changes do not take care of their babies and may engage in verbal or physical negative behaviors. Thus, maternal attachment does not occur in a healthy way, and problems may occur in the baby's emotional, mental, physical, social, and language development (9).

In this study, we aimed to investigate the frequency of postpartum depression and maternal attachment status in a low socioeconomic level region during the Covid-19 pandemic.

MATERIAL and METHODS

Women who gave birth at Muş State Hospital were evaluated between 1 January 2021 and 28 February 2021. The women who came to the follow-up visit on the 10th postpartum and agreed to participate in our study voluntarily were included. Our participants were selected from people over the age of 18, Turkish speaking, literate, able to understand what they read, and fill out the questionnaire on their own. Persons with a known history of psychiatric illness during or before pregnancy were excluded from the study. Also, stillbirth, neonatal death, and participants whose babies were in neonatal intensive care tested positive for COVID-19 during pregnancy were excluded from the study. Sociodemographic characteristics and the participants' maternal and fetal outcome information were recorded during the questionnaire. The evaluation was done with Edinburgh Postpartum Depression Scale (EPDS) and Maternal Attachment Scale (MAI). Approvals from the Ministry of Health and the local ethical commission (514/194/49) were obtained. Our study was conducted with 200 women who gave birth as a cross-sectional prospective.

Patients' age, gravity, parity, height, weight, weight gained during pregnancy, medical history, previous or ongoing psychological illness and drug use, alcohol, and cigarette use, obstetric follow-up regarding any complications for fetus or mother, socioeconomic status, spousal support, sleeping disorder, type of delivery, need for hospitalization longer than 48 hours, neonatal intensive care unit admissions were recorded. None of our participants used alcohol or drugs, and people with known psychiatric disorders were also excluded from the study. Body Mass Index (BMI) was calculated by dividing weight (kg) by height (m) squared. According to BMI, were divided into three classes normal weight (<25), overweight (25-29.9 kg/m2), and obese (≥30 kg/m2). Socio-economically, according to October 2020 Turkey Statistics data, those with a monthly income below the hunger limit of 2482 TL were recorded as low income, those with a monthly income of 8085 TL above the poverty line were recorded as high, and their families with an income between 2482-8085 TL were recorded as a medium.

Edinburgh Postpartum Depression Scale (EPDS); Responses consisting of 10 items and four options, which can be evaluated in less than 5 minutes, are scored between 0-3; the lowest score that can be obtained from the scale is 0, and the highest score is 30 (9). The Turkish adaptation was made by Engindeniz, and the threshold value of the scale was found to be 12 (10). Scores of this value and above indicate high-risk mothers for the development of postpartum depression, and further investigation is required. The reason why we preferred it in our study was the fact that sleeplessness, which is frequently seen independently of depression in the postpartum period, does not affect the outcome, as it is a scale that is evaluated quickly and easily. In our study, participants with an EPDS score of 12 and above were considered high risk. And they were referred to the psychiatry outpatient clinic for evaluation in terms of depression and expert support.

Maternal Attachment Scale (MAI); measures adaptation to motherhood and attachment to the baby with maternal emotions and behaviors. High scores indicate high attachment. The lowest score to be obtained from the scale is 26, and the highest score is 104 (11). Its Turkish adaptation was made by Kavlak (12).

While evaluating the findings obtained in the study, SPSS (Statistical Package for Social Sciences) for Windows 10.0 program was used for statistical analysis. Student's t-test was used to compare the descriptive statistical methods (mean, standard deviation, frequency) while evaluating the study data, as well as the normally distributed parameters in the comparison of quantitative data; Mann Whitney U and Kruskal Wallis tests were used for intergroup comparisons of non-normally distributed parameters. A Chi-square test was used to compare qualitative data. The results were evaluated at the 95% confidence interval, a significance level of $p<0.05$.

RESULTS

The mean age of the puerperal group was 26.38±6.07, mean BMI was 28.06±2.67, mean weight gained during pregnancy was 12.91±4.62, mean gestational week was 38.09±2.66, mean gravida was 3.02 ±1.91, parity means 2.68±1.67, living child mean 2.65±1.64, Edinburgh scores mean 10.33±5.52 and maternal attachment scores mean 98.91±43.88 (Table 1).

When the BMI groups of the participants were examined, 12 women were in the normal weight group, 158 of them were in the overweight group, and 30 women were in the obese group. When the parity conditions are examined, 58 women are in the Primipar group, and 142 women are in the Multipar group.

Eighty-six of the participants have sleeping disorders, 174 women get support from their spouses, 4 of them smoke, 195 women do not have a chronic disease, and 5 women have a chronic disease. While the income status of 112 women is low income, 77 women are medium income, and 11 women are high income. Considering their educational status, 80 people are primary school graduates, while 34 people are university graduates. There are 49 patients who need prolonged hospitalization. When Edinburgh groups are examined, 117 people are in the low-risk group, while 83 people are in the high-risk group (Table 2).

BMI group, Parity Status, Mode of Delivery, Sleeping problem, Spousal support, Smoking, Chronic Disease, Income Status, Educational Status, Edinburgh group status, EPDS scores, and MAI scores were compared. In the group with normal BMI, the mean of EPDS was lower than the other two groups. The mean EPDS in the group with sleep problems was higher than those without sleep problems.

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While the mean of EPDS is higher in those, who do not receive support from a spouse, the mean of maternal attachment in those who receive support from a spouse is higher than in those who do not receive support from a spouse. The Edinburgh average of those with good income status is lower than those with middle income.

The mean of maternal attachment of those who do not need prolonged hospitalization is higher than those who are hospitalized. The mean maternal attachment of those in the EPDS high-risk (≥12 points) group was lower than those in the EPDS low-risk (<12 points) group (Table 3).

Table 1: Demographic data of the Patients

	Mean	s.s.	Median
Age	26,38	±6,07	25,00
Height (Cm)	163,04	±5,10	163,00
Weight (Kg)	74,52	±6,98	74,00
BMI (Body Mass Index)	28,06	±2,67	27,64
Weight gained during pregnancy	12,91	±4,62	13,00
Gestational week of delivery	38,09	±2,66	38,00
Gravity	3,02	±1,91	3,00
Parity	2,68	±1,67	2,00
Living Child	2,65	±1,64	2,00
EPDS scores	10,33	±5,52	10,00
Maternal Attachment Inventory (MBI)	98,91	±43,88	98,00

Table 2: Descriptive statistics

		n	%
BMI (Body Mass Index)	Normal (<25)	12	(6,00)
	Overweight (25-29,9)	158	(79,00)
	Obese (≥30)	30	(15,00)
Parity	Primipar	58	(29,00)
	Multipar	142	(71,00)
Type of delivery	Vaginal delivery	150	(75,00)
	Cesarean section	50	(25,00)
Sleeping disorder	No	114	(57,00)
	Yes	86	(43,00)
Spousal support	No	26	(13,00)
	Yes	174	(87,00)
Smoking	No	196	(98,00)
	Yes	4	(2,00)
Chronic disease	No	195	(97,50)
	Yes	5	(2,50)
Level of Income	Low	112	(56,00)
	Medium	77	(38,50)
	High	11	(5,50)
Level of education	Primary school graduate	80	(40,0)
	High school graduate	86	(43,00)
	University graduate or higher	34	(17,00)
Long hospital stay	No	151	(75,50)
	Yes	49	(24,50)
EPDS Group	Low risk	117	(58,50)
	High risk	83	(41,50)

Table 3: Comprasion of EPDS and MAI scores for each them

		EPDS				MAI			
		Mean	s.s	Median	p	Mean	s.s	Median	p
BMI (Body Mass Index)	Normal (<25)	5,00	±3,46	4,50	**0,002**[1]	100,08	±4,10	101,00	0,104[1]
	Overweight(25-29,9)	10,73	±5,37	10,00		99,59	±49,21	98,00	
	Obese (≥30)	10,37	±6,02	10,00		94,83	±8,79	96,50	
Parity	Primipar	10,02	±6,05	10,00	0,523	106,02	±80,59	98,50	0,394
	Multipar	10,46	±5,31	10,00		96,01	±7,96	98,00	
Type of delivery	Vaginal delivery	10,39	±5,44	10,00	0,797	100,13	±50,27	98,00	0,866
	Cesarean section	10,18	±5,83	10,00		95,24	±10,81	98,50	
Sleeping disorder	No	8,58	±5,36	8,50	**<0,001**	96,27	±8,61	99,00	0,325
	Yes	12,66	±4,87	13,00		102,41	±66,24	97,50	
Spousal support	No	12,54	±5,35	13,00	**0,038**	93,23	±8,41	95,00	**0,007**
	Yes	10,01	±5,49	10,00		99,76	±46,90	99,00	
Smoking	No	10,39	±5,56	10,00	0,265	98,86	±44,33	98,00	0,140
	Yes	7,75	±2,50	7,50		101,25	±3,59	102,50	
Chronic disease	No	10,35	±5,54	10,00	0,698	99,01	±44,44	98,00	0,285
	Yes	9,60	±5,37	10,00		95,00	±4,85	94,00	
Level of İncome	Low	9,62	±5,41	10,00	**0,012**[1]	101,42	±58,04	98,50	0,944[1]
	Medium	11,69	±5,58	12,00		95,83	±8,94	98,00	
	High	8,18	±4,53	8,00		94,91	±12,57	98,00	
Level of schooling	Primary school graduate	9,15	±3,72	10,00	0,662[1]	95,38	±8,67	97,00	0,734[1]
	High school graduate	9,88	±6,07	10,00		105,99	±74,55	99,00	
	University graduate or higher	10,93	±5,71	10,00		95,88	±8,68	98,00	
Long hospital stay (> 48 hour)	No	10,36	±5,53	10,00	0,908	99,25	±50,32	98,00	**0,024**
	Yes	10,24	±5,58	10,00		97,86	±8,31	100,00	
Edinburgh group	Low risk	6,56	±3,43	7,00	**<0,001**	103,19	±56,43	100,00	**<0,001**
	High risk	15,66	±2,89	15,00		92,88	±10,26	95,00	

DISCUSSION

The pandemic process has negatively affected the psychological state of the entire world population. In studies investigating the effect of the pandemic on anxiety, depression, and quality of life in the world, it was found that different groups were affected to different degrees (13-15). Although the incidence of PPD was found to be 10-15% in general, the rate of postpartum depression was found to be 35.5% in a group performed in Ankara and applied EPDS (16). In another study conducted in Istanbul during the pandemic period, EPDS was found to be 12% similar to the pre-pandemic period (17). In a study conducted in Italy during the quarantine period, PPD was found to be 44% (22). In our study, 41.5% were found in the risky group in terms of postpartum depression, according to EPDS. This situation can be since our participants are from a low socioeconomic group and may have been more negatively affected by the pandemic process. The fact that the group with a good income level had a significantly lower EPDS score than the other groups indicates that there may be a relationship between income status and depression. In previous studies, it has been suggested that individuals in the lower socioeconomic class have a higher incidence of mental disorders such as depression than those in the middle and upper socioeconomic class (18,19).

When we look at the literature, Although there are studies stating that there is a relationship between obesity and postpartum depression in general, there are also studies claiming that there is no relationship (20,21). In our study, consistent with the literature, it was concluded that the risk of PPD increased in mothers with an increased BMI. It has been stated that sleep health during pregnancy and postpartum may have an effect on anxiety and depression (23). In our study, EPDS scores were found to be significantly higher in expectant mothers with sleep problems.

Close environment support reduces the mother's duties and responsibilities and provides psychological relief (24). In our study, it was observed that support from the spouse both decreased the EPDS scores and increased the MAI scores, making a positive contribution to mother-infant adjustment.

Mother-infant attachment is a special relationship between mother and infant that develops over time and can be affected by many factors. Studies have shown that early skin-to-skin contact, staying in the same room with the mother and baby, and breastfeeding regularly increase the adjustment of mother and baby(25). In our study, it was observed that the MAI scores of the mothers who stayed in the hospital longer than 48 hours decreased. Reducing the length of stay in the hospital can strengthen the mother-infant relationship.

Postpartum depressive symptoms were examined, and it was found that mothers with high scores had poor adjustment to the maternal role and mother-infant adjustment (26,27). Similarly, women who had higher EPDS scores had lower MAI scores in our study too.

CONCLUSION

In the study we conducted in a region with a low socioeconomic level during the pandemic period, We determined that PPD rates were considerably increased, and this situation negatively affected maternal attachment. We think that encouraging spousal support can decrease depression scores and increase maternal attachment. By encouraging spouses and social support to mothers, depressive symptoms can be reduced. Evaluating postpartum women for depression and providing professional support to the risky group can prevent the devastating effects of depression.

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Ethical approval: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by Local Ethical Committee. All procedures performed in studies with human participants met the ethical standards of the Institutional Research Commission and the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical standards.

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Short term blood pressure variability and diastolic function in middle-aged normotensive individuals

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ABSTRACT

Objective: Blood pressure variability (BPV), a non-conventional blood pressure parameter, has been shown to contribute to hypertensive target organ damage but its association with diastolic dysfunction is unknown. The present study investigates the association of BPV and left ventricular diastolic dysfunction (LVDD) in middle-aged normotensive individuals.

Materials and Methods: 264 normotensive patients aged between 45 and 65 were enrolled. 24-hour ambulatory blood pressure monitoring was performed, and BPV was defined as the standard deviation of systolic blood pressure measurements. Patients were divided into three groups according to BPV tertiles. Echocardiographic and tissue doppler diastolic function parameters were compared among the groups.

Results: Mean ages of the patients were 50.41 and similar among groups. Mitral inflow E/A (Tertile 1 vs 2 vs 3: 1.10[0.33] vs 1.05 [0.22] vs 1.02 [0.30], p=0.02) and average tissue doppler mitral annular E' velocity (12 [2] vs 10.5 [1.85] vs 10 [1.55], p=0.02) were highest in the tertile 1 and lowest in the tertile 3. Average E/E' (Tertile 1 vs 2 vs 3: 7.2 [2.2] vs 8.1 [3.2] vs 9.3 [2.9], p<0.001) was lowest in the tertile 1 and highest in the tertile 3. In addition, there was a positive correlation between BPV and Average E/E' (Rs =0.401, p<0.001). In contrary, E/A (Rs =- 0.286, p<0.001) and average E' (Rs =- 0.451, p<0.001) were negatively correlated with BPV.

Conclusion: BPV is positively correlated with average E/E' and negatively correlated with E/A and average E'. Further studies are required to elucidate the relationship between BPV and LVDD.

Keywords: blood pressure variability, left ventricular diastolic dysfunction

INTRODUCTION

Blood pressure is a dynamic parameter that continuously fluctuates over time due to the interaction of cardiovascular regulatory mechanisms and environmental, physical, and emotional factors (1). Blood pressure variability (BPV), a measure of blood pressure fluctuation, has emerged as a non-conventional blood pressure parameter and has been shown to contribute to hypertensive target organ damage independent of the absolute blood pressure levels, but it is rarely assessed in daily clinical practice(2).

Blood pressure variability can be classified as very short term (beat to beat), short term (24-hour ambulatory monitoring), mid-term (day by day in-home blood pressure monitoring), and long term (e.g., variability among clinical visits). Short-term BPV is associated with increased cardiac, vascular, and renal events (2).

Left ventricular diastolic dysfunction (LVDD) is characterized by increased viscoelastic chamber stiffness and impaired relaxation, which may lead to elevated filling pressures and diastolic heart failure (3). The Association of diastolic dysfunction and hypertension is well established, but the role of BPV in LVDD is unknown (4).

The present study investigates the association between short-term BPV in 24-hour ambulatory blood pressure monitoring and LVDD in middle-aged normotensive individuals.

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MATERIAL and METHODS

264 normotensive patients aged between 45 and 65 who were admitted to cardiology outpatient clinics and had 24-hour ambulatory blood pressure monitoring between January 2017 and September 2021 were enrolled in the study. Patients with hypertension or on antihypertensive drugs, atrial fibrillation, more than mild valvular heart disease, left ventricular hypertrophy, left ventricular ejection fraction < 55%, clinical heart failure, coronary artery disease, obesity, and diabetes mellitus were excluded from the study. Patients were divided into three groups according to BPV tertiles. Echocardiographic and tissue doppler diastolic function parameters were compared among the groups. All participants have given informed consent, and the study protocol was approved by the Institutional Ethics Committee.

24-hour ambulatory blood pressure monitoring was performed, and BPV was defined as the standard deviation of systolic blood pressure measurements. Normotension was defined as office blood pressure <140/90 mmHg, mean daytime blood pressure < 135/85, night-time blood pressure <120/70 and mean 24-hour blood pressure < 130/80 mmHg. Obesity was defined as body mass index > 30 kg/m2. Diabetes mellitus was defined as antidiabetic medication use, fasting blood glucose > 126 mg/dl or HbA1c > 6.5%.

Hospital records were used to obtain the patients' medical history and demographic information. Venous blood samples were drawn for basic hematologic and biochemical analysis. Two-dimensional, m-mode, doppler, and tissue doppler echocardiography (Toshiba Artida, Toshiba Medical Systems Co., Japan) were performed in the left lateral position according to the European Association of Cardiovascular Imaging recommendations (BB). Pulse wave doppler imaging was performed in the apical four chamber view with a sweep speed of 50 mm/s, sample volume of 1-3 mm, and averaged over three cardiac cycles. Mitral inflow velocities including peak early filling (E) velocity, late diastolic filling (A) velocity, E/A ratio, deceleration time (DT-time between peak and end of the E wave), and isovolumic relaxation time (IVRT-time between aortic valve closure and mitral valve opening) were recorded. In tissue doppler imaging, early (E') and late (A') diastolic velocities of the mitral annulus were recorded by placing sample volume at the insertion of mitral leaflets to septal and lateral walls.

SPSS Statistics version 18.0 for Windows (SPSS Inc., Chicago, IL) was used for statistical analysis. The distribution pattern of the continuous variables was determined by using The Kolmogorov-Smirnov method. According to the distribution pattern, continuous data were presented as mean and standard deviation or median and interquartile range. The one-way ANOVA was used to compare data with normal distribution, and the Kruskal-Wallis test was applied to compare the data without normal distribution. Bonferroni correction was used for multiple comparisons. Categorical variables were compared with the chi-square test. Spearman's correlation analysis was used to assess the correlation between BPV and diastolic function parameters. A two-tailed p value < 0.05 was considered to be statistically significant.

RESULTS

The mean age of the patients was 50.41 and similar among groups along with gender, hyperlipidemia, and body mass index. Serum levels of fasting glucose, creatinine, lipoproteins, and thyroid-stimulating hormone were also similar (**Table 1**).

Two dimensional and doppler echocardiographic examination revealed that left ventricular ejection fraction, wall thicknesses, left ventricular diameters, left ventricular mass index, deceleration time, tricuspid regurgitation velocity, right ventricular diameters, and tricuspid annular plane systolic excursion were similar among groups in. Mitral inflow E/A (Tertile 1 vs 2 vs 3: 1.10[0.33] vs 1.05 [0.22} vs 1.02 [0.30], p=0.02) and average tissue doppler mitral annular E' velocity (12 [2] vs 10.5 [1.85] vs 10 [1.55], p=0.02) were highest in the tertile 1 and lowest in the tertile 3. Average E/E' (Tertile 1 vs 2 vs 3: 7.2 [2.2] vs 8.1 [3.2] vs 9.3 [2.9], p<0.001) was lowest in the tertile 1 and highest in the tertile 3 (**Table 2**).

In post hoc analysis, the difference between tertile 1 and 3 for mitral inflow E/A (p=0.01) and average E' (p=0.008) was significant. For average E/E', difference between tertile 1 and 2 (p=0.003), tertile 1 and 3 (p<0.001) and tertile 2 and 3 (p=0.001) were significant. In addition, there was a positive correlation between BPV and Average E/E' (Rs =0.401, p<0.001).

In contrary, E/A (Rs =- 0.286, p<0.001) and average E' (Rs =- 0.451, p<0.001) were negatively correlated with BPV (**Figure 1**).

Table 1. Baseline characteristics of the groups

Variables	Blood Pressure Variability Tertile1 (n=88)	Tertile2 (n=88)	Tertile3 (n=88)	*P Value*
Age(years)	50.86 ± 9.18	50.23 ± 11.98	50.14 ± 9.42	0.787
Gender (Male)	49 (55.7)	51 (58.0)	49 (55.7)	0.645
Hyperlipidemia (n, %)	14 (15.9)	12 (13.6)	13 (14.8)	0.488
BMI (kg/m^2)	22.99 (3.43)	22.49 (7.62)	22.61 (5.34)	0.766
Glucose (mg/dl)	88.05 ± 28.42	87.50 ± 30.21	88.14 ± 31.75	0.688
Creatinine (mg/dl)	0.79 ± 0.18	0.78 ± 0.22	0.76 ± 0.21	0.877
Cholesterol (mg/dl)	186 (88)	181 (92)	184 (100)	0.729
LDL (mg/dl)	121 (54)	116(71)	118 (64)	0.516
HDL (mg/dl)	48 (21)	47 (18)	48 (20)	0.853
Triglycerides(mg/dl)	125 (72)	122 (64)	124 (71)	0.738
Hemoglobin (g/L)	14.52 ± 1.30	14.32 ± 2.52	14.10 ± 1.25	0.626
WBC (x 10^3/ml)	6.25 ± 1.57	6.63 ± 1.39	6.41 ± 1.65	0.344
TSH	1.80 (1.91)	1.70 (1.90)	1.70 (0.90)	0.566

BMI, body mass index; LDL, low density lipoprotein cholesterol; HDL, high density lipoprotein cholesterol; WBC, white blood cell; TSH, thyroid stimulating hormone.

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Table 2. Echocardiographic parameters of the groups

Variables	Blood Pressure Variability Tertile1 (n=88)	Tertile2 (n=88)	Tertile3 (n=88)	*P Value*
Left atrium (mm)	30 (5)	31 (2)	32 (6)	0.422
IV Septum (mm)	9 (2)	9 (2)	9 (2)	0.998
Posterior Wall (mm)	9 (2)	9 (2)	9 (2)	0.986
LVEDD (mm)	42 (4)	43 (3)	43 (5)	0.842
LVESD (mm)	26 (5)	27 (4)	27 (4)	0.874
LVEF (%)	64 (4)	65 (5)	65 (6)	0.752
LVMI	72 (20)	74 (13)	75 (18)	0.685
E/A	1.10 (0.33)	1.05 (0.22)	1.02 (0.30)	**0.02**
IVRT	94 (12)	97 (10)	99 (10)	0.054
DT	175 (32)	181 (36)	178 (36)	0.453
Average E’	12 (2)	10.5 (1.85)	10 (1.55)	**0.02**
Average E/E’	7.2 (2.2)	8.1 (3.2)	9.3 (2.9)	**<0.001**
TRV (m/s)	2.1 (0.6)	2.2 (0.5)	2.2 (0.5)	0.683
RV diameter (mm)	29 (5)	29 (4)	29 (7)	0.838
TAPSE	22 (6)	23 (5)	22 (5)	0.888

IV, interventricular; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; TRV, tricuspid regurgitation velocity; RV, right ventricle; TAPSE, Tricuspid Annular Plane Systolic Excursion.

Table 3. 24-hour ambulatory blood pressure monitoring parameters.

Variables	Blood Pressure Variability Tertile1 (n=88)	Tertile2 (n=88)	Tertile3 (n=88)	*P Value*
Office SBP	126.55 ± 18.69	127.73 ± 16.80	126.36 ± 14.08	0.866
Office DBP	78.22 ± 11.26	77.87 ± 10.45	77.98 ± 12.18	0.912
Mean 24h SBP	122.89 ± 16.30	121.98 ± 18.25	122.24 ± 14.74	0.886
Mean 24h DBP	74.15 ± 7.84	73.88 ± 7.24	74.32 ± 8.54	0.834
Mean daytime SBP	124.45 ± 16.32	124.18 ± 14.48	124.88 ± 18.54	0.788
Mean daytime DBP	76.20 ± 8.12	75.94 ± 6.24	76.10 ± 7.48	0.847
Mean night-time SBP	119.70 ± 16.49	119.27 ± 28.04	119.32 ± 16.84	0.911
Mean night-time DBP	72.69 ± 9.42	72.87 ± 11.12	72.90 ± 8.98	0.892
Blood pressure variability	7.89 ± 0.88	9.22 ± 1.51	13.14 ± 2.34	**<0.001**
Non-dipper pattern	24 (27.3)	25 (28.4)	26 (29.5)	0.127

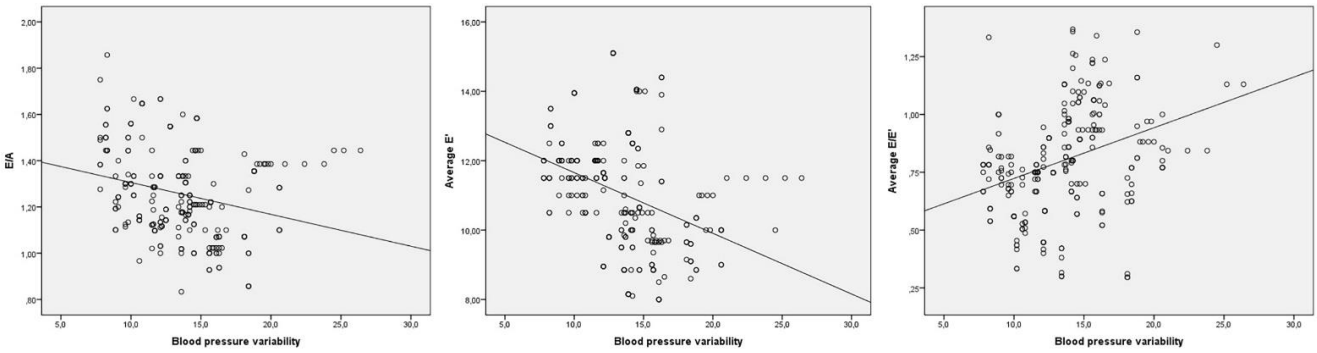

Figure 1. Correlation analysis between blood pressure variability and diastolic parameters.

DISCUSSION

In the present study, we demonstrated for the first time that higher BPV is positively correlated with E/E’ and negatively correlated with E/A and E’ in normotensive individuals. To the best of our knowledge, no study in the literature suggests a relation between BPV and LV diastolic parameters.

Diastolic dysfunction is characterized by impaired relaxation, reduced left ventricular diastolic distensibility, and filling of the myocardium, resulting incomplete cardiac chamber filling in the absence of an increase in the left atrial pressure. Consequently, higher atrial pressures may lead to diastolic heart failure symptoms (5).

Although several other risk factors such as coronary artery disease, obesity, and diabetes mellitus are implicated, hypertension is the most important risk factor for the development of LVDD in the community (4). Hypertension-induced inflammatory activation and endothelial dysfunction were shown to be associated with LVDD (6). Particularly, decreased nitric oxide-cyclic guanosine monophosphate-protein kinase G signaling predisposes cardiomyocytes to develop hypertrophy and high diastolic resting tension (7).

Blood pressure oscillates over the short and long-term periods. Oscillation of the blood pressure within 24 hours is called short-term BPV (8).

Early studies demonstrated that short-term BPV is increased in hypertensive patients and is related to cardiovascular risk (9,10). Subsequently, accumulated evidence showed that BPV is linked to end organ damage in the general population as well as hypertensive individuals (11). Short-term BPV was also found to be associated with cardiovascular morbidity and mortality (12-15).

Moreover, the PAMELA study showed that cardiovascular mortality was higher in patients with greater erratic blood pressure variations during 24 hours (13). In a study using microneurographic nerve traffic recording in peripheral nerves, Narkiewicz et al. demonstrated that sympathetic activity is directly linked with 24-hour BPV in normotensive individuals (16). It is also known that increased sympathetic activity may play a role in the development and progression of structural cardiovascular alterations such as endothelial dysfunction and left ventricular hypertrophy (17). Therefore, increased sympathetic activity and endothelial dysfunction are probably the cause of diastolic dysfunction in normotensive individuals with higher BPV.

The present study has several limitations. First, this is a single-center study. Second, cardiac magnetic resonance and novel echocardiographic techniques such as myocardial strain imaging were not available and not used.

CONCLUSION

In conclusion, in normotensive individuals, BPV is positively correlated with average E/E' and negatively correlated with E/A and average E'. Further studies are required to elucidate the relationship between BPV and diastolic functions.

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Ethical approval: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by Local Ethical Committee. All procedures performed in studies with human participants met the ethical standards of the Institutional Research Commission and the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical standards.

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Role of the inflammatory activity in haemodialysis patients with COVID-19

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ABSTRACT

Objectives: It is known that haemodialysis (HD) patients are older and have more co-morbidities, and therefore they are very susceptible against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Inflammatory activity plays an important role in coronavirus disease 2019 (COVID-19), and the intensity of inflammatory response makes the severity of COVID-19 worse. Biomarkers related to infection such as procalcitonin (PCT), C-reactive protein (CRP), ferritin, albumin, troponin I, D-dimer, white blood cell (WBC), neutrophil, lymphocyte, and platelet play an important role in the inflammatory response of COVID-19. Our objective is to compare these biomarkers between healthy individuals with COVID-19 (HI-COVID-19) and haemodialysis (HD) patients (HP-COVID-19).

Methods: 50 patients diagnosed with COVID-19 were included in this cross-sectional and monocentric retrospective study. The population of this study was separated into two groups: Group 1 consisted of HI-COVID-19 (n=27), and Group 2 consisted of HP-COVID-19 (n=23). Demographic data, basic clinical characteristics, and laboratory tests were recorded during the application. Group 2 participants were chosen from those whose biomarkers such as ferritin (<200 ng/mL), CRP, PCT, ferritin, albumin, D-dimer, troponin I, WBC, neutrophil, lymphocyte, and platelet were within the normal range three months before (prior to having COVID-19).

Findings: When Group 2 and Group 1 were compared in terms of gender, age, presence of lung uptake, and fever, there was no difference. Five HP-COVID-19 patients lost their lives. There were no deaths in the other group. There was a statistically significant difference. Comorbid diseases such as diabetes mellitus (DM), coronary artery disease (CAD), and hypertension (HT) were significantly higher in Group 2. It was observed that CRP, PCT, troponin I, D-dimer, and ferritin from biochemical parameters were higher in Group 2, and platelet and albumin were higher in Group 1. Although WBC and neutrophil elevations and low lymphocytes were detected in Group 2, it was statistically not significant. Tocilizumab and convalescent plasma use were significantly higher in Group 2.

Conclusions: The strength of inflammatory activity in HP-COVID-19 can be estimated by observing serum levels of biomarkers such as CRP, PCT, ferritin, albumin, D-dimer, troponin I, WBC, neutrophil, lymphocyte, and platelet.

Keywords: Haemodialysis, Coronavirus Disease 2019, C-reactive protein, procalcitonin, lymphocyte

INTRODUCTION

Novel Coronavirus Disease 2019 (COVID-19), which has evolved from the infection with Severe Acute Respiratory Syndrome Coronavirus 2 Virus (SARS-CoV-2), outbreaked in Wuhan, China, in December 2019. COVID-19 has rapidly spread to the other parts of China and other countries (1,2). Kidney failure is a violent medical situation with a high prevalence of comorbid conditions, including heart disease and diabetes mellitus (DM), which heavily affect the elderly(3). According to the China National Data System (4), 579,381 haemodialysis (HD) patients were reported in 2018, with 33,795 of them in Hubei Province. Patients with HD have a higher sensitivity to SARS-CoV-2 pneumonia than the general population since they are old and have more medical history. While most patients had asymptomatic or only mild symptoms, approximately 15-20% of them required hospitalization, and less than 5% of them developed severe illness,

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which is the manifestation of acute respiratory distress syndrome (ARDS) and multiple organ failure (MOF), for which intensive care support is generally required and frequently provide a poor prognosis (5). The pathophysiology of COVID-19 is not entirely defined yet, and the lack of effective treatments creates a need to urgently enforce novel therapeutic strategies which will be developed by considering the pathophysiological assumptions. By binding angiotensin-converting enzyme-2 to human cells, the SARS-CoV2 spike protein induces cellular infection (6). The inflammasome in the host cell is activated by cellular infection and viral replication, resulting in the release of pro-inflammatory cytokines and cell death due to the pyroptosis, with the following release of a damage-related molecular pattern that amplifies the inflammatory response (7, 8). In COVID-19, one of the systems that result in ARDS and MOF is excessive cytokine release in response to viral infection, often known as cytokine release syndrome or cytokine storm (7). However, the cytokine release and inflammatory response in severe COVID-19 is currently known as incompetent.

Inflammatory activities and cytokine release of the individuals who do not have any diseases and those who have chronic kidney disease (CKD) and receive HD (with comorbid diseases) were reacted differently when they fell ill with COVID-19. It is possible that the severity of COVID-19 disease is affected by this difference. When the literature is examined, it is concluded that the HPs-COVID-19 and HIs-COVID-19 were not compared in terms of inflammatory activities and cytokine storm. In this regard, to our knowledge, this study will be the first in the literature. Our aim in this study was to compare these two groups in terms of the serum levels of the biomarkers associated with infection, such as CRP, PCT, ferritin, albumin, D-dimer, troponin I, WBC, neutrophil, lymphocyte, and platelet.

MATERIAL and METHODS

Patients and methods

Study groups: In this study, all participants were divided into two different groups by us.

Group 1: The inclusion criteria were healthy individuals who had COVID-19 (HIs-COVID-19); among the 1300 patients who were admitted to our Infectious Diseases and Clinical Microbiology Clinic, 27 HIs-COVID-19 patients were selected as healthy individuals with COVID-19. Data such as population characteristics and clinical and biochemical data were recorded following patient admission. The exclusion from the HIs-COVID-19 group were the patients with neoplastic diseases, hypertension (HT), cardiovascular diseases, CKD, asthma, obesity diseases, chronic obstructive pulmonary disease (COPD), DM, hematologic diseases, inflammatory disorders, smokers, and under herbal/drug therapy.

Group 2: Haemodialysis patients with COVID-19 (HD-COVID-19) formed the second group of our study. In addition, the 23 HPs-COVID-19 were also selected from 150 patients and accepted into our nephrology clinic. Data such as population characteristics and clinical and biochemical data were recorded following patient admission.

The inclusion criterion for HD-COVID-19 was that the patient had undergone CKD and continued to receive HD therapy for six months. Etiological causes of the kidney disease in Group 2 can be listed as follows; DM, HT, coronary artery disease (CAD), iatrogenic cause, kidney stone, glomerulonephritis, and Fabry disease. There was also a patient with a history of cerebral vascular obstruction (CVO). In this study, patients with acute renal impairment were excluded. Users of angiotensin converting enzyme inhibitors and angiotensin receptor inhibitors were not included in this study. We have selected the participants in Group 2 among those with the biomarkers, such as ferritin (<200 ng/mL), CRP, PCT, ferritin, albumin, D-dimer, troponin I, WBC, neutrophil, lymphocyte, and platelet within the normal range up to three months ago (before falling ill with COVID-19).

Laboratory tests: Patient data, as well as routine biochemical parameters, complete blood count, and demographics, were extracted from available medical records. Blood samples were collected after a twelve-hour fasting period. WBC, neutrophil, lymphocyte, and platelet analyses were conducted using blood samples that had been collected in tubes with EDTA, using an automatic blood counter (Mindray BC6800 Auto Haematology Analyzer Device [Shenzhen Mindray Bio-Medical Electronics Co. Ltd., Shenzhen, P.R, China]).

Biochemical biomarkers, such as serum glucose, urea, creatine (Cre), albumin, lactate dehydrogenase (LDH), and CRP, were analyzed by spectrophotometer, using a Beckman Coulter Chemistry Analyzer AU5800 Device (Beckman Coulter Mishima K.K., Tokyo, Japan).

The fluorescence immunoassay technique was used to conduct an analysis of PCT using a GP Getein 1600 Immunofluorescence Quantitative Analyzer (Getein Biotechnology Co., Ltd. Jiangsu, China).

Ferritin, troponin I, and creatine kinase (CK-MB) were analysed by immunoassay using an ADVIA Centaur XP immunoassay system (Siemens Healthineers, Erlangen, Germany).

D-dimer analysis was conducted using blood samples that had been collected in tubes with Na-citrate (1:9) analyzed with an immunoassay technique using an AQT90 FLEX Immunoassay Analyzer (Radiometer Medical ApS, Bronshoj, Denmark).

Prothrombin time (PT), activated partial thromboplastin time (aPTT), and international normalized ratio (INR) analyses were conducted using blood samples that had been collected in tubes with Na-citrate (1:9) and analyzed by the clot, chromogenic, or immune turbidimetric techniques using an STA Compact Max Analyzer (Diagnostica Stago, Asnieres, France)

Statistical Analysis: The analysis was carried out using the SPSS software (version 20.0). Categoric variables have been identified as absolute numbers. In this study, continuous variables were reported as median values or mean ± standard deviation and ranges. Fisher Exact Test, Mann-Whitney U, and Chi-Square Test were used among intragroup comparisons. $P < 0.05$ was found to be statistically significant.

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RESULTS

The study included 50 patients, of which 27 were HIs-COVID-19, and 23 were HPs-COVID-19. Twenty-three of the 150 HD patients who were monitored at our HD center were suffering from COVID-19. Twenty-three of the participants were male, and 27 were female. The average ages of the participants were 63.26±12.2. Forty-three participants had positive real-time reverse transcriptase-polymerase chain reaction (RT-PCR), while the remaining seven were diagnosed due to clinical, laboratory, and radiological analyses; 47 of the participants had positive pulmonary findings. There were no pulmonary results for three participants. Group 2 and Group 1 were compared in terms of gender, age, whether or not pulmonary involvement was present, and whether or not they had a fever, which were found to have no difference. Five HPs-COVID-19 (one female, four males) were deceased. No death was observed in the other group. The difference among the groups was statistically significant.

Dyspnea was significantly present in Group 1. In Group 2, comorbid diseases, such as DM, CAD, and HT, were significantly elevated. Although hospitalization time was longer in Group 2, it was not statistically significant. Whereas all Group 1 members were followed up with hospitalization, nine HPs-COVID-19 were followed up as outpatients. Two HPs-COVID-19 were deceased when they applied to the emergency service. The rest of Group 2 agreed to be hospitalized. The outpatient HPs-COVID-19 recovered within 10 to 15 days on average. While the period between the occurrence of symptoms and the start of treatment or hospitalization was five to seven days for Group 1, it was identified as three to five days for Group 2. The history of contact was statistically significant in Group 1. One HP-COVID-19 was diagnosed with CVO, while another participant had a COPD diagnosis, but it was not statistically significant. Pulmonary involvement was observed with chest computed tomography (CT) in the majority of the two patient groups (excluding two HIs-COVID-19 and one HP-COVID-19). **Table 1** summarizes all participants' demographic and general characteristics.

Table 1: Demographical and general characteristics of all participants

Parameter	Group 1 n:27	Group 2 n:23	p-value
Age (years) (mean±SD)	64.67±8.61	61.61±15.16	0.430
Gender (F/M)	13/14	14/9	0.368
History of contact (no/yes/unknown)	4/22/1	0/13/10	<**0.001****
Did family members contract with COVID-19? (no/yes/unknown)	10/15/2	8/15/0	0.742
Fever (no/yes)	16/11	9/14	0.256
Cough (no/yes)	4/23	4/19	0.805
Dyspnea (no/yes)	7/20	16/7	**0.002***
Hemoptysis (no/yes)	25/2	23/0	0.494
Sputum (no/yes)	26/1	20/3	0.322
Anosmia (no/yes)	25/2	22/1	0.653
Fatigue (no/yes)	0/27	0/23	0.465
Muscle pain (no/yes)	0/27	1/22	0.460
Diarrhea (no/yes)	22/5	15/8	0.196
CAD	27/0	9/14	<**0.001****
HT	27/0	4/19	<**0.001****
DM	27/0	16/7	**0.002***
CVO	27/0	22/1	0.460
COPD	27/0	22/1	0.460
RT-PCR (no/yes)	0/27	7/16	**0.002***
Finding in CT Thorax (no/yes)	2/25	1/22	0.646
Hospitalization (days)	6.89±2.75	9.7±14.88	0.384
Death (no/yes)	27/0	18/5	**0.003***
Tocilizumab (Using/Not Using)	1/27	7/16	**0.004***
Convalescent plasma (Using/Not Using)	1/27	6/17	**0.003***

**<0.001, *<0.05, CAD, coronary artery disease; HT, hypertension; DM, diabetes mellitus; CVO, cerebrovascular obstruction; chronic obstructive pulmonary disease (COPD); RT-PCR, real-time reverse transcriptase-polymerase chain reaction; CT, computerized tomography.

Table 2: Symptoms and findings of all participants

Parameter	No (n, %)	Yes (n, %)
Fever	25 (50)	25 (50)
Cough	8 (16)	42 (84)
Dyspnea	23 (46)	27 (54)
Hemoptysis	48 (96)	2 (4)
Sputum	46 (92)	4 (8)
Anosmia	47 (94)	3 (6)
Fatigue	0	50 (100)
Muscle pain	1 (2)	49 (98)
Diarrhea	37 (74)	13 (26)

Fever, cough, dyspnea, fatigue, and muscle pain occurred in most patients. The primary symptom in the patients was fatigue. Hemoptysis, sputum, anosmia, and diarrhea were the least observed symptoms. Symptoms and outcomes for all participants are summarised in T**able 2**.

Although WBC, neutrophil, and low lymphocyte elevations were found in Group 2, they were not statistically significant. While the parameters such as platelet and albumin were identified higher in Group 2, the parameters such as urea, CRP, Cre, PCT, troponin I, D-dimer, and ferritin were identified higher in Group 2. Comparing laboratory parameters across groups is summarized in **Table 3**.

DISCUSSION

Our HD unit is made up of 150 permanent HD patients. A total of 23 of these patients (15.3%) were diagnosed with COVID-19. Five (21.7%) of the 23 HPs-COVID-19 are deceased. In Group 2, co-morbidities were identified as statistically higher.

The ratio of patients deceased due to HD was 3.3%. There were no side effects of HCQ in any of our deceased patients. Among the deceased HD patients, male dominance was prominent (four of the five patients were male and one female), which is consistent with previous studies (9, 10).

All members in groups 1 and 16 of 23 HPs-COVID-19 received positive RT-PCR results. Seven HPs with COVID-19 underwent thoracic CT in addition to respiratory symptoms. The most common defect in chest radiography was the ground-glass opacity, which is similar to the previous reports 9. As documented in the literature, (11) the majority of patients presented with symptoms such as cough, fever, dyspnea, muscle pain, and fatigue.

While all Group 1 members were followed up with hospitalization, fourteen HPs-COVID-19 accepted hospitalization.

Two patients have deceased when they applied to the emergency service. Seven HPs-COVID-19 were followed up as outpatients because they did not agree to be hospitalized. Outpatients recovered over a long period of time, averaging 10 and a half days. The difference between the onset of symptoms and the onset of treatment or hospitalization was less for Group 2. Group 2 was continually hospitalized in our hospital and was diagnosed by medical staff sooner. Recovery plasma and tocilizumab were found to be used primarily in Group 2 (p=0.003, p=0.004, respectively). These findings confirm that the infection process is heavy and that cytokine release is severe in this group of patients. According to Wan et al. (12) cytokine storm is necessary for the development of COVID-19, and as a result, severe complications and the possibility of death.

The fifth edition of "Diagnosis and Treatment of COVID-19" recommends that cytokine levels be carefully monitored in order to improve treatment efficiency and reduce mortality (13).

While not statistically significant, the identification of high and low WBC and neutrophil lymphocytes in Group 2 is consistent with cytokine inflammation and tempest. Hypoalbuminemia, thrombocytopenia, and height in the serum of biomarkers, such as CRP, PCT, ferritin, troponin I, and D-dimer in Group 2 is an indicator of severe inflammation and quick processing of coagulation cascade in this group. The changes in these biomarkers, which play a role in the inflammation process and coagulation cascade, are compatible with the cytokine release and severe inflammation activity.

We will try to explain the general effects of uraemia and kidney disease on the immune system. The uremic toxins may be responsible for acquired immunity disruptions in patients with CKD was reported by the old observation data that uremic serum put into cell cultures reduces T-lymphocyte proliferation after the administration of the stimulation using phytohemagglutinin (14).

Table 3: Laboratory characteristics of all participants

Parameter	Group 1 n:27	Group 2 n:23	P value
Glucose (mg/dL)	107 (79-217)	113 (83-252)	0.514
WBC (x10^9/L)	7.92±4.59	9.07±6.41	0.553
Neutrophile (x10^9/L)	5.91±4.18	7.24±6.04	0.454
Lymphocyte (x10^9/L)	1.38 (0.40-3.36)	1.19 (0.36-7.3)	0.129
Platelet (x10^9/L)	245.40±105.41	155.34±57.21	<**0.001****
Ure (mg/dL)	31 (13-61)	100 (25-62)	<**0.001****
Cre (mg/dL)	0.69 (0.42-1.25)	5.9 (0.1-17)	<**0.001****
Albumin (g/L)	40.16±2.98	33.97±4.64	<**0.001****
LDH (U/L)	318.07±161.60	284.61±104.68	0.599
PCT (ng/mL)	0.02 (0.0-16)	0.8 (0.0-36.61)	<**0.001****
Troponin I (ng/mL)	0.01 (0.0-50)	0.06 (0.0-0.70)	<**0.001****
CRP (mg/L)	13.80 (1.2-114)	85 (4-113)	**0.002***
CK-MB (ng/mL)	0.18 (0-300)	0.68 (0-5)	0.103
D-dimer (µg/L)	384 (111-1170)	1248 (200-5800)	<**0.001****
INR	1.03 (0.0-1.31)	1.1 (0.0-2.5)	0.198
Ferritin (ng/mL)	278.80 (22-1655)	1500 (31-1655)	<**0.001****

**<0.001, *<0.05, WBC, white blood cell; Cre, creatinine; LDH, lactate dehydrogenase; PCT, procalcitonin; CRP, C-reactive protein; CK-MB, creatine kinase-MB; INR, international normalized ratio.

It has been discussed that T-lymphocyte apoptosis has been affected by both the permeability and the composition of the dialysis membrane (15). Acquired immunity disturbances in HD individuals are widespread and varied. They have arisen from complications of chronic renal failure, therapeutic interventions, uremia per se, and HD procedure for their treatment. The present data affirm that these problems of acquired immunity cover the antigen-presenting cell (APC) and T-lymphocyte primarily. While APC is preactivated, the T lymphocyte-dependent immune response is weak, which tends to predispose to infections (16). We emphasized the complex effects of uremia and kidney disease on the immune system. The effects of COVID-19 disease on the immune system are still unknown. We performed this study to solve this mystery.

We will also mention some published studies that are consistent with the findings obtained in this study. Because patients with HD have disarrangements of T- and B-cell function, patients may have uncommon presentations (17, 18). It was reported by Huang et al. (19). that depressed total lymphocytes, high LDH, and prolonged PT levels were reported as the most common laboratory aberrances in COVID-19 pneumonia. Although not statistically significant, serum lymphocyte level in patients with HD was observed as low. (In Group 2, the average serum lymphocyte level was $1.19x10^9$/L, and in Group 1, it was $1.38\ x10^9$/L).

According to Huang et al. (20), a blood albumin level of 35 g/L at presentation increases the probability of death in COVID-19 by at least 6-fold. They proposed that, in addition to lymphocyte count and comorbidities, lower albumin levels on admission can be used to predict the outcome of COVID-19. Group 2 had significantly decreased serum albumin levels ($p<0.001$).

On admission, CRP, PCT, and IL-6 levels increased significantly as 65.0 percent, 5.7 percent, and 67.9% in the patients, respectively. The proportion of patients with elevated levels of IL-6, PCT, and CRP was significantly higher in severe COVID-19 pneumonia than in mild COVID-19 pneumonia, which is consistent with Professor Li Lanjuan's term "cytokine storm", which emphasizes the importance of inflammatory factors in the progression from mild to severe disease (21). Average serum PCT and CRP levels in Group 2 were found significantly lower ($p<0.001$, $p=0.002$, respectively).

Serum ferritin, characteristic of hemophagocytic lymphohistiocytosis, commonly recognized as a complication of viral infection, is nearly associated with poor recovery of COVID-19 patients, and those with disturbed lung lesions are more probably to have incremented ferritin levels (22). While our patients had ferritin<200 ng/mL before they were fell ill with COVID-19 disease, it increased to an average of 1500 ng/mL during the COVID-19 period ($p<0.001$).

It is demonstrated that patients having an elevated cardiac troponin-I level in the first 24 hours of admission have remarkably higher in-hospital mortality when compared to the patients having a normal troponin-I level. We should note that there are various hypotheses in relation to a myocardial injury that is linked with COVID-19, as represented by high troponin-I compatible with previous observations associated with the outbreaks of the Middle East respiratory syndrome (MERS) and SARS. Microangiopathy, myocarditis, cytokine storm, and myocardial infarction are among these mechanisms (23). In COVID-19 patients, elevated baseline D-dimer levels are linked to inflammation and have a limited predictive value for thrombosis (24). High blood troponin I and D-dimer levels were significant ($p<0.001$, $p<0.001$, respectively) in Group 2, and serum troponin I and D-dimer levels were also found to be extremely high in Group 2 who have deceased.

In Younes Zaid et al. (25) both thrombosis and inflammation are accepted as the clinical manifestations that were monitored during the infection of SARS-CoV-2. They can be fatal, and a better understanding of COVID-19's cellular and molecular effectors could lead to novel therapeutic options for people who are currently not vaccinated. Platelets can interact with viruses, causing thrombosis and inflammation. They looked at platelets in a group of patients with non-severe and severe COVID-19 who had platelet counts in the lower range (but not thrombocytopenic). SARS-CoV-2 RNA appears to be linked to patient platelets, and platelets describe pro-inflammatory chemicals and are hyperactivated in COVID-19, according to their findings. Although the platelets of the Group 2 were observed within the normal range, it was lower than Group 1 ($p<0.001$). This demonstrates that the inflammatory activity was severe.

Our study had certain limitations. The first limitation was that because we had an insufficient number of patients, it is required to conduct a more comprehensive study to generalize the changes in the inflammatory, thrombosis, and coagulation markers that occurred in the patients with HD to all HD patients. The second limitation was that it is required to check serum IL-6, IL-1β, TNF, and IL-10 levels in terms of the cytokine storm or release. We did not evaluate these levels because we do not examine these cytokines in our laboratory. We demonstrated the diagnosis of cytokine release or storm with the clinic and changes in inflammation, coagulation, and thrombosis biomarkers. The third limitation was that because some of our patients with HD did not accept being hospitalized and due to the occasional difficulties in supplying convalescent plasma and tocilizumab, we could not study the role of these treatments in suppressing the cytokine release. However, we mostly used tocilizumab and convalescent plasma in patients with HD.

CONCLUSION

The comorbid diseases-rich HD patients' inflammatory activities and cytokine release were higher when they contracted COVID-19 than individuals without any diseases. Cytokine storm brings about ARDS or MOF, which gives rise to physiological relapse and death. If the serum levels of the biomarkers, such as CRP, PCT, albumin, ferritin, D-dimer, troponin I, WBC, neutrophile, lymphocyte, and platelet, are known and in case of clinical suitability; this may enable us to understand the inflammatory response activity, foresee that the patient may sustain severely and provide the possibility to take the precaution against the complications associated with the COVID-19.

Author Contributions: ZK, FA: Study design, Literature review, Data collection and/or processing, Analysis and/or interpretation, **ZK:** Writing, Revision

Acknowledgments: None

Conflict of interest: The Declaration of Helsinki was followed in this single-center, cross-sectional retrospective investigation upon obtaining consent from the local ethical committee. Informed verbal consent was obtained from all participants.

Ethical approval: The present study was approved by Batman Education and Research Hospital Clinical Research Ethics Committee of Clinical Studies dated 23.03.2021 and 267 decision number.

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Evaluation of Efficacy and Failure of High Flow Nasal Cannula Therapy in Paediatric Emergency Service and Pediatric Intensive Care Unit

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ABSTRACT

Objective: High-flow nasal cannula oxygen therapy (HFNC) improves gas exchange and decreases work of breathing in patients with acute respiratory distress. We aimed to discuss the indications for HFNC in children of all ages and diagnoses and to evaluate the efficacy and risk factors for failure of HFNC therapy in children with acute respiratory distress and failure in a paediatric emergency service and paediatric intensive care unit (PICU).

Material and Methods: A total of 191 patients aged one month to 18 years treated with HFNC between October 1, 2018, and July 1, 2020, in the Paediatric Emergency Service and PICU were included in the study. Demographic and clinical characteristics, underlying chronic diseases, HFNC treatment success, and treatment failure of the cases were recorded.

Results: One hundred ninety-one children were included in the study, of whom 70 (36.6%) were female, and the median age was 13 months (1-204). The most common indication of HFNC treatment was bronchopneumonia (n=83, 43,5 %). HFNC treatment succeeded in 81.7 % (n=156) of the patients. It was observed that the two most successful patient groups were acute bronchiolitis and pneumonia. The failure rate was 18.3 % (35 of 191 children). The most common underlying comorbidity was bronchopulmonary dysplasia (BPD) (19, 9.9%). There was a statistically significant difference seen on Glasgow Coma Scale (GCS) and lactate value in blood gas in the first hour of the treatment in the group with unsuccessful results ($p<0.05$). During the HFNC treatment, 28 patients (14.7%) required invasive mechanical ventilation (IMV), and seven patients (3.7%) required non-invasive mechanical ventilation (NIMV).

Conclusion: HFNC is a reliable non-invasive treatment modality that is easily tolerated by children and has effective use in many critical diseases. Our study found that HFNC therapy could be initiated as the first-line therapy for various aetiologies of acute respiratory distress in a paediatric emergency service and PICU and all age groups. It was emphasized that transition to other treatment modalities should not be delayed in the cases predicted to be unsuccessful.

Keywords: High-flow nasal cannula, child, acute respiratory distress, paediatric intensive care unit

INTRODUCTION

The reason for over 9 million paediatric emergency service admission is related to respiratory tract diseases. It accounts for approximately 36% of paediatric emergency service admissions. More than 1.5 million children a year are hospitalized due to this issue (1, 2). Pulmonary and extrapulmonary pathologies (congestive heart failure, myocarditis, central nervous system infection, status epilepticus, metabolic diseases, sepsis) may cause respiratory distress. Oxygenation is used in many conditions with a high fraction of inspired oxygen (FiO_2) requirements like carbon monoxide poisoning, pre-intubation, post-extubation, sepsis, acute laryngotracheobronchitis, acute asthma attack, pneumonia, and acute bronchiolitis. The primary parameters are tachypnea, tachycardia, hypoxemia, and respiratory distress. Improvement in vital signs and decline in respiratory distress is not always observed with conventional oxygen treatment (3).

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HFNC treatment allows heated and humidified oxygen to be applied by determining oxygen concentration through a wide nasal cannula with high flow. Oxygen concentration can be increased to nearly 100%, and humidified oxygen temperature can be regulated between 34-37°C, allowing mucociliary clearance to be increased and secretions to be removed easily (3). HFNC has been shown to improve airway resistance and lung compliance, eliminate nasopharyngeal dead space and decrease work of breathing. Effective use of HFNC therapy in infants with respiratory distress, there are many studies showing that it reduces intubation rates and length of stay in PICU. However, few studies highlight the indications for HFNC use, efficacy, and failure factors in older children (4).

Our study aimed to predict HFNC treatment failure in the early period at different diagnosis groups causing respiratory distress and to determine the factors that may indicate not being late for other treatment modalities.

MATERIAL and METHODS

Our study was designed as a single-center retrospective cohort study. Our study included 191 patients aged one month to 18 years who underwent HFNC treatment in the paediatric emergency service and paediatric intensive care unit between October 1, 2018, and July 1, 2020. Acute respiratory distress was defined as hypoxemia (SpO_2<94%) and signs of respiratory distress (increased respiratory rate and heart rate, agitation, change of consciousness, colour changes, nose flaring, retractions, and wheezing) despite standard-flow oxygen therapy.

All patients received standard-flow oxygen therapy before the transition to HFNC therapy. The same brand of nasal cannula and sets were used in paediatric emergency service and PICU, with a flow rate of 1-60 L/min, FiO_2 21-100%, airflow temperature in the range of 34-37°C. FiO_2 was adjusted to reach pulse oximetry (SpO_2) between 92 and 97%, and the flow setting was based on the patients' body weight.

The data registration form noted demographic characteristics of patients, HFNC treatment indication, underlying chronic diseases, treatment success, length of stay in hospital (LOS), and mortality. We also monitored clinical and laboratory parameters, including GCS, respiratory rate per minute (RR/min), heart rate per minute (HR/min), modified respiratory distress assessment instrument score (m-RDAI), SpO_2, SpO_2/FiO_2 (S/F) ratio, venous blood gas for pH and pCO_2 at the beginning and the first hour of the HFNC treatment.

HFNC failure was defined as the need for escalation to NIMV or IMV. The treating physician decided whether escalation of treatment was necessary, but it generally occurred if FiO_2>0.6 or a worsening clinical condition. The patients whose HFNC treatment was discontinued and discharged from the hospital were considered successful.

Statistical Analysis: Statistical analysis was conducted with Statistical Programme Social Sciences (SPSS) 26 package program. Frequency and percent values were used for categorical data.

If the continuous variables complied with normal distribution, mean and standard deviation values were given; on the other hand, if they were not in conformity with normal distribution, their median, minimum and maximum values were stated.

While the continuous variables were analysed in the two groups, the evaluation was carried out with T-test independent groups if they complied with normal distribution; however, it was evaluated with the "Student T" test in independent groups. In assessing consecutive data that were not compatible with normal distribution, the Wilcoxon test was used for independent groups, and the Mann Whitney U test was utilized in independent groups. The significance level was approved as p<0.05 in terms of statistics in our study.

RESULTS

Seventy (36.6%) of the 191 children were female, and the median age was 13 months (1-204). One hundred and two (53.4%) of the 191 children had underlying medical conditions. The most common underlying comorbidity was bronchopulmonary dysplasia (BPD) (19, 9.9%), followed by neurologic disorder, cerebral palsy (CP) (17, 8.9%), and wheezy child (16, 8.4%).

The most common indication for the use of HFNC therapy was pneumonia (83, 43.5%), followed by acute bronchiolitis (49, 25.8%). There were no significant differences in gender, indication, and PRISM III score between the two groups. The success of HFNC treatment in the group ⩽24 months was 88.6%; while it was detected at 69.1% in the group >25 months, the difference between both age groups was statistically significant. The demographics of the 191 children are summarized in **Table I**.

There were significant improvements in RR/min, HR/min, SpO_2, S/F ratio, pH, pCO_2, and lactate values in the first hour of the successful HFNC period (p<0.05) (**Table II**). A statistically significant difference was only seen in GCS when RR/min, HR/min, m-RDAI score, GCS, SpO_2, S/F rate of 35 patients with unsuccessful HFNC were evaluated at the beginning and 1 hour of the treatment (p<0.05). There was a statistically significant difference in the lactate value of 35 patients with HFNC failure who were examined in the baseline and 1st-hour blood gas parameters (p<0.05) (**Table III**).

The two patient groups in which HFNC treatment was most successful were pneumonia (41.7%) and acute bronchiolitis (30.8%) (**Table I**). During the HFNC treatment, 35 patients needed escalation of respiratory support, including 7 (3.7%) who received NIMV and 28 (14.7%) who received intubation with mechanical ventilation. The reasons for treatment failure were a rise in work of breathing, desaturation, weakening of protective airway reflexes, and hemodynamic instability.

While there was no statistically significant difference between successful and unsuccessful groups in terms of duration of HFNC use, there was a significant difference in the length of stay (LOS) in the hospital. No patient was lost during the HFNC treatment process.

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Table I. Demographic characteristics, HFNC indications, success and failure conditions

Patient characteristics	Total n=191(%)	Successfull group n=156(%)	Failure group n=35(%)	P value
Sex				0.947
Female	70 (36.6%)	57 (36.5%)	13 (37.1%)	
Male	121 (63.4%)	99 (63.5%)	22 (62.9%)	
Age				
≤24 months	123 (64.4%)	109 (88.6%)	14 (11.4%)	**0.001**
>25 months	68 (35.6%)	47 (69.1%)	21 (30.9%)	
HFNC indications				0.641
Bronchiolitis Bronchopneumonia	49 (25.8%)	48 (30.8%)	1 (2.9%)	
Lobar pneumonia	83 (43.5%)	65 (41.7%)	18 (51.4%)	
Asthma	16 (8.4%)	12 (7.7%)	4 (11.4%)	
Croup	6 (3.1%)	6 (3.9%)	0 (0%)	
Sepsis	2 (1%)	2 (1.3%)	0 (0%)	
Status epilepticus	14 (7.3%)	8 (5.1%)	6 (17.1%)	
Post-extubation	6 (3.1%)	2 (1.3%)	4 (11.4%)	
Other Indications	6 (3.1%)	5 (3.1%)	1 (2.9%)	
	9 (4.7%)	8 (5.1%)	1 (2.89%)	
PRISM III score	8.70±4.40	8.56±4.32	10.25±4.60	0.112
Escalation of therapy				
NIMV	7 (3.7%)		7 (3.7%)	
IMV	28 (14.7%)		28 (147%)	
Duration of HFNC (day) median (min-max)	2(1-39)	3(1-21)	2(1-39)	0.377
Hospital LOS (day) median (min-max)	5(1-390)	4(1-34)	26(2-390)	**<0.001**

LOS: Length of stay, IMV: Invasive mechanical ventilation, NIMV: Non-invasive mechanical ventilation, HFNC: High flow nasal cannula

Table II. The findings of patients with successful HFNC treatment

Variables	Baseline HFNC treatment Mean (± SD)	First hour HFNC treatment Mean (± SD)	P value
HR/min	147.47 (24.6)	134.14 (18.37)	**0.001**
RR/min	53.67 (15.67)	45.81 (12.85)	**<0.001**
SpO_2	93.4 (5.86)	97.65 (2.29)	**0.001**
S/F rate	194.81 (39.93)	207.86 (32.5)	**<0.001**
pH	7.38 (0.12)	7.41 (0.09)	**0.001**
pCO_2 (mmHg)	36.41 (14.15)	33.62 (9.79)	**0.001**
HCO_3	21.58 (4.12)	22.42 (4.13)	**0.001**
Lactate (mmol/L)	2.25 (1.27)	1,36 (1.09)	**0.001**
	Median (Range)	**Median (Range)**	
GCS	15 (8-15)	15 (12-15)	**0.001**
m-RDAI	6 (3-10)	5 (1-8)	**0.001**

HFNC, high-flow nasal cannula; HR/min heart rate per minute; RR/min, respiratory rate per minute; SpO_2, pulse oximetry; S/F ratio, SpO_2/FiO_2 ratio; GCS: Glasgow coma scale, m-RDAI; modified respiratory distress assessment instrument score (m-RDAI),

Table III. The findings of patients with HFNC treatment failure

Variables	Baseline HFNC treatment Mean (± SD)	First hour HFNC treatment Mean (± SD)	P value
HR/min	145.46 (17.09)	143.14 (18.97)	0.370
RR/min	47.49 (15.72)	47.94 (16.70)	0.776
SpO2	93.14 (4.82)	93.83 (4.64)	0.295
S/F rate	188.42 (37.98)	184.62 (37.41)	0.485
pH	7.37 (0.14)	7.34 (0.16)	0.152
pCO2(mmHg)	38.43 (19.01)	43.45 (22.44)	0.080
HCO3	22.89 (6.68)	23.19 (6.39)	0.150
Lactate (mmol/L)	2.10 (1.86)	1.84 (2.23)	**0.043**
	Median (Range)	**Median (Range)**	
GCS	14 (7-15)	12 (4-15)	**0.048**
m-RDAI	5 (3-9)	6 (3-9)	0.845

HFNC, high-flow nasal cannula; HR/min heart rate per minute; RR/min, respiratory rate per minute; SpO_2, pulse oximetry; S/F ratio, SpO_2/FiO_2 ratio; GCS: Glasgow coma scale, m-RDAI; modified respiratory distress assessment instrument score.

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DISCUSSION

Acute respiratory failure is one of the most important causes of mortality and morbidity. Therefore, early diagnosis and effective treatment are essential. Upper airway pathologies include epiglottitis, laryngotracheitis, subglottic stenosis, foreign body aspiration; lung pathologies like asthma, bronchiolitis, pneumonia, cystic fibrosis; neuromuscular diseases; traumas lead to respiratory failure (5). Oxygen treatment is the most substantial part of treating respiratory distress and respiratory failure. HFNC is a safe, non-invasive, and well-tolerated treatment modality by children used in patients when conventional oxygen treatment is inadequate (3). The number of patients ⩽24 months was 121 (64.4%) in this study. Since the effectiveness and safety of HFNC were proven with studies, it was initiated to be used in many patient groups, especially with bronchiolitis (6-7-8). We found that a higher success rate of HFNC treatment in the ⩽ 24 months is related to the higher incidence of acute bronchiolitis in this age group. Nevertheless, studies related to HFNC use in asthma, pneumonia, croup, neurological diseases, muscle diseases, and cardiac reasons before intubation and post-extubation (9). In a study on HFNC treatment, post-extubation and conventional oxygen treatments were compared by Akyıldız et al., extubation failure rates were found as 4% with HFNC treatment and 22% with conventional oxygen treatment, and HFNC treatment was shown to reduce post-extubation failure risk (10). In studies by Hoffman et al., pneumonia was the most common indication of HFNC treatment (11). The most common indication for the use of HFNC therapy was pneumonia (83, 43.5 %), followed by acute bronchiolitis (49, 25.8%) in our study. In a study; of the patients who had been applied to HFNC treatment in PICU, there was an underlying chronic disease in 55,7 % of patients, and the most commonly seen chronic disease was neuromotor disease at 28.2 % (6). In our study, one hundred and two (53.4%) of the 191 children had underlying medical conditions. The most common underlying comorbidity was bronchopulmonary dysplasia (BPD) (19, 9.9%), followed by neurologic disorder, cerebral palsy (CP) (17, 8.9%). HFNC treatment success rate shows a difference in many studies. Its reason can be indications in its use, age groups, differences in application, and underlying chronic diseases. Success rates of HFNC in literature were varying between 60-94% (12,13,14,8,15,16). In this study, the success rate of HFNC is 82%, and it is similar to the literature. When we look at the treatment results of HFNC treatment indications, acute bronchiolitis forms the most widely used and successful indication in the literature (17). Pneumonia (n=77, 49.4%) and acute bronchiolitis (n=48, 30.8%) were the two most successful indications in the present study. Numerous studies are associated with a length of stay in HFNC treatment. The duration of treatment varies according to underlying comorbid conditions. In a study performed on patients with bronchiolitis by Goh et al., it has been indicated that HFNC treatment reduces hospital stay; however, it does not decrease the LOS in PICU (18). In a study carried out by Mckiernan et al., the average hospital stay in the intensive care unit decreased from 6 days to 4 after HFNC treatment in infants with bronchiolitis (19). In a study carried out by Alessandro et al., it has been seen that long-term HFNC treatment was more successful in patients (15). While there was no significant difference between successful and unsuccessful groups in terms of HFNC treatment duration, it was reported that the hospital length of stay was longer in the unsuccessful group. While HFNC treatment duration was three days in those with no underlying comorbidities, the median hospital LOS was five days. When the median HFNC treatment duration was five days in those with underlying chronic disease, the median hospital stay was seven days. The group with chronic disease had longer hospital stays because they had underlying conditions, and those illnesses were related to specific treatment requirements.

A decrease in RR/min, HR/min, and an increase in SpO2 and S/F ratio in the first hour predict that the treatment will be successful (19). We also observed a decrease in RR/min and HR/min in the first hour. It is essential to follow the SpO2 and S/F ratios in demonstrating the efficacy of treatment in patients treated with HFNC. Studies have shown that S/F ratios are a safe indicator of early NIMV failure in children (20). In a prospective study that a total of 204 cases with HFNC treatment were involved owing to acute respiratory failure by Can et al., the S/F rate elevated in the first hour remarkably, and it was displayed that being over 200 mmHg of S/F rate was a significant criterion in predicting HFNC treatment success (21). We observed a significant increase in SpO2 and S/F ratios in the first hour of treatment in the HFNC successful group. In a study performed by Er et al., after there was no response to HFNC treatment in paediatric emergency service, it was found that if the S/F rate was below 195 in the first hour, it was an early predictor of HFNC treatment failure (22).

In our study, the S/F ratio was below 190 in the first hour of the treatment in the HFNC failure group. When the baseline and first hour data of the HFNC failure group was assessed, a statistically significant difference was only observed in GCS and lactate. We think that the deterioration in GCS in patients with poor airway protective reflexes associated with underlying neurological diseases was significant in estimating failure as other parameters. M-RDAI is a clinical scoring system including wheeze, retraction, RR/min, and skin colour used in many studies regarding bronchiolitis. A study that analyzes the alteration of the m-RDAI score with HFNC treatment stated that treatment failure was higher in inpatient groups with an mRDAI score of >5 and emphasized the importance of m-RDAI score in the prediction of treatment achievement (15). While the m-RDAI score median value was six before the treatment, it was 5 in the first hour of the treatment, and it displayed a significant reduction in HFNC successful group. If possible, blood gas monitoring is an important follow-up parameter to evaluate the efficiency of ventilation and oxygenation in respiratory failure. In a study that Söğütlü et al. assessed the efficacy of HFNC treatment, there was no significant difference in pH and pCO_2 before and after the treatment (3). In a study that Vural et al. evaluated 131 patients who had been applied HFNC treatment in PICU, while there was no significant difference in pH and pCO_2 in blood gases of cases, a significant difference was established in their blood lactate levels (6). In the present study, while a statistically significant difference was observed in pH, pCO_2, HCO_3, and lactate values in the patient group with successful results, a significant difference was observed statistically in only the blood lactate levels of the patient

group with failure. Blood lactate value is a fast, simple, measurable parameter in determining tissue hypoxia, and it has prognostic importance. The significant difference in lactate values in the baseline and first hour blood gas parameters in the HFNC failure group; has been associated with conditions such as shock, seizures, and hypoxemia, leading to decreased oxygen delivery to tissues.

There are many studies related to intubation and mortality during HFNC treatment. While HFNC treatment use was related to reducing intubation and IMV rate in PICU, no alteration occurred in mortality in studies performed (23-24).

In a study, it has been indicated that there was an intubation need in 12% of the patients who had been applied HFNC (25). However, in the present study, 28 (14.7%) patients were intubated; other NIMV methods were used in 7 (3.7%) patients.

HFNC treatment has been used increasingly in respiratory failure in paediatric patients. However, more comprehensive, randomized, and controlled studies are required to determine its reliability and effectiveness more precisely and ascertain the factors affecting the utilization failure of HFNC, ensure the early transition to other treatment modalities and reduce hospital stay and cost.

Limitations: The main limitations of our study are that it was designed retrospectively, and data quality was dependent on file contents. As it was a retrospective study, patients' long-term flow and FiO2 values could not be accessed, and the onset and endpoint of HFNC treatment and FiO2 values could not be indicated in the study. Our study did not include the patients whose data were inadequate or could not be accessed.

CONCLUSION

We think that HFNC can be initiated as the first-line therapy for all age groups of children with various aetiologies of acute respiratory distress in paediatric emergency service and PICU. Further prospective studies are needed to evaluate the risk factors for failure in different clinical conditions and the reliability of long-term use.

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Ethical approval: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by Local Ethical Committee. All procedures performed in studies with human participants met the ethical standards of the Institutional Research Commission and the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical standards.

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Factors affecting preoperative sleep quality in patients undergoing myomectomy and hysterectomy

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ABSTRACT

Objective: In this study, preoperative subjective sleep quality (SP) and the factors which affect the SP were investigated in patients who underwent myomectomy and hysterectomy.

Material and Methods: A total of 172 patients were included in the present study; 67 patients undergoing myomectomy and 105 undergoing hysterectomies were evaluated. Pittsburgh Sleep Quality Index (PSQI), Beck Anxiety Inventory (BAI), and Beck Depression Inventory (BDI) were used preoperatively to evaluate subjective sleep quality, anxiety, and depression, respectively. The patients were classified into two groups according to sleep quality score: good quality (PSQI $\leqslant$ 5) and poor quality (PSQI > 5).

Results: Overall, 56.4% of patients reported poor sleep quality with a PSQI score > 5. The total PSQI score, BAI score, subjective sleep quality, sleep latency, sleep duration, sleep disturbances, and the use of sleeping medication of the patients undergoing hysterectomy were significantly higher than those undergoing myomectomy ($p < 0.05$). Age (odds ratio [OR] = 1.082; 95% confidence interval [CI], 1.012–1.157; $p = 0.021$), operation type (OR = 1.071; 95% CI, 1.015–1.149; $p = 0.035$), and BAI score (OR = 1.097; 95% CI, 1.073–1.294; $p = 0.001$) were significantly associated with poor sleep quality. Logistic regression analysis showed that age, the BAI score, and the type of surgery were significantly associated with poor sleep quality.

Conclusion: The preoperative sleep quality of patients was significantly associated with the surgical procedure, patient age, and patient anxiety. Preoperative sleep quality of patients who underwent hysterectomy was worse than those who underwent myomectomy.

Keywords: Gynecological surgery, preoperative anxiety, Pittsburgh sleep quality index, sleep quality

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INTRODUCTION

Sleep quality is important for general health, as it affects the quality of life and daytime functioning (1). It is affected by many factors, including age, gender, and physical and psychological health. Poor sleep quality has been reported in hospitalized patients due to psychiatric disorders, anxiety about surgical or diagnostic procedures, and medical or surgical problems (2,3). Perioperative sleep disturbance is a common problem that affects a large number of patients undergoing surgery (4,5). About 8.8-79.1% of patients suffer from sleep disturbances before surgery (6).

Studies have shown that sleep disturbances during the preoperative period are associated with anxiety, pain, the magnitude of the surgery, the type and duration of the procedure, and the severity of the disease (7,8). The size of the surgical intervention is a factor affecting the sleep quality of patients, which is worse for patients requiring major surgery than those in need of a minor or intermediate-level surgical procedure (e.g., open cholecystectomy or colonic resection) (9). In one study, the quality of sleep the night before thoracic surgery was profoundly affected; although age and the timing of surgery were strong predictors of poor sleep, no relationship was found between sleep quality and the type of surgery (8).

It has been reported that preoperative sleep quality is most adversely affected by fear of the unknown, organ loss, and anxiety about being disabled after a major surgical intervention (10). Sleep disturbances and anxiety are prevalent among women undergoing hysterectomy, as loss of the uterus can be a major psychological trauma (11).

The purpose of this study was to evaluate the preoperative sleep quality of patients who underwent myomectomy and hysterectomy and to determine the factors affecting sleep.

MATERIAL and METHODS

This cross-sectional study was conducted at Zekai Tahir Burak Women's Health Education and Research Hospital between August 2018 and May 2019. The hospital's institutional review board approved the study (permission number: 37/2018), and all patients provided written informed consent before their enrollment.

The study enrolled 172 patients, and they were recruited from the gynecology outpatient clinic with abnormal uterine bleeding or pelvic pain; all were scheduled for hysterectomy or myomectomy. A semi-structured anamnesis was taken from all patients to evaluate existing sleep disorders, including obstructive sleep apnea syndrome, chronic insomnia, and excessive daytime sleepiness.

Patients with these sleep disorders were excluded from the study. Patients with mental, psychological, neurological, or cardiac disorders (history taken from the medical records) and those using sedatives or hypnotics within two months before hospitalization were also excluded. The patients had no known previous risk factors for sleep disturbance, and all underwent elective surgery. None of the patients were taking any medications before surgery. All patients had American Society of Anesthesiologists scores of 1-2.

The Pittsburgh Sleep Quality Index (PSQI) was used to evaluate the patients' subjective sleep quality over the prior month. Anxiety and depression symptoms were evaluated using the Beck Anxiety Inventory (BAI) and the Beck Depression Inventory (BDI), respectively. Total PSQI, BAI, and BDI scores were compared in myomectomy and hysterectomy groups.

The patients were classified into two groups according to sleep quality, i.e., a group without sleep disturbances (PSQI ≤ 5) and a group with sleep disturbances (PSQI > 5). Age, BMI, initial complaint, operation type (hysterectomy or myomectomy), and BAI and BDI scores were compared between the two groups.

The PSQI is a standardized self-administered questionnaire used to assess subjective sleep quality. The PSQI was designed by Buysee et al. and consists of 19 self-rated questions measuring seven components, including sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleep medication, and daytime functioning (12).

Each item of the questionnaire was scored from 0 to 3, and the scores were summed to give a total score of 0 to 21. A total PSQI score of 5 or higher indicated poor sleep, whereas a score below 5 indicated good sleep quality.

The PSQI was validated for Turkish people in 1997 by Agargun et al. (13).

The BAI is a short 21-item questionnaire that assesses the severity of anxiety. The total score ranges from 0 to 63 (0-9 points, normal; 10-18 points, slight to moderate anxiety; 19-29 points, moderate to severe anxiety; and 30-63 points, very severe anxiety). The scale was first developed by Beck. (14). The validity and reliability of BAI in the Turkish population were assessed by Ulusoy et al. (15).

The BDI is a 21-item questionnaire evaluating the presence and severity of depression. A higher score indicates more severe depression (0-9 points, minimal depression; 10-18 points, slight depression; 19-29 points, moderate depression; 30-63 points, severe depression).

Statistical analysis

Statistical analysis was performed using SPSS for Windows, version 21.0 (SPSS Inc., Chicago, IL, USA). The Kolmogorov-Smirnov test was used to determine whether continuous variables were normally distributed. Where applicable, continuous variables are expressed as mean ± standard deviation or median (range). Categorical variables are expressed as numbers (percentages). The chi-square test and Student's t-test were used to evaluate the associations between the categorical and continuous variables.

Multivariate logistic regression analysis was performed to evaluate the effect of various risk factors on sleep quality. The variables used in the regression included patient age, BMI, type of operation (myomectomy vs. hysterectomy), and BAI and BDI scores. P-values<0.05 were considered statistically significant for all tests.

RESULTS

A total of 220 patients were hospitalized for myomectomy or hysterectomy during the study period. Of these, 30 with medical or psychological problems and 18 who refused or were unable to complete the questionnaires were excluded from the study. Of the remaining 172 patients, myomectomy was planned in 67 (39%) and abdominal hysterectomy in 105 (61%). The mean age of the patients was 43.78 ± 7.55 years, and the mean BMI was 28.36 kg/m2.

The total PSQI score, BAI score, subjective sleep quality, sleep latency, sleep duration, sleep disturbances, and use of sleeping medication of the patients undergoing hysterectomy were significantly higher than those undergoing myomectomy ($p < 0.05$). There was no significant difference in the BDI score between the two groups (**Table 1**).

Overall, 43.6% of the patients reported that their sleep was unaffected; however, 56.4% reported poor sleep quality with a PSQI score > 5. Comparative results of patients without a sleep disturbance (PSQI ≤ 5) and patients with a sleep disturbance (PSQI > 5) are given in Table 2. The mean ages of the patients without and those with a sleep disturbance were 44.2 ± 5.1 years and 48.1 ± 5.8 years, respectively ($p < 0.001$). The PSQI score increased with age.

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While 74 (76.3%) of the patients who underwent hysterectomy had a PSQI score > 5, only 23 (23.7%) of the patients who underwent myomectomy had a PSQI score > 5 (p = 0.001). Patients who were hospitalized for hysterectomy had worse sleep quality than those hospitalized for myomectomy. Anxiety also adversely affected sleep quality (p = 0.001) (**Table 2**).

A logistic regression analysis was performed to evaluate the risk factors for sleep quality.

Table 3 summarizes the outcomes of the logistic regression analysis. Age (odds ratio [OR] = 1.082; 95% confidence interval [CI], 1.012–1.157; p = 0.021), operation type (OR = 1.071; 95% CI, 1.015–1.149; p = 0.035), and BAI score (OR = 1.097; 95% CI, 1.073–1.294; p = 0.001) were significantly associated with poor sleep quality. As the BAI score increased, the PSQI score increased, and sleep quality decreased. According to logistic regression, age, anxiety, and the surgical procedure were important predictors of poor sleep.

Table 1. Comparison of sleep quality, anxiety and depression of patients between the myomectomy and hysterectomy groups

Characteristic	Myomectomy N=67 (%)	Hysterectomy N=105 (%)	*P value*
PSQI			
Total score	4.9±2.3	7.2±2.9	0.001
Subjective sleep quality	0.7±0.7	1.3±0.9	0.001
Sleep latency	1.1±0.7	1.6±0.8	0.001
Duration of sleep	0.4±0.6	0.8±0.7	0.001
Habitual sleep efficiency	0.4±0.8	0.6±0.8	0.112
Sleep disturbances	1.3±0.5	1.9±0.7	0.001
Use of sleeping medication	0.1±0.4	0.3±0.5	0.006
Daytime dysfunction	0.6±0.9	0.8±0.7	0.105
PSQI			
≤ 5 (without sleep disturbance)	44 (65.7)	31 (29.5)	0.001
> 5 (with sleep disturbance)	23 (34.3)	74 (70.5)	
Total BAI score	10.1±6.2	13.2±5.3	0.001
Total BDI score	12.6±7.2	11.3±5.7	0.190

PSQI:Pittsburgh Sleep Quality Index; BAI:BECK Anxiety Inventory; BDI:BECK Depression Inventory; Data presented as frequency (percentage) or mean±standart deviation (SD); p <.05 is considered statistically significant.

Table 2. Sleep disturbances according to age, BMI, symptom category, type of operation, anxiety and depression

Variable	PSQI ≤ 5 N=75 (%)	PSQI > 5 N=97 (%)	*P value*
Age (years)	44.2±5.1	48.1±5.8	0.001
BMI	29.4±4.5	28.3±3.7	0.080
Symptom category			
Bleeding	43 (57.3)	56 (57.7)	0.958
Pain	32 (42.7)	41 (42.3)	
Operation type			
Myomectomy	44 (58.7)	23 (23.7)	0.001
Hysterectomy	31 (41.3)	74 (76.3)	
BAI score	9.47±6.1	13.69±5.3	0.001
BDI score	10.6±7.2	11.7±5.7	0.265

BMI:body mass index; PSQI:Pittsburgh Sleep Quality Index; BAI:BECK Anxiety Inventory; BDI: BECK Depression Inventory; Data presented as frequency (percentage) or mean±standart deviation (SD); p < 0.05 is considered statistically significant.

Table 3. Logistic regression analysis of risk factors for poor sleep quality

Variables	OR	CI 95%	*P value*
Age (years)	1.082	1.012-1.157	0.021
BMI (kg/m^2)	0.953	0.879-1.033	0.244
Symptom category	1.622	0.597-4.407	0.643
Operation type	1.071	1.015-1.149	0.035
BAI score	1.097	1.073-1.294	0.001
BDI score	0.448	0.341-1.428	0.175

BMI: Body Mass Index; BAI: BECK Anxiety Inventory; OR: odds ratio; CI: confidence interval; p < 0.05 is considered statistically significant.

DISCUSSION

In this cross-sectional study, we evaluated preoperative subjective sleep quality in patients who underwent myomectomy and hysterectomy and the factors that influenced it. Important associations were observed between preoperative sleep quality and age, anxiety, and the type of surgery. It was previously unknown whether sleep disturbances before gynecologic surgery were affected by the type of surgery. Our prospective design allowed us to examine the relationship between sleep quality during the preoperative period and the type of surgical procedure. Few studies on preoperative sleep quality are available in the gynecological surgery literature (11,16). The most notable finding of our study was that patients undergoing hysterectomy had worse preoperative sleep quality than those undergoing myomectomy. The age of the patients and the BAI score also were significant predictors of poor sleep quality.

This study showed that sleep quality was severely affected before surgery in 56.4% of patients who were operated on for benign uterine surgery. The prevalence of poor sleep quality was compatible with previous studies; Wang et al. reported that 51% of breast cancer patients scheduled for breast surgery were affected by poor sleep before surgery (17). Orbach-Zinger et al. reported poor sleep quality in 68% of women before a cesarean operation (18). Sleep disturbances are frequently reported by hospitalized patients. Jolfaei et al. evaluated sleep quality in such patients (19). The mean PSQI score was 8.8 ± 4.8, and 70.8% of the patients were poor sleepers (PSQI > 5) in their study, which was higher than in our study.

In the present study, we subjectively evaluated the sleep quality of the patients during the previous month using the PSQI. The PSQI was significantly higher in patients undergoing hysterectomy procedures than those who underwent myomectomy procedures. During this one month, the decision for surgery, the method of surgery, and detailed information thereon may have affected sleep quality. Knowledge of an impending operation may be a risk factor for sleep disturbance. The higher rates of sleep disturbance in patients undergoing hysterectomy compared with myomectomy may be explained by fertility or organ loss. Concerns about organ loss and sterility due to surgery may be an important factor explaining poor preoperative sleep quality. Sheizaf et al. evaluated preoperative sleep patterns in women undergoing gynecologic endoscopic surgery for benign conditions (16). Although age and stress level before sleep were significant predictors of poor sleep, the type of planned surgery did not affect the quality of sleep in that study.

No consensus has been reached on whether patient age is a risk factor for sleep disturbance before surgery. In our study, sleep quality decreased as the patient age increased. These results are similar to findings reported by Sheizaf et al. (16). However, age was not cited as a risk factor for sleep quality in previous studies (7,9,17).

Anxiety is one of the most frequently observed psychological reactions among patients awaiting surgery (20,21).

Preoperative anxiety and stress are frequently observed in studies of patients undergoing elective surgery. In a study that investigated the effectiveness of the preoperative sleeping period on the preoperative anxiety level, fewer sleeping hours increased the level of anxiety (22). Here, we determined that preoperative anxiety status was significantly correlated with poor sleep quality; as the BAI increased, the PSQI score also increased.

Study Limitations

There are several limitations of our study. First, there are many factors that affect patient sleep quality, including hormone levels and nutritional status, as well as cultural, physical, psychological, and ethnic factors. In this study, we investigated only a subset of these factors. Second, the PSQI assessment was subjective. Preoperative sleep quality was not evaluated using objective methods such as polysomnography and actigraphy. Third, we did not evaluate sleep quality during the postoperative period because we aimed to evaluate sleep quality exclusively during the preoperative period.

CONCLUSION

The preoperative sleep quality of patients is significantly associated with the surgical procedure, patient age, and patient anxiety. Preoperative sleep quality of patients who underwent hysterectomy was worse than those who underwent myomectomy. Patients scheduled for hysterectomy should be evaluated in terms of sleep quality and anxiety using preoperative assessment scales.

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Ethical approval: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by Local Ethical Committee. All procedures performed in studies with human participants met the ethical standards of the Institutional Research Commission and the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical standards. This study was approved by the Ethics Committee of the Zekai Tahir Burak Women's Health Education and Research Hospital, Ankara (ethics committee no: 37/2018).

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The effect of previous SARS-Cov-2 infection positivity on Gynecological Surgery: A Tertiary Hospital Experience

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ABSTRACT

Objective: The study aimed to investigate whether a history of preoperative SARS-CoV-2 infection differs in terms of peroperative complications and prognosis in patients who had undergone gynecological surgery in the last one year compared to patients who did not.

Materials and Methods: This retrospective case-control study included 632 patients who underwent laparotomic, laparoscopic, urogynecological and oncological surgeries for various indications between July 2020 and July 2021. The patients were divided into two groups according to positive and negative SARS-CoV-2 RT-PCR (Real-time Polymerase Chain Reaction) test results performed preoperatively. The two groups were compared in terms of demographic characteristics, the operation performed, the type of anesthesia applied during the operations, the status of blood transfusion, operation and hospitalization times, and intraoperative and postoperative complications.

Results: While 5.5% (n=35) of the patients had positive SARS-CoV-2 RT-PCR test results in the preoperative period (group 1), 94.5% (n=597) had negative SARS-CoV-2 RT-PCR test results preoperatively. The following parameters, including age, body mass index (BMI), gravida, parity, number of smokers, and number of patients with the comorbid disease, were similar between the two groups. Moreover, no difference was detected in terms of mean hospitalization time, mean operative time, and the number of patients with intraoperative-postoperative complications between the two groups. However, there was a significant difference between the groups in terms of blood product transfusion requirement [0 patients (0%) vs. 55 patients (9.2%) (p=0.05)].

Conclusion: History of SARS-CoV-2 infection in gynecological surgery does not affect intraoperative and postoperative complications except blood product transfusion requirement.

Keywords: SARS-CoV-2 infection, gynecological surgery, complication

INTRODUCTION

COVID-19 disease (SARS-CoV-2) spread rapidly from the city of Wuhan in China to the whole world in December 2019, was declared a pandemic by the World Health Organization (WHO) in March 2020 and started to be seen rapidly in our country in the same period. Since the disease is seen in a wide spectrum from asymptomatic carriage to severe pneumonia resulting in mortality, all elective surgical interventions within the scope of routine health care services had to be postponed. In a statement published in March 2020 by the American College of Surgeons (ACS), all gynecological-oncological diseases were recommended to be treated as triage, except for some emergency operations such as ectopic pregnancy, adnexal torsion, and emergency cerclage (1). In the next period, because the pandemic was relatively under control, the epidemic curve was flattened, and the vaccination programs, as of March 2021, elective surgical operations could also be performed within the framework of certain rules (2). The long delay of elective surgical interventions has also delayed the study of the effect of SARS-CoV-2 infection on surgery. Therefore, there are very few studies in the literature. In a published multicenter study, it was reported that a history of SARS-CoV-2 infection in patients who had undergone benign gynecological surgery did not cause an increase in the rate of postoperative complications (3). However, due to the limited number of studies, this issue continues to be discussed.

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Our aim in this study is to investigate whether the history of COVID-19 affects intraoperative and postoperative complications in patients who underwent surgery for gynecological reasons.

MATERIAL and METHODS

The data of 925 patients hospitalized in Etlik Zübeyde Hanım Gynecology Training and Research Hospital Gynecology Service were analyzed retrospectively between July 2020 and July 2021. Patients who underwent laparotomic, laparoscopic, urogynecological and oncological surgery for various indications in the gynecology clinic within the date range determined were included in the study. Patients hospitalized for medical treatment only (menorrhagia+anemia, pelvic inflammatory disease, vulvar abscess) and patients who underwent minor surgical procedures (endometrial sampling under anesthesia, operative/diagnostic hysteroscopy, conization/Loop Electrosurgical excision procedure [LEEP], suturation for postcoital bleeding) were excluded from the study. At the end of the review process, 632 patients whose data were available were included in the study. A total of 293 patients, 127 patients who were discharged after receiving medical treatment and 161 patients who underwent minor interventional procedures, were excluded from the study. In addition, five patients were not included in the study because their data were missing (**Figure 1**).

Operation preparation, hospitalization, and discharge procedures were planned in accordance with the ACS Recommendations (4) and the Turkish Ministry of Health's SARS-COV-2 Pandemic Working Guide in Health Institutions and Infection Control Precautions (5) for the patients whose operations were performed in accordance with their indications. In the preoperative period, the patients were screened for SARS-COV-2 symptoms, and SARS-COV-2 PCR tests were performed within 48 hours before the operation after hospitalization. Accompaniment was not accepted. Intraoperative anesthesia, surgery, and allied health personnel team used PPE (personal protective equipment) appropriately. Early recovery procedures were preferred in the postoperative period, and early discharge was planned.

Demographic data of the included patients; Age, gravida, parity, body mass index (BMI), smoking, and comorbid diseases were recorded. The operation performed, type of anesthesia applied during the operations, blood transfusion status, operation and hospitalization times, intraoperative and postoperative complications were recorded. The data of the whole study group were compared by dividing them into two groups as positive and negative SARS-CoV-2 RT-PCR (Real-time Polymerase Chain Reaction) test results performed at any time preoperatively.

Statistical Analysis

SPSS 22.0 (IBM Corp, Armonk, NY, USA) program was used for statistical analysis. The mean, standard deviation, and percentage of the data were used. Non-parametric tests (Mann-Whitney U) were used to compare variables that did not fit a normal distribution, and parametric tests (Student's t-test) were used to compare variables with normal distribution. The Chi-square test was used to compare categorical data between groups. $p<0.05$ was considered statistically significant.

RESULTS

While 35 (5.5%) of the 632 patients included in the study had positive SARS-CoV-2 RT-PCR test results in the preoperative period (group 1), the preoperative SARS-CoV-2 RT-PCR test results of the remaining 597 (94.5%) patients were negative (group 2). It was determined that 35 patients underwent surgery at least 22 days and at most 330 days after the SARS-CoV-2 RT-PCR positive results in the preoperative period [Median 134 (22-330)].

The following parameters including age (50.26±8.27 vs 48.19±9.54, p=0.21); BMI 28.23±3.49 vs 28.12±4.53, p=0.89); gravida [3 (0–9) vs 3 (0–11), p=0.20)]; parity [3 (0–8) vs 2 (0–8) (p=0.10)]; number of smokers [5 patients (14.2%) vs 60 (10%) (p=0.42)]; the number of patients with comorbid disease [10 patients (28.6%) vs 154 patients (25.2%) (p=0.71)] were similar between two groups. Hypertension was the most common comorbid disease in both groups. (17.3% vs 13.4%). Demographic findings are shown in **Table 1**.

In the preoperative period, the most frequently performed operation in the first group was Total Abdominal Hysterectomy (TAH) performed in 8 (22.8%) patients, while the most frequently performed operation in the other group was TAH and Bilateral Salpingoopherectomy performed in 132 (22.1%) patients. There was no significant difference between the groups in terms of the surgeries performed (p=0.89). In the first group, 29 (82.9%) patients were operated on by general anesthesia and 6 (17.1%) patients by spinal anesthesia; in the other group, there were 500 (83.8%) patients who were administered general anesthesia and 97 (16.2%) patients who were administered spinal anesthesia.

There was no significant difference between the groups in terms of the type of anesthesia applied during the surgery (p=0.88). In the first group, blood products were not transfused during and after the operation; however, blood products were transfused in 55 (9.2%) patients in the other group, and a significant difference was found between the groups in terms of blood product transfusion requirement (p=0.05).

There was no difference in terms of mean hospitalization time [2.66±1.11 days vs. 2.95±2.14 days, (p=0.42)], mean operative time [1.92±0.58 vs 1.86±0.63 hours, (p=0.56)], number of patients with intraoperative-postoperative complications [1 patient (2.9%) vs 52 patients (8.3%), (p=0.24)] between the two groups. In the first group, the hematoma was observed in one patient in the postoperative follow-up, and no additional surgical intervention was performed on the patient. The most common complication in the other group was fever, which was observed in 14 (2.3%) patients. These patients were consulted to Infectious Diseases, and when the SARS-CoV-2 RT-PCR samples were negative, appropriate follow-up and treatment were planned. The intraoperative and postoperative findings of the patients are shown in **Table 2**.

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Figure 1. Flowchart of patients

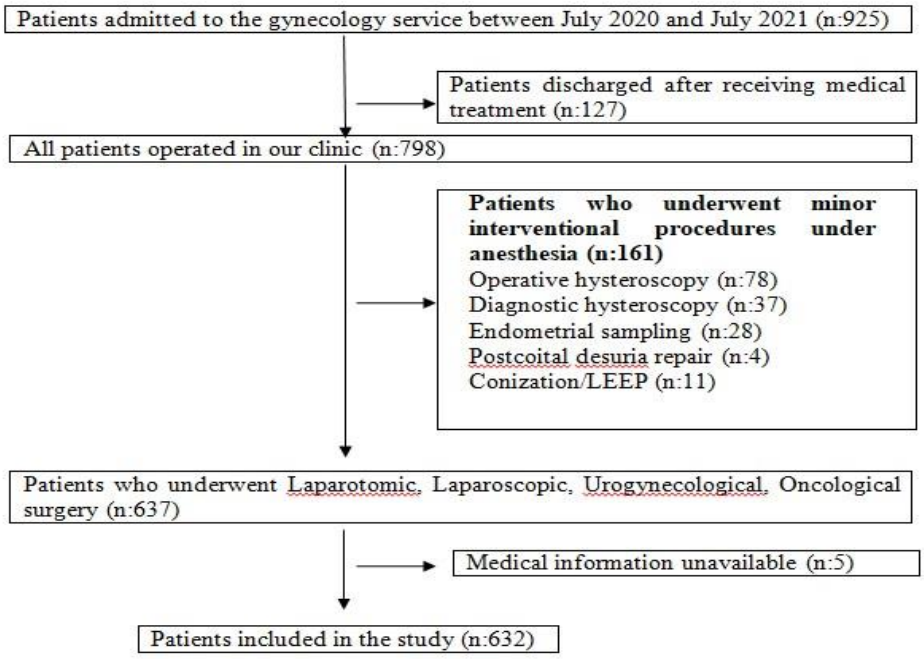

Table 1. Demographic data of the patients

Parameters	Total (n:632)	Grup 1 Preoperative RT PCR pozitivity (n:35)	Grup 2 Preoperative RT PCR negativity (n:597)	P
Age (mean±SD) (year)	48.1±9.48	50.26±8.27	48.19±9.54	0.21*
BMI (mean±SD) (kg/m^2)	28.13±4.48	28.23±3.49	28.12±4.53	0.89*
Gravida (mean±SD)	3.03±1.77	3.40±1.57	3.01±1.78	0.20*
Parity (mean±SD)	2.43±1.26	2.77±1.33	2.41±1.26	0.10*
Smoking (number, %)				0.42**
No	567 (89.7)	30 (85.8)	537 (90)	
Yes	65 (10.3)	5 (14.2)	60 (10)	
Additional Disease (number, %)				0.71**
no	468 (74.1)	25 (71.4)	443 (74.8)	
Asthma	12 (1.8)	-	12 (2.0)	
DM	16 (2.5)	2 (5.7)	14 (2.3)	
DM+ HT	29 (4.6)	1 (2.8)	28 (4.7)	
Epilepsy	1 (0.1)	-	1 (0.1)	
Fibromyalgia	2 (0.3)	-	2 (0.3)	
hypothyroidism	2 (0.3)	-	2 (0.3)	
HT	86 (13.6)	6 (17.3)	80 (13.4)	
CAD	3 (0.4)	-	3 (0.5)	
Cholelithless	2 (0.3)	-	2 (0.3)	
Breast Ca	1 (0.1)	-	1 (0.1)	
Migraine	2 (0.3)	-	2 (0.3)	
MS	1 (0.1)	-	1 (0.1)	
Panic attack	1 (0.1)	-	1 (0.1)	
Psoriasis	2 (0.3)	1 (2.8)	1 (0.1)	
RA	2 (0.3)	-	2 (0.3)	
Vertigo	2 (0.3)	-	2 (0.3)	

DM; Diabetes, HT; Hypertension, DM HT; Diabetes and Hypertension, CAD; Coronary Artery Disease, MS; Multiple Sclerosis, RA; Rheumatoid Arthritis
mean±SD; mean ±std deviation, * Student's t-test ** Chi-square test

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Table 2. Intraoperative and postoperative data of the patients

Parameters	Total (n:632)	Grup 1 Preoperative RT PCR pozitivity (n:35)	Grup 2 Preoperative RT PCR negativity (n:597)	p
Type of Surgery Performed, number, %				
Myomectomy	37 (5.9)	-	37 (6.2)	
Tubaovarian Abscess Surgery / Laparoscopy	6 (0.9)	-	6 (1)	
Tubaovarian Abscess Surgery/Laparotomy	5 (0.8)	-	5 (0.8)	
Unilateral Salpingooopherectomy/Laparotomy	29 (4.6)	3 (8.6)	26 (4.4)	
Ovarian detorsion/Laparotomy	3 (0.5)	-	3 (0.5)	
Sacrohysteropexy	3 (0.5)	1 (2.9)	2 (0.3)	
Anteroposterior repair+perineoplasty	30 (4.7)	2 (5.7)	28 (4.7)	
Total Abdominal Hysterectomy (TAH)	124 (19.7)	8 (22.8)	116 (19.4)	0.89*
TAH + Bilateral Salpingooopherectomy	139 (22)	7 (20)	132 (22.1)	
Vaginal Hysterectomy	59 (9.3)	2 (5.7)	57 (9.5)	
Total Laparoscopic Hysterectomy	72 (11.4)	6 (17.1)	66 (11.1)	
Unilateral Salpingoopherectomy/Laparoscopy	35 (5.5)	-	35 (5.9)	
Ovarian cystectomy/Laparoscopy	23 (3.6)	1 (2.9)	22 (3.7)	
Trans-vaginal-tape operation	26 (4.1)	3 (8.6)	23 (3.9)	
Staging surgery	34 (5.4)	2 (5.7)	32 (5.4)	
Bartholin Cyst Excision	7 (1.1)	-	7 (1.1)	
Anesthesia (number, %)				
General	529 (83.7)	29 (82.9)	500 (83.8)	0.88**
Spinal	103 (16.3)	6 (17.1)	97 (16.2)	
Transfusion (number, %)				
No	577 (91.2)	**35 (100)**	542 (90.8)	**0.05****
Yes	55 (8.8)	-	**55 (9.2)**	
Hospitalization time (days) (mean±SD)	2.93 (±2.10)	2.66 (±1.11)	2.95 (±2.14)	0.42*
Operation time (hours) (mean±SD)	1.86 (±0.63)	1.92 (±0.58)	1.86 (±0.63)	0.56*
Complications (number, %)				
No	581 (91.9)	34 (97.1)	547 (91.7)	0.24**
Postoperative complication				
Fever	14 (2.2)	-	14 (2.3)	
Dyspnea	12 (1.9)	-	12 (2)	
Cuff hematoma	4 (0.7)	-	4 (0.7)	
Hematoma	2 (0.3)	1 (2.9)	2 (0.3)	
Wound infection	10 (1.6)	-	9 (1.5)	
Ileus	3 (0.5)	-	3 (0.5)	
Intraoperative complication				
Bladder Injury	6 (0.9)	-	6 (1)	

DISCUSSION

In this study, which included a large number of patients in the field of gynecological surgery, the importance of previous SARS-CoV-2 infection in terms of surgical results and the risk of postoperative complications was investigated. There was no difference between the groups in terms of demographic characteristics and intraoperative and postoperative complications. Only the postoperative blood transfusion requirement was found to be higher in the group that had not had a previous SARS-COV-2 infection.

The COVID-19 epidemic, which has caused serious mortality and morbidity all over the world and in our country in the last two years, has led to many changes in the field of gynecological surgery, such as surgical operation indication, operation type, postoperative follow-up. Elective surgical operations were postponed with the first attack of the pandemic. Except for gynecological emergency operations such as ectopic pregnancy rupture and adnexal torsion, gynecological and oncological operations can be performed by forming a triage.

Therefore, it is seen that there are few studies on the effect of SARS-CoV-2 on general gynecological surgery in the first year of the pandemic (3,6). In this period, publications in the field of gynecological oncology were dominant (7, 8, 9, 10). Ayhan et al. reported the perioperative incidence of SARS-CoV-2 as 6.7% in patients who underwent major gynecological cancer surgery. While the need for intensive care and mechanical ventilation in patients with perioperative SARS-CoV-2 was 8.7% and 4.3%, respectively, the mortality rate was reported as 0% (7). In a multicenter study in which 200 patients who underwent gynecologic oncologic surgery were retrospectively evaluated by Dursun et al.; SARS-CoV-2 was not found in any of the patients preoperatively, PCR positivity was observed at a rate of 1% postoperatively, and the mortality rate was again found to be 0% (9). Comparing gynecological and oncological surgeries performed before and during the COVID-19 pandemic, Akıllı et al. found similar intraoperative and postoperative complication rates, but the previous SARS-CoV-2 history was not evaluated in the study (10).

Similar to the study of Akıllı et al., a study comparing oncological surgeries performed before and during the pandemic, both intraoperative and postoperative complication rates were found to be similar; only the duration of hospitalization was found to be shorter during the pandemic (5.6±3.3 vs. 8.5±9.3 days) (8).

Laparoscopic surgery has decreased significantly during the SARS-CoV-2 pandemic because the SARS-CoV-2 virus is not only an aerosol-transmitted infectious agent but also can be detected in body fluids and pneumoperitoneum and can even spread to the operating room during insufflation (11-14). In subsequent studies, it was reported that there was no vertical transmission in the urinary and genital system of women who contracted SARS-CoV-2 and in pregnant women (15, 16). Jones et al. investigated the SARS-CoV-2 antigen in peritoneal and vaginal fluid in preoperative SARS-CoV-2 PCR negative women who underwent laparotomic and laparoscopic surgery. Postoperative PCR positivity was detected in one patient (1%), and PCR-antibody (past infection) was detected in 4 patients (13%). No virus was found in any patient's peritoneal and vaginal samples, including the PCR positive patient. Thus, it was emphasized that laparoscopic surgeries can be performed safely during the pandemic (17). Kale et al. found the rate of postoperative SARS-CoV-2 development to be 0.39% in the first 14 days and 0.5% in the 15-30 days in 765 patients who underwent elective gynecological and oncological surgery. Toptas et al. published the peroperative COVID-19 development rate as 1.4% (4/276) in the gynecology clinic in the first year of the pandemic, and only 1.8% of healthcare workers were found to be positive for COVID-19 in this process (18). The most comprehensive COVID study in this area is a multicenter study involving 3423 patients. In the study, the effects of the previous SARS-CoV-2, peroperative and postoperative SARS-CoV-2 exposure on complications were examined, and 43 patients (1.3%) with a positive history of SARS-CoV-2 and 39 patients (1.1%) who developed postoperative SARS-CoV-2 was detected. The rate of perioperative complications was found to be similar between patients with and without a history of SARS-CoV-2 (3). In our single-center study with a very large number of patients, patients with a history of SARS-CoV-2 were compared with patients who did not have SARS-CoV-2 before, and complication rates were found to be similar to the literature. Only the need for blood transfusion was found to be significantly higher in the group that did not have SARS-CoV-2. The reason for this increase may be the relatively few patients with a positive history of SARS-CoV-2 and the fact that patients known to have had SARS-CoV-2 were evaluated and treated before. In the light of these findings, it can be said that elective surgery does not have a serious effect on the transmission of SARS-CoV-2 and can be performed safely.

The study's limitations are that the hospital is not a pandemic hospital and the study is a retrospective study.

CONCLUSION

We think that having a SARS-CoV-2 infection does not have a significant effect on the results of gynecological surgeries in terms of complications. Considering that its impact will continue in the coming years, we think that elective gynecological surgical operations should not be postponed.

Author Contributions: AÖ, HI, BT, and OY: Project design, Patient examinations. **AÖ, BT, and MD:** Data analyses and Literature review. **AÖ, HI, and MD:** Manuscript preparation, Revisions.

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Non-Necrotizing Granulomas in Bone Marrow Biopsy of a Patient with Bicytopenia: Brucellosis Case

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ABSTRACT

Objective: Brucellosis has the ability to mimic a variety of multisystem illnesses, exhibiting a wide range of clinical polymorphism that frequently leads to misdiagnosis and treatment delays, thus raising the risk of complications. In cases of brucellosis, hematologic abnormalities might manifest as anemia, leukopenia, thrombocytopenia, lymphomonocytosis, hemolytic anemia, disseminated intravascular coagulation, and pancytopenia.

Material and Methods: In this study, we presented the bone marrow biopsy findings of a brucellosis case.

Case: For ten days, a 19-year-old male patient with fever, exhaustion, weight loss, loss of appetite, and stomach pain was taken to the emergency room. A bone marrow aspiration and biopsy were conducted because of the patient's indications and symptoms. Brucella melitensis was isolated in the blood and bone marrow cultures on the 7th day.

Conclusion: Brucellosis, one of the most common zoonoses in the world and our country, can occur with a wide variety of complications.

Keywords: Brucellosis, fever, non-necrotizing granuloma, cytopenia, bone marrow, hepatosplenomegaly

INTRODUCTION

Brucellosis is an important disease that is endemic in all regions of our country and affects both the animal industry and human health. It is a zoonotic disease caused by Brucella spp., a gram-negative bacteria. Brucellosis; can affect many systems, as well as the reticuloendothelial system and bone marrow. Any organ or tissue in the body may be infected with Brucella. Hematological findings such as anemia, leukopenia, thrombocytopenia, lymphocytosis, hemolytic anemia, diffuse intravascular coagulation, and pancytopenia can be encountered in patients with brucellosis infection (1). One of the possible causes of cytopenias in brucellosis is granuloma formation in the bone marrow (2). A granuloma is a group of mononuclear phagocytes that is compact and well-organized. Granuloma cells serve as both a protector and a destroyer for the host (1). In this study, we presented the bone marrow biopsy findings of a brucellosis case.

CASE

A 19-year-old male patient, who was previously healthy and dealing with animal husbandry, was admitted to the emergency room with fever, fatigue, weight loss, loss of appetite, and abdominal pain for ten days. Physical examination revealed abdominal tenderness and hepatosplenomegaly. Bone marrow aspiration and biopsy were performed because the patient’s signs and symptoms were insisted in the inpatient service; his thrombocyte count dropped to 35x103/µL, hemoglobin to 9g/dL, and white blood cell to 1970/µL. Rose Bengal test was positive, Brucella tube agglutination test was positive at 1/640 titer. Brucella melitensis isolation was detected on the 7th day in the blood and bone marrow culture examination. Doxycycline 2x100 mg/day and rifampicin 600 mg/day were administered as treatment. In the microscopic examination of bone marrow sections, age-appropriate normocellular tissue was detected. Non-necrotizing granuloma formation characterized by the accumulation of epithelioid histiocytes in a focal area was observed in Figure 1.

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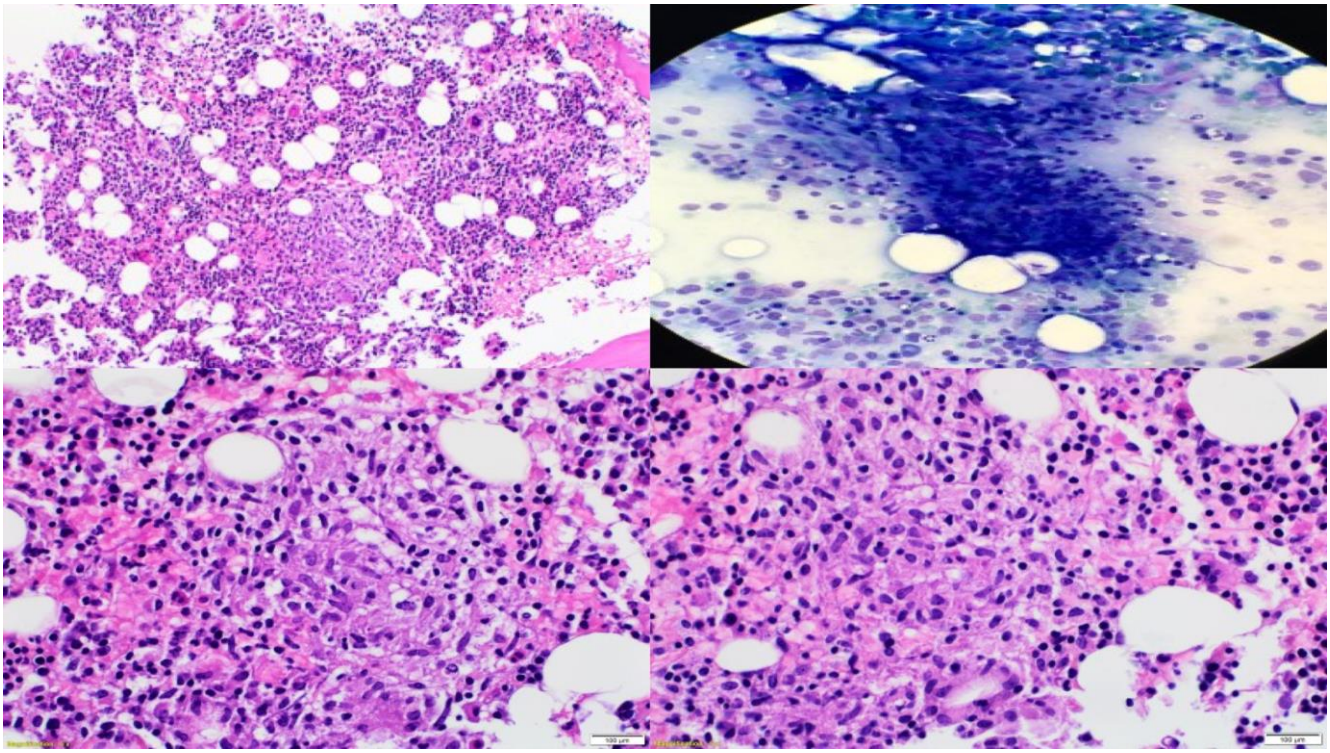

Figure 1. A) An age-appropriate normocellular bone marrow tissue (Hematoxylin-eosin staining: x100). B) Non-necrotizing granulomas in Brucellosis in bone marrow aspiration (May-Grunewald-Giemsa Stain;200x) C/D) Non-necrotizing granuloma characterized by accumulation of epitheloid histiocytes in a focal area (Hematoxylin & Eosin staining; 400x)

On the 10th day of the treatment, the patient's laboratory findings and symptoms improved, and the treatment was planned to be completed to 6 weeks. When the treatment was completed, the patient's symptoms regressed. At the end of 6 weeks, leukocyte hemoglobin and thrombocyte values were found to be within the normal range.

DISCUSSION

Brucella species are encapsulated Gram-negative coccobacilli that cause abortion and infertility in wild and domestic animals. Brucella melitensis is the most common pathogen found in sheep and goats, and it is also the most commonly implicated pathogen in human illness. In addition to direct contact with sick animals, transmission occurs through the consumption of unpasteurized dairy products. Human-to-human transmission has been documented through breast milk (3). Brucella spp. isolation from a sterile location, such as blood or bone marrow, confirms the diagnosis. Although the rate of blood isolation fluctuates, it is now believed to be around 50% (4).

The vague clinical symptoms make diagnosis difficult. Fever, night sweats, malaise, joint pain, and weight loss are the most prevalent symptoms, with hepatosplenomegaly and lymphadenopathy detected on examination (5). Increased inflammatory markers, liver enzymes, and hematological abnormalities such as pancytopenia are also possible accompanying findings. The pathophysiology of pancytopenia in brucellosis is unclear; however, it appears to be complex. Hypersplenism, hemophagocytosis, bone marrow hypoplasia, and bone marrow granulomatous lesions, as well as immunological damage, appear to be key factors in the development of these abnormalities (6, 7).

Brucella species can induce pancytopenia by directly inhibiting proliferating marrow cells, causing parasitized macrophages to release inhibitory mediators and stimulating lymphocytes to release inhibitory mediators (8).

The incidence of pancytopenia in brucellosis patients ranges from 3% to 21% (9). Studies related to bone marrow involvement of Brucella infection have been performed. Al-Eissa et al. reported that 110 children's hematologic alterations during the active course of brucellosis infection and found pancytopenia in 14% of them (10).

Akbayram et al. reported that Brucella infection was accompanied by pancytopenia in 25 (13.3%) of 187 children (8). Non-necrotizing granuloma formation in bone marrow biopsy is generally a rare finding. From an aspect of the department of infectious diseases, the differential diagnosis for Coxiella burnetii, Ebstein Barr Virus infection, Leishmaniasis, Histoplasmosis, Bartonellosis, and Mycobacterial diseases should be made. Non-necrotizing granulomas have also been reported in Brucellosis (11, 12).

In the case we presented, it was observed that pancytopenia developed together with the symptoms. In the patient's bone marrow biopsy, non-necrotizing granuloma formation, characterized by the accumulation of epithelioid histiocytes in the focal area, was observed. Studies have reported that all patients recovered completely, and peripheral blood counts returned to normal 2 to 6 weeks after antibiotic treatment of brucellosis (8, 13).

CONCLUSION

Brucellosis, one of the most common zoonoses in the world and our country, can occur with a wide variety of complications. Because the clinical signs of brucellosis are so variable and ambiguous, it might be mistaken for other illnesses. As a result, clinical diagnosis of this illness is difficult. Our study emphasizes the importance of a bone marrow biopsy, bone marrow culture, and a thorough clinical history in determining the diagnosis.

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Ethical approval: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by Local Ethical Committee. All procedures performed in studies with human participants met the ethical standards of the Institutional Research Commission and the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical standards.

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A case of Transvaginal NOTES (vNOTES) hysterectomy. Multidisciplinary minimal invasive approach for all aspects

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ABSTRACT

Objective: Minimally invasive procedures for gynaecologic diseases are used widely and provide advances in surgical equipment. All surgical procedures aim for better significant benefits for patients. As multiple-port laparoscopic surgeries are minimally invasive procedures, but multiple skin incisions and port-site pain cause anxiety for some patients. Umbilical single-port surgeries developed with advanced technological equipment like flexıble optics and reticulated graspers. Single-port surgeries decreased skin incision and multiple port-site pain concerns.

Case: In this study, a 74-years-old, postmenopausal female had P2G2 descensus uteri, subtotal uterine prolapse. Complaints were about vaginal mass disturbing life quality associated with bladder incontinence. vNOTES Hysterectomy performed. Case: vNOTES Hysterectomy was performed and spinal anaesthesia was used as a regional anaesthesia (RA) for the procedure. vNOTES allow for safe surgery for ovarian and adnexal structures and visual exploration in the abdominal cavity.

Conclusion: vNOTES Hysterectomy allows safe surgery, especially for elderyl and uterine prolapse cases.

Keywords: vNOTES Hysterectomy, Uterine Prolapse, Regional Anaesthesia

INTRODUCTION

Minimally invasive procedures in gynaecologic diseases are used widely and provide advances in surgical equipment. All surgical procedures aim for better significant benefits for patients. As multiple-port laparoscopic surgeries are minimally invasive procedures but multiple skin incisions and port-site pain cause anxiety for some patients. Umbilical single-port surgeries developed with advanced technological equipment like flexıble optics and reticulated graspers. Single -port surgeries decreased skin incision and multıple port-site pain concerns.

flexible transgastric peritoneoscopy firstly described by Kalloo et al in 2004 in a porcine model (1). After different experiments have demonstrated the feasibility and safety of peritoneal access via transgastric, transanal, transurethral, and transvaginal routes, NOTES entered clinical practice attentively (2).

The transvaginal NOTES (vNOTES) approach is a combination of classic vaginal surgery and laparoendoscopic single-site surgery. Transvaginal routes by NOTE surgery allows safe entry, simple closure, and are less complicated. Recently vNOTES in various gynaecologic surgeries were applied successfully.

CASE

A 74-years-old, postmenopausal female had P2G2 descensus uteri, subtotal uterine prolapse. She complained about vaginal mass disturbing life quality associated with bladder incontinence. Pelvic Organ Prolapse Quantification system (POP–Q) was used after emptied bladder, the measurements are taken when the Valsalva maneuver is performed while the patient is in the dorsal lithotomy position Grade 3 – halfway past hymen prolapsus detected. Using abdominal ultrasonography endometrial echo line is atrophic and bilateral small ovaries determined. Carotid endarterectomy for stenosis and chronic obstructive pulmonary disease were in the patient's medical history. Antihypertensive agents and inhaled corticosteroids beclomethasone have been used. According to The American Society of Anaesthesiologists (ASA) the case is classified as ASA3. Spinal anaesthesia was used as a regional anaesthesia (RA).

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vNOTES hysterectomy

The patient was prepared in the dorsal lithotomy position. Surgical field was sterilized and draped.

A Foley catheter was inserted for urinary drainage. Vaginal retractors placed and cervix grasped with tenaculum. For hydro dissection, 20 cc saline solution was injected. The circular incision of the vaginal mucosa around the cervix was performed by a scalpel. Colpotomies were performed anteriorior and posterior. Bilateral sacrouterine ligaments were grasped and cut as in the standard procedure of vaginal hysterectomy. Gelpoint V-Path (Applied Medical, Rancho Santo Margarita, CA) was inserted through the anterior and posterior colpotomy spaces and reached the pelvic cavity.

After the vaginal procedure, laparoscopic approach with 10 mm Hg CO2 insufflated for providing pneumoperitoneum. And rigid zero-degree telescope was inserted for optical imaging (Karl Storz visualization system; Karl Storz Tuulingen, Germany). Disposable laparoscopic grasping forceps and laparoscopic bipolar 5 mm sealing electrosurgical device, Voyant (VT) (Applied Medical, Rancho Santa Margarita, CA, USA) were used during the procedure. The uterine vessels, ovarian ligaments, adnexal structures, and Fallopian tubes were removed bilaterally caudally to cranially. After the resection of the uterus, ovaries, and tubes, all structures removed through the vaginal opening. And vaginal vault was sutured continuously with a Vicryl 1-0 suture (Ethicon, Piscataway, NJ, USA).

The patient's pain was minimal, mobilized 6 hours after surgery. The patient was discharged two days after surgery.

DISCUSSION

Laparoscopic hysterectomy (LH) and vaginal hysterectomy (VH) are minimally-invasive hysterectomy procedures. Both are associated with less pain, less visible scar formation, and less postoperative adhesion formations. Post-operative infection risk is low, and recovery is fast compared with hysterectomy through a laparotomy (3).

The disadvantages of vaginal hysterectomy when compared with laparoscopic hysterectomy are: salpingo-oophorectomy during the vaginal hysterectomy may be difficult because of the higher and deeper position of the adnexa, so this technique requires an experienced surgeon's skill (4).

During the laparoscopic procedure, surgeons can explore the whole abdominal cavity before and after hysterectomy procedures but at vaginal hysterectomy abdominal cavity visualisation is till the vaginal cuff closure. vNOTES allows for safe surgery for ovarian and adnexal structures and visual exploration in the abdominal cavity. Also, vNOTES approach avoids port site complications like scars, and wound infection and incisional herniation (5, 6), and reduces postoperative hospital stay.

The anaesthetic technique: Usually general anaesthesia is preferable for abdominal laparoscopic procedures. The safety of the use of spinal anaesthesia for abdominal laparoscopic procedures was reported in several studies (7, 8).

Spinal anaesthesia for laparoscopic surgery gives rise to shorter recovery time, spontaneously breathing and comfortable post-operative analgesia.

CONCLUSION

Combining regional anaesthesia and vNOTES surgery can provide a multidisciplinary, minimally invasive approach.

Author Contributions: GÇU, ŞB: Study design, Literature review, Data collection and/or processing, Analysis and/or interpretation, **GÇU:** Writing, Revision

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Medical providers should return the medical data ownership to the patient –a blockchain ledger solution. Opinion.

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ABSTRACT

Objective: Patients who paid for data generation, either privately or by public insurance or taxation systems, don't keep and don't have easy access to their health records. Furthermore, centralized databases that govern Big Data of health records are vulnerable to hostile breaches. Therefore, the current practice of medical data accumulation and sharing can potentially interfere with the fundamental personal rights of ownership, even endanger patients' health on one side, and provide uncompensated profit to third parties.

Material and Methods: The technical solution to this inherent problem might be storing personal medical data on the blockchain platform.

Conclusion: This method can decentralize the data accumulation, provide a high level of security of the collected data, and immutability of the stored data.

Keywords: blockchain; Big Data; medical records; patient rights; bioethical issues

INTRODUCTION

Most of the current medical records are kept on digital platforms owned by the medical providers. This data is generated following patients' evaluation and treatment and financed by direct payments or private or governmental insurance programs. Generally, the patients provide private and governmental funding sources directly or through taxation. Therefore the situation exists when the patients who paid for the generation of data regarding their health don't keep and don't have easy access to their records. Furthermore, the crucial data exchange among medical providers is not always readily available. Additionally, the administrator of the database can manipulate the data. The centralized databases are vulnerable to hostile breaches. Thus, the current medical databases endanger their real owners, i.e., patients, because of insufficient availability and security. This is not a theoretical but rather a real threat, supported by the recent hacking of data in the US hospitals, UK NHS databases, and the recent attack on the medical records database in Hillel Yafe Hospital in Israel. Moreover, the centralized accumulation of the medical records by the medical providers generates Big Data accumulation. This financial asset can be traded and provide economic benefit for the institutions without compensation and approval by the patients who are the actual owners of these assets (**Figure 1**).

Therefore, the current practice of medical data accumulation and sharing can potentially interfere with the fundamental personal rights of ownership, even endanger patients' health on one side, and provide uncompensated profit to third parties. Recently this issue was further emphasized by the concern on the attempts of commercial third parties to mine clinical data from medical providers' databases.

MATERIAL and METHODS (Possible solution)

The solution to this inherent problem should be based on the following principles [1,2,3]:

- Decentralization of the data accumulation
- High level of security of the collected data
- Immutability of the stored data

These factors are the blockchain platforms' data storage and transfer characteristics. By utilizing this data storage method, sophisticated encryption should achieve security. If the keys to the data are available only to the patients, the control of Big Data by the medical institutions will be omitted. The miscommunication between health providers will become irrelevant since all the information will be solely in the patient's hands and can be used only for their own medical and financial benefit (**Figure 2**).

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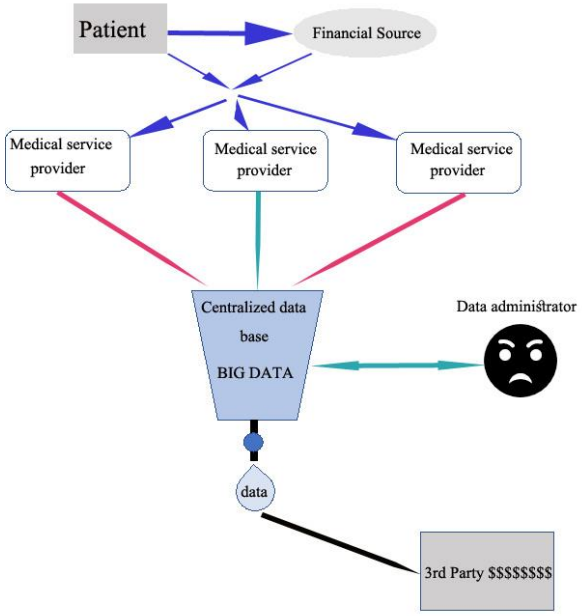

Figure 1: The problem - the medical data is centralized and governed by medical service providers—no financial benefit for the patient.

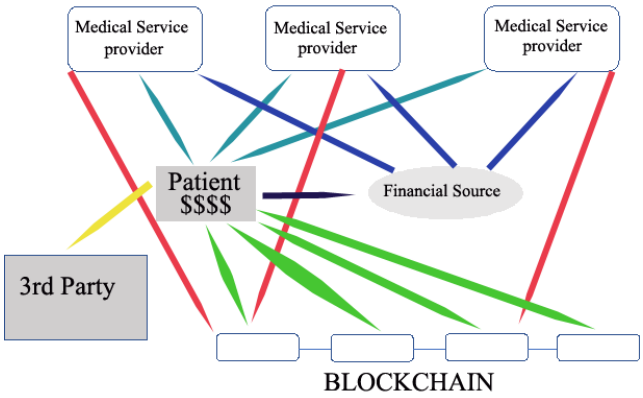

Figure 2: The solution – the medical data is kept on the uncentered blockchain, can be accessed only by the patient, can't be manipulated, and used without patients' permission.

DISCUSSION

Blockchain technology is relatively new and mainly used for financial transactions. Its implementation for health care data storage should overcome several technical obstacles and be appropriately regulated.

On the technical side, the main issue that should be resolved is encrypting a high volume of data, including imaging and high-speed transfer of the data on the blockchain platform.

The blockchain storage of medical records should be thoroughly regulated. The policymakers should consider its theoretical advantage for security and personal ownership.

CONCLUSION

Storing patient records on a blockchain platform can decentralize the data accumulation, provide a high level of security of the collected data, and immutability of the stored data.

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Ethical approval: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by Local Ethical Committee. All procedures performed in studies with human participants met the ethical standards of the Institutional Research Commission and the 1964 Declaration of Helsinki and its subsequent amendments or comparable ethical standards.

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