

Factors increasing mortality in Echinococcosis patients treated percutaneously or surgically. A review of 1,143 patients: a retrospective single center study

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Abstract. – OBJECTIVE: While cystic echinococcosis (CE) is a serious problem in under-developed countries, it also becomes a serious public health problem in developed countries due to recent migration and population movements. This study aimed to investigate the relationship between pregnancy, multi-organ involvement, treatment methods, and emergency surgery (unfollowed patients), with mortality in patients with CE who underwent surgical or percutaneous treatment.

PATIENTS AND METHODS: In this study, demographic characteristics, pregnancy status, organ involvement, development of relapse and anaphylaxis, need for intensive care and mortality rates of patients with CE treated with percutaneous or surgical methods at Harran University Hospital between January 1997 to January 2022 were investigated.

RESULTS: Of the 1,143 patients who underwent surgery or percutaneous treatment for CE, 18 were pregnant. Mortality was found to be significantly higher in pregnant patients with CE ($p<0.001$). Mortality was significantly higher in those who developed anaphylaxis ($p<0.001$). In percutaneous treatment, recurrence ($p<0.001$) and anaphylaxis ($p=0.026$) were found to be significantly higher. Mortality was found to be three times higher in patients without follow-up who were operated on urgently ($p=0.108$).

CONCLUSIONS: CE is a disease that can occur at any age and can be fatal. Although multi-organ involvement and percutaneous treatment may be associated with recurrence, they do not directly increase mortality. The mortality is high, especially in pregnant women with pulmonary CE. Cardiac involvement, brain involvement and anaphylaxis increase mortality. Mortality is higher in patients without follow-up who are operated on urgently.

Key Words:

Echinococcosis, Percutaneous, Anaphylaxis, Pregnancy, Mortality.

Introduction

Cystic echinococcosis (CE) is a parasitic infectious disease caused by the zoonotic transmission of organisms belonging to the *Echinococcus* genus, and the causative agent is usually *Echinococcus granulosus*¹. The incidence of CE in Turkey is 0.8-11%, and 0.8-6.6 individuals out of 100,000 undergo surgical treatment for CE^{2,3}. The infection may remain asymptomatic until adulthood in cases without complications. Imaging methods and serological tests are available for diagnosis. In humans, 60-80% of the cases are seen in the liver, 10-30% in the lungs and 10-15% in the rest of the body. Multi-organ involvement is rare⁴.

Surgical and percutaneous treatment options are available for certain cysts, pursuant to the diagnostic classifications of the World Health Organization (WHO)⁵. In medical treatment, the first option is albendazole⁶. Anaphylaxis may develop due to the perforation of the cyst as a result of spontaneous rupturing or during cyst aspiration⁷. The post-operative mortality rate ranges between 0% and 2%⁸.

Limited data are available on the effect of CE on pregnant women, yet CE can have a substantial effect on the morbidity and mortality in pregnant women⁹.

The present study investigated whether a relationship exists between pregnancy, multi-organ involvement and mortality in patients with CE treated by surgical or percutaneous methods. In addition, the effect of emergency surgery on mortality in patients without follow-up was evaluated.

Patients and Methods

The present study was approved the Local Ethics Committee (Date of Approval: 10 January 2021, Session No. 01, HRÜ: 22/01/08). In accordance with the Declaration of Helsinki, all patient

data were anonymized. The data of 1,143 patients clinically and radiologically pre-diagnosed with CE at the Harran University Medical Faculty Hospital and treated with surgical or percutaneous methods under general anesthesia between January 1997 and January 2022 were evaluated. Age, sex, pregnancy status (of patients >18 years of age), involved organ(s), relapse status, urgency for surgery, preference for open surgery or percutaneous method, anesthetic medications and methods, occurrence of anaphylaxis, blood product requirements, post-operative period intensive care needs, and mortality rates of the patients were recorded. The study data were retrieved from the patient files and anesthesia forms.

Direct abdominal X-ray in standing position, chest X-ray, ultrasonography (USG), computed tomography (CT) and magnetic resonance imaging (MRI) were used for radiological diagnoses and determination of relapse. USG and MRI were used as needed for the diagnoses and follow-up of pregnant women.

For general anesthesia, propofol or thiopental were preferred as the hypnotic, fentanyl, or remifentanyl hydrochloride as the opioid, rocuronium bromide as the muscle relaxant and sevoflurane or desflurane as the inhaler anesthetic.

In patients who develop anaphylaxis, 8 L/min 100% oxygen and 0.01 mg/kg intravenous (IV) adrenaline were administered, and fluid resuscitation was performed with a 20 mL/kg crystalloid solution. Two mg/kg methyl prednisolone and 1 mg/kg IV pheniramine maleate were administered. The administration of 0.005 mg/kg IV adrenaline was repeated at 3-minute intervals for patients whose hemodynamic parameters did not improve.

Statistical Analysis

The Statistical Package for the Social Sciences Version 25.0 (IBM Corp., Armonk, NY, USA) software was used to analyze the study data. Chi-square test was used to investigate the significance of intergroup differences for the categorical variables. A p -value <0.05 was considered as statistically significant across all the tests.

Results

Of the 1,143 patients, who received surgical or percutaneous treatment in our hospital for CE, 370 (32.4%) were men and 773 (67.6%) were women. The ages of the patients ranged between 0 and 111 years. The mean age was 33.08 ± 18.81 years. To-

tally, 877 (76.72%) patients were >18 years of age, of which 639 (72.9%) were women and 18 (2.8%) were pregnant (Table I) (Figure 1).

Upon examination of the involved organs in the patients, isolated liver and lung involvements were observed in 690 (60%) and 270 (24%) patients, respectively. The frequency of involvement of the other organs and multi-organ involvements are shown in Table I. Two of the deceased patients were pregnant, and there was a statistically significant relation between pregnancy and mortality ($p < 0.001$) (Tables II, III). Intra-operative anaphylaxis occurred in nine patients (0.8%), and one of them died ($p < 0.001$). Of the patients who developed anaphylaxis, two had undergone percutaneous treatment and seven had undergone surgical treatment ($p = 0.026$). Three (14.5%) of the deceased patients underwent surgery under emergency conditions ($p = 0.108$) (Tables II, III). There was no significant relationship between the number of involved organs and mortality ($p = 0.270$). Relapse was observed in 123 (10.8%) patients during the follow-up period. There was no mortality in the relapsed cases ($p = 0.296$) (Table II). Ninety-one patients who underwent CE-related operation were admitted to the intensive care unit (ICU) for a duration of 1-8 days, 35 (3.1%) of whom received blood/blood products (erythrocyte suspension, platelet, fresh/frozen plasma, etc.) during the intra-/post-operative period. There was no significant relationship between the duration of stay in the ICU and mortality ($p = 0.345$). Of the nine (0.8%) deceased patients, seven had single-organ involvement and two had multi-organ involvement; all of them had undergone open surgery ($p = 0.471$).

Discussion

CE is a serious public health problem in developing countries, especially in regions that earn a living from animal husbandry, and also in developed countries because of the recent migration and population movements⁶. In Turkey, the incidence of CE is 0.8-11%³. Every 0.8-6.6 individuals out of 100,000 undergo CE-related surgical operations². Our research reflects current data on CE, which is endemic in our region.

Owing to its slow progression, only 10-20% of the patients are diagnosed with CE during the childhood period^{6,10}. Şanlıurfa is one of the cities in Turkey with the highest child population. The fact that the proportion of patients aged <18 years of age was 23.27% in our study ($n = 266$), which is slightly higher when compared with relevant studies¹⁰ in the

Table I. Demographic data and distribution of involved organs.

| | Number of patients (n) | Percentage (%) |
|---|------------------------|----------------|
| Sex distribution of the patients | | |
| Men | 370 | 32.4 |
| Women | 773 | 67.6 |
| Total | 1143 | 100 |
| Age distribution of the patients | | |
| Mean age | 33.08 | |
| Standard deviation | 18.81 | |
| Minimum | 0.30 | |
| Maximum | 111.00 | |
| Sex distribution of the patients >18 years of age | | |
| Men | 238 | 27.1 |
| Women | 639 | 72.9 |
| Pregnant patients >18 years of age | | |
| Pregnancy (-) | 621 | 97.2 |
| Pregnancy (+) | 18 | 2.8 |
| Single-organ (isolated) involvement | | |
| Liver | 690 | 60 |
| Lung | 270 | 24 |
| Spleen | 34 | 3.0 |
| Kidney | 25 | 2.2 |
| Brain | 17 | 1.5 |
| Heart | 4 | 0.3 |
| Soft Tissue | 4 | 0.3 |
| Ovary | 1 | 0.1 |
| Two-organ involvement | | |
| Lung Liver | 49 | 4.3 |
| Liver Spleen | 16 | 1.4 |
| Heart Lung | 9 | 0.8 |
| Liver Kidney | 6 | 0.5 |
| Liver Ovary | 5 | 0.4 |
| Lung Kidney | 3 | 0.3 |
| Liver Pancreas | 1 | 0.1 |
| Liver Soft tissue | 1 | 0.1 |
| 2+ organ involvement | | |
| Liver Lung Spleen | 5 | 0.4 |
| Liver Lung Heart | 3 | 0.3 |
| Total | 1,143 | 100 |

literature, is indicative of the endemic nature of the disease. This present study also important in that it draws attention to the possibility of a large number of asymptomatic cases that may remain silent for many years in the regions, which has a large population of children and adolescents. The fact that there are possibly many asymptomatic cases that may remain undiagnosed for many years in Turkey and similar countries, whose population is composed of a high proportion of children and young people, contributes to the importance of our study.

Previous studies¹⁰ have reported single-organ involvement in 85-90% of the CE cases. Similarly,

the rate of single-organ involvement was 91.4% in the present study. In approximately 5-13% of the cases, two organs may be affected simultaneously¹¹. Consistently, in the present study, the number of cases with two-organ involvement was 90 (7.9%). The concurrent involvement of more than two organs (multi-organ involvement) is rare and accounts for > 5% of the cases in endemic areas⁴. Although this study was conducted in an endemic region, only eight (0.7%) patients presented with multi-organ involvement, which is a low rate when compared with the relevant studies⁴ in the literature.

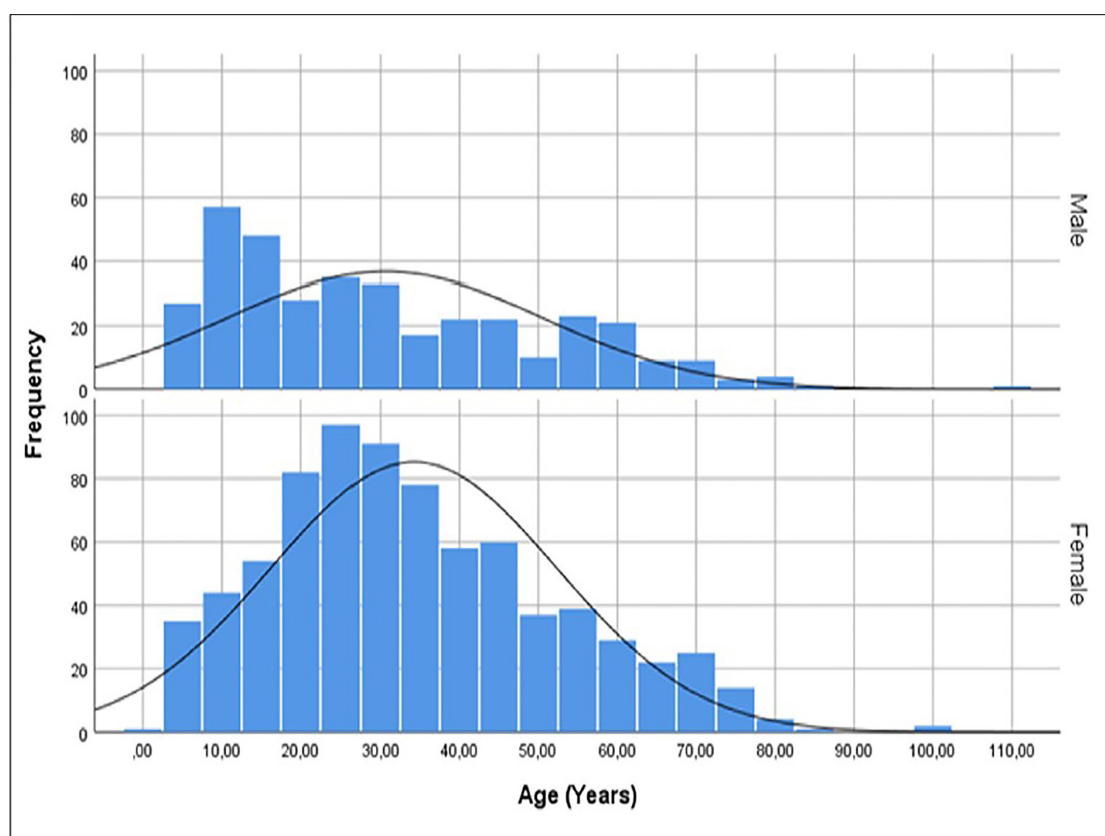


Figure 1. Age distribution of CE patients according to sex (CE: cystic echinococcosis).

The most commonly affected organ is the liver (50-70%) due to the nature of portal blood flow, followed by the lungs (20-30%)¹⁰. In the present study, the liver and lungs were the first and second most commonly affected organs [n=776 (67.8%) and n=339 (29.6%), respectively]. The spleen is involved less commonly (1%)¹². In our study, isolated and combined spleen involvements were seen in 34 (3%) patients and 21 (1.8%) patients, respectively. Isolated renal CE is clinically very rare (2-3%)¹³. Isolated and combined renal involvements were seen in 25 (2.2%) patients and 9 (0.8%) patients, respectively (Table I).

Brain involvement occurs in 1-2% of patients with CE, usually in children¹⁴. In our study, the brain involvement was observed in 17 (1.5%) patients, 53% of whom were children. Brain involvement was in the form of isolated brain involvement in all patients. In this study, the youngest patient (4 months and 5 days old) underwent operation after a preliminary diagnosis of hydrocephalus, and histopathological examination indicated intracranial CE. This case is important because the development of CE in the brain at such an early age is very rare.

Isolated cardiac involvement is very rare and accounts for approximately 0.02-2% of all the CE cases¹⁵. In our study, a similar rate of isolated cardiac involvement was also observed (4 patients, 0.3%). In the present study, the frequency of multi-organ involvement, including the heart, was higher when compared with the isolated heart involvement (Table I).

CE diagnosis is often coincidental and is primarily *via* patient history, clinical examination, serology and imaging¹⁰. In our study, 89.23% (n=1,020) of the patients were randomly diagnosed. As regards the diagnosis of patients who presented to different clinics of our hospital with non-specific complaints, the post-examination clinically suspected cases were referred to the necessary laboratory and radiological tests (serology, USG, CT, and MRI). CE pre-diagnosis was surgically confirmed in all the cases in our study, which can be explained by the fact that the hospital resides in an endemic region and that the clinicians are highly experienced in CE cases.

Certain cysts are merely followed up, whereas others receive medical, surgical, or combined treatment options pursuant to the diagnostic classifications of the WHO⁶. Even among respected

Table II. Mortality rates.

| | Alive (n) | Dead (n) | Percentage (%) | <i>p</i> |
|---|--------------------------|--------------------------|----------------|----------|
| Relationship between duration of stay in intensive care unit and mortality | | | | |
| 1 Day | 45 | 7 | | 0.345 |
| 2 Days | 36 | 1 | | |
| 4 Days | 1 | 0 | | |
| 8 Days | 1 | 0 | | |
| Pregnancy–Mortality relationship | | | | |
| Pregnancy (+) | 16 | 2 | | <0.001 |
| Pregnancy (–) | 1,118 | 7 | | |
| Relationship between involved organs and mortality | | | | |
| 1 Organ | 1,038 | 7 | 91.4 | 0.270 |
| 2 Organs | 88 | 2 | 7.9 | |
| 2+ Organs | 8 | 0 | 0.7 | |
| Relationship between open surgery/percutaneous treatment and mortality | | | | |
| Percutaneous treatment | 62 | 0 | | 0.471 |
| Open surgery | 1,072 | 9 | | |
| Relationship between relapse and mortality | | | | |
| Relapse (–) | 1,011 | 9 | | 0.296 |
| Relapse (+) | 123 | 0 | | |
| Relationship between anaphylaxis development and mortality | | | | |
| Anaphylaxis (–) | 1,126 | 8 | 99.2 | <0.001 |
| Anaphylaxis (+) | 8 | 1 | 0.8 | |
| Elective/emergency surgery distribution | | | | |
| Elective | 977 | 6 | 85.5 | 0.108 |
| Emergency | 166 | 3 | 14.5 | |
| Relapse rates | | | | |
| | Relapse – (n) | Relapse + (n) | | <0.001 |
| Percutaneous treatment | 44 | 18 | | |
| Open surgery | 976 | 105 | | |
| Relationship between anaphylaxis development and open surgery and percutaneous methods | | | | |
| | Anaphylaxis + (n) | Anaphylaxis – (n) | | 0.026 |
| Percutaneous treatment | 2 | 60 | | |
| Open surgery | 7 | 1074 | | |
| Percutaneous treatment/open surgery/age distribution | | | | |
| | <17 years | >18 years | | |
| Percutaneous treatment | 14 | 48 | 5.43 | |
| Open surgery | 252 | 829 | 94.57 | |

authorities, management of the disease worldwide is not standardized, and treatment options are controversial¹⁶. According to a recent meta-analysis by Velesco-Tirado et al¹⁷ on the medical treatment of echinococcosis, current treatment modalities of CE (pharmacological therapy, pre- and/or post-operative chemotherapy, surgery, percutaneous method) were stated to be controversial. In addition, according to this meta-analysis, it is stated that the results may be better when the treatment with surgery or

percutaneous approach is combined with chemotherapy¹⁷. In a study comparing treatment with percutaneous and surgical approaches, higher clinical efficacy, lower complication rates, lower mortality and disease recurrence were observed in treatment with the percutaneous approach¹⁸. In our study, it was found that although percutaneous treatment was associated with relapse ($p<0.001$), it did not directly increase mortality ($p=0.471$). Because of the many different approaches and different outcomes,

Table III. Distribution of the nine dead patients.

| | | | Pregnancy | | | | |
|-----------|-------------|-----|--------------|------|-----------|------|---|
| | | | No | | Yes | | |
| | | | Mortality | | Mortality | | |
| | | | Alive | Dead | Alive | Dead | |
| Elective | Anaphylaxis | No | Surgery | 895 | 5 | 12 | 1 |
| | | | Percutaneous | 59 | 0 | 1 | 0 |
| | | Yes | Surgery | 2 | 0 | 0 | 0 |
| | | | Percutaneous | 2 | 0 | 0 | 0 |
| Emergency | Anaphylaxis | No | Surgery | 156 | 1 | 3 | 1 |
| | | | Percutaneous | 0 | 0 | 0 | 0 |
| | | Yes | Surgery | 4 | 1 | 0 | 0 |
| | | | Percutaneous | 0 | 0 | 0 | 0 |

randomized controlled multidimensional studies comparing treatment approaches are needed to improve the clinical management of CE. In our study, on the other hand, the factors that increase mortality in patients treated with surgical or percutaneous approaches are discussed.

Patients treated with surgical (95%) or percutaneous (5%) approaches under general anesthesia were included in our study. One of the most important complications associated with the surgical procedures is relapse, which occurs in 2-15% of the operated patients^{19,20}. In our study, relapse was seen in 123 (10.8%) patients during the follow-up period. Although follow-up periods of up to 5 years are considered adequate to evaluate relapse risk, some sources recommend follow-up *via* imaging procedures for a 10-year duration⁶. The patients who underwent surgical treatment in our hospital were asked to visit the clinic once a year for undergoing laboratory tests, USG, CT and MRI as necessary, depending on the surgical localization.

Percutaneous aspiration or biopsy can be performed in limited cases, where other methods fail due to anaphylaxis risk or the secondary spread potential of the infection. In the relevant literature, percutaneous treatment has also been reported to be associated with anaphylaxis risk²¹. In our study, anaphylaxis occurred in 2 (3.22%) of the 62 patients treated percutaneously. The relationship between percutaneous therapy and anaphylaxis was significant ($p=0.026$).

Anesthesiologists significantly contribute to preventing early disease complications and in their diagnosis and treatment in case of occurrence. Adequate operating room and intensive care preparations are required prior to the sur-

gery. Preparation for pre-operative anesthesia includes invasive monitoring, the preparation of the necessary blood, and blood products and volume extenders²². In our study, the patients were evaluated through a multidisciplinary approach by the anesthesiologist, and necessary anesthesia and intensive care preparations were made during the pre-operative period. General anesthesia was applied to all of our patients under operating room conditions. Despite all precautions and technological developments, 0-2% mortality can be seen in patients with CE^{6,23}. Consistent with the relevant studies^{6,23} in the literature, the mortality rate was 0.8% in this study. In this study, 2.2% of those with lung involvement, 5.9% of those with brain involvement, and 20% of those with heart-lung involvement died. This result is indicative of the fact that mortality rates were statistically significantly higher in case of vital organ involvement, including the heart, lungs, and brain ($p<0.001$). However, there was no significant relationship between the duration of stay in the ICU ($p=0.345$), number of involved organs ($p=0.270$), relapse ($p=0.296$) and mortality (Table II).

Anaphylaxis is a fatal complication of CE and may occur as a result of spontaneous or iatrogenic cyst rupture¹⁹. Although rare, the mortality rate is high upon its occurrence. Ye et al²⁴ reported that anaphylactic shock developed during surgery in 18 of the 1,426 patients and that a higher risk of anaphylaxis was seen in patients with CE who had pulmonary involvement. In our study too, anaphylaxis occurred mostly in patients with CE who had pulmonary involvement. Anaphylaxis was statistically significantly associated with a high degree of mortality in patients with CE ($p<0.001$). Early

detection of anaphylaxis is challenging in patients under general anesthesia and requires close monitoring of the patient's status and cooperation of the surgical team. Sudden decrease in peripheral oxygen saturation during cyst puncture, deep hypotension, bradycardia, especially in the upper part of the body; widespread erythema, skin and mucosal lesions should suggest anaphylaxis and the patient should be treated urgently.

Relevant studies^{25,26} in the literature have reported a CE incidence in pregnancy of 1/20,000-1/30,000. In such patients, the cysts can rupture and cause anaphylactic shock and bleeding as they enlarge due to cellular immunity suppression during pregnancy and secretion of steroid hormones. In pregnant patients, it is possible to surgically excise or percutaneously drain the cyst during the early period. Cases treated surgically after the termination of pregnancy have also been reported⁹. Of the 18 (2.8%) pregnant patients in our study, 2 (11.11%) died after diffuse acute respiratory distress (ARDS) that developed within 4 days postoperatively. In our study, mortality in pregnant women with CE was found to be statistically significantly higher ($p<0.001$).

All of the patients who were operated on urgently were patients who were diagnosed incidentally ($n=166$). And the mortality rate for these patients (although not statistically significant, $p=0.108$) was three times higher than for patients undergoing elective surgery. This result also reveals the importance of diagnosis and follow-up of CE disease.

CE, which continues to be a medical and economic problem worldwide in the 21st century, may remain asymptomatic for many years with atypical locations from an early age. Emergency surgery increases mortality rates in patients diagnosed incidentally and without follow-up. Hence, screening programs should be developed to address this issue. Non-specific clinical findings should not escape the attention of clinicians in geographies where CE is not endemic. We believe that close patient follow-up by the anesthesiology team with a multidisciplinary approach will contribute positively towards reducing mortality and morbidity in patients with CE. We further opine that multi-organ involvement may be associated with relapse but is not a direct factor for increasing the mortality.

Limitations

There were several limitations in our study. Our study was retrospective. Furthermore, some information of the patients could not be accessed *via*

the digital environment, and the follow-up of the patients in the pediatric age group still continues. Some of the pediatric patients with CE involving both lungs were treated surgically at different time points and were considered as relapsed cases.

Conclusions

In conclusion, especially in pregnant women with pulmonary CE, in people with vital organ involvement such as heart-brain-lung, in emergency surgeries, and in case of anaphylaxis, mortality rates increase. Therefore, special guidelines should be developed for the early diagnosis and follow-up of patients with CE, especially pregnant women with CE, and the results should be supported by larger patient series studies.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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Ethics Approval

This study was approved by the Harran University Faculty of Medicine Ethics Committee (Date of Approval: 10 January 2021, Session No. 01, HRÜ: 22/01/08).

Informed Consent

Informed consent was not required due to the retrospective nature of the study.

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Data Availability

The data supporting this article are available from the corresponding author on reasonable request.

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Authors' Contribution

Erdoğan Duran designed the research, analyzed and interpreted the data, conducted the research, and prepared the article; Başak Pehlivan reached the data, analyzed, and interpreted the data. All authors read and approved the final version of the manuscript.

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