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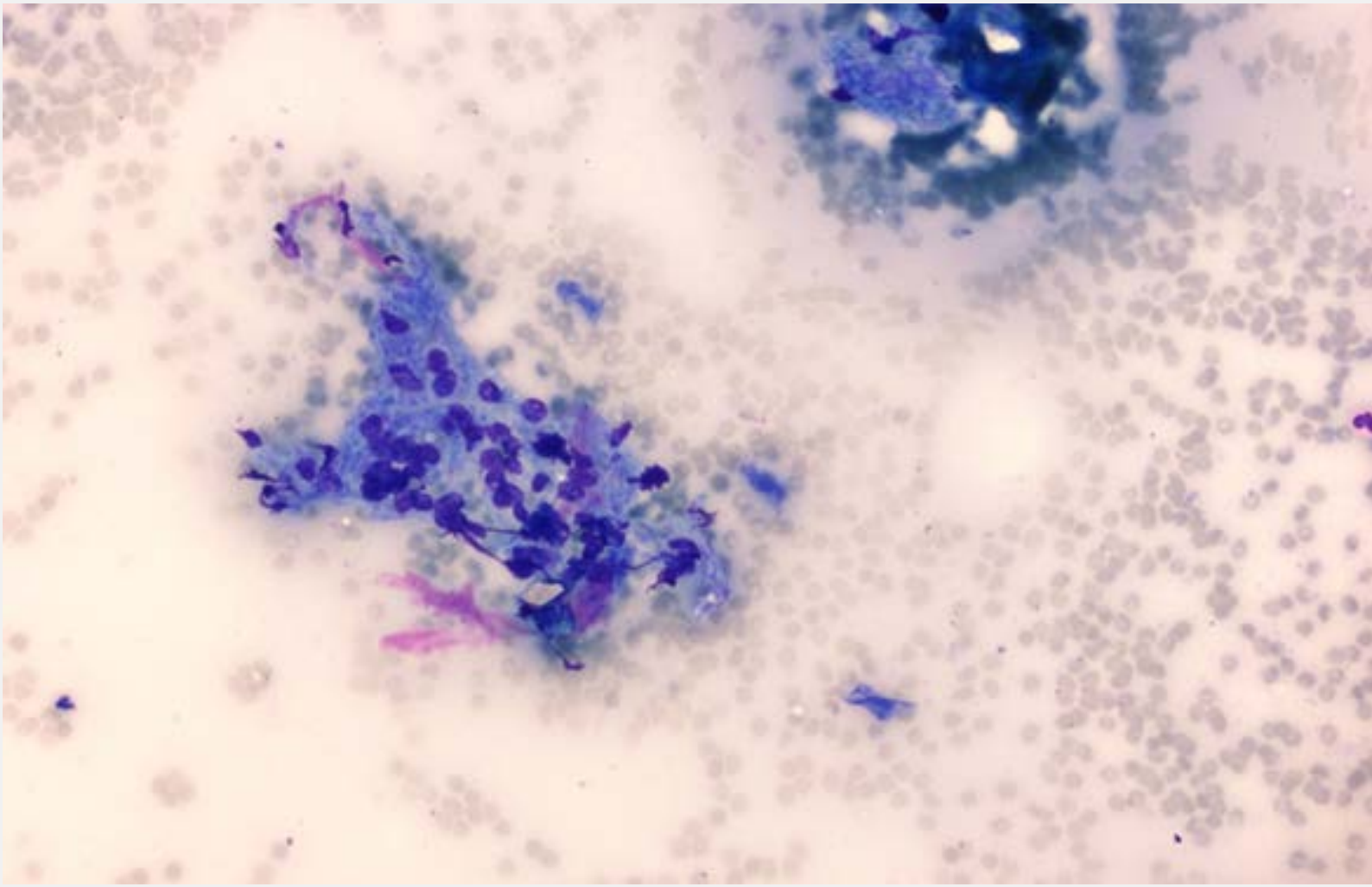

## High Lights

- Ultrasound-guided lateral sagittal infrac lavicular block in patient with flexion contracture
- Prevalence of HIV infection in young male candidates scheduled for military recruitment
- The effects of 2-aminoethyl diphenylborinate on L-Arginine induced acute pancreatitis
- Anomalous origin of Left Coronary Artery from Pulmonary Artery

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# Contents

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Letter to Editor Doi: 10.17546/msd.68142

# Ultrasound-guided lateral sagittal infraclavicular block in a patient with flexion contracture

Onur Palabiyik[1*]

Dear Editor,

Lateral sagittal infraclavicular block (LSIB) is a technique of regional anesthesia that is frequently used for anesthesia and analgesia in lower arm surgery. After ultrasound (US) had started to be used in the practice of anesthesia, peripheral nerve blocks (PNBs) could be applied more easily and with less risk. Besides, US emerges as an essential source for PNBs in cases of the nerve stimulator is not possible to use. In this present, we showed that US-guided LSIB was successfully applied for finger amputation in a patient with flexion contracture of the left hand due to previous cerebrovascular disease (CVD), which we do not be able to correctly provide the muscle response to nerve stimulator.

An 80-years female patient was scheduled for finger amputation. The patient had a flexion contracture in her left hand, which had not motor activities, as sequel due to the previous CVD for seven years. The patient had edema and laceration advancing to bone tissue, which were caused by the compression of the two rings, in her third finger of the left hand (Figure). The patient had normal physical examination and laboratory findings. To provide surgical anesthesia and postoperative analgesia, US-guided LSIB was decided. Following informed consent, electrocardiography, non-invasive blood pressure, and pulse oximeter were instituted in the operation room. Intravenous (IV) access was provided. The patient was sedated with 2 mg midazolam intravenously and lied in the supine position with left arm adducted and turned her head to opposite side. After all aseptic precautions, US probe was placed as in-plane technique near the entry point of the needle where is stated as the intersection between the clavicle and the coracoid process. The axillary artery and chords of nerves were identified. A 100 mm 21 G nerve stimulation needle was introduced caudally in a sagittal plane and 45° from the skin on a horizontal plane as in the same plane with the probe. After 2 ml of 0.25% bupivacaine and 1% lidocaine mixture was given under the skin, the needle was advanced and placed through the posterior to the axillary artery. We were reached to the goal at a depth of 5 cm from the skin. After no blood within negative aspiration had seen, 15 ml of 0.25% bupivacaine and 1% lidocaine mixture were injected intermittently.

The spread of local anesthetic mixture as surrounding the artery was observed during the injection period. When the adequate sensory block was achieved, the surgery was allowed. The surgery lasted 40 minutes was uneventfully completed. The patient had not needed additional analgesia and sedation during the surgical procedure. First analgesic requirement time was about 8 hours. The patient was discharged uneventfully.

The infraclavicular block is suggested as the safer and more effective technique in PNB for lower arm surgery (1). LSIB, which was developed by Klaastad et al. (2), is often preferred because of applying easily and with less risk of complication. LSIB is applied with nerve stimulator or US. US provides to view the nerves and the advancing of the needle during the injection that obtains increasing the success rate of the block and reducing the complications (3,4). By visualizing the spread of local anesthetic with US, PNBs can be applied with low dose local anesthetic.

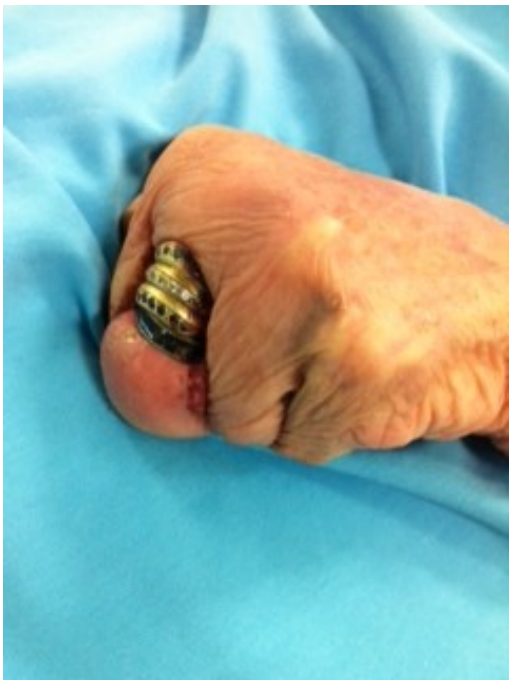

**Figure:** The patient's left hand with flexion contracture like clenched fist

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Additionally, PNBs can be applied only with US in some conditions; such as nerve stimulation is not possible, muscle response to nerve stimulation could not be accurately obtained and appropriate position of patient was not available for PNB (5). We applied a successful anesthesia with USG-guided LSIB. As a result, US-guided LSIB may be applied an effective and safe anesthesia in lower arm surgery in the patient with a sequel of the previous CVD.

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Review Article Doi: 10.17546/msd.27074

# The Role of MRCP on Management of the Acute Biliary Pancreatitis

Melih Yuksel[1]*, Murat Yıldar[2], Erdogan Bulbul[3]

## Abstract

Acute pancreatitis (AP) an acute inflammation of the pancreas is the most common cause of admission to hospital because of acute gastro-intestinal tract in the USA. In etiology, factors such as cholelithiasis, alcohol, drugs, hypertriglyceridemia, and sphincter of oddi dysfunction play a role. Acute biliary pancreatitis (ABP) constitutes %40 of all pancreatitis cases. The management of patients with ABP are vital for the cases in which choledocholithiazis exists. This review focuses on the management of such patients. The timing of ERCP and the use of MRCP was investigated in this review. For this review, various studies and reviews were critically evaluated

**Keywords:** Acute Biliary Pancreatitis, Endoscopic Retrograde Cholangiopancreatography, Common bile duct, Magnetic Resonance Cholangiopancreatography

## Introduction

Acute pancreatitis (AP), an acute inflammation of the pancreas, is the most common cause of admission to hospital because of acute gastro-intestinal tract pathologies in the USA [1, 2]. According to recent studies, the probability of encountering AP is between 4.9 and 73.4 per one hundred thousand cases [3, 4]. The incidence of AP cases has been increased. Moreover, their potential effects on patients and society are expected to increase too [1]. The mortality rate is approximately % 4-7 for all cases, whereas it is % 20-30 for severe cases [5]. In etiology, factors such as cholelithiasis, alcohol, drugs, hypertriglyceridemia, and sphincter of oddi dysfunction play a role. Additionally, after Endoscopic Retrograde Cholangiopancreatography (ERCP) treatment, AP may develop [6].

Acute biliary pancreatitis (ABP) constitutes %40 of all pancreatitis cases. ABP was first defined in 1901 by Opie [7]. The obstruction in ampulla caused by gallstones passing to duodenum is held responsible for pathogenesis [7, 8], which is temporary in general [9]. However, impacted gallstones in ampulla may cause progression of disease. The disease can be treated within a few days by supportive therapy for the cases in which the biliary obstruction is temporary. On the other hand, the management of the disease is vital for the cases in which choledocholithiazis exists. ERCP is known as golden standard for diagnosis and treatment of common bile duct (CBD) stone [10].

Authors hold a common belief that ERCP must be performed at the soonest time possible, ideally during within the first 24 hours for cholangitis cases. Nonetheless, for the other situations, it is suggested that other imaging methods should be used with the aim of diagnosing, because ERCP is invasive. Today, Endoscopic Ultrasonography (EUS) and Magnetic Resonance Cholangiopancreatography (MRCP) are the most commonly used imaging methods for the diagnosis of CBD stone [11].

MRCP is a non-invasive technique for evaluating the biliary tract and pancreatic canal. It was described by Wallner et al in 1991 using the T2 weighted gradient-echo sequence [12]. Because of the low signal-noise ratio and susceptibility to motion, demonstration of non-dilated bile duct was limited. It is possible to obtain higher quality images with newer techniques including the rapid acquisition with relaxation enhancement (RARE) and half-Fourier acquisition single shot turbo spinecho (HASTE). Also the images can be acquired within a breath-hold period. Additionally, visibility of the bile ducts can be increased with the use of ranitidine and glucagon [13, 14].

MRCP is a highly sensitive and specific noninvasive method for detection of CBD Stones [15]. This non-invasive technique is comparable with ERCP which is standard reference for detecting CBD stone, in acute biliary pancreatitis (Figure 1) [16]. Compared to different modalities, MRCP has a higher sensitivity than transabdominal ultrasonography (US)

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and computed tomography, similar to intraoperative cholangiography and lower than EUS [17].

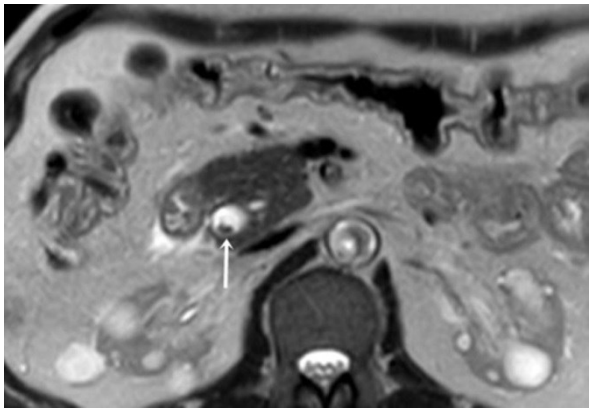

**Figure 1A.** Axial T2 image shows the hypointense stone (white arrow) in the CBD

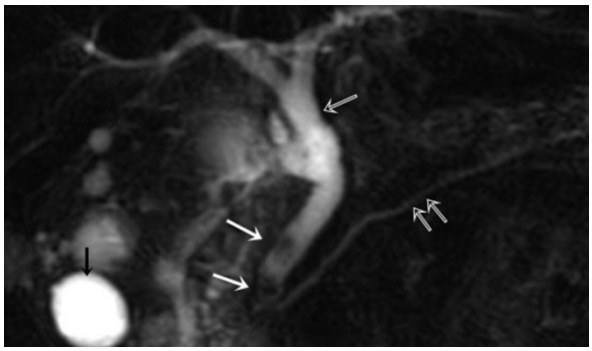

**Figure 1B.** Coronal MRCP image demonstrates the stones (white arrows) in the distal CBD. Open arrow and double open arrows show the CBD and pancretic duct, respectively. Black arrow demonstrates an incidental renal cyst

MRCP does not need for radiation, intravenous contrast material, anesthesia or sedation and provides the evaluation of surrounding anatomy. ERCP is an invasive procedure and may cause complications but can be used for both diagnostic and therapeutic purposes. Despite EUS is less invasive than ERCP, it is operator dependent and not widely available [6].

There are some limitations of MRCP. Statitionary fluid, metallic clips and fragments within the surrounding area, crossing defect of right hepatic artery or severely narrowed duct can cause image artifacts. MRI, by employing MRCP, has the advantage of detecting CBD stone down to 3 mm diameter and pancreatic duct disruption while providing high-quality imaging for diagnostic and / or severity purposes. In patients with low to moderate risk, MRCP or EUS can be used preoperatively [18]. Sensitivity of detecting CBD stones smaller than 3mm decreases when the bile duct is dilated [6].

The timing of ERCP and the use of MRCP are controversial at the management of patients with ABP [10]. According to studies conducted on patients with ABP, it is stated that biliary duct stones may fall spontaneously into duodenum over time [6]. Because of the reasons mentioned above, a comprehensive review needed to be conducted

## Methods

A PubMed search was performed using the terms pancreatitis [MeSH Terms]) AND pancreatitis [Title/Abstract]) AND MRCP [Title/Abstract]) AND Acute [Title/Abstract]. The titles were scanned manually and articles of interest regarding use of MRCP were reviewed.

## Discussion

During the assessment of patients with acute pancreatitis, the role of MRCP has been highly debatable. According to some studies, a temporary biliary obstruction may both lead a biliary pancreatitis attack. In addition, post-mortem studies found that patients who died of necrotizing pancreatitis had stones in the CBD [18]. It has been validated by the recent studies that early ERCP within the 24 hours of admission decreases morbidity and mortality in patients with AP complicated by biliary sepsis. However, it is claimed that ERCP is expected to be used for screening CBD stone only if there is considerable evidence and conditional recommendation. In the non-existence of cholangitis and / or jaundice, MRCP or EUS is more feasible approach for diagnosis [19].

CBD stone can be detected by using EUS. EUS is a highly sensitive test and can be another option to MRCP which is not as accurate as EUS while detecting tinier gallstones or sludge [20]. However, MRCP is a beneficial method for detecting retained stones in CBD [11]. The role of MRCP in biliary pancreatitis has been examined by many researches in the past several decades. Some studies have asserted that MRCP images should be taken routinely, whereas it is suggested in some other studies that they should be used selectively. Authors, stating that MRCP images should be used routinely, assert that the sensitivity of transabdominal ultrasonography (USG) and cholestatic enzymes is low.

In a retrospective study carried out by Barlow et al., 256 patients with ABP were examined and the median time to MRCP from admission was found to be 4 days (interquartile range: 2.5–9.5 days). MRCP was applied to 173 of patients and in 30% (52/173) of patients, CBD stone was observed. During the admission, CBD stone was detected in 5 patients who had not a biliary dilatation at USG and had completely normal liver function tests. So, it was suggested that MRCP images should be taken for each patient with the aim of minimizing the risk of CBD stone [21]. Neri et al. used MRCP imaging for all 47 patient having ABP and not having CBD stone at USG and cholestasis. It was discovered that 13 of those patients had CBD stone (13/47) and proposed that routine MRCP images should be taken from the patients with ABP [22].

Telem et al. examine 114 patients with ABP retrospectively. In this study, the correlation between and the existence of CBD stone and variables such as

the diameter of CBD stone measured by USG, Alkaline Phosphatase (ALP), gamma-glutamyl transferase (GGT), total bilirubin(TBIL), direct bilirubin(DBIL) were investigated and 69 patients were assessed with MRCP and ERCP. The optimal laboratory values were found as follows : CBD⩾9 mm; ALP⩾250 U/l; GGT⩾350 U/l; TBIL⩾3 mg/dl; and DBIL⩾2 mg/dl. Moreover, the correlation was observed between five variables and CBD stone (OR:53.1 p< 0.001). In addition, the correlation between four variables and CBD stone was found to be 8.97 (p=0.004). On the other hand, in patients having any combination of one to three variables, there existed no developing correlation with persistent CBD stone. According to findings above and the results of laboratory examinations, it can be said that selective use of MRCP not only reduces the need for ERCP but also helps to prevent unnecessary MRCP imaging [23]. Mofidi et al. investigated 249 patients suspected of having stones in CBD retrospectively. They used ERCP imaging for 57 of patients and MRCP imaging for 46. They stated that the use of MRCP was appropriate for screening biliary tract for the patients with APB and selective use of MRCP might help to diminish the requirement of ERCP and hospital admissions [24].

It is widely accepted that CBD stones may pass spontaneously in many patients when ERCP is used unnecessarily [19). Waele et al. examined 104 patients with ABP in detail. They discovered CBD stone in 21 of 104 (20.2%) patients taken MRCP images [6). Additionally, they used MRCP during the first day of admission and found CBD stones in 2 of 4 patients (50%). After that, they discovered that 6 of 21 patients (28.6%) had CBD stones within 48 hours of admission. In the following days; day 2 + 3, day 4 + 5 and day 6 + 7, the rate of CBD stones was 23.1% (6/26), 25.0% (6/24) and 12.5% (1/8) consecutively. The total incidence of CBD stone was found to be 8.0% (2/25) after 7 days. As a result, they explained that the incidence of CBD stone considerably decreased after acute attack and the reason for this might be explained as spontaneous stone migration.

Çavdar et al. offered a different perspective. They used MRCP screening for 60 patients between 1-4 days after admission and reassessed the patients with CBD stone after 7 days by using MRCP. At the first image, they detected CBD stone in 20 patients. After 7 days, they performed MRCP again and realized that 4 of the patient did not have CBD stone (4/20). The 16 of the patients with CBD stone, detected by MRCP, were applied ERCP. Additionally, they used ERCP imaging because of suspected clinical and laboratory findings for 2 of 4 patients who were not detected CBD stone during MRCP. They declared that controlled MRCP might prevent %10 of ERCP attempt, which could be unnecessary, and suggested that MRCP screening should be performed at the first week of acute attack for patients with ABP [10].

In conclusion, the number of the studies investigating the use of MRCP for diagnosing CBD stone for the patients with ABP is relatively low. In some of these studies, it was suggested that MRCP should be used routinely, however according to others, the use of MRCP should be selective.

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# Hyperemesis gravidarum, socio-cultural factors and maternal short psychiatric status

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## Abstract

**Objective:** This study sought to investigate the associations between Hyperemesis Gravidarum and both sociocultural factors and psychiatric status.
**Material and Methods:** A prospective non-randomized cohort design was employed. A total of 79 patients with Hyperemesis Gravidarum and 71 healthy pregnant women were enrolled. The study and control groups were compared according to results on the Brief Psychiatric Rating Scale and sociocultural factors specific to the region.
**Results:** Anxiety, somatic concern, tension, depressive mood, hostility, motor retardation, uncooperativeness, and blunted effect were found to be statistically significantly higher in patients with Hyperemesis Gravidarum ($p< 0.01$ and $p<0.05$). Furthermore, pregnant women living in extended families had statistically higher anxiety scores than those residing in nuclear families ($p < 0.05$).
**Conclusion:** Psychiatric status as well as sociocultural factors specific to the society in which the individuals live should be taken into account in assessments of patients with Hyperemesis Gravidarum.

**Key words:** Brief Psychiatric Rating Scale; Extended Families; Hyperemesis Gravidarum

## Introduction

Hyperemesis gravidarum (HG) is characterized by persistent nausea and vomiting associated with advanced dehydration and metabolic and biochemical problems (1). A significant endocrine feature of HG is the presence of substantially higher levels of human chorionic gonadotropin. However, the etiology and pathophysiology of the disease have yet to be explained and can comprise psychosocial as well as biological factors (1). HG is most likely a multifactorial condition and has been associated with many risk factors (such as female infant, ethnicity, maternal psychiatric status, body mass index, socioeconomic status) (2).

Individuals in society can be affected, either directly or indirectly, by a range of social, economic, or demographic factors. For example, the negative effects of socio-economic status and several demographic factors (e.g., job loss, financial difficulties, educational or career problems) on psychological impairment in pregnant women have been reported in previous studies (3-8) and potential links between these factors and HG have also been examined. However, evaluations of the association between HG and sociocultural factors have thus far been limited.

Sociocultural practices such as polygamy and living in extended families, which are frequently seen in the Southeast region of Anatolia, could play a major role in the health and well-being of expectant mothers, as might an unwanted marriage or unplanned pregnancy. Given this context, this study was conducted on pregnant women living in Southeast Anatolia to evaluate the relationship between HG and the psychological status of pregnant women, as well as the effects of sociocultural factors specific to the study population on the development of HG

## Material and Methods

This prospective study included females diagnosed with hyperemesis gravidarum who were hospitalized at Batman State Hospital department of obstetric and gynecology and Bakirkoy Dr. Sadi Konuk Teaching Hospital Department of obstetric and Gynecology. Approval for the study was granted by the Research local Ethics Committee. The study sample comprised 79 pregnant women with HG (study group) and 71 healthy pregnant women (control group) who were recruited into the study from march 2014 to august 2014. Informed consort form vas obtained from each participants. The

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participants in the study and the control groups were matched by age, parity, body mass index (BMI), and gestational weeks at hospital admission. Women with gastrointestinal disease, thyroid disease, gestational trophoblastic disease, psychiatric illness, or any other acute or chronic disease were excluded. Those who had previously received psychiatric treatment were also excluded. In this study, HG was defined as persistent vomiting in early pregnancy, not due to other causes (e.g., gastroenteritis), requiring any of the following: in-patient admission, day stay with intravenous fluids, nasogastric feeding (at home or in hospital), or vomiting associated with the loss of 5% of the individual's weight on presentation. Women with oral intake intolerance and ketonuria (i.e., ketone values of 3+ to 4+ as assessed with a urine dipstick test) were hospitalized. A comprehensive medical history was obtained from each participant, and laboratory evaluation tests were applied for renal function, serum electrolytes, and full blood count. A fetal sonogram was also obtained to confirm gestational age. Data were collected at the time of admission, using a series of forms completed in face-to-face interviews by the same physician (MBS, YC and AO). The patient information form was used to obtain clinical and demographic data related to expectant mothers. Standard inpatient management of HG was carried out, where all patients with HG were initially rehydrated with intravenous fluids and given intravenous anti-emetics. Oral intake was resumed based on clinical judgment. Patients were discharged once they were rehydrated and capable of maintaining adequate oral intake. All of the participants were asked to complete the Brief Psychiatric Rating Scale (BPRS) (9). The BPRS evaluation was conducted by a psychologist (AO). A further 6 questions were asked to evaluate sociodemographic characteristics which were felt to be unique to the region. These questions were: "How many concurrent marriages did your father have?", "How many siblings have you got?", "Is your marriage voluntary or unwanted?", "Did you want the pregnancy you currently have?", "What kind of a family do you have? Is it a nuclear or extended family?", and "If you live in a large family, do you feel anxious?". Plural marriage was defined as having a number of equal partners at the same time. Marriages that occurred after divorce or the loss of a partner were not considered plural. A nuclear family was defined as a family unit comprising a couple and their own children, whereas a large extended family, as also consisting of a mother, father, or sibling of the pair. Statistical analysis was performed using the Number Cruncher Statistical System (NCSS) 2007 and the Power Analysis and Sample Size (PASS) 2008 Statistical Software (Utah, USA). In order to evaluate differences on the BPRS between the two groups, the Mann-Whitney U test was applied. To assess intergroup differences on sociocultural factors, Pearson's Chi-square, Fisher's Exact, and Yates Continuity Correction tests were performed where appropriate, with a statistical significance level of $p = 0.05$ and 0.01

## Results

A total of 79 pregnant women with HG (study group) and 71 healthy pregnant women (control group) were enrolled in the study. All of the women were unemployed and were primary school graduates. The demographic characteristics of the participants are shown in further detail in Table 1. Approximately 13.3% of the women (n = 20) had 6 siblings or fewer, while 86.7% (n = 130) had more than 6. The father of the participant was polygamous in 16.7% of cases (n = 25) and the husband in 3.3% of cases. The living conditions were in a nuclear family for 54% of the women (n = 81), and 46% had extended families. Approximately, 20.7% (n = 31) had unwanted marriages and 75.3% stated that the pregnancy was planned (Table 2). A comparison of the control and study groups did not reveal any statistical differences between the groups in terms of unwanted marriages, unplanned pregnancies, family type, number of siblings, and having a polygamous father or husband. The rate of discontent from living in an extended family was significantly higher among patients with HG ($p < 0.01$) (Table 3). Anxiety, somatic concern, tension, depressive mood, hostility, motor retardation, uncooperativeness, and blunted effect were also found to be significantly higher in patients with HG ($p < 0.01$) (Table 4). Pregnant women living in extended families had statistically higher anxiety scores than those living in nuclear families ($p < 0.05$) (Table 5).

**Table 1.** Participant characteristics

| Characteristics | Min–Max | M ± SD |
|---|---|---|
| Week | 4–14 | 8.98 ± 2.3 |
| Gravidity | 1–10 | 3.72 ± 2.24 |
| Parity | 1–8 | 2.99 ± 1.71 |
| Abortion | 1–4 | 1.41 ± 0.74 |
| Cesarean | 1–3 | 1.42 ± 0.67 |
| Vaginal birth | 1–8 | 3.00 ± 1.72 |

**Table 2.** Family characteristics of participants

| | | n | % |
|---|---|---|---|
| Number of siblings | ≤ 6 siblings | 20 | 13.3 |
| | > 6 siblings | 130 | 86.7 |
| Polygamous father | | 25 | 16.7 |
| Polygamous husband | | 5 | 3.3 |
| Family type | Nuclear | 81 | 54.0 |
| | Extended | 69 | 46.0 |
| Voluntary marriage | | 119 | 79.3 |
| Voluntary pregnancy | | 113 | 75.3 |

**Table 3.** Comparison of demographic characteristics between study and control groups. [a]Yates Continuity Correction [b]Fisher's Exact Test [c]Pearson's Chi-squared **p < 0.01

| | | Hyperemesis Gravidarum (HG) | | p |
|---|---|---|---|---|
| | | HG (+) (n = 79) | HG (-) (n = 71) | |
| | | n (%) | n (%) | |
| Number of siblings | ≤ 6 siblings | 12 (15.2) | 8 (11.3) | 0.642 [a] |
| | > 6 siblings | 67 (84.8) | 63 (88.7) | |
| Polygamous father | | 14 (17.7) | 11 (15.5) | 0.884 [a] |
| Polygamous husband | | 4 (5.1) | 1 (1.4) | 0.370 [b] |
| Family type | Nuclear | 37 (46.8) | 44 (62.0) | 0.063 [c] |
| | Extended | 42 (53.2) | 27 (38.0) | |
| Discontent from living in an extended family | | 34 (81.0) | 9 (33.3) | 0.001 [a,]** |
| Voluntary marriage | | 60 (75.9) | 59 (83.1) | 0.380 [a] |
| Voluntary pregnancy | | 54 (68.4) | 59 (83.1) | 0.057 [a] |

**Table 4.** Comparison of BPRS[a] scores between study and control groups. Mann-Whitney U Test *p < 0.05 **p < 0.01

| | HE (+) | | HE (-) | | [d]p |
|---|---|---|---|---|---|
| | Min-Max (Median) | Mean±SD | Min-Max (Median) | Mean±SD | |
| Somatic conern | 0-6 (3) | 2.48±1.68 | 0-4 (1) | 1.10±1.21 | 0.001** |
| Anxiety | 0-5 (4) | 3.16±1.80 | 0-4 (1) | 1.07±1.05 | 0.001** |
| Emotional Withdrawal | 0-5 (0) | 0.75±1.29 | 0-4 (0) | 0.44±0.79 | 0.369 |
| Conceptual Disorganization | 0-3 (0) | 0.11±0.45 | 0-0 (0) | 0.00±0.00 | 0.018* |
| Guilt Feelings | 0-4 (0) | 0.47±0.97 | 0-4 (0) | 0.55±0.98 | 0.490 |
| Tension | 0-5 (1) | 1.39±1.29 | 0-3 (0) | 0.49±0.84 | 0.001** |
| Mannerisms and Posturing | 0-1 (0) | 0.04±0.19 | 0-2 (0) | 0.04±0.26 | 0.753 |
| Grandiosity | 0-2 (0) | 0.10±0.34 | 0-2 (0) | 0.07±0.35 | 0.278 |
| Depressive Mood | 0-6 (1) | 1.38±1.37 | 0-5 (0) | 0.38±0.96 | 0.001** |
| Hostility | 0-3 (0) | 0.22±0.59 | 0-1 (0) | 0.01±0.12 | 0.005** |
| Suspiciousness | 0-4 (0) | 0.49±1.11 | 0-6 (0) | 0.34±1.05 | 0.296 |
| Hallucinatory Behavior | 0-1 (0) | 0.01±0.11 | 0-0 (0) | 0.00±0.00 | 0.343 |
| Motor Retardation | 0-4 (0) | 0.53±1.02 | 0-1 (0) | 0.01±0.12 | 0.001** |
| Uncooperativeness | 0-3 (0) | 0.30±0.72 | 0-2 (0) | 0.06±0.29 | 0.005** |
| Unusual Thought Content | 0-3 (0) | 0.09±0.43 | 0-4 (0) | 0.06±0.47 | 0.224 |
| Blunted Affect | 0-4 (0) | 0.33±0.78 | 0-3 (0) | 0.06±0.37 | 0.002** |
| Excitement | 0-5 (0) | 0.24±0.91 | 0-3 (0) | 0.04±0.36 | 0.043* |
| Disorientation | 0-2 (0) | 0.03±0.23 | 0-1 (0) | 0.01±0.12 | 0.947 |
| Total score | 0-45 (10) | 12.13±8.53 | 0-31 (3) | 4.73±4.77 | 0.001** |

**Table 5.** Comparison of anxiety scores between study and control groups. M = Mean, SD = Standard Deviation [a]Mann-Whitney U Test *p < 0.05

| | Family type | | | | [a]p |
|---|---|---|---|---|---|
| | Nuclear (n=81) | | Extended (n=69) | | |
| | Min-Max (Median) | Ort±SD | Min-Max (Median) | Ort±SD | |
| Anxiety | 0-5 (1.0) | 1.79±1.55 | 0-5 (3.0) | 2.62±2.01 | 0.013* |

## Discussion

It is not apparent if psychiatric disorders induce HG symptoms or if HG symptoms have a negative effect on psychiatric status. Moreover, there is also the possibility that these two issues occur independently, but affect each other (10). In a study by Uguz et al. (11) anxiety and mood disorders were found to be statistically higher among pregnant women with HG than in healthy controls. In another study (12) involving Turkish patients with HG, the main findings were that the prevalence rates of psychiatric diagnosis among women in their study population were higher than those in the general population.

Several difficulties arise in ascertaining the effects of sociodemographic variables or in assessing the relationship between psychological problems and HG (10). For example, economic and sociological problems, such as that of unemployment, have been clearly linked to negative psychological outcomes in countries with a low level of economic development, unequal income distributions, or weak unemployment protection systems (12, 13). In a study conducted in Oslo (14), being an immigrant was found to be an independent factor, strongly correlated with HG. In that study population, adaptation and other social problems related to migration may have had a negative effect on physical health. In another study in Berlin (15), researchers reported that immigrant women were 4 to 5 times more likely than native-born women to have HG. At the same time, immigrant pregnant women had longer hospitalization periods for treatment. In a previous study in Turkey (16), patients with HG were evaluated in terms of educational attainment, economic status, and whether or not the pregnancy was planned. In that study, educational attainment was found to be higher in the HG group. No differences existed between the study and control groups in terms of other features, including economic status and whether pregnancies were planned, although anxiety and depression scores were higher in the HG group. However, it is difficult to determine the effects of social traditions and customs on psychological health and wellbeing, due to the difficulty of reaching a reliable source and the lack of clear definitions and classifications concerning these parameters.

Different studies have been conducted with regard to the effects of demographic factors on HG. In the current study, assessment was made of the sociodemographic factors and sociocultural characteristics specific to the region where the study population lived. The study and control groups were both compared in terms of sociodemographic features. The anxiety disorder rate was statistically higher among participants living in extended families than in those residing with nuclear families. Living in an extended family had a negative effect on the women's psychological health and seemed to aggravate HG symptoms. While the extended family type is frequently seen in the region where the study was performed (i.e., Southeast Anatolia), these results suggested that living in an extended family significantly affected the development of HG among the women in this study population. Hence, long-term hospitalization may present a viable option or reasonable approach to treating HG among these patients, as the negative effects of living with the extended family may be alleviated.

Although the planned pregnancy rate was higher in the control group, this difference was not statistically significant. These results suggested that unplanned pregnancies may have a negative effect on maternal perceptions rather than the actual status of health. With further research on an extensive number of patients, the association between unplanned pregnancy and maternal perceptions on psychological status may be more clearly defined. One of the most prominent sociodemographic features of this study population was polygamy. Although the prevalence of this practice has decreased in recent years, it is still relatively frequent and is more common in the urban districts of Southeast Anatolia. Polygamy is a sociological feature that could have negative effects on the psychological status of women in this area (17). In the current study, there were 4 HG patients and 1 in the control group whose husbands practiced plural marriage. Unfortunately, the effect of polygamy on maternal psychological status and HG could not be statistically evaluated in our study because of the inadequate number of patients in this sample. Another sociological feature of Southeast Anatolia is that of unwanted marriages, which include arranged and/or early marriages.

This sociological factor was examined in greater depth in this study, and no statistical differences were observed between HG patients and healthy pregnant women

This study had several limitations, including the relatively small sample of HG patients and the limited duration of observation. These limitations may have restricted the assessments of relationships between several traditional parameters specific to the study population (e.g., the practice of polygamy) and those of HG. However, to the best of our knowledge, this is the first study to examine sociodemographic factors specific to the region of Southeast Anatolia in pregnant women with HG, and it can be considered to contribute to existing literature on the effects of these significant factors on the development of the condition.

## Conclusion

In conclusion, patients with HG should be evaluated in terms of sociodemographic factors, economic status, and family type. Detailed assessments of regional-specific sociodemographic factors are needed, as these factors could have a significant influence on the management of HG symptoms.

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**Conflict of Interest:** The authors declare that they have no conflicts of interest.

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# Prevalence of HIV infection in young male candidates scheduled for military recruitment and whole population in Turkey

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## Abstract

**Objective:** The aim of this study is to investigate the epidemiology and recent incidence of HIV infection among young male candidates scheduled for military recruitment and whole young population in Turkey, a country previously known as markedly low prevalence of HIV infection.
**Materials and Methods:** In the present study, the medical records from respective health institutions between the years 2007 and 2013 of male candidates scheduled for recruitment from recruitment offices serving under the National Defence Ministry of Turkish Republic, diagnosed with HIV infection and as such judged as unfit for service were requested.
**Results:** While the total number of new HIV/AIDs cases in 2000 was 157, a fourfold increase (589) was recorded in the year 2010, and reaching 1,068 by the year 2012. Considering, data from the national statistics, in the year 2013 (including the month of November), a total of 7050 HIV positive cases were reported and of all the cases 4,931 (72%) consisted of males. At the same time, an important part of this group falls into the 18-45 year group category.
**Conclusion:** As a conclusion, the prevalence of HIV infection in Turkey remains still low as compared to that of current global figures but the case numbers of HIV positive candidates of recruits and young people in the whole population are increasing alarmingly in significant manner due to every new coming year. So, programs targeted at identifying high risk groups and increasing the testing rates and preventive measures about HIV infection should be improved and developed

**Key words:** HIV infection, Acquired Immunodeficiency Syndrome, Military Personnel

## Introduction

Human Immunodeficiency Syndrome (HIV) was first described in 1980 and a rapid increase in the number of cases across the globe has been observed over the years1. Till date, it continues to be one of the most important infectious epidemics with tragic outcomes. Trends in adult infection differ among regions. Millions of people have already been affected by this disease in North America, Europe, previous countries of the Soviet-Russia (USSR) and sub-saharan Africa. The epidemic continues to disproportionately affect sub-saharan Africa, home to about 70% of all new cases (1). Most new HIV infections occur among sexually active middle aged males. Around the world, 5 million young people ages 15-24 are living with HIV (2). Young people ages 15-24 represent 41 percent of all new HIV diagnoses, and 890,000 acquire HIV each year (3).The aim of this study is to investigate the epidemiology and recent incidence of HIV infection among young male candidates scheduled for military recruitment in Turkey, a country with a markedly low prevalence of HIV infection

## Materials and Methods

In the present study, the medical records from respective health institutions between the years 2007 and 2013 of male candidates scheduled for recruitment from recruitment offices serving under the National Defence Ministry of Turkish Republic, diagnosed with HIV infection and as such judged as unfit for service were requested. The database was interrogated for information on their age, previous history of immigration in a foreign country/migration to a foreign country, use of anti-retroviral therapy (ART), how HIV was first diagnosed, and level of education.

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Therefore, personal communications regarding all HIV positive cases that were recorded in these recruitment offices between 1988 and 1999, specifically cases with a positive history of immigration in a foreign country (longer than 5 years; mostly European countries) and that of the first reported cases in military recruits in Turkey were sought (Personal communication with Ret. Mil. Med Drs; Eray Nedim ILICAK & Ömer Hilmi Alga-Kocaeli/TR).

In addition to the above, epidemiological data of all HIV cases for the past 30 years were obtained from the official website of the "Directorate General Primary Health Care Services and Communicable Disease Control, department of Sexually transmitted diseases of Ministry of Health, Republic of Turkey". All reported cases of HIV infection from 1985 till December 2013 (Both AIDS and HIV positive cases) and their distribution according to age, gender and year are included in this dataset (Tables 1, 2) (4). The study was reviewed by the Council of Medical Ethics Gulhane Military School of Medicine & Hospital, Ankara, Turkey and ethical approval was received (July 03, 2013 / Session No: 23).

## Results

The first HIV positive case in a military recruit was first reported in an individual who had a positive history of foreign country immigration and was undergoing training at the center for candidates of recruits, Burdur, Turkey in 1988. Screening for HIV positive cases at Burdur, continued till 1999 and more HIV positive cases with a positive history of foreign country immigration were identified over the specified period. During this 11 year period (1988-1999), between 2000 and 3000 candidates scheduled for military recruitment were screened for HIV infection annually. The officially confirmed sero-positivity rate of HIV infection (contracted from abroad) was found to vary between 1 and 4 candidates per 2000 to 3000 Turkish candidates of recruits having story of living abroad for at least 5 years. (Source: Data from personal communications).

Data on HIV positive cases was obtained from health records from military recruitment offices and retrospectively evaluated. Although this can be a reason for data loss, almost all data on HIV positive cases reported from 2007 to 2013 were retrieved for the study. Totally, 160 cases were detected as candidates of recruits having HIV infection. All the subjects enrolled in to the analysis were males. The mean age of the subject was 29.063 ± 8.044 and varied 17 to 49 years old.

Sixteen (10%) of the 160 cases were subjects who had completed a 4-year degree program from the university. The remaining were either primary or high school graduates. A positive history of work and foreign immigration in Germany, France, Holland and Belgium and other European countries was present in one-third of the cases. The other two-thirds consisted of domestic cases ("authoctonous cases"). ART usage present in at least 17% (27/160) of the cases.

HIV sero-positivity was detected in 27.5% of the subjects during the diagnostic work up to investigate complaints such as weakness, long term diarrhea, lymphadenopathy in the head and neck regions, and genital warts. In another 27.5% of the cases, diagnosis was arrived at during laboratory investigations made after risky sexual contact and routine examinations conducted at cells and prisons. Diagnosis was encountered in 20% of the cases during the serological tests performed after blood transfusion, 25% of the cases during preoperative laboratory screening and in the course of carrier examinations.

Reported professional history of the subjects revealed >80% working in the entertainment, tourism or construction industry. While the annual rate of reported HIV positivity or AIDS cases among recruits varied between 1 and 4 in the period of 1988-1999 years, a marked increase was observed during the following years after 1999. In the year of 2013, the number of HIV positive cases among for about 500.000 candidates of recruits scheduled for recruitment had reached 37 (Figure 1). This means 7.4/ 100000 incidence rate. On the other hand in the same year the number of HIV positive cases among all Turkish population which is 76 667 864 person according to the most recent Census data (5) had reached for about 1200. This figure represents 1.56 / 100000 as an incidence rate

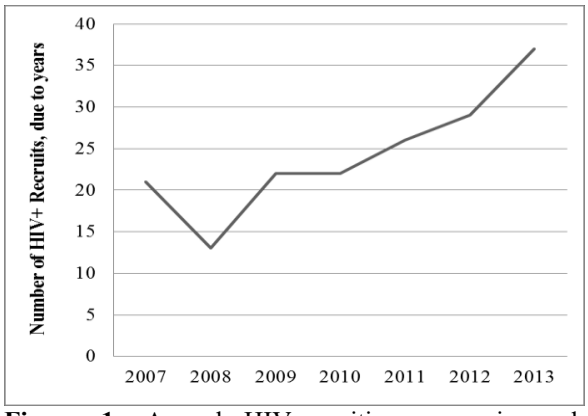


**Figure 1:** Annual HIV positive cases in male candidates scheduled for military recruitment in Turkey (2007-2013)

**Table 1:** Distribution of AIDS cases and HIV seropositivity across the years in Turkey (According to the statistics provided by the Health Ministry of the Turkish Republic)

| YEAR | HIV(+) | AIDS | TOTAL |
|---|---|---|---|
| 1985 | 0 | 3 | 3 |
| 1986 | 1 | 1 | 2 |
| 1987 | 32 | 8 | 40 |
| 1988 | 21 | 11 | 32 |
| 1989 | 22 | 11 | 33 |
| 1990 | 23 | 13 | 36 |
| 1991 | 27 | 24 | 51 |
| 1992 | 36 | 29 | 65 |
| 1993 | 47 | 33 | 80 |
| 1994 | 48 | 35 | 83 |
| 1995 | 59 | 28 | 87 |
| 1996 | 92 | 35 | 127 |
| 1997 | 95 | 38 | 133 |
| 1998 | 82 | 42 | 124 |
| 1999 | 89 | 28 | 117 |
| 2000 | 111 | 46 | 157 |
| 2001 | 137 | 45 | 182 |
| 2002 | 136 | 41 | 177 |
| 2003 | 136 | 46 | 182 |
| 2004 | 175 | 58 | 233 |
| 2005 | 246 | 46 | 292 |
| 2006 | 253 | 44 | 297 |
| 2007 | 345 | 24 | 369 |
| 2008 | 390 | 53 | 443 |
| 2009 | 437 | 66 | 503 |
| 2010 | 516 | 73 | 589 |
| 2011 | 632 | 78 | 710 |
| 2012 | 973 | 95 | 1068 |
| 2013 (First 6 months) | 545 | 42 | 587 |
| **TOTAL** | **5706** | **1096** | **6802** |

## Discussion

Since the first reported case of HIV in 1980, the widespread of this infectious epidemic across the globe has been observed and a marked increase in the number of cases annually is well known with over 35.2-38.8 million people carrying the infection as of the year 2012. Regions with a higher incidence and prevalence include; sub-Saharan Africa, south and South-Eastern Asia and Latin America. Additionally, HIV infection is also common and keeps its importance in the neighboring countries and regions of Turkey (Middle East, North Africa, Western Europe, Central Europe and Central-Asia) (1, 6).

**Table 2:** Distribution ff Reported Cases Of HIV/AIDS By Age-Group And Gender. (01 October 1985-20 June 2013)

| Age Groups | Male | Female | Unknown Gender | TOTAL |
|---|---|---|---|---|
| 0 | 19 | 11 | | 30 |
| 1.Nis | 15 | 23 | | 38 |
| 5.Eyl | 11 | 9 | | 20 |
| Eki.14 | 10 | 7 | | 17 |
| 15-19 | 50 | 54 | | 104 |
| 20-24 | 410 | 320 | | 730 |
| 25-29 | 733 | 380 | | 1113 |
| 30-34 | 867 | 325 | | 1192 |
| 35-39 | 754 | 215 | | 969 |
| 40-49 | 1090 | 245 | | 1335 |
| 50-59 | 559 | 153 | | 712 |
| 60+ | 275 | 69 | | 344 |
| Unknown | 138 | 58 | 2 | 198 |
| **TOTAL** | **4931** | **1869** | **2** | **6802** |

The first case of HIV infection in Turkey was reported in 1985. According to global rates, a climb in the number of newly reported cases has been shown over the past years. The aim of this study was to investigate the prevalence of HIV infection in a potentially risky population group known to pose a greater risk to the spread of this fatal infection; young male candidates scheduled for military recruitment and also determine whether or not there an increase in the sero-positivity of HIV/ AIDS in Turkey currently exists.

Compared to previous years, attention has been drawn to an increase in the number of HIV positive cases among candidates of military recruits. One major drawback or limitation of the study is its retrospective nature which exposes it to the possibility of inaccuracies in data collection. Nevertheless, with the inclusion of official statistical data from the nationally recognized health authority, the Turkish Ministry of Health we managed to minimize the degree of error in data collection.

The first case of HIV infection in candidates scheduled for recruitment in Turkey was reported in individuals who had lived or worked abroad for a longer duration. These were individuals who applied to the Burdur Military Barracks for the fulfillment of the National Military obligation assignment in 1988, and tested positive for HIV infection during the screening tests conducted as part of military general health assessment exercise. Following that year screening tests for HIV infection among candidates of military recruits continued at the same center till 1999.

After the presence of HIV infection was well noted, screening tests at the Burdur Military Barracks was stopped followed by confirmatory tests that led to the drafting a protocol exempting all subjects who tested positive from military duty.

One of the striking findings from our study is that almost all of the subjects who tested positive for HIV infection (90%-100%) towards the year 2000 were individuals who had lived or worked abroad with Western Europe being the most common region of foreign abode. Domestic HIV positive cases among recruits began to be reported after the year 2000. At least one third of the subjects enrolled in the study had a positive history of foreign country immigration either as an immigrant or a worker. Within the years of 1961 and 1975, most young Turkish citizens migrated to European countries specifically Germany for work and greener pastures (7). During the years following this period, although the migration rate of Turkish Citizens from Turkey to Europe had decreased, a staggering figure of around 4 million Turkish Citizens are known to currently reside in Europe. Some of the citizens and their offsprings were known to have contracted HIV infection in most European countries before their return back to Turkey. On the other hand, currently an important proportion (17%) of all HIV positive patients (recruits and non-recruits) in Turkey are known to be foreigners (8). Another contributory factor was the illegal migration of Sex workers (Natasha) from the former Soviet Union and Eastern Europe to Turkey during the early 1990. These illegal migrants, who lived in the Northern part of the country with bigger cities like Istanbul being a major area of settlement, fostered the uncontrollable spread of HIV infection across all the regions in Turkey (9).

Also, the enormous boost in the Turkish tourism sector after 1985, contributed to the spread of the infection by foreign tourists whose numbers increased rapidly over the said period in the Aegean and Mediterranean coasts. Risky Activities such as unprotected sexual contacts among the natives and tourists promoted the widespread of HIV infection. In a tourist friendly country like Turkey, the number of visitors has increased greatly over the past decade to over 20 million annually. One out of four of these tourists originate from Eastern or Central Europe and Commonwealth of Independent States and Baltic States (CEE/CIS). The high prevalence of HIV infection in these neigh boring countries (CEE/CIS), puts the Turkish population under risk (10). As of the year 2013, the number of visiting tourists in Turkey had increased two fold over the past decade reaching a record annual figure of 39.224.000 tourists. Therefore, this can be a contributory factor to the increase in the incidence of HIV infection among the youth In Turkey, and also specifically young male candidates scheduled for millitary recruitment.

The incidence of sexually transmitted diseases is known to be high not only among subjects who practice unprotected sex but also in drug addicts of intravenous drug use (11-12). Turkey is not known as a producer of drugs, however remains one of the countries which is used as a means of transport of drugs to other countries. The past years have seen a rapid rise in the number of young IV drug users in Turkey. As of 1999 the number of drug IV drug users in Turkey was reported to be only 2,682 persons. According to results from a recent study in 2010, the number of patients receiving care and treatment at various hospitals for the treatment of drug addiction and abuse has reached 135,000. A closer look at the figures during the past 11 years reveal frightening figures. Evaluation of the patients under treatment for drug abuse according to age and first exposure to drugs revealed the following; < 15 years (10.72%), 15-19 years (31.5%), 20-24 years (28.5%) 25-29% (14.2%), 30-34 years (7%) 35-39 years (4.8%) (“Turkish Drug Report-2010)” (13). The situation reflects the role drug abuse and addiction among male recruiters has got to play in increasing HIV seropositivity. Findings from our study revealed that 25% of the subjects were IV drug users. In terms of HIV infection all risk factors discussed above are specifically reflective among males with the 18-45 age groups.

The Republic of Turkey's Ministry of Health, approved the inclusion of HIV/AIDS into the list of Notifiable diseases in 1986. According to statistical findings from the Turkish Ministry of Health only 3 case of HIV/AIDs cases were reported for the first time in 1985. A gradual annual increase in the number of cases was observed after 1985. The figures however reveal how serious the increase in HIV/AIDs seropositivity in Turkey is. While the total number of new HIV/AIDs cases in 2000 was 157, a four fold increase (589) was recorded in the year 2010, and reaching 1,068 by the year 2012. These figures in comparisons to the previous decade ("y of 2002") have seen a four fold increase (400%). Twenty six percent (26%) of the HIV positive cases are seen among the 15-29 year group. For this age group, evaluation of figures from the past five years (2007 till 2012) shows an annual increase of 86% in HIV seropositivity rates. Considering, data from the national statistics, in the year 2013 (including the month of November), a total of 7050 HIV positive cases were reported and of all the cases 4,931 (72%) consisted of males (14). At the same time, an important part of this group falls into the 18-45 year group category. A sexually hyperactive group category that fit best as candidates for military recruitment.

In Turkey, regulations regarding blood donation and blood banks of 1986, serological tests country-widely performed as part of pre-operative evaluation (by the y of 1987) and compulsory

serological tests for pre-marital counseling (y of 2003) have helped reduce transmission of HIV infection via the blood to blood/ blood products route to virtually zero. Most of the cases are transmitted via unprotected sexual intercourse. In this respect, Turkey falls on top of the list of risky countries due several factors it possess such as lack of sex education among the populated youth, a higher rate of migration by the citizens to abroad, enormous increase in the tourism sector, its location in terms of drug trade and an increase in IV drug users thus increasing the incidence and prevalence of HIV seropositivity in Turkey. Since the year 2013, an estimated number of 1200 cases recorded when compared to the general population appears certainly low according to the most of the countries in the world however an increase of around 15-35% new HIV positive cases annually is considerably high. With this increasing trend in HIV seropositivity, Turkey is now counted among regions like Eastern Europe and Central Asia where the spread of HIV is considered to be rapid. With this rate of increase, the number of cases will be expected to reach a level where the risk of transmission will remain high within the society (authoctonous cases) without the effect of exogenous factors such as migrating abroad. Since an increase in the prevalence of HIV/AIDs will be more evident among sexually active young males and as such affect them most, this effect on candidates scheduled for military recruitment has become inevitable. To site an extreme example, due to the high HIV seropositivity prevalence of about 30% in the general population of South Africa and some other countries, millitary recruits and their other companions are encountering problems recruiting and keeping healthy soldiers in their armies. In some South African countries, HIV positivity among soldiers is known to be around 10%."A staggering seven out of ten military deaths in South Africa are AIDS-related, according to government figures released in 2002. Uganda's defence force lost more soldiers to AIDS than to fighting in two decades of war with the Lord's Resistance Army. In Zambia, AIDS-related illnesses have killed more military personnel since 1983 than died in all its military operations combined, including the bloody independence struggle. AIDS-related illnesses have killed mainly the more senior, experienced and difficult-to-replace ranks, due to the higher prevalence of HIV among older soldiers. Large numbers of soldiers on extended sick leave and unfit for active duty, further weaken military capability" (15).

## Conclusion

As a conclusion, the prevalence of HIV infection in Turkey remains still low as compared to that of current global figures. However,. the case numbers of HIV positive candidates of military recruits and young people in the whole population are increasing continuously in significant manner due to every new coming year. Thus, continuous increase in the number of newly reported cases is a big concerning issue.

Programs targeted at identifying high risk groups and increasing the testing rates should be improved and developed. And since asymptomatic carriers form a greater part of infected patients, diagnostic procedures and protocols aimed at early detection of disease and risk reduction should be developed for early treatment and management in such patients. The need for organizations such as "Voluntary Counselling and test Centers" a Turkish nongovernmental organization founded in the year 2007 that aims at delivering free counselling and HIV testing to interested individuals of the society, to be continued and supported is vital. Involving candidates scheduled for military recruitment in blood donation campaigns and other screening programs could be useful in the early detection of HIV positive cases. The need to continue previously commenced programs such as the family planning education program for military personnel which was started in 2007 is increasing.

While the rate of HIV infection has been successfully kept under control in most parts of the world, a staggering rise in these rates in neighboring countries of Turkey demands that, individuals of whom most are young, visiting these regions as tourists or for work purposes should be educated and well informed regarding the risks and preventive measures involved. Giving more importance to sexually transmitted diseases as part of the primary health care program will be of unequivocal benefits (16).

For this, the ministry of health including all other health organizations and nongovernmental organizations have a big role to play. In addition the need for participation of an effective media should be evaluated

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# Relationship among the HDLc, NonHDLc/ HDLc ratio and Gilbert's Syndrome

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## Abstract

**Objective:** We investigated the relationship between HDL-cholesterol levels that is indirect marker of ApoA-I production in liver, Non-HDL-cholesterol that is indirect marker of ApoB and GS
**Methods:** HDLc, NonHDLc/HDLc Ratio levels were investigated in subjects with GS (n=148) and compared to healthy controls (n=148).
**Results:** Age and BMI distributions were similar between the two groups. HDLc levels were lower in GS than the healthy controls (p=0.012). However, TC, Non-HDLc, Non-HDLc/HDLc levels were higher in GS than the healthy controls (p=0.002, p=0.001, p<0.001, respectively). In correlation analysis, UB were negatively mildly correlated with HDLc (r=−0.191, p=0.001) and positively correlated with TC (r=0.436, p<0.001), Non-HDLc (r=0.511, p<0.001) and Non-HDLc/HDLc (r=0.512, p<0.001) in the whole group.
**Conclusions:** The contrary of previously studies, we would like to suggest that bilirubin is a only antioxidant agent that protects from cardiovascular disease, but not physiological hypolipidemic agent

**Key words:** Gilbert's syndrome (GS), Unconjugated hyperbilirubinemia (UB), HDL cholesterol, Non-HDL-cholesterol, NonHDLc/HDLc ratio.

## Introduction

Gilbert's syndrome (GS) is characterized by intermittent unconjugated hyperbilirubinemia in the absence of haemolysis or underlying liver disease. It is a relatively common condition in the general population (3–17%), depending on the ethnicity studies (1). In most subjects, the hyperbilirubinemia of GS manifests itself during adolescence or early adulthood. The total serum bilirubin concentration usually rises and fluctuates between 20 and 50 µmol/l but rarely exceeds 85 µmol/l (2). Gilbert syndrome is the result of a defect in the promotor of the gene that encodes the enzyme uridine diphosphoglucuronate-glucuronosyltransferase 1A1 (UGT1A1), which is responsible for the conjugation of bilirubin with glucuronic acid. A number of studies have reported that gilbert syndrome is negatively associated with the prevalence of cardiovascular disease (CVD) (3, 4). However, the mechanisms of decreased frequency of atherosclerotic disease in GS are not entirely known but probably multifactorial.

ApoA-I is produced by the liver and acquires free cholesterol and phospholipid from liver and peripheral cells to form high density lipoprotein (HDL) cholesterol. An inverse relationship between the level of HDL cholesterol and the presence or development of coronary heart disease (CHD) is well established (5).

Non-HDL-cholesterol, which is estimated by subtracting HDLc from total cholesterol, corresponds closely to measurements of ApoB (6). With respect to the NonHDLc/ HDLc ratio, the UK Prospective Diabetes Study found NonHDLc/HDLc ratio to be better than NonHDLc as a predictor of coronary heart disease (CHD) in patients with type 2 diabetes (7). A recent observational study also demonstrated that the NonHDLc/HDLc ratio is a better marker than the apoB/apoA1 ratio for identifying metabolic syndrome and insulin resistance (8). In the present study, we investigated the relationship between HDL-cholesterol levels that is indirect marker of ApoA-I production in liver, Non-HDL-cholesterol that is indirect marker of ApoB and GS. In order to prevent any interference of confounding factors for inflammation or atherosclerosis, we studied a specifically selected group having no additional disorders such as hypertension, diabetes mellitus or obesity

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## Materials and Methods

### Subjects

We recruited a total of one hundred forty eight male patients with GS from the outpatient clinic of the department of Cardiology and Internal Medicine, Diyarbakır Military Hospital. Age, sex and body mass index (BMI) matched one hundred forty eight male healthy volunteers were studied as control group. The diagnosis of GS was made by unconjugated hyperbilirubinemia (UB> 1 mg/dl). Eligibility criteria were as follows (3); no evidence of haemolysis (normal full blood count and lactate dehydrogenase [LDH]), normal liver enzyme test results (aspartate aminotransferase [AST], alanine aminotransferase [ALT] and male sex. Subjects were excluded if they had a history of liver disease, diabetes mellitus, renal disease, alcoholism, cholelithiasis, coronary heart disease, haemolysis, haemoglobinopathy, positive hepatitis B surface antigen (HBsAg) or anti-hepatitis C virus (HCV) test, or had used any drugs in the past two weeks. All patients with GS were asymptomatic. The study was approved by the local ethics committee of Gulhane School of Medicine and all participants signed informed consent.

### Samples

All blood samples were collected from an antecubital vein, using Vacutainer® tubes (collected in clot activator and EDTA separately) between 08:00 and 09:00 AM after an overnight fasting. All serum and plasma samples were protected from light.

### Laboratory investigations

Total and direct bilirubin levels were measured by Olympus AU400 auto-analyser using reagents from Olympus Diagnostics (Hamburg, Germany). UB was calculated by the Formula (UB=total bilirubin−conjugated bilirubin). Also, glucose, total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDLc), low-density lipoprotein cholesterol (LDL-C), LDH, AST, ALT and ALT levels were measured by the enzymatic methods with Olympus AU400 auto-analyser using reagents from Olympus Diagnostics (Hamburg, Germany). LDL-C was calculated by Friedewald's formula (9).

### Statistical analysis

Results are reported as the mean±SD. Kolmogorov Smirnov test was used to determine the distribution characteristics of variables. Differences between groups were tested for significance by independent samples t test. To determine the relationship between GS and HDLc variable, multivariate linear regression models were used. The relationship between variables was analysed by Pearson correlation. Differences were considered significant at $p<0.05$. All data were analysed using SPSS 22.0 (SPSS Inc., Chicago, IL, USA).

## Results

The characteristics of the patients and the controls are summarized in Table 1. Age and BMI distributions were similar between the two groups. FBG, LDL-C, TG, AST, ALT levels were also similar in two groups. TC, HDLc, Non-HDLc, Non-HDLc/HDLc levels were different. HDLc levels were lower in GS than the healthy controls ($p=0.012$) (Table 1). However, TC, Non-HDLc, Non-HDLc/HDLc levels were higher in GS than the healthy controls ($p=0.002$, $p=0.001$, $p<0.001$, respectively) (Table 1). In correlation analysis, UB were negatively mildly correlated with HDLc ($r=-0.191$, $p=0.001$) and positively correlated with TC ($r=0.436$, $p<0.001$), Non-HDLc ($r=0.511$, $p<0.001$) and Non-HDLc/HDLc ($r=0.512$, $p<0.001$) in the whole group (Figure 1). On the other hand in subgroup analysis no significant association were found between UB and other parameters investigated. In multivariate linear regression analysis taking account HDLc as a dependent variable, HDLc were associated with UB (Beta:-0.181,t:19.322, $p=0.002$) .

## Discussion and Conclusion

To the contrary of our knowledge, the present study shows for the first time TC ($r=0.436$, $p<0.001$), non-HDLc ($r=0.511$, $p<0.001$) and non-HDLc/HDLc ($r=0.512$, $p<0.001$), well known mediators of initial stages of atherosclerosis, was higher in subjects with GS when compared to healthy controls.

These novel findings must be carefully evaluated in the pathogenesis of atherogenesis in GS. Because of several studies have reported an inverse relationship between the presences of CAD and circulating bilirubin levels (10, 11). In 1994, Schwertner et al. were the first to observe a significant inverse correlation between bilirubin plasma concentrations and the prevalence of CAD. This important finding indicated that a lower than normal serum bilirubin concentration is associated with the presence of ischemic heart disease (10). Moreover, Vitek et al. recently showed that GS subjects have low prevalence of CAD and presumed chronic hyperbilirubinemia prevent the development of CAD by increasing the serum antioxidant capacity (3). But these findings suggest that antioxidant capacity of serum bilirubin.

In aspect of liver, ApoA-I is produced by the liver and acquires free cholesterol and phospholipid from liver and peripheral cells via the ATP-binding cassette transporter A1 (ABCA1) to form nascent (discoidal) HDLc particles. But HDLc levels were lower in GS than the healthy controls in our study ( $p=0.012$). HDL-cholesterol levels is indirect marker of ApoA-I production in liver. Therefore, production of nonlipidated apoA-I may be decreased by UB in the liver and mature HDLc particles could be reduced

**Table 1.** Basic characteristics of the study population.

| | Gilbert (n=148) | Control (n=148) | P value |
|---|---|---|---|
| **Age (years)** | 29.9±12.9 | 36.3±14.7 | .073 |
| **Creatinine (mg/dL)** | 0.88±0.27 | 0.78±0.17 | .051 |
| **Fasting Glucose (mg/dL)** | 87.8±12.7 | 89.3±12.6 | .950 |
| **ALT (IU/L)** | 25.5±15.8 | 21.7±12.1 | .051 |
| **AST (IU/L)** | 27.5±10.3 | 24.9±8.3 | .077 |
| **UB (mg/dL)** | 1.49±0.47 | 0.41±0.18 | <.001 |
| **TC (mg/dL)** | 175.0±44.7 | 116.2±33.1 | .002 |
| **Triglyceride (mg/dL)** | 112.7±83.6 | 131.9±74.3 | .564 |
| **HDL (mg/dL)** | 44.9±13.9 | 50.7±17.7 | .012 |
| **LDL (mg/dL)** | 107.6±34.4 | 115.9±34.2 | .776 |
| **NonHDL (mg/dL)** | 130.1±41.7 | 65.5±27.6 | .001 |
| **NonHDL/HDL** | 3.2±1.4 | 1.4±0.7 | <.001 |
| **Hgb (g/dL)** | 15.1±1.6 | 14.3±6.7 | .193 |
| **Hct (%)** | 43.5±6.3 | 41.8±5.1 | .547 |
| **RBC (K/uL)** | 5.3±0.6 | 4.9±0.6 | .394 |
| **Plt (K/uL)** | 243±57 | 284±66 | .057 |
| **MCV (fL)** | 84.5±6.8 | 86.9±4.9 | .051 |
| **RDW (%)** | 12.6±1.3 | 12.9±1.0 | .134 |
| **WBC (K/uL)** | 6.5±2.1 | 7.2±2.0 | .238 |
| **Lymphocyte (K/uL)** | 2.1±1.2 | 2.8±0.8 | .026 |
| **Neutrophil (K/uL)** | 3.8±1.7 | 3.9±1.5 | .083 |

Abbreviations: UB- unconjugated bilirubin; TC- total cholesterol; HDL– high-density lipoprotein cholesterol; LDL – low-density lipoprotein cholesterol; Hgb- hemoglobin; Hct- hematocrit; RBC- red blood cell; Plt- platelets; MCV- mean corpuscular volume; RDW- red cell distribution width; WBC – white blood cell. Independent samples t test. Values are given as mean ± standard deviation.

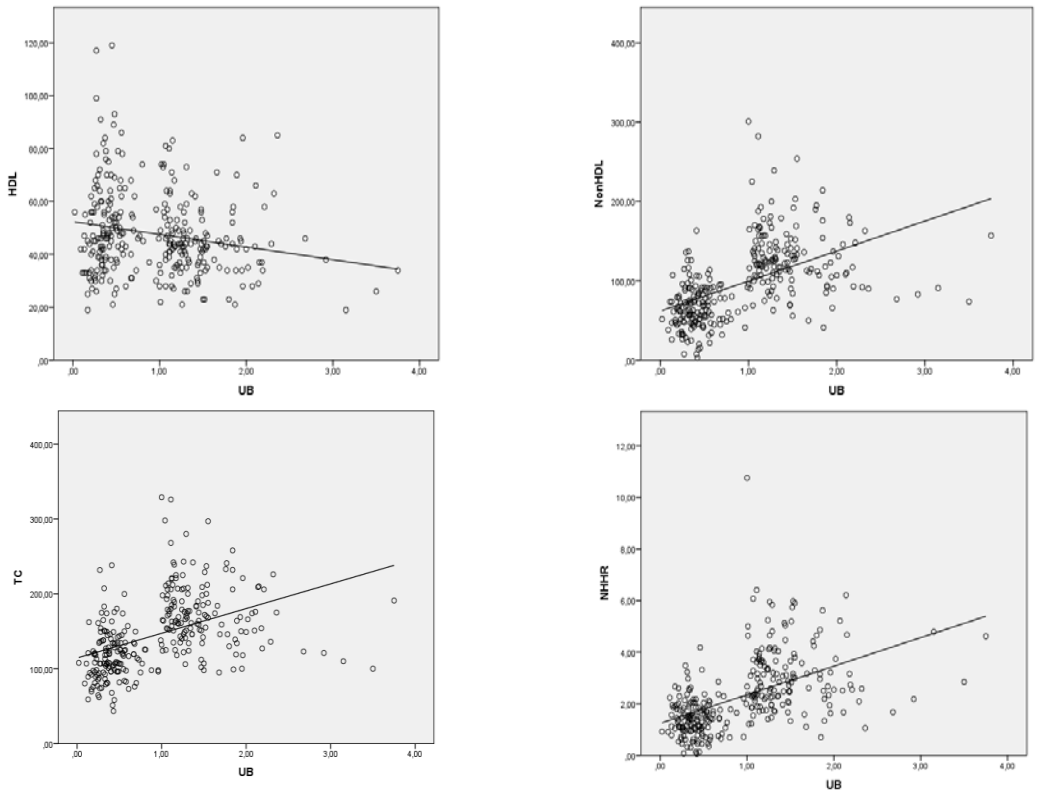


**Figure 1.** The Pearson correlation analysis in whole group. UB were negatively mildly correlated with HDLc (r=−0.191, p=0.001) and positively correlated with TC (r=0.436, p<0.001), non-HDLc (r=0.511, p<0.001) and non-HDLc/HDLc (r=0.512, p<0.001) in the whole group.

There is no data on the association between the NonHDLc/HDLc ratio and the GS, and also findings that about total lipid profile are controversial (12-15). The NonHDLc/HDLc ratio captures atherogenic lipid abnormalities other than LDLc including abnormalities in lipid particles such as small dense LDL, very low-density lipoproteins (VLDL), and HDLc similarly to that of ApoB/A1 (8). In our study, non-HDLc level as a marker of ApoB levels were found higher in the GS than the healthy controls. These findings may suggest that non-HDL cholesterol esters are taken up by endocytosis into hepatocytes is defective in the GS.

In this study, we found that GS was significantly associated with an increased risk of TC, non-HDLc and non-HDLc/HDLc. At first glance, these findings could appear unexpected. Because several studies have reported an inverse relationship between the presence of CAD and circulating bilirubin levels (10,11,16). But the contrary of these studies (10,11,16), we would like to suggest that bilirubin is a only antioxidant agent that protects from cardiovascular disease, but not physiological hypolipidemic agent

## Conclusion

The contrary of previously studies, we would like to suggest that bilirubin is a only antioxidant agent that protects from cardiovascular disease, but not physiological hypolipidemic agent. Our study has several limitations. Because of the narrow selection criteria, the sample size was small. Hence, our data may not be representative for all subjects with GS.

**Conflict of Interest:** The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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# The Effect of Ezetimibe on Plasma Viscosity, Fibrinogen and Lipid Profile

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## Abstract

**Objective:** The aim of this study is to reveal the effect of ezetimibe monotherapy on plasma viscosity and fibrinogen levels in hyperlipidemia.
**Material and Methods:** A study group of 31 hyperlipidemic patients was treated for twelve weeks with a monotherapy of ezetimibe 10 mg/day. A healthy control group of 31 individuals with normal plasma lipid profile was also admitted to the study. PV, fibrinogen and fasting lipid parameters were evaluated. PV was measured by Harkness Capillary Viscometer.
**Results:** PV and fibrinogen levels decreased significantly with ezetimibe monotherapy ($p<0.01$). Total cholesterol and low density lipoprotein (LDL) levels were statistically significantly lower than ezetimibe monotherapy group ($p<0.001$), whereas high density lipoprotein (HDL) level was significantly higher than ezetimibe monotherapy group ($p<0.01$). HDL level increased significantly in ezetimibe monotherapy group ($p<0.01$). PV and fibrinogen levels of the control group were lower than ezetimibe monotherapy group before treatment ($p<0.01$ and $p<0.001$; respectively). Besides, fibrinogen level of control group was significantly lower than ezetimibe monotherapy group after treatment ($p<0.01$). Total cholesterol and LDL levels of control group were lower than ezetimibe monotherapy group before and after treatment ($p<0.001$ and $p<0.01$; $p<0.001$, respectively). HDL level of control group was significantly higher than ezetimibe monotherapy group before treatment ($p<0.01$).
**Conclusions:** Ezetimibe monotherapy ameliorates lipid profile and PV parameters in hyperlipidemic individuals. Increased PV and deteriorations in lipid profile may induce endothelial damage in cardiovascular diseases. Being a biophysical mechanical marker, PV may be useful for diagnosis, treatment and follow-up of hyperlipidemic patients treated with ezetimibe monotherapy.

**Key words:** Ezetimibe; viscosity; fibrinogen; hyperlipidemia

## Introduction

Cardiovascular diseases related with atherosclerosis are the leading causes of worldwide mortality [1]. Prolonged dyslipidemia ends up with the initiation of atherosclerosis [2]. Hemorheological factors, such as viscosity, are significant in determining blood flow characteristics and play an important role in the pathogenesis of thrombotic events and, therefore, cardio- and cerebro-vascular diseases.

The source of cholesterol that affects lipid profile depends majorly on intestinal absorption of dietary and biliary cholesterol [3]. Ezetimibe, which is the first member of a new class of selective cholesterol absorption inhibitors and is found to inhibit acylcoenzyme A, has positive effects both on lipid profile and cardiovascular events [4,5]. Moreover, ezetimibe monotherapy may be a favourable option acting as a non-synthetic agent having few side-effects. Ezetimibe diminishes cholesterol absorption by 40% to 50% [6], and reduces low density lipoprotein (LDL) levels by approximately 18 % [7,8]. Despite the fact that cholesterol has deteriorating effects over blood flow [9], the impacts of ezetimibe monotherapy on plasma viscosity (PV) have not been fully elucidated in the literature.

Recently, studies concerning blood flow in atherosclerosis reveal that atherogenesis is further accelerated by impaired blood flow. PV plays an important part in the formation and progression of atherosclerotic lesions [10]. PV is a major determinant of capillary blood flow through the microcirculation - an increase in blood viscosity (BV) reduces blood

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flow in the circulation. Elevated PV may contribute to tissue damage by impairing microcirculatory flow due to shear stress damage at the blood-endothelial interface [10-14].

Either PV and/or fibrinogen have been defined as atherogenic risk factors for cardiovascular diseases. Fibrinogen is generally accepted as a factor that has the greatest effect on PV [10]. Fibrinogen, which is one of the plasma proteins, has a pronounced impact on PV despite its lower concentration than albumin and globulin. The reason why fibrinogen is responsible of 22% for the PV can be elucidated by its asymmetry and big molecular structure. As being an acute phase reactant, high fibrinogen levels might result from underlying pathologies including endothelial dysfunction and inflammation and may consequently increase PV [15]. Hypercoagulability and decreased fibrinolysis are often encountered in the clinical field related with cardiovascular diseases [16,17].

The aim of our study is to reveal the effect of ezetimibe monotherapy on plasma viscosity and fibrinogen levels which were analyzed in hyperlipidemic patients and compared with the control group. Thus, variations in plasma viscosity and fibrinogen were analyzed in the ezetimibe monotherapy applied hyperlipidemic group and compared with the control group.

## Materials and Methods

This study was performed with 31 hyperlipidemic patients [male (M) / female (F): 17/14; mean age: 47 ± 8 years; body mass index (BMI): 25.8 ± 3.1 kg/m$^2$] admitted to the Outpatient Clinic of Family Medicine at Istanbul University, Cerrahpasa Medical Faculty between September 2007 and September 2008. Asymptomatic patients with LDL cholesterol levels that needed to be treated according to the Adult Treatment Panel III (ATP III) guidelines were enrolled in the study. A group of healthy controls with normal total and LDL cholesterol levels and matched for body weight (BMI: 26.4 ± 4.6 kg/m$^2$), age (mean: 44 ± 9 years), and sex (M/F: 14/16) was included. Routine biochemical parameters were measured both in ezetimibe monotherapy and control groups. Patients in the ezetimibe monotherapy group were treated with ezetimibe 10 mg/day for twelve weeks, while no intervention was given to the control group. A full medical history was obtained from each individual. Physical examination, 12-lead electrocardiogram and echocardiography were performed. Patients were excluded from the study if they had alcohol abuse or smoked heavily (>10 cigarettes/day), if they were pregnant or if they had diabetes mellitus, liver insufficiency, serious renal disorders (serum creatinine >1.6 mg/dL), myocardial infarction, unstable angina, coronary revascularization, a clinical history of cardiovascular disease, peripheral vascular surgery, a percutaneous interventional procedure, acute cerebrovascular disease, or deep venous thrombosis. They were also excluded if they were treated with statins, antioxidant vitamins, or other herbal drugs. The protocol for sample collection was approved by Istanbul University, Cerrahpasa Medical Faculty, Ethical Commitee. The study was performed in accordance with the Helsinki Declaration, and informed consent was obtained from all patients and controls prior to their inclusion in the study.

After 12 hours of overnight fasting, venous blood samples were drawn into chilled dry polypropylene tubes containing one-tenth volume of 0.1 M sodium citrate without venous stasis. After immediate centrifugation (3000 g) for 10 min at 4°C, plasma was stored at -70°C until assayed for determination of the parameters. Serum was used directly for measurements of routine biochemical parameters and lipid profile. Total cholesterol, high density lipoprotein (HDL), LDL, very low density lipoprotein (VLDL) and triglyceride levels were analyzed within lipid profile. All reagents were analytical grade and purchased from Sigma (St. Louis, MO, USA) and Merck (Darmstadt, Germany). All parameters were analyzed in all samples together in a single batch, after the protocol was finished (control and patient samples were analyzed in the same batch).

Fibrinogen was assessed using Clauss method with MDA180 device (Trinity Biotech Company) and expressed as mg/dL.

Blood samples for PV measurements were drawn into vacutainers with potassium EDTA as anticoagulant and were processed in two hours following collection in accordance with the committee of hemorheology standardization [18]. PV was measured by Harkness capillary viscometer (Coulter Electronics LTD Serial Number 6083, England) at 37°C, which allows measurement of sizes as low as 0.5 ml within 1 min. The flow rate, measured in seconds (s), of each plasma sample (Tp) was compared with that of distilled water (Tw) to obtain the relative plasma viscosity (coefficient of variation, 1,00%). For quality control, measurements were compared with tap water. PV measurements were carried out in triplicate. The PV was expressed as in milliPascal × seconds (mPa.s; 1 mPa.s = 1 centipoise).

$$P_v = \eta_w \frac{T_p(s)}{T_w(s)} \qquad \eta w = 0.693 \text{ mPa.s}$$

### Statistical analysis

For each variable, values were expressed as mean ± standard error of the mean. Statistical calculations were performed with the NCSS 2007 program. Besides standard descriptive statistical calculations (mean and standard deviation), paired t-test was used in the assessment of pretreatment and

post-treatment values, and the Chi square test was performed during the evaluation of qualitative data. The Pearson correlation test was used for determination of correlation between biochemical parameters and other variables.

## Results

The demographic characteristics of the patients and controls were expressed as means ± SEM in the methods section. There were no significant differences in demographic data (gender, age, BMI, systolic and diastolic blood pressure) and biochemical parameters (hemoglobin, hematocrit, C-reactive protein (CRP), fasting blood glucose, hemoblobin A1c (HbA1c), alanine aminotransferase (ALT), aspartate aminotransferase (AST) and creatinine) between the two groups (Table 1). Twelve weeks of monotherapy with ezetimibe caused an improvement in the lipid profile, in accordance with the literature.

The value of PV decreased significantly from 1.31 ± 0.17 mPa.s to 1.26 ± 0.13 mPa.s in the ezetimibe monotherapy group after the treatment period ($p<0.01$). The value of PV in the control group was measured as 1.24 ± 0.10 mPa.s with a significant value compared with ezetimibe monotherapy group before treatment ($p<0.01$).

Ezetimibe monotherapy significantly reduced fibrinogen level by 11% after 90 days of treatment. Fibrinogen level of the ezetimibe monotherapy group decreased from 352.3 ± 36.2 mg/dL to 310.7 ± 37.1 mg/dL after ezetimibe monotherapy ($p<0.01$). Fibrinogen level of the control group was measured as 268.52 ± 47.4 mg/dL, compared statistically significantly with ezetimibe monotherapy group before treatment ($p<0.001$). Fibrinogen level of the control group was measured significantly lower than the ezetimibe monotherapy group after treatment ($p<0.01$).

Total cholesterol level and and LDL level of the ezetimibe monotherapy group both decreased statistically significantly from 280.75 ± 27.98 mg/dL to 241.77 ± 31.07 mg/dL and from 180.36 ± 26.30 mg/dL to 142.48 ± 25.93 mg/dL, respectively ($p<0.001$). Total cholesterol level of the control group (192.06 ± 12.54 mg/dL) was measured statistically significantly lower than the ezetimibe monotherapy group before treatment and significantly lower than the ezetimibe monotherapy after treatment ($p<0.001$ and $p<0.01$, respectively). LDL level of the control group (110.46 ± 22.10 mg/dL) was measured statistically significantly lower than the ezetimibe monotherapy group both before and after therapy ($p<0.001$). HDL level increased significantly from 43.83 ± 10.58 mg/dL to 46.27 ± 11.02 mg/dL in the ezetimibe monotherapy group ($p<0.01$). HDL level of the control group revealed significantly lower results than the ezetimibe monotherapy group before treatment ($p<0.01$). VLDL level in the ezetimibe monotherapy was measured as 28.51 ± 10.85 mg/dL and 26.46 ± 13.82 mg/dL before and after treatment with no statistical significance, respectively. VLDL level in the control group was measured as 25.42 ± 11.15 mg/dL. Trigyceride levels in both ezetimibe monotherapy and control group did not show any statistical significance with levels of 140.25 ± 61.54 mg/dL, 132.82 ± 72.34 mg/dL and 113.28 ± 52.67 mg/dL with no significance, respectively. The effects of ezetimibe monotherapy on PV, fibrinogen and lipid profiles are summarized in Table 2.

**Table 1.** Demographic data and biochemical parameters of ezetimibe monotherapy and control groups.

| | Ezetimibe Monotherapy Group (n: 31) | | Control Group (n:30) | p |
|---|---|---|---|---|
| **Gender (Male / Female)** | 17 / 14 | | 14 / 16 | |
| **Age (years)** | 47 ± 8 | | 44 ± 9 | |
| | **Before Therapy** | **After Therapy** | | |
| **BMI (kg/m$^2$)** | 25.8 ± 3.1 | | 26.4 ± 4.6 | NS |
| **SBP (mmHg)** | 129 ± 9 | | 127 ± 6 | NS |
| **DBP (mmHg)** | 82 ± 6 | | 72 ± 4 | NS |
| **Hemoglobin (mg/dL)** | 14.02 ± 2.5 | 14.35 ± 1.52 | 13.72 ± 1.24 | NS |
| **Hematocrit (%)** | 40.75 ± 4.92 | 41.48 ± 4.68 | 43.5 ± 4.21 | NS |
| **CRP (mg/L)** | 3.1 ± 0.9 | 2.8 ± 0.7 | 3.3 ± 0.6 | NS |
| **Fasting blood glucose (mg/dL)** | 89 ± 8 | 85 ± 6 | 87 ± 9 | NS |
| **HbA1c (%)** | 5.9 ± 0.5 | 5.7 ± 0.3 | 5.6 ± 0.4 | NS |
| **ALT (U/L)** | 23.1 ± 5.8 | 22.7 ± 4.3 | 20.4 ± 7.2 | NS |
| **AST (U/L)** | 20.2 ± 3.7 | 19.6 ± 3.4 | 21.5 ± 6.8 | NS |
| **Creatinin (mg/dL)** | 0.91 ± 0.12 | 0.86 ± 0.28 | 0.81 ± 0.21 | NS |

Values are represented as (mean ± SEM). BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; CRP: C-reactive protein; HbA1c: hemoglobin A1c; ALT: alanine aminotransferase; AST: aspartate aminotransferase; NS: non-significant.

The Pearson correlation test was used for determination of correlation between parameters and variables. A statistical positive correlation was found between PV and fibrinogen in the study group before treatment with ezetimibe monotherapy (r = + 0.429; p = 0.026). There was no correlation between PV and lipid profile in the ezetimibe monotherapy group before treatment. Despite the fact that there was statistically reduction in PV, fibrinogen, total cholesterol and LDL levels in the ezetimibe monotherapy group after treatment, no correlation was found between these variables. A statistical positive correlation was found between PV and fibrinogen in the control group (r = + 0.299; p = 0.078).

## Discussion

In our study, we observed that with three months of ezetimibe monotherapy; PV, fibrinogen, total cholesterol and LDL levels decreased significantly. Ezetimibe monotherapy resulted in a decrease in PV levels by 3.8%. Ezetimibe monotherapy significantly reduced fibrinogen levels by 12% at the end of the treatment period. There was also a reduction in total cholesterol by 14.2% and in LDL by 21.3%. The assessment of blood sample of the control group was not repeated after 12 weeks, since no intervention was given to the control group.

As we could reach the literature, we didn't encounter the studies related with the effects of ezetimibe monotherapy on PV. In our study, we focused on the investigation of the effects of ezetimibe monotherapy on PV and fibrinogen.

Ezetimibe is known as the first member of a new class of selective cholesterol absorption inhibitors. Several studies revealed that ezetimibe monotherapy combined with statins and other anti-hyperlipidemic agents have a positive influence in lipid-lowering [4,5,19]. It is well known that prolonged hyperlipidemia, increased PV and fibrinogen levels could be affected in the pathologic process in cardiovascular diseases [9,14,20].

The fact that blood flowing has more important roles in subsequent cardiovascular events is a widely accepted data in the literature [21]. Similarly with the literature, we found out that PV was higher in ezetimibe monotherapy group before treatment than control group. PV decreased to values almost reaching control group after treatment with ezetimibe monotherapy. Plasma is a cell-free or cell-depleted marginal layer adjacent to the endothelium of the vessel wall. Thus, PV points out the qualitative and quantitative assessment of the endothelium layer [22]. In their study on 27 patients with cerebrovascular diseases Laszlo et al. [23] found out that in chronic cerebrovascular patients with hyperlipidemia who were treated with atorvastatine 10 mg daily for 3 months, plasma total cholesterol level was reduced by 28%, LDL cholesterol level was decreased by 40% and BV was improved ($p<0.05$). They concluded that besides lipid lowering, atorvastatin may improve hemorheological parameters, platelet aggregation and endothelial dysfunction after short-term and long-term therapy. Van der Loo et al. [20] reported that atorvastatin 80 mg/daily for 6 months was not more effective in decreasing major hemorheologic parameters like PV, red cell aggregation and BV in comparison with lower doses of statin usage in peripheric arterial disease patients.

Atherosclerosis consists of early and late phases within a process of coagulation and fibrinolysis pathologies and complications [5]. Only a few studies have been reported on the effect of ezetimibe monotherapy on PV, fibrinogen and fibrinolytic activity. In our study, fibrinogen decreased significantly in ezetimibe monotherapy group after treatment. Fibrinogen level in control group was statistically significantly lower than ezetimibe monotherapy group before treatment. Being one of the plasma proteins, fibrinogen has a pronounced effect on PV. The increase in fibrinogen levels might result from underlying pathologies including endothelial dysfunction and inflammation [15]. Yano et al. [24] concluded that patients with high fibrinogen could encounter with an increase in cardiovascular

**Table 2.** The effect of ezetimibe monotherapy on plasma viscosity, fibrinogen and lipid profile.

| | Ezetimibe Monotherapy Group (n: 31) | | Control Group (n:30) |
|---|---|---|---|
| | Before Therapy | After Therapy | |
| **Plasma viscosity (m.Pa.s)** | 1.31 ± 0.17 | 1.26 ± 0.13 † ** | 1.24 ± 0.10 † ** |
| **Fibrinogen (mg/dL)** | 352.3 ± 36.2 | 310.7 ± 37.1 † ** | 268.52 ± 47.4 † ***, ‡ ** |
| **Total Cholesterol (mg/dL)** | 280.75 ± 27.98 | 241.77 ± 31.07 † *** | 192.06 ± 12.54 † ***, ‡ ** |
| **HDL (mg/dL)** | 43.83 ± 10.58 | 46.27 ± 11.02 † ** | 50.17 ± 15.41† ** |
| **LDL (mg/dL)** | 180.36 ± 26.30 | 142.48 ± 25.93 † *** | 110.46 ± 22.10 † ***, ‡ *** |
| **VLDL (mg/dL)** | 28.51 ± 10.85 | 26.46 ± 13.82 | 25.42 ± 11.15 |
| **Triglyceride (mg/dL)** | 140.25 ± 61.54 | 132.82 ± 72.34 | 113.28 ± 52.67 |

Values are represented as (mean ± SEM). HDL: high density lipoprotein; LDL: low density lipoprotein; VLDL: very low density lipoprotein, †: Statistical comparison before treatment; ‡: Statistical comparison after treatment; * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

morbidity and mortality. PV and fibrinogen level build up the vital functions of the vessel wall and their increase has been shown to be responsible for starting endothelial damage. The ability of ezetimibe to decrease fibrinogen level has been pointed out by Krysiak et al. [5]; and supports its role in hemorheologic mechanisms. Turfaner et al. [25] found out that the balance between fibrinolytic markers was maintained and fibrinolysis was prevented by ezetimibe monotherapy. Thus, the decrease in fibrinogen might be due to the improvement of profibrinolytic activity. In their study of the effect of ezetimibe and simvastatin on hemostasis, Krysiak et al. [5] stated that ezetimibe monotherapy reduced fibrinogen levels by 18.9% after 90 days of treatment. Because, even it has small differences, in the plasma levels of fibrinogen was associated with the effect of ezetimibe on clinical manifestation.

Studies have shown that there is a correlation between PV and cholesterol levels of the individuals. PV correlates strongly with cholesterol status of the individuals [10]. In a study held by Ercan et al. [26] hypercholesterolemic patients were declared to have significantly higher PV, LDL and triglyceride levels compared with normocholesterolemic patients; and HDL was significanly lower in hypercholesterolemic patients than in normocholesterolemic patients . Kikuchi et al. [4] pointed in their study of postprandial hyperlipidemia and hyperglycemia that the reductions in LDL with ezetimibe monotherapy was thought to have resulted from the inhibition of cholesterol absorption. Besides, Miyashita et al. [19] reported that ezetimibe monot herapy significantly decreased LDL levels by 23%. Similarly with the literature, our study revealed that ezetimibe monotherapy reduced fibrinogen, total cholesterol and LDL and increased HDL in hyperlipidemic patients. There was statistical decrease in levels of PV together with fibrinogen and improvement in lipid profile in ezetimibe monotherapy group after treatment; however no correlation was analyzed with PV between these parameters. Thus, this fact might be evaluable in considering the PV as an independent variable.

## Conclusion

Ezetimibe monotherapy may be a favourable option for the treatment of the patients with hyperlipidemia via its effects over PV and fibrinogen. Depending on the fact that PV is a marker of the hemorheologic and fibrinolytic features of both the endothelium and blood, the amelioration of PV in individuals treated with ezetimibe is a promising result. It should be taken into account that it may not be as effective as statin monotherapy on some parameters like LDL cholesterol and fibrinogen levels [4, 19, 27]. Ezetimibe monotherapy administration may be considered in order to decrease atherogenic events encountered in cardiovascular diseases with its improving effects on PV. Since effects of statin monotherapy and statin-ezetimibe combination therapy on plasma viscosity have been evaluated in several other concomitant studies, we only compared the plasma viscosity values before and after ezetimibe monotherapy in the ezetimibe monotherapy group which has been rarely done in the literature and we did not include another statin therapy group.

As a result, being a non-invasive, repeatable and economic parameter plasma viscosity might be evaluated as one of cardiovascular risk factors and be assessed as a biomechanical / biophysical marker in the efficiency of the diagnosis, treatment and follow-up of hyperlipidemia.

**Limitations:** The limitation of our study is the absence of flow mediated dilatation assessment of our study and control group. Another limitation is that the rheologic and lipid parameters of the control group were only assesed once. It could have been measured at the end of the study to detect the changes that result from the life-style, although they were on a stable diet. We evaluated plasma viscosity, lipid status and fibrinogen in hyperlipidemic patients with ezetimibe monotherapy. The positive effects of ezetimibe monotherapy on human health have not been elucidated thoroughly. The pleiotropic benefits of ezetimibe should be assessed in detail with large-scale studies.

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# Optimal cytoreduction is the only independent prognostic factor for survival in women with ovarian clear cell carcinoma

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## Abstract

**Objective:** To evaluate the clinicopathological characteristics, treatment methods, survival, and prognosis of ovarian clear-cell carcinoma (OCCC).
**Material and Methods:** All patients with OCCC who were treated between January 1998 and October 2012 were retrospectively reviewed. After the exclusion criteria, a total of 39 women were included in the present study. Univariate and multivariate analyses were used to identify the risk factors for overall survival (OS) and progression-free survival (PFS).
**Results:** The majority of the patients were at stage I disease (n=21 [24.3%]). All patients underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy. Additionally only pelvic, and pelvic plus para-aortic lymphadenectomy was done in 8 (20.5%) and 19 (48.8%) women, respectively. Optimal cytoreductive surgery was achieved in 26 (66.7%) patients. Recurrences occurred in 11 (28.2%) patients. The median follow-up period was 51 months (range 4 – 132 months). The 5-year PFS and OS rates were 47% and 54%, for all patients. The 5-year OS rates for women with early (stage I and II) and advanced (stage III and IV) stage disease were 56.4% and 38.1%, respectively. Multivariate analysis confirmed optimal cytoreduction as the only independent predictor of OS [Odds ratio (OR) 21.212, 95% confidence interval (CI) 5.259–85.556, ($p<0.001$)]
**Conclusion:** Optimal cytoreductive surgery is the only independent good prognostic factor for survival in patients with OCCC.

**Keywords:** ovarian clear-cell carcinoma, survival, optimal cytoreduction, chemotherapy

## Introduction

Ovarian cancer is the most lethal malignancy of the genital tract (1). Epithelial ovarian cancer (EOC) accounts for 90–95% all ovarian cancer types. Ovarian clear cell carcinoma (OCCC) is a rare subtype of EOC, constituting approximately 5% to 25% of cases (2,3). These tumors were first described and originally named as ‘mesonephroma ovarii’ due to the patological findings including hobnailed clear-cells with an immature glomerular pattern (Fig 1) (4).

Unlike other subtypes, OCCC is more likely to be diagnosed at an earlier stage and occur unilaterally (5-7). They are generally associated with poor prognosis and distinct clinical features compared to other subtypes of EOC (5). An association between endometriosis and OCCC was described and nulliparous women are considered to be at higher risk like women with most subtypes of EOC (6,8,9).

The traditional management approach for OCCC is comprehensive surgical staging (surgical treatment consisted of hysterectomy, removal of the adnexae, and/or lymphadenectomy [pelvic and/or para-aortic], infracolic omentectomy or omental sampling, and/or tumor cytoreduction, if needed), followed by chemotherapy (CT).

However, no standard treatment method exists particularly in early-stage diseases (3). Besides, type of surgery and adjuvant treatment methods can vary from author to author depending on the experience and patient characteristics.

In the current study, we analysed the clinicopathological characteristics, treatment methods, survival, and prognosis of 39 women with OCCC

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## Materials and Methods

### Patients

A retrospective review was conducted for all patients who had undergone surgery for OCCC between January 1998 and October 2012. This study was performed in accordance with the ethical standards of the Declaration of Helsinki and was approved by the local ethics committee of our institution. Patients who did not undergo surgery and patients with missing data were excluded. Besides, women with mixed-type OCCC or another primary cancer were not included in the study.

### Data collection

Demographic data, such as age at diagnosis, clinical stage, parity, menopausal status, surgical and neo-adjuvant and/or adjuvant treatment details, perioperative and postoperative complications, follow-up data, and laboratory findings such as serum cancer antigen 125 (CA 125) levels were obtained from medical records. Histopathological findings, including, cytological analysis, primary tumor diameter (PTD), existence or non-existence of ovarian capsule rupture, pelvic (P) and/or para-aortic (PA) lymph node involvement, and the size and location of extra-uterine metastatic tumors were retrieved from surgical pathology and cytology reports. All of the pathology slides were reviewed by an experienced gynaecologic pathologist.

### Surgical technique

All of the patients underwent laparotomy. Total abdominal histerectomy (TAH) with bilateral salpingo-oopherectomy (BSO), and cytolopathological analysis of ascitic fluid were performed in all cases. Infragastric omentectomy was performed in most cases whereas resection of peritoneal implants by stripping the pelvic, abdominal, and/or diaphragmatic peritoneum was performed in some eligible cases. The decision to perform systematic P and PA lymphadenectomy was determined by the surgical team. No lymph nodes were sampled in some patients, only the P or PA nodes were sampled in some patients, bilateral P lymph node dissection (LND) was applied in some patients, and some patients underwent bilateral P and PA LND. Colorectal, small bowel, and upper abdominal organ resections were also performed when necessary. The general goal was to remove as much of the tumor as possible to achieve optimal cytoreduction, which was defined as residual disease $\leqslant$1 cm according to the Gynecologic Oncology Group (GOG). Staging criteria were determined postoperatively based on the 2009 International Federation of Gynaecology and Obstetrics (FIGO) staging system.

### Neo-adjuvant and adjuvant treatment

The CT regimens were as follows: Patients were administered 3 courses of paclitaxel/carboplatin or docetaxel/carboplatin as neo-adjuvant chemotherapy (NAC) regimens. Paclitaxel was administered at a dose of 175 mg/m2 in association with carboplatin at an area under the curve of 5 or 6 (AUC 5 or 6). Docetaxel was administered at a dose of 75 mg/m2 in association with carboplatin (AUC 5 or 6). Courses were repeated every 3 weeks. Four patients underwent debulking surgery following neo-adjuvant chemotherapy (NAC). To complete the full treatment regimen of 6 cycles, women in the NAC group received 3 cycles postoperatively. The patients who did not undergo NAC, received 6 cycles of CT as adjuvant CT. The reported reasons for primary therapy with NAC were extra-abdominal disease verified by imaging methods and extensive intra-abdominal disease that was deemed unresectable by the primary surgical team. In addition, NAC was administered when the patients could not tolerate radical surgery due to advanced age, poor general condition, and/or the presence of comorbidities. Adjuvant therapy was administered to patients based on stage, age, nodal metastasis status, performance status, and the presence/absence of medical comorbidities.

### Clinical follow-up

The patients returned for follow-up evaluations every 3 months for the first 2 years, every 6 months for the next 3 years, and annually thereafter. Follow-up evaluations consisted of physical and vaginal examinations, vaginal cytology, ultrasound scanning and assessment of serum CA 125 values. Computed tomography or magnetic resonance imaging was performed annually. Progression-free survival (PFS) was defined as the time from the date of primary surgery to the detection of recurrence or the latest observation. Overall survival (OS) was defined as the time interval from the date of surgery to death or last contact.

### Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics 22.0 (SPSS Inc., Chicago, IL). The variables were assessed using visual (histograms, probability plots) and analytical methods to determine whether they were normally distributed. Continuous data (presented as the mean±SD and median [min-max]) were analysed using the Mann-Whitney U test for non-normal data. The chi-square test (Pearson's chi-square and Pearson's exact chi-square tests) was used to compare the proportions between groups. Univariate and multivariate logistic regression models were used to identify the risk factors. The Kaplan-Meier method was used to generate the survival curve, and comparisons were performed with the log rank test. A p-value $<0.05$ was defined as statistically significant.

## Results

A total of 39 patients with OCCC fulfilling the inclusion criteria were included in the present study. The median age at diagnosis was 54 years (range, 34–72 years), and 32 (82%) women were postmenopausal. Abdominal bloating and pain (89.7%) were the most common presenting complaints. Twenty-one patients (53.8%) presented with FIGO stage I disease, 3 (7.7%) with stage II disease, and 15 (38.5 %) with stage III disease. Besides, 24 (61.5%) patients were categorised as early stage (stage I and II) and 15 (38.5 %) patients were categorised as advanced stage (stage III and IV). The median serum CA-125 lev¬el was 269 U/mL (range 7-4031). Majority of the patients (89.7%) had serum CA-125 lev¬els ⩾35 U/ml. All patients had ascites at laparotomy; 26 (66.7%) had <500 cc and 13 (33.3%) had ⩾500 cc. The demographic findings and clinico-pathological characteristics are summarised in table 1.

Among 39 patients, 12 (30.8%) underwent TAH+BSO. Omentectomy were performed in all women except in 3 who had undergone only TAH+BSO. 8 (20.5%) underwent TAH+BSO and P lymphadenectomy, 19 (48.8%) underwent TAH+BSO and P plus PA lymphadenectomy. Optimal cytoreductive surgery was achieved in 26 (66.7%) patients. Adjuvant treatment was administered to 35 patients whereas 4 women (13.2%) received NAC alone who had stage IIIC disease. The median PTD was 8 cm. (range, 3-24 cm). PTD were ⩽8 cm in 11 (28.2%) patients and >8 cm in 28 (71.8%).

In the present study, the univariate analysis pointed out that early stage disease and optimal cytoreduction were the significant prognostic factors for both PFS (p=0.021, and p<0.001, respectively) and OS (p=0.007 and p<0.001, respectively). Multivariate analysis confirmed optimal cytoreduction to be the only independent predictor of OS [Odds ratio (OR) 21.21, 95% confidence interval (CI) 5.25–85.55, (p<0.001)] (Table 2) (Fig 2). No independent factors shown to affect PFS.

The median follow-up period was 51 months (range 4 – 132 months). The 5-year PFS and OS rates for all patients were 47% and 54%, respectively. The 5-year OS rates for women with stage I, II, and III disease were 57%, 50%, and 38.1% (Fig 3). On the other hand the 5-year OS rates for early and advanced stage were 56.4% and 38.1%, respectively. Recurrences developed in 11 (28.2%) patients, of whom 3 had stage I; 1 had stage II, and 7 had stage III disease. There was only one vaginal cuff recurrence. The rest of the recurrences were outside the P cavity (only PA recurrence in 5, peritonitis carcinomatosa in 3, liver recurrence in 1, and PA, supraclavicular and inguinal recurrences in 1 patient).

## Discussion

Ovarian clear cell carcinomas are rare tumors that have poorer outcomes and considered as one of the most aggressive ovarian tumor for they are potentially resistant to traditional platinum-based CT (5,10). In the present study, the median age at diagnosis (54 years) was similar to that reported in many previous studies (11-13). Besides, 15.3 % of patients were nulliparous however nulliparity has been reported to account for more than 50% of all cases in majority of the studies with the exception of the two reports (17% and 45%, respectively) (12,13). The reported incidence of endometriosis in patients with OCCC ranges from 8% to 55% (14-16). In line with the literature (8-55 %), endometriosis has been reported in 20.5 % of patients in our study. The percentage of OCCC patients who presented at stages I and II disease was 61.5 % which has been reported to be significantly higher (53% to 66% of patients with OCCC) compared to other subtypes of EOC (6-8,14,17-19). Five-year survival rates in stages I and II OCCC vary from 50% to 73% in the reported series. In our study, the 5-year OS rates for women with stage I, and II disease were 57%, and 50% respectively.

**Table 1.** Clinical, surgical and histopathological characteristics of the study population (n=39)

| **Characteristic** | **n (%)** |
|---|---|
| Age (years) | 54 [34-72] |
| Menopause | |
| Yes | 32 (82) |
| No | 7 (28) |
| FIGO stage | |
| I | 21 (53.8) |
| II | 3 (7.7) |
| III | 15 (38.5) |
| CA-125 U/mL | 269 [7-4031] |
| PTD | |
| ≤ 8 cm | 11 (28.2) |
| >8 cm | 28 (71.8) |
| Amount of ascitic fluid | 11 (15.4) |
| ≤ 500 mL | 26 (66.7) |
| > 500 mL | 13 (33.3) |
| Optimal cytoreductive surgery | |
| Yes | 26 (66.7) |
| No | 13 (33.3) |
| Recurrence | |
| Yes | 11 (28.2) |
| No | 28 (71.8) |
| PFS | 24 [1-132] |
| OS | 35 [4-132] |

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; PTD, primary tumor diameter; OS, overall survival; PFS, progression-free survival. Values for the continuous variables are median (min-max). Values for the categorical variables are the number/total number of cases (%).

**Table 2.** Univariate and multivariate analysis of overall survival in the patients with ovarian clear cell carcinoma

| Characteristic | Univariate model | | Multivariate model | |
|---|---|---|---|---|
| | | p-value | OR (95% CI) | p-value |
| Age at surgery (≤54 vs. >54 years) | | 0.603 | | |
| PTD | | | | |
| ≤8 cm | reference category | | | |
| >8 cm | | 0.333 | | |
| FIGO stage | | | | |
| early stage | reference category | | | |
| advanced stage | | 0.021 | | |
| Optimal cytoreductive surgery | | | | |
| No | reference category | | reference category | |
| Yes | | <0.001 | 21.21(5.25–85.55) | <0.001 |
| Ascites | | | | |
| ≤500 cc | reference category | | | |
| >500 cc | | 0.274 | | |

Abbreviations: OR, odds ratio; CI, confidence interval; LVSI, lymphovascular space invasion; PTD, primary tumor diameter; MI, myometrial invasion; FIGO, International Federation of Gynecology and Obstetrics. A p-value of <0.05 was considered to be statistically significant.

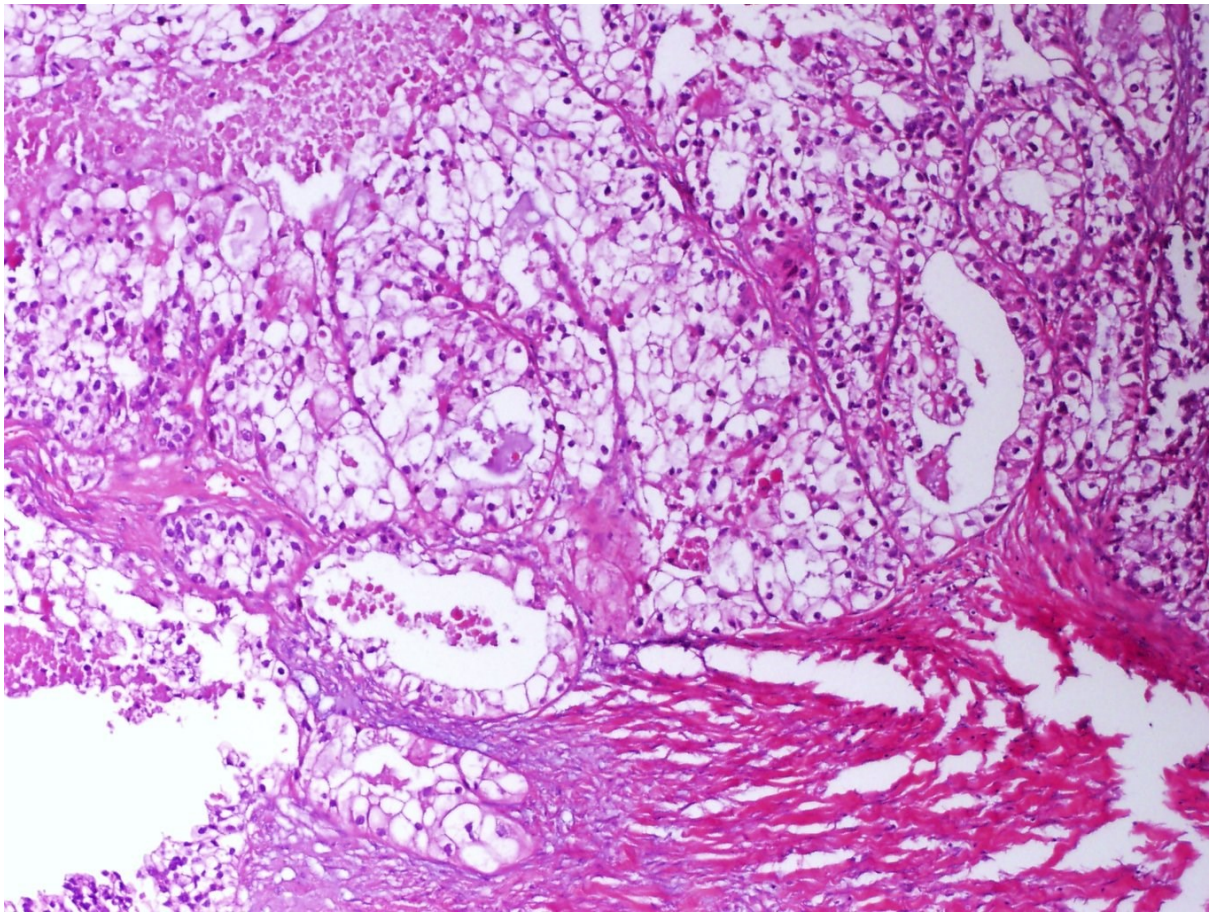

**Figure 1.** Clear cell of the ovary, depicting the characteristic tubulo-cystic histologic pattern (100 ×)

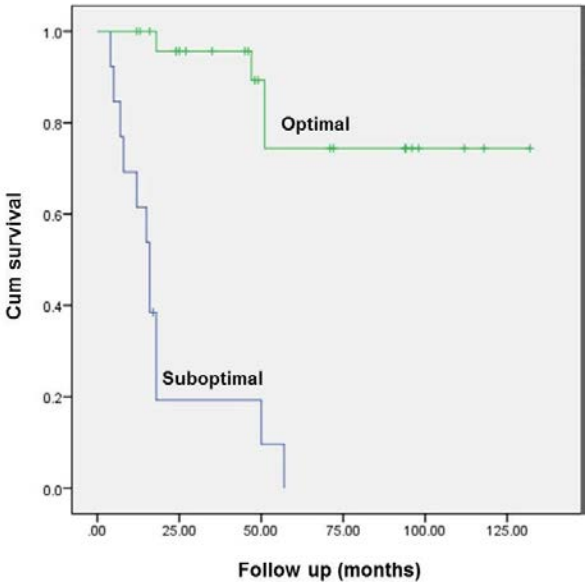


**Figure 2.** Kaplan–Meier curves of the clinical outcome. Overall survival of all patients (n=39) when grouped according to cytoreduction (optimal vs. suboptimal)

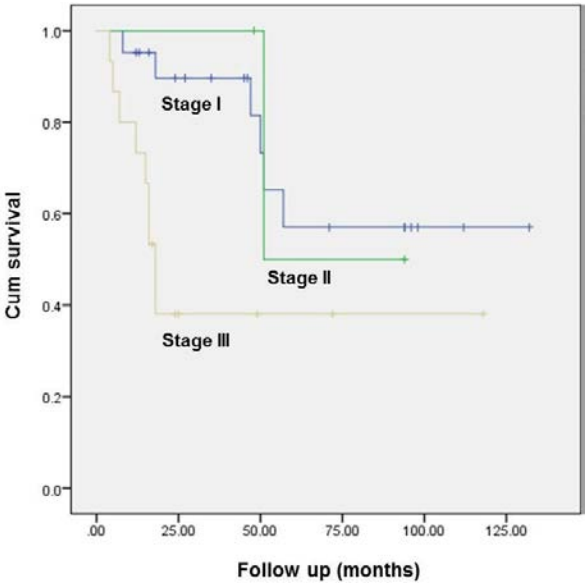


**Figure 3.** Kaplan–Meier curves of the clinical outcome. Overall survival of all patients (n=39) when grouped according to stage

In a study by Mizuno et al. positive cytology, ascitic volume, residual tumor, and serum CA-125 level were the significant factors of survival on univariate analysis (20). CA-125 and residual tumor are popular prognostic factors that have prognostic impact in women with EOC (21-25). However, the low positivity rates of CA 125 in patients with OCCC, makes it a less useful prognostic marker in clinical practice. In the present study, the univariate analysis showed that early stage disease and optimal cytoreduction were the significant prognostic factors. Mizuno et al. have also evaluated the patients with multivariate analysis for the first time in literature and found that early stage, ⩽100 ml ascitic volume, and no residual tumor were independent prognostic factors (20). In our study, less than 1cm residual tumor was considered as optimal cytoreduction and it has been found to be the only independent favorable prognostic factor of OS.

There are some studies suggesting chemoresistant behaviour of OCCC. Behbakht et al. showed that 37% of patients with stage I OCCC who were subjected to platinum-based adjuvant CT relapsed (19). In support of this concept, in another study by Gorai et al. it was pointed out that cell-lines of OCCC have chemoresistence to cisplatin in cell culture (26). Besides, Kita et al. showed that 60% of patients with stage II disease who had macroscopic residual tumor died within 9 months after initial surgery and adjuvant cisplatin-based CT (14).

In the light of the results of previous reports and our study, optimal cytoreductive surgery and the presence of residual tumor have a strong impact on the prognosis of the patients with OCCC owing to the fact that these tumors are mostly chemoresistant. Consequently the general goal should be to remove as much of the tumor as possible to achieve no residual tumor or optimal cytoreduction, and even at an early clinical stage, patients should undergo complete staging surgery.

The limitations of this study are its retrospective nature, and some patients were treated by non-gynaecological oncologic surgeons and therefore patients were treated with different types of surgical approaches over the 15-year time period. Retrospective cohort studies are subjected to selection bias, recall bias, and unknown confounding variables, which may negatively impact the accuracy of the results. Moreover, during the 15-year study period, significant improvements in surgical techniques and adjuvant treatment may have also affected the results.

Lastly, the data did not allow definitive and comparative analyses assessing the heterogeneity of the different adjuvant therapy regimens and the information on chemoresistance was lacking. Despite these limitations, relatively a large number of patients diagnosed with this rare disease, with similar demographic characteristics were included in this study. Besides, good follow-up data were available. Additionally, the surgeries were performed at a single institution, and all pathological slides were reviewed by an experienced gynaecologic pathologist. All of these factors most likely increased the validity of the results and mitigated the limitations.

## Conclusion

Our study demonstrated that optimal cytoreduction to be the only independent prognostic factor for survival in women with OCCC. Considering the chemoresistant behaviour of OCCC, complete staging surgery and optimal cytoreduction surgery remains the primary treatment modality. Therefore, quality of life issues, operability and the most appropriate and effective treatment regimens should also be considered for management. Further improvements in survival rates require the optimization of adjuvant therapy modalities.

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# The effects of 2-aminoethyl diphenylborinate on L-Arginine induced acute pancreatitis in the rats

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## Abstract

**Objective:** The aim of the study is to investigate the protective effect of 2-aminoethyl diphenylborinate on an acute pancreatitis model through an experimental study.
**Materials and Methods:** 30 Spraque-Dawley male rats were randomly divided into three groups: Sham, Pancreatitis and Pancreatitis + 2-APB. Pancreatitis was induced by L-arginine administration. The therapeutic agent 2-APB was enjected i.v. at a dose of 2 mg/kg 10 min before pancreatitis induction. From blood samples, superoxide dismutase (SOD), malondialdehyde (MDA), total antioxidant capacity, tumor necrosis factor alpha, interleukin-6, aspartate aminotransferase , alanine aminotransferase and creatinine levels were measured and the rats were sacrificed subsequently. Tissue samples were evaluated histopathologically. TUNEL staining method was used to visualize apoptotic cells.
**Results:** 2-APB significantly reduced serum MDA and creatinine levels in pancreatitis + 2-APB group. Unfortunately, SOD levels reduced significantly, too. Edema and hemorrhage in pancreatic tissue were lower, necrosis and fibrosis were higher in the 2-APB administered group. Additionally, in 2-APB given group, it was found that vacuolisation, epithelial desquamation, and congestion reduced in renal tubular epithelial. The number of apoptotic cells did not change in the pancreatic tissue in TUNEL staining.
**Conclusions:** 2-APB reduces renal damage caused by acute pancreatitis. However, protective effect has not been on pancreatic tissue with 2-APB administered group. Although 2-APB, which was shown to prevent the degradation of kidney functions due to pancreatitis, do not minimize the pancreas tissue damage, it can improve the prognosis of pancreatitis by reducing the damage of distant organs

**Key words:** 2-aminoethyl diphenylborinate, acute pancreatitis, kidney, oxidative stress, antioxidants

## Introduction

Acute pancreatitis is a nonbacterial inflammatory process which may affect pancreas, peripancreatic tissues and distant organs. Normally, it is self-limiting but it sometimes may lead to serious medical conditions such as systemic inflammatory response syndrome, sepsis, multiple organ failure and death (1). Some factors such as age, ischemia-necrosis and comorbid diseases affect the prognosis. Another factor affecting the prognosis is the increase of oxygen free radicals (ROS). ROS affects prognosis by causing damage to both pancreas and distant organs (2).

Intracellular and mitochondrial Ca2 + concentrations, which increase in relation to ATP concentrations decreasing during ischemia, play an important role in ischemic cell damage and ROS increase (3). Store-operated calcium channels (SOCs) are the members of ion channel family that enables the transition of Ca2 + to the intracellular space and located in the membrane of many cells (3-6). 2-aminoethyl diphenylborinat (2-APB) inhibits the entry of calcium into the cell from the extracellular space by blockading SOCs (4). Additionally, it prevents ischemic cell damage by contributing to intracellular calcium hemostasis.

In some studies conducted earlier, it was mentioned that SOCs blockade of renal efferent arteriole myocytes increases blood flow by doing vasodilatation (6, 7). However, in this experimental study, the effect of 2-APB on acute pancreatitis was examined. Our hypothesis was that the 2-APB can

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provide vasodilation in pancreatic arterioles through SOCs channel blockade, which may be useful over the course of pancreatitis by increasing pancreatic blood flow. Thus, we expected to have an antioxidant effect. In our study, as a sign of the protective effect, the biochemical markers of antioxidant activity in serum samples were primarily measured. And then histopathological examination was conducted.

## Materials and Methods

### Chemicals

2-APB (Sigma-Aldrich), L- arginine (Sigma-Aldrich), ketamin (Ketalar-Pfizer) and xylazine (Alfazyne, EGE-VET)

### Animals and treatment protocol

The approval of Çanakkale onsekizmart University Ethical Committee of Animal experiments was granted before the study was conducted. Animals were allowed ad libitum access to food and drink up to the study. In addition, animals were treated humanely throughout the protocol according to national health institution guidelines and rules about the care and use of laboratory animals.

30 Spraque-Dawley male rats were randomly divided into three groups: Sham, Pancreatitis and Pancreatitis + 2-APB. Pancreatitis was induced by 2 doses of 1,5 g/kg of L-arginine which was administered intraperitoneally at a 1 hour interval. The therapeutic agent 2-APB was used intravenous at a dose of 2 mg/kg 10 min before pancreatitis induction. Anesthesia was performed with i.m. ketamine/xylazine (90/10 mg/kg) injection. All rats were sacrificed in 24 h after experimental procedure. After this, blood samples were collected through inferior vena cava, kidney-pancreas was excised, and the rats were sacrificed subsequently. Superoxide dismutase (SOD), malondialdehyde (MDA), total antioxidant capacity (TAS), tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and creatinine levels were measured from blood samples, Renal and pancreatic tissue samples were evaluated histopathologically. Apoptotic cells visualization was evaluated by TUNEL staining method.

### Proinflammatory cytokines, Antioxidant enzymes, MDA, AST, ALT and creatinine measurement

Blood samples were kept for 2 h at room temperature to ensure proper clotting. The samples were then centrifuged at 2500 g at 4 ºC for 15 min and stored at -20 °C until analysis.

Double sandwich Elisa kits (eBioscience USA) were used to measure serum concentrations of tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6). The samples were incubated with xanthine oxidase solution for 1 h at 37 °C to measure SOD activity in serum. Absorbance was read at 490 nm to generate superoxide anions. SOD activity was determined as the inhibition of chromagen reduction. In the presence of SOD, superoxide anion concentration reduced by yielding less colorimetric signal. SOD activity was shown in %. Lipid peroxidation was determined using the procedure described by Yoshioka et al (8), in which MDA, an end product of fatty acid peroxidation, reacts with TBA to form a colored complex with a maximum absorbance at 532 nm. TAS of the serum was determined by using an automated measurement method with a commercial available kit developed by Rel. The antioxidative effect of the sample against the potent free radical reactions initiated by the reduced hydroxyl radical was measured by this method. The results were explained as mmol Trolox equiv/L. ELISA plates were measured using a microplate reader at 450 nm. Serum ALT (Archem, A2221, Istanbul, Turkey) and AST (Archem, A2212, Istanbul, Turkey) activities were measured by commercial available kits at a Biochemistry Auto Analyzer (Sinnowa D280, China). Likewise, serum creatinine (Archem, A2162, Istanbul, Turkey) levels were measured similarly by using commercial available kits at the same Auto Analyzer.

### Histological analysis

Kidney and pancreas tissue specimens were sliced transversely, fixed in formalin solution (10%), dehydrated in alcohol and embedded in paraffin. Sections at 5-µm thick were taken using a microtome and stained with hematoxylen-eosin. A pathologist who was blind to the groups examined the specimens and investigated dispersion of kidney and pancreas.

### TUNEL staining for detection of apoptotic cells

Apoptotic cells in the pancreas sections were identified using TUNEL assay by an observer who was blind to the group assignments. TUNEL staining was performed using a TUNEL assay kit according to the manufacturer's instructions (ApopTaq Peroxidase In Situ Apoptosis Detection Kit; S7101-KIT, Millipore) decrease.

### Statistical Analysis

Data was presented as means ± SD. All statistical analyses were performed on SPSS 20.0. The one-way ANOVA was used to test for differences among groups. Tukey's HSD test was used for multiple comparisons. P values $< 0.05$ were considered significant.

Table 1: The mean levels of serum samples and statistical results in all experimental groups

| Groups | SOD (%) | MDA (mmol/L) | TAS (mmol trolox equiv./L) | TNF-α (pg/mL) | IL-6 (pg/mL) |
|---|---|---|---|---|---|
| **Sham** | 64,75±1,32 | 15,34±0,67 | 2,20±0,25 | 31,04±6,80 | 15,01±3,81 |
| **Pancreatitis** | 66,68±0,80* | 24,08±5,49* | 2,30±0,24 | 23,79±1,47* | 19,39±2,08* |
| **Pancreatitis+2 APB** | 61,60±2,29*† | 19,70±2,17*† | 2,41±0,16 | 22,46±2,60* | 16,51±2,98 |

Results are expressed as the mean ± standard deviation. * P < 0.05 compared with the sham group.
† P < 0.05 compared with the pancreatitis group.

Table 2: The mean levels of serum samples and statistical results in all experimental groups

| Groups | AST (U/L) | ALT (U/L) | Creatinine (mg/dL) |
|---|---|---|---|
| **Sham** | 224,50±36,73 | 83,80±43,17 | 0,43±0,06 |
| **Pancreatitis** | 122,10±44,32* | 48,30±11,70* | 0,58±0,06* |
| **Pancreatitis + 2 APB** | 79,00±9,51*† | 48,50±4,95* | 0,45±0,06*† |

Results are expressed as the mean ± standard deviation. * P < 0.05 compared with the sham group.
† P < 0.05 compared with the pancreatitis group.

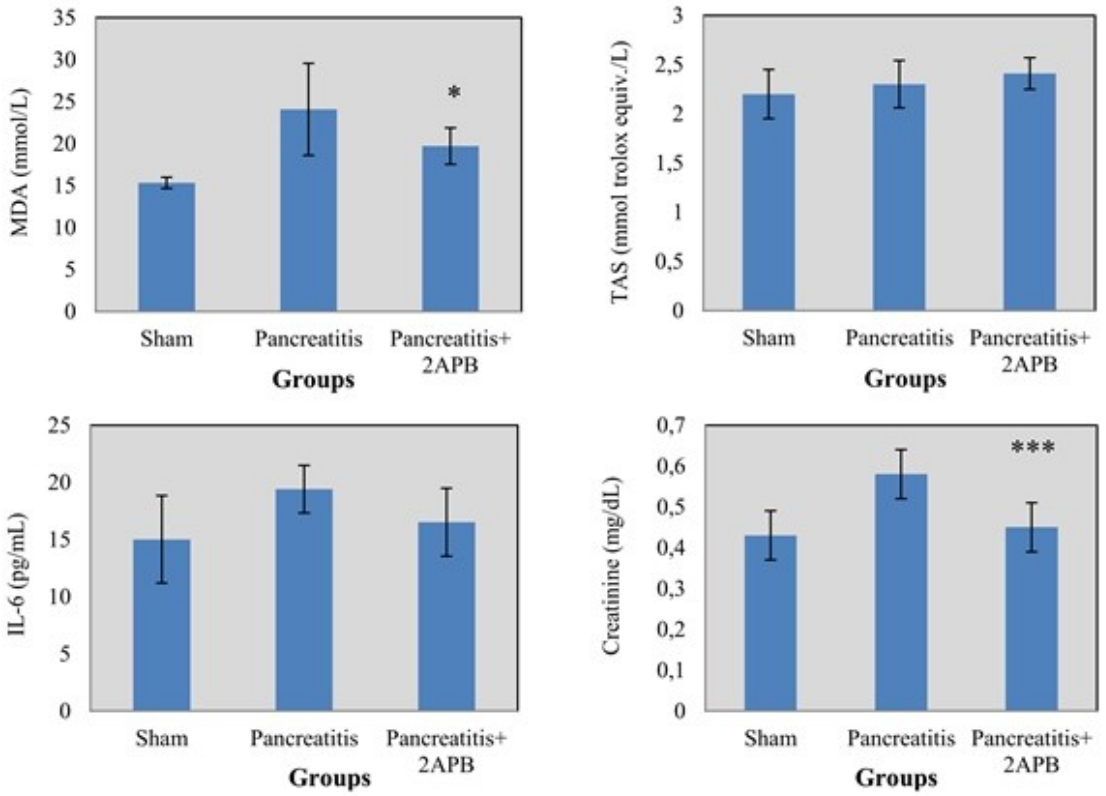


**Figure 1.** Mean serum MDA, TAS, IL-6, and Creatinine levels in all experimental groups. Data are expressed as the mean ± standard deviation. *P < 0.05 compared with the Pancreatitis group, ***P < 0.001 compared with the Pancreatitis group.

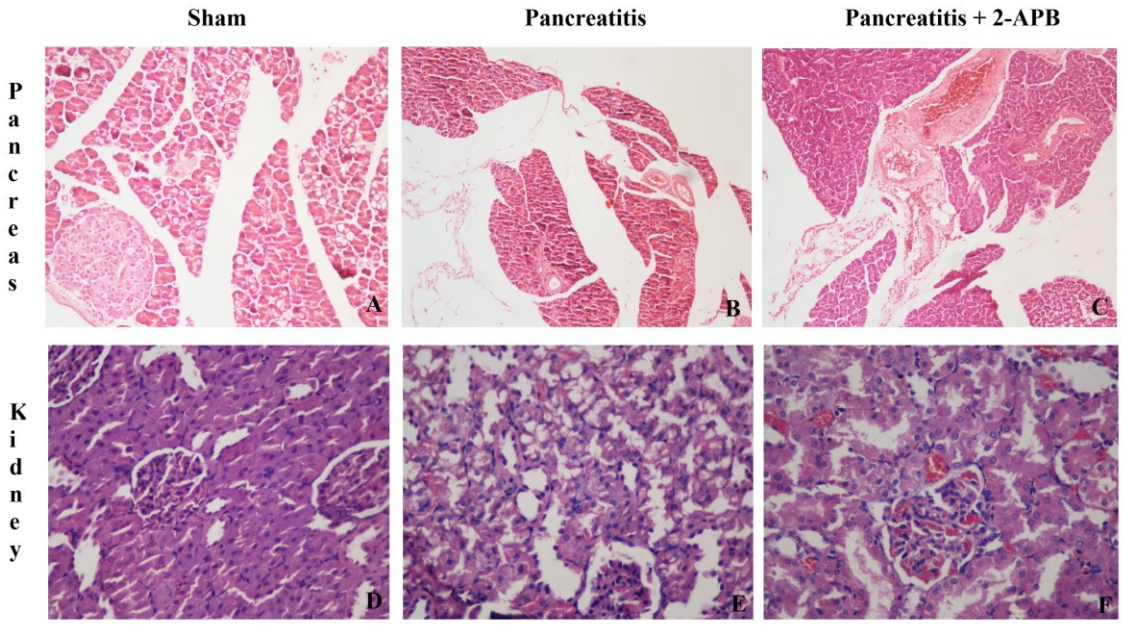


**Figure 2.** Histopathologic examination with hematoxylin-eosin of pancreatic tissue shown in images (A), (B) and (C) (magnification, X200, X100 and X100 respectively ). Kidney tissue shown in images (D),(E) and (F) (magnification, X400).

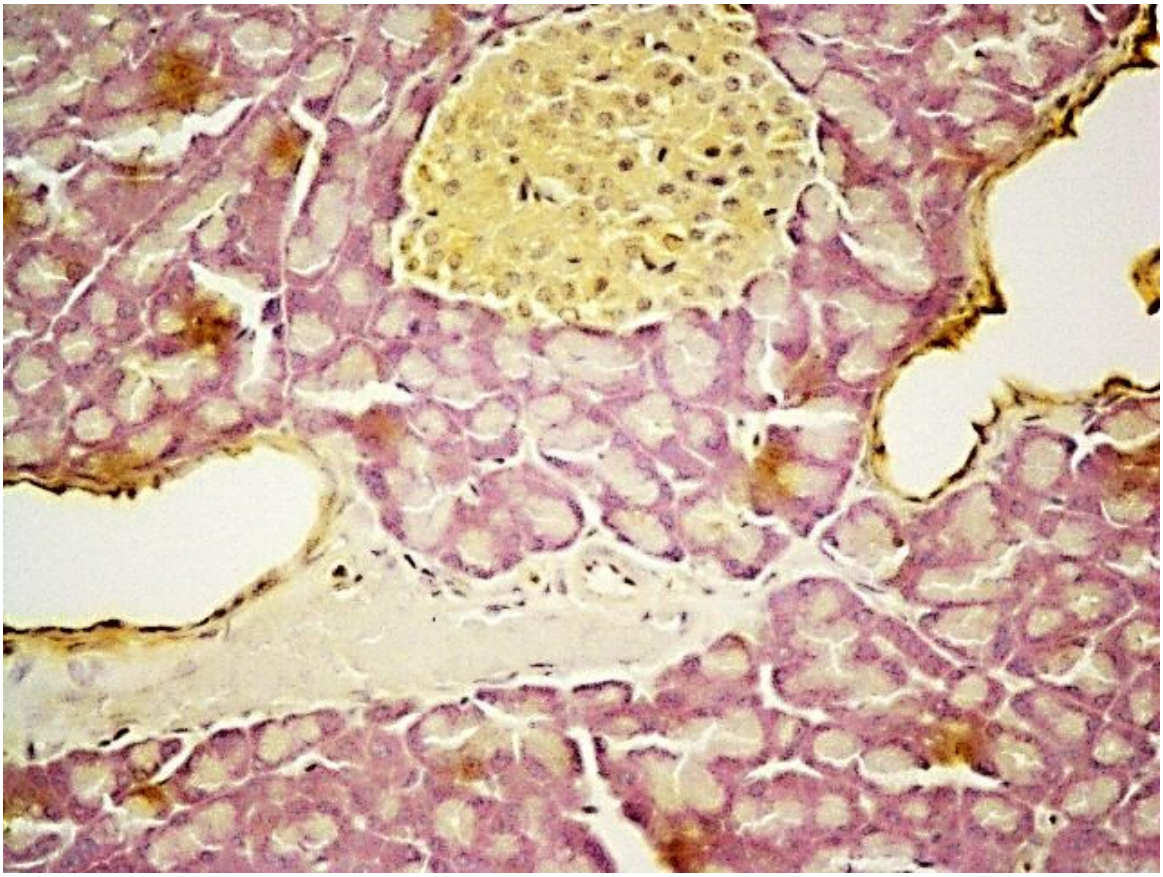

**Figure 3.** TUNEL analysis for apoptotic cells in Pancreatitis group. TUNEL-positive cells were not encountered (magnification, X400).

## Results

**The effect of 2-APB on TNF-α and IL-6 levels**

Mean values of TNF-α in the serum were significantly lower in the pancreatitis group than in the sham group (p=0.002). Mean values of IL-6 in the serum were significantly higher in the pancreatitis group than in the sham group (p=0.009). The pancreatitis induced increase in IL-6 and it was attenuated in the 2-APB administrated group (p= 0.105). However, decrease in TNF-α was relatively induced (Table 1 and Figure 1).

**The effect of 2-APB on SOD, TAS and MDA levels**

Mean levels of SOD and TAS in the serum were higher in the pancreatitis group than in the sham group (p=0.030 and p=0.557, respectively). Pancreatitis induced increase in TAS induced in the 2-APB administrated group (p=0.542). However, SOD levels decreased (p<0.001). Mean levels of MDA in the serum were higher in the pancreatitis group than in the sham group (p<0.001). The pancreatitis that induced increase in this marker was significantly attenuated in the 2-APB administrated group (p=0.021) .The results are shown in Table 1 and Figure 1.

**The effects of 2-APB on AST, ALT, creatinine levels and histopathological results**

AST and ALT levels in the serum were lower in the Pancreatitis group than in the sham group (p<0.001 and p=0.013, respectively). AST levels were significantly lower in the group administrated 2-APB compared to the pancreatitis group (p=0.021). However, levels of ALT did not change (p=1.000), (Table 2). Mean serum level of creatinine was significantly elevated in the pancreatitis group compared to the sham group (p<0.001). Serum levels of creatinine significantly decreased in 2-APB administrated group compared to the pancreatitis group (p<0.001), (Table 2 and Figure 1).

Examination of pancreatic tissue sections stained with hematoxylen and eosin in the pancreatitis group revealed edema, hemorrhage, leukocyte infiltration. Edema and hemorrhage in pancreatic tissue were lower, while necrosis and fibrosis were higher in the 2-APB administered group. Examination of kidney tissue sections stained with hematoxylen and eosin in the pancreatitis group revealed vacuolization and desquamation of tubular epithelial cell and bleeding around the intertubular region and blood vessels. Severity of kidney tissue damage in the group administered 2-APB was lower than in the pancreatitis group (Figure 2).

***Effects of 2-APB on TUNEL staining***

TUNEL-positive cells were not encountered in the pancreas from pancreatitis group (Figure 3).

## Discussion

2-APB reduces renal damage caused by acute pancreatitis. However, protective effect has not been on pancreatic tissue. Results of the present study have demonstrated that 2-APB can be used as an effective agent for reducing distant organ injury on pancreatitis as 2-APB significantly reduced creatinine levels in this study.

Up to now, several experimental pancreatitis models have been proposed and various drugs have been tested in order to reduce morbidity and mortality in acute pancreatitis. One of these models is formed with L-Arginine (9). Rakonczay Z et al. explained 300 mg/100 g as an appropriate dose for L-arginine in the induction of severe acute pancreatitis (10). Thus, 300 mg/100 g dose L-arginine was used to form acute pancreatitis in our study.

The pathogenesis of acute pancreatitis is multifactorial. It is stated in the studies that excessive production of oxygen free radicals and increase in cytokine levels are effective in the pathogenesis (2). Excessive production of ROS may damage cells by causing protease activation and lipid peroxidation. In this study, it was found that MDA level, which is an indicator of lipid peroxidation, decreased by means of 2-APB treatment (11).

Endogenous antioxidants such as SOD and endogenous antioxidant systems that involve these components protect cells from ROS damage. When ROS production increases, levels of antioxidant systems decrease (12). In our study, TAS levels increased once 2-APB was given.

In the studies conducted, it has been demonstrated that ROS causes the release of proinflammatory cytokines by stimulating macrophage, and these cytokines induce the inflammatory response which increases tissue damage. Proinflammatory cytokines such as TNF-α and IL-6 have an important role in the damage occurring in both tissue and distant organs by inducing polymorphomononuclear leukocytes activation and infiltration (13). In our study, only IL-6 levels decreased with 2-APB treatment.

Excessive ROS, proinflammatory cytokine release, or hypovolemia can cause kidney damage in acute pancreatitis (14). In our study, it was discovered that vacuolisation in renal tubular epithelial, desquamation and congestion in intertubular regions increased after pancreatitis. However, it was observed that the complaints decreased with 2-APB treatment. Additionally, after pancreatitis, it was seen that renal functions impaired probably due to increased systemic renal tubular injury, which caused an increase in serum creatinine levels. However, with 2-APB treatment, significant reduction of creatinine levels was observed.

## Conclusions

It was revealed in this study that the presence of 2-APB showed antioxidant activity in acute pancreatitis. However, the protective effect of this activity on pancreas was not shown in this study. Although 2-APB, whose protective effect on the degradation of kidney functions caused by pancreatitis was demonstrated, cannot minimize damage in pancreas tissue, it can improve the prognosis of pancreatitis by reducing the damage distant organs.

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**Conflict of interest statement:** Authors declare that there is no financial support or relationships that may pose potential conflict of interest.

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# Anomalous origin of left coronary artery from pulmonary artery; Congenital anomaly presenting with dyspnea. A rare case study

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## Abstract

Anomalous origin of left coronary artery from pulmonary artery (ALCAPA) is rare congenital anomaly. Most of these patients die is infancy. Presentation in adulthood is very rare. Clinical manifestation in teenagers or young adult contains arrhythmia, myocardial perfusion likely causes significant chest pain and these symptoms of myocardial ischemia may be misinterpreted as routine infantile colic and sudden death.

**Keywords:** Anomalous origin of left coronary artery from pulmonary artery

## Introduction

Anomalous origin of left coronary artery from pulmonary artery (ALCAPA) is a rare lesion with an estimated incidence of between 1 in 30000 and 1 in 300000. It is frequently lethal in early infancy with some reports suggesting a mortality rate as high as 90% in first year of life.

## Case

Our case is an adult survivor of ALCAPA diagnosed at our hospital. The patient is a 55 years old female with history of effort dyspnoea (FC=II) from a few years ago. Patient has history of 12 time gestation 8 deliveries without any problem. Physical examination was normal only an II/VI systole murmur auscultate in left sternal border. Vital sign was normal. CXR was not remarkable. ECG was normal. Two dimensional echo revealed moderate mitral regurgitation and moderate left ventricular dilatation and mild LV dysfunction with EF about 45-50%, but it not seen any clue of ALCAPA. Then patient went for coronary angiography that revealed typical anatomy of ALCAPA. On cardiac CT angiography, typical anatomy of ALCAPA was detected.

## Discussion and Conclusion

ALCAPA is rare lesion with an incidence of about 1 in 100000 accounting for 0.25% of congenital heart disease(1). The anomalous left main connects most often to the sinus of Valsalva immediately above the left of posterior cups of pulmonary trunk and rarely from that above the right cup. Collateral between right & left coronary arteries always presents and grossly visible mainly is adults. Left ventricle is always hypertrophied and greatly dilated. Diffuse LV fibrosis is always present and patients dying in infancy usually leave evidence of anterolateral myocardial infarction. A considerable amount of LV dysfunction in infants must be ischemic in origin. There are some reasons for mitral regurgitation. There may be extensive fibrosis and sometime calcification in papillary muscles. Endocardial fibro-elactosis may involve mitral valve (2).

In patients who survive into adulthood, collateral circulation from right coronary artery is apparently adequate to prevent sever left ventricular failure (3). Presentation is often delayed beyond age 20 years. About half have effort dyspnoea. Occasionally a mitral regurgitation dominates clinical picture. Resting ECG is always abnormal with ST-T segment changes or evidence of old anterolateral infarction. Exercise ECT usually shows ischemic changes thallium is usually abnormal. CXR may be normal or shows cardiomegaly (4). Echocardiography (2-D) is the principle tools for diagnosis.

It may show enlarged RCA or dilated LV or abnormal regaining of LM from pulmonary trunks. Angiography shows more collateral in adults than infants and shows near normal or mildly decreased LV function. Coronary angiography is considered the gold standard technique for diagnosis (5). Most patients who survive infancy continue to be at risk of death from chronic heart failure and those who survive until the fourth decade occasionally die suddenly once diagnosis of ALCAPA is established.

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Early surgical correction including difference type of construction a two artery coronary system for prevention of complication and increase of survival is indicated (6).

**Conflict of Interest:** The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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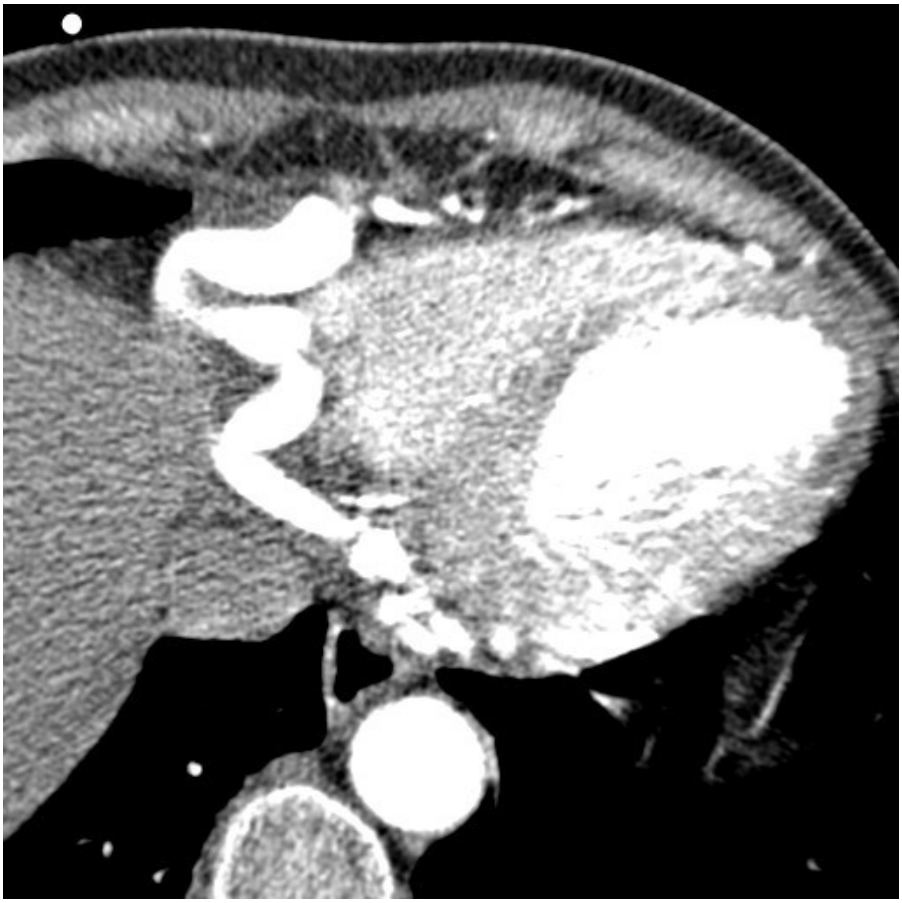

**Figure 1.** Computed Tomographic angiography showing dilated right coronary artery with continuation with left coronary artery.

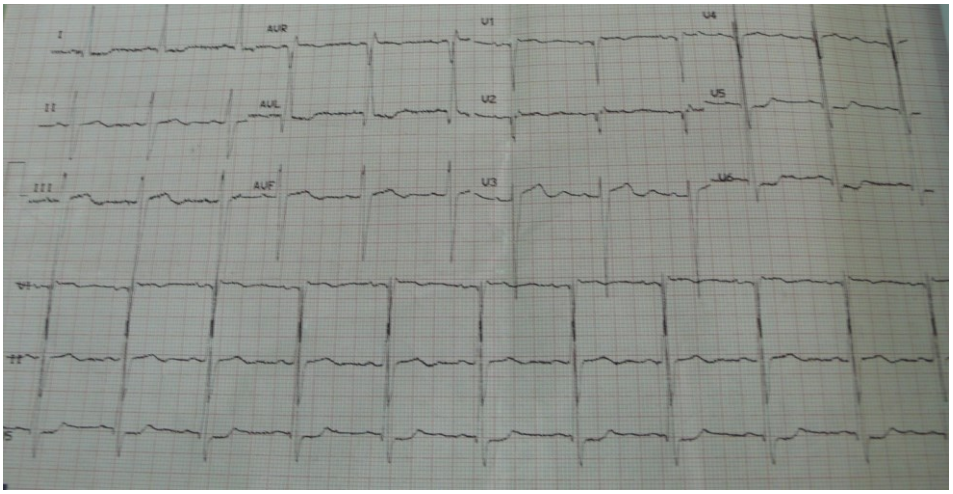


**Figure 2.** ECG is showing normal pattern view.

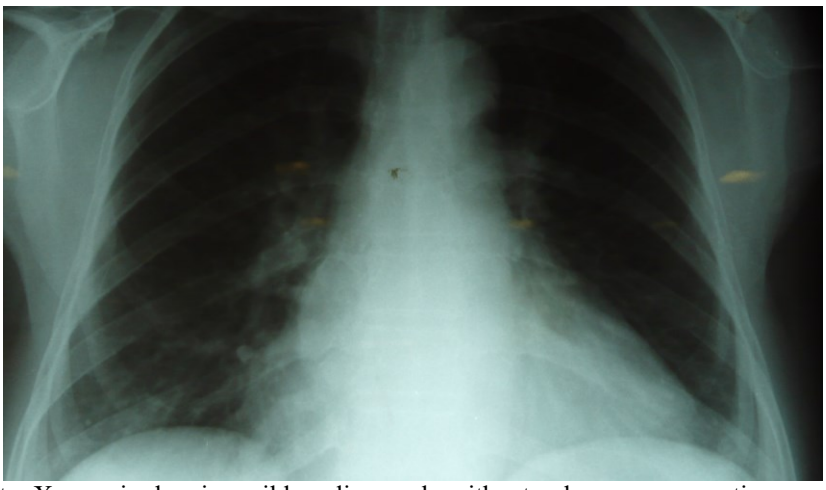

**Figure 3.** Chest – X – ray is showing mild cardiomegaly without pulmonary congestion.

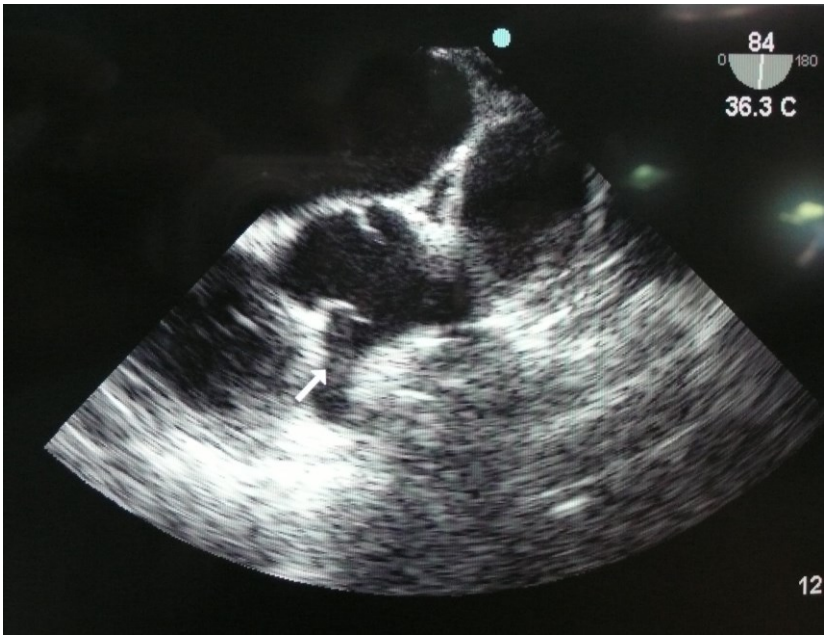


**Figure 4.** Trans – Thorasic – Echocardiography shows dilated right coronary artery without evidence of left coronary artery.

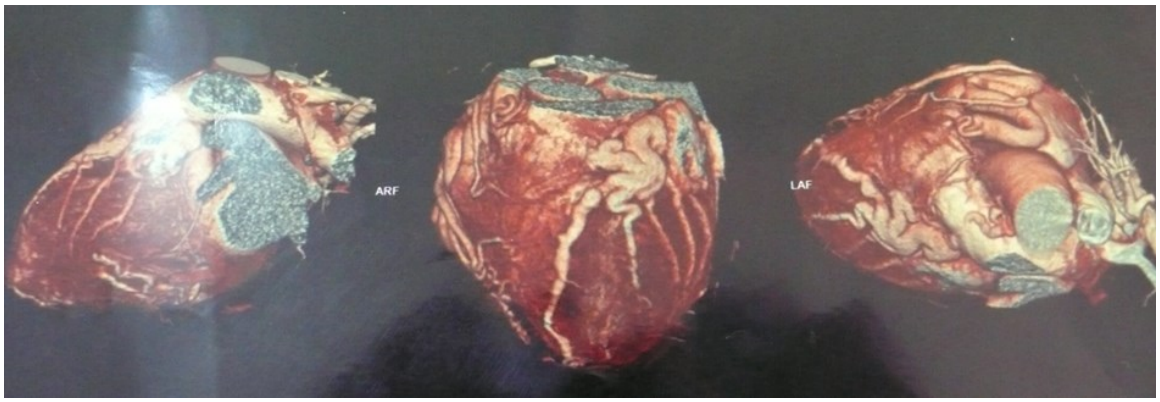


**Figure 5.** Comptuded tomographic angiography shows much dilated right coronary artery with normal origin of aorta and abnormal origin of left coronary artery from pulmonary artery.

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# Approach to hydatid cyst rupture patient who administered with anaphylactic shock

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## Abstract

Hydatid cyst is a parasitic disease, which can involve liver, lungs, spleen, kidneys, orbita, heart, brain and bones. In case of rupture it can cause anaphylactic reactions, shock and cardiovascular collapse. Cyst hydatid is a very common health problem in our country among 30-50 year-old males therefore it is essential to include it in the differential diagnosis idiopathic anaphylactic shock.

**Key words:** Hydatid cyst rupture, Anaphylactic shock

## Introduction

Hydatid cyst is a parasitic disease, caused by Echinococcus granulosus, which can involve liver (%85-90), lungs (%10-30), spleen (%10), kidneys, orbita, heart, brain and bone and in case of rupture it can cause anaphylactic reactions, shock and cardiovascular collapse (1-6).

## Case

In this study we present a 34 year-old male with no known systemic disease who was admitted with loss of consciousness, erythematous rashes, which do not fade with palpation, 70/50 mmHg arterial blood pressure, generalized edema, and no response to pain and no peripheral pulse. Patient had spontaneous eye opening.

He was administered 1mg intravenous adrenalin twice, was oxygenized and given intravenous fluid and admitted to the ICU (Intensive Care Unit) where he was administered intravenous 1.5mg/kg methyl prednisolone and 45.5mg feniramin maleate.

Skin lesions were regressive over the umbilicus and there was generalized distension over the abdomen. White cell count was 27.000/mm3, AST:201 U/L, ALT:237 U/L. After patient became hemodynamically stable ultrasound investigation was made and cystic lesions with septas (78x92mm in the left lobe of the liver and 113x98,2mm in the spleen) were detected.

Immediate surgery was planned. Patient was administered 1 mg/kg lidocain HCL, 2 mg/kg propofol, 0.6 mg/kg esmeron, 1 µcg/kg fentanyl and was intubated. Maintenance of anesthesia during surgery was provided with %2 sevoflurane in $\%50O_2/50N_20$. Cystectomy was performed in the liver and was irrigated with %3 NaCl. It was detected that the cyst, which involved the entire splenic fossa, was ruptured and splenectomy was performed. At the end of surgery, inhalation anesthetics were terminated. Skin lesions returned to normal, patient opened his eyes spontaneously within 4 minutes and after his respiration became sufficient he was transferred to ICU. In postoperative 36th hour the abnormalities in the hemogram and blood biochemistry recovered and patient was discharged.

## Discussion and Conclusion

Spontaneous, intraoperative or posttraumatic rupture of cyst hydatid causes fluid with highly antigenic features to mix into the circulation and cause anaphylactic shock (**3-6**). Cyst hydatid is a very common health problem in our country among 30-50 year-old males. We are in the opinion that it is important to include hydatid cyst rupture in differential diagnosis of idiopathic anaphylactic shock

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# The significance of lower extremity FDG PET/CT imaging in patients with unknown primary tumor

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## Abstract

If a suspicious finding for primary site of an unknown primary tumor (UPT) is found in limited whole-body FDG PET/CT imaging area, imaging of lower extremities is generally not performed in routine practice. This approach may not be true. In this case, FDG PET/CT imaging was performed in patient with UPT. The limited whole-body FDG PET/CT images showed an increased FDG uptake in a thyroid nodule which was seemed to be a primary lesion at first sight. But similar FDG PET/CT findings might be observed in benign thyroid nodules. So we also acquired FDG PET/CT images of the lower extremities. Then, a mass showing increased FDG uptake was seen in the left thigh. On histopathologic examination, the thyroid nodule was found to be benign and the left thigh mass was diagnosed with a malignant (hemangiopericytoma). This case demonstrates contribution of lower extremity FDG PET/CT imaging to detection of primary site of UPTs in suspected situations

**Key words:** Positron emission tomography, unknown primary tumor, field of view, lower extremity, hemangiopericytoma

## Introduction

Unknown primary tumor (UPT) is described as a proven malignity with unidentified primary origin (1). UPTs account for approximately 5% of all malignancies and it is the fourth most common cause of death from cancer (2,3). Diagnosis of the primary origin is essential for the treatment of the patient. Nowadays, 2-(18F) fluoro-2-deoxy-D-glucose (FDG) positron emission tomography/computed tomography (PET/CT) whole-body imaging is widely used for this purpose (1). Even though FDG PET/CT is entitled as whole-body imaging, the scanning is routinely performed between the base of skull and upper-mid thigh (4). Nevertheless, it is the right approach to image true whole-body in case of tumors having high risk for the involvement of scalp, skull, brain, or lower extremities (5). In this report, we aimed to emphasize that the significance of adding lower extremity to the FDG PET/CT imaging area in patients with UPT

## Case

The patient was a 60-year-old female with complaints of cough, exhaustion, and weight loss for two months.

Thorax CT scan revealed multiple regular-bordered and round-shaped bilateral pulmonary nodules, of which the largest one had a diameter of 15 mm. The nodules had been thought to be metastatic, and FDG PET/CT scanning was performed for the metabolic characterization of the nodules and also for the diagnosis of a potential primary tumor. The limited whole-body FDG PET/CT images showed multiple bilateral pulmonary nodules, in which the largest one had a dimensions of 17x15 mm and a maximum of standardized uptake value (SUVmax) of 4 (Figure 1). Also, an increased FDG uptake was seen in a regular-bordered and round-shaped left lobe thyroid nodule with the dimensions of 10x10 mm and a SUVmax of 6.1 (Figure 2 and 3).

Although the thyroid nodule seemed to be a primary lesion at first sight, it was possible to observe similar FDG uptake patterns on PET/CT in benign thyroid nodules. Therefore, the FDG PET/CT images of the lower extremities were also acquired. A lobulated mass with millimetric calcifications between the posterior thigh muscles in the left lower extremity with the dimensions of 75x54x114 mm and increased heterogeneous FDG uptake with a SUVmax of 10 were seen (Figure 3 and 4).

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Fine needle aspiration biopsy was taken from the thyroid nodule. On thyroid fine needle aspiration cytology examination, although the aspiration material was hypocellular, the thyrocytes seen were benign. (Figure 5).

The thigh mass was gone to fine needle aspiration cytology first and it was excised totally. Then it was diagnosed histopathologically as intermediate grade malignant soft tissue sarcoma in the structure of hemangiopericytoma (Figure 6).

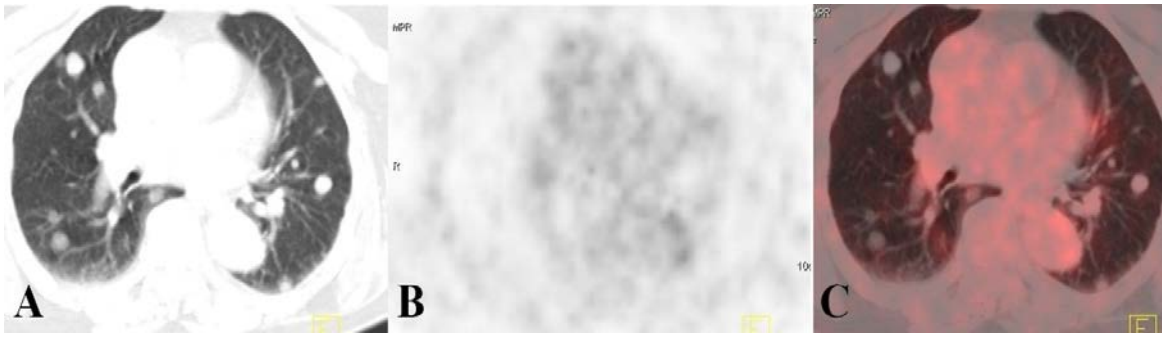


**Figure 1.** Multiple bilateral pulmonary nodules on axial CT (A), PET (B) and PET/CT (C) images.

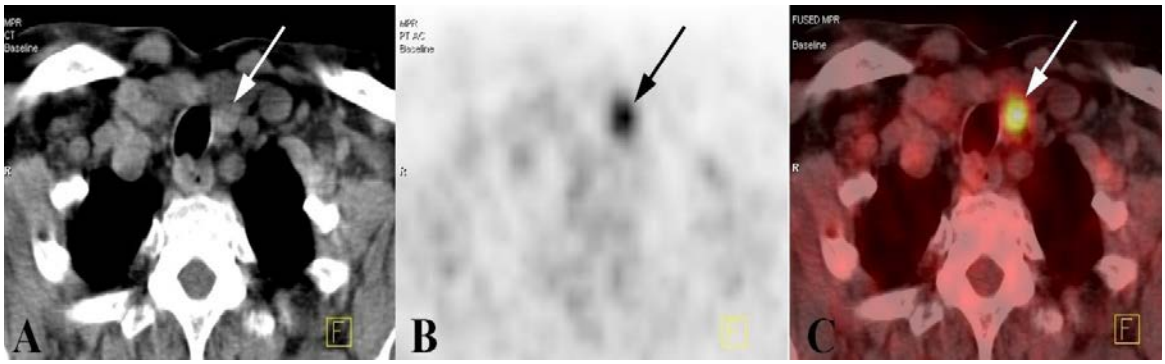


**Figure 2.** Thyroid nodule in the left lobe on axial CT (A), PET (B) and PET/CT (C) images (arrows).

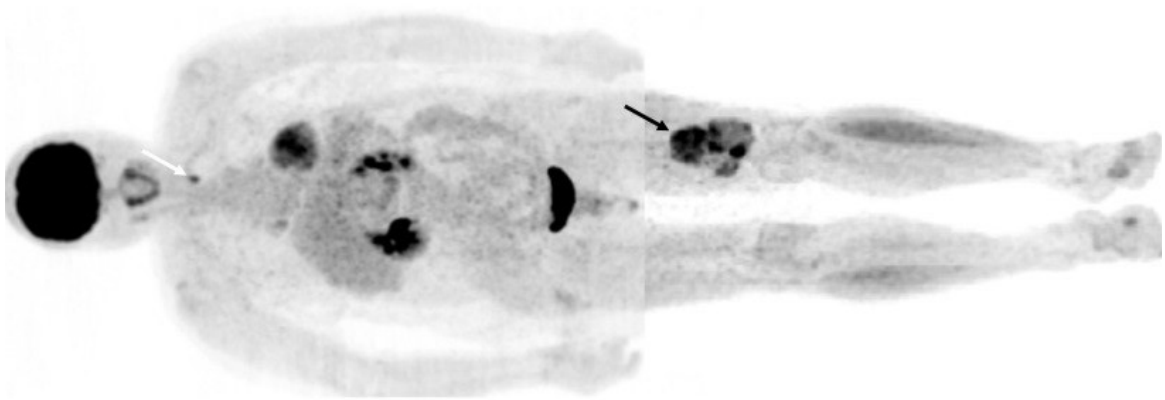

**Figure 3.** Maximum intensity projection (MIP) image of the patient. White arrow shows thyroid nodule in the left lobe and black arrow shows lobulated mass between the posterior thigh muscles in the left lower extremity.

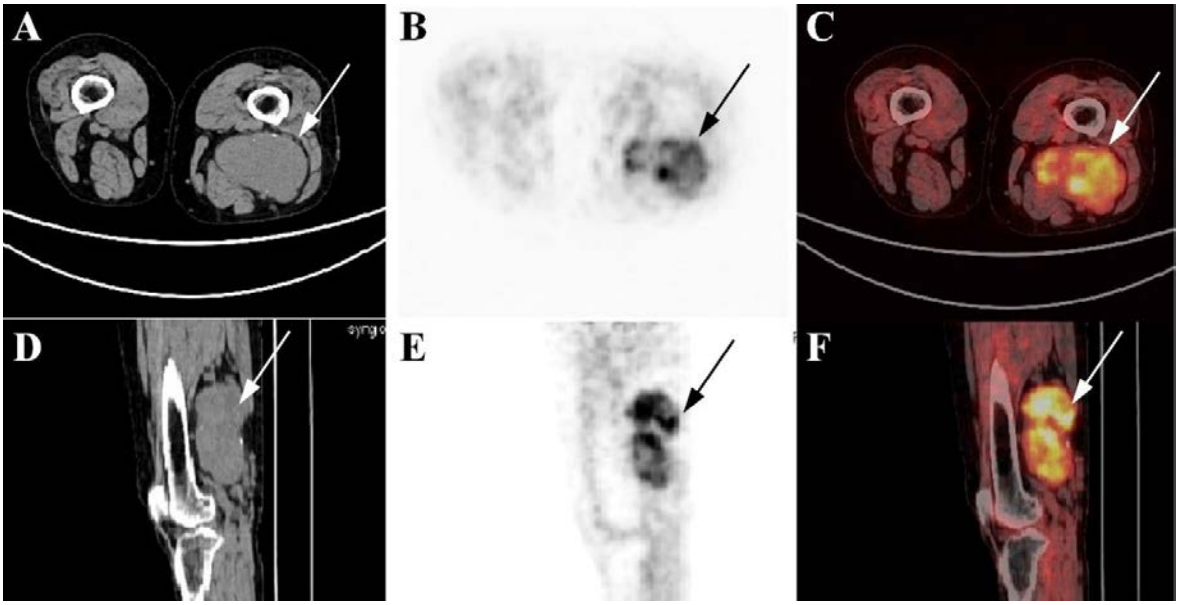


**Figure 4.** Lobulated mass between the posterior thigh muscles in the left lower extremity on axial CT (A), PET (B), PET/CT (C) and sagittal CT (D), PET (E) and PET/CT (F) images

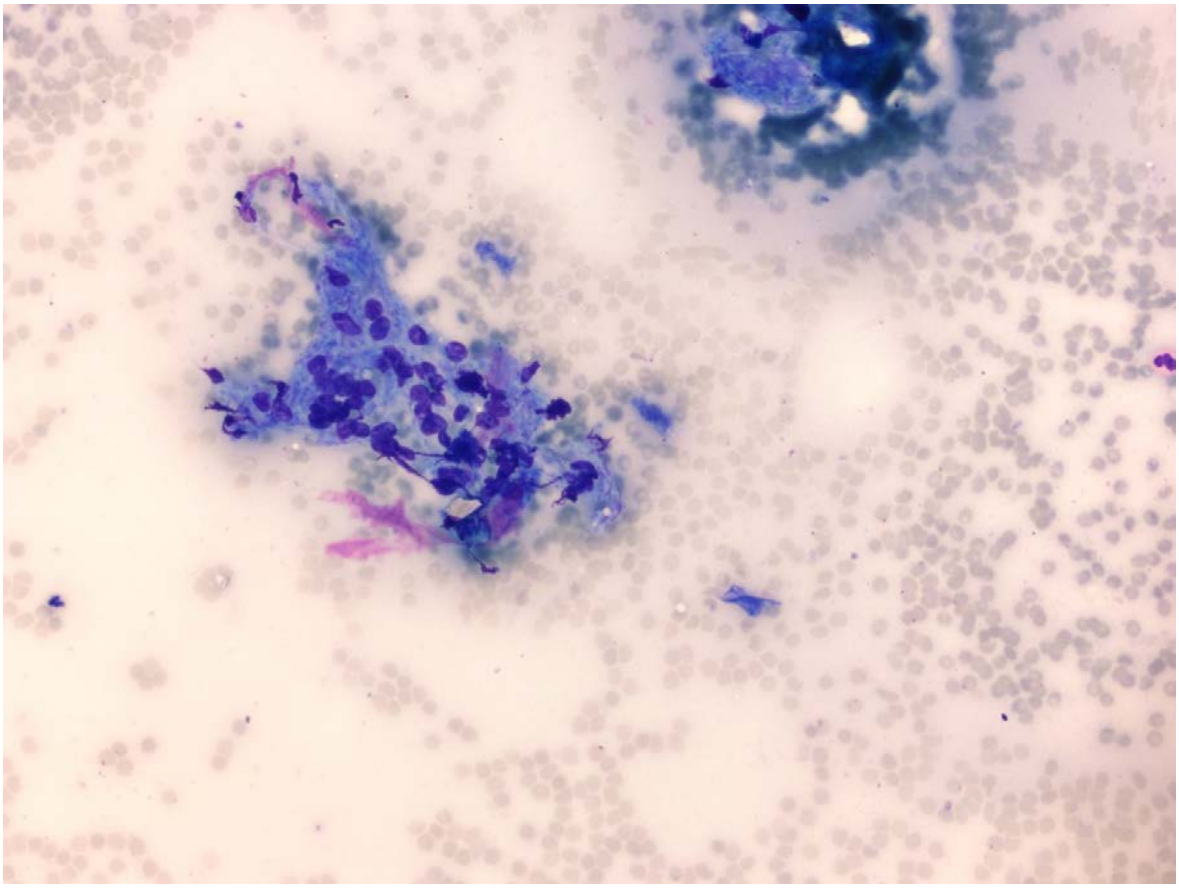

**Figure 5.** Benign-looking thyrocytes.

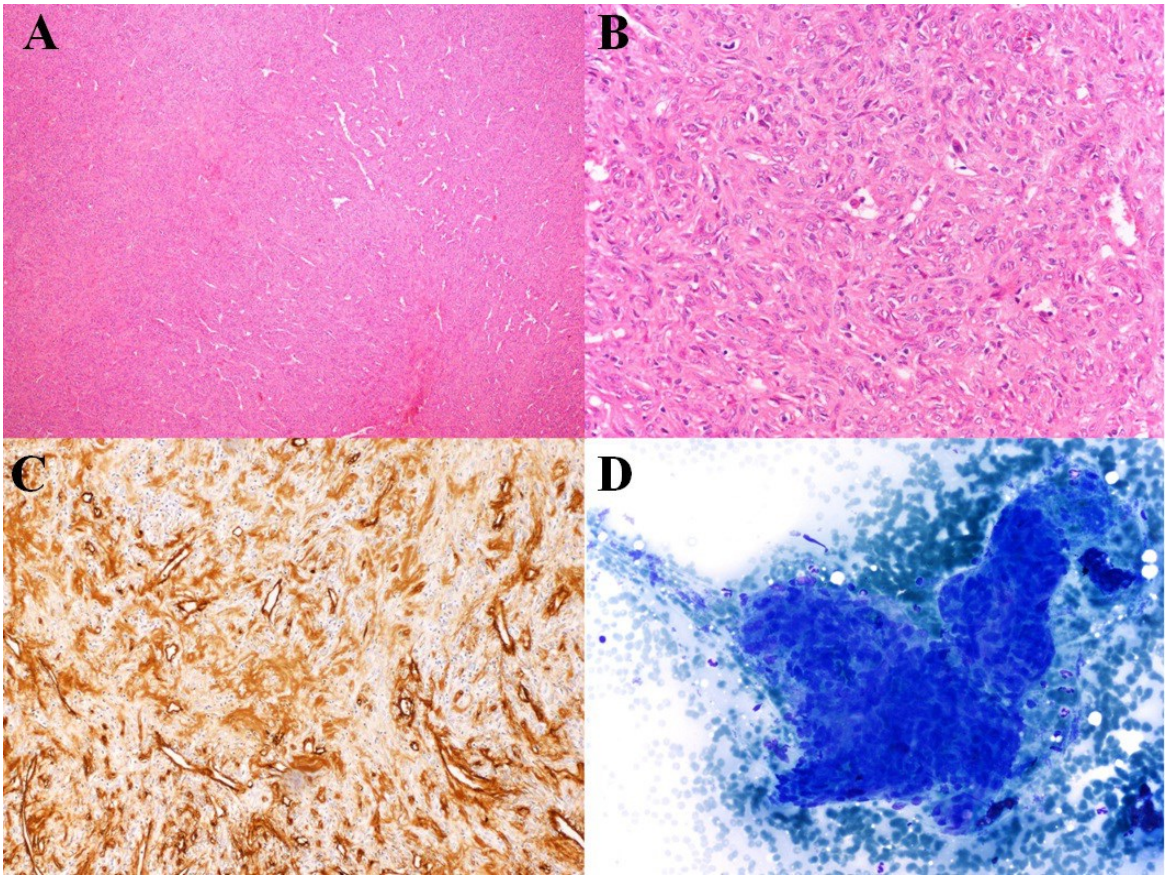


**Figure 6.** Spindle cell tumor having arborizing vascular structures (H&E,×40) (A). Spindle cells with moderately cellular tumor (H&E,×200) (B). Tumor cells stained with Factor VIII antibody (Factor VIII, x100) (C). Cohesive spindle-shaped cell cluster on cytology (MGG, x200) (D).

## Discussion and Conclusion

In literature, there are several reports about the inclusion of other body parts to the limited whole-body area on FDG PET/CT imaging (4,6-13). However, only two of them have evaluated the clinical contributions of the lower extremity imaging (4,9). In the study performed by Osman et al., the lower extremity imaging did not result in any change in terms of the stage of the disease in 14 patients with UPT (4). Sebro et al. studied 46 patients with UPT and reported that the lower extremity scanning changed the tumor stage in only one patient (9).

In our literature review, we did not identify any study that has revealed any primary origin by means of the lower extremity FDG PET/CT scanning in patients with UPT. Besides, there is no clear statement in the main FDG PET/CT guidelines about including the lower extremities in FDG PET/CT imaging in patients with UPT (5,14,15). For this reason, there are various implementations in the nuclear medicine clinics and there is no standard imaging procedure for this indication.

Some clinics perform limited whole-body scanning, paying no attention to the detection of a primary lesion. And, some clinics include other body parts if a primary tumor is not detected in limited whole-body field of view. If a suspicious primary lesion is found in the limited whole-body scan, then imaging of other body parts are generally not performed. This case represents that this kind of approach may not be true.

In conclusion, this case demonstrates the contribution of adding lower extremity to the limited whole-body imaging area on FDG PET/CT imaging for the detection of the primary site of UPT in case primary tumor is not found or the determined primary focus has any doubt in the limited whole-body imaging area

**Conflict of Interest:** The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. We thank Ahmet Yilmaz from Dicle University Medical Faculty for his invaluable help the manuscript's publishing process.

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