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

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# The place of inferior vena cava diameter and proBNP levels in determining the fluid balance of medical intensive care patients

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ABSTRACT

Objective: Fast and accurate detection of fluid balance in intensive care patients is of special significance. Many different methods are used to determine the fluid balance. In this study, we aimed to determine the fluid balance of patients in the medical intensive care unit using measurement of the inferior vena cava diameter and pro-brain natriuretic peptide (proBNP).

Patients and Methods: Patients admitted to the medical intensive care unit between September 2013 and February 2014 were enrolled in the study. Inferior vena cava diameter was measured with a portable ultrasonography, according to guidelines published by the American Echocardiography Association. For pro BNP measurement, samples were taken simultaneously with ultrasonography.

Results: One hundred and twenty-six patients (70 male,55.6%) were enrolled for the study. Mean age was 57.8 ± 19.8 (18-89 years). Ninety-six (76.2%) patients were receiving mechanical ventilation support. Mean proBNP levels were 10645.88 ± 12731.08 pg/ml. There was no statistically significant difference between proBNP levels in patients according to the fluid status. Collapsibility index was not statistically different according to the volume status (p=0.75).

Conclusion: proBNP levels were not correlated with the fluid balance. proBNP levels and inferior vena cava diameters were negatively but weakly correlated.

Keywords: Fluid balance, Inferior vena cava diameter, proBNP, Ultrasonography

## 1. INTRODUCTION

Assessment of fluid balance is one of the most important management procedures for critical care patients. Previously, the Swan–Ganz catheter has been used to assess the volume status of the patients; however, it lost popularity due to its invasiveness [1]. The surviving sepsis campaign guidelines in 2012 recommend using central venous pressure (CVP), but it is not recommended anymore in Sepsis 3 because of its poor correlation to the volume status of the patients [2].

In t recent years non-invasive assessment is becoming popular in critical care settings. Respiratory variations in the inferior vena cava measured by ultrasonography is one of them [3]. Ultrasound is quite simple, and it can be evaluated by medical or non-medical staff following short-term instructions [4]. Also, ultrasound provides results simultaneously with the procedure. Additionally, inferior vena cava ultrasonography is well known as a tool of point-of-care for restrictive fluid therapy in heart failure or fluid removal in hemodialysis [5].

Brain Natriuretic Peptide (BNP) is a hormone whose active form is C-Terminal BNP with 32 amino acids, which is released as a 108 amino acid prohormone due to excessive stress in the heart muscle cells. The 76 amino acid N-Terminal proBNP is released in proteolysis, in which the active state of the hormone occurs [6]. It is used to evaluate and monitor heart failure. The place of BNP in fluid therapy in the intensive care unit is still a matter of debate.

In this study, we aimed to determine the fluid status of patients in the medical intensive care unit using measurement of the inferior vena cava diameter and proBNP.

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## 2. PATIENTS and METHODS

The study is an observational descriptive study. We included all patients hospitalized in the Medical Intensive Care Unit (ICU) of the Marmara University Education and Research Hospital between September 2013 and February 2014 who provided an informed consent and were over 18 years of age after the approval of the Institutional Ethics Committee of Marmara University School of Medicine (Approval number: 09.2013. 0262). Patients' demographic characteristics, comorbidities, medication they were taking, vital signs, mechanical ventilator parameters and fluid status as measured by intake-output follow-ups were recorded.

Ultrasonography was performed by a certified researcher on intensive care ultrasonography, using a Mindray M5 brand portable ultrasonography device according to the guidelines of the American Echocardiography Association [7]. The right atrium was detected with a subcostal approach, the inferior vena cava was imaged, and measurements were made using M-Mode 1 cm above the joining point of the hepatic vein. By recording the diameters in inspiration and expiration, collapsibility and distensibility indexes were calculated as previously described in the literature [8]. For ProBNP, samples were taken simultaneously with ultrasonography and measurements were made by enzyme immunoassay method [9].

Primary end point was to determine the association of the inferior vena cava diameter indices, proBNP levels and the fluid status of patients.

### Statistical Analysis

All statistical analyses were made using the PSPP program (free software). Data are given as mean ± standard deviation and frequencies when appropriate. The Kolmogorov-Smirnov test was used to evaluate whether the distribution of data was normal. Correlation analysis was performed for the relationship between the diameter of the inferior vena cava and proBNP and the follow-up. Since the data in the subgroups were not normally distributed, the Mann-Whitney U test, one of the non-parametric tests, was used. The Kruskall-Wallis test was used when the means of more than two groups were compared. In all analyses, $p < 0.05$ value was taken as the limit for statistical significance.

## 3. RESULTS

Between September 2013 and February 2014, 126 patients (70 males, 55.6%) with a mean age of 57.8 ± 19.8 (18-89 years) were included in the study. Ninety-six (76.2%) patients were receiving mechanical ventilatory support. Sixty-three (65.6%) of these were on invasive, 33 (34.4%) were on non-invasive ventilation. Thirty-six (37.5%) of the patients who received mechanical ventilator support were in pressure support ventilation (PSV) mode, 23 (24%) in pressure controlled synchronized intermittent mandatory ventilation (P-SIMV), and 36 (37.5%) in adaptive support ventilation (ASV) mode. Average external positive end expiratory pressure (PEEP) was calculated as 5.4 ± 0.9mmHg. The demographic and clinical characteristics of the patients included in the study are summarized in Table I.

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

| Parameters | Value |
|---|---|
| Number of patients | 126 |
| Demographics | |
| Male gender, n (%) | 70 (55.6%) |
| Age (years) | 57.8 ± 19.8 |
| Age (years), median (min-max) | 62 (18-89) |
| Mechanical ventilation support, n (%) | 96 (76%) |
| IMV support, n (%) | 63 (50%) |
| NIV support, n (%) | 33 (26.1%) |
| External PEEP ($cmH_2O$) | 5.4 ± 0,9 |
| Modes of mechanical ventilation, n (%) | |
| PSV, n (%) | 36 (37.5%) |
| P-SIMV, n (%) | 23 (24%) |
| ASV, n (%) | 36 (37.5%) |
| CMV, n (%) | 1 (%1) |
| APACHE II | 24.3 ± 8.1 |
| Fluid balance (ml) | +635.8 ± 933.8 |
| proBNP (pg/ml) | 10645.9 ± 12731.1 |
| Ejection fraction (%) (95% CI) | 48.4 ± 3.6 (44.1 – 52.8) |

*IMV: invasive mechanical ventilation, NIV: noninvasive mechanical ventilation, PEEP: positive end expiratory pressure, PSV: pressure support ventilation, P-SIMV: Pressure targeted synchronized intermittent mandatory mechanical ventilation, ASV: Adaptive support ventilation, CMV: controlled mechanical ventilation, 95% CI: 95% Confidence interval*

According to input-output follow-ups (IOF) , the average fluid balance of the patients included in the study was found to be +635.8 ± 993.8 ml. When the patients were grouped according to IOF, 26 (20.6%) patients were found to be in negative fluid balance and 100 (79.4%) patients were found to be in positive fluid balance. The mean fluid balance of patients with positive fluid balance according to IOF was calculated as +958.9 ± 742.8 ml, and the mean fluid balance of those with negative fluid balance was calculated as – 582.2 ± 443.8 ml. Although the proBNP level increased in the group with positive fluid balance, there was no statistically significant difference between both groups (11705 vs 6362 respectively, p=0.153). In the subgroup analysis performed excluding patients with systolic dysfunction (EF <55%) on echocardiography, proBNP levels tended to increase as the fluid balance shifted to the positive side, but no statistically significant difference was found (p=0.256).

The mean end-inspiratory inferior vena cava diameter was 1.23 ± 0.81 cm, and the mean end-expiratory inferior vena cava diameter was 1.76 ± 0.65 cm. The best limit value for the collapsibility index to show the fluid balance was shown as 50% in previous studies. When the fluid balance averages of both groups were compared, the fluid balance of those with a collapsibility index over 50% tended to increase, but no statistically significant difference was found. However, proBNP levels were found to be higher in patients with collapsibility index less than 50% (Table II). A statistically significant negative


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correlation was found between the calculated collapsibility indexes of the patients and the measured proBNP levels (r = –0.409 p <0.01); as the proBNP levels increase, the collapsibility index decreases (Figure 1).

***Table II**. proBNP levels according to the collapsibility index*

| Collapsibility index (n) | proBNP (pg/ml), mean±SD (95% CI) |
|---|---|
| <50% (82) | 12938.8 ± 13549.9 |
| | (95% CI: 9658 – 16218,5) |
| ≥ 50% (44) | 5939.6 ± 9504.9 |
| | (95% CI: 2623.2 – 9256) |

*SD: standard deviation, CI: 95% Confidence interval*

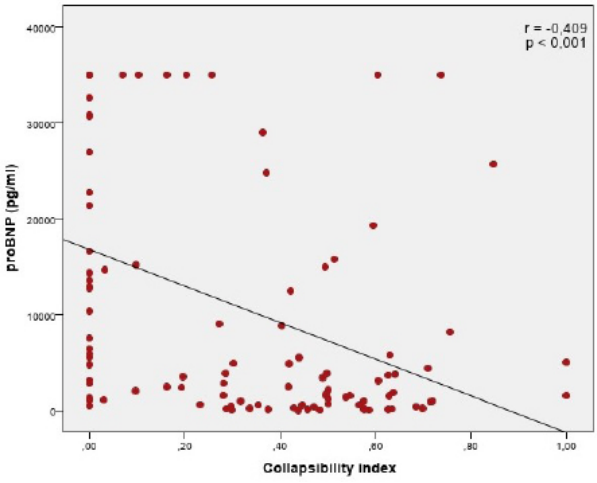


***Figure 1.** Collapsibility index and proBNP relationship*

## 4. DISCUSSION

In our study, the place of the inferior vena cava diameter measured ultrasonographically and the collapsibility index derived from it and the proBNP level were investigated in determining the fluid balance in patients in the medical ICU. According to the results, as the positivity in fluid balance increased, proBNP levels tended to increase and the collapsibility index decreased, but the changes found did not reach statistical significance. However, a negative, weak but statistically significant relationship was found between the diameter of the inferior vena cava and proBNP level in determining the fluid balance.

In our study, although, proBNP levels tend to increase as the fluid balance shifts to the positive side, we could not show a significant relationship between proBNP levels and fluid balance. The use of proBNP in evaluating the fluid balance is mostly used in dialysis patients. In a study evaluating the hydration status of hemodialysis patients, proBNP was used to assess fluid status in relation to the diameter of the inferior vena cava [10]. In a study evaluating bioimpedance and proBNP level in peritoneal dialysis patients, it was stated that proBNP levels could be used to show fluid status such as bioimpedance and guide treatment [11]. Tapolyai et al., concluded that there was an exponential relationship between bioimpedance measurements and proBNP levels in dialysis patients [12].

The qualitative assessment of inferior vena cava diameter indices has also been carried out in a prospective study which demonstrated that they offer a rapid, non-invasive way to evaluate volume status in critically ill patients [13]. However, in our study we were unable to demonstrate similar results. Two meta-analyses showed that inferior vena cava ultrasonography is a reliable parameter for hypovolemia and has a great value in predicting fluid responsiveness [14, 15]. However, other meta-analyses on inferior vena cava ultrasonography concluded that it is not a reliable method to predict fluid responsiveness [16, 17]. Hence, the effectiveness of inferior vena cava ultrasonography to predict volume status or fluid responsiveness has not yet reached a conclusion.

In studies evaluating the fluid status of intensive care patients in the literature, the inferior vena diameter was mostly compared with CVP. Zhang et al., in their study of 32 patients who had undergone gastrointestinal surgery, the fluid status of the patients was evaluated with CVP and the inferior vena cava diameters were evaluated by a researcher who was blind to the results. As a result, a correlation was found between CVP measurements and inferior vena cava diameters (r = 0.585, p <0.05) [18]. In this study, as only a very small number of patients had central lines to evaluate CVP (eight patients) we were unable to make such a comparison.

In our study, we found a negative, weak but statistically significant relationship between inferior vena cava diameters and proBNP levels. In addition, when we divided the patients into two groups with a 50% limit value of the collapsibility index, we found a statistically significant difference between the groups in favor of those with a collapsibility index of less than 50%. The reason for using the 50% limit is that it was reported as the most successful limit value in demonstrating fluid balance in previous studies [19]. This finding shows that the collapsibility index and proBNP levels are in agreement with each other in determining the fluid balance.

According to our knowledge, there is no study in the literature evaluating proBNP levels and inferior vena cava diameter in medical intensive care patients. Current studies have been conducted in heart failure patients. In a study investigating the correlation of the inferior vena cava diameter and natriuretic peptides in heart failure patients, a positive but weak relationship was found (r = 0.27, 95% CI: 0.05-0.47; P = 0.01) [20]. In a study evaluating the re-admissions of patients hospitalized with the diagnosis of acute decompensated heart failure after discharge, it was reported that patients with high proBNP levels at discharge and with larger inferior vena cava diameters at presentation had earlier and more frequent hospitalizations [21]. In a study conducted in our country, the treatment responses of patients admitted to the emergency department with acute heart failure were evaluated with the inferior vena cava collapsibility index and there was a statistically significant difference between


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pre-treatment collapsibility indexes and post-treatment collapsibility index (p <0.001), but there was no difference between proBNP levels [22].

### Limitations

The limitations of this study should be acknowledged. First, invasive assessments of fluid status were very limited in the current study. Thus, comparisons between invasive methods and inferior vena cava ultrasonography could not be made. However, the correlation between invasive techniques and inferior vena cava ultrasonography has already been shown in previous studies as mentioned earlier. Secondly, there was no consecutive measurement during or after fluid therapy. Therefore, no comment could be made on changes in the indeces.

### Conclusion

In conclusion, as the positivity in fluid balance increases, proBNP levels tend to increase, and the collapsibility index tends to decrease. In addition, a weak negative but statistically significant relationship was found between the proBNP level and the collapsibility index, and it was shown that these two parameters were compatible with each other in evaluating the fluid balance.

### Compliance with Ethical Standards

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

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# p-Coumaric acid has an ameliorative effect on peptic ulcer: a macroscopic, microscopic and biochemical analysis

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ABSTRACT

Objective: p-Coumaric acid is commonly found in edible plants in nature and is known to be an effective antioxidant. This study aimed to investigate the therapeutic effects of p-coumaric acid on ethanol-induced gastric ulcer model

Materials and Methods: After an 18-hour starvation period, the ulcer was induced in male Sprague-Dawley (250-300) rats by intragastric administration of 75% ethanol. An hour after ulcer induction, p-coumaric acid (250 mg/kg) suspended in 1 ml tween-80 was administered intragastrically. The control and ulcer groups received 1 ml tween-80. One hour later, all rats were euthanized and stomach samples were collected for macroscopic examination, histological evaluation, and measurement of myeloperoxidase (MPO) activity, malondialdehyde (MDA), and glutathione (GSH) levels.

Results: Ethanol induction resulted in gastric epithelial and mucosal injury, increased MPO activity and MDA levels; and decreased GSH levels. Treatment with p-coumaric acid at a dose of 250 mg/kg markedly improved the gastric injury macroscopically, microscopically, and biochemically due to decreasing MPO activity and MDA levels while increasing GSH levels.

Conclusion: p-Coumaric acid markedly ameliorated the gastric epithelial and mucosal injury induced by ethanol. The therapeutic effects of p-coumaric acid could be due to its antioxidant properties and protective role against GSH depletion and neutrophil accumulation.

Keywords: p-Coumaric acid, Ulcer, Ethanol, Antioxidant, Neutrophil

## 1. INTRODUCTION

p-Coumaric acid is one of the three isomers of coumaric acid, which is a member of the hydroxycinnamic acid family. It is found in a variety of edible plants, vegetables, vinegar, wine, and barley grain in free or bound form. p-Coumaric acid and other phenolic acids are known to be powerful antioxidants [1]. Recent interest in phenolic acids stems from their potential capacity to diminish tissue damage caused by oxidative stress [2]. It has been discovered that pre-treatment of animals with p-coumaric acid is helpful in reducing cerebral ischemia reperfusion (IR) induced injuries, oxidative stress, size of infarction and neuronal vulnerability to death [3]. Moreover, it has been proposed that p-coumaric acid can block oxidative modification of low-density lipoprotein (LDL), which is a necessary step in atherosclerosis [4]. p-Coumaric acid also suppresses dyslipidemia, hepatosteatosis and oxidative stress in obese rats and has an adipogenic effect [5]. Recent investigations have also shown that p-coumaric acid has anti-cancer [6,7] and anti-inflammatory [8] effects. Recently, reduction in acid pro-inflammatory cytokines [tumor necrosis factor-α, interleukin (IL)-1β, IL-6, and IL-17], and inflammatory enzymes (inducible nitric oxide and cyclooxygenase-2) by p-coumaric acid has been shown in arthritic rats [9]. Kilani-Jaziri S, et al., demonstrated that p-coumaric acid augments the killing activity of isolated natural killer cells and cytotoxic T cells, and possibly activates B cells along with enhanced humoral immunity [10].

Ulcer is defined as a disruption in the mucosa, which extends through the muscularis mucosae, and is surrounded by acute and chronic inflammation. Each year, peptic ulcer disease affects 4 million people around the world [11]. Although, the pathophysiology is not yet fully understood, it is accepted that peptic ulcer results from an imbalance between defensive mechanisms of the mucosa and other aggressive factors

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[12]. Acid secretion, pepsin secretion, and parietal cells are among aggravating factors; whereas mucus secretion, mucosal regeneration, prostaglandins and gastric blood flow are examples of protective factors [13]. Some factors such as excessive alcohol consumption, H. pylori infection and prolonged non-steroid anti-inflammatory drug treatment destroy the balance, which is easier in genetically predisposed individuals.Ingestion of excessive ethanol could induce gastric mucosal injury by stimulating mucosal epithelial cell apoptosis, inflammatory reaction and oxidative stress in gastric tissue [14]. Ethanol solubilizes the protective mucus via proteolytic and hydrolytic actions, and increases the concentration of hydrochloric acid and pepsin. It produces reactive oxygen species (ROS) that alter cell structure and function. These factors eventually damage the membrane and lead to ulceration [15]. Anti-oxidant agents are effective in peptic ulcer disease treatment due to their ROS scavenging and cytoprotective activities. No previous study has analyzed the anti-ulcer effects of p-coumaric acid at microscopic and biochemical levels, which makes this study unique in terms of revealing the underlying mechanisms.

Our aim was to determine the therapeutic effects of p-coumaric acid on ethanol-induced gastric ulcer models at macroscopic, microscopic and biochemical levels.

## 2. MATERIAL and METHODS

### *Animals*

Sprague-Dawley rats were provided by the Acibadem Mehmet Ali Aydinlar University (ACU) Animal Center. Male rats (300–350 g; n = 7–8 per group) were housed at a constant temperature (22 ± 1 °C) at a humidity of 65-70% with 12 h light/dark cycles. Rats were fed standard pellet chow and water *ad libitum*. All protocols were approved by ACU Local Ethics Committee for Animal Experiments (ACU-HADYEK 2017/2).

### *Induction of ulcer and treatment protocol*

Following 18-h starvation, rats were divided into 4 groups. Rats were given 75% ethanol (ulcer and ulcer + p-coumaric acid groups) or saline (control and p-coumaric acid groups) by oral gavage under light isoflurane anesthesia. One hour before ethanol or saline administration, rats were treated with either 1 ml 10% tween-80 (ulcer and control groups) as vehicle or p-coumaric acid (Sigma-Aldrich C9008, Merck, Germany; 250 mg/kg; suspended in 10% tween-80) (p-coumaric acid and ulcer + p-coumaric acid groups) per oral (Table I). Barros, et al., showed that the dose of 250 mg/kg of p-coumaric acid reduced the macroscopic lesion index most compared to other doses [16]. Therefore, the dose of 250 mg/kg p-coumaric acid was used for treatment in the study. One hour after ulcer induction, all rats were euthanized by cutting the aorta and removing the heart under deep isoflurane anesthesia. Stomach samples were collected for macroscopic examination, histological evaluation, microscopic scoring and biochemical analyses. For histological evaluation the stomach samples were examined under light microscopy and for biochemical analyses tissue-associated myeloperoxidase (MPO) activity as the indicator of neutrophil infiltration, malondialdehyde (MDA) which is the end-product of lipid peroxidation and endogen antioxidant glutathione (GSH) levels were measured.

***Table I.*** *Experimental protocol*

| | 10:00 | 11:00 | 12:00 |
|---|---|---|---|
| **Control** | Tween-80 | Saline | Euthanasia |
| **p-coumaric acid** | p-coumaric acid 250 mg/kg | Saline | Euthanasia |
| **Ulcer** | Tween-80 | Ethanol | Euthanasia |
| **Ulcer + p-coumaric acid** | p-coumaric acid 250 mg/kg | Ethanol | Euthanasia |

### *Macroscopic scoring*

Macroscopic scoring was performed by an observer who was blind to the study using a semi-quantitative scale of 0 to 3. A score of 0 indicated a normal mucosa. A score of 1 indicated that there were a total number of 1 to 4 small petechiae observed on the stomach. A score of 2 indicated 5 or more petechiae or hemorrhagic streaks up to 4 millimeters in length. A score of 3 indicated erosions longer than 5 millimeters, or confluent hemorrhages [17].

### *Histological evaluation and microscopic scoring*

For light microscopic examination, stomach samples were placed in 10% formalin solution, dehydrated through ascending alcohol series (70%, 90%, 96% and 100%), cleared in xylene and embedded in paraffin. For each animal, four randomly taken tissue sections (5 µm) were stained with hematoxylin and eosin (H&E). The slides were examined under a AxioCam MRc5 photomicroscope (Zeiss, Germany). The photos of the samples were taken via the camera of the photomicroscope itself. The criteria for scoring were epithelial desquamation, mucosal hemorrhage, glandular damage and eosinophilic infiltration. Each specimen was scored using a scale ranging from 0 to 3 (0: none, 1: mild, 2: moderate, and 3: severe) for each criterion. The total score was 12. Histologic examination and scoring were performed by an observer (S.A.) who was unaware of the treatment groups [18].

### *Measurement of MDA and GSH levels*

Stomach samples were homogenized in 10 volumes of ice-cold 10% trichloroacetic acid and centrifuged at 3000 rpm for 15 min at 4 °C and then removed supernatants were re-centrifuged at 9000 rpm at 4 °C for 8 min. In order to detect MDA levels, the samples combined with thiobarbituric acid boiled for 15 minutes. Lipid peroxide levels were expressed in terms of MDA equivalents as nmol MDA per g tissue [19]. GSH was determined by a spectrophotometric method which is the modification of Ellman procedure [20]. Briefly, removed supernatant was added to a mixture composed of 2 ml of 0.3 mol/l $Na_2HPO_4$-$2H_2O$ solution and 0.2 ml dithiobis-nitrobenzoate solution (0.4 mg/ml in 1% sodium citrate). Immediately, the absorbance of the mixture was measured at 412 nm. GSH levels were calculated using an extinction coefficient of 1.36 x $10^4$M/cm. Results are expressed in micromoles GSH per gram tissue.


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### *Measurement of MPO activity*

Myeloperoxidase activity, an indicator of neutrophil accumulation, was assessed by measuring the $H_2O_2$-dependent oxidation of o-dianisidine 2HCl. One unit of enzyme activity was defined as the amount of MPO present that causes a change in absorbance of 1.0 unit $min^{-1}$ at 460 nm and 37 ºC and expressed in units per g tissue [21]. Gastric tissue samples were homogenized for a minute in a solution containing potassium phosphate buffer ($K_2HPO_4$) and hexadecyltrimethylammonium bromide (HETAB). They were centrifuged at 12000 rpm at 4 ºC for 10 minutes and the supernatants were discarded. Then, pellets were mixed with a solution of $K_2HPO_4$, HETAB and Ethylenediaminetetraacetic acid (EDTA) with re-homogenization for 15 seconds. Finally, oxidation reaction of o-Dianisidine in the presence of $H_2O_2$ was conducted with the mixture and MPO activity was measured spectrophotometrically according to the reaction. MPO activity was expressed as U/g tissue.

### Statistical Analysis

All data expressed as means ± S.E. parameters were compared using two-way analysis of variance (ANOVA) followed by Tukey-Kramer multiple comparison tests. Values of $p<0.05$ were regarded as significant. Calculations were done using the InStat statistical analysis package (GraphPad Software, San Diego, CA, USA).

## 3. RESULTS

### *Macroscopic and microscopic lesion scores*

When compared with the vehicle-treated control group, the ethanol-induced ulcer group had significantly high macroscopic ($p<0.001$) and microscopic ($p<0.001$) lesion scores (Fig.1). When compared with the untreated ethanol-induced ulcer group, the ulcer group treated with p-coumaric acid had significantly reduced macroscopic (2.55±0.20 and 1.4±0.4; respectively) ($p<0.05$) and microscopic (10.33±0.62 and 3.17±0.6; respectively) ($p<0.001$) lesion scores (Fig.1). In terms of macroscopic scoring, the ulcer group had severe hemorrhage and a lot of petechiae. Treatment with p-coumaric acid decreased the gastric lesions observed macroscopically and reduced the macroscopic lesion score significantly when compared with the untreated ulcer group. The ulcer-free group treated only with p-coumaric acid (0.17±0.02) had a similar macroscopic lesion score with the control (Fig.1A). In microscopic examination p-coumaric acid treatment also decreased the microscopic scores compared with ulcer group given vehicle. Unexpectedly, only p-coumaric acid given rats (4.33±0.33) had slightly higher microscopic score than control group (Fig.1B). This might be driven from slight inflammatory cell infiltration due to the effect of p-coumaric acid that increases blood flow.

In terms of histological evaluation, the control group had regular gastric mucosa with surface epithelium and glandular epithelium. In the ulcer group, there was severe damage of surface epithelium and glandular epithelium with hemorrhagic regions and desquamated cells. The ulcer-free group treated with only p-coumaric acid had slight degeneration of gastric epithelium and moderate inflammatory cell infiltration. The ulcer group treated with p-coumaric acid showed minor damage at surface epithelium and gastric glands, and eosinophilic infiltration was reduced significantly (Fig. 2).

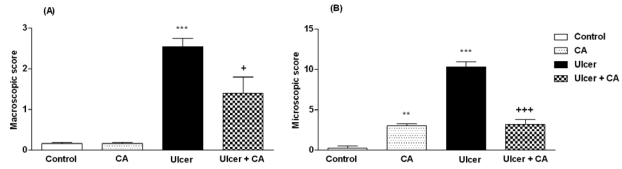


*Fig 1. Macroscopic (A) and microscopic (B) lesion scores in control, coumaric acid (CA), ulcer and ulcer + coumaric acid (ulcer + CA) groups. *** p<0.001 compared with control group. + p<0.05, +++ p<0.001 compared with ulcer group. The results are expressed as the mean ± S.E.M.*

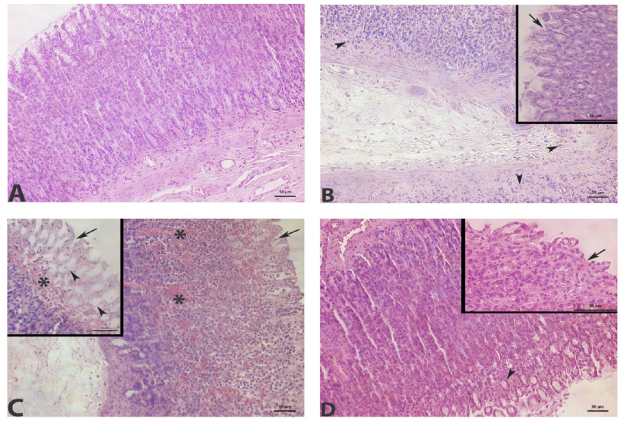


*Fig 2. Histological analysis of the tissue samples by hematoxylin and eosin staining (A-D). (A) Regular gastric mucosa with surface epithelium and glandular epithelium in the control group. (B) Slight degeneration of gastric epithelium (→) and moderate inflammatory cell infiltration (▶) in the coumaric acid group. (C) Severe damage of surface epithelium (→) and glandular epithelium (▶) with hemorrhagic regions (*) and desquamated cells in the ulcer group. (D) Minor damage at surface epithelium (→) and gastric glands (▶) in the ulcer combined with coumaric acid treatment group. H&E staining, scale bars: 50 µm (x20), inset: 20 µm (x40).*

### *MDA and GSH levels*

As expected, the ulcer group was characterized by a significant increase in gastric MDA level along with a concomitant decrease in GSH content. Increase in MDA (13.07±0.88) with ethanol administration considering the control group (6.99±0.97) ($p<0.001$) decreased significantly with p-coumaric acid treatment (8.85±0.43) ($p<0.01$) (Fig.3A). The endogenous antioxidant GSH was lower in the ulcer group (1.06±0.06) compared to the control (1.89±0.09) ($p<0.05$) and treatment with


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p-coumaric acid (2.01±0.28) prevented gastric GSH depletion (p<0.05) (Fig.3B). Only p-coumaric acid administration had similar values with control group for both MDA and GSH measurement (9.32±0.73 and 1.68±0.18; respectively).

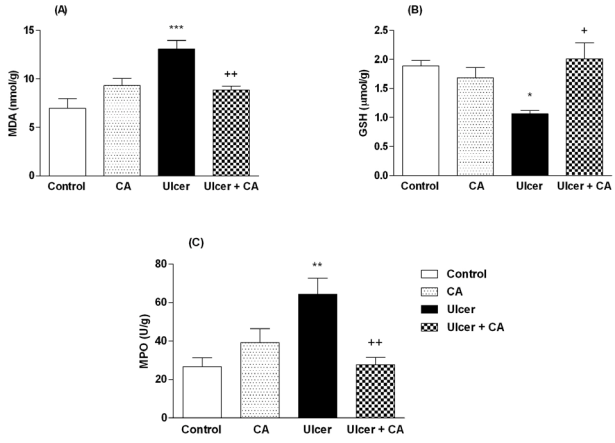


***Fig 3.*** *(A) Malondialdehyde (MDA) levels, (B) Glutathione (GSH) levels, (C) Myeloperoxidase (MPO) activity in control, coumaric acid (CA), ulcer and ulcer + coumaric acid (ulcer + CA) groups determined by procedures explained above. *p<0.05, **p<0.01, ***p<0.001 compared to the control group. + p<0.05, ++ p<0.01 compared to the ulcer group. The results are expressed as the mean ± S.E.M.*

### *MPO activity*

Ethanol administration resulted in an increase in MPO activity in the ulcer group (64.22±8.57) compared with control group (26.69±4.55) (p<0.01). Elevated MPO activity was reduced by the p-coumaric acid treatment (27.7±3.8) significantly (p<0.01) (Fig.3C). p-Coumaric acid treatment without ethanol administration (39.16±7.2) increased MPO activity slightly; however there was no significant difference with control group.

## 4. DISCUSSION

Peptic ulcer is a disease characterized by an imbalance between the factors that damages the mucosa and those for its protection, resulting in a lesion of the lining of the upper digestive tract. When the gastric mucosa is exposed to noxious agents such as alcohol, the extent of gastric damage depends upon the balance between the factors [22]. p-Coumaric acid is widely distributed in plants and mushrooms, and shows various biological activities as anti-oxidant, anti-tumorogenesis and anti-inflammatory effects [23].The results of the study demonstrate that p-coumaric acid treatment markedly improved the ethanol induced gastric injury, as confirmed by histological evaluation and biochemical assays as a measure of the extent of the inflammatory response. The extent of injury was significantly reduced by p-coumaric acid treatment as assessed by macroscopic and microscopic scores. MPO activity as a marker of recruitment of neutrophils was suppressed in p-coumaric acid treated group. Moreover, p-coumaric acid treatment reduced MDA content increased by ethanol administration and gastric GSH levels, which were depleted in ethanol consumed rats, were preserved with p-coumaric acid treatment.

p-Coumaric acid is a hydroxycinnamic acid derivative that was found to be an effective antioxidant in different in vitro assays including superoxide anion radical scavenging, hydrogen peroxide scavenging and metal chelating activities [24]. As shown before, 250 mg/kg p-coumaric acid diminished the lesion index, the total area of the lesion and the percentage of lesion in ulcer induced rats. However, anti-ulcer activity of p-coumaric acid at the microscopic level and the biochemical parameters related to inflammation were investigated for the first time in the present study. The current study revealed that p-coumaric acid decreased macroscopic and microscopic scores and histological results demonstrated that the ingestion of p-coumaric acid ameliorated the gastric injury induced by ethanol.

Ethanol-induced gastric injury is a key experimental model commonly utilized for preclinical assessment of agents with potential anti-ulcer activity since ethanol has been regarded as a leading cause of gastric ulcer in humans [25]. The effect of ethanol on gastric mucosa is a complicated process and it is associated with multiple pathologies. Ethanol has the tendency to create ulcers via oxidative pathways, which lead to solubilization of protective mucus, increase in hydrochloric acid (HCl) and pepsin concentrations and cell apoptosis in gastric tissue. The result of one of these oxidative pathways is the production of ROS, which play a major role in the ulcer mechanism. ROS decrease the pH levels in stomach and speed up the oxidation process, therefore causing ulceration in the mucosa [26].

There are several potential sources of ROS production by the inflamed tissues. These may include the epithelial cells, the microvascular endothelium or the inflammatory cells. As the inflammatory cells, activated neutrophils can induce tissue injury via the release of various toxic metabolites, including ROS and proteases [27]. Neutrophil infiltration to injured gastric mucosa can be indicated by MPO activity. MPO, found in lysosomes of neutrophils, monocytes and macrophages, is one of the enzymes responsible for catalyzing ROS generation [28]. As shown before, these harmful actions can be blocked by antioxidant substances which scavenge the free radicals and detoxify the organism [29]. In the present study, increased MPO levels with ethanol administration were depressed with the p-coumaric acid treatment. This decline in the MPO activity which represents the protective effects of p-coumaric acid against neutrophil accumulation in gastric tissue was shown for the first time in this study in the literature.

Meanwhile, ROS generated by activated leukocytes trigger mucosal damage via lipid peroxidation and via depletion of the antioxidant defenses such as reduced GSH. Highly reactive compound, MDA, produced by peroxidation of lipids also increases during formation of ethanol induced ulcers [30]. In the study increased MDA levels because of ethanol ingestion were reduced by p-coumaric acid treatment. On behalf of its antioxidant effects, p-coumaric acid decreased MDA levels, possibly via its scavenging effect [31].

Glutathione levels were preserved in the p-coumaric acid treated ulcer group. This suggests that the protective effects of p-coumaric acid include prevention of the depletion of GSH, which is an endogen antioxidant. GSH content in gastric tissue reveals anti-oxidant capacity and it is used as marker for tissue injury and oxidative stress. In the present study depleted gastric GSH with the ethanol administration was preserved by p-coumaric acid. Due to its reducing properties, GSH protects the cells against injuries promoted by free radicals, radiation, ultraviolet light, besides removing products of lipid peroxidation [32].

As a result, our study showed the beneficial and anti-ulcer effect of p-coumaric acid against ethanol induced gastric damage. The healing effects of p-coumaric acid could be due to its preventive effect of neutrophil accumulation, lipid peroxidation and GSH depletion. On the basis of our findings, it could be suggested that p-coumaric acid can be a therapeutic choice for gastric ulcer.

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### Compliance with Ethical Standards

**Ethical Approval:** All protocols were approved by ACU Local Ethics Committee for Animal Experiments (ACU-HADYEK 2017/2).

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**Conflict of Interest:** The authors declare that there are no conflicts of interest.

**Author Contributions:** M.K. and G.O. contributed to the conception and design. M.K., G.O., M.Y., Z.N.U., E.A., S.O., S.C., M.A.E, N.A. performed experiments and did data collection, M.K. and S.A. analyzed data. M.K., G.O., M.Y., Z.N.U., E.A., S.O., S.A. contributed to the writing and M.K. did the critical revision of the article. All authors approved the final version of the article.

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# Association of polypharmacy with postural instability and impaired balance in community-dwelling older adults in Turkey

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ABSTRACT

Objective: Polypharmacy, an important geriatric syndrome, has been shown to be an independent risk factor for falling. However, the data about effects of polypharmacy on balance is lacking. We aimed to evaluate the effects of polypharmacy and inappropriate drug usage on balance in older adults.

Patients and Methods: Fifty-one patients using ≥ 5 drugs and 50 patients using < 5 drugs were included in the study. Inappropriate drug usage of the patients was evaluated by Beers criteria. Postural stability and risk of falling was investigated by using Biosway Portable Balance System (BPBS). Activities and functional status of the patients were assessed by using Short Physical Performance Battery (SPPB) and Activities Specific Balance Confidence Scale (ABC). All patients underwent comprehensive geriatric assessment.

Results: Age, gender, hand grip strength, SPPB scores of the patients were similar between polypharmacy and control groups (all had $p>0.05$). ABC score was higher in polypharmacy group than control ($p<0.01$). Overall, anterior-posterior, medial-lateral stability index and eyes closed firm surface scores detected in BPBS were higher, indicating worse stability in the polypharmacy group than control ($p<0.05$). Limit of stability score was lower in the polypharmacy group than control ($p=0.03$). Rates of polypharmacy and inappropriate drug usage were higher in patients with a history of falling than without ($p<0.01$, $p<0.01$, respectively). In multivariate analysis model, polypharmacy was found to be an independently correlated parameter for impaired balance (OR 24.31; 95%CI 3.05-193.91; $p<0.01$).

Conclusion: This study has demonstrated that polypharmacy might be a related factor for impaired balance. Struggling with polypharmacy and inappropriate drug usage should be one of the most important part of comprehensive geriatric assessment.

Keywords: Balance, Elderly, Falling, Polypharmacy

## 1. INTRODUCTION

Approximately one third of the patients over 65 years have experienced at least one falling every year and about 10% of the cases result in serious injury causing major morbidity and mortality in this population [1, 2]. The health expenditures due to fall-related injuries are progressively increasing [3, 4]. Polypharmacy is generally defined as using 5 or more drugs and a number of drugs have been shown to be associated with an increased risk of falling in geriatric population [5-7]. As well as the number of the drugs, inappropriate medications are also important in older adults that may lead to increased risk of drug-drug interactions and various side effects [8-10].

Postural stability is a complex process that requires the combination of multiple neurological sensory and motor components to maintain the body balance [11]. Maintaining postural stability diminishes with age and this facilitates falls in older adults [12]. Biosway Portable Balance System (Biodex Inc. Shirley, New York) (BPBS) is a device that assesses balance and its sub-parameters such as postural stability, limit of stability (LOS) and risk of fall via modified Clinical Test of Sensory Integration and Balance (m-CTSIB). The system provides valid, reliable, and repeatable objectives measures of a patient's neuromuscular control and ability to balance on a firm and/or unstable surface. There are some studies showing the predictive effect of BPBS on risk of falling for elderly population in literature [13]. This system enables the objective assessment of the balance and consists of a balance platform connected to computer software. Performances of the patients were assessed and the computer gives automatically goal values for each person.

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Although, the association between polypharmacy and falling risk is well known, the data about the association between polypharmacy and balance problems detected with BPBS is lacking. In the light of this knowledge, this study was carried out to evaluate the effects of polypharmacy and inappropriate drug usage on balance problems detected by using BPBS and falls in elderly patients.

## 2. PATIENTS and METHODS

Patients aged 65 years and over who applied to the geriatric outpatient clinic at a university hospital between 2015 and 2016 were included in this study. The participants were divided into two groups as 51 patients using 5 or more drugs as study group and 50 patients using less than 5 drugs as control group. All patients underwent comprehensive geriatric assessment including Mini Nutritional Assessment – Short Form [14], Katz activities of daily living [15], Lawton Brody instrumental activities of daily living [16], Mini Mental State Examination [17], Yesavage Depression Scale [18] and clock drawing tests. Hand grip strength was measured by grip strength dynamometer, (Grip D produced by Takei / Made in Japan) with dominant hand. Measurements were repeated for three times after 10 second intervals and maximum hand grip strength value was recorded. The number of drugs and the comorbidities of the participants were also recorded. Inappropriate medication usage was identified by using Beers criteria [8-10]. All patients were included in the study after their informed consents were obtained. The exclusion criteria were history of orthopedic surgery (presence of prosthesis), vestibular, neurological and rheumatologic diseases, diabetic neuropathy documented both symptoms and electromyography, bone fracture due to falls in the last 6 months, having severe joint deformity and not cooperating to BPBS measurement.

### *Assessment of risk of falling, postural stability and limit of stability*

Risk of falling, postural stability and LOS were assessed by using BPBS (Biodex Inc. Shirley, New York) [19]. This system enables the objective assessment of the balance and consists of a balance platform connected to computer software. Each participant was given the information about the test and one trial evaluation was performed before recording the results. The patients participated in the balance assessment with bare feet. The position of the foot was determined by adjusting the position in which an individual can stand in balance with minimal effort. The coordinate location on the platform, age and height of the participants were recorded to the device. The risk of fall was assessed with m-CTSIB test, in 4 conditions as standing on a firm and foam surface with eyes open and closed (preferred test protocol: eyes open firm surface, eyes closed firm surface, eyes open foam surface and eyes closed foam surface). The duration of each condition was 20 seconds. The higher Sway Index score points out the more unstable patients. Postural stability was evaluated by the assessment of the patients' ability to keep a moving point on the screen of the BPBS. The test was repeated for three times with each part taking 20 seconds. Overall stability index (OSI), anterior-posterior stability index (APSI) and medial-lateral stability index (MLSI) scores were measured. Higher values indicate worse stability. LOS was measured by assessment of ability of patient moving through a blinking ball and back to the screen by shifting the body weight on the platform. Performances of the patients were assessed according to the LOS scores. The test was repeated three times. The computer gives automatically goal values for each person's LOS test. The system reliability for postural stability and LOS were tested with 25 healthy elderly volunteers in bilateral standing (two sessions on consecutive weeks).

### *Assessment of physical activity and fear of falling*

Activities and functional status of the patients were assessed by using Short Physical Performance Battery (SPPB) [20]. The scores ranged from 0 (worst performance) to 12 (best performance). Activities Specific Balance Confidence Scale (ABC) was also performed. Patients were asked 16 questions in this scale to indicate their level of confidence in doing the activity without losing their balance or becoming unsteady. They selected one of the percentage points on the scale from 0% to 100% [21]. Arithmetic mean of the total score was taken.

### *Biochemical evaluation*

Fasting plasma glucose, high density lipoprotein, low density lipoprotein, total cholesterol, triglyceride, blood urea nitrogen, creatinine, sodium, potassium, calcium, total protein, albumin, thyroid stimulating hormone, free t4, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, alkaline phosphatase, bilirubin, vitamin B12, folic acid, 25 (OH) vitamin D, C reactive protein levels, erythrocyte sedimentation rate and complete blood count were measured.

### *Ethics*

Ethical approval for the research was obtained from the Ethics Committee of Kecioren Training and Research Hospital, Ankara, in 2015 and informed consent was obtained from each participant conforming to the Helsinki Declaration.

### Statistical Analysis

Statistical analysis was performed by using Statistical Package for Social Sciences (SPSS) for windows 15.0 software. Numerical parameters were assessed by histogram and Kolmogorov – Smirnov test to evaluate whether the variables had normally distribution or not. Categorical variables were presented as frequencies and percentage. Comparison of continuous numerical parameters between two groups was done by using Student's T or Mann-Whitney U tests according to the distribution of the parameters as normal or skew distribution, respectively. Categorical parameters were compared with Chi-square test. Detection of the independent associated factors affecting falls in geriatric patients was made by binary logistic regression analysis. In the regression analysis model, the parameters that were different (p value lower than 0.05) between patients with and without history of falling in the previous year


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before the study conducted were included. Receiver Operating Characteristic (ROC) analysis was applied to detect the optimum drug number which may increase the falling in geriatric patients. P value < 0.05 was considered as statistically significant.

## 3. RESULTS

Median age of the study population was 72 years (min-max: 65-86) and 55.4 % of patients were female. Age, sex, hand grip strength and usage of walking aid were similar between groups. Mean body mass index (BMI) of patients in the polypharmacy group was higher than control group (p<0.01). SPPB total scores were similar between groups. ABC scores were lower in the polypharmacy group (p=0.01). The demographic characteristics, clinical features and laboratory parameters of patients are summarized in Table I.

***Table I.*** *Demographic characteristics, co-morbidities and baseline laboratory findings of the patients*

| | All groups n=101 | Polypharmacy group n=51 | Control group n=50 | p value |
|---|---|---|---|---|
| **Age, years** | 72 (65-86) | 72 (65-86) | 71(65-85) | 0.09 |
| **Sex (%Female)** | 55.4 | 52.9 | 58 | 0.61 |
| **BMI, kg/m2** | 29.6 ± 4.4 | 30.8 ± 4.1 | 28.5 ± 4.5 | <0.01 |
| **Handgrip strength, kg** | 24.8 ± 8.8 | 23.9 ± 9.5 | 25.6 ± 8.1 | 0.35 |
| **Mobilization (% walking aid)** | 5.9 | 5.9 | 6 | 1.00 |
| **History of falling (%)** | 18.8 | 35.3 | 2.0 | <0.01 |
| **SPPB score** | 8.4 ± 1.7 | 8.1 ± 1.5 | 8.7± 1.8 | 0.08 |
| **ABC score** | 85.3 (0-100) | 91.83 (40-100) | 80.67 (0-100) | <0.01 |
| **Co-morbidities, n (%)** | | | | |
| *Hypertension* | 68 (67.3) | 47 (92.2) | 21 (42.0) | <0.01 |
| *Diabetes mellitus* | 35 (34.7) | 35 (68.6) | 0 (0.0) | <0.01 |
| *Coronary artery disease* | 12 (11.9) | 11 (21.6) | 1 (2.0) | <0.01 |
| **Biochemical parameters** | | | | |
| *Fasting plasma glucose(mg/dL)* | 100 (70-294) | 113 (78-294) | 94 (70-198) | <0.01 |
| *Hb (g/dL)* | 13.3 ± 1.6 | 13.04 ± 1.4 | 13.60 ± 1.8 | 0.08 |
| *Vitamin B12 (pg/mL)* | 376 (117-1887) | 376 (117-1887) | 359 (164-1823) | 0.82 |
| *25 OH vitamin D (µg/L)* | 21.4 (5.9-79.6) | 22.3 (5.9-79.6) | 19.1 (9.0-44.7) | 0.32 |
| *TSH (mIU/mL)* | 1.8 (0.5-14.0) | 1.8 (0.5-9.7) | 1.8 (0.5-14.0) | 0.90 |

*BMI: Body Mass Index, SPPB: Short Physical Performance Battery, ABC: Activities Specific Balance Confidence Scale, Hb: Hemoglobin, TSH: Thyroid stimulating hormone. The numerical parameters are shown as mean ± standard deviation or median (min-max) according to the distribution pattern of the variables.*

The rate of inappropriate drug usage according to the Beers criteria was 22.8% in the study population and only 4% of the study population was using at least one drug that may increase the risk of falling. Rate of previous history of falling was higher in the polypharmacy group compared to control (35.3% versus 2%, p<0.001). Comprehensive geriatric assessment scores are shown in Table II.

***Table II.*** *The results of comprehensive geriatric assessment test parameters between study and control groups*

| | Polypharmacy group n=51 | Control group n=50 | p value |
|---|---|---|---|
| **Katz ADL** | 6 (5-6) | 6 (5-6) | >0.05 |
| **Lawton-Brody IADL** | 8 (5-8) | 8 (4-8) | >0.05 |
| **MNA-SF** | 14 (10-14) | 14 (5-14) | 0.046 |
| **MMSE** | 30 (25-30) | 29 (25-30) | 0.014 |
| **YDS** | 0 (0-8) | 2 (0-11) | <0.001 |
| **6 m gait speed, m/sn** | 5 (3.1-13.2) | 7 (3.5-28.1) | <0.001 |
| **Hand grip strength, kg** | 25.6 ± 8.1 | 23.9 ± 9.4 | >0.05 |

*ADL: Activities of daily living, IADL: Instrumental activities of daily living, MNA-SF: mininutritional assessment-short form, MMSE: minimental state examination, YDS: Yesavage depression scale, The numerical parameters are shown as mean ± standard deviation or median (min-max) according to the distribution pattern of the variables.*

When the patients were classified according to the history of falling, the rate of polypharmacy was seen to be higher in the patients with history of falling than without (94.7% versus the 40.2%, p <0.01). The incidence of hypertension, diabetes mellitus and hypothyroidism were found to be higher in patients with a history of falling than without (p = 0.02, p <0.01 and p = 0.04, respectively). Inappropriate drug usage, according to Beers criteria was also more frequent in patients with history of falling than without (52.6% versus 15.9%, p <0.01).

Impaired balance and increased risk of falling were observed in the polypharmacy group. Eyes closed firm surface score was higher in the polypharmacy group than control (p=0.042). All postural stability index scores were found to be higher in the polypharmacy group compared to control (p<0.01, p=0.03, p<0.01, respectively). LOS score was significantly lower in the polypharmacy group (34 min-max: 15-81 vs. 39 min-max: 18-60, p=0.03). Results of BPBS are shown in Table III.

***Table III.*** *Comparison of BPBS results between polypharmacy and control groups*

| | Polypharmacy group | Control group | P value |
|---|---|---|---|
| **EOFS** | 0.53 (0.26-1.81) | 0.50 (0.25-1.13) | 0.19 |
| **ECFS** | 0.82 (0.45-2.58) | 0.70 (0.30-1.87) | **0.04** |
| **EOSS** | 1.23 (0.72-4.14) | 1.16 (0.75-2.65) | 0.50 |
| **ECSS** | 2.96 (1.87-4.73) | 2.94 (1.42-5.52) | 0.66 |
| **OSI** | 0.50 (0.20-4.30) | 0.40 (0.20-1.0) | **<0.01** |
| **APSI** | 0.40 (0.10- 3.10) | 0.30 (0.10- 1) | **0.03** |
| **MLSI** | 0.20 (0.0-2.90) | 0.20 (0.0-0.70) | **<0.01** |
| **LOS** | 34 (15-81) | 39 (18-60) | **0.03** |

*EOFS: eyes open firm surface ECFS: eyes closed firm surface EOSS: eyes open soft surface ECSS: eyes closed soft surface OSI: overall stability index APSI: anterior-posterior stability index MLSI: medial-lateral stability index LOS: limits of stability. All the variables are shown as median (min-max) according to the distribution pattern.*

In multivariate analysis model, polypharmacy was found to be an independently correlated parameter for falling (OR 24.31; 95%CI 3.05-193.91; p<0.01) (Table IV). As a result of ROC analysis, > 2 drugs use was identified as a cut-off for fall risk (94.7% sensitivity and 59.76% specificity, 35.3% positive predictive and 98% negative predictive value, AUC 0.747, p<0.05).

***Table IV.*** *The independently related factors of impaired balance are shown in these multivariate analysis models.*

| Parameters | OR | 95% Confidence Interval | | p value |
|---|---|---|---|---|
| | | Lower limit | Upper limit | |
| ***Model 1**** | | | | |
| **Polypharmacy** | 24.31 | 3.05 | 193.91 | 0.003 |
| ***Model 2*** ** | | | | |
| **Diabetes mellitus** | 7.89 | 1.99 | 31.34 | 0.003 |
| **Inappropriate drug usage** | 11.05 | 2.39 | 51.10 | 0.002 |

****Model 1:*** *The parameters those had p value lower than 0.05 when comparing between patients with and without falling history were included in this multivariate model. The parameters were polypharmacy, hypertension, diabetes mellitus, hypothyroid, body mass index, walking speed, eyes closed firm surface, overall stability, anterior-posterior stability, medial-lateral stability and limits of stability indexes, mini-nutritional assessment-short form, mini-mental state examination, Yesavage geriatric depression scale and fasting blood glucose.* ** ***Model 2:*** *Instead of polypharmacy, inappropriate drug usage according to Beers criteria was included in this multivariate analysis model.*

## 4. DISCUSSION

In this study, we have found that polypharmacy would be a related factor for impaired balance and falling in the geriatric population regardless using of a drug that may increase the risk of falling. Additionally, rate of polypharmacy and incidence of inappropriate drug usage were higher in patients with falling history. To our knowledge, this is the first study examining the relationship between polypharmacy and balance with BPBS in older adults.

Falls are one of the major health issues among the older population. Falls are often accompanied by complications such as fractures, long term disability, loss of independence and increased risk of mortality. Polypharmacy is one of the most significant fall risk factor in the older adults [22]. Recently, Zaninotto, et al., showed that the risk of hospitalization due to a fall increased with polypharmacy [23]. In this study, similar with the literature, we have found a positive correlation between polypharmacy and falling risk. Kojima, et al., mentioned that taking 5 or more drugs was a significant risk for falls [24]. Our results have shown that taking two or more drugs is significantly related with increased fall risk in geriatric patients. Additionally, in our study, it has been found that behind the polypharmacy, inappropriate drug use is also an important related factor for falls in elderly population. Especially, serotonin reuptake inhibitors, tricyclic antidepressants, neuroleptics, benzodiazepines, anticonvulsants, class 1A antiarrhythmic drugs, digoxin and diuretics are associated with increased falls [6, 25]. We could not find a relation between drug subclasses and fall risk. This finding may be derived from small sample size of the study.

We found that, in the polypharmacy group ABC scores were lower and rate of previous history of fall was higher than control. Previously, researchers found an inverse relation between balance confidence and impaired balance [2]. Also, community-dwelling older adults with fear of falling have demonstrated decreased performance on measures of balance and gait [27]. Lajoie, et al., showed that those individuals with a fall history were more affected by the fear of falling and more restricted in daily activities [28]. Similar to the literature, we found impaired balance and low gait speed in the polypharmacy group.

Body mass index values were higher in the polypharmacy group. Obesity prevalance was increased among geriatric population in recent years. Both aging and obesity could result in multiorgan dysfuntion that leads to increased chronic diseases and polypharmacy.

Multimorbidities are common in the elderly and these lead to increase in the risk of polypharmacy and related adverse drug reactions. The incidence of chronic diseases such as hypertension, diabetes mellitus and hypothyroidism were found to be higher in polypharmacy group and patients with a history of falling. Although, diabetes mellitus incidence was higher, diabetic neuropathy documented both by symptoms and electromyography did not exist in the polypharmacy group. Additionally, model 1 shows that the polypharmacy is an independently associated factor for impaired balance in the elderly patients irrespective of having diabetes mellitus, hypertension, body mass index, etc.

In older adults, polypharmacy effects many disease processes, with balance function being one of the most susceptible. Evaluation of the older patients with a balance disorder is critical for these patients [29]. To assess balance situation, postural stability of the patients was evaluated by BPBS [19]. In our study, OSI scores were found to be higher in patients with polypharmacy. OSI is believed to be the most reliable indicator of postural stability and higher scores indicate poorer stability [19]. Hsieh, et al., previously reported that, patients with knee osteoarthritis displayed higher OSI than controls, therefore displayed lower postural stability [30]. In the polypharmacy group, also, sway index, measured at a condition eyes closed firm surface, was higher than control group demonstrating that firm surface might be related with impaired balance. However, in previous studies, soft foam surface has been shown to be related with poor balance assessment results that challenges with our results [31]. This finding may be due to the eyes condition (open or closed) while using the device [32]. In our study, no impaired balance was detected in patients using BPBS device while their eyes open regardless of the characteristics of the surface.

Additionally, our results showed that limits of stability scores were worse in the polypharmacy group. Limit of stability is defined as the maximum angle a person's body can achieve from vertical position without losing balance [19]. Lower LOS values point out the unstable patient. It has been demonstrated that hip muscles strength that contributes to balance is reduced with ankle

dysfunction. Also, fatigue of ankle plantar flexors and dorsiflexors have shown to significantly influence sway parameters and postural control [33]. Additionally, these authors mentioned that, due to the impairment in the large muscles of the ankle, the smaller muscles of the foot compromise for maintaining the stability. In the elderly as well as polypharmacy, these findings may be due to the sarcopenia in the lower extremity muscles.

The study had several limitations. The information about the falls of the patients was evaluated retrospectively. Prospective analysis including falls history of the patients should be performed with larger studies. This study was not in a longitudinal manner. Secondly, falls were self-reported. Because of that, some of the patients may have not remembered the all fallings. Thirdly, the underlying causes of previous falls history of our patients had not been exactly explored. The reason for that is the assessment of falls was made retrospectively.

In conclusion, polypharmacy is a remarkable problem leading to balance problems and falls in geriatric population. Falls related injuries take great place in health care expenditures. In evaluation of the older adults presenting with balance problems, polypharmacy and inappropriate drug usage should be kept in mind and questioned separately.

### Compliance with Ethical Standards

**Ethical Approval**: The study protocol was approved by the Ethics Committee of Kecioren Training and Research Hospital, Ankara, in 2015 and informed consent was obtained from each participant conforming to the Helsinki Declaration.

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# Correlation of PAPP-A values with maternal characteristics, biochemical and ultrasonographic markers of pregnancy

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## ABSTRACT

Objective: Our aim is to investigate whether there is a correlation of pregnancy-associated plasma protein A (PAPP-A) values with other variables in pregnancy and maternal characteristics.

Materials and Methods: We retrospectively analyzed the relation between the PAPP-A levels, demographics, biochemical and ultrasonographic markers of the first trimester screening of 11,842 pregnant women seen at a tertiary hospital between November 2002 and November 2008.

Results: A significant difference between PAPP-A values of the diabetic and non-diabetic pregnant women were observed (p=0.0005, Mann-Whitney U test). In terms of weight, crown-rump length, Beta-hCG values, significant differences were observed between low and medium level PAPP-A subgroups and between low and high level PAPP-A subgroups. PAPP-A levels were found to differ significantly between the pregnant women of Caucasian origin and other racial origins.

Conclusions: Pregnant women with different ethnic and medical backgrounds have different PAPP-A values and other markers of the aneuploidy screening. To make patient specific risk predictions, understanding these interactions and differences is important. Future studies are needed to understand the pathopyhsiology behind these differences.

Keywords: Pregnancy-associated plasma protein A (PAPP-A), Maternal characteristics, Aneuploidy screening, Biochemical markers, Ultrasonographic markers

## 1. INTRODUCTION

Pregnancy-associated plasma protein A (PAPP-A) is one of the markers used in aneuploidy screening. It can be used alone or with other markers. Used alone, low PAPP-A levels can indicate adverse pregnancy outcomes such as small for gestational age babies, preterm delivery, intrauterine growth retardation and large for gestational age babies in high PAPP-A levels [1-3]. High levels of PAPP-A (PAPP-A more than 4 multiples of median (MoM) are rarely observed and there are a few studies on the outcomes of pregnancies with extremely high PAPP-A levels (More than 5 MoM) [4].

Previous studies demonstrated that there is an effect of different PAPP-A levels on maternal characteristics [5-8]. Westergaard et al., found statistically significant correlation between PAPP-A concentrations and maternal weight, placental weight, fetal sex and gravidity [5]. Several studies showed that PAPP-A level is higher in women of Afro-Caribbean, South Asian and East Asian racial origin, than in Caucasian women [7,8].

The relation between gestational diabetes and PAPP-A is an active research area [9]. Syngelaki et al., reported that PAPP-A levels of patients who developed gestational diabetes were 5.1–30.8% lower than other pregnant women [10]. Lovati et al. showed that low PAPP-A was associated with gestational diabetes mellitus (DM) and lower values were found in insulin dependent diabetic women [11].

The objectives of this study with its large cohort is to identify and quantify the effects of maternal characteristics and biochemical and ultrasonographic markers of first trimester screening on PAPP-A levels to make better predictions for pregnancy outcome and therefore to give better counselling and follow up.

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## 2. MATERIALS and METHODS

We retrospectively collected first trimester screening data from 11,824 singleton pregnant women followed between November 2002 and November 2008 after approval by the Yale University Ethics Commitee (September 23, 2008, protocol number HIC 080.900.4229). In this study group, there were only 23 pregnancies (0.18%) with PAPP-A above 5 MoM .

As part of first trimester aneuploidy screening, free beta human chorionic gonadotrophin (Beta-hCG) and PAPP-A measurements of pregnant women were collected. Free Beta-hCG and PAPP-A were measured using IMMULITE 1,000 analyzer (BioDPC, USA). The concentrations of these markers were converted to MoMs. Features such as age, weight, diabetes status, age group risk, down syndrome risk, nuchal translucency (NT), and crown-rump length (CRL) were recorded.

Mean, median, minimum and maximum values of 11,842 patients' age, weight, gestational week, crown-rump length (CRL), nuchal translucency (NT), PAPP-A, beta-hCG, age group risk and Down syndrome risk values were calculated. Log10 transformation was applied to MoM values of NT, free Beta-hCG, and PAPP-A.

### Statistical Aalysis

Statistical analysis was performed on a computer using statistical program for social sciences version 22.0 (IBM SPSS Statistics Base 22.0). 11,842 patients were divided into subgroups according to PAPP-A levels, diabetes status and race. Mean, median, minimum and maximum values were recalculated. Mann-Whitney U test was used to test whether the variables used in the study were significant. The significance level was set to 95%. Log-transformed data were also analyzed in this study to normalize the distribution of the residuals, as required for the linear regression and as it is a widely used method in this field. P-values less than 0.05 were considered statistically significant.

## 3. RESULTS

First, we analyzed the characteristics of 11,842 patients (Table I), and the characteristics of the subgroups that we created according to the pregnant women's diabetic status (Table II). As shown in Table II, there was a significant difference between PAPP-A MoM values of the diabetic and non-diabetic pregnant women (p = 0.0005). For diabetic pregnant women, mean of PAPP-A MoM was 1.03, while for non-diabetic pregnant women, this value was 1.18. Same statistical difference was also observed between PAPP-A log10MoM values of the diabetic and non-diabetic pregnant women (p=0.0005). For diabetic pregnant women, mean of PAPP-A log10MoM was – 0.06, while for non-diabetic pregnant women, this value was 0.002. Another statistically significant difference was found between the weights of pregnant and non-diabetic pregnant women (p <0.0001). For diabetic pregnant women, mean of weight was 89.4 kg, while for non-diabetic pregnant women, this value was 70.5 kg.

***Table I.*** *Maternal and pregnancy characteristics of study population*

| Characteristics | All patients | | |
|---|---|---|---|
| | N | Mean (SD) | Median (min-max) |
| **Age (years)** | 11842 | 31.76±5.46 | 32(14-53) |
| **Weight (kg)** | 11842 | 70.87±17.1 | 66.6(36.5-182) |
| **Gestational week** | 11842 | 11.5±0.82 | 12(10-14) |
| **CRL (mm)** | 11842 | 61.3±8.5 | 61.3(36-79.3) |
| **NT MoM** | 11842 | 1.04±0.3 | 1(0.3-6.28) |
| **PAPP-A MoM** | 11842 | 1.1±0.7 | 1(0.06-12.4) |
| **Beta-hCG MoM** | 11842 | 1.07±0.43 | 1.01(0.05-5.01) |
| **PAPP-A (log10MoM)** | 11842 | 0.0016±0.24 | 0(-1.22-1.09) |
| **Beta-hCG (log10MoM)** | 11842 | -0.00056±0.17161 | 0.0043(-1.3-0.699) |
| **Age group risk** | 11842 | 390.81±252.15 | 340(4-1200) |
| **Ds_risk** | 11842 | 5023.38±5543.5 | 2800(2-20000) |

*CRL: Fetal crown-to-rump length, NT:Nuchal translucency, hCG: human chorionic gonadotropin, MoM: Multiples of median, Ds: Down syndrome.*

***Table II.*** *Maternal and pregnancy characteristics of diabetic status-based subgroups*

| Characteristics | Diabetic | | | Non-Diabetic | | | p (Mann Whitney U test) |
|---|---|---|---|---|---|---|---|
| | N | Mean (SD) | Median (min-max) | N | Mean (SD) | Median (min-max) | Diabetic and non-diabetic |
| **Age (years)** | 185 | 31.28±6.33 | 32(16-46) | 11657 | 31.7±5.44 | 32(14-53) | 0.385 |
| **Weight (kg)** | 185 | 89.4±24.5 | 85.3(47.9-182) | 11657 | 70.5±16.7 | 66.6(36.5-172.4) | **<0.00001*** |
| **Gestational week** | 185 | 11.5±0.85 | 11(10-13) | 11657 | 11.5±0.8 | 12(10-14) | 0.543 |
| **CRL (mm)** | 185 | 60.42±9.22 | 60.8(38-79.3) | 11657 | 61.3±8.5 | 61.3(36-79.3) | 0.182 |
| **NT MoM** | 185 | 1.04±0.3 | 1.01 (0.55-2.51) | 11657 | 1.04±0.3 | 1(0.3-6.28) | 0.953 |
| **PAPP-A MoM** | 185 | 1.03±0.72 | 0.85 (0.16-5.67) | 11657 | 1.18±0.7 | 1.01(0.06-12.4) | **0.00049*** |
| **Beta-hCG MoM** | 185 | 1.07±0.43 | 1.01 (0.16-2.86) | 11657 | 1.07±0.43 | 1.01(0.05-5.01) | 0.825 |
| **PAPP-A (log10MoM)** | 185 | -0.06±0.26 | -0.07 (-0.79-0.75) | 11657 | 0.002±0.24 | 0.004(-1.22-1.09) | **0.00049*** |
| **Beta-hCG (log10MoM)** | 185 | -0.006 ±0.18 | 0.004 (-0.79-0.45) | 11657 | -0.0004 ±0.17 | 0.0043(-1.3-0.69) | 0.825 |
| **Age group risk** | 185 | 416.25±277.8 | 360(11-890) | 11657 | 390.4±251.7 | 340(4-1200) | 0.289 |
| **Ds_risk** | 185 | 4431.13±5219.5 | 240(8-20000) | 11657 | 5032.78±5548 | 2800(2-20000) | 0.055 |

*CRL: Fetal crown-to-rump length, NT: Nuchal translucency, hCG: human chorionic gonadotropin, Ds: Down syndome, MoM: Multiples of median, *Using Mann-Whitney U test, statistical significance at p<0.05.*


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We then divided our dataset into the following three subgroups according to the PAPP-A levels; low PAPP-A (PAPP-A level < 4), medium PAPP-A (4 < PAPP-A level < 5), and high PAPP-A (PAPP-A level > 5). Table III identifies the characteristics of these subgroups. Significant differences were observed between low PAPP-A level subgroup and medium PAPP-A level subgroup in terms of weight, CRL, Beta – hCG MoM, Beta-HCG log10MoM values (p values of Mann-Whitney U test<0.05). Similarly, significant differences were observed between low PAPP-A level subgroup and high PAPP-A level subgroup in terms of weight, Beta-hCG MoM, Beta-hCG log10MoM values (p values of Mann-Whitney U test<0.05). Mean of weight was 70.79 kg for low PAPP-A level subgroup, while this value was 91.84 kg for high PAPP-A level subgroup.

***Table III.*** *Maternal and pregnancy characteristics of PAPP-A level-based subgroup*

| | Subjects with PAPP-A level < 4 (Low) | | | 4 < PAPP-A level < 5 (Medium) | | | PAPP-A level > 5 (High) | | | p (Mann-Whitney U test for PAPP-A levels) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | Mean (SD) | Median (min-max) | N | Mean (SD) | Median (min-max) | N | Mean (SD) | Median (min-max) | Low-Medium | Low-High | Medium-High |
| **Age (years)** | 11762 | 31.76±5.46 | 32(14-53) | 52 | 31.7±5.43 | 32(21-40) | 28 | 32.67±4.11 | 33.5(25-42) | 0.905 | 0.479 | 0.606 |
| **Weight (kg)** | 11762 | 70.79±16.97 | 66.6(36.5-182) | 52 | 77.9±19.2 | 71.4(48.8-135) | 28 | 91.84±35.21 | 90.11(47.45-161.53) | **0.005*** | **0.005*** | 0.217 |
| **Gestational week** | 11762 | 11.55±0.82 | 12(10-14) | 52 | 11.25±0.7 | 11(10-13) | 28 | 11.35±0.85 | 11(10-13) | 0.006 | 0.144 | 0.722 |
| **CRL (mm)** | 11762 | 61.39±8.57 | 61.3(36-79.3) | 52 | 57.07±8.53 | 57.3(41-79.3) | 28 | 59.3±9.9 | 59.1(45.2-77.3) | **0.001*** | 0.224 | 0.356 |
| **NT MoM** | 11762 | 1.04±0.3 | 1(0.3-6.28) | 52 | 1.1±0.34 | 1.05(0.5-2.39) | 28 | 0.98±0.33 | 0.97(0.31-1.84) | 0.222 | 0.327 | 0.162 |
| **Beta-hCG MoM** | 11762 | 1.07±0.42 | 1.01(0.07-5.01) | 52 | 1.34±0.5 | 1.21(0.37-3.02) | 28 | 1.46±0.73 | 1.37(0.05-3.41) | **<0.0001*** | **0.001*** | 0.661 |
| **Beta-hCG (log10MoM)** | 11762 | -0.001±0.17 | 0.0004 (-1.15-0.69) | 52 | 0.09±0.17 | 0.08(-0.43-0.48) | 28 | 0.08±0.32 | 0.13(-1.3-0.5) | **<0.0001*** | **0.001*** | 0.661 |
| **Age group risk** | 11762 | 390.9±252.1 | 340(4-1200) | 52 | 393.9±261.9 | 340(50-850) | 28 | 341.6±210.3 | 265(35-760) | 0.995 | 0.404 | 0.505 |
| **Ds_risk** | 11762 | 5011.6±5532.4 | 2800(2-20000) | 52 | 6983±7096.1 | 3050(20-20000) | 28 | 6321.78±6105.6 | 3100(310-20000) | 0.081 | 0.146 | 0.972 |

*CRL: Fetal crown-to-rump length, NT: Nuchal translucency, hCG: human chorionic gonadotropin, Ds: Down syndome, MoM: Multiples of median, *Using Mann-Whitney U test, statistical significance at p<0.05.*

***Table IV.*** *Maternal and pregnancy characteristics of racial origin based subgroups*

| | Caucasian Patients (C) | | | Afro-Caribbean Patients (A) | | | Patients of Other Ethnicities (O) | | | P (Mann Whitney U test for diabetic yes and no) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | Mean (SD) | Median (min-max) | N | Mean (SD) | Median (min-max) | N | Mean (SD) | Median (min-max) | C-A | C-O | A-O |
| **Age (years)** | 8807 | 32.3±5.11 | 33(15-53) | 1046 | 29.4±6.37 | 29(15-46) | 1989 | 30.4±5.82 | 31(14-45) | **<0.0001*** | **<0.0001*** | **<0.0001*** |
| **Weight (kg)** | 8807 | 70.7±16.3 | 66.6(40.15-172.4) | 1046 | 81.5±20.9 | 78.02 (45.17-182.06) | 1989 | 65.7±15.6 | 62.05(36.5-161.5) | **<0.0001*** | **<0.0001*** | **<0.0001*** |
| **Gestational week** | 8807 | 11.5±0.8 | 11(10-14) | 1046 | 11.7±0.86 | 12(10-13) | 1989 | 11.6±0.8 | 12(10-14) | **<0.0001*** | **<0.0001*** | **0.002*** |
| **CRL (mm)** | 8807 | 61.2±8.49 | 61.1(36-79.3) | 1046 | 62.16±8.87 | 62.1(36-79.3) | 1989 | 61.5±8.7 | 61.5(36.1-79.3) | **0.001*** | 0.089 | 0.095 |
| **NT MoM** | 8807 | 1.04±0.32 | 1(0.3-6.28) | 1046 | 0.98±0.25 | 0.95(0.31-2.78) | 1989 | 1.06±0.32 | 1.02(0.41-4.74) | **<0.0001*** | 0.04 | **<0.0001*** |
| **PAPP-A MoM** | 8807 | 1.14±0.66 | 0.98(0.06-8.32) | 1046 | 1.45±1.01 | 1.21(0.16-12.4) | 1989 | 1.18±0.73 | 1(0.08-6.24) | **<0.000001*** | 0.269 | **<0.0001*** |
| **Beta – hCG MoM** | 8807 | 1.06±0.41 | 1(0.09-4.37) | 1046 | 1.21±0.52 | 1.11(0.05-5.01) | 1989 | 1.07±0.42 | 1.01(0.11-3.3) | **<0.0001*** | 0.170 | **<0.0001*** |
| **PAPP-A (log10MoM)** | 8807 | -0.006±0.23 | -0.0087(-1.22-0.92) | 1046 | 0.075±0.27 | 0.08(-0.79-1.09) | 1989 | 0.00038±0.25 | 0(-1.09-0.79) | **<0.0001*** | 0.269 | **<0.0001*** |
| **Beta – hCG (log10MoM)** | 8807 | -0.006±0.16 | 0(-1.04-0.64) | 1046 | 0.04±0.18 | 0.04(-1.3-0.69) | 1989 | 0.00043±0.16 | 0.004(-0.95-0.51) | **<0.0001*** | 0.170 | **<0.0001*** |
| **Age group risk** | 8807 | 365.09±240.05 | 310(4-900) | 1046 | 494.17±282.6 | 525(11-900) | 1989 | 450.36±263.25 | 430(14-1200) | **<0.0001*** | **<0.0001*** | **<0.0001*** |
| **Ds_risk** | 8807 | 4679.9±5271.3 | 2600(2-20000) | 1046 | 6660.5±6405.7 | 4300(11-20000) | 1989 | 5683.2±5998.2 | 3200(2-20000) | **<0.0001*** | **<0.0001*** | **<0.0001*** |

*CRL: Fetal crown-to-rump length, NT: Nuchal translucency, hCG: human chorionic gonadotropiN, Ds: Down syndome, MoM: Multiples of median, *Using Mann-Whitney U test, statistical significance at p<0.05.*

We also divided our dataset into the following three subgroups according to the racial origin. 74.3%, 8.8%, 16.8 % of the 11,842 subjects were Caucasian, Afro-Caribbean, other, respectively. Table IV summarizes the characteristics of these subgroups. Significant differences were observed between all pairs in terms of weight, gestational week, NT MoM, PAPP-A MoM, Beta-hCG MoM, PAPP-A log10 MoM, Beta-hCG MoM, age group risk, Down syndrome risk values. There was a significant difference in CRL between the Caucasian and Afro-Caribbean subgroups ($p < 0.05$). While the mean of CRL was 61.1 for Caucasian subgroup, this value was 62.16 for Afro-Caribbean subgroup.

We looked at the correlation between fetus NT values and PAPP-A MoM values of pregnant women whose PAPP-A MoM values were grouped as low-normal (less than 4), high (between 4 and 5) and very high (greater than 5) (Figure 1). There was no significant correlation between PAPP-A MoM and fetus NT measurement in these groups (r=0.04, 0.4, 0.1 for PAPP-A low-normal, high, very high subgroups, respectively).

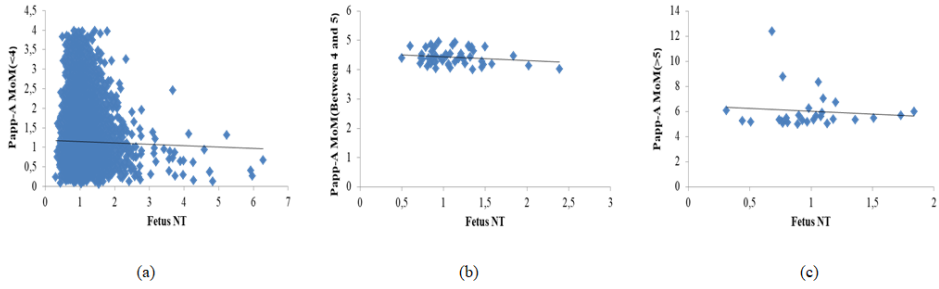


***Figure 1.*** *Correlation between fetus nuchal translucency (NT) values and PAPP-A MoM (multiples of median) values of pregnant women. PAPP-A MoM values were grouped as (a) low-normal (less than 4), (b) high (between 4 and 5) and (c) very high (greater than 5).*

In addition no correlation was observed between PAPP-A MoM and NT values for racial origin groups (r= 0.009, 0.029, 0.029, for Caucasians , Afro-Caribbean's,other ethnicities, respectively) (Figure 2). There was no correlation between PAPP-A MoM and CRL values for racial origin groups (r= 0.04, 0.06, 0.03 for Caucasians, Afro-Caribbeans, other ethnicities, respectively) (Figure 3).

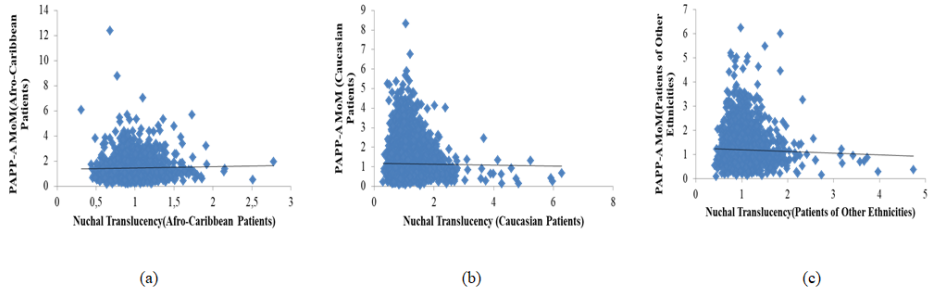


***Figure 2.*** *Correlation between PAPP-A MoM (multiples of median) values and nuchal translucency (NT) values for different racial origin groups, i.e. (a) Afro-Caribbean Patients, b) Caucasian Patients, c) Other Patients*

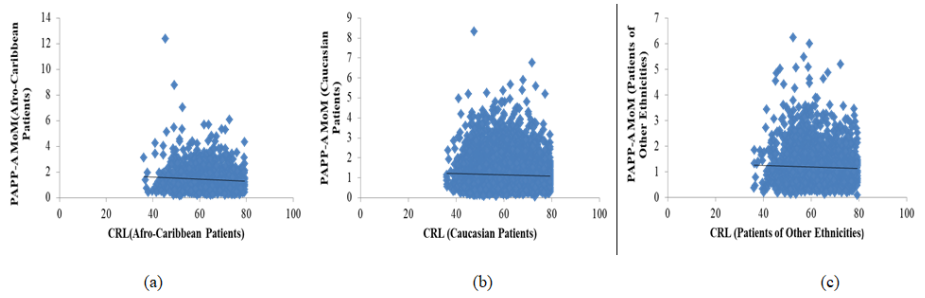


***Figure 3.*** *Correlation between PAPP-A MoM (multiples of median) values and fetal crown-to-rump length (CRL) values for different racial origin groups, i.e., (a) Afro-Caribbean Patients, b) Caucasian Patients, c) Other Patients*

## 4. DISCUSSION

Pregnancy-associated plasma protein A values are used in predicting pregnancy outcomes, so using accurate cut-off values according to patient's characteristics is important to avoid misinterpretation of results. We found similar results with the previous studies [5-7], that there was a racial difference; Caucasians had lower PAPP-A values than Afro-Caribbeans and other racial groups. In aneuploidy screening one does not fit all, and more studies are needed to make specific charts for different ethnic groups.

Gestational diabetes is another factor that affects PAPP-A levels. Again in line with previous studies [8,9], we also found that PAPP-A levels were significantly lower in pregnant women with diabetes. As expected, the weights of the women in the diabetes group were higher than the non-diabetics regardless of ethnic background. Pregnant women must be counseled about healthy diet.

Pregnancy-associated plasma protein A is a protease for insulin like growth factors (IGF) and acts as an important regulator in their function [10]. IGFs stimulate growth and decrease glucose levels. It is therefore reasonable to observe low PAPP-A levels in diabetic pregnant women.

When we looked at correlations between CRL, NT and ethnic differences, we found that there was a small but significant difference in NT and CRL measurements between fetuses of different ethnic origin. Intrauterine fetal growth charts developed by Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) [12], INTERGROWTH [13] and WHO [14] also showed that the percentile cut-points for SGA and LGA varied among the studies. Both environmental and genetic factors are hypothesized to cause differences in body size and proportion [15] , but still determinants of fetal growth are not fully understood [16,17].

Our study with its large cohort of pregnant women coming from different ethnic origins provides useful data for examining the relationship between certain demographic factors, diabetes, CRL, NT and PAPP-A levels. Adjusting the normal values for different backgrounds is important to make accurate patient specific risk predictions [18]. Understanding its interaction with other pregnancy markers and demographics may help us better understand PAPP-A physiology and function in pregnancy.

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### Compliance with Ethical Standards

**Ethical Approval:** The study was approved by Yale University, School of Medicine Ethics Committee (September 23, 2008, protocol number HIC 080.900.4229).

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**Author contributions:**Research idea, data collection, literature search, reviewing of analysis results, writing: H.K.,

Data mining, statistical analysis, drawing the tables and figures, writing, literature search: O.G.U.,

Statistical analysis, literature search: J.H.,

Data mining, statistical analysis, reviewing and editing of the manuscript, literature search: B.B.G. We confirm that the final version of the article has been read and approved by all named authors.

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# Ultrasound shear-wave elasticity and magnetic resonance diffusion coefficient show strong inverse correlation in small fibroadenomas

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ABSTRACT

Objective: Stiffness of breast lesions helps distinguish malignant from benign solid masses. Stiffness can be quantitatively measured by magnetic resonance and ultrasound imaging using apparent diffusion coefficient (ADC) and shear-wave elastography (SWE) techniques, respectively. This study aims to analyze correlations between SWE and ADC in biopsy-proven small fibroadenomas.

Patients and Methods: Shear-wave elastography and ADC measurements of 50 fibroadenomas were evaluated retrospectively. Mean patient age was 41±13 years (range 27-63). All lesions had maximum diameters of ≤20 millimeters. Correlations between intralesional ADC, lesion-parenchyma ADC ratio, intralesional SWE, SWE heterogeneity index and lesion volume were analyzed.

Results: Mean values of lesions were as follows: ADC=1.71±0.22 x10-3mm2/s, ADC ratio=1.04±0.09, maximum SWE=73.4±28.8 kPa, minimum SWE=43.9±21.8 kPa and SWE heterogeneity index =29.4±12.7 kPa. There was a strong inverse correlation between fibroadenoma ADC and SWE values (rho = – 0.746, p <0.01). Significant correlations were also found between fibroadenoma volume and ADC (rho = – 0.525, p <0.05) and SWE (rho = 0.840, p <0.01).

Conclusion: Apparent diffusion coefficient and SWE values show strong inverse correlation in small fibroadenomas. If proven threshold values for lesion characterization are revealed, ultrasonographic SWE and diffusion-weighted MRI have potential to be used interchangeably.

Keywords: Apparent diffusion coefficient, Fibroadenoma of breast, Magnetic resonance imaging, Ultrasound shear-wave elastography

## 1. INTRODUCTION

Stiffness of breast lesions helps distinguish malignant from benign solid masses. Tissue stiffness can be quantitatively and objectively assessed by magnetic resonance and ultrasound imaging using apparent diffusion coefficient (ADC) and shear-wave elastography (SWE) techniques, respectively. Diffusion-weighted magnetic resonance imaging (DW-MRI) is based on random diffusivity principle of water molecules. Diffusivity is impeded within dense and highly cellular tissues and can be quantitatively measured as ADC values. Ultrasound SWE, on the other hand, uses acoustic energy pulses to generate shear waves causing transient displacements in tissue which are then measured as shear moduli as absolute measures of tissue elasticity. Both techniques have previously been proven to be useful adjuncts in determining malignancy risk of large solid breast masses [1, 2]. This study, on the other hand, aims to analyze correlations between SWE and ADC in a rather overlooked category of breast lesions, namely biopsy-proven small fibroadenomas.

## 2. PATIENTS and METHODS

Approval for the study was obtained from the Ethics Committee of Marmara University, School of Medicine with the decision numbered 2018.478. A total of 50 consecutive female patients with biopsy proven solitary fibroadenomas of maximum diameter ≤20 millimeters within a one year period, from May 2018 till May 2019, were included after consenting to usage of relevant medical information in written form during follow-up clinical visits. Routine pre-biopsy diagnostic magnetic resonance and ultrasound studies were reviewed for ADC and SWE measurements.

Diagnostic breast MRI were realized using a 1.5 Tesla scanner (Optiva, General Electrics, USA) with the patient in prone position and both breasts in bilateral 16-channel phased array dedicated breast coils. DW-MRI examination was performed using a pre-contrast axial single-shot echo planar imaging (EPI) sequence with fat suppression and b values of 0, 400, and 800 s/mm$^2$. TR/TE was 6055/69 ms and FOV was 350 mm. A 3.5 mm slice thickness and

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a matrix of 128x96 was employed. ADC maps were automatically calculated by MRI scanner. ADC measurement of lesions were performed using specialized software (AW Volume Share, version 5, General Electrics, USA) by manually placing region of interest (ROI) on the largest cross-section of lesions (Figure 1). ADC values were recorded in units of $mm^2/s$ and control ADC measurements from contralateral breast parenchyma were also made in order to obtain a lesion to parenchyma ADC ratio.

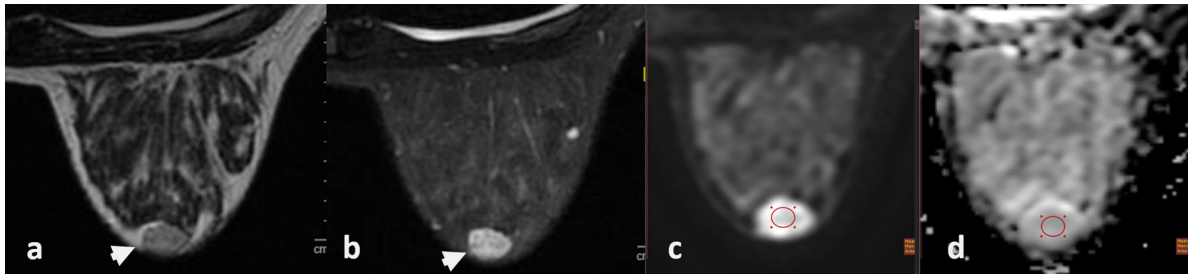


***Figure 1.*** *A 27-year-old female presenting with enlarging periareolar mass. (a) T2-weighted axial and (b) Fat-saturated T2-weighted axial images delineate a well-circumscribed oval retroareolar lesion (arrowheads). (c) Diffusion-weighted imaging and (d) corresponding Apparent Diffusion Coefficient maps show restricted water diffusion within the lesion. ADC measurements are performed using a free-hand elliptical ROI (ovals).*

Pre-biopsy SWE of lesions was performed using a 12-16 MHz linear probe and a dedicated ultrasound system (Logic S8, General Electrics, USA) by a single operator who had over 15 years of experience in breast imaging and previous practice of SWE in different patient populations. Sonoelastographic measurements were made with the transducer held perpendicular to the skin while applying minimal pressure during one single breath-hold. A standard circular ROI of $2.25mm^2$ area was used and intralesional maximum and minimum elasticity ($E_{max}$ and $E_{min}$) were measured in units of kilopascals (kPa) (Figure 2). Lesion volume was calculated using formula for spheroid volume, i.e. $V = 4/3 \times \pi \times r1 \times r2 \times r3$; and SWE heterogeneity indices (HI) were calculated according to formula $HI = E_{max} - E_{min}$.

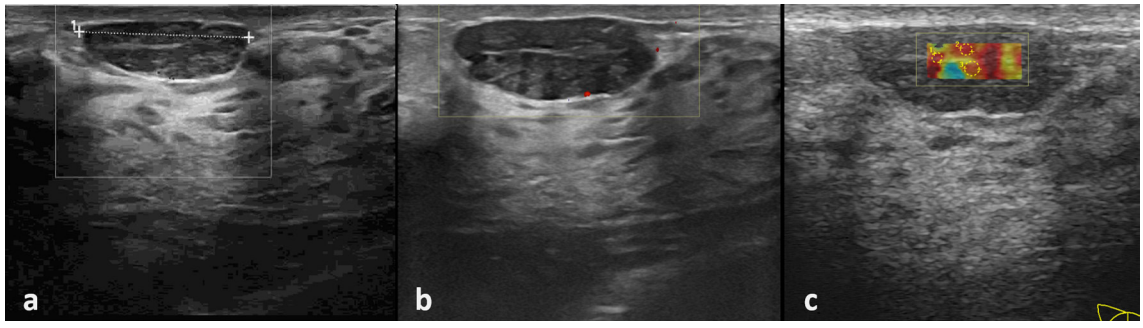


***Figure 2.*** *(a) Ultrasound image of retroareolar mass of the same patient. (b) Lesion had interval enlargement within one-year clinical follow-up, and was therefore sampled. Pathological diagnosis was consistent with fibroadenoma. (c) Shear-wave elastography of the lesion.*

### Statistical Analyses

Statistical analyses were performed using a commercially available software package (SPSS Advanced Statistics module, version 21.0, IBM, USA) and potential correlations among ADC measurements, i.e. intralesional ADC and lesion-to-parenchyma ADC ratio ($ADC_{ratio}$), and SWE values, namely $E_{max}$, $E_{min}$ and HI, were sought. Correlation strength was categorized based on Spearman's correlation coefficient obtained from analyses (Table I). The Mann-Whitney U test was used to compare continuous data between groups. The results were evaluated at a 95% confidence interval. $p < 0.05$ was considered significant.

***Table I.*** *Strength of linear relationship corresponding to correlation coefficient value (Spearman's rho).*

| Correlation coefficient value (rho=) | Strength of correlation |
|---|---|
| 0.80 – 0.99 | Very Strong |
| 0.60 – 0.79 | Strong |
| 0.40 – 0.59 | Moderate |
| 0.01 – 0.39 | Poor |

## 3. RESULTS

Patient ages ranged from 27 to 63 years (mean 41±13 years). Mean lesion volume was 735 $mm^3$ while median volume was


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434 $mm^3$ and volumes ranged from 113 to 3751 $mm^3$. Mean ADC of lesions was 1.71±0.22 $x10^{-3}$ $mm^2/s$ (range 1.37 to 2.11 $x10^{-3}$ $mm^2/s$). Mean lesion to normal parenchyma ADC ratio was 1.04±0.9 and ranged from 0.90 to 1.21. Mean elasticity measurements of lesions were as follows: $E_{max}$=73.4±28.8 kPa (range 41-133 kPa), $E_{min}$=43.9±21.8 kPa (range 15-84 kPa) and HI=29.4±12.7 kPa (range 12-61 kPa).

A strong inverse correlation was found between ADC and $E_{max}$ of fibroadenomas (rho = – 0.746, p <0.01) (Figure 3). Additionally, there were a strong inverse correlation among mean ADC and $E_{min}$ (rho = – 0.661, p=0.003) and a moderate inverse correlation between ADC and HI (rho = – 0.538, p=0.001). $ADC_{ratio}$ and $E_{max}$ had a moderate inverse correlation (rho = – 0.525, p <0.01) (Figure 4). There were no statistically significant correlations among $ADC_{ratio}$ and $E_{min}$ or HI (rho = – 0.335, p=0.013 and rho = – 0.248, p=0.071, respectively).

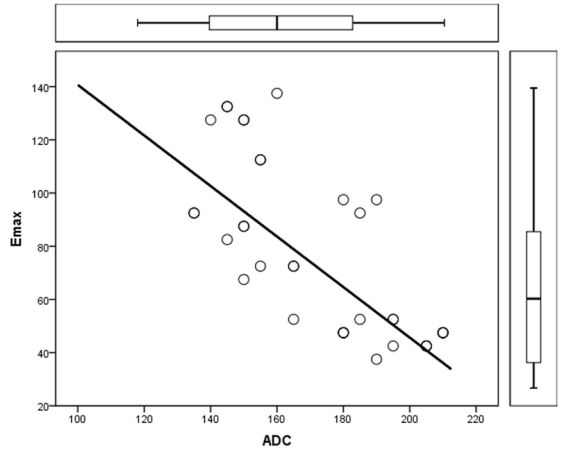


***Figure 3**. A strong inverse correlation was found between apparent diffusion coefficient (ADC) and maximal elasticity (Emax) of fibroadenomas (Spearman's rho = – 0.746, p <0.01). ADC is presented in units of $x10^{-5}$ $mm^2/s$.*

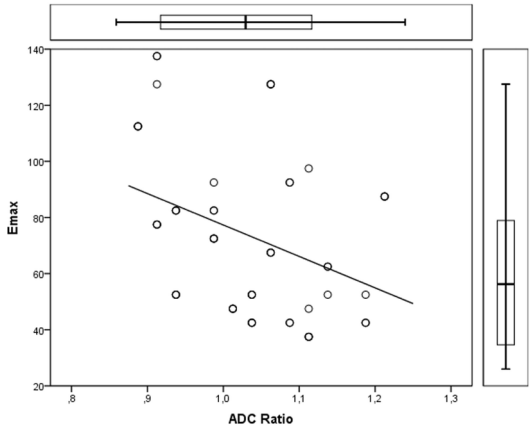


***Figure 4.** Lesion to parenchyma ratio of apparent diffusion coefficient ($ADC_{ratio}$) and maximal elasticity ($E_{max}$) of fibroadenomas had a moderate inverse correlation (Spearman's rho = – 0.525, p <0.01). $E_{max}$ is presented in units of kPa.*

ADC had a moderate inverse correlation with fibroadenoma volume (Spearmans rho = – 0.520, p<0.001) (Figure 5). There was no statistically significant correlations among $ADC_{ratio}$ and fibroadenoma volume (p=0.12). On the other hand, fibroadenoma volumes were positively and strongly correlated with SWE measurements; Spearman's rho were 0.840, 0.680 and 0.745 for $E_{max}$, $E_{min}$ and HI, respectively (p<0.001 in all analyses) (Figure 6).

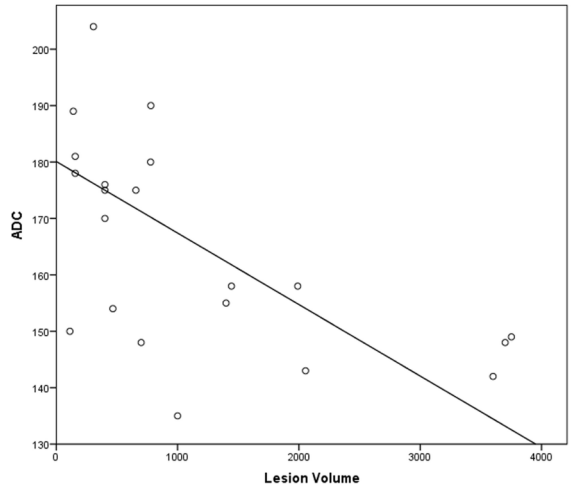


***Figure 5.** Apparent diffusion coefficient (ADC) showed a moderate inverse correlation with fibroadenoma volume (Spearman's rho = – 0.520, p<0.001). Volumes are presented in units of $mm^3$ and ADC in units of $x10^{-5}$ $mm^2/s$.*

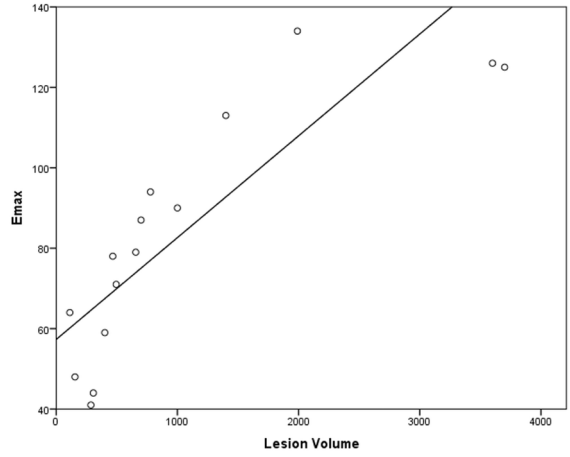


***Figure 6.** Lesion volumes were positively and strongly correlated with maximal elasticity (Emax) measured in fibroadenomas (Spearman's rho=0.840, p<0.001). Volume is presented in units of $mm^3$ whereas $E_{max}$ is in units of kPa.*

There was no statistically significant correlation between patient age and SWE or ADC measurements of fibroadenomas (p = 0.23 and p = 0.47, respectively).

## 4. DISCUSSION

This study demonstrated a strong inverse correlation among ADC and SWE measurements of biopsy-proven small fibroadenomas, implying that ultrasound SWE has potential to be used interchangeably with diffusion-weighted MRI of such masses. ADC and SWE measurements also had significant correlation with lesion size, but not with patient age.

A previous study also showed significantly correlated lesion elasticity and ADC values. ADC values of malignant lesions was reported to be significantly lower than those of benign masses (0.94 versus 1.31 $x10^{-3}$ $mm^2/s$) and elasticity of lesions were also correlated with fibrosis grade histologically [3]. Our study population, comprising solely small biopsy-proven fibroadenomas, had comparable ADC measurements ranging from 1.37 to 2.11 $x10^{-3}$ $mm^2/s$. There were no correlation between patient age and fibroadenoma stiffness in another study [4]. This was also concordant with results of our study.

In our study, lesion volume was significantly correlated with both ADC and SWE measurements. This was in accordance with a previous study which also demonstrated that size of tumor was correlated with its stiffness. In the mentioned study, mean elasticity of larger cancers, i.e. those with diameter >15 mm, was 167 kPa whereas it was 109 kPa for smaller malignancies [5]. In regard to fibroadenomas, a prior study proposed that major predictor of a lesion's stiffness was its size and thus different SWE thresholds were required for malignancy differentiation in lesions of differing sizes [4]. Another study proposed cut-off SWE values of 65 and 75 kPa for small and larger lesions, respectively [6]. This proposal is, on the other hand, not in accord with our study in which maximal elasticity of small fibroadenomas ranged from 41to 133 kPa with a mean elasticity of 73.4±28.8 kPa.

SWE has proven to increase accurate characterization of lesions. In fact, stiffness of large and symptomatic breast masses are more easily assessed with SWE when compared to clinically occult lesions [2, 7]. But, on the other hand, utility of SWE in assessment of malignity has certain caveats. Benign breast masses generally have lower SWE measurements than malignant lesions. But, still there is a wide grey-zone between these proposed cut-off values for benignity and malignancy. In a large cohort, SWE measurements of less than 80 kPa indicated benignity with a specificity of 80% and 120 kPa was proposed as malignancy threshold [8]. Furthermore, there is no widely accepted elasticity threshold for malignancy detection yet. Due to histologic characteristics of certain neoplasms, there is significant overlap of elasticity of malignant and benign lesions. Several studies have indeed proposed very different cut-off values for malignancy [5, 9-11]. Most breast cancers are stiff and have mean elasticity over 50 kPa at SWE. Cancers falsely cleared as benign by SWE are mostly small lesions, i.e. less than 10mm in diameter, and low grade. Pure ductal carcinomas in situ are constitutionally softer than invasive cancers. Thus, a small and soft mass as shown by SWE may as well be an early cancer; so in such cases, it is advisable to use the biopsy option more liberally [12].

Another potential limitation SWE in differentiation of malignancy is that SWE may not be able to calculate lesion elasticity accurately in certain occasions. This occurs due to extremely diminished tissue deformation as seen in large and rigid infiltrative cancers which result in falsely low measurements because ultrasound cannot penetrate such highly attenuating scirrous tissues. This condition has potential to be confused as a low reading due to a lesion's benignity [2, 12]. In such cases, diffusion MRI and ADC mapping is indeed more valuable.

In conclusion ADC and SWE measurements have strong inverse correlation in small fibroadenomas which implies, in select cases, a potential of ultrasonographic SWE to be used interchangeably with diffusion-weighted magnetic resonance imaging.

### Compliance with Ethical Standards

**Ethical Approval**: Approval for the study was obtained from the Ethics Committee of Marmara University, School of Medicine with the decision numbered 2018.478. Written informed consent was obtained from all patients.

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

**Author contributions:** Both authors were actively involved in data collection, analysis, and the writing of the manuscript.

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# Neurosurgical aspects of falls from flat-roofed houses

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ABSTRACT

Objective: This study analyzed the current incidence and characteristics of neurosurgical injuries after falls from flat-roofed houses in Adiyaman.

Patients and Methods: This retrospective study evaluated data of 31 patients who fell from flat-roofed houses and consulted the neurosurgery unit between January and December 2017 at Adiyaman University Hospital, Turkey. Mann–Whitney U test and Spearman coefficient were used for statistical analysis.

Results: There were 19 male and 12 female patients [mean age, 16.8 (range: 1–78) years; <18 years = 77%]. The 2017 crude rate of falls in Adiyaman was 5/100,000 cases. Mean fall height was 2.8 ± 1.0 (2–6) m. The number of cases is significantly higher in months with temperature >33°C (June–September) than those <33°C (p = 0.006). The most common pathology on initial computed tomography was isolated linear fracture (38%). Five patients (2 cranial, 3 spinal) underwent surgery. All patients, except one, reported no or acceptable symptoms in their first outpatient clinic visit. The overall mortality rate was 0%.

Conclusion: High falls from flat-roofed houses are still a common cause of neurosurgical injury. However, the current incidence in Adiyaman is currently not as high as the rates 20 years ago in Diyarbakir, a neighboring city with similar lifestyles.

Keywords: Fall, Flat-roofed houses, Incidence, Injury, Neurosurgery, Trauma

## 1. INTRODUCTION

In hot summer months, the residents of Southeastern Turkey mostly prefer sleeping on the top of flat-roofed houses instead of sleeping inside the house. This is a centuries-old common tradition in the Mesopotamia region that corresponds to Southeastern Turkey, Syria, and Iraq and extends to Kuwait and certain parts of Saudi Arabia. Besides sleeping, the roof of these village houses is a part of daily activities where women dry and store foods; it also serves as a playground for children. This results in a year-long incidence of falls from such roofed houses [1].

Flat-roofed houses are not specific to the Middle East region; in addition, they are commonly encountered in shantytowns worldwide, particularly in South American countries such as Brazil [2] or Asian countries such as Pakistan [3].

Previously, falls from flat-roofed houses were considered the second leading cause of death from accidental injuries in our region [1]. However, the incidence of such fall-related injuries has been drastically declining in the last few years. Therefore, this study aimed to analyze the current incidence and characteristics of fall-related neurosurgical injuries in a Southeastern Turkey city named Adiyaman.

## 2. MATERIALS and METHODS

This was a retrospective study including the prospectively collected data of 31 patients admitted to the emergency department after a fall from flat-roofed houses and consulted to the neurosurgery unit between January 2017 and December 2017 at Adiyaman University Hospital, Adiyaman, Turkey. This hospital is the only tertiary referral trauma center in the entire Adiyaman province with a neurosurgery department. Collected data included age, sex, date, and location of the incident, neurosurgical pathology on the initial computed tomography (CT), height of fall, landing material, reason of fall, the initial Glasgow Coma Scale (GCS) score, treatment modality, type of surgical intervention, types and treatments of associated non-neurosurgical pathologies, total experienced CT count, total

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days of hospitalization in the intensive care unit (ICU) and in the ward, prognosis, and follow-up.

Data for the Turkish population were obtained from the Turkish Statistical Institute [4]. The catalogs studied were as follows: 1590 population of provinces by years (2000–2017) and 1587 population of province/district centers and towns/villages by years and sex (1927–2017). Temperature data were acquired from Accuweather Inc. (PA, USA) [5]. Radiological data were obtained from the reports of a full-time radiology consultant, and the images were double-checked by two consultant neurosurgeons.

### Statistical Analysis

Quantitative variables were compared using the Mann–Whitney *U* test. Correlations between quantitative variables were estimated using Spearman coefficient. IBM SPSS Statistics V21.0 was used for the statistical analysis, and *P* value less than 0.05 was considered statistically significant.

The study was reviewed and approved by Adiyaman University Institutional Review Board (document no:176-21).

## 3. RESULTS

### *Incidence and demographics*

A total of 31 patients (19 males, 12 females) (Table I) who fell from flat-roofed houses were admitted to the emergency department and consulted to the neurosurgery department. The mean age of all patients was 16.8 (range: 1–78) years; 77% (n: 24) were below 18 years. The overall population of Adiyaman in 2017 was 615,076, giving a crude rate of 5 new cases of falls from flat-roofed houses per 100,000 cases (Table II).

***Table I.*** *Clinical characteristics of patients with falls from flat-roofed houses*

| | No. of Cases (%) |
|---|---|
| **Demographics** | |
| Total number of patients | 31 |
| Male | 19 (61%) |
| Female | 12 (39%) |
| Mean age (range) | 16.8 (1-78) |
| Pediatric | 24 (77%) |
| Adult | 7 (23%) |
| **Findings on Initial CT** | |
| **Cranial** | **25 (81%)** |
| Isolated Linear Fracture | **12** |
| Frontal | 8 |
| Parietal | 2 |
| Occipital | 2 |
| Isolated Depressed Fracture | **4** |
| Parietal | 2 |
| Frontal | 2 |
| Linear Fracture + EDH | **3** |
| Temporal | 2 |
| Frontal | 1 |
| Linear Fracture + SDH | **1** |
| Frontal | 1 |
| Linear Fracture + Contusion | **2** |
| Temporal | 1 |
| Occipital | 1 |
| SAH | **2** |
| Diffuse axonal injury | **1** |
| **Spinal** | **6 (19%)** |
| Compression fracture | 5 |
| Burst fracture | 2 |
| **Number of patients who underwent surgery** | 5 (16%) |
| **Number of patients who underwent spine surgery** | 3/6 (50%) |
| **Number of patients who underwent cranial surgery** | 2/25 (8%) |
| **Mortality** | 0 |
| **Associated Pathologies** | **8** |
| Extremity Fracture | 5 |
| Ocular Trauma | 1 |
| Rib Fracture | 1 |
| Retroperitoneal Hematoma | 1 |

*EPH: Epidural hematoma, SDH: Subdural hemorrhage, SAH: subarachnoid hemorrhage*

The fall incidence for Adiyaman was calculated by dividing the number of new cases that were prospectively collected in 2017 by the population of Adiyaman in 2017. The two studies that give information about falls from flat-roofed houses in Diyarbakir were conducted between January 1997 and May 2001 and between January 2005 and December 2008, respectively. The mean yearly incidence was calculated by dividing the total number of cases in 4.4 and 4 years, respectively, by the average population in the given time period. The obtained rates are divided by 4.4 and 4, respectively, to get a mean yearly incidence. Given the lack of yearly case numbers in the given studies, the calculated mean yearly incidence is not an exact number but a close (Table II).

***Table II.*** *Crude rate of falls from flat-roofed houses*

| | Adiyaman | Diyarbakir [1] | Diyarbakir 2 [8] |
|---|---|---|---|
| Population in 2017 | 615,076 | - | - |
| Average population between 1997-2001* | - | 1,328,064 | - |
| Average population between 2005-2008 | - | - | 1,452,000 |
| Total falls | N/A | 1643 | 1056 |
| Neurosurgical consultancy | 31 | 839 | N/A |
| Rate for 100.000[a] | - | 28.1** | 18.1 |
| Rate for 100.000[b] | 5.0 | 14.3** | - |

*N/A: Not available *Average population calculated by the population in 2000 and 2001 because of incomplete data before 2000. **May be slightly higher because the study comprises only winter months in 2001, which may have a lower patient density compared to summer months. [a]For falls in total population in a year. [b]For falls requiring neurosurgical consultancy in the total population in a year.*

### *Characteristics of fall incidents*

All incidents occurred in villages, and all were accidents (no suicidal intent was detected). Twelve of the patients (38%) landed on concrete and the remaining on soil. The mean height of the falls was 2.8 ± 1.0 (2–6) m. There was a significant positive correlation between monthly highest temperature and the number of cases (r = 0.6, p = 0.03). The number of cases was significantly higher in months with temperature above 33°C (June–September) than those below 33°C (p = 0.006, Table III).

***Table III.*** *Distribution of cases according to months*

| 2017 | Jan | Feb | Mar | Apr | May | June* | July* | Aug* | Sept* | Oct | Nov | Dec |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Highest Temperature (°C) | 12 | 18 | 20 | 26 | 33 | 39 | 41 | 43 | 40 | 27 | 21 | 18 |
| No. of cases | 2 | - | 1 | - | - | 4 | 7 | 6 | 6 | 1 | 3 | 1 |

*The number of cases is significantly higher in months with the highest temperature (above 33°C) and marked with an asterisk (*) (p = 0.006).*

### *Clinical data*

The results are summarized in Table I. Twenty-five patients (80%) had a cranial injury; however, no patient simultaneously had a cranial and a spinal injury. The initial GCS score was 14.2 ± 1.2 (10–15). The most common pathology on initial CT was isolated linear fracture (38%), and the most commonly fractured bone was the frontal bone. One patient simultaneously had a burst and compression fracture on the T11 and L2 levels, respectively. Three patients had a multiple level spinal injury, and T12 was the most commonly affected vertebra level in three patients. Five patients experienced an extremity fracture (3 upper, 2 lower extremity), and no surgeries were performed for the associated anomalies. The overall mortality rate was 0%. Five patients (16%, 2 cranial, 3 spinal) underwent surgery. Among them, two underwent "single-level decompression (laminectomy + foraminotomy) + fusion (2 levels up, 2 levels down)" on day 0 of the incident, and one patient underwent "one-level kyphoplasty" for the refractory lumbar pain on the third month after the incident. For cranial injuries, a child underwent surgery for the depressed frontal fracture for cosmetic reasons, and another child with an initial GCS score of 12/15 underwent an emergent surgery for the temporal fracture + epidural hematoma. The mean CT count during hospitalization was 2 ± 1.06 (1–5). Twenty-seven patients (87%) were hospitalized, among which 13 (41%) had an ICU stay. The mean stay in the ward and ICU was 5.6 ± 5.6 (1–22) and 2.4 ± 2.0 (1–8) days. All patients were discharged with full recovery, except one adult woman who fell when she went up to the rooftop to collect some dried food and fell after being butted by a goat. She was paraplegic before and after the surgery, and no functional recovery was observed on her follow-up in five months. All patients were noted to have none or acceptable symptoms in their first outpatient clinic visit on the first month of the fall. The patient who underwent a kyphoplasty has had a decreased visual analog scale score from 6/10 (preoperative) to 2/10 (on postoperative 3 months).

## 4. DISCUSSION

Unintentional injuries are among the top 10 death causes in the USA and are responsible for 5% of overall deaths [6]. Falls can cause serious injuries with high morbidity and mortality; they comprise 21% of all major trauma mechanisms in a recent epidemiological study [7]. Published articles regarding the epidemiological features of falls from flat-roofed houses in Southeastern Turkey are very few [1, 8, 9]. Unfortunately, incidence data about these falls in Adiyaman in the past years is not available; therefore, this is one of the major limitations that prevent from making a more accurate comparison between the present and past years. For comparison, we used two studies conducted in the Diyarbakir province between January 1997 and May 2001 and between January 2005 and December 2008 [1, 8]. We excluded the study conducted in the Batman province as it covered only a seven-month period, which is not adequate for a yearly incidence calculation [9]. The comparison of the incidence of the falls from flat-roofed houses in the Diyarbakir and Adiyaman provinces are acceptable because they are close neighbors and have similar lifestyles, traditions, and demographic characteristics for centuries.

The epidemiological data is summarized in Table II. Yagmur et al., have reported 1.643 patients who fell from flat-roofed

houses between January 1997 and May 2001 [1]. We calculated a mean yearly incidence of 28.1 for overall patients and 14.3 for patients with neurosurgical pathologies. Icer et al.,reported 1,056 falls between January 2005 and December 2008 in Diyarbakir, giving a mean yearly incidence of 18.1 [8]. Another limitation is that these studies conducted in Diyarbakir do not provide the exact number of patients in each year during the study period; therefore, our calculations are not exact but a close approximation. In regard of this data, we can obviously comment that the incidence of falls from flat-roofed houses decreased approximately 1.5 times in Diyarbakir in 12 years (between 1997 and 2008). The incidence for neurosurgical patients in 2017 in our study was almost three times lower than that in the study conducted in Diyarbakir (Table II). We identified three possible reasons for a low incidence in our study:

(1) In 2000, Turkey had a population of 67,803,927, among which 23,797,653 (35%) were living in villages. On the other hand, in 2017, only 6,049,393 (7%) among 80,810,525 people were living in villages [4]. There is a significant drop in the village population in Turkey, where most of the fall-related injuries occur.

(2) Studies that aim to emphasize the importance and identify the risk and preventive factors (compulsory building of pitch-roofed houses or of a barrier around flat roofs, beds, and/or roof stairs, locking of roof door to prevent children from using the roof as a playground) of such situations might create public awareness for the prevention of such accidents [1,8,9].

(3) The use of air conditioning may have been increased over the past 20 years in Turkey.

Falls from flat-roofed houses were the second leading cause of death from accidental injuries in Diyarbakir, accounting for more than 117 deaths (33.7% of 329 traumatic deaths) during 1997 [1]. We did not face any mortality during our study period, possible because of a relatively lower mean height of fall, lower percentage of patients that fell on concrete, and lack of any suicide attempts.

## Conclusion

Although, falls from flat-roofed houses remain an important cause of morbidity, their current incidences in Adiyaman in Southeastern Turkey is currently not as high as that 20 years ago in Diyarbakir, a neighboring city with a similar lifestyle. Possible precautions may further decrease the incidence of such fall-related injuries to more acceptable rates.

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## Compliance with Ethical Standards

**Ethical Approval:** The study was reviewed and approved by Adiyaman University Institutional Review Board (document no:176-21).

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**Conflict of Interest:** None of the authors have any conflict of interest to declare regarding the article.

**Author Contributions:** Concept and Design – CS, SCY, NU, AO; Supervision – AO; Data Collection and Processing – CS, SCY, SK, LTS, ID, TO, ArO, NU; Analysis and Interpretation – CS, OAS; Literature Search – CS, ArO, TO; Writing Manuscript – CS, OAS; Critical Review – SCY, NU, SK, AO. All authors approved the final version of the article.

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# The effect of vaginal cleansing performed with normal saline solution or povidone-iodine before elective caesarean section on postoperative maternal morbidity and infection: A prospective randomized controlled study

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## ABSTRACT

Objective: The present study was designed to determine the effect of vaginal cleansing performed with saline solution or povidone-iodine before elective cesarean section on postpartum maternal morbidity and postoperative infection.

Patients and Methods: One hundred and eighty primiparae, awaiting elective caesarean section, were assigned into the following three groups, Group1 (saline solution vaginal cleansing for 30s, n:60); Group2 (povidone-iodine vaginal cleansing for 30s, n:60); Group3 (control group, n:60).

Results: There were statistically significant differences between the 3 groups in terms of the median values for the postoperative C-reactive protein (CRP) and fever, and visual analogue scale (VAS) score ($p<0.001$). The median value for the postoperative CRP level was 26.5 mg/dl, 59.5mg/dl and 62.3mg/dl in the saline solution, povidone-iodine and control groups respectively. The median value for the VAS score was 3,4 and 4; the incidence of the patients with fever >38°C was 1.7%, 3.4% and 10% in the saline solution, povidone-iodine and control groups, respectively.

Conclusion: Vaginal cleansing with normal saline solution or povidone-iodine before caesarean section significantly reduced postoperative pain, fever, and CRP levels. Cleansing of the vagina before cesarean section clinically reduced the number of postcaesarean wound site infections, and endometritis; however, the reduction was not statistically significant.

Keywords: Caesarean section, Maternal morbidity, Postoperative infection, Vaginal cleansing, Saline solution, Povidone-iodine

## 1. INTRODUCTION

Caesarean section is one of the most commonly performed surgical operations in the world. Postpartum infection morbidity, one of the most common complications after caesarean section, not only poses a serious problem to maternal physiological and psychological wellbeing but also imposes a significant burden to the national economy [1].

Among the causes of infectious morbidity after caesarean section are endometritis, surgical site infection (SSI) and fever. The prevalence of postnatal endometritis is 6-27%. It is 10 times more common in caesarean delivery than in vaginal delivery [2]. Clinically, 5-24% of the postnatal endometritis cases are accompanied by postoperative fever and uterine fundal tenderness and is usually treated with antibiotics administered intravenously. The major concern is that endometritis might result in bacteremia, sepsis, pelvic inflammatory disease or tubo-ovarian abscess. Although, this complication is rare, it is the cause of 0.06% of maternal mortality. Even though, the incidence of surgical site infection (SSI) after caesarean section varies from one clinic to another, it generally ranges between 2% and 19%, and it usually occurs within the first week of postpartum [2, 3].

Most of the infections are caused by the cervicovaginal flora via ascending route [4]. Prolonged premature rupture of membranes, prolonged labor, frequent vaginal examinations and bacterial vaginosis increase the incidence of infection [5]. Today, postoperative infection cannot be eliminated completely, even if modern broad-spectrum antibiotics are administered for preoperative prophylaxis. Bacteria in the vaginal flora,

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particularly enterococci, are resistant to antibiotic cefazolin [4]. Therefore, in addition to antibiotic prophylaxis, preoperative cleansing of the vagina with povidone – iodine is a safe, inexpensive and an easy method in the elimination of bacteria and fungi, and reduces the risk of postoperative infections [6, 7]. A ten-minute preoperative cleansing of the vagina with povidone-iodine reduces not only the anaerobic Gram-positive bacilli, Gram-negative bacilli but also aerobic and anaerobic Gram-positive cocci, particularly Enterococcus [8, 9].

Although, there are publications emphasizing that vaginal cleansing performed before caesarean section decreases the incidence of morbidity due to postoperative ascending infections [10-12], there are other studies stating that vaginal cleansing does not have any effect [1, 13-16].

In the literature, there are studies indicating that uterine and abdominal washing with normal saline during caesarean section reduces postoperative endometritis and surgical site infections [17, 18]. Today, in Turkey, vaginal cleansing performed with normal saline solution and antiseptics like povidone-iodine before elective caesarean section is not performed routinely.

This randomized prospective study was conducted to determine the effect of vaginal cleansing performed with normal saline solution or povidone-iodine before caesarean section on postpartum maternal morbidity and postoperative infections.

## 2. PATIENTS and METHODS

The Clinical Research Ethics Committee of School of Medicine, Medipol University approved the study. The management of the university hospital where the study was conducted gave its written permission to conduct the study before the data collection phase (Reference number: 108400098-604.01.01-E.1468). After the participants were informed about the purpose of the study, their written consent was obtained.

Three thousand pregnant women applied to gynecology outpatient clinic of a private hospital for childbirth between January 2019 and January 2020. Of them, 1400 were primiparous and 1600 were multiparous pregnant women. The universe of the study was 1000 pregnant women who applied for planned caesarean delivery in this date range. Of them, 300 pregnant women underwent a primary caesarean section and 700 underwent a secondary caesarean section. One hundred and eighty primiparous pregnant women wanted to have elective caesarean section. The primary caesarean section rate was 10%. The caesarean section rates in muliparous was 46% and primiparous was 17%. The sample size of the study was calculated using the G * Power (version 3.1). A literature review demonstrated that vaginal cleansing had an effect on postpartum maternal morbidity [19]. Accordingly, when the maternal morbidity was taken into consideration in determining the sample size of the study, the minimum sample size was determined as 150 people (n = 50 for each group) (confidence interval: 95%, test power: 80.9% and effect size: f = 0.2586919) Considering the possibility of refusals, withdrawals and/or losses in the study, it was decided to include 60 participants in each group, and then the study sample was selected.

The inclusion criteria were as follows: being between the ages of 20 and 40, being in the gestational age of 37-42 weeks, having a singleton pregnancy, undergoing elective cesarean section and absence of an active infection. The exclusion criteria were as follows: having preterm labor, premature rupture of membranes, positive bacterial vaginosis and / or group B streptococcus culture within 2 weeks before caesarean section, undergoing emergency caesarean section (due to ablatio placentae, placenta previa, chorioamnionitis, acute fetal distress, placental abnormalities, active hemorrhage), having a chronic disease (e.g. diabetes mellitus, thyroid function, hypothyroidism, cardio vascular problems), regular drug use, long-term steroid therapy, body temperature above 38°C, severe anemia and allergic reaction to the agents used.

Randomization of the women who met the inclusion criteria (n=180) was carried out by simple randomization using three groups of sealed envelopes with labeled notes. The women were asked to choose one of the envelopes which were labeled Group 1 (normal saline solution vaginal cleansing for 30 s n:60), Group 2 (povidon-iodine vaginal cleansing for 30 s, n:60) and Group 3 (control group, n:60) (Figure 1).

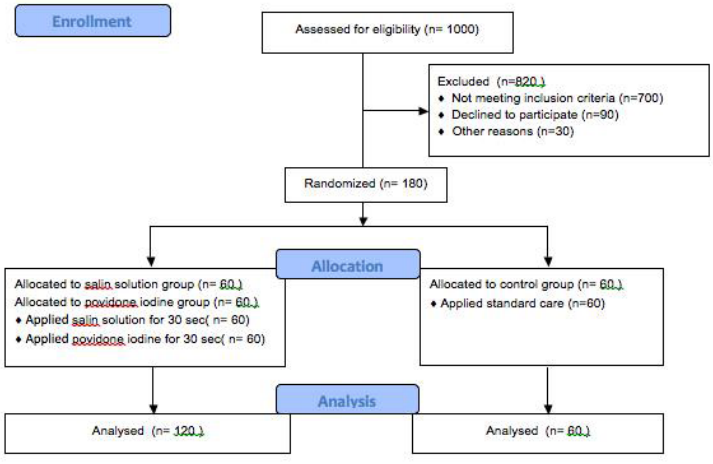


***Figure 1.*** *Randomization of participants*

All the patients were administered adequate general anesthesia and then they were catheterized with Foley's catheter under aseptic conditions. After catheterization, all the vaginal walls and fornices of the participants in Group 1 and 2 were cleaned with sterile square gauze impregnated with 50 ml of normal saline solution or povidone-iodine solution, respectively. The cleaning agents were applied to 360 degrees of the vaginal walls and fornices by the surgical doctor for 30 sec. No vaginal cleansing solution was used for the pregnants in the control group. Skin cleansing of all the patients in the 3 groups was performed with an abdominal scrub. All the patients were given intravenous push with 2 g cephazolin sodium for prophylaxis at the time of umbilical cord clamping during the operation. All the patients underwent the same standard preoperative preparation, and they were operated by the same surgical team. All the participants underwent routine postoperative care.

The participants' demographic data, preoperative hemoglobin (Hgb), hematocrite (Hct), leukocyte (WBC) values, duration of surgery, postoperative 24$^{th}$ hour C-reactive protein (CRP), procalcitonin (PCT) values and fever values, postoperative first week endometritis and surgical site infection findings were assessed and their postoperative 6$^{th}$ and 24$^{th}$ hour pain levels were assessed by the Visual Analogue Scale (VAS). Serum procalcitonin (PCT) levels were measured using an immunoluminometric assay (LUMI test PCT kit: Brahms Diagnostica, Berlin, Germany) and recorded as ng/ml. Serum CRP concentrations were assayed using a Cobas 6000 analyzer with c501 module (Roche, Switzerland) and recorded as mg/dL. VAS was developed and used by Bond and Pilowsky in 1966 for the first time [20]. VAS is a 10-cm ruler with "no pain" at one end and "worst pain" at the other end. The evaluation of VAS is defined as no pain: 0 cm, mild pain: 0.5 cm-3.0 cm, moderate pain: 3.5 cm – 6.5 cm, and severe pain: 7.0 cm – 10.0 cm. It is thought to be the most suitable scale for the determination of acute pain severity because it provides faster results and it is easy to understand [20].

Endometritis was defined as postoperative temperature of > 38°C or at least twice uterine tenderness and persistent offensive lochia 24 hours after birth. Surgical infection was based on a diagnosis of erythema or wound edge separation with purulent discharge involving the caesarean incision site that requires antibiotics therapy and wound care. Postoperative febrile morbidity was defined as temperature of 38 ° C and greater after the first 24 h of surgery in the absence of other clinical findings suggestive of infection (chest infection, urinary tract infection, breast engorgement, etc.).

### Statistical Analysis

Data were analyzed with the IBM SPSS V23. Whether the data was normally distributed was examined with the Shapiro-Wilk test. Kruskal Wallis test was used for the comparison of the data without normal distribution. The chi-square test was used for the analysis of the categorical data according to the groups. Analysis results were presented as a median value (min-max) for the quantitative data and frequency (percentage) for the categorical data. P-values less than 0.05 were considered statistically significant.

## 3. RESULTS

The median age of the participants varied from one group to another (p<0.001). There were no differences between the groups in terms of median height and weight values, and education and income levels (p=0.513, p=0.528, p> 0.05) (Tables I and II).

***Table I.*** *Comparison of parameters by groups*

| | Saline Group Median (min-max) | Povidone-iodine Group Median (min-max) | Control group Median (min-max) | Total* Median (min-max) | p |
|---|---|---|---|---|---|
| Age (year) | 30.5 (21 - 41)b | 28.5 (19 - 39)a | 27 (20 - 40)a | 30 (19 - 41) | <0.001 |
| Height:(cm) | 162.5 (157 - 176) | 162 (150 -175) | 162 (155 -180) | 162 (150 -180) | 0.513 |
| Weight(kg) | 78 (60 - 105) | 80 (65 - 98) | 76.5 (65 - 90) | 78 (60 - 105) | 0.528 |

*a-b: between the groups with the same letter, there is no difference, * Median (min-max)*

***Table II.*** *Comparison of demographic data by groups*

| | Saline n (%) | Povidone- iodine n (%) | Control n (%) | Total* n (%) | p |
|---|---|---|---|---|---|
| **Educational attainment** | | | | | 0.527 |
| Literate but not a graduate of any school | 2 (3.3) | 0 (0) | 1 (1.7) | 3 (1.7) | |
| Primary school | 27 (45) | 22 (36.7) | 18 (30) | 67 (37.2) | |
| High school | 21 (35) | 30 (50) | 29 (48.3) | 80 (44.4) | |
| University | 9 (15) | 6 (10) | 10 (16.7) | 25 (13.9) | |
| Postgraduate | 1 (1.7) | 2 (3.3) | 2 (3.3) | 5 (2.8) | |
| **Income status** | | | | | 0.104 |
| Income lower than expenses | 4 (6.7) | 5 (8.3) | 4 (6.7) | 13 (7.2) | |
| Income equal to expenses | 41 (68.3) | 49 (81.7) | 38 (63.3) | 128 (71.1) | |
| Income higher than expenses | 15 (25) | 6 (10) | 18 (30) | 39 (21.7) | |

**n(%)*

There were no statistically significant differences between the 3 groups in terms of the median values of the preoperative Hgb, Hct and WBC, duration of surgery, values of PCT at the postoperative 24$^{th}$ hour, and the VAS score for pain at the postoperative 6$^{th}$ hour (p>0.05). There were differences between the groups in terms of their postoperative median CRP values (p <0.001). While the median value for the postoperative CRP level was 26.5 mg/dL in the normal saline solution group, it was 59.5 mg/dL in the povidone iodine group and 62.3 mg/dL in the control group. There were differences between the groups in terms of the VAS score for pain at the postoperative 24$^{th}$ hour (p<0.001) (Table III).

***Table III.*** *Comparison of laboratory and clinical parameters by groups*

| | Saline group Median (min-max) | Povidone-iodine group Median (min-max) | Control group Median (min-max) | Total* Median (min-max) | p |
|---|---|---|---|---|---|
| Preoperative Hgb (g/dL) | 12.1 (9.2 - 14.2) | 12.3 (8.9 - 14.2) | 12 (9.2 - 14.4) | 12.1 (8.9 - 14.4) | 0.703 |
| Preoperative Hct% | 36 (29 - 42) | 36.5 (25.9 - 42) | 36 (28 - 41) | 36 (25.9 - 42) | 0.411 |
| Preoperative WBC (x 109/L) | 11.4 (8.8 - 13.8) | 11 (7.2 - 17) | 10.2 (6.1 - 17) | 11 (6.1 - 17) | 0.079 |
| Postoperative 24th hour CRP(mg/dL) | 26.5 (7 - 100)b | 59.5 (10 - 170)a | 62.3 (9 - 170)a | 46.3 (7 - 170) | <0.001 |
| Postoperative 24th hour PCT(ng/ml) | 0 (0 - 0.3) | 0.1 (0 - 0.7) | 0.1 (0 - 0.5) | 0.1 (0 - 0.7) | 0.059 |
| VAS score postoperative 6thhour | 4 (2 - 7) | 4 (2 - 7) | 5 (3 - 7) | 4 (2 - 7) | 0.072 |
| VAS score postoperative 24th hour | 3 (1 - 7)b | 4 (1 - 8)a | 4 (2 - 9)a | 4 (1 - 9) | <0.001 |
| Duration of operation | 30 min (20-60) | 30 min (20-45) | 30 min (25-45) | 30 min(20-60) | 0.520 |

*a-b: between the groups with the same letter, there is no difference, * Median (min-max)*
*Hgb: Hemoglobin g/dL, Hct: hematocrit %, WBC: White blood cell, CRP: C-Reactive Protein, PCT: Procalcitonin, VAS: Visual Analogue Scale (VAS).*

There were no statistically differences between the three groups in terms of postoperative endometritis and wound site infection rates (p>0.05). The incidence of endometritis was 1.7%, 1.7% and 3.3% in the normal saline solution, povidone iodine and control groups, respectively. The incidence of surgical site infection was 3.3%, 3.3% and 6.7% in the normal saline solution, povidone-iodine and control groups, respectively. There were statistically differences between the three groups in terms of the postoperative fever levels (p<0.05). While the percentage of the patients with fever >38°C in the normal saline solution group was 1.7%, it was 3.4% in the povidone-iodine group and 10% in the control group.

***Table IV.*** *Comparison of infectious morbidity findings by groups*

| | Saline group n (%) | Povidone-iodine group n (%) | Control group n (%) | Total* n (%) | p |
|---|---|---|---|---|---|
| Postoperative endometritis | | | | | |
| Yes | 1 (1.7) | 1 (1.7) | 2 (3.3) | 4 (2.2) | 0.774 |
| No | 59 (98.3) | 59 (98.3) | 58 (96.7) | 176 (97.8) | |
| Postoperative surgical site infection | | | | | |
| Yes | 2 (3.3) | 2 (3.3) | 4 (6.7) | 8 (4.4) | 0.593 |
| No | 58 (96.7) | 58 (96.7) | 56 (93.3) | 172 (95.6) | |
| Postoperative fever >38° C | | | | | |
| Yes | 1 (1.7) | 2 (3.3) | 6 (10) | 9(15) | **<0.05** |
| No | 59 (98.3) | 58 (96.7) | 54(90) | 51(85) | |

*n(%)

## 4. DISCUSSION

In the present study, the median age of the participants varied from one group to another. Except for their median age, that the three groups were similar in terms of their socio-demographic characteristics (height, weight, parity, educational attainment and income status) is important for the reliability of the study. The results of the present study are consistent with those of Göymen et al.'s study [19]. In the present study, there were no statistical differences between the groups regarding the duration of surgery, preoperative Hgb, Hct and WBC values, levels of PCT at the postoperative 24$^{th}$ hour, and VAS score for pain at the postoperative 6$^{th}$ hour.

Although, there were statistically significant differences between the 3 groups in terms of the median values for the postoperative infection parameters CRP and fever, and VAS score for pain at the postoperative 24$^{th}$ hour, the highest level of difference was observed in the normal saline solution group. The median value for the postoperative CRP level was 26.5 mg/dL, 59.5 mg/dL and 62.3 mg/dL in the normal saline solution, povidone-iodine and control groups, respectively. The median value for the VAS score for pain at the postoperative 24$^{th}$ hour was 3, 4 and 4 in the normal saline solution, povidone-iodine and control groups, respectively. The incidence of the patients with fever >38°C was 1.7%, 3.4% and 10% in the normal saline solution, povidone iodine group and control groups. There were no statistically significant differences between the 3 groups in terms of the incidence of postoperative endometritis and wound site infections. In general, we believe that waiting for clinical diagnoses (endometritis, wound site infection, etc.) in postoperative infection detection is not an objective in assessing the effectiveness of vaginal cleansing. In our study, more sensitive parameters such as postoperative CRP levels, postoperative fever and postoperative pain were investigated. Thus, evaluation and

early treatment can be done without having to wait for clinical symptoms.

There are publications emphasizing that vaginal cleansing performed before caesarean section decreases the incidence of morbidity due to postoperative ascending infections [10-12]; however, in other studies, it is stated that vaginal cleansing does not have any effect [1, 13-16].

In their meta-analysis, Haas et al., in 2018, investigated 3403 women who had vaginal cleansing with different preparations before caesarean section in terms of postoperative infection morbidity in 11 studies and found that the postpartum endometritis risk as 8.7% in the control group and 3.8% in the vaginal cleansing group (average risk ratio (RR) 0.36, 95% confidence interval (CI) 0.20 to 0.63, 10 trials, 3283 women, moderate quality of evidence). On the other hand, they found no difference between the groups in terms of postoperative fever and wound site infections [10]. In their meta-analysis which included 16 studies with 4,837 women, Caissutti C et al., determined that precaesarean vaginal cleansing decreased the post-caesarean endometritis rate but it did not have any effect on wound site infections and postoperative fever [12]. Unlike the present study, there was a decrease in the endometritis rate in the two meta-analyses. We think that this decrease stemmed from the fact that the authors of the meta-analyses did not perform subgroup analysis and therefore they could not exclude the women with premature ruptured membranes whose active labor started.

Yıldırım G et al., found that vaginal cleansing before caesarean section significantly reduced post-operative endometritis risk in the povidone iodine washed group compared to the control group but there was no statistical difference between the two groups when excluding the patients with membrane rupture before delivery [1].

In another study, although, vaginal cleansing with povidone iodine before caesarean section reduced clinical postoperative fever, endometritis and surgical site infections, the difference was not statistically significant. While the postoperative endometritis rate which was 14.0% before the implementation decreased to 11.7% after the implementation (p=0.49, OR:0.77, CI:0.36–1.62), the postoperative fever decreased from 22.3% to 18.3% (p=0.256, OR:0.70, CI:0.37–1.30) . The infectious wound site complications were 4.5% and 5.8% before and after the implementation, respectively (p=0.76, OR:1.07, CI:0.69–3.64) [16]. These findings are consistent with those of the present study.

In some studies in which vaginal cleansing before caesarean section was performed with saline in the control group and with chlorhexidine in the experimental group, no statistically significant difference was determined in terms of postoperative endometritis [21, 22], which probably stemmed from the fact that they did not have a control group not undergoing vaginal cleansing but that they accepted the saline group as a control group. Guzman et al., performed vaginal cleansing with saline solution and povidone iodine before caesarean section and found that the intervention reduced the rate of post-caesarean endometritis. They also determined that the rates of post-caesarean cellulitis were similar in the two groups [23].

In the present study, in the normal saline solution group, one of the two experimental groups, normal saline solution was found to cause a significant decrease in the postoperative fever, CRP and pain levels compared to the povidone iodine and control groups. As for the postoperative endometritis and surgical site infections, although, vaginal cleansing with normal saline solution before caesarean section led to a decrease clinically, the difference was not statistically significant.

In the literature, the effects of vaginal cleansing performed before caesarean section on postoperative infectious morbidity were generally investigated without discriminating between emergency and elective caesarean section cases. However, the number of studies investigating the effect of preoperative vaginal cleansing on postoperative maternal morbidity in primiparous women undergoing elective caesarean section is limited. Similar to the present study, in their study, Göymen et al., found that in primiparous women undergoing elective caesarean section, pre-operative vaginal cleansing with povidone iodine and chlorhexidine reduced postoperative pain and that CRP values at the 24$^{th}$ hour were lower [19].

Although, vaginal cleansing before caesarean section is more effective in decreasing postoperative infection morbidity in women with premature ruptured membranes whose labor started, this study also showed that vaginal cleansing performed with normal saline solution or povidone iodine solution just before birth in primiparous women undergoing elective caesarean section statistically significantly decreased postoperative pain, fever and CRP levels, which is a biochemical marker of infection, compared to the women in the control group. The beneficial effects, safety, simplicity and low cost of the intervention support its adoption as a method to reduce maternal morbidity.

### Strengths and Limitations of the Study

The present study has some strengths. In order to eliminate all study biases, microbiological measurements were performed for all the participants before caesarean section, and those with infection were excluded from the study. On the other hand, the present study had some limitations as well. The size of the sample was relatively small. Another limitation was that it included only primiparous women whose active labor did not start. Therefore, we recommend that future studies should be conducted excluding these limitations.

## Conclusion

In the present study, it was determined that vaginal cleansing performed with normal saline solution or povidone-iodine led to a statistically significant decrease in postoperative pain, fever and CRP levels which is a biochemical marker of infection in primiparous women undergoing elective caesarean section compared to the women in the control group. It was also determined that vaginal cleansing clinically reduced the number of post-caesarean surgical site infections and endometritis;

however, the reduction is not statistically significant; thus, to generate statistically significant evidence on the issue, large-scale studies should be performed.

### Compliance with the Ethical Standards

**Ethical Approval**: The Clinical Research Ethics Committee of School of Medicine, Medipol University approved the study. The management of the university hospital where the study was conducted gave its written permission to conduct the study before the data collection phase (Reference number: 108400098-604.01.01-E.1468).

All the procedures were performed in accordance with rules regarding studies involving human participants by taking into account the ethical standards of the institutional and/or national research committee and the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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**Informed Consent:** After the participants were informed about the purpose of the study, their written consent was obtained.

**Author Contributions:** D.K.G.: Project development, data collection, manuscript writing, data analysis

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# Effectiveness of dry needling in the treatment of neck pain and disability associated with myofascial trigger points

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## ABSTRACT

Objective: The aim of this study is to evaluate the effectiveness of dry needling (DN) with fast-in and fast-out technique for myofascial trigger points (MTrPs) in the upper trapezius muscle associated with neck pain.

Patients and Methods: Patients aged 18-70 years, who have had neck pain at least one active MTrP in the upper trapezius muscle treated with DN, were included in the study. Pain and disability were assessed with Numeric Rating Scale (NRS) and Neck Disability Index (NDI) before treatment (T0), after first session (T1) and after last session (T2). Number of MTrPs where DN was performed and the number of DN sessions were recorded. Patients were evaluated based on the minimal clinically important change (MCIC) scores for NRS and NDI.

Results: A total of 76 patients (Female: 67, Male: 9) were included in the study. Median number of DN sessions was 3 and median of MTrPs that DN performed was 4. Both NRS and NDI showed significant improvement at T1 and T2. More than 90% of patients had MCIC at T1 and T2.

Conclusion: Dry needling with fast-in and fast-out technique is effective for pain and disability management in patients with neck pain due to MTrPs.

Keywords: Dry needling, Myofascial trigger points, Neck pain, Neck disability

## 1. INTRODUCTION

A myofascial trigger point (MTrP), defined as a hyperirritable nodule in a taut band of the muscle, is a neuromuscular dysfunction caused by the unaccustomed overload of the muscles [1]. The compression of the trigger point is painful, provokes the characteristic referred pain and sensation of the patient, and may cause sensory, motor and autonomic symptoms [2]. Repetitive minor microtraumas, acute musculoskeletal injuries, sudden eccentric or concentric contractions, postural and emotional stress, compressive loading and dehydration are thought to play a role in its etiology. Although, the underlying mechanism of the MTrP has not been clearly defined, inappropriate activity of acetylcholine (ACh) at the neuromuscular junction is the most accepted hypothesis [3]. The inhibition of ACh esterase and upregulation of ACh receptors, as well as the excessive release of ACh, are associated with the development of taut bands and trigger points due to a sustained sarcomere contraction which leads to increased metabolism, local ischemia and hypoxia [4]. Consequently, the increased release of algogenic and sensitizing substances from the damaged tissues causes peripheral and central sensitization [5-7]. There are two types of MTrPs: active and latent [8]. While active MTrPs are spontaneously painful, latent MTrPs are painful with palpation and motion but not spontaneously. However, both may result in decreased range of motion, muscle weakness and dysfunction, and reproduce the symptoms of a variety of chronic pain disorders such as tension-type headache, migraine, temporomandibular joint disorders, mechanical neck pain, shoulder pain, lateral epicondylalgia, low back pain, plantar fasciitis and chronic pelvic pain [2,7].

Dry needling (DN) is a commonly used and increasingly interested non-pharmacological treatment method in which a filiform needle is used to penetrate the MTrP and disrupt the

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integrity of dysfunctional endplates located near the MTrP [9]. It is considered that DN creates biochemical and neurophysiological changes at and near the MTrP and normalizes the hypersensitive structures [4,9]. There are different types of DN: fast-in and fast-out needling such as pistoning (dynamic model), leaving the needle in situ (static model) and rotating the needle several revolutions [6]. There is a debate as to which technique is ideal due to a lack of high-quality studies [6,10]. Although, it is conflicting in the literature, some authors suggested that to elicit local twitch response (LTR), an involuntary spinal cord reflex, is important for effectiveness of dry needling [11].

In the literature, there are a growing number of studies which report that DN of the trapezius muscle has beneficial effects on pain, cervical range of motion, functions and quality of life [12]. However, more research is needed, since the optimal number, duration and intensity of DN has yet to be determined for the successful treatment.

This study aims to evaluate whether there is a significant change in the pain and neck disability scores of patients with fast-in and fast-out DN technique, and to assess the number of sessions required to achieve the optimal treatment.

## 2. PATIENTS and METHODS

The study protocol was approved by the local ethics committee of Marmara University School of Medicine (approval number 09.617). The study was conducted in accordance with the principles of the Declaration of Helsinki.

### *Study Design*

Patients who had DN therapy at Marmara University Hospital and Sultan Abdulhamid Han Training and Research Hospital, Department of Physical Medicine and Rehabilitation, between January 2019 and January 2020, were retrospectively scanned from hospital records. Patients aged 18 to 70 years who presented with neck pain, had at least one active MTrP in the upper trapezius muscle and were treated with DN were included. The exclusion criteria were major trauma documented from the medical history, cervical radiculopathy, pregnancy, inflammatory, hormonal and neurological disorders, and severe psychiatric illness.

Patients who had baseline (T0), after first treatment session (T1) and after last session (T2) data were included in the study. The required data included the following: Numeric Rating Scale (NRS) for pain intensity and Neck Disability Index (NDI) for disability assessment. NRS is an 11-point numeric scale which ranges from 0 (no pain) to 10 (worst pain imaginable). NDI is a 10-item scale where each item is scored from 0 to 5, with the total score being the sum of all item scores; higher scores reflect more severe disability. Its validity and reliability has been studied in the Turkish population [13]. NDI was categorized as no disability (0-4), mild (5-14), moderate (15-24), severe (25-34) and complete (35-50) disability [14]. A minimal clinically important change (MCIC) for NRS and NDI in patients with neck pain has been reported to be 2.5 and 3.5, respectively (15).

### *Procedure*

Dry needling was performed for each MTrP in the upper trapezius, using a 25 x 0.25 mm acupuncture needle with a guided tube, once a week by two physicians with more than 5 years' experience in DN.

The method described by Hong was used. The needle was inserted into the active MTrP. When the first LTR was obtained, multiple rapid insertions of the needle were performed, in and out of the MTrP with fast-in and fast-out technique to get more LTRs [16,17]. The procedure was performed while the patients were lying in the prone position. A combination of stretching and strengthening exercises were recommended to all patients.

The number of MTrPs on which DN was performed and the number of DN sessions were recorded.

### Statistical Analysis

The IBM SPSS Statistics 22 (SPSS IBM, Turkey) program was used for statistical analysis. The normality of the parameters was assessed with the Shapiro-Wilk test. Mean, median, standard deviation, minimum, maximum and frequency were used as the descriptive statistical methods. The Friedman test was used for repeated comparisons and the Wilcoxon signed test was performed with a Bonferroni correction for pairwise comparisons. The Spearman test was performed for correlation analysis. Results were evaluated at a 95% confidence interval, $p < 0.05$ significance level. After Bonferroni correction $p < 0.017$ was considered statistically significant.

## 3. RESULTS

Overall, 76 patients fulfilling the inclusion criteria (Female: 67, Male: 9), among a total of 104 patients who had trapezius DN applied due to neck pain, were included in the study. The demographic and clinical data are summarized in Table I.

The median number of DN sessions performed was 3, although, in 3 patients only one session of DN was performed because the patients' pain and disability recovered totally. The median number of MTrP that DN was performed on was 4 (Table I).

***Table I.*** *Clinical and demographic data of the patients*

| | | |
|---|---|---|
| Age $_{(years)}$ (mean±SD) (min-max) | | 40.72±11.66 (22-70) |
| Gender (Female/Male) | | 67/9 |
| Comorbidities | Hypertension (n) | 13 |
| | Diabetes mellitus (n) | 6 |
| | Hypothyroidism (n) | 1 |
| Symptom duration $_{(months)}$ (median) (min-max) | | 12 (2-48) |
| Number of DN sessions (median) (min-max) | | 3 (1-10) |
| Number of MTrP (median) (min-max) | | 4 (2-6) |

*DN: Dry Needling, MTrP: Myofascial trigger point, min: minimum, max: maximum*

Neck pain and disability scores had significantly reduced at T1 and T2 (Figure 1) (Table II). When MCIC was analysed for NRS


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and NDI, more than 90% of patients had MCIC at T1 and T2 (Table III).

***Table II**. Pain and disability outcomes of the patients*

| | | NRS | NDI |
|---|---|---|---|
| T0 median (min-max) | | 7 (5-10) | 18 (8-35) |
| T1 median (min-max) | | 3 (0-7) | 8 (0-28) |
| T2 median (min-max) | | 3 (0-8) | 4 (0-28) |
| p* | | **0.000** | **0.000** |
| p** | T0-T1 | **0.000** | **0.000** |
| | T0-T2 | **0.000** | **0.000** |

**Friedman test, **Wilcoxon signed-rank test*
*NDI: Neck Disability Index, NRS: Numeric Rating Scale, min: minimum, max: maximum*
*T0: baseline, T1: after first treatment session, T2: after last treatment session*

***Table III.** Clinical important change of pain and disability scores*

| | T0-T1 (n=76) | T0-T2 (n=73) |
|---|---|---|
| $NRS_{MCIC}$ n(%) | 69 (90.7) | 67 (91.7) |
| $NDI_{MCIC}$ n (%) | 72 (94.7) | 71 (97.2) |

*NDI: Neck Disability Index, NRS: Numeric Rating Scale, MCIC: Minimal Clinical Important Change, T0: baseline, T1: after first treatment session, T2: after last treatment session*

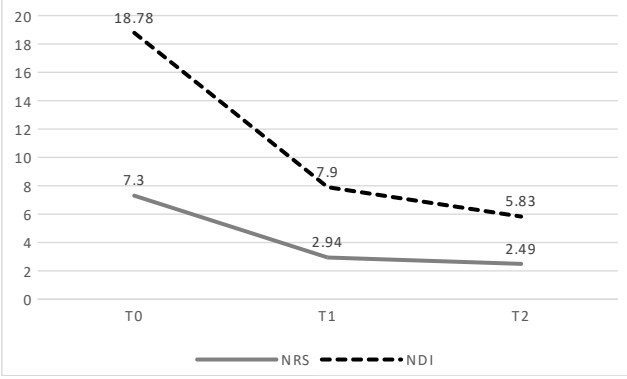


***Figure 1.** Pain and disability score change over time*

There was a moderate positive correlation between symptom duration, number of DN sessions and number of MTrP. There is a weak negative correlation between symptom duration and change of NRS and NDI. A weak positive correlation was detected between the number of DN sessions and change of NDI. In addition, there was a moderate positive correlation between the number of MTrP on which DN was performed and change of NDI (Table IV).

***Table IV.** Correlation analysis between dry needling parameters and change of pain, disability scores*

| | | Symptom duration | Number of DN session | Number of MTrP |
|---|---|---|---|---|
| Symptom duration | p | - | **0.000** | **0.000** |
| | r | | **0.503** | **0.514** |
| Number of DN session | p | **0.000** | - | **0.000** |
| | r | **0.503** | | **0.447** |
| Number of MTrP | p | **0.000** | **0.000** | - |
| | r | **0.514** | **0.447** | |
| NRS T0-T1 | p | **0.035** | 0.669 | 0.766 |
| | r | **-0.242** | -0.050 | -0.035 |
| NRS T0-T2 | p | **0.046** | 0.839 | 0.606 |
| | r | **-0.234** | 0.024 | -0.061 |
| NDI T0-T1 | p | 0.282 | 0.113 | **0.000** |
| | r | 0.125 | 0.183 | **0.488** |
| NDI T0-T2 | p | **0.030** | **0.002** | **0.000** |
| | r | **0.255** | **0.365** | **0.469** |

*Spearman test, DN: Dry Needling, MTrP: Myofascial trigger point, T0: baseline, T1: after first treatment session, T2: after last treatment session*

There were no recorded early or delayed procedure-related complications except post needling local soreness, which lasted no longer than 72 hours.

## 4. DISCUSSION

This study revealed that DN of MTrP on the trapezius muscle is an effective method in patients with neck pain. In the past two to three decades, there have been an increasing number of studies in which the beneficial effects of DN have been demonstrated on neck disability and pain [12,18-23]. However, different types of DN modalities were used in these studies. Therefore, the optimal treatment modalities are unknown and more studies are required in this trending topic to provide more information. In this study, we used fast-in and fast-out technique and aimed to obtain LTRs. Although, there is an expert opinion about this technique which suggests that it is more beneficial than other techniques, evidence regarding the efficiency of fast-in and fast-out technique is limited in the literature [6]. In accordance with previous studies, the current study showed that pain and disability scores of patients were significantly improved after both first and last session with DN using fast-in and fast-out technique [23,24]. Additionally, for the interpretation of treatment effects, it is not only important to know whether the results of outcome measurements are significantly changed, but also whether these changes are meaningful for patients (15,25) . MCIC is strongly recommended for evaluation of relevant changes in clinical practice and research. In this study, we used the cut-off points of 3.5 for NDI and 2.5 for NRS which were determined by patients and clinicians as MCIC for patients with neck pain in a previous study [15]. Based on these values, more than 90% of patients had minimal clinical improvement for both outcome measures in this study.


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One of the frequent questions about DN is how many sessions should be applied [6]. In the current study, the number of DN sessions was in line with previous studies, ranging from 1 to 10 with a median of 3 [6,23]. We limited the number of DN to a maximum of 10, otherwise the maximum number of DN would have been higher than 10. We also demonstrated that the number of DN sessions correlated with symptom duration and the number of MTrPs. This also supports the idea that, while subacute MTrPs resolve with less number of DN sessions, chronic MTrPs require more sessions [6]. This result was thought to be related with the central sensitization mechanism of MTrPs. It has been suggested that MTrPs cause a continued peripheral nociceptive afferent bombardment into the dorsal root ganglia, dorsal horn neurons and central nervous system; therefore, the presence of multiple MTrPs, or the presence of MTrPs for a long time, may lead to spinal and supra-spinal sensitization [26], Although, DN is considered to be able to reduce central sensitization by reducing peripheral nociception and dorsal horn neuron activity, and by activating central pain-inhibitory pathways, the treatment of patients with central sensitization is more difficult than those without central sensitization [7]. Short term improvements in pain may occur in patients with central sensitization; however, treatment modalities which have beneficial effects on central sensitization should be considered, to improve patients in the long term. In patients who have beneficial effects on pain with DN but require a multiple number of DN, as in the current study, clinicians should be aware that the effectiveness of DN may be short due to central sensitization.

### Limitations

First of all, a control group, treated with other DN techniques or other treatment methods such as physical therapy, ischemic compression and manual therapy, could not be included in this study due to its retrospective design. In addition, we were not able to supervise whether patients performed exercises regularly, as recommended by physicians. Secondly, we did not evaluate the long-term results of DN which might have been essential, especially for patients where DN was performed 10 times. We consider that these patients might have had central sensitization and the duration of DN efficacy in these patients would therefore have been shorter than others.

### Conclusion

This study demonstrated that DN with fast-in and fast-out technique should be considered in the management of patients with neck pain due to MTrPs. It has beneficial effects on both pain and disability. More randomized control studies are needed to compare DN techniques and modalities and also to evaluate related factors with the efficacy of DN.

### Compliance with Ethical Standards

**Ethical Approval:** All procedures performed in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Ethics Committee of Marmara University School of Medicine (approval number: 09.617).

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# Validity and reliability of the Sports Nutrition Knowledge Questionnaire for the Turkish athletes

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ABSTRACT

Objective: The aim of this research is to determine validity and reliability of Sports Nutrition Knowledge Questionnaire (SNKQ) for the Turkish athletes.

Materials and Methods: A total of 210 participants (n = 125 elite athletes and n = 85 Nutrition and Dietetics Department senior students) aged 19-30 years were enrolled in the research. SNKQ was evaluated utilizing the psychometric criteria to determine the reliability of items, test-retest reliability and known groups validity, by significance test (Independent Samples t-Test) of the difference between the two groups. After two weeks, SNKQ was applied again to some participants (n = 42) with the purpose of assuring test-retest reliability.

Results: The Sports Nutrition Knowledge Questionnaire was detected as valid and reliable according to the high internal consistency value (Kuder Richardson-20 (KR-20) = 0.927) and high test-retest reliability intraclass correlation coefficient (ICC = 0.974). The difference between SNKQ total scores of athletes (36.0 ± 8.1) and Nutrition and Dietetics Department students (59.1 ± 5.98) was statistically significant; thus, the known groups validity was obtained ($p < 0.001$).

Conclusion: The Sports Nutrition Knowledge Questionnaire is valid and reliable. It can be easily used to determine the nutrition knowledge level of the Turkish athletes.

Keywords: Sports nutrition, Knowledge, Reliability and validity, Athletes

## 1. INTRODUCTION

Adequate and balanced nutrition is essential for athletic performance [1]. In addition, special nutritional strategies may increase performance by supporting adaptations in exercise [2,3]. However, some nutrients are inadequate in diets of the athletes who do not consume a sufficient amount of fruits, vegetables, and dairy products. [4-8]. Nutrition knowledge is one of the factors that influence food choice. Knowledge has defined both consciousness and the facility to practice this consciousness when it comes to people opting for healthy food on a daily basis [9]. It has been observed that athletes are misinformed about the roles of proteins, vitamins and mineral supplements [10], as well as current recommendations on carbohydrate intake [11]. Coaches also lack knowledge about the energy density of nutrients, supplementation and the role of proteins [12]. The inadequacy of athletes' nutrition knowledge may affect their performance negatively [13]. Thus, assessing nutrition knowledge properly is crucial yet challenging. Therefore, designing measurement instruments are required to assess nutrition knowledge. Content validity, known groups validity and reliability – named psychometric criteria – of the questionnaire should be identified. The questionnaire should include all directions [hydration, recovery, supplements, etc.] of the subject [sports nutrition knowledge] to be measured to ensure content validity. Known groups validity assesses whether the questionnaire designates dissimilar scores between groups. Reliability means that the questionnaire can be used in different times. Test-retest method is used to guarantee reliability [14-16]. There are valid and reliable instruments measuring general or sports nutrition knowledge of athletes and coaches in different countries [4, 17-22]. Some of these were developed for the athletes who were in different branches, such as cross-country runners [4], track and field athletes [18], ultra-endurance athletes [19]. Calella et al., developed a questionnaire for Italian adolescent and adult athletes. De Souza et al., designed a tool for

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German adolescent athletes [20, 21]. Trakman et al., developed a questionnaire consisting of 6 subdivisions [weight management, macronutrients, micronutrients, sports nutrition, supplements, and alcohol] by using different statistical analysis method from other studies [22]. Although, some of the questionnaires used in studies in the sports field in Turkey were developed or modified, none of them had enough psychometric measurements. Therefore, they were not valid or reliable [23-32]. Sports Nutrition Knowledge Questionnaire (SNKQ) was developed by Zinn et al.for the rugby coaches in New Zealand [17]. SNKQ was also used in other samples such as rugby coaches [33], college students in Iran [34], coaches in England and the USA [35, 36]. Blennerhassett et al., modified and validated the questionnaire for ultra-endurance athletes [19].

A valid and reliable sports nutrition knowledge questionnaire is considered essential in determining the nutrition level of the Turkish athletes. Inadequate nutrition knowledge can negatively affect sports performance. Hence, by taking questionnaire results of the athletes into consideration, the athletes can be provided with the required nutritional recommendations so as to support their performance. Currently, no sports nutrition knowledge instrument with enough psychometric measurements exists in Turkey. This is why, this study aims to assess validity and reliability of the Sports Nutrition Knowledge Questionnaire (SNKQ) for the Turkish athletes.

## 2. MATERIALS and METHODS

### *Participants*

Two hundred and ten participants were enrolled in the study. Of the participants, one hundred and twenty-five athletes (X ± SD = 20.2 ± 2.07 years) were recruited from the Center of Athlete Training and Health Research of the Ministry of Youth and Sports alongside 85 Nutrition and Dietetics senior students (X ± SD = 22.5 ± 1.20 years) were recruited from two universities in Ankara, Turkey. For the purpose of evaluating the known groups validity, Nutrition and Dietetics senior college students known to have a high level of nutrition knowledge were included. The athlete group participating in the study consisted of different sports branches such as martial arts and technical sports; wrestling (n = 23), archery (n = 15), fencing (n = 7), team sports and aerobic sports; basketball (n = 7), volleyball (n = 16), athletics long distance (n = 2), futsal (n = 12), anaerobic sports; weightlifting (n = 4), track and field (n = 24), gymnastics (n = 5), canoe (n = 10). The participants signed the informed consent form before partaking in the study. The inclusion criteria for the participants were to be healthy and not to be following a special diet. Participants with any eating disorders and chronic diseases were excluded. The remaining participants completed a personal information questionnaire and SNKQ with face to face interview method. This project was approved by the Hacettepe University Ethics Board and Commission (approval no: GO 17/788).

***Table I.*** *Characteristics of the participants*

| Variables | Athletes (n = 125) | | Nutrition and Dietetics Students (n = 85) | | |
|---|---|---|---|---|---|
| **Age (years), X ± SD** | 20.2 ± 2.07 | | 22.5± 1.20 | | p=0,001** |
| **Gender** | n | % | n | % | p<0,001* |
| Male | 83 | 66.4 | 4 | 4.7 | |
| Female | 42 | 33.6 | 81 | 95.3 | |
| **Education level** | N | % | N | % | p<0,001* |
| Secondary school | 32 | 25.6 | - | 0.0 | |
| High School | 83 | 66.4 | 85 | 100.0 | |
| University | 10 | 8.0 | - | 0.0 | |

SD = standard deviation, X = mean, *chi square test **student t test, Mann-Whitney U test

### *Adaptation of Sports Nutrition Knowledge Questionnaire*

In this study, SNKQ consisting of 88 items was adapted for the Turkish population [17]. SNKQ was translated into Turkish, ensuring translation validity by using standard back translation method. According to a group of 5 registered dietitians' suggestions, the foods that are non-consumable in Turkey were adjusted to conform to the eating habits of Turkish society regarding their suitable equivalents. To serve this purpose, "creamed rice" was converted into "rice pudding". Vitamin water and some brand names of some energy drinks were changed as they are not common in Turkey. "Edam cheese" was replaced "white cheese". "Cheddar cheese" was changed as "fresh kassari cheese". "Margarine containing polyunsaturated fat" was switched to "margarine". "Marmite" a kind of yeast paste consumed in New Zealand, was replaced with "jam". Some unfamiliar food brands were not included in the questionnaire. Instead of the word "player", the word "athlete" was preferred. Eventually, researchers applied SNKQ to 25 athletes as a pilot study. The feedbacks were evaluated and the final version of the questions was formed in accordance with the written and verbal notifications. The study expert group reevaluated the content validity of the questionnaire. The questionnaire consisted of five subsections related to general and sports nutrition, "nutrients", "fluids", "recovery", "weight management", "supplements". All participants completed the personal information questionnaire and SNKQ. Items were scored as "1" for each item answered as "correct", and "0" for items that were answered "incorrectly" or "not sure". The difference between the mean scores of athletes and Nutrition and Dietetics students was statistically evaluated. For the reliability of the questionnaire, the internal consistency of the subsections and the entire SNKQ, and the test-retest reliability were evaluated. SNKQ was applied to some of the participants (n=24 athletes, n=18 students) after 2 weeks (the best time period not to remember the answers and make big changes in the responses for test-retest) [14].


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### Statistical Analysis

In the statistical evaluation of the data obtained from the research, IBM SPSS Statistics for Windows version 23.0 program was used. Distribution of the numerical data were checked by applying Kolmogorov-Smirnov test. The Independent Samples t-Test was used to test the significance of the difference between the two means. The data was summarised by using number (n) and percentage (%) for categorical variables, and average ($\bar{X}$), standard deviation (SD), median (M) and minimum – maximum values (min-max) for numerical variables. To determine the items incompatible with the questionnaire, the item-total correlation was used. Kuder-Richardson-20 (KR-20) coefficient, a special case of Cronbach's Alpha in which the items are binary variables (usually scored as 0 or 1), was used to determine the internal consistency [37]. Kuder Richardson-20 value > 0.70 was considered to be acceptable. The test-retest reliability was evaluated by using intraclass correlation coefficient ($R_1$-ICC). $R_1$-ICC was evaluated as 0.95-1.00 excellent, 0.85-0.94 high, 0.70-0.84 moderate, 0.00-0.69 unacceptable [38]. The validity of the scale was evaluated with known groups validity by the significance test (Independent Samples t-Test) of the difference between the two groups [15, 16]. The results were considered as statistically significant when the p-value was below 0.05 [38].

## 3. RESULTS

### *Characteristics of the Participants*

The characteristics of the participants are presented in Table I. Athletes (n = 125) and Nutrition and Dietetics senior students (n = 85) completed the SNKQ. The majority in the study consisted of male athletes (n = 83, 66.4%) and female Nutrition and Dietetics students (n = 81, 95.3%). The mean age of the athletes was 20.2 ± 2.07 years and the mean age of the Nutrition and Dietetics students was 22.5 ± 1.20 years. Sixty-six point four percent of the athletes and all students are high school graduates.

### *Adaptation of Sports Nutrition Knowledge Questionnaire*

The ability of each individual item to discriminate between people with different levels of knowledge was measured by correlating the score on each item with the overall test score. The item-total correlation revealed that 10 items were completely incompatible with the questionnaire. As a result, 10 items with the item-all correlation value of – 0.10-0.10, not contributing to the questionnaire, were excluded with expert (biostatistician) advice. Internal reliability was calculated separately for the different subsections by using Kuder Richardson-20. Nutrients: 0.924; fluids: 0.402; recovery: 0.643; weight management: 0.599; supplements: 0.730 values were obtained. Intraclass correlation coefficient was applied for the test-retest reliability to 42 participants retaking SNKQ after two weeks (Table II).

***Table II.*** *Total and subsections of Sports Nutrition Knowledge Questionnaire (SNKQ) internal reliability (KR-20) and test-retest reliability coefficient (R1-ICC).*

| | Internal reliability (KR-20) | Test-retest Reliability (R1-ICC) | | |
|---|---|---|---|---|
| SNKQ sections | All participants (n= 210) | Athletes (n= 24) | Nutrition and Dietetics Students (n= 18) | All (n= 42) |
| Total | 0.927 | 0.909 | 0.823 | 0.974 |
| Nutrients | 0.924 | 0.634 | 0.798 | 0.946 |
| Fluids | 0.402 | 0.676 | 0.760 | 0.735 |
| Recovery | 0.643 | 0.860 | 0.881 | 0.916 |
| Weight management | 0.599 | 0.799 | 0.729 | 0.904 |
| Supplements | 0.730 | 0.834 | 0.879 | 0.888 |

There were strong, positive correlations in all subsections (ranging 0.735-0.946) and the whole questionnaire (0.974). Therefore, the 78 item SNKQ was found reliable. The SNKQ total scores of Nutrition and Dietetics senior students (59.1 ± 5.98) and athletes (36.0 ± 8.1) were found to be statistically different ($p < 0.001$) ; thereby demonstrating that the known groups validity was confirmed. Nutrition and Dietetics senior students scored better than the athletes in the subsections of nutrients, recovery, weight management, and supplements subsections (Table III) ($p < 0.001$).

***Table III.*** *SNKQ total score and subsections scores*

| | Athletes (n=125) | | | Nutrition and Dietetics Students (n=85) | | | |
|---|---|---|---|---|---|---|---|
| SNKQ scores (maximum) | X ± SD | M | (Min- max) | X ± SD | M | (Min-max) | p value* |
| Nutrients (40) | 18.7 ± 5.16 | 19 | (6-31) | 35.5 ± 2.78 | 36 | (41-73) | <0.001 |
| Fluids (7) | 3.7 ± 1.47 | 4 | (0-7) | 3.9 ± 1.77 | 4 | (28-41) | 0.214 |
| Recovery (8) | 3.8 ± 1.60 | 4 | (0-8) | 6.2 ± 1.28 | 6 | (0-7) | <0.001 |
| Weight management (14) | 8.0 ± 1.89 | 8 | (3-12) | 10.8 ± 1.83 | 11 | (2- 8) | <0.001 |
| Supplements (9) | 1.5 ± 1.71 | 1 | (0-9) | 2.8 ± 2.33 | 2 | (0- 9) | <0.001 |
| Total score (78) | 36.0 ± 8.1 | 36 | (14-57) | 59.1 ± 5.98 | 59 | (41-73) | <0.001 |

*SD = standard deviation, M = median, *Student t test was used for analysis.*


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## 4. DISCUSSION

Adequate nutrient intake and healthy food habits are crucial for athletes to ensure optimal performance. Therefore, the main point of the assessment of SNKQ is to raise the awareness of healthy dietary habits and improve nutritional knowledge in Turkish athletes. Therefore, professional athletes must have a high sports nutrition knowledge level. In Turkey, no sports nutrition knowledge instrument with enough psychometric measures exists. Since, a questionnaire needs to be valid, reliable and capable of accurate measurement, psychometric criteria are important [16]. Thereby, SNKQ in this study meets the basic psychometric criteria for reliability and validity. Therefore, this study is expected to set an example for many future studies.

This study aims to improve validity and reliability of the SNKQ for the Turkish athletes. To begin with, the wording of the questions ensured by the expert study group (dietitians) clarified for content validity. Some items with low item total correlation coefficient were excluded from the questionnaire due to their insufficient contribution to measuring nutrition knowledge. It was considered that participants could misinterpret or misperceive these items.

In our study, as observed in Table II, the internal reliability value (K-20: 0.927) was found high and test-retest reliability coefficient value (R1-ICC: 0.974) was found excellent in the overall questionnaire. Kuder Richardson-20 (KR-20) coefficient, a special case of Cronbach's alpha, was used to determine the internal reliability of the information survey which had only one correct answer. Kuder-Richardson value > 0.70 was considered acceptable. $R_1$ ICC was evaluated as 0.95-1.00 excellent, 0.85-0.94 high, 0.70-0.84 moderate, 0.00-0.69 unacceptable [38]. Considering these results, SNKQ measures nutrition knowledge properly and consistently.

In our study, internal consistency values of the subsections ranged between 0.402-0.924. Whereas, internal reliability for the "nutrients" (0.924) and "supplements" (0.730) subsections were acceptable, "weight management" (0.599) and "recovery" (0.643) subsections were under 0.7. Similarly, it is observed that the internal consistency values are within the range of 0.34-0.97 in other studies [19, 39, 40]. In a study investigating the validity and reliability of the general nutrition knowledge questionnaire in Turkey, the internal consistency values of the subsections were found to be between 0.43-0.89 [39]. Likewise, in Spendlove et al.'s study, the internal consistency values were determined between 0.4-0.95 [40]. Thus, it is common for some subsection values to be under 0.7 in nutrition knowledge questionnaires [19, 39, 40].

In this study, the internal consistency value in "fluids" subsection (0.402) was low, which is attributed to the low number of items (7 items) as well as different content (exact knowledge questions-practical questions) in multiple choice questions. It is stated that when the number of items increases, the internal reliability is affected; and thus, it also increases [38]. Moreover, individuals' disinterest in the subject of fluids and their lack of knowledge on this subject – such as sports drinks and basic hydration techniques – are believed to have lead these results. Additionally, in other studies the SNKQ scores in the fluid subsection were found to be low [19, 34, 35]. In another study, the mean percentage of correct responses about fluids was only 47.3% in coaches [35]. To ensure content validity, the instrument must have subsections dealing with different subjects [14]. A person knowledgeable about one of the subjects may not be sufficiently versed in another subject; therefore, some subsections with low values can be regarded acceptable. Also, the necessity of a high internal consistency value in the evaluation of structures such as attitudes and opinions rather than knowledge is emphasized [41].

As observed in Table II, test-retest correlation coefficient values which are very close to 1.00 indicate a perfect correlation in the overall questionnaire (0.974) and "nutrients" (0.946) subsection of our study. Test-retest correlation coefficient values are high in "recovery" (0.916), "weight management" (0.904) and "supplements" (0.888) subsections and moderate for the "fluids" (0.735) subsection.

The two groups (athletes and Nutrition and Dietetics students) with different levels of nutrition knowledge were included in our study to evaluate known groups validity. Nutrition and Dietetics students were included in the study as the known group, in order to determine the validity of the SNKQ. Similarly, there are many studies using known groups validity method which includes Nutrition and Dietetic students or dietitians [17, 20, 39, 40, 42-44].

As displayed in Table III, the total SNKQ scores of Nutrition and Dietetics students and athletes were found to be statistically different, with Nutrition and Dietetics senior students achieving a statistically higher score than professional athletes ($p< 0,001$). Consequently, the known groups validity was obtained. In Turkey, Nutrition and Dietetics students have practical training in their senior year following a three-year-theoretical training. Yet, not all professional athletes are able to receive an education on nutrition. Athletes studying at the Physical Education and Sports College or Faculty of Sports Science have a chance to attend a limited number of courses on nutrition. In line with these results, it is also possible to consider that athletes prioritize improving their fitness, strength and attention while ignoring importance of nutrition. Similarly, in the study of Zinn and colleagues, the total SNKQ scores were statistically significant in 5 different groups of dietitians (74.6 points), university employees (51.7 points), nutrition and dietetics students (71.6 points) and sports students (49.7 points) [$p <0.001$]. Nutrition and Dietetics students and dietitians achieved the highest scores [17]. In other studies, the scores of the students of the Nutrition and Dietetics department and/or the dietitian group were discovered to be considerably higher than the rest [17, 20, 39, 40, 42-44].

As seen in Table III, Nutrition and Dietetics senior students achieved statistically higher scores than professional athletes in "nutrients", "recovery", "weight management" and "supplements" subsections. The scores were not statistically different in the fluids subsection. Fluids are one of the specific subjects concerning sports nutrition. Some Nutrition and Dietetics students are thought not to have taken the elective sports nutrition course in


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the Nutrition and Dietetics Department in Turkey. In addition, all professional athletes may not be able to receive education on nutrition. These conditions are considered to have prevented the participants from accessing current knowledge about liquids and hydration.

Some limitations which may influence the results of the study exist. Firstly, since the questionnaire contains different types of questions, it was not suitable for factor analysis, which is one of the methods of construct validity. Likewise, factor analysis was absent in the study of Zinn et al., from which the questionnaire was taken, as well as the study of Blennerhassett et al. that validate SNKQ [17, 19]. Secondly, the convergent validity method was not utilized due to the fact that there was not a valid and reliable sports nutrition knowledge questionnaire in Turkey to be compared with the SNKQ. The results of the psychometric measurements were limited to the conditions under which the data were collected. Future studies are needed to test the validity of the questionnaire in different sports branches and various levels of athletes. When collecting data, participants completed the sports nutrition knowledge questionnaire without intervention. The possibility that participants' guessing the answers to the questions can be another limitation even though the "not sure" option was included to minimize it.

## Conclusion

Sports Nutrition Knowledge Questionnaire was found to be valid and reliable. The final questionnaire has 78 questions and five subsections (nutrients, fluids, recovery, weight management, and supplements). It can be applied to the Turkish athletes performing in different sports branches so as to correctly determine their sports nutrition knowledge. It can be employed in future studies to investigate the relationship between nutrition knowledge and sports performance. Experts in the fields of sports and nutrition can easily use SNKQ.

## Compliance with Ethical Standards

**Ethical Approval**: This project was approved by the Hacettepe University Ethics Board and Commission (approval no: GO 17/788).

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# Evaluation of different respiratory samples and saliva for the detection of SARS CoV-2 RNA

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ABSTRACT

Objective: We aimed to analyse the positivity rate and cycle threshold values indicating viral loads for SARS CoV-2 among different respiratory specimens and also to evaluate the diagnostic efficacy of saliva samples.

Materials and Methods: We included combined oropharyngeal and nasopharyngeal swab (cONS), sputum, and tracheal aspirate (TA) specimens of patients. Unpreserved saliva samples were collected prospectively from hospitalized patients within 72 hours of admission. SARS CoV-2 RNA was extracted by using Bio-Speedy viral nucleic acid buffer than RT-PCR was performed with Bio-Speedy COVID-19 qPCR detection kit.

Results: Retrospective evaluation revealed SARS CoV-2 RNA in 19.66% of cONS (n: 5819), 30.77% of sputum (n: 39), 29.41% of TA samples (n: 34) from 4812 patients. In the majority (86.72%) of the samples, the first cONS sample was positive. Consecutive cONS and sputum/TA samples were investigated in 52 patients of whom 11 were positive with either of these samples. Saliva positivity was detected in 60% of cONS positive (n: 20) and 30% of cONS negative (n: 12) patients.

Conclusion: Although, cONS samples show the greatest diagnostic guidance, repeated sampling from multiple sites of the respiratory tract increases the possibility of COVID-19 diagnosis. Saliva samples might be considered as an alternative specimen.

Keywords: SARS CoV-2, COVID-19, RT-PCR, Upper respiratory samples, Saliva, Cycle threshold

## 1. INTRODUCTION

In December 2019, a new coronavirus was identified in a group of patients in Wuhan, China [1]. Originally named as 2019 new coronavirus (novel Coronavirus, 2019-nCoV), the virus is currently named as severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) by the International Committee on Taxonomy of Viruses (ICTV), and the disease caused by this virus is named as coronavirus disease 2019 (COVID-19) [2].

Since, the World Health Organization (WHO) declared the outbreak as a Public Health Emergency of International concern on January 30, 2020; COVID-19 affected 63, 719, 213 cases and 1, 482, 084 deaths were recorded by December 3, 2020 [3]. The first case was detected on March 10, 2020 in Turkey, 513, 656 cases and 14, 129 deaths have been declared by the Turkish Ministry of Health, on December 2, 2020 [4].

The current diagnostic method is the detection of SARS CoV-2 RNA by reverse transcriptase polymerase chain reaction (RT-PCR) from clinical materials. The nasal swab (NS) refers to flocked swab stick sampling of the anterior nasal cavity and the nasopharyngeal swab (NPS) involves the introduction of a flocked swab stick deep into the nasopharynx (beyond the hard-soft palate transition) to achieve direct contact with the posterior nasopharyngeal mucosal wall [5]. Zou et al., compared 72 NS/NPS specimens across various days of illness in 18 COVID-19 patients and concluded that NPS technique is time-consuming, resource intensive, and unsuitable for mass testing in a pandemic situation [6]. Although, sampling by oropharyngeal swab (OPS) is easier, it has a low negative predictive value. Xie et al., reported that only 9 out of 19 (47%) OPS from ultimately seropositive COVID-19 patients were positive, calling attention to the importance of repeated sampling from multiple sites, including the lower respiratory system, in order to increase the diagnostic yield [7]. At present, the United States Centers for Disease Control and Prevention also recommends that nasopharyngeal and oropharyngeal flocked swabs should be

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used for the collection of specimens for SARS CoV-2 viral detection. While these methods have their limitations, both allow rapid up-scaling for mass testing and detection, as part of most countries' greater strategy to proactively test, isolate and contact-trace infected cases [8]. Turkish Ministry of Health diagnostic guideline advises using combined oropharyngeal and nasopharyngeal swab (cONS) samples from clinically suspected cases for diagnosis [9]. Lower respiratory sampling methods lack rapid up-scaling potential but the superiority of sputum for SARS CoV-2 viral detection was echoed by Pan et al., who demonstrated that sputum samples generally showed higher viral loads than throat swabs [10]. Tracheal aspirates (TA) may be obtained via suction from an indwelling endotracheal tube in mechanically ventilated patients, or direct tracheal suction of tracheotomized patients. Comparisons of upper respiratory samples vs. endotracheal aspirates in a cohort of 16 intubated COVID-19 patients showed that the latter had significantly higher viral RNA values compared to NS and OPS samples [11].

Recently, alternative strategies for specimen collection, including home collection by patients themselves have also been considered [12]. Testing saliva as an alternative first-line screening test especially in the face of shortages of swabs and personal protective equipment is advised [13]. To et al., reported that 20 of 23 (87%) patients who had SARS CoV-2 detected by RT-PCR in NPS or sputum also had SARS CoV-2 detectable in saliva [14].

Herein, we shared our experience of COVID-19 laboratory diagnosis during the pandemic. We analyzed the positivity rate among upper and lower respiratory tract specimens, compared viral load indicated by cycle threshold (Ct) values of RT-PCR assays, and evaluated the diagnostic efficacy of saliva samples.

## 2. MATERIALS and METHODS

We examined cONS, sputum and TA specimens collected from COVID-19 suspected patients admitted to Marmara University Pendik Training and Research Hospital between March 23 and September 15, 2020. Although, it is not included in our routine diagnostic procedures, we also evaluated saliva samples prospectively from a small group of hospitalized patients within 72 hours of admission.

cONS samples were taken from patients with acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath) with either a history of travel to a location reporting community transmission of COVID-19 disease or having been in close contact with a confirmed COVID-19 case in the last 14 days before symptom onset; or a patient with severe acute respiratory illness requiring hospitalization without an alternative diagnosis that fully explains the clinical presentation. Sputum samples were obtained from patients with productive cough and TA specimens were taken from mechanically ventilated patients. cONS samples were taken into a transfer tube containing viral transport medium whereas sputum samples and TA samples were put into a 25 ml sterile cup without viral transport media (VTM).

To obtain unpreserved saliva samples, patients were asked not to have any food or drink 30 minutes before collection, to pool saliva in their mouth for 1-2 minutes, and spit 1-2 mL of saliva into a sterile cup without VTM. Patient selection was done randomly regardless of severity of the infection. All samples were transferred to the laboratory within a basic triple packing system [15].

Viral RNA was extracted by using Bio-speedy® viral nucleic acid buffer (Bioexen LTD, Istanbul, Turkey) and RT-PCR was performed with Bio-speedy® COVID-19 qPCR detection kit, Version 2 (Bioexen LTD, Istanbul, Turkey) using primers and probes targeting the RNA-dependent RNA polymerase (RdRp) gene fragment in a LightCycler® 96 System (Roche, Switzerland). Each 20 µL reaction mixture contained 5 µL of Oligo Mix, 10 µL of 2X Prime Script Mix, and 5 µL of RNA as the template. The thermal cycling condition was 15 minutes at 45°C for reverse transcription, 3 minutes at 95°C for PCR initial activation, and 45 cycles of 5 seconds at 95°C and 35 seconds at 55°C according to the manufacturer's instructions (Bioexen LTD, Istanbul, Turkey). Oligo Mix contains internal control (IC) targeting the Human RNase P gene as an extraction control. A positive and negative control were included in each run to generate a valid result. A Ct value of less than 40 was defined as a positive result. Analytical and clinical performance of the kit was determined by the "Turkish Ministry of Health, General Directorate of Public Health, Department of Microbiology Reference Laboratories and Biological Products (HSGM)". The analytical sensitivity of the kit is 99.4% and its specificity is 99.0%.

The study protocol was approved by both the Turkish Ministry of Health (Protocol Number:2020-05-05T12_38_13) and the Institutional Review Board and Ethics Committee of Marmara University, Faculty of Medicine (Protocol Number: 09.2020.620).

### Statistical Analysis

Statistical analyses were performed by using SPSS version 21.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were presented as percentages and medians (IQR) in data without normal distribution. We used the Mann-Whitney U test to compare continuous variables for independent groups. All tests were two-tailed; P values of $< 0.05$ were considered to indicate statistical significance.

## 3. RESULTS

Among 4812 suspected COVID-19 patients, 1053 cases (532 male, 521 female) were confirmed positive by RT-PCR assay. The median age was 40 years (IQR:0-95). The most common symptom was cough (66.22%), followed by dyspnea (31.69%) and fever (31.66%). The majority of the patients (%59.79) had been in close contact with a positive patient in the last 14 days before symptom onset (Table I).


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***Table I.*** *Characteristics of patients with confirmed diagnosis of COVID-19 (n: 1053)*

| Gender | n | % |
|---|---|---|
| Male | 532 | 50.50 |
| Female | 521 | 49.50 |
| **Age, years** | **Median** | **IQR** |
| Male | 40 | 0-90 |
| Female | 38 | 0-95 |
| Total | 40 | 0-95 |
| **Presenting signs and symptoms** | **n** | **%** |
| Cough | 697 | 66.22 |
| Dyspnea | 334 | 31.69 |
| Fever | 333 | 31.66 |
| **Epidemiological characteristics** | **n** | **%** |
| Contact with positive patient | 519 | 59.79 |
| Travel history | 7 | 0.91 |

SARS CoV-2 RNA has been investigated in cONS samples (n: 5819), sputum (n: 39), and TA (n: 34) samples from 4812 patients with suspected COVID-19 infection. Positivity was detected in 19.66% of cONS, 29.41% of TA, and 30.77% of sputum samples. Ct values of cONS samples were lower than sputum and TA samples, indicating higher viral loads (Table II).

***Table II.*** *Detection rates of SARS CoV-2 RNA from different respiratory tract samples. (cONS: combined oropharyngeal and nasopharyngeal swab, TA: tracheal aspirate)*

| | Sample Type (n) | | | |
|---|---|---|---|---|
| | cONS (5819) | Sputum (39) | TA (34) | TOTAL (5892) |
| Positive test result, n (%) | 1144 (19.66) | 12 (30.77) | 10 (29.41) | 1166 (19.79) |
| Cycle threshold, median (IQR) | 27.00 (14-40) | 30.05 (21-39) | 30.00 (24-39) | 27.17(14-40) |

The results of repetitive cONS samples collected within 72 hours were evaluated retrospectively. In the majority of the patients (86.72%) SARS CoV-2 RNA was detected in the first collected cONS sample. Out of 689 patients with initial negative results, the second test was performed. For these patients, the test results were positive in 98 cases (9.36%). Thirty-nine patients (3.72%) were found to have a positive RT-PCR result after two consecutive negative results. Two patients were tested positive by four repeated RT-PCR tests. Totally 139 patients (13.28%) were diagnosed with COVID-19 through repetitive samples taken within maximum nine days (Table III).

***Table III.*** *Positivity rate of the repetitive cONS samples from COVID-19 suspected patients*

| | Negative | Positive | |
|---|---|---|---|
| | n: [a] | n: 1047 | % |
| 1. Sample | 4792 | 908 | 86.72 |
| [b]2. Sample | 591 | 98 | 9.36 |
| [b]3. Sample | 114 | 39 | 3.72 |
| [b]4. Sample | 15 | 2 | 0.19 |

*[a]since there are overlapping negative results obtained from the same patients, total number of negative samples were not added, [b]repetitive cONS samples were collected within 72 hours. The maximum number of days of sample collection (1st – 4th ) was nine.*

Consecutive cONS and sputum or TA samples from 52 patients were investigated for the presence of SARS CoV-2 RNA. Eleven of 52 patients were found to be positive with either of these samples (Table IV). Detection time for SARS CoV-2 RNA in lower respiratory tract specimens (8 sputum, 3 TA) after the first clinical symptom varied 3 to 12 days. The difference in time between cONS and lower respiratory tract samples collection varied from 1 to 10 days. Whereas, in only four patients both cONS and sputum samples (patients 1-4) and in only one patient both cONS and TA samples (patient 5) were positive. The median Ct value was 30.00 (IQR: 25.85-39.92) in sputum and TA samples and 25.00 (IQR: 18.01-26.39) in cONS samples. Cycle threshold values detected from cONS samples were significantly lower than sputum and TA samples ($p<0.05$). Seven patients' (patient no: 2-6 and 10, 11) clinical condition was severe, requiring oxygen support or admission to the intensive care unit (Table V).

***Table IV.*** *Comparison of SARS CoV-2 RT-PCR results in consecutive cONS and lower respiratory tract samples (sputum and tracheal aspirate) (n=52)*

| | | Sputum/TA Samples | | |
|---|---|---|---|---|
| | | Positive n (%) | Negative n (%) | Total n (%) |
| cONS Samples | Positive n (%) | 5 (71.43) | 2(28.57) | 7 (100.0) |
| | Negative n (%) | 6 (13.33) | 39 (86.67) | 45 (100.0) |
| | Total n (%) | 11 (21.15) | 41 (78.85) | 52 (100.0) |

*cONS: combined oropharyngeal and nasopharyngeal swab, TA: tracheal aspirate*

***Table V.*** *Comparison of consecutive cONS and SARS CoV-2 RNA detected sputum/TA samples*

| No | Specimen type | Result | Ct value* | Days from symptom onset to test |
|---|---|---|---|---|
| 1 | cONS | P | 22.98 | 4 |
| | Sputum | P | 28.25 | 6 |
| 2* | cONS | P | 18.01 | 2 |
| | cONS | N | | 11 |
| | Sputum | P | 32.90 | 12 |
| 3* | cONS | P | 22.27 | 2 |
| | Sputum | P | 31.43 | 10 |
| 4* | cONS | P | 26.39 | 0 |
| | Sputum | P | 30.93 | 5 |
| 5* | cONS | P | 26.04 | 3 |
| | TA | P | 30.40 | 4 |
| 6* | cONS | N | | 2 |
| | Sputum | P | 29.46 | 6 |
| 7 | cONS | N | | 1 |
| | Sputum | P | 39.92 | 3 |
| 8 | cONS | N | | 2 |
| | Sputum | P | 36.19 | 3 |
| 9 | cONS | N | | 0 |
| | Sputum | P | 25.85 | 3 |
| 10* | cONS | N | | 0 |
| | TA | P | 27.97 | 4 |
| 11* | cONS | N | | 5 |
| | TA | P | 34.33 | 12 |

**clinical condition was severe, hypoxic and/or intensive care unit admission, cONS: combined oropharyngeal and nasopharyngeal swab, N: negative, P: positive, TA: tracheal aspirate, *p<0.05.*

***Table VI.*** *Comparison of cONS and saliva samples*

| NO | Specimen type | Result | Ct value* | Days from symptom onset to test |
|---|---|---|---|---|
| 1 | cONS | P | 25.42 | 7 |
| | Saliva | N | | 8 |
| 2 | cONS | P | 21.95 | 5 |
| | Saliva | P | 27.79 | 8 |
| 3 | cONS | P | 23.20 | 0 |
| | Saliva | P | 31.00 | 2 |
| 4 | cONS | P | 27.59 | 0 |
| | Saliva | N | | 1 |
| 5 | cONS | P | 22.12 | 9 |
| | Saliva | N | | 12 |
| 6 | cONS | P | 26.03 | 4 |
| | Saliva | P | 30.80 | 6 |
| 7 | cONS | P | 23.56 | 2 |
| | Saliva | P | 29.15 | 3 |
| 8 | cONS | P | 29.60 | 4 |
| | Saliva | P | 26.79 | 6 |
| 9 | cONS | P | 26.13 | 6 |
| | Saliva | P | 22.73 | 8 |
| 10 | cONS | P | 23.45 | 0 |
| | Saliva | N | | 3 |
| 11 | cONS | P | 29.89 | 5 |
| | Saliva | P | 31.92 | 8 |
| 12 | cONS | P | 29.73 | 5 |
| | Saliva | N | | 8 |
| 13 | cONS | P | 19.24 | 1 |
| | Saliva | N | | 2 |
| 14 | cONS | P | 23.02 | 4 |
| | Saliva | P | 24.27 | 5 |
| 15 | cONS | P | 25.58 | 4 |
| | Saliva | P | 20.08 | 4 |
| 16 | cONS | P | 36.74 | 10 |
| | Saliva | P | 30.24 | 11 |
| 17 | cONS | P | 29.10 | 0 |
| | Saliva | P | 31.27 | 3 |
| 18 | cONS | P | 17.37 | 5 |
| | Saliva | N | | 6 |
| 19 | cONS | P | 31.21 | 7 |
| | Saliva | N | | 8 |
| 20 | cONS | P | 32.91 | 8 |
| | Saliva | P | 21.18 | 10 |

*cONS: combined oropharyngeal and nasopharyngeal swab, N: Negative, P: Positive* :p>0.05.*

We compared the diagnostic validity of saliva samples (n: 20) collected prospectively from patients whose cONS samples were tested positive. In 12 (60%) patients positivity was detected in both samples. Detection time for SARS CoV-2 RNA positivity in saliva after first clinical symptom varied from one to twelve days. The median Ct value was 25.50 (IQR: 17.37-36.74) in cONS samples and 28.00 (IQR: 20.08-31.00) in saliva samples (Table VI). Cycle threshold values detected from cONS samples were lower than saliva samples, the difference was not found statistically significant (p>0.05). We also added 12 saliva samples from patients whose cONS samples were tested negative for SARS CoV-2 RNA despite strong clinical suspicion. Surprisingly, in 4 (30%) patients saliva samples were found to be positive (data not shown) even after 20 days from the symptom onset.

## 4. DISCUSSION

In this study, we found that the most common symptom was cough (66.22%), followed by dyspnea (31.69%) and fever (31.66%) in patients with suspected COVID-19 infection (Table I). SARS CoV-2 RNA has been investigated in cONS samples (n: 5819), sputum (n: 39), and TA (n: 34) samples from 4812 patients with suspected COVID-19 infection. Retrospective analysis of our patients revealed a 19.66% positivity rate for cONS samples (1144 of 5819), 29.41% for TA samples (10 of 34), and 30.77% for sputum samples (12 of 39) (Table II).

The course of COVID-19 varies among individuals ranging from asymptomatic infection to severe respiratory failure [16]. Common symptoms of the disease are fever, cough, slight dyspnea, sore throat, fatigue and headache, therefore, it is difficult to differentiate COVID-19 from other respiratory diseases [17]. According to the WHO interim guideline, the primary and preferred method for diagnosis is the collection of upper respiratory tract samples via nasopharyngeal and oropharyngeal swabs [2]. The use of bronchoscopy is not recommended as the aerosol that is generated poses a substantial risk for both patients and healthcare staff and tracheal aspiration can be used to collect respiratory specimens in intubated patients [18]. One of the earliest papers about laboratory diagnosis published in February 2020 compared the positive ratio of SARS CoV-2 nucleic acid amplification test results from different samples including oropharyngeal swab, blood, urine, and stool of 19 patients. The positive ratio of nucleic acid detection was only 47.4% in oropharyngeal swab samples, with no positivity in the blood and urine samples [7]. Testing of respiratory samples from multiple sites seems to improve the sensitivity and reduce false-negative test results. Wang et al., reported that bronchoalveolar lavage fluid specimens showed the highest positive rates (14 of 15; 93%), followed by sputum (72 of 104; 72%), nasal swabs (5 of 8; 63%), and pharyngeal swabs (126 of 398; 32%) [19]. Lui et al., reported a 38.25% positivity rate of nasal, and pharyngeal swab samples (n: 4818) and 49.12% positivity of sputum (n: 57) samples [20].

During the pandemic, about 40,000 RT-PCR tests have been performed on a daily basis in Turkey and a test kit, validated by The Turkish Ministry of Health, General Directorate of Public Health, Department of Microbiology Reference Laboratories and Biological Products (HSGM), was distributed to 129 authorized diagnostic laboratories. Viral RNA-based tests are the best option to diagnose an acute illness. The true clinical sensitivity of PCR tests is unknown. It is important to remember that the accuracy of the test is affected by the quality of the sample, days from symptom onset to test (very early or late in the infection), technical reasons (virus mutation or PCR inhibition), and whom to test.

In this study, we detected lower Ct values of cONS samples than sputum and TA samples, indicating higher viral loads (Table II).

The first study to analyze serial samples (throat swabs, sputum, urine, and stool) from two patients in Beijing revealed that the viral loads in throat swab and sputum samples peaked at around 5–6 days after symptom onset, ranging from around 10, 000 to 10, 000, 000 copies/mL during this time [10]. A recent and very comprehensive study estimated the viral loads in more than 3000 samples collected from 96 patients analyzed the temporal change in viral loads and the correlation between viral loads in different sample types and disease severity. In the respiratory samples, the median duration of the virus in patients with severe disease (21 days, 14-30 days) was significantly longer than in patients with mild disease (14 days, 10-21 days; P=0.04). Patients with severe disease had significantly higher viral loads than patients with mild disease. In the mild group, the viral load was greater during the initial stages of the disease, reached a peak in the second week from disease onset, and was followed by lower loads. In the severe group, however, the viral load in respiratory samples continued to be high during the third and fourth weeks after disease onset [21].

In the majority of our patients (86.72%) SARS CoV-2 RNA was detected in the first cNOS sample whereas in only 13.28% of the patients' positive results were obtained in consecutively taken samples within 9 days and only 0.19% of the patients 4$^{th}$ sample was required for positivity (Table III). Repetitive specimens should be tested in patients with negative RT-PCR and high suspicion or probability of infection to reduce false-negative results. Li et al., reported a potentially high false-negative rate of RT-PCR testing for SARS CoV-2 in the 610 hospitalized patients from whom 241(39.5%) patients were finally confirmed with COVID-19 with at least one positive RT-PCR test result [22]. Among the 384 patients with initial negative results, the second test was performed and the test results were positive in 48 cases (12.5%), seven patients were eventually confirmed with COVID-19 by three repeated swab PCR tests, four were confirmed by four repeated tests, and one was confirmed by five repeated tests. In another reported case, the third time RT-PCR test result for pharyngeal swab specimen from an infected patient turned to be positive after two previous negative results of the PCR test.

We also analyzed consecutive cONS and sputum samples or TA samples from 52 patients. Six lower respiratory tract samples (4 sputum, 2 TA) were found to be positive while cONS samples were found negative (Table IV). Therefore, if a negative result is obtained from a patient with a high suspicion for COVID-19, if possible the lower respiratory tract specimens should be tested. In 7 of 11 patients' clinical condition was severe requiring oxygen support or admission to the intensive care unit. Detection time for SARS CoV-2 RNA in lower respiratory specimens after symptom onset varied 3 to 12 days. The median Ct value was 30.00 (IQR: 25.85-39.92) in sputum and TA samples and 25.00 (IQR: 18.01-26.39) in cONS samples. Cycle threshold values detected from cONS samples were significantly lower than sputum and TA samples ($p<0.05$). Lower Ct values detected in cONS samples compared to lower respiratory tract specimens were inconsistent with the findings of the previous studies [19, 23]. We assume that this might be related to the manual extraction method and the performance of our RT-PCR kit for lower respiratory tract samples.

Additionally, we investigated the diagnostic value of saliva as a non-invasive specimen in a small group of hospitalized patients. SARS CoV-2 RNA was detected in 12 of 20 (60%) cONS positive and 4 of 12 (30%) cONS negative patients. Median Ct value was 25.50 (IQR: 17.37-36.74) in cONS samples and 28.00 (IQR: 20.08-31.00) in saliva samples indicating cONS contains a higher viral load. Similar to our results, the median Ct value was found to be lower in NPS compared to saliva in the study performed by Williams et al. and McCormick-Baw et al. [13, 24]. Saliva samples were found to be positive in 4 (30%) of 12 patients whose cONS samples were tested negative (data not shown). Ct values of four saliva samples were 28.54, 29.89, 29.90 and 31.27 (Median: 29.89, IQR: 28.54-31.27). Previous studies have reported that positive salivary results can be detected from the patients even when their pharyngeal swabs tested negative [13, 24-26]. In our study saliva was found to be positive even after 20 days of the initial symptoms that might alert people about the possibility of transmission through their saliva by close contact.

In a conclusion, the efficacy of the PCR test in the diagnosis of COVID-19 infection is greatly dependent on the pre-analytical phase including patient selection, material collection, and extraction method of RNA and performance of the RT-PCR test kit.

In this study, the preliminary findings of the diagnostic value of saliva for COVID-19 infection also were shared. Further research with larger sample size on saliva efficacy for detecting COVID-19 is needed for confirmation. Although, NPS samples show greatest diagnostic guidance, saliva testing might be an alternative screening test in the face of shortages of swabs and personal protective equipment.

## Compliance with Ethical Standards

### Ethical approvals

**The Turkish Ministry of Health Approval:** The study protocol was approved by the Turkish Ministry of Health (Protocol Number:2020-05-05T12_38_13).

**Institutional Approval**: The study protocol was approved by the Institutional Review Board and Ethics Committee of Marmara University, Faculty of Medicine (Protocol Number: 09.2020.563).

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**Author contributions:** R.C.S.: Method determination, doing PCR test, analyse PCR results, manuscript preparation, D.G.: Doing PCR test, analyse PCR results, manuscript preparation, B.E.S.: Patient selection, sample collection, medical record collection, V.K. : Patient selection, manuscript preparation, A.K.: Method determination, patient selection, manuscript preparation. All authors have read and approved the final version of the article.

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# Experiences of patients who had undergone coronary artery bypass graft surgery with strengths-based nursing care

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ABSTRACT

Objective: Strengths-based nursing is a new approach and care philosophy and it is still unclear how it affects patients in the surgery period. The aim of this study was to determine the experiences of patients who had undergone coronary artery bypass graft surgery managed with this philosophy.

Patients and Methods: This qualitative study consisted of 23 patients who had undergone coronary artery bypass graft surgery in the Cardiovascular Surgery Department of a university hospital in Izmir, Turkey. The data were collected using Individual Identification Form, Semi-structured Interview Forms, SWOT Analysis Form and Classification of Qualitative Strengths Form. Thematic data analysis was used to evaluate patient answers to the research questions.

Results: According to the analyses performed, seven main themes consisting of "Perception of Being Strong", "Perception of Being Weak", "Care Process", "Effects of Heart Disease", "Reason for the Occurrence of the Disease", "Need for Knowledge" and "Solution Seeking" were determined in the preoperative interviews, and five main themes consisting of "Perception of Being Strong", "Perception of Being Weak", "Surgery", "Care Process" and "Education" were determined in the postoperative interviews.

Conclusion: This new philosophy in patient management has positive effects because it increases patients' hopes for life, healing and facilitating adaptation to the surgical procedure.

Keywords: Coronary artery bypass graft surgery, Patient, Experience, Strengths-based nursing care.

## 1. INTRODUCTION

Many people die for various reasons including cardiovascular diseases (CVDs) in the world every passing year, and CVDs rank first among the causes of death around the world. According to data of the World Health Organization (WHO), 17.9 million people died from CVDs in 2016, and CVDs constituted 31% of all global deaths [1]. Coronary artery disease (CAD) is the most common among CVDs nowadays, coronary artery bypass graft surgery (CABGS) is the most commonly used method to reduce mortality and symptoms and to prolong life in the surgical treatment of CAD [2]. While surgical intervention performed by this method has therapeutic and positive effects on patients, it can also be observed to cause physiological, psychological and social changes. Physiological, behavioral, environmental and socioeconomic factors play a role in the effective management and nursing care of chronic diseases. The patients found ways to cope with the process by changing their environment, motivating themselves and reducing their demands. They found that the psychological effects of the disease could be coped by self-control, with the support of family, friends and spouse [3-5]. For these reasons, patients may need support to manage their symptoms and improve the prognosis in the surgical process.

In recent years, in these patients who underwent CABGS, the main goals of health care were to provide early mobilization, to reduce possible complication rates, to overcome deficiencies, to improve compliance to treatment and the quality of life and to ensure early discharge. It is necessary to ensure the participation of patients in their care and to encourage them to take part in their care in order to achieve these goals [6]. For quality patient management, to provide holistic care to individuals in the surgical process, to allow individuals to take a decision, and to

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teach them to use their resource mobilization skills (focusing on individuals' strengths) are among the roles and responsibilities of the nurse [6,7]. Strengths-Based Nursing Care (SBNC), published by Gottlieb in 2014, was a new philosophy of thinking in nursing and based on positive, the best and best working areas [8]. According to this philosophy, nurses and health professionals are charged with the responsibility of helping individuals find their own strengths to deal with both everyday challenges and adversities that threaten their integrity, that is, their sense of wholeness as well as the intactness of their lives [9].

This study will be a guide for health teams with respect to improving the quality of life of individuals, ensuring their participation in their own care and their compliance to treatment, and preventing possible complications. Besides, this study is considered a contribution to the literature as no study using this philosophy in patients undergoing heart surgery has been observed so far.The aim of this study was to determine experiences of patients undergoing coronary artery bypass graft surgery with SBNC.

## 2. MATERIALS and METHODS

A qualitative design was used with the purpose of explaining and describing facts of a phenomenon or an experience [10] using the participants' own language and staying close to the data [11]. The researcher is interested in the personal experiences of the participant and examines the perceptions of the individual and the meanings attributed to the events using in-depth interviews with patients.

### *Study Population*

This qualitative study consisted of 23 patients undergoing coronary artery bypass graft surgery in the Cardiovascular Surgery Department of a university hospital in Izmir, Turkey. Purposive sampling method was used in participant selection. Twenty-three patients who agreed to participate in the study, over18 years old, undergoing CABG for the first time, were hospitalized at least two days before surgery and were physically and psychologically qualified to have an interview were included. Patients who met the inclusion criteria were invited to the study by face to face method on the first day of hospitalization. The researcher gave detailed information about herself and the study and consent was obtained from the patients to participate in the current study. In total, 32 patients were invited to the study, a total of 9 patients were excluded, including 5 patients who refused to participate in the study and 4 patients who retracted from surgery. Twenty-three patients agreed to participate.

Research ethics board approval for this research was obtained from the Scientific Ethic Committee of a university (Ethics Committee approval no. 2015-86) and written permission was taken from the Administration of the University Hospital where the study was to be conducted. Written and verbal permissions of the patients who agreed to participate in the study were obtained. Patients were told that they could withdraw at any stage of the research and the 'Principle of Respect for Autonomy' was fulfilled. It was stated that the information obtained in the research would be kept confidential and the 'Principle of Confidentiality and Protection of Confidentiality' was fulfilled. Ethical principles were fulfilled based on the 'Principle of Beneficence and Nonmaleficence'.

### *Data Collection Tools*

Before the interview questions were prepared, international literature was reviewed and the relevant qualitative and quantitative studies were used [2,6,12,13]. Before starting to collect data, a total of 5 experts consisting of Faculty Members of Anthropology, Sociology, Curriculum and Instruction and Surgical Nursing were consulted for their opinions about the questions, and the questions were rearranged and finalized in line with the suggestions.

The data were collected in both processes before and after surgery, when the patient was interactive and communicative in the surgical process; since it is a whole that includes preoperative, intraoperative and postoperative management. The data were collected using the individual identification form (Socio-demographic Characteristics), semi-structured interview forms, Strengths, Weaknesses, Opportunities and Threats (SWOT) analysis form and the form of classification of qualitative strengths (Knowledge and Wisdom, Courage, Humanity, Justice, Moderation and Superiority).

The preoperative semi-structured interview form included the following questions:

-How has your illness affected you from physiological, psychological and social aspects?

-How did you decide to have surgery?

-What are your strengths, and the factors that make you weak?

-How do you think your strengths will affect your care process?

The postoperative semi-structured interview form included the following questions:

-What do you feel about your surgery?

-Were you able to use your strengths in accordance with the care provided to you during surgery?

-How did you use them?

-How did bringing your strengths into the forefront affect your recovery?

-What are your future expectations for using your strengths?

### *Data Collection Method*

The data were collected by conducting in-depth interviews on the day the patients were admitted to the clinic and the day they were discharged, and using individual trainings which are valid and reliable learning tools received from 10 experts consisting of 5 Faculty Members of Surgical Nursing and 5 Cardiovascular Surgery Nurses. The interviews with patients were conducted with preoperative and postoperative semi-structured interview forms by the first researcher. She was trained in qualitative methods and attended formal training courses including


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Qualitative Research Methods, Qualitative Data Analysis: Analysing Qualitative Interviews, Body Language, Effective Communication and Diction. She had worked as a nurse in the cardiovascular surgery service. In-depth interviews were conducted alone with the patient in the patient room or in the meeting rooms (depending on the request of the patient) in the clinic (Figure 1).


***Figure 1.*** *Data collection chart*

Data collection was maintained up to the stage at which the concepts and processes that could be the answer to the research questions began to repeat (saturation point). As the study progressed, data saturation was assessed by the research group by evaluating the richness of the data being collected, whether new substantive codes were being elicited, and whether new thematic categories were emerging. When saturation was considered to have been reached, a further three interviews were undertaken to confirm no new substantive codes were elicited. The interviews were audio recorded, transcribed verbatim, and validated by relistening to the recording by the researcher. The mean length of the interview was 53 minutes (min.45-max.72) on the day the participants were admitted to the clinic in the preoperative period, and 38 minutes (min.32-max.50) on the postoperative discharge day. The data collection was performed between August-November 2015 in the Cardiovascular Surgery Department of a university hospital.

### Data Analysis

Thematic data analysis was used to evaluate answers to the research questions [14]. The data management was assured using the NVivo 12. All interviews were transcribed verbatim word by word. Transcribed data were read and reread, and commonalities between the transcripts were noted and led to the development of themes [14]. Themes were analyzed for connections across emergent themes and were validated through comparison with the original data sources until data saturation occurred. Participant narratives and words served to inform the naming of themes [14]. Expert opinion was obtained from the clinical psychiatrist to determine the strengths of the patients and the factors that make them weak, transcripts were returned to participants and individual trainings were provided in accordance with the needs that emerged through the interviews. Quotations were translated to English, and throughout the analysis process, the patterns were discussed with all authors until consensus was reached. Examples of quotations are illustrated in the text and numbered from 1 to 23, representing all participants.

## 3. RESULTS

The average age of the patients participating in the study was 60.91±9.67 years. Of the patients, 73.9% were male, 95.7% were married, 56.5% were primary school graduates and retired, 95.7% had social security, 56.5% had previously undergone surgery and 87.0% were on continuous medication. The mean hospitalization day of the patients participating in the study was 12.73±2.75 days.

The results consisted of two parts. The first part included qualitative data including experiences for the preoperative period (Figure 2), and the second part for the postoperative period (Figure 3).

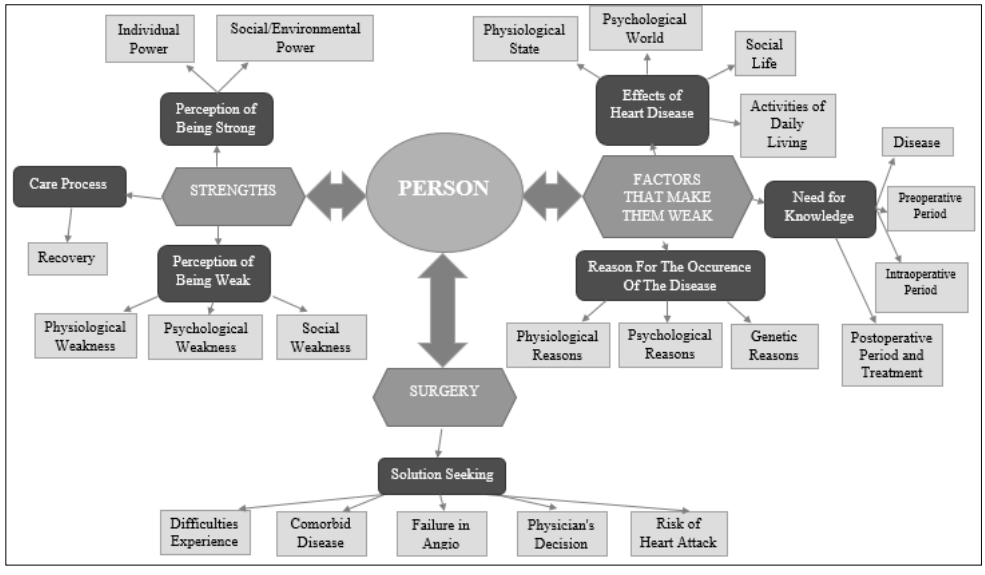


***Figure 2.*** *Categories, main themes and sub-themes of the preoperative period*

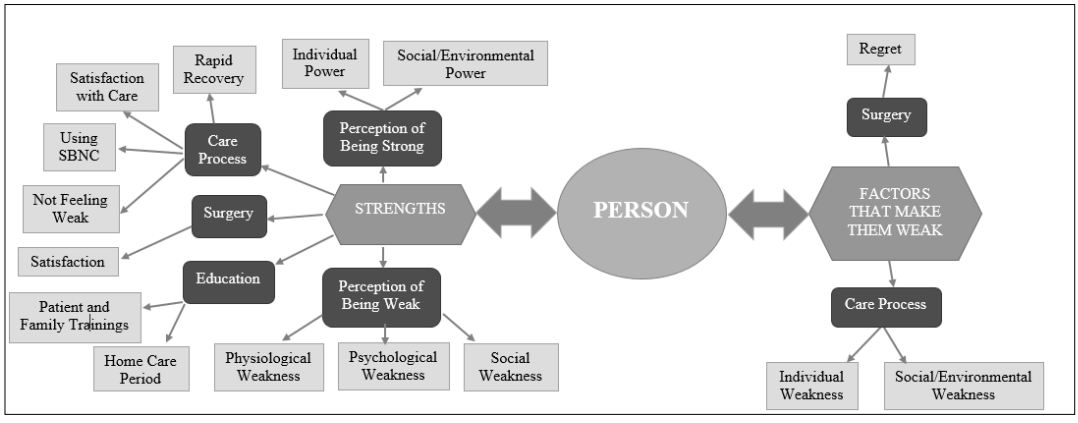


***Figure 3.*** *Categories, main themes and sub-themes of the postoperative period*


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According to the analyses performed, three categories consisting of 'Strengths', 'Factors That Make Them Weak' and 'Surgery' were determined in the preoperative period and two categories consisting of 'Strengths' and 'Factors That Make Them Weak' were determined in the postoperative period. According to the analyses performed, seven main themes consisting of "Perception of Being Strong", "Perception of Being Weak", "Care Process", "Effects of Heart Disease", "Reason for the Occurrence of the Disease", "Need for Knowledge" and "Solution Seeking" were determined in the preoperative interviews, and five main themes consisting of "Perception of Being Strong", "Perception of Being Weak", "Surgery", "Care Process" and "Education" were determined in the postoperative interviews.

### *A. Results of the preoperative period*

According to the interviews conducted in the preoperative period, 7 main themes consisting of 'Perception of Being Strong', 'Perception of Being Weak', 'Care Process', 'Effects of Heart Disease', 'Reason for the Occurrence of the Disease', 'Need for Knowledge', and 'Solution Seeking' were determined in the categories of 'Strengths', 'Factors That Make Them Weak' and 'Surgery', and their sub-themes were created.

### *A.1. Strengths*

This category consisted of the main themes of "Perception of Being Strong", "Perception of Being Weak" and "Care Process".

*Perception of being strong*

This consisted of two sub-themes including "Individual Power" and "Social/Environmental Power". Most of the patients and their relatives expressed being strong as "Being Rich (n=10)", "Struggling (n=7)" and "Being Healthy (n=7)".

*Perception of being weak*

It consisted of three sub-themes including "Physiological Weakness", "Psychological Weakness" and "SocialWeakness". Most of the patients and their relatives expressed "Being Weak (n=4)" as "Giving Up (n=6)", "Failing (n=5)" and "Insufficiency of the Person and His/Her Family, Being Passive in Everything".

*Care process*

This consisted of one sub-theme"Recovery". The patents expressed "Positive Effect (n=15)" by stating that "their strengths would positively affect the care process, which would give them experience and would strengthen them" and "Hope (n=14)" by stating that "their strengths increased their hope for recovery, morale and recovery would affect each other, and they would feel the effect of care with their strengths over time".

### *A.2. Factors that make them weak*

This category consisted of the main themes of "Reason for the Occurrence of the Disease", "Effects of Heart Disease" and "Need for Knowledge".

*Reason for the occurrence of the disease*

This consisted of three sub-themes including "Physiological Reasons", "Psychological Reasons" and "Genetic Reasons". They expressed "Family History (n=4)", "Stress (n=3)" and "Decrease in Physical Movement (n=2)" while describing the reasons for the occurrence of the disease.

*Effects of heart disease*

This consisted of four sub-themes including "Physiological State", "Psychological World", "Social Life" and "Activities of Daily Living". Most of the patients described the effects of heart disease as "Fatigue (n=16)", "Chest Disorders (n=15)", "Pain (n=14)" and "Restriction in Social Life (n=13)".

*"…when I went 50-100 meters, I was immediately squeezing my chest, there was burning on the chest, sweating started and came over me, I was sitting due to sweating for a 5-10 min. I was breathing and then I got up and walked again." (P.1)*

*Need for knowledge*

This consisted of four sub-themes including "Disease", "Preoperative Period", "Intraoperative Period" and "Postoperative Period and Treatment". While patients' needs for knowledge concerning the surgical process were described, they expressed that "They did not know anything and nobody told them (n=20)" about the preoperative and postoperative periods.

*"…The tests will be finished and then they will perform surgery … I have no other information." (P.20)*

### *A.3. Surgery*

This category consisted of the main theme of "Solution Seeking" since patients considered surgery as a solution.

*Solution seeking*

It consisted of five sub-themes including "Difficulties Experienced", "Comorbid Disease", "Failure of Coronary Angiography", "Physician's Decision" and "Risk of Heart Attack". The patients mostly described the decision-making process for surgery as "Physician's Decision (n=14)", "Risk of Heart Attack (n=4)" and "Failure of Coronary – – Angiography (n=3)".

*"…Well, my doctor told, I said you know better. He said that surgery was needed and the sooner would I, the better would I be. I also said you know better than me" (P.11)*

### B. Results of the postoperative period

The themes of the participants in the postoperative period were determined under the groups of "Strengths and Factors that Make Them Weak", and their main and sub-themes were created. 5 main themes consisting of 'Perception of Being Strong', 'Perception of Being Weak', 'Surgery', 'Care Process' and 'Education' were determined in the groups of "Strengths" and "Factors that Make Them Weak" in the postoperative interviews.


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### *B.1. Strengths*

This category consisted of the main themes of "Perception of Being Strong", "Perception of Being Weak", "Surgery", "Care Process and Education".

*Perception of Being Strong*

It consisted of two sub-themes including "Individual Power" and "Social/Environmental Power". In the postoperative period, most of the patients and their relatives mostly described their thoughts and behaviors about the perception of being strong and what being strong meant to them as "Being Healthy (n=11)", "Self-Sufficiency (n=8)" and "Environmental Support (n=5)".

*"Being self-sufficient, being strong. How can I say? (Thinking…) I mean it is to get up from this bed by drawing strength from me without my wife, being able to walk alone, in other words, to use my strength to meet my needs …". (P.2)*

*Perception of being weak*

It consisted of three sub-themes including "Physiological Weakness", "Psychological Weakness" and "Social Weakness". Most of the patients expressed the perception of being weak as "Giving Up (n=5)" and "Being Weak (n=6)".

*"Giving up in the face of difficulties... not struggling." (P.7)*

*"Self-release, to give up life." (P.13)*

*Surgery*

The patients were asked to complete the sentences of I am glad I had surgery because…., "Satisfaction" that would be appropriate for them, and the statements of the patients were structured in accordance with the following two sub-themes under the third main theme "Surgery".

The patients mentioned 3 concepts including "Getting Healthy (n=12)", "Risk of Heart Attack (n=8)" and "Fear of Death (n=6)" under the sub-theme of "Satisfaction" while describing their thoughts and feelings about having surgery.

*"I am glad I had surgery because I would constantly feel uneasy for a heart attack …but now, I've had surgery and I'm getting better slowly. I feel better, I believe that I will be better …". (P.15)*

*Care Process*

It consisted of four sub-themes including "Rapid Recovery", "Satisfaction with Care", "Using SBNC" and "Not Feeling Weak". While the patients were describing the effects of their strengths on the care process, they mostly talked about the sub-themes "Rapid Recovery (n=25)", "Satisfaction with Care (n=25)" and "Using SBNC (n=21)" expressing that "they recovered faster than expected", "they were pleased because of the increased courage" and "they would use the SBNC in all areas".

*"It has affected positively. It made me recover faster, my self-confidence has increased, I have started to feel stronger, how can tell, I am happy." (P.21)*

*"I am so glad. I never imagined it before I came here. I liked the fact that you asked my opinion in every respect. It impressed me that I recovered more quickly and was very pleased in this respect." (P.13)*

*Education*

It consisted of two sub-themes including "Patient and Family Trainings" and "Home Care Period". While the patients were describing their thoughts and behaviors related to the effect of individual patient and family trainings on the care process, they mostly talked about the sub-themes "Patient and Family Trainings (n=12)" and "Home Care Period (n=7)" expressing that "it had a positive effect and was very beneficial" and "it was very good for them to have a written document".

*"Our doctor told us a little, but we had some questions to ask, of course you told them. One forgets with the excitement of being discharged. Thank you very much for the information and books you provided." (P.19)*

### *B.2. Factors that make them weak*

This category consisted of the main themes of surgery and care process.

*Surgery*

The patients were asked to complete the sentences of I wish I had not had surgery because… .. "Regret" that would be appropriate for them, and the statements of the patients were structured in accordance with two sub-themes under the third main theme "Surgery".

While the patients were describing their thoughts and feelings about having surgery, under the sub-theme of regret, one of the patients expressed his regret by stating that he had never stayed in hospital previously and therefore he wish he had not had surgery.

*"I wish I had not had surgery because I have never stayed in hospital, but I had a risk of death, therefore I had to stay."(P.12)*

*Care process*

Care process, which was the second main theme, consisted of two sub-themes including "Individual Weakness" and "Social/Environmental Weakness". While the patients were describing their thoughts and behaviors related to their strengths and the factors that make them weak in the care process and the methods of coping with them, they mostly expressed difficulty in "Physical Activity (n=7)" and "Intensive Care Unit (n=7)".

*"I felt weak in the intensive care unit, well, I was naked with a hose in my mouth, it was cold, it is too cold in there … But I did not give up, I said to myself "you would achieve this" … do this job, I immediately started the exercises, my feet warmed, it was good when my legs moved. Then I said that Mrs. Nurse was telling the truth (laughs….". (P.11)*

## 4. DISCUSSION

The discussion section consists of patients' feelings and thoughts, strengths and the factors that made them weak in the preoperative and postoperative processes. On the preoperative period in this study, patients indicated that they could get support from their families, relatives, environment and physicians in coping with this process and adapting to the process. In the study of Mooney, et al., 70% of coronary artery surgery patients stated that they had difficulty in maintaining a regular social life [15]. Bergvik, et al., indicated that coronary artery surgery patients needed the support of their relatives to plan activities and perform these activities in their daily lives [16]. It was determined that coronary artery surgery patients had significant deteriorations in daily life, social relations and psychology [3,15,16]. Coping strategies under strengths are important in adapting to the chronic state [3,15]. This process is consistent with Knowledge and Wisdom, Courage and Superiority capacity, the ability to predict the future with the impressions of the individual about past experiences, one of basic principles on which the SBNC is based. These results describe patients' "Individual Centered Care, Empowering the Individual, Holistic, Individual and Personalized Care, Health Promotion and Disease Prevention and Collaborative Care" capacity, one of basic principles on which the SBNC is based.

On the preoperative period in this study, within the framework of "Knowledge and Wisdom, Courage, Superiority and Moderation" of the SBNC which constituted the basis of the study, the reasons for patients to decide on surgery were expressed as the risk of heart attack, failure of coronary angiography, difficulties experienced, comorbid diseases and physician's decision. The decision for surgery is considered as an experience that threatens the patient both physiologically and psychologically. However, the patients who will undergo surgery feel scared and anxious since they do not have information about the surgical process [15-17]. In the literature and in this study, it appears that the patients who are scheduled for surgery do not have enough information about the surgical process and they need to get more knowledge [5,15-18]. Nevertheless, it is reported that the training given to patients in this process is limited and usually provided by the physician [15,19]. However, the nurse has important responsibilities in ensuring coordination within the team and in the planning and implementation of training on the surgical process and discharge [17,19]. In this study, when patients who underwent CABG were asked where they were informed about CAD and the surgical process, most of the patients indicated that they did not receive any information. After the individual and family trainings provided by the researcher in accordance with the SBNC, most of the patients indicated that those trainings were very useful and they would use SBNC in preoperative surgical patients.

On the postoperative period in this study, most of the patients indicated that they effectively coped with disease and surgery. These statements explain the principle of "Courage, Moderation and Superiority" expressing the individual's belief in the ability to achieve a behavior, one of the basic principles on which the SBNC is based. Leegaard and et al. (2008) indicated that the internal factors affecting the compliance of patients with CAD and treatment were personality, and the external factors were social activity, family, friend relations and support of health care professionals [4]. Physiological, behavioral, environmental and socioeconomic factors play a role in the effective management of chronic diseases [3]. Mohammadi, et al., indicated that the patients found ways to cope with the process by changing their environment, motivating themselves and reducing their demands and that the psychological effects of the disease could be coped with by self-control, family, friends and spouse's support [20]. Emotional health is important in coping with CAD. According to the "Knowledge and Wisdom, Courage and Superiority" capacity, one of the basic principles on which the SBNC is based, patients set targets in the postoperative period by coding their past experiences with thoughts and symbols and making future plans. Some patients indicated that "they were further encouraged after surgery", "they were able to realize some thoughts that they could not do before the surgery", "they could express themselves better", "this situation made them happy" and "they felt like a newborn". It is stated that post-traumatic growth is more frequently observed in those with life-threatening diseases such as cancer and CAD, and in these studies, individuals achieve growth in many areas such as self-perception, life philosophy, and mental development in the post-operative period [21]. The individual learns to make and implement plans for the future based on his past experiences, accepts the process and adapts to the post-operative process with Content Centered Care, Collaborative Care and Empowerment Movements and Health Promotion and Disease Prevention, and Determination, Positive Thinking and Perseverance.

On the postoperative period another result obtained from this study was that getting individual centered care increased patient satisfaction and improved the feeling of confidence between health worker and patient. Patient satisfaction expressed at the end of the surgical period in line with individual-centered care is a complex concept affected by various factors and is one of the most important indicators of the quality patient management [12]. In some studies, it was also found that interpersonal communication and behavior of staff regarding the treatment process and information about the disease increased patient satisfaction [5,17,19]. SBNC offers nurses the opportunity to provide individual and holistic care to patients, in this respect, the use of the philosophy in this patient group is important. SBNC increases patients' compliance with the surgical process by revealing their strengths and empowers them and also reveals their weaknesses and gives them the opportunity to turn them into strengths, and facilitates their compliance to the surgical process.

### Strengths and Limitations

Human factor constitutes the strengths of qualitative studies. Patients' experiences are closely associated with their culture and past experiences. As the first author of the present study has clinical experience in the field of cardiovascular nursing, the analysis of the data was carried out continuously discussing and reflecting on identified main themes and sub-themes to


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decrease the risk of research bias. The translated quotations and the pattern of the data and interviews were further discussed until consensus was reached within the whole research team, which confirms the dependability of the data. Multiple researchers analyzing the data independently then conjointly established credibility and trustworthiness of the data. The use of various data collection methods (interviews and written reflections) preserved credibility, providing multiple constructions of the data, and enhanced the richness of the interpretation. Furthermore, the transferability is enhanced by the detailed description of the design of the study, the analysis of the data and the rich description of the context and findings. Nevertheless, the fact that the study provided an opportunity to examine in depth the experiences of CABGS patients and was the first study using SBNC made the results of the study unique and valuable and constituted the strength of the study. However, we acknowledge that it is a single centre study, which might limit transferability. The fact that the results obtained as a result of the study were based on the patients' own statements constituted the factors that made the study weak, therefore, the results of the study cannot be generalized.

### Conclusion

According to SBNC, the strengths that were mostly expressed by the patients provided with care were the "desire to manage the surgical process", "ability to provide basic physiological and safety needs", "hope for life", "strong desire to learn" and "having family support". It was concluded that the factors that made individuals most weak in the surgical process were the "lack of knowledge about disease and treatment process", "limitation of physical and social activity" and "being in the intensive care unit". The patients emphasized that they were satisfied with the care provided in accordance with this philosophy in the surgical process. This new philosophy in patient management is effective because it increases patients' hopes for life, healing and facilitating adaptation to the surgical procedure. In the future, education and training about CABGS must focus on patient needs regarding the surgical process and encourage them to take part in their care. In line with these results, it is recommended to use SBNC for different diseases and processes and to discuss the results.

### Compliance with Ethical Standards

**Ethical approval:** Approval for the study was obtained from the Scientific Ethics Committee of a University (Ethics Committee Approval No. 2015-86). Written permission was taken from the Administration of University Hospital where the study was to be conducted. Informed consent was obtained from all individual participant included in the study.

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# Cost-effectiveness analysis of arthroscopic surgery versus open surgery in rotator cuff repair

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ABSTRACT

Objective: This study aimed to compare the open and arthroscopic rotator cuff tear treatment methods in terms of cost-effectiveness.
Materials and Methods: This study includes a prospective method of a total of 104 patients, 52 with open surgery and 52 with arthroscopic surgery, in the treatment of rotator cuff tears. Cost calculations of the treatment methods were obtained from patient invoices. Oxford Shoulder Score and Short Form-36 Health Survey Questionnaire were used for effectiveness calculations. The cost-effectiveness comparison was conducted using the Incremental Cost Effectiveness Ratio (ICER) assessment. The difference between costs of open and arthroscopic surgery was analyzed using the SPSS 23.0 package program, with Mann-Whitney U test.
Results: The average cost per patient was 4,838.7 Turkish Liras (TL) (866.22 USD) in open surgery and 5,770.33 TL (1,033.00 USD) according to the exchange rate at the time of writing, in arthroscopic surgery. Oxford Shoulder Score was 21.15 in open surgery and 20.83 in arthroscopic surgery. Short Form-36 Health Survey Questionnaire score was 61.92 in open surgery and 63.17 in arthroscopic surgery. The ICER calculated according to the Oxford Shoulder Score was – 2,912.37 TL (521,37 USD), while the ICER calculated according to the General Health Perception sub-scale of Short Form-36 was 745.57 TL (133,47 USD). In addition, statistical significant difference was found between the surgery, medication, medical and surgical materials, hospitalization and average cost of those treated with open surgery and those treated with arthroscopic surgery ($p<0.05$).
Conclusion: There was no statistically significant difference between the efficacy scores of the treatment groups. However, there was statistically significant difference between costs of the treatment groups.
Keywords: Rotator cuff injuries, Rotator cuff repair, Cost-effectiveness

## 1. INTRODUCTION

The largest part of the shoulder joint function is performed by the rotator cuff [1]. The rotator cuff muscles and the extrinsic shoulder muscles are located around the shoulder joint to perform a specific rotational motion [2]. The tear of the rotator cuff is the most common musculoskeletal injury to the shoulder [3] and is the common cause of shoulder pain and shoulder disability [4]. Shoulder pain (16%), was shown as the third most common pain in the musculoskeletal system after knee pain (19%) and low back pain (23%) [5,6].

Pain in shoulders causes a significant socioeconomic burden; disability of the shoulder can impair the ability to work or perform household tasks and can result in time off work [5]. It is estimated that there are 4.5 million outpatient visits in the United States of America (USA) each year for shoulder pain, and these are usually associated with rotator cuff pathologies [7]. According to the Ministry of Health (MoH) in Turkey in "First 100 Hospitals in All Branches Report (2017)", the number of patients admitted to the Orthopedics and Traumatology units constitutes about 5% of all patients [8]. In rotator cuff tears, the ability of the shoulder joint to function as well as the ability to perform basic activities are impaired. Rotator cuff tear also causes significant labor shortages, loss of movement, reduced quality of life, and increased health care costs [9,10].

Rotator cuff tear is characterized by shoulder pain, and it is a cause of pain and disability among adults. Conservative and surgical treatment options are available for the treatment of rotator cuff diseases. The importance of pain in treatment decision-making has yet to be determined, particularly since psychosocial factors have been demonstrated to play a more important role in patient-reported pain and function than

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tear severity [11,12]. The conservative method includes combinations of rest, exercise, physiotherapy and painkillers [13,14]. Without repair, the rotator cuff has limited capacity to heal; conservative treatment often yields a satisfactory outcome, however the main disadvantages of a non-surgical approach are tear progression, ongoing pain, and deterioration in function over time [15,12].

The heal of the rotator cuff is associated with an improvement in function. The optimal treatment option for symptomatic rotator cuff tears is unknown and for many years there has been conflicting evidence as to which is the most effective method. Arthroscopic surgery causes less damage to surrounding soft tissues such as the deltoid, and has the theoretical advantage of causing less postoperative pain while permitting earlier mobilization [16]. Surgical methods include arthroscopic or open surgical procedures [17]. The use of these methods varies depending on the type of tear and the condition of the patient and tissue [18]. The costs and the effects on the quality of life of patients of these surgical treatment methods, which can be applied to similar patient groups, are different. Rotator cuff repair is a very costly operation [19]. As with all health services, increasing costs in rotator cuff repair is a worldwide phenomenon. Therefore, it is becoming more important to reduce healthcare delivery costs [20]. The dissimilar costs of the treatment methods used in the treatment of the same disease, as well as the different effects on the quality of life of the patients, necessitates the comparison between alternative methods. Given the increasing costs and scarce resources, there is a need to make comparisons between different rotator cuff tear treatment methods, which is itone of the major health problems. Rotator cuff surgery is one of the most widely performed orthopedic surgical procedures, and surgery volume is on the rise [21].

In this study, we aimed to compare the open and arthroscopic rotator cuff tear treatment methods in terms of cost-effectiveness analysis. We hypothesized that arthroscopic rotator cuff tear surgery would be more cost-effective than open surgery.

## 2. MATERIALS and METHOD

In this study, we aimed to compare open and arthroscopic rotator cuff tear treatment methods with cost-effectiveness analysis. The study was approved by the Ethical Committee of the Faculty of Health Sciences, Ankara University (approval number: 56786525-050.04.04/7564). This study utilizes the prospective research method, it has been conducted between September 2018 and April 2019. One hundred and four patients who met the inclusion criteria and each group who underwent open and arthroscopic surgery were included in the study. The surgeons used their usual preferred method of repair. Inclusion criteria were (1) the patients who had shoulder pain between 4 and 6 months, (2) had a tear ≤ 3 cm, (3) the tear had been confirmed with magnetic resonance imaging (MRI) and ultrasound findings. Exclusion criteria were (1) had massive tears, (2) previous surgical procedure on either shoulder, (3) preceding trauma. Patients operated on with the arthroscopic method were treated with tendon bone fixation. Informed consent was obtained from each patient prior to surgery.

In this study conducted from the perspective of the public funded health care system cost data were obtained from hospital information system. The average cost of open and arthroscopic surgical treatment methods was calculated based on the invoiced amounts for each group of patients. Besides, the invoice amounts were classified under the headings of the operation, medicaments, medical and surgical materials, medical imaging and hospitalization expenses and their share in total expenses was calculated.

The Oxford Shoulder Score and Short Form 36 Health Survey Questionnaire scoring systems were used to measure the effectiveness criteria in the study. The Oxford Shoulder Score commonly used for quality of life in orthopedics was applied. The Oxford Shoulder Score has been shown to correlate well with the Short Form 36 ($r>0.5$) [19]. The Oxford Shoulder Score is a scale developed to evaluate the functional status of patients with certain shoulder problems [22]. It consists of 12 questions, each with five answer options, where 1 represents the best and 5 the worst [23]. The total score of the 12 questions gives the Oxford Shoulder Score for each individual. Scores from each question are combined to achieve a single score on a scale where 48 represents the best and 0 represents the worst [24,25,19]. This indicates severe shoulder arthritis at score 0 to 19, moderate to severe shoulder arthritis at score 20 to 29, mild to moderate shoulder arthritis at score 30 to 39 and satisfactory joint function at score 40 to 48 [25].

The Short Form 36 Health Survey Questionnaire consists of 36 questions measuring health status in three categories: functional ability, welfare and general health. The health status of the person is measured in eight sub-parameters. Functional ability category consists of sub-parameters of physical function, social function, limitation due to physical problems, limitation due to emotional problems; welfare category consists of sub-parameters of emotional well-being, energy-fatigue, body pain and general health category consists of sub-parameter of general health perception. Each item response is on a 6-point scale (from "always" to "never"). The total score is calculated by reversing the answers into two items (third and fifth), adding the scores and converting the raw scores to a scale ranging from 0 to 100 [20]. The scale gives a separate total score for each subscale instead of a single total score. A higher score means better health [25,26].

### *Data Analysis*

The invoices of patients treated between September 2018 and April 2019 were examined and the costs of alternative treatment methods for the reimbursement institution were calculated. Reduction was not performed because the data were collected prospectively and did not cover a short time.

The aim of surgical treatment is to minimize deterioration in shoulder function and this significantly increases the quality of life of the patient. After surgery, patients are taken under a rehabilitation programme for the first year [15,27,12]. In this

study for the comparison of the effect of treatment methods, Oxford Shoulder Score and Short Form 36 measurement tools were applied to both groups the 16th week after surgery.

### Statistical Analysis

To determine whether there is a univariate end value in the data set, z values outside the range of – 3 to +3 were examined. To investigate the univariate normality, descriptive statistics of the scores obtained from Oxford Shoulder Score and Short Form 36 scales and of the cost were calculated and histograms were drawn for their distribution. From the descriptive statistics of these distributions, it is necessary to provide the univariate normality assumption considering the mean, mode and median and skewness and kurtosis coefficients. As a result, it was seen that the univariate normality assumption was not provided by considering the mean, mode and median and skewness and kurtosis coefficients. Also, the normality hypothesis was tested by the Shapiro-Wilk and Kolmogorov-Smirnov tests. In the selection of significance tests, whether the distributions were normal or not was taken into consideration. According to these results, the Mann-Whitney U test was used to analyze whether the mean scores of the two non-normally distributed groups were different, in order to test whether the effectiveness scores of arthroscopic and open surgical methods differ. The ICER was used to compare the treatment methods with cost-effectiveness analysis. The 95% confidence intervals (95% CI) were calculated, with statistical significance set at $P < 0.05$.

## 3. RESULTS

During the research period, 52 patients treated with open surgery and 52 patients treated with arthroscopic surgery were included in the study. Of the patients treated with arthroscopic surgery, 63.46% were female and 36.54 were male. The ages of the patients in this group ranged between 38-82 and the mean age was 58.3. 67.31% of the patients treated with open surgery were female and 32.69% were male. The ages of the patients ranged from 37 to 80 years with a mean age of 57.62 years. It was seen that the groups were distributed homogeneously. The mean hospitalization duration was 2.70 days in arthroscopic surgery while it is 3.23 days in open surgery.

***Table I.*** *Cost accounts*

| Types of Treatment | Types of Expenses | Operation | Medicaments | Medical Imaging | Medical and Surgical Materials | Hospitalization | Total | Mann-Whitney U | p |
|---|---|---|---|---|---|---|---|---|---|
| Open Surgery | Total (TL) | 147,732.61 | 9,533.17 | 296.40 | 89,053.22 | 4,980.00 | 251,595.40 | 1,917.00 | 0.000 |
| | Share in Total Expense (%) | 58.72 | 3.79 | 0.12 | 35.4 | 1.98 | 100.00 | 2,381.00 | 0.000 |
| | Average Cost per Patient (TL) | 2,841.01 | 183.33 | 5.70 | 1.712.56 | 95.77 | 4,838.37 | 764.00 | 0.000 |
| Arthroscopic Surgery | Total (TL) | 211,447.21 | 6,319.89 | 296.40 | 77,763.68 | 4,230.00 | 300,057.18 | 917.00 | 0.002 |
| | Share in Total Expense (%) | 70.47 | 2.11 | 0.10 | 25.92 | 1.41 | 100.00 | 440.00 | 0.000 |
| | Average Cost per Patient (TL) | 4,066.29 | 121.54 | 5.70 | 1,495.46 | 81.35 | 5,770.33 | 808.00 | 0.000 |

Table I shows the cost findings related to treatment methods. The average cost of treatment with open surgery per patient is 4,838.7 TL (866.22 USD). Surgical intervention with 58.72% and medical equipment expenses with 35.4% have the highest share in this cost. The average cost of treatment with arthroscopic surgery per patient is 5,770.33 TL (1,033.00 USD). 70.47% of this amount is for surgical intervention and 25.92% of it consists of medical equipment expenses.

***Table II.*** *Statistical analysis of open and arthroscopic surgery costs*

| Types of cost | Open Surgery (TL) | Arthroscopic Surgery (TL) | Mann-Whitney U | p |
|---|---|---|---|---|
| Operation | 2,841.01 | 4,066.29 | 138.00 | 0.000 |
| Medicament | 183.33 | 121.54 | 1,826.50 | 0.002 |
| Medical Imaging | 5.70 | 5.70 | 1,352.00 | 1.000 |
| Medical and Surgical Materials | 1,712.56 | 1,495.46 | 1,941.50 | 0.000 |
| Hospitalization | 95.77 | 81.35 | 1,690.00 | 0.019 |
| Average Cost | 4,838.37 | 5,770.33 | 1,352.50 | 0.000 |

Table II shows statistical analysis of open and arthroscopic surgery costs. Statistically significant difference was found between operation, medication, medical and surgical materials, hospitalization and average cost of those treated with open surgery and those treated with arthroscopic surgery ($p<0.05$). However, there was no statistically significant difference between the medical imaging cost of the treatment groups ($p>0.05$).

***Table III.*** *Results of cost-effectiveness analysis*

| Treatment Methods | Cost (TL) | Additional Cost (TL) | Effectiveness (Oxford Shoulder Score) | Additional Effectiveness (Oxford Shoulder Score) | Effectiveness (Short Form-36) | Additional Effectiveness (Short Form-36) | Incremental Cost Effectiveness Ratio (Cost difference/ Oxford Shoulder Score difference) | Incremental Cost Effectiveness Ratio (Cost difference/Short Form-36 difference) | Cost/Effectiveness (Oxford Shoulder Score) | Cost/Effectiveness (Short Form-36) |
|---|---|---|---|---|---|---|---|---|---|---|
| **Open Surgery** | 4,838.37 | | 21.15 | | 61.92 | | | | 228.76 | 78.14 |
| **Arthroscopic Surgery** | 5,770.33 | 931.96 | 20.83 | -0.32 | 63.17 | 1.25 | – 2,912.37 | 745.57 | 277.02 | 91.35 |

Table III shows the results of the cost-effectiveness analysis. According to the results of the analysis, arthroscopic surgery requires an additional cost of 931.96 TL (166.84 USD) compared to open surgery. No statistically significant difference was found between the Oxford Shoulder Scores of those treated with open surgery and those treated with arthroscopic surgery (Mann-Whitney U:1,468; $p>0.05$). There was no statistically significant relationship between the Short Form 36 General Health Perception sub-scores of patients treated with both surgical methods. (Mann-Whitney U:1,352.5; $p>0.05$). When the Oxford Shoulder Score values were compared; arthroscopic surgery was found to be 0.32 units less effective than open surgery. When the Short Form 36 General Health Perception sub-scores were evaluated, arthroscopic surgery was found to be 1.25 units more effective than open surgery.

The incremental cost-effectiveness ratio calculated according to the Oxford Shoulder Score was found to be – 2,912.37 TL (521.37 USD). In this case, the cost per additional unit effectiveness by arthroscopic surgery compared to open surgery was – 2,912.37 TL (521.37 USD). The negative value of the ICER indicates that treatment with arthroscopic surgery does not provide additional efficacy. Compared to open surgery, arthroscopic surgery with its high cost and low efficiency was not found to be cost-effective. According to the General Health Perception sub-scores of Short Form 36, ICER was calculated as 745.57 TL (133.47 USD). In this case, an additional unit cost of TL 745.57 is required for another unit improvement in general health status in arthroscopic surgery compared to open surgery. The costs of the treatment methods were divided by the effectiveness scores and the cost of one unit of effectiveness was determined. To gain one unit of effectiveness concerning the Oxford Shoulder Score, an additional cost of 228.76 TL (40.95 USD) is required in open surgical treatment; and in arthroscopic surgery, an additional cost of 277.02 TL (49,60 USD) is required to gain one unit of effectiveness concerning the Oxford Shoulder Score. However, for a one-unit increase in the Short Form 36 General Health Perception sub-score, an additional cost of 78.14 TL (13,99 USD) arises in open surgery, and an additional cost of 91.35 TL (16,35 USD) arises in arthroscopic surgery.

## 4. DISCUSSION

Despite the frequent application of rotator cuff repair, there is no consensus on the best repair technique The appropriate rotator cuff tear surgical treatment is still controversial and patients who undergo surgery have two options as open or arthroscopic treatment. Therefore, focusing on rotator cuff surgery, there has been a significant reduction in failure rate [16,28]. Increased treatment costs in health care have led to the necessity of cost-effectiveness comparisons between alternative surgical methods. Mather et al., found that surgical and continuous non-operative rotator cuff repair methods are cost effective in all age groups [17]. This finding indicates the curability of each patient. In rotator cuff repair which is very commonly performed, cost-effectiveness evaluations were made between various treatment methods. The overall cost-effectiveness of rotator cuff repair [22], surgical and non-surgical methods and cost-effectiveness of alternative surgical methods have been the research question of many studies [28-30]. In this study, open and arthroscopic repair methods were compared in terms of cost and effectiveness.

When the studies comparing the cost of open and arthroscopic surgery methods in literature are examined, generally open surgery is found to have a lower cost than arthroscopic surgery [29,30,17,31]. In our study also, the cost of open surgery was found to be lower than the cost of arthroscopic surgery. This difference in costs is due to surgical intervention and medical equipment expenses (Table I). Hui et al., concluded in their study that the majority of the cost difference between surgical methods stems from implants and consumables [29]. Narvy et al., reported that the main cost driver factor in rotator cuff repair surgeries is the suture anchor cost [31], Murphy et al., reported that other equipment costs (except anchors) were statistically


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significant requiring £77 additional cost for arthroscopic surgery procedure [32].

In our study, the Oxford Shoulder Score was used to measure the clinical efficacy of treatment groups, and the Short Form 36 Health Survey Questionnaire, General Health Perception sub-scale was used to measure general health perception. Dawson et al., have demonstrated a good correlation between Oxford Shoulder Score and Short Form 36 in rotator shoulder tear efficacy measurement [19]. In our study, it was concluded that open surgery had higher value in terms of Oxford Shoulder Score and Short Form 36 General Health Perception sub-scale value was higher in arthroscopic surgery. There was no statistically significant relationship in terms of effectiveness scores of the surgical methods ($p > 0.05$). In the literature, treatment methods have been evaluated with various effectiveness measurement tools and some studies do not detect any differences in the effectiveness of treatment methods [32,33,16,17]. Churchill et al., in their study comparing the duration of surgery, determined the time in the mini-open group (103 minutes) to be significantly shorter than the entire arthroscopic group (113 minutes) [34]. In a cost-effectiveness study performed among surgical methods in nineteen hospitals in the United Kingdom, effectiveness scores were measured at 2 weeks, 8 weeks, 8 months, 12 months, and 24 months after surgery. The Oxford Shoulder Score increased in 24 months from 25 to 42.5 in the open group and from 26.3 to 41.7 in the arthroscopic group. However, there was no difference between open repair and arthroscopic repair in terms of clinical efficacy or cost-effectiveness [17].

### Limitations

This study should be reviewed within the framework of certain limitations. The cost-effectiveness assessment of treatment methods was carried out from the perspective of the reimbursement agency. Performing economic assessments also with patients, service providers and community perspectives will provide evidence-based information for more stakeholders. To compare the effectiveness of treatment methods, the scales were administered only once four months after surgery. Evaluating the differences between the measurements by applying the effectiveness scales before surgery and certain periods after surgery will provide more clear results.

### Conclusion

In this study, treatment with arthroscopic surgery was found to be more costly in rotator cuff tear repair compared to open surgery. No statistically significant difference was found between the effectiveness scores of the treatment methods. However, there was statistically significant difference between the costs of the treatment groups. According to the Oxford Shoulder Score which is a clinical efficacy measurement tool, arthroscopic surgery was not found to be cost-effective in terms of shoulder health compared to open surgery. Treatment with arthroscopic surgery was found to be more effective compared to open surgery, although its cost was higher in terms of general health perception according to Short Form 36.

### Compliance with Ethical Standards

**Ethical Approval:** The study was approved by the Ethical Committee of the Faculty of Health Sciences, Ankara University (approval number: 56786525-050.04.04/7564).

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**Conflict of Interest**: The authors, their immediate families, and any research foundations with which they are affiliated have not received any financial payments or other benefits from any commercial entity related to the subject of this article.

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# The effect of HPV analysis on the ASC/SIL ratio which is one of the quality control criteria for PAP smears

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ABSTRACT

Objective: The high number of smear tests has a workload on pathologists/cytopathologists, which raises the concern for the quality of diagnoses. The application of high-risk human papillomavirus (hr-HPV) analyses with the PAP smear has begun to contribute to the clinical practice. In this study, we aimed to show the effect of hr-HPV analysis on the results of PAP smear via atypical squamous cell/squamous intraepithelial lesion (ASC/SIL) ratio on the quality standards.

Materials and Methods: A total of 12799 cervical cytology reports, between 2014-2016, from the Pathology Department of Marmara University Hospital, were included. Between November 2014 and May 2016, hr-HPV analysis was performed on a total of 4307 cases with Hologic Aptima HPV™, USA. Smear diagnoses before and after the start of the HPV test application were recorded.

Results: The cytology diagnoses, during when hr-HPV screening was not performed, were: negative for intraepithelial lesion or malignancy (NILM) 99.4%, atypical squamous cells of undetermined significance (ASCUS) 0.6%, low-grade squamous intraepithelial lesion (LSIL) 0.2%, ASC-H 0.04%, and high-grade squamous intraepithelial lesion (HSIL) 0.13%. The cytology diagnoses that were evaluated with HPV test were as follows: NILM 93.67%, ASCUS 2.31%, LSIL 2.82%, ASC-H 0.3%, and HSIL 0.91%. ASC/SIL ratio has been dropped from 1.9 to 0.7 after the initiation of hr-HPV use.

Conclusion: During the period without hr-HPV analysis, the ASC/SIL ratio was 1.9. Later with the initiation of hr-HPV screening this ratio decreased to 0.7. This shows that knowing HPV test results affects and improves the quality of the laboratory diagnoses.

Keywords: ASC/SIL ratio, Quality, PAP smear, HPV analysis

## 1. INTRODUCTION

The widespread adaptation of cervical smear (PAP smear) screening programs led to the diagnosis and treatment of squamous intraepithelial lesions (SIL). It has been used since the 1950s and this caused a dramatic decrease in cervical cancer incidence. The PAP smear has not lost its reputation even after the introduction of the human papillomavirus (HPV) vaccine, due to its population-wide effect and affordable cost in comparison to HPV vaccines. The high number of smear tests, on the other hand, has a workload burden on pathologists/cytopathologists, which raises the concern for the quality of diagnoses. In recent years, the application of high-risk HPV (hr-HPV) analyses (HPV DNA and/or mRNA) reflexively or simultaneously with the PAP smear has begun to contribute to the clinical practice [1,2 ].

Atypical squamous cells of undetermined significance (ASCUS] and atypical squamous cells, cannot exclude a high-grade lesion (ASC-H) categories of Bethesda Classification are sometimes overused by those who sign-out a high number of smears. Some quality control measures have been developed to overcome this bias, such as the ASC/SIL ratio [3-6].

In this study, we aimed to show the effect of hr-HPV analysis on the results of PAP smear assessment in general and via ASC / SIL ratio on the quality standards.

## 2. MATERIALS and METHODS

A total of 12799 cervical cytology reports, between 2014-2016, from the Pathology Department of Marmara University Hospital, were included. Between November 2014 and May 2016, hr-HPV analysis was performed on a total of 4307 cases with Hologic Aptima HPV (Hologic Panther, USA™). Smear

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diagnoses before and after the start of the HPV test application were recorded.

The study protocol was approved by the Institutional Ethics Committee of Marmara University, School of Medicine.

### Statistical Analysis

The distribution of cases according to Bethesda Classification and HPV test usage were compared using Chi-square test. For statistical analysis "The jamovi project (2020). jamovi. (Version 1.6) [Computer Software]. Retrieved from https://www.jamovi.org. " was used.

These distributions were significantly different ($\chi^2 = 321.1944$, df = 4, $p<0.001$), where the ratios of non-negative for intraepithelial lesion or malignancy (NILM) diagnoses (atypical epithelial cells) were more common in the cases with known hr-HPV results.

## 3. RESULTS

The mean age of the patients were 40.4 ± 12.2 years (min: 16, max: 94). The cytology diagnoses, during when hr-HPV screening was not performed, were: NILM 99.4% (n=8422), ASCUS 0.6% (n=51), low grade squamous intraepithelial lesion (LSIL) 0.2% (n=17), ASC-H 0.04% (n=3), and high grade squamous intraepithelial lesion (HSIL) 0.13% (n=11). The distribution of cytology diagnoses that were evaluated with HPV test were as follows: NILM 93.67% (n=4023), ASCUS 2.31% (n=99), LSIL 2.82% (n=121), ASC-H 0.3% (n=13), and HSIL 0.91% (n=39).

These distributions were significantly different ($p<0.0001$), where the ratios of non-NILM diagnoses were more common in the cases with known hr-HPV results.

ASC/SIL ratio has been dropped from 1.9 to 0.7 after the initiation of hr-HPV use.

## 4. DISCUSSION

Human papillomavirus (HPV) PCR technique continues to be one of the most popular topics of the recent cytology literature. Its use in cervix cancer screening, both alone and together with cytology, is widely studied [7,8]. HPV test has been included in the American Society for Colposcopy and Cervical Pathology guidelines to refer positive patients to colposcopy [9].

The PAP smear and the hr-HPV results should not be considered as separate diagnoses. Currently, PAP smear and HPV analysis are performed and reported simultaneously (co-test) in many centers. In the co-test, the pathologist/cytopathologist has the chance to evaluate the smear by knowing the HPV result. Whether this affects the pathologist's final decision in the diagnosis of PAP smear is also a matter of debate [3,10]. In our department, after the initiation of hr-HPV tests, we detected a significantly higher number of cellular anomalies (non-NILM) ($p<0.0001$). However, how the increase in non-NILM diagnoses changes the diagnostic quality of the laboratory is also important.

The Bethesda Classification classifies ASC as cells showing cytologic changes suggestive of the SIL but not enough for a definitive diagnosis of SIL [5]. ASC is a diagnosis of uncertainty and many laboratories monitor their ASC rates to ensure that it is not overused. The ASC categories (ASCUS and ASC-H) should be less than 5% of cases to ensure avoiding their misuse [5]. For interlaboratory comparisons and comparing cervical dysplasia ratios in different populations, ASC/SIL ratio is used, which is calculated as the number (or percentage) of ASCUS and ASC-H cases divided by LSIL, HSIL, and malignant cases. If this ratio is over 3, then it is regarded as the overuse and potential misuse of ASC categories [3,5,6,11,12].

In our laboratory, during the period without hr-HPV analysis, the ASC/SIL ratio was 1.9. Later with the initiation of hr-HPV screening this ratio decreased to 0.7. This shows that knowing HPV test results affects and improves the quality of the laboratory diagnoses. Our ASC/SIL ratio was lower than recommended standard in both periods. These results lead us to think whether the recommended ASC/SIL ratio in co-test performing laboratories remain as 3 or should it be lowered. Further studies comparing ASC/SIL ratios in different co-test performing laboratories are required.

### Compliance with Ethical Standards

**Ethical Approval:** The study protocol was approved by the Institutional Ethics Committee of Marmara University, School of Medicine.

**Financial Support**: The author has no relevant financial information to disclose.

**Conflict of Interest:** The author has no potential conflicts to declare.

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Short Communication

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# A preliminary study evaluating trans-fat content of pastries in socioeconomically disadvantaged communities of Istanbul

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ABSTRACT

Objective: Trans-fatty acids (TFAs) pose several risks to human health. World Health Organization recommends the elimination of trans-fat consumption through limiting their use as less than 2g/100g fat. In line with this recommendation, Turkey recently passed a new regulation securing the content of TFAs as less than 2g/100g fat in industrially produced foods. The objective of this study was to determine the proportion of high TFA (>2 g/100g fat) in pastries among socioeconomically disadvantaged communities of Istanbul before the regulation was put into force.

Materials and Methods: Eight socioeconomically disadvantaged districts were chosen from Istanbul and from each district three neighborhoods with the lowest land values were identified. Pastry samples were collected from 72 shops. TFA content was analyzed at Scientific and Technological Research Council of Turkey (TUBITAK) Marmara Research Center by the ISO 12966-2:2011 method. $p<0.05$ was set as the level of statistical significance.

Results: The median (25th-75th percentile) value of TFAs was 0.19g/100g (0.04g/100g – 0.30g/100g). None of the samples exceeded the level of 2g/100g. There was no difference in TFA content between the districts ($p>0.05$).

Conclusion: Our findings indicate that Turkey could easily comply with the legislative limit of 2%. Still, the compliance should continuously be evaluated in diverse populations of the country.

Keywords: Trans-fatty acids, Elimination, Pastry

## 1. INTRODUCTION

Trans-fatty acids (TFAs) are unsaturated fats containing at least one trans-double bond. TFAs can either occur naturally in animal sources such as meat and milk products or they can be industrially produced by partial hydrogenation of vegetable oils. Industrially produced TFAs are present in a variety of products as margarines, chocolates, bakery products and fried foods. They are used widely in the food supply because they extend the shelf life of products, maintain their structure after re-heating and are cheap [1-3].

Despite their wide use TFAs pose several health risks on human health. Consumption of TFAs leads to a 34% increase in all-cause mortality and a 28% increase in cardiovascular disease mortality [3,4]. There are also some studies indicating the association of TFAs with diabetes mellitus, abdominal obesity, breast and colon cancer, cognitive impairment, Alzheimer's disease, allergy, pre-eclampsia, disorders of nervous system, and impaired vision in infants [1,5]. Just by eliminating the use of TFAs 540.000 coronary heart disease deaths can be prevented worldwide every year [6]. Since, industrially produced TFA-containing products cost less, low income communities are even more likely to consume them. Therefore, in order to address the health inequality problems that might arise from TFA consumption, elimination policies need to be implemented globally [1,2].

World Health Organization (WHO) targets the elimination of industrially produced TFAs from the global food supply by 2023 with an aim to reduce the disease risk and positively influence the overall nutritional quality. This translates to limiting the consumption of TFAs to less than 1% of the total daily energy which is less than 2.2g daily intake for a 2000-kcal diet. The recommended strategy is either to ban the use or to set up a mandatory limit of less than 2g of industrially produced TFAs per 100g of total fat [3,7].

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In Turkey, there have been some voluntary initiatives requiring the labeling of the TFA content of food products higher than 2%. However, there have been no comprehensive regulatory actions to limit the TFA content up until recently. On 7th of May 2020 the Ministry of Agriculture and Forestry passed a new regulation which restricts the content of TFAs as less than 2g/100g fat for foods intended for the final consumer, including the products supplied for retail. The new regulation will enter into force as of December 31 2020 [8].

The objective of this study was to evaluate the TFA content of local pastry products before the regulation was implemented. The main aim was to determine the proportion of high TFA (>2 g/100g fat) pastries (*börek**) among socioeconomically disadvantaged communities of Istanbul. We studied pastries because an earlier survey revealed that bakery products had the highest TFA contents [9]. However, to our knowledge among the bakery products, local-made pastries were not evaluated previously.

## 2. MATERIALS and METHODS

The sampling unit was pastry shops located in socioeconomically disadvantaged communities of Istanbul. The sample size was calculated as 72 pastry shops assuming the proportion of high TFA use (>2 g/100g fat) in pastries as 25%, a confidence level of 95% and a margin of error of 10%.

The minimum $m^2$ unit land values published annually by the Revenue Administration were used in order to identify the socioeconomically disadvantaged communities of Istanbul [10]. Sampling was carried out in three stages. In the first stage, eight districts with low land values were chosen among the 39 districts in Istanbul. In the second stage, from each chosen district, three neighborhoods with the lowest land values were identified. In the last stage, three public schools (one primary, one secondary and one high school) were chosen from each neighborhood. Researchers visited the schools and identified the pastry shops that were located closest to each school. Pastry samples (without meat) were collected from 72 shops. TFA content was analysed at Scientific and Technological Research Council of Turkey (TUBITAK) Marmara Research Center by the ISO 12966-2:2011 method. TFA values were defined as grams per 100g fat.

This study was approved by the Institutional Clinical Research Ethics Committee of Marmara University, School of Medicine (document no: 09.2019.778).

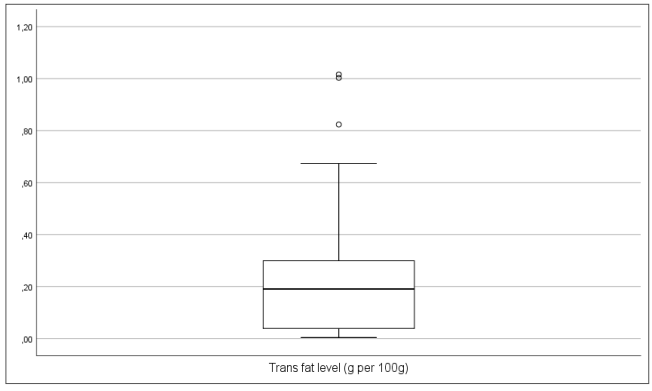
### Statistical Analysis

Descriptive statistics were presented as medians, 25th-75th percentiles, minimum and maximum values. Continuous variables between multiple groups were analyzed by the Kruskal Wallis test since the data did not follow the normal distribution. A p-value less than 0.05 was set as the level of statistical significance.

* *Börek: Savory pastry product from Turkish cuisine*

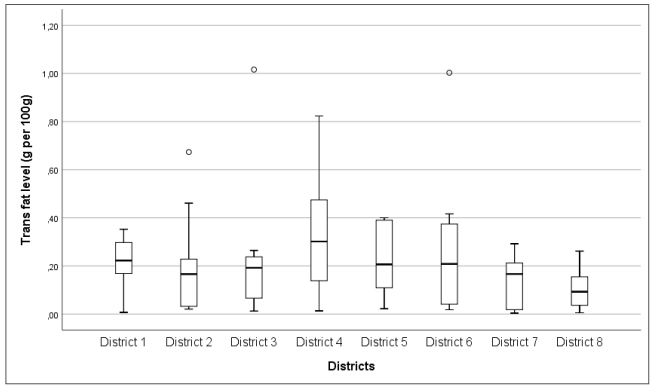
## 3. RESULTS

The median (25th-75th percentile) value of TFAs was 0.19g/100g (0.04g/100g – 0.30g/100g). The minimum and the maximum values were 0.004g/100g and 1.06g/100g, respectively. None of the samples exceeded the level of 2g/100g. All the samples except two had TFA content less than 1g/100g. Figure 1 presents the box plot graph of the TFA levels among the 72 pastries. There was no difference in TFA content between the eight districts (p>0.05). TFA levels by district are presented in Figure 2.




º Outliers

***Figure 1.*** *Trans-fat level (g per 100g) in pastries*




º Outliers

***Figure 2.*** *Trans-fat level (g per 100g) in pastries by district (p>0.05)*

## 4. DISCUSSION

The present study evaluated the TFA content of 72 pastry samples obtained from eight low income neighborhoods of Istanbul. Among all industrially produced food, bakery and pastry products were shown to pose a special risk for TFA exposure in different countries [9,11-15]. A study carried out in Canada identified bakery products as the major source of TFAs among healthy pregnant women [11]. A study evaluating pastry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products in the Polish market indicated that approximately one third of the samples had more than 2% of TFAs [12].

Another study carried out in Zurich revealed that fine bakery products had the highest TFA values [13]. Home-made food sold by street vendors might also be a source of TFAs. A study evaluating street food in an urban environment in Moldova documented that home-made pastries had a high TFA content. The authors reported that for some of the pastries, one serving had over half the daily WHO upper limit for TFA [14]. Similar findings were also reported from Turkey. Karabulut assessed the frequently consumed foods and determined that bakery products had the highest TFA contents ranging from 0.99 to 17.77g/100g fat [9].

To our knowledge this is the first comprehensive study with a focus of evaluating TFA content of pastries which make up an important portion of bakery products in Istanbul, Turkey. Our findings indicate that the TFA content was less than 2g/100g in all of the pastry samples. All samples, except two had TFA content less than 1g/100g. These results support the fact that Turkey could easily comply with the recommendations of the WHO's REview, Promote, Legislate, Assess, Create, Enforce (REPLACE) Initiative. WHO had developed REPLACE Initiative as a roadmap strategy for countries in order to eliminate the TFAs from the global food supply. One of the actions recommended in the REPLACE Initiative is to implement regulatory actions in order to eliminate industrially produced TFAs. Countries can either set a mandatory limit of 2 g/100g of total fat or totally ban partially hydrogenated oil through classifying them as unsafe [3]. Research had indicated that among policies aimed at reducing TFAs, bans or setting mandatory limits were identified as the most effective, economical, and equitable policy approach [16]. Denmark used this strategy and limited industrially produced TFAs in foods to a maximum of 2% in 2004 and had successfully reduced the exposure to a high TFA diet at the individual level [17].

Our study has some limitations. Firstly, the level of TFAs were evaluated for only a special type of pastry (börek). Hence, there might be other bakery products that pose a risk for TFA exposure which were not assessed in this study. Another limitation is related to the setting of the study. We evaluated the pastries marketed in selected neighborhoods in eight districts of Istanbul. The city has quite a heterogeneous market for food commodities which necessitate a broader assessment. We also collected samples from pastry shops only, and neither the products sold by street vendors nor the home-cooked pastries were evaluated. Nevertheless, assessing high number of samples at a period close to the introduction of the new regulation in Turkey provided up-to-date information on the TFA content of a product that is widely consumed by Turkish consumers [18].

Our study revealed that pastries, which might have been an important source of dietary TFAs, had TFA levels less than 2%. This finding shows that Turkey could easily comply with the legislation limit of 2% TFAs. Granting, compliance to the regulation should continuously be evaluated through monitoring the TFA content of different food products in diverse populations of the country.

### Compliance with Ethical Standards

**Ethical Approval:** This study was approved by the Institutional Clinical Research Ethics Committee of Marmara University, School of Medicine (document no: 09.2019.778).

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**Conflict of interest:** The authors declare no conflict of interest.

**Authors' Contrubition**: Concept and Design: P.A., Z.B.K., T.G., U.P.S., M.G., E.D., Supervision: T.G., E.D., Resources: M.G., E.D. Materials: P.A., Z.B.K., T.G., U.P.S., M.G., E.D., Data Collection and Processing: L.Q., O.C., E.R., R.F., Analysis and Interpretation: P.A.,, Z.B.K.,, E.R., R.F., Literature Search: P.A., E.R., R.F., Writing the Article: P.A., L.Q., O.C., Critical Review: P.A., Z.B.K., T.G., E.D. All authors approved the final version of the article.

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Case Report

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# Severe facial fractures due to airbag deployment without utilization of a seat belt: A case report

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## ABSTRACT

This report is about a man of 25 years old (175 cm, 90 kg) who sustained bilateral Le fort I, II, and III fractures because of an inflating car airbag. Despite the fact that airbags harshly reduce both the mortality and morbidity from crashes as intercept frontal collisions, but with increasing use of airbags, increasing number of injuries caused by these devices is inevitable. Reports about serious injuries and even death due to airbag deployment highlight the necessity for a modification in design and speed of airbag deployment for accidents with various speeds.

Keywords: Airbag-mediated injury, Le fort fractures, Motor vehicle accident, Nasal defect

## 1. INTRODUCTION

Traffic accidents are one of the most important reasons for human injuries and deaths in many countries [1]. Strategies have been developed over the years to decrease the risk of death and serious injuries caused by motor vehicle accidents. Some of these useful strategies include speed limits, seat belt wearing, and use of airbags in vehicles. Although, there is no doubt that airbags decrease the risk of death and injury caused by motor vehicle accidents, airbag deployment injuries, including the head and neck injuries, have been broadly reported [2-4]. Le Fort fractures are those types of fractures in the face related to the maxillary bone and the surrounding structures in a usually horizontal and bilateral, transverse or pyramidal ways [5]. Here, we present a very rare case of three types of Le Fort fractures with closed fractures of mandible, condylar process, and nasal bones caused by airbag deployment. The patient was operated using open reduction internal fixation (ORIF) and nasal reconstruction surgery methods.

## 2. CASE REPORT

A 25-year-old man (175 cm, 90 kg) came to the emergency department approximately 1 hour after being involved in a motor vehicle crash. He did not fasten the seat belt while travelling at a high speed (140 Km/hr) and had an accident with a deviated car and frontal airbag deployed (Figure 1). Obvious fractures of the head and neck were detected on his plain radiographs (Figure 2). The patient was taken for computed tomography (CT) scan for more information when obvious fractures were detected (Figure 3).

The final diagnosis was bilateral Le fort I, II, and III fractures. In addition, closed fractures of mandible, condylar process, and nasal bones were detected on external examination using ICD-10 fracture codes [6]. After 4 days of hospitalization in the plastic and reconstructive surgery department, the patient was operated through ORIF surgery by using plates and screws (Figure 4). Also, after 4 months, nasal reconstruction surgery was performed for his nasal defects. Written informed consent was obtained from the patient for publication of individual information and photographs in an academic journal.

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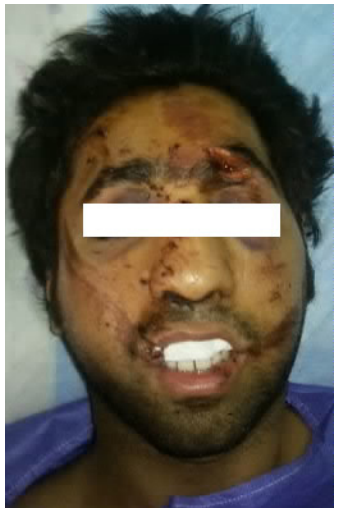

***Figure 1.*** *The patient before the surgery*

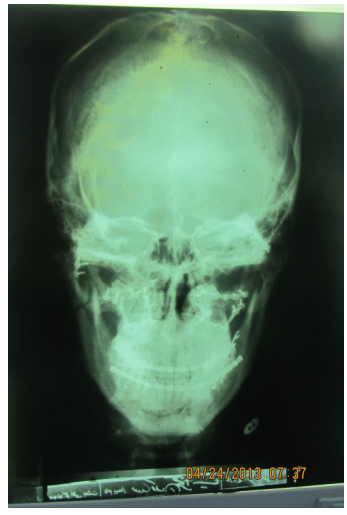

***Figure 2.*** The *head and neck radiography before the surgery*

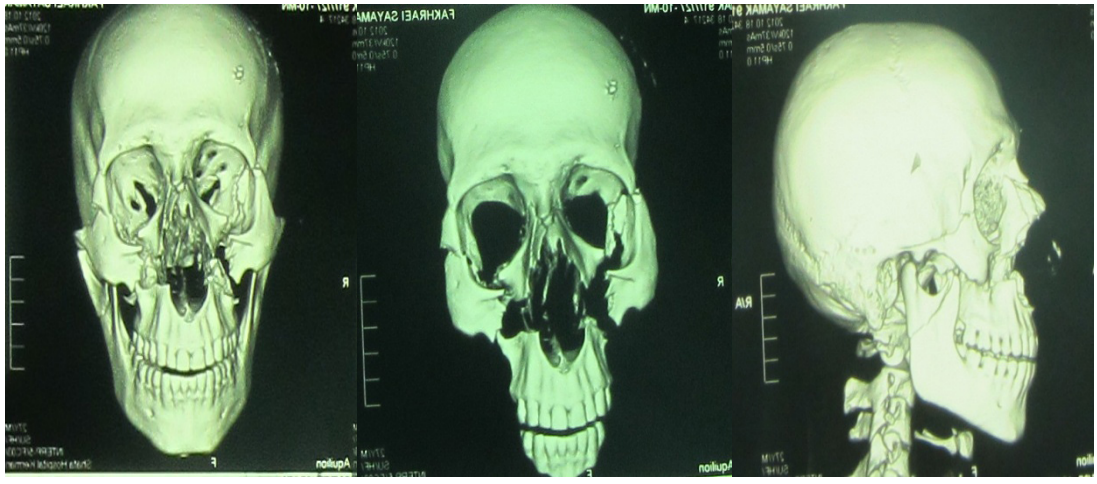

***Figure 3.*** *Pre-operation of the facial CT scans*

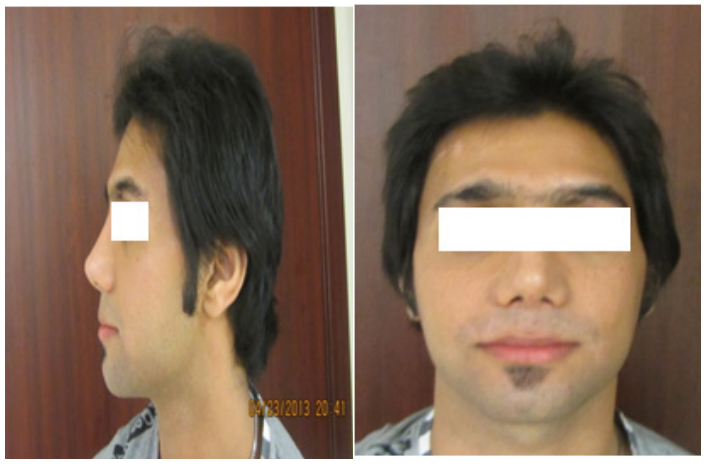

***Figure 4.*** *Six months after ORIF surgery and rhinoplasty*


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## 3. DISCUSSION

Airbag was introduced in 1953 and became available in motor vehicles in 1973 [7]. The injuries caused by deploying airbags depend on pressure of the deployed airbag, accident severity and fastening the seat belt or not [7, 8]. However, several researchers have shown that using airbags decrease mortality rate in most frontal crashes up to 20-30 percent [8]. In a frontal accident, airbag deployment and wearing a seatbelt reduced the risk of death by over 80% [9]. Yet, considerable evidence has shown that airbags can be as a source of morbidity and mortality in specific conditions. Moreover, with the increase in the use of vehicles equipped with airbags, injuries caused by airbags may occur more frequently. Therefore, more awareness about injuries caused by airbags can help solve this problem.

In the above-mentioned case, the driver had not worn the seat belt and consequently he was hit by the airbag full-force (Iranian vehicle: Samand Soren). In fact, since he did not fasten seat belt, he was thrown toward the deploying airbag. Therefore, such direct force caused the bilateral Le fort I, II, and III fractures and closed fracture of mandible and nasal bones. There are many reports about head injuries caused by airbags, such as facial trauma [4] and temporomandibular joint injury [3]. However, the present study reported one of the extensive injuries and fractures of head related to airbag deployment.

Not wearing seat belts when airbags deployed, hit by a low-power airbag in comparison to hit by a powerful airbag, inflate unnecessarily in low speed crashes and moving children to the forward seats were described as some reasons that increased the suspicion of airbag related injuries [2,10-12]. Some other ways to reduce these damages include changing steering wheel to reduce the use of airbags in frontal accidents, use of educational programs to ensure the correct utilization of seat belts, and development of smart airbags.

In conclusion, it is necessary to know that the head and neck are exposed to risk more than other parts of the body in the frontal impacts resulting from airbag deployment (especially if a seat belt is not worn). Therefore, conducting researches is essential for improvement of airbag designs especially for prevention of the head and neck injuries.

### Compliance with Ethical Standards

Written informed consent was obtained from the patient.

**Finacial Support:** The authors have no relevant financial information to disclose.

**Conflict of Interest:** The authors declare that they have no conflict of interests.

**Authors Contibutions:**

Study conception and design: M. A.,

Acquisition of data: M. A.,

Analysis and interpretation of data: M. A.,

Drafting of manuscript: M. A., F. H.

Critical revision: F. H. Both authors approved the final version of the article.

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# A rare cause of respiratory distress in a newborn: Pneumomediastinum

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## ABSTRACT

Pneumomediastinum is an uncommon cause of neonatal respiratory distress and occurs in approximately 2.5 per 1000 live births. Although, the most common cause of pneumomediastinum is an underlying lung disease, it can be seen in newborns who undergo resuscitation during delivery without a predisposing factor. Initial diagnosis by chest X-ray can be difficult in some cases. The "spinnaker-sail sign" is an uncommon radiological appearance of pneumomediastinum. Careful conservative management can result with spontaneous resolution without long-term sequelae. In this case report, we present a neonate who developed pneumomediastinum.
Keywords: Newborn, Birth trauma, Pneumomediastinum, Respiratory distress, Spinnaker-sail sign

## 1. INTRODUCTION

Pneumomediastinum is an uncommon cause of neonatal respiratory distress and occurs in approximately 2.5 per 1000 live births [1]. Spontaneous pneumomediastinum is usually caused by alveolar rupture resulting from a sudden increase in the thoracic pressure. Although, the most common cause of pneumomediastinum in children is an underlying lung disease, it can be seen in neonates who require resuscitation during delivery without a predisposing factor [2]. In this case report, we aimed to present a neonate who underwent resuscitation in the delivery room and developed pneumomediastinum.

## 2. CASE REPORT

A baby girl was born at 37 weeks of gestation with a birth weight of 3675 g to a 37-year-old multiparous mother by vaginal delivery. She required positive pressure ventilation by T-piece due to respiratory distress after delivery. The baby's 1$^{st}$ and 5$^{th}$ minute APGAR scores were 7 and 9, respectively. Due to respiratory distress, the baby was admitted to the neonatal intensive care unit. The physical examination revealed caput succedaneum, edematous eyelids, petechiae, and ecchymosis around the eyes. Breath and heart sounds were decreased on the right hemithorax. Crepitation was palpated bilaterally on the neck and upper chest wall due to subcutaneous emphysema. Moro reflex was poor on the right side but the grasp reflex was present on the right hand. Due to grunting and tachypnea, she was intubated and placed on mechanical ventilation with minimal settings. Empiric antibiotics, ampicillin and gentamicin were commenced to cover the risk of sepsis due to respiratory distress. The laboratory test results were as follows, total leucocyte count: 12000/m$^3$ hemoglobin: 15.1 gr/dl, thrombocyte count: 149000/m$^3$, C-reactive protein: 9.4 mg/L (0-5), procalcitonin: 19.6 µg/L (0-2); blood gas analysis, pH: 7.19, $CO_2$: 58 mmHg, $HCO_3$: 21.6 mEq/L, base excess: 8.2 mEq/L, lactate: 2.3 mmol/L. Pneumomediastinum was suspected due to a spinnaker-sail sign on the chest X-ray that was otherwise unremarkable (Figure 1).

A few hours after birth, the infant became hypotensive and dopamine infusion was started. Within 24 hours, the baby was clinically stabilized and her blood gases were within normal ranges. She was extubated at the end of the first day and was on $FiO_2$ of 25%. Her computed tomography (CT) findings showed pneumomediastinum without any mediastinal mass (Figure 2). Cranial and abdominal ultrasonographies were unremarkable.

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The image of pneumomediastinum persisted for three days and regressed spontaneously (Figure 3). She was consulted to physical therapy and orthopedics departments due to brachial plexus injury. The baby was discharged on the 7th day of life. In the second month, her physical examination was totally normal including the chest X-ray (Figure 4).

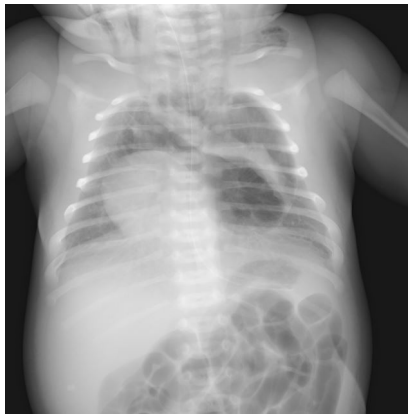

***Figure 1.*** *The chest X-ray on admission to Neonatal Intensive Care Unit*

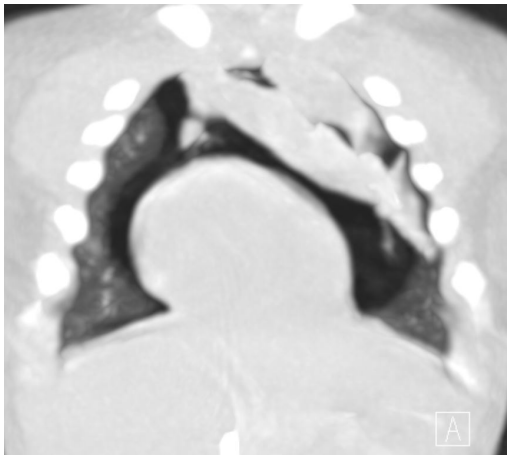

***Figure 2.*** *The CT scan of the patient on day 2*

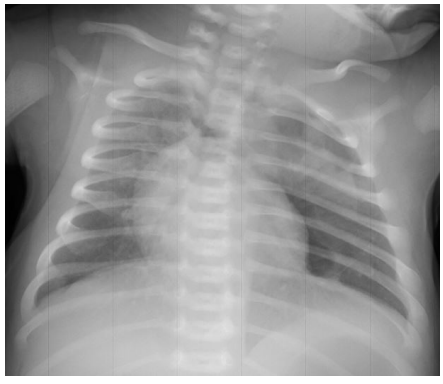

***Figure 3.*** *The chest X-ray before discharge*

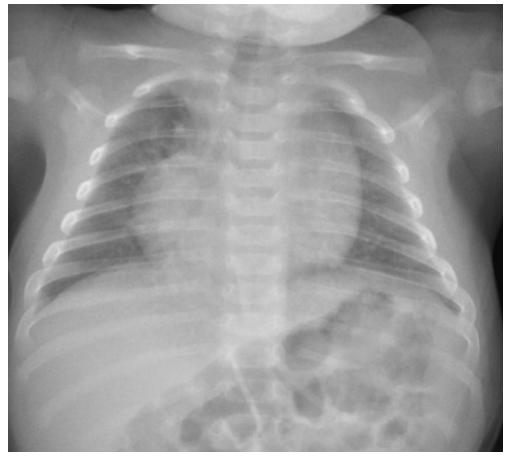

***Figure 4.*** *The chest X-ray at two months*

Written informed consent was obtained from the family for publication of this case report and accompanying images.

## 3. DISCUSSION

Pneumomediastinum is a benign, self-limiting condition in neonates [3]. It occurs in approximately 2.5 per 1000 live births [1]. It occurs due to increases in alveolar pressure and air leakage to the mediastinum. Spontaneous pneumomediastinum has no association with mechanical ventilation for respiratory distress syndrome, tracheal or esophageal injury [4]. It is frequently associated with nonspecific birth-related trauma [5]. Most of the babies diagnosed with pneumomediastinum are asymptomatic at birth for that reason some studies reported lower incidences (1.7 per 1000 live births) [6,7]. Our case, who was symptomatic at birth, had signs of respiratory distress and required positive pressure ventilation by T-piece for 15 seconds. Additionally, she had brachial plexus injury.

Steele et al., evaluated chest X-rays of 550 babies within two hours after birth and diagnosed 13 pneumothorax and/or pneumomediastinum cases [1]. The incidence was higher (8%) in intubated infants. The incidence of pneumomediastinum was detected in 2.3% and 1% in vaginal and caesarean section deliveries, respectively. According to their study, apparent predisposing or associated factors included intubation, congenital anomalies, and meconium-stained amniotic fluid while no significant correlation was found for prematurity, dysmaturity, small size for age, caesarean section, or hyaline membrane disease [1,3].

The babies are usually diagnosed on plain chest X ray. The radiographic signs of pneumomediastinum include pneumopericardium, continuous diaphragm sign, continuous

left diaphragm sign, Naclerio's V sign, and spinnaker-sail sign [5,8]. The "spinnaker-sail sign" might be accepted as an ominous sign in a term neonate, especially if it is accompanied by pneumopericardium and pneumoperitoneum [9]. This uncommon sign, where the thymic lobes are displaced superiorly and laterally by pneumomediastinum should not be confused with the thymic sail sign which is a normal finding in infants [10]. The "spinnaker-sail sign" was detected on the chest X-ray in some cases who required bag valve mask ventilation due to continued dyspnea similar to our case who also required resuscitation by T-piece [5,7].

The diagnosis can be difficult in some cases. Chest X-ray can be negative in up to 30% of cases [11]. For the exclusion of mediastinal masses, a CT scan can be used [7]. In our patient's chest X-ray, the typical "spinnaker-sail sign" due to the elevation of the thymus confirmed the diagnosis of pneumomediastinum. The presence of any mediastinal mass was ruled out by CT.

Pneumomediastinum resolves with supportive conservative treatment, with or without oxygen therapy, in most of the cases [3]. Similar to the cases reported in the literature, our case had a spontaneous resolution [7]. Deterioration of the clinical status due to pneumothorax, subcutaneous interstitial emphysema, and the need for drainage and mechanical ventilation had been reported in severe cases [3,9].

Pneumomediastinum is a rare cause of respiratory distress and initial diagnosis by chest X-ray can be difficult in some cases. Timely diagnosis of spontaneous pneumomediastinum is important. Pneumomediastinum should be considered especially in patients with respiratory distress who underwent resuscitation after a traumatic delivery. The "spinnaker-sail sign" is an uncommon radiological appearance of pneumomediastinum. Careful conservative management can result in spontaneous resolution without long-term sequelae.

**Compliance with the Ethical Standards**

Written informed consent was obtained from the family for publication of this case report and accompanying images.

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**Author Contributions:** SGK conceived the case report, drafted the manuscript and carried out the literature search. HO and SGK prepared the figures, have expert knowledge in this area and made critical revisions. AM, HB, and EO have expert knowledge in this area and made critical revisions. All authors read and approved the final manuscript.

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Case Report

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# Is renal abscess still a problem?

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## ABSTRACT

Renal abscess, the accumulation of infected fluid in the kidney, is a rare condition seen in children as well as adults. It leads to long term hospital admission and antibiotic use. Early diagnosis is an important factor in the outcome of renal abscess because the management may differ. Urinalysis test results and radiologic imaging findings of the patients who are admitted to hospital with complaints of fever, vomiting, abdominal pain or flank pain are important for the early diagnosis. Undertreated cases have high risk for renal scar formation. In this paper, we aim to present three pediatric patients, who showed the complication of renal abscess and were treated with long term antibiotic use without a need for surgical drainage.
Keywords: Urinary tract infection, Renal abscess, Children

## 1. INTRODUCTION

Vesicoureteral reflux (VUR) and recurrent urinary tract infection (UTI) are still among the most common etiologies of end-stage renal disease in Turkey. Renal abscess, the accumulation of infected fluid in the kidneys is a rare condition and usually seen in immune-compromised children and children with UTI caused by mostly resistant microorganisms that are not treated properly and promptly. It leads to long term hospital admission and antibiotic use [1]. Lober nefronia, also known as acute focal bacterial nephritis, is the localized infection of the kidney without abscess formation and must be considered in differential diagnosis [2]. Here, we report three cases with renal abscess who were hospitalized and treated with long term antibiotherapy at our hospital in 2018.

## 2. CASE REPORTS

### Case 1

A four-year-old girl was admitted to hospital with fever, abdominal pain and vomiting and did not respond oral antibiotic treatment for 3 days. During physical examination, suprapubic tenderness and fever were present. She had a history of hospitalization because of UTI when she was 3.5 months old. Laboratory findings revealed leukocytosis, mild elevation in renal function tests and pyuria. In urine culture taken by transurethral catheterization 10.000 cfu/ml *Escherichia Coli* was present. Renal ultrasonography (US) revealed normal sized kidneys with increased parenchymal echogenicity in the upper pole of the left kidney and perinephritic liquid collection. Abdominal magnetic resonance imaging (MRI) showed a renal abscess measuring 30x27 mm in the left kidney (Figure-1a). Grade 3 VUR to the left kidney and grade 1 VUR to the right kidney were detected in voiding cystourethrography (VCUG) performed on the 26th day of antibiotherapy. Technetium 99m-dimercaptosuccinic acid (99mTc DMSA) renal scan performed on the 16th day of the treatment revealed a well circumscribed lesion in the left kidney, and separated functions were normal. Abscess could not be drained. She was successfully treated with intravenous antibiotic, ceftriaxone treatment initiated first and then teicoplanin was added when urine culture result was available. Treatment was completed in 35 days and abscess formation totally disappeared. Control DMSA scan one year after acute episode showed the disappearance of cortical lesion and revealed only contour deformity in the left kidney, separated functions were still normal. Informed consent form was obtained from her parents.

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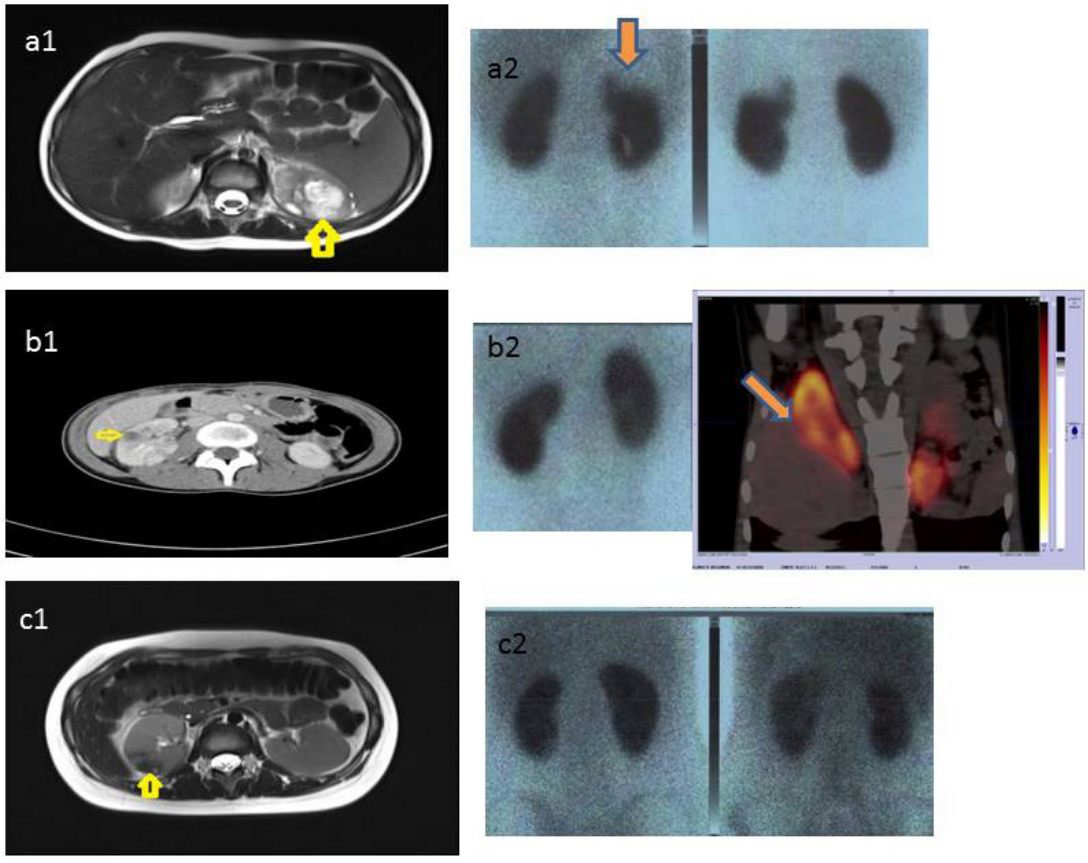


***Figure 1.*** *Renal abscess formation of the three cases (arrows). a, c. Abdominal magnetic resonance and DMSA scans of case 1 and 3 respectively b. Computed tomography, DMSA and coronal SPECT CT scans of case 2.*

### Case 2

A previously healthy 17 years old girl admitted to hospital with the complaints of nausea, vomiting, fever and malaise for five days. On physical examination, costovertebral angle tenderness was present. Laboratory findings revealed leukocytosis, anemia, mild elevation in renal function tests and pyuria. In urine culture obtained by clean catch method >100.000 cfu/ml *Escherichia Coli* was present. Renal US revealed normal sized kidneys with 15 mm diameter non perfused area in the middle of the right kidney. Computed tomography showed renal abscess formation measuring about 13 mm in the right kidney (Figure-1b). She was successfully treated with intravenous ceftriaxone for 14 days and followed by oral cefixime for 7 days. 99mTc DMSA scan was performed on the 7th day of antibiotherapy and it revealed well circumscribed lesion in the right kidney, separated functions were normal. Abscess formation totally disappeared with medical treatment. Control DMSA scan one year later revealed contour deformity in the right kidney but not scarring as we observed in the first patient, separated functions were also normal. Informed consent form was obtained from her parents.

### Case 3

A previously healthy 16 years old girl admitted to hospital with the complaints of nausea, vomiting, fever, malaise and right side flank pain for seven days. On physical examination costovertebral angle tenderness was present. Laboratory findings revealed elevated C-reactive protein (CRP) level. Her creatinine level increased up to 5.6 mg/dl in the follow up and returned to the normal level without any need to renal replacement therapy. There was no pyuria in urinalysis and urine culture obtained by clean catch method was sterile. Renal US revealed normal sized kidneys with renal abscess formation in the right kidney. Abdominal MRI showed renal abscess measuring 40x35 mm (Figure-1c). VCUG performed on the 11th day of antibioteraphy was normal. 99mTc DMSA renal scan performed on the 17th day of the treatment and did not reveal cortical scarring but background activity was increased. She was first treated with ceftriaxone, and then treatment upgraded to piperacillin and vancomycin according to urine culture result and finally switched to meropenem when she developed acute kidney injury. Abscess formation totally disappeared with medical treatment administered for 28 days. Control DMSA scan one year later revealed hypoactive area in the upper pole of the right

kidney, separated functions were normal. Informed consent form was obtained from her parents.

## 3. DISCUSSION

Urinary tract infection is one of the most common bacterial infections in children especially in infancy and mostly it is uncomplicated and can be treated by oral or iv antibiotics. It ranges from lower urinary tract infections to acute piyelonephritis (APN), acute lober nephronia and renal abscess. The association between UTI and congenital abnormalities, like VUR, may put children at high risk for APN and subsequent renal scarring [3].

Acute lober nephronia, also known as acute focal bacterial nephritis (AFBN) was first radiologically described in 1979 [4]. It is an acute, localized non-liquefactive infection of the kidney caused by bacterial infection generally affecting one or more renal lobules. It is considered as at the midpoint in the spectrum of upper UTI between APN and intrarenal abscess [5]. The diagnosis of AFBN is dependent on radiologic imaging. Acute focal bacterial nephritis is characterized by hypoperfused wedged-shaped or round and space-occupying lesions in the kidney, exhibiting no capsule [6-8]. Acute focal bacterial nephritis is associated with higher incidence of renal scarring in comparison to APN. It must be treated by long course intravenous antibiotics at least 2 to 3 weeks [9]. Bitsori, et al., evaluated 25 pediatric patients (27 episodes), 21 with AFBN, one with abscess and three with pyonephrosis and suggested at least 1 week of intravenous treatment and a total antibiotic course of 3 weeks in patients with AFBN [10].

Renal abscess is the most complicated form of UTI. In renal abscess, the infected material is localized in the parenchyma. It is often caused by ascending infections of the lower urinary tract by gram negative organisms or hematogenic spread. Clinical symptoms are similar to APN and AFBN. Laboratory investigation reveals leukocytosis and elevated CRP levels [11]. Our first two patients both had leukocytosis and elevated CRP levels, third patient only had elevated CRP level. Urinalysis generally shows pyuria or may be normal if it is caused by hematogenic spread or if the patient received antibiotics before performing urinalysis and urine culture. There may or may not be growth in the urine culture test. Bitsori, et al., demonstrated abnormal urinalysis in 16 (59%) and *Eschericia coli* bacteriuria as a leading pathogen in 12 (44%) episodes [10]. Similarly, in our two patients *Escherichia Coli* was the predisposing cause of renal abscess formation. The urinalysis of our third patient was also normal and urine culture was sterile. Our patient did not have a history of receiving antibiotic treatment before performing urinalysis and her blood culture was also sterile excluding hematogenic spread.

Renal and perirenal abscess management includes medical treatment, percutaneous drainage, surgical drainage (open surgery), and nephrectomy. Dalla Palma, et al. and Lee, et al., confirmed that renal abscesses of 50 mm diameter or less can completely regress after long term medical treatment. Although, antibiotic therapy is the mainstay of the treatment, percutaneous or surgical drainage of abscesses larger than 50 mm in diameter is suggested. According to some authors, drainage treatment of the abscesses 30-50 mm in diameter should be planned, especially if there is no response to the antibiotic treatment [12, 13]. Similarly, all of our patients were successfully treated by long term antibiotic use. None of them needed invasive surgical treatments.

Acute interstitial nephritis (AIN) is a common cause of acute kidney injury (AKI) associated with drugs, infections or unknown causes. AIN associated with infections constitute a proportion of %5-10 of all AIN cases and its frequency decreased after widespread of antibiotic use. Bitsori, et al., revealed a reversible increase of creatinine in 15 (55%) episodes [10]. The gold standard of diagnosis of AIN is kidney biopsy. Treatment consists supportive therapy and treating underlying infections, it has been reported that steroid treatment is beneficial for total recovery [14]. Our third patient's creatinine level also increased up to 5 mg/dl in the follow up and recovered by supportive treatment. We suspected infection associated AIN for this patient. Since the renal functions of the patient quickly regressed, we did not perform a renal biopsy to confirm it.

In conclusion, early diagnosis is an important factor in the outcome of renal abscess. Urinalysis and radiologic imaging of the patients who admitted to hospital with complaints of fever, vomiting, abdominal pain or flank pain is important for the early diagnosis. It should be kept in mind that we cannot exclude renal abscess even if the urinalysis is normal. Undertreated cases have the risk for development of renal scarring.

### Compliance with the Ethical Standards

Written informed consents were obtained from the parents for publication of these case reports and accompanying images.

**Financial Support**: The authors have no relevant financial information to disclose.

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

**Author Contributions:** M.S. : Coordinated and supervised data collection, drafted the initial manuscript, reviewed and revised the manuscript, I.G.: Conceptualized and designed the cases, coordinated and supervised data collection, N.C., S.G. and N.Y. : Had active roles in the diagnosis and treatment of the patients, R.E.: Evaluated radiological images of the patients, H. A. : Critically reviewed and revised the manuscript. All authors read and approved the final version of the article.

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