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# The role of using antitussive for premedication of bronchoscopy antitussive treatment in bronchoscopy: a randomized, double-blind, placebo-controlled trial

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## ABSTRACT

**Aims**: The cough affects adversely the comfort of patient and process during fiberoptic bronchoscopy. Various studies have been made to prevent cough during bronchoscopy. However, there is no any medication that usage of it becomes definite. The influence of usage codeine in bronchoscopy premedication in addition to the midazolam on the comfort of patient and physicians is examined .

**Methods**: 96 patients made bronchoscopy for various indications were included to the study. The study was carried out as a prospective, placebo-controlled and double-blind. The patients were divided into two groups. Group 1 (n=48) 20 mg fenocodeine tablets divided into 4 doses were administered one day before process. Group 2 (n=48) the placebo tablets divided four dose were administered one day before process. Both of two groups were administered midazolam before procedure. Topical anesthesia was administered as needed during the operation and its doses were recorded. Two questionnaire form that examined the level of comfort of patients and physicians, the amount of secretion and the severity of cough with a visual analogue scale (VAS) were prepared and they were immediately completed after procedure.

**Results**: In both groups, any complication wasn't occurred that require to terminate the process. In the scala evaluated by patients given fenocodein, the amount of cough was statistically significantly low (p=0.026). In the scale evaluated by doctors, the amount of secretion was lower (p=0.02). Comfort level of doctor was found significantly higher in Group 2 (p=0.02).

**Conclusion**: It was determined that the amount of secretion and cough had decreased and the level of comfort had increased when fenocodeine was given with midazolam prior to bronchoscopy

**Keywords**: Bronchoscopy, codeine, premedication

Turkish Toraks Society presented as a poster at the 17th Annual Congress.

## INTRODUCTION

Fiberoptic bronchoscopy (FOB) is an interventional process usually performed under topical anesthesia and appropriate sedation. It can be provided better toleration for patients with drugs administered before the process.[1-5]

During FOB cough adversely affects the comfort of patient and process. In studies to prevent cough that occurs during bronchoscopy, the effectiveness of various drugs were investigated. However, there is not any definitive medication have been resulted. Opioids; because of their analgesic, antitussive and anxiolytic effects are used as combination with other sedative agents in bronchoscopy.[6]

In this study, the group which was given codeine that has weak opioid property with midazolam was compared with the group given midazolam alone. The effect of sedation on patients cough, secretion and level of comfort during the procedure was investigated.

## METHODS

Ninetysix patients performed bronchoscopy for various indications were included in the study. The study was performed as a prospective, placebo-controlled and double-blind. The study was carried out with the permission of İstanbul Kartal Dr. Lütfi Kırdar Training and Research Hospital Scientific Researches Evaluation Ethics Committee (Date: 22.01.2013, Decision No: 1). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

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### The Study Exclusion Criteria

Pregnant women, younger than 18 years old, patients who didn't give consent for bronchoscopy and /or patients with high risk or with contraindications for bronchoscopy, patients with contraindications for fenocodeine and midazolam weren't included in our study.

The age, gender, smoking history, the comorbidities of patient, the indication for bronchoscopy, the arterial blood pressure values, the pulse measurement, the oxygen saturation in room air, the doses of topical anesthesia and midazolam were recorded.

Bronchoscopy was performed by 2 physicians. There were also 2 physicians during the procedures.

As a result the process and the amount of secretions evaluated the same bonkoscopists.

10% lidocaine as a topical anesthesia was applied to the patient's nose and oropharynx by spraying. Lidocaine diluted with saline was applied to the trachea and bronchial system during the process. During bronchoscopy; blood pressure, pulse and oxygen saturation of the patients were monitored.

Midazolam was administered 1-2 mg as an initial dose considering age and weight of patients, at 5-10 minutes before procedure, it was administered as a1 mg dose upon necessity.

Patients were randomized in two groups by bronchoscopy nurse. Doctor and patient were not aware of the patient's group.

Patients were divided into 2 groups.

Group 1: Group with midazolam and fenocodein tablets

Group 2: Group with midazolam and placebo

3 doses fenocodein each 20 mg tablet in 8 hours intervalles were given to Group 1 patients one day before bronchoscopy and the fourth dose was given 2-3 hours before process. Tree doses placebo were given to group 2 patients in 8 hours intervalles one day before bronchoscopy and the fourth placebo tablet was given 2-3 hours before process.

Necessary diagnostic procedures were applied according to the lesions seen during bronchoscopy, all procedures performed and complications emerged during the process were recorded.

During the procedure, The Ramsey Sedation Scale was used to define the level of sedation of patient.

After the process was finished, the forms prepared for the patient and bronchoscopist were filled individually under the supervision of a bronchoscopy nurse.

It was charted from the patients and the doctors to mark the cough, secretion and degree of comfort on a visual analogue scale 100 mm in lenght. The highest values were located on the right side of the scale (100) and the lowest values were located on the left side.

### Statistical Analysis

Statistical Analysis: SPSS 16,0 software (Statistical Package for Social Sciences for Windows) was used for the statistical analysis of the data obtained from this study. Chi-square and Fisher's exact test were used for the comparison of qualitative datas, student T-test was used for the comparison of quantitative datas. Results were assessed at 95% confidence interval and significance was assessed as $p<0.05$

## RESULTS

Totally 96 patient were included to the study that 21 (21.9%) of them were female (21.9%), 75 (78.1%) of them were male. The mean age of the patients was 56.9±1.4 (range: 28-82 years).

The most common indication for bronchoscopy was lung cancer. The indications for bronchoscopy are shown in **Table 1**. The procedures performed during bronchoscopy are shown in **Table 2**.

**Table 1. The indications for bronchoscopy**

| | Group 1 (Fenocodeine n:48) | Group 2 (Placebo n:48) | Total (n=96) |
|---|---|---|---|
| Lung cancer | 22 | 25 | 47 |
| Tuberculosis | 7 | 1 | 8 |
| Interstitial lung disease | 5 | 6 | 11 |
| Hemoptysis | 10 | 4 | 14 |
| Solitary pulmonary nodule | 1 | 2 | 3 |
| Pneumonia | 2 | 2 | 4 |
| Tuberculosis+lung cancer | 1 | 2 | 3 |
| Pneumonia+lung cancer | 0 | 2 | 2 |
| Atelectasis | 0 | 2 | 2 |
| Pleural efusion | 0 | 1 | 1 |
| Cystic hydatic | 0 | 1 | 1 |
| Total | 48 | 48 | 96 |

Patients were divided into 2 groups. In Group 1, there were 48 patients (50%), in Group 2 there were 48 (50%) patients. There was no significant difference in between two groups in terms of the distributiun of age, gender and additional diseases (**Table 3**).

**Table 3. The distribution of age, gender, and the additional disease**

| | Group 1 n (%) | Group 2 n (%) | P |
|---|---|---|---|
| Gender | | | 0.8 |
| Female | 10 (20.8) | 11 (22.9) | |
| Male | 38 (79.2) | 37 (77.1) | |
| Additional diseases | 23 (51) | 22 (49) | 0,5 |
| Age | 55.5±14.5 | 58.4±12.9 | 0.3 |

**Table 2. Procedures in bronchoscopy**

| | Group 1 (Fenocodeine n:48) | Group 2 (Placebo n:48) | Total |
|---|---|---|---|
| Bronchial lavage | 20 (41.7%) | 10 (20.8%) | 30 (31.2%) |
| Endobronchial biopsy+bronchial lavage | 8 (16.7%) | 15 (31.2%) | 23 (24%) |
| Transbronchial biopsy | 1 (2.1%) | 0 | 1 (1%) |
| Transbronchial biopsy+bronchoalveolar lavage+broncihal lavage | 2 (4.2%) | 4 (8.3%) | 6 (6.2%) |
| Endobronchial biopsy+transbronchial biopsy+bronchoalveolar lavage | 1 (2.1%) | 1 (2.1%) | 2 (2.1%) |
| Endobronchial biopsy+bronchial lavage+brush | 6 (12.5%) | 2 (4.2%) | 8 (8.3%) |
| Bronchoalveolar lavage+brush | 8 (16.7%) | 15 (31.2%) | 23 (24%) |
| Endobronchial biopsy +transbronchial biopsy +bronchoalveolar lavage | 1 (2.1%) | 0 | 1 (1%) |
| Bronchial lavage+bronchoalveolar lavage | 1 (2.1%) | 1 (2.1%) | 2 (2.1%) |
| Total | 48 | 48 | 96 |

When two groups were compared in terms of bronchoscopy duration midazolam dose, local anesthetic dose and Ramsey Sedation Scale there was no significant difference between them (**Table 4**).

**Table 4. The comparision of the groups in terms of bronchoscopy time, midazolam dose, local anesthetic dose and the Ramsey Sedation Scale**

| | All patients mean±SD | Group 1 mean±SD | Group 2 mean±SD | p |
|---|---|---|---|---|
| Bronchoscopy time (min) | 11.2±4.6 | 11.4±5.2 | 11.06±4 | 0.709 |
| Midazolam dose (mg) | 2.12±0.5 | 2.1±0.5 | 2.2±0.5 | 0.225 |
| Anesthetic dose (mg) | 165±68.9 | 175±67.5 | 155±69.4 | 0.144 |
| Ramsey Sedation scale | 2.2±0.7 | 2.3±0.7 | 2.1±0.6 | 0.309 |

In the visual analogue scale that assessed by the patients, the amount of cough was 61.72±24.40 mm in Group 1, 50.39±24.56 mm in Group 2. The patients were given fenocodein showed the amount of cough much less than the group were given with placebo. The difference between two groups was statistically significant (p<0.02) (**Table 5**).

**Table 5. The comparison of the visual analog scale scores of the groups**

| Patient | | | |
|---|---|---|---|
| **Value of VAS** | **Fenocodein (Grup1) mean±SD** | **Placebo (Grup 2) mean± SD** | **p** |
| Secretion (mm) | 62.72±24.88 | 53.66±22.68 | 0.065 |
| Cough (mm) | 61.72±24.40 | 50.39±24.56 | 0.026 |
| Comfort (mm) | 61.60±23.12 | 55.25±20.94 | 0.16 |

In the visual analog scale assessed by the doctors, the amount of secretion in Group 1 patients given fenocodein was 65±15.27 mm and in Group 2 received placebo was 57.04±18.60 mm. Accordingly in the group given fenocodein the amount of secretion was much less, but the difference between the two groups was not statistically significant (p=0.02).

The comfort of the doctors was 61.93±22.20 mm in Group 1 and 51.52±22.98 mm in Group 2 respectively. Accordingly, in Group 1 the comfort level of the doctor was evaluated more higher, the difference between the two groups was statistically significant (p=0.02)

In both groups, a complication hasn't developed to require the termination of the process.

## DISCUSSION

It is aimed that to increase the comfort of the patient and physician (cough, secretion, dyspnea sensation, patient compliance, process duration, etc.) and to reduce drug use for sedation and to take the best results for the process by using the premedication before bronchoscopy.

Several opioid antitussive drugs were investigated as well as to suppress the cough, but failed to reach a definitive conclusion for the routine use of these drugs.[7-11]

The most common drugs used for sedation are benzodiazepines, propofol, and opioids.[6]

Midazolam is preferred by doctors because of the rapid half-life time and affecting short duration.[12] Although this drug makes the process easier in many ways, it has no effect on cough and secretion.

Opioids are used in pain management for many years; analgesic, antitussive and anxiolytic effects. This group of drugs preferred to use alone due to the short half-life and rapid start-up period, is limited during bronchoscopy, they are used in combination with other analgesic agents.[13-15]

Haga T et al.[16] have performed bronchoscopy by applying deep sedation. In this study, patient satisfaction was evaluated. No significant difference was found between the two groups with and without deep sedation applied with midazolam.

There are several studies, that is about addition to midazolam, other sedative drugs.

Some studies show that the more effective the co-administration of the agent than the administered alone.[17,18]

The apply of midazolam and opioid or propofol reduce the amount of cough and reduce the dose of topical anesthetic. Thus they increase the patient tolerance.[19,20]

In the study by Crawford et al.[21] were compared with a group given propofol and midazolam to a group given fentanyl. In this study, the advantages of rapid onset and short duration of propofol have been reported. However it is recommended that propofol should be used for patients requiring deep sedation and it should be used under the responsibility of the anesthesiologist.[6] But opioids can be used safely by the bronchoscopist.

In a study of Tsunezuka et al.[22] in 1999; patients received midazolam were divided into 2 groups; as a group given a placebo and the other group given codeine phosphate. Finally it was determined that the necessity of local anesthesia was less in the group given codein .This finding was interpreted because of developing cough less in the group given codein.

Tsunezuka et al. claimed that the administration of opioid with midazolam is beneficial for both the patient and the doctor.

As there was no significant reduction in the need of local anesthesia in our study, the results of this study supports that cough is less in the group given codein when it is assessed by visual analog scale.

In the Tsunezuka and his colleagues study codein was given 60 minutes before process. The half-life of Codeine phosphate is 2-3 hours. Also to reach maximum concentration in plasma a drug must be given until 4-5 half-life time.Therefore in our study fenocodein tablets given were initiated the day before process, 20 mg fenocodein tablets were given at 8 hours intervals three times and the final dose was given 2 hours before process. Thus, it was intended to reach the highest concentration in plasma.

In another study done by Stolz et al.[23] in 2004, midazolam and hydrocodone 5 mg IV had been administered to one group patients, midazolam and placebo had been administered to another group patients. As a result of the study; it was reported that in the group given midazolam and hydrocodone the less cough and the better patients tolerance.

Although the antitussive effect of codeine is less than hydrocodone, it is very important that our study determines that in the group given codein cough is less.[24]

The oral use, the any side effects no seen, the easy achievability of codeine in our country, show that it can take place as a cough-reducing drug in our bronchoscopy practice.

In the study of Stolz et al.[19] with Tsunezuka et al.[22] it wasn't specified that there was no significant decrease in the oxygen saturation levels in the group given opioid. In our study, no significant difference was developed in oxygen saturation level during process for both groups too.

## CONCLUSION

As a result of our study, it has been indicated that the addition of oral fenocodein to the midazolam sedation reduced cough and increased the comfort of the patient and the physician and not caused any side effects extension . Therefore it was concluded that fenocodein is an effective and reliable drug that can be used to decrease the cough during the bronchoscopy process. It is convinced that fenocodein can be used routinely before bronchoscpy process after the results of other major studies that will be made in the future.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

The study was carried out with the permission of İstanbul Kartal Dr. Lütfi Kırdar Training and Research Hospital Scientific Researches Evaluation Ethics Committee (Date: 22.01.2013, Decision No: 1).

### Informed Consent

All patients signed and free and informed consent form.

### Referee Evaluation Process

Externally peer-reviewed.

### Conflict of Interest Statement

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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### Author Contributions

All of the authors declare that they have all participated in the design, execution and analysis of the paper and that they have approved the final version.

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Original Article

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# A retrospective analysis of postoperative geriatric patients with hip fracture; the reasons for admission to ICU

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## ABSTRACT

**Aims**: Geriatric patients with hip fracture experience high rates of mortality and morbidity. The purpose of this study was to analyse the epidemiology, complications and reasons for admission to ICU of the postoperative geriatric patients undergoing hip fracture surgery.

**Methods**: Patients aged 60 years and over who were operated on for hip fractures were retrospectively examined. Demographic characteristics, type of anesthesia (general/regional), operation time, and complications were recorded from the patients' files.

**Results**: The median age of the patients included in the study was 78.9±8.39 (min 60-max 100). It was observed that 71.6% of the patients were women, 13 patients received general anesthesia, and the rest received regional anesthesia. It was determined that 56.2% of the patients were admitted to intensive care. It was found that the surgery duration of patients admitted to intensive care was longer, and their average age and ASA scores were higher.

**Conclusion**: In our study, besides to the development of perioperative complications, age >80 years, ASA score 3 and 4, and long operation time were found to be the most important factors that required patients to be admitted to intensive care.

**Keywords**: Geriatric, hip fracture, critical care, general anaesthesia, spinal anaesthesia

## INTRODUCTION

With the increase in the elderly population, the number of operations performed for femoral fractures is also increasing. The surgical plan of these patients should be meticulously planned starting from the admission to the emergency department. The medical treatment process should be planned and followed by a multidisciplinary team including an emergency medicine specialist, orthopedist, anesthesiologist, intensive care specialist, nurse, physiotherapist, social worker and dietician. In this way, it is possible to achieve fewer complications and shorter hospitalisations.[1,2] In people with hip fracture, mortality in the first year is higher in older men than in women compared to the normal population. In female patients, mortality increases with advancing age and increasing number of systemic diseases. Scientific studies are generally aimed at analysing the factors affecting mortality and morbidity. The predictive roles of preoperative laboratory data and demographic data of the patient in terms of postoperative mortality have been investigated.[3-6] Timely planning of measures that can be taken by identifying postoperative mortality markers and effective intervention can prevent possible complications in these patients and reduce morbidity and mortality. Anesthesiologists have an important role in planning the necessary preparations by looking at these parameters in the preoperative evaluation of patients. Postoperative follow-up of patients in intensive care is an important issue that should be evaluated by anesthesiologists in the preoperative period. However, intensive care units should be used with caution because of their high costs, limited capacity and risk of infection.[6-8] In this study, we aimed to contribute to the literature by analysing the effect of anesthesia method on the perioperative process and possible risk factors for intensive care unit admission.

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## METHODS

The study was carried out with the permission of Keçiören Training and Research Hospital Clinical Researches Ethics Committee (Date: 08.04.2015, Decision No: 784). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

### Statistical Analysis

Continuous variables were expressed as mean±standard deviation, categorical variables as number and percentage. In the intergroup analysis of continuous variables, normality analysis of the variables was performed with the Kolmogorov-Smirnov goodness of fit test. In paired group comparisons, the T-test was used when the data were compatible with normal distribution, and the Mann Whitney U test was used when the data were not. Within-group comparisons were made with Wilcoxon signed ranks test. Chi-square test (Fisher's exact test where necessary) was used for the comparison of categorical data. Analyses were performed with IBM SPSS Package Program version 24.0 (IBM Corporation, Armonk, NY, USA). Statistical significance level was considered as $p<0.05$.

## RESULTS

When compared according to the type of anesthesia [general and regional anesthesia(spinal/ spinal-epidural combined anesthesia)], it was found that there was no significant difference between patients in terms of ASA score, peroperative complication, peroperative hypotension and respiratory depression rates ($p>0.05$). During surgery bradycardia developed in 30.8% of patients who had general anesthesia and in 10.1% of patients had regional anesthesia ($p=0.046$) (**Table 1**).

**Table 1. Comparison of some preoperative and intraoperative clinical characteristics of the patients according to anesthesia type**

| | Anesthesia Type | | | | Total | | p |
|---|---|---|---|---|---|---|---|
| | Spinal-epidural combined | | General anesthesia | | | | |
| | n | % | n | % | n | % | |
| **ASA** | | | | | | | 0.515* |
| 2 | 22 | 12.3 | 3 | 3.1 | 25 | 13.0 | |
| 3 | 136 | 76.0 | 9 | 69.2 | 145 | 75.5 | |
| 4 | 21 | 11.7 | 1 | 7.7 | 22 | 11.5 | |
| **Peroperative complication** | | | | | | | 0.263* |
| No | 99 | 55.3 | 5 | 38.5 | 104 | 54.2 | |
| Yes | 80 | 44.7 | 8 | 61.5 | 88 | 45.8 | |
| **Peroperative hypotension** | | | | | | | 0.919* |
| No | 99 | 55.3 | 7 | 53.8 | 106 | 55.2 | |
| Yes | 80 | 44.7 | 6 | 46.2 | 86 | 44.8 | |
| **Peroperative bradycardia** | | | | | | | 0.046** |
| No | 161 | 89.9 | 9 | 69.2 | 180 | 93.8 | |
| Yes | 18 | 10.1 | 4 | 30.8 | 6 | 3.1 | |
| **Respiratory depression** | | | | | | | 0.869** |
| No | 177 | 98.9 | 13 | 100.0 | 190 | 99.0 | |
| Yes | 2 | 1.2 | 0 | 0.0 | 2 | 1.0 | |
| **Total** | 179 | 100.0 | 13 | 100.0 | 192 | 100.0 | |

* Chi-square Test, **Fisher's Exact Test

When some clinical characteristics of a total of 108 patients hospitalised in the intensive care unit were compared according to the type of anesthesia, no significant difference was found between who had general anesthesia and had regional anesthesia (spinal/ combined spinal-epidural anesthesia) in terms of blood transfussion, noradrenaline use, mechanical ventilator use, duration of intensive care unit stay and outcome (discharge or exitus) (**Table 2**). The mean age of fracture patients hospitalised in the intensive care unit (ICU group) (80.38±7.84 years) was statistically significantly higher than that of patients hospitalised in the orthopedic ward (Ward group) (77.13±8.77 years) ($p=0.012$). The proportion of patients aged 80 years and over hospitalised in the intensive care unit was 58.3%, whereas it was 47.7% in the ward. It was found that the rate of hospitalisation in the intensive care unit increased with increasing age ($p=0.020$). ASA 3 and 4 rates were significantly higher in ICU group (93.6%) compared to Ward group (78.5%) ($p=0.009$). There was a statistically significant difference between ICU group and Ward group according to the type of surgery and type of anesthesia ($p=0.017$ and $p=0.042$, respectively). While 10.2% of those transferred to the intensive care unit received general anesthesia, this rate was only 2.4% in those admitted to the ward. The rates of peroperative complications and peroperative hypotension were statistically significantly higher in ICU group ($p<0.001$). No significant difference was found in terms of gender, fracture mechanism, operated side and the rates of peroperative bradycardia (**Table 3**).

**Table 2. Comparison of some clinical characteristics of patients admitted to intensive care unit according to anesthesia type**

| | Anesthesia Type | | | | Total | | p |
|---|---|---|---|---|---|---|---|
| | Spinal-epidural combined | | General anesthesia | | | | |
| | n | % | n | % | n | % | |
| **Blood replacement** | | | | | | | 0.803* |
| No | 67 | 69.1 | 8 | 72.7 | 75 | 69.4 | |
| Yes | 30 | 30.9 | 3 | 27.3 | 33 | 30.6 | |
| **Use of inotropes** | | | | | | | 0.722** |
| No | 94 | 96.9 | 11 | 100.0 | 105 | 97.2 | |
| Yes | 3 | 3.1 | 0 | 0.0 | 3 | 2.8 | |
| **Use of mechanical ventilation** | | | | | | | 0.806** |
| No | 95 | 97.9 | 11 | 100.0 | 106 | 98.1 | |
| Yes | 2 | 2.1 | 0 | 0.0 | 2 | 1.9 | |
| **Duration of ICU stay (days)** | | | | | | | 0.813* |
| 1 | 76 | 78.4 | 15 | 15.5 | 85 | 78.7 | |
| 2 | 15 | 15.5 | 1 | 9.1 | 16 | 14.8 | |
| ≥3 | 6 | 6.2 | 1 | 9.1 | 7 | 6.5 | |
| **Sonuç** | | | | | | | 0.898** |
| Referral | 96 | 99.0 | 11 | 100.0 | 107 | 99.1 | |
| Exitus | 1 | 1.0 | 0 | 0.0 | 1 | 0.9 | |
| **Total** | 97 | 100.0 | 11 | 100.0 | 108 | 100.0 | |

* Chi-square Test, **Fisher's Exact Test

There was no significant difference between ICU group and Ward group in terms of time to operation and hospitalization ($p>0.05$). The operation times were significantly higher in ICU group (92.40±35.09 min.) compared to Ward group (79.94±31.81 min.). On the contrary, preoperative and postoperative hemoglobin levels were found to be significantly lower in ICU group. The operation times were significantly higher in ICU group. Postoperative hemoglobin levels were found to be statistically significantly lower than basal preoperative levels in both groups ($p<0.001$) (**Table 4**).

**Table 3. Comparison of sociodemographic and some clinical data of patients according to hospitalization in intensive care unit**

| | Admission to intensive care unit | | | | Total | | p |
|---|---|---|---|---|---|---|---|
| | No | | Yes | | | | |
| | n | % | n | % | n | % | |
| **Age** | | | | | | | 0.020* |
| 60-69 | 18 | 21.4 | 10 | 9.3 | 28 | 14.6 | |
| 70-79 | 26 | 31.0 | 35 | 32.4 | 61 | 31.8 | |
| 80-89 | 36 | 42.9 | 52 | 48.1 | 88 | 45.8 | |
| 90 ≤ | 4 | 4.8 | 11 | 10.2 | 15 | 7.8 | |
| **Sex** | | | | | | | 0.413* |
| Female | 48 | 57.1 | 68 | 63.0 | 116 | 60.4 | |
| Male | 36 | 42.9 | 40 | 37.0 | 76 | 39.6 | |
| **ASA** | | | | | | | 0.009* |
| 2 | 18 | 21.4 | 7 | 6.5 | 25 | 13.0 | |
| 3 | 58 | 69.0 | 87 | 80.6 | 145 | 75.5 | |
| 4 | 8 | 9.5 | 14 | 13.0 | 22 | 11.5 | |
| **Fracture mechanism** | | | | | | | 0.903* |
| Falling down | 78 | 92.9 | 102 | 94.4 | 180 | 93.8 | |
| Traffic accident | 3 | 3.6 | 3 | 2.8 | 6 | 3.1 | |
| Pathological fracture | 3 | 3.6 | 3 | 2.8 | 6 | 3.1 | |
| **Operated side of the body** | | | | | | | 0.114* |
| Left leg | 47 | 56.0 | 48 | 44.4 | 95 | 49.5 | |
| Right leg | 37 | 44.0 | 60 | 55.6 | 97 | 50.5 | |
| **Type of surgery** | | | | | | | 0.017* |
| PFNA | 31 | 36.9 | 30 | 27.8 | 61 | 31.8 | |
| PTN | 34 | 40.5 | 31 | 28.7 | 65 | 33.9 | |
| PFN | 8 | 9.5 | 27 | 25.0 | 35 | 18.2 | |
| Other | 11 | 13.1 | 20 | 18.5 | 31 | 16.1 | |
| **Anesthesia type** | | | | | | | 0.042** |
| Spinal-epidural-combined | 82 | 97.6 | 97 | 89.8 | 179 | 93.2 | |
| General anesthesia | 2 | 2.4 | 11 | 10.2 | 13 | 6.8 | |
| **Peroperative complication** | | | | | | | <0.001* |
| Yes | 58 | 69.0 | 46 | 42.6 | 104 | 54.2 | |
| No | 26 | 31.0 | 62 | 57.4 | 88 | 45.8 | |
| **Peroperative hypotension** | | | | | | | <0.001* |
| Yes | 60 | 71.4 | 46 | 42.6 | 106 | 55.2 | |
| No | 24 | 28.6 | 62 | 57.4 | 86 | 44.8 | |
| **Peroperative bradycardia** | | | | | | | 0.231* |
| Yes | 77 | 91.7 | 93 | 86.1 | 170 | 88.5 | |
| No | 7 | 8.3 | 15 | 13.9 | 22 | 11.5 | |
| **Total** | 84 | 100.0 | 108 | 100.0 | 192 | 100.0 | |

* Chi-square Test, **Fisher's Exact Test

## DISCUSSION

As a result of our study, it was observed that there were many factors determining intensive care unit hospitalisation in patients operated for femoral fracture. The presence of perioperative complications, advanced age, ASA >3, and long duration of surgery were determined as factors that increased the risk of ICU hospitalisation.

There is little evidence to support the use of either method of anesthesia for hip fracture. One meta-analysis found no significant difference in complications between regional and general anesthesia except for acute renal failure.[9] Recent meta-analyses have also reported no statistically significant difference in 30-day mortality between the two methods of anesthesia.[10-15] In one of these studies, 30-day mortality and the incidence of deep vein thrombosis were lower in the regional anesthesia group, although not statistically significant, and the incidence of myocardial infarction, confusion and postoperative hypoxia was also lower. Although the operation time was shorter in operations performed under general anesthesia, there was a tendency towards cerebrovascular events and intraoperative hypotension in these patients. The incidence of postoperative hypoxia was 35.7% in patients under regional anesthesia and 48.3% in general anesthesia.[11] In a study by Neuman et al.[16] 666 patients under spinal anesthesia and 769 patients under general anesthesia were compared. When 60-day mortality in older adults undergoing hip fracture surgery was examined, it was found to be 3.9% in the spinal anesthesia group and 4.1% in the general anesthesia group. Both types of anesthesia were found to be similar in terms of mortality and ambulation. Among the patients we followed within the scope of our study, no deaths occurred in patients who received general anesthesia, while only one patient died in patients who received regional anesthesia. When we looked at the perioperative complications, we found that the incidence of complications was higher in the general anesthesia group. The incidence of hypotension during the operation was similar in both groups, while bradycardia was more common in the general anesthesia group. While all patients under general anesthesia were extubated, 2 patients under regional anesthesia were intubated due to respiratory depression and required mechanical ventilator support. While our study was compatible with the literature in terms of mortality, hemodynamic complication findings were not compatible with the literature. This may be due to the small number of patients who had general anesthesia among the patients included in the study. During the period included in the study, regional anesthesia was administered to the majority of the patients, while general anesthesia was administered much less frequently, and regional anesthesia was preferred by anesthesiologists in our clinic. This may be considered as a limitation of our study.

Rashiq et al.[17] reported that the need for blood transfusion was associated with female gender, preoperative low Hb level, presence of comorbidities and long surgical duration, and that blood loss and the need for transfusion were less in regional anesthesia. Morgan et al.[15] found that less blood transfusion was performed in patients who had spinal anesthesia in their analysis of 11 years of records registered in the UK database. However, in two large-scale meta-analyses, the need for postoperative blood transfusion was found to be similar in both types of anesthesia.[11,16] In our study, similar to the meta-analyses, the need for blood transfusion was similar in both groups. There seems to be no consensus on the effect of anesthesia method on blood transfusion.

**Table 4. Comparison of the mean values of some clinical data of the patients according to the status of hospitalization in the intensive care unit**

| | Hospitalized in service | | Hospitalized in intensive care unit | | p |
|---|---|---|---|---|---|
| | Min-max | Mean±Sd | Min-max | Mean±Sd | |
| Time until the operation (day) | 1-9 | 3.50±1.89 | 1-11 | 3.29±2.11 | 0.406** |
| Surgery time (minutes) | 30-180 | 79.94±31.81 | 40-180 | 92.40±35.09 | 0.012** |
| Duration of hospital stay (days) | 3-17 | 8.45±4.05 | 3-25 | 7.86±3.93 | 0.587** |
| Preoperative hemogram (mg/dl) | 9.3-17 | 12.32±1.81 | 8.6-15.7 | 11.79±1.66 | 0.039* |
| Postoperative hemogram (mg/dl) | 1-9 | 10.50±1.84 | 1-9 | 9.90±1.68 | 0.024** |
| | p<0.001*** | | p<0.001*** | | |

* T Test, **Mann Whitney U Test, *** Wilcoxon signed ranks test (comparison of preoperative and postoperative hemogram values within each group)

Morgan et al.[15] in their retrospective study of 8144 patients, 24.6% of the patients were in the 84- 89 age range. In the study of Neuman et al.[16] the mean age was 78 years and found to be similar in terms of additional systemic diseases, and when the ASA scores of the patients in both groups were analysed, it was observed that 60% of the patients were ASA 3. In the study of Kanar et al.[18] the mean age was found to be 80 years. In our study, 45.8% of the patients were between the ages of 80-89 years and 31.8% were between the ages of 70-79 years, 75% were ASA 3 and 11.5% were ASA 4, and in this respect, our study was compatible with the literature. Patients who were operated for hip fracture were elderly, had additional systemic diseases and had high risk ASA scores.

The elderly are special patient group and anesthesia management should be meticulously planned. In these patients, cardiopulmonary reserve, nutrition, anticoagulation, polypharmacy should be taken into consideration in preoperative evaluation and necessary tests and consultations should be planned.[19] Early intervention, early mobilisation and physiotherapy are the primary goals for possible adverse outcomes. Therefore, optimum conditions should be prepared for the patient with a multidisciplinary approach and the surgical process should be managed by providing effective analgesia from the preoperative period.[20,21]

The need for follow-up and treatment in the intensive care unit in the postoperative period should be discussed and planned in the preoperative period. However, sometimes complications that develop during the operation may cause unexpected intensive care unit requirement. Kanar et al.[18] compared 118 patients over 65 years of age who were operated on for proximal femur fracture, divided into two groups: those followed up in the ward and in the intensive care unit, and evaluated the possible risk factors. There was no difference between the two groups in terms of gender and type of operation. Although no statistically significant difference was found in terms of blood transfusion in patients hospitalised in the ICU, it was reported that more blood transfusions were performed in patients referred to the ICU. Similarly, in our study, no significant difference was found between patients hospitalised in the intensive care unit and patients followed in the ward in terms of gender and type of surgery. However, we found that the preoperative and postoperative control Hb values of patients hospitalised in the ICU were statistically significantly lower.

Early surgical intervention and early mobilization are preferred by orthopedists. Delay in surgery may increase complications such as pain, myocardial infarction due to increased sympathetic activity, embolism, atelectasis, and infection.[20,21] In our study, when the time from fracture to surgery was analysed, no statistically significant difference was found between patients hospitalised in the intensive care unit and in the ward. The length of surgical time has been reported as a risk factor that increases the risk of complications and blood transfusion.[17] Consistent with the literature, we found that the mean surgical time was statistically significantly higher in our patients hospitalised in the intensive care unit compared to patients transferred to the ward.

The presence of comorbidity is an important risk factor for postoperative morbidity and mortality. In our study, 48.1% of the patients hospitalised in the intensive care unit were 80-89 years old and 10.2% were over 90 years old, which was significantly higher compared to patients who did not require intensive care unit hospitalisation. The risk of comorbidity increases with age. When the ASA scores of the patients were examined, it was found that 80.6% of the patients hospitalised in the intensive care unit were ASA 3 and 13% were ASA 4, which were significantly higher. In addition, the percentage of patients receiving general anesthesia was found to be higher in patients hospitalised in the intensive care unit. In a study, patients who were planned for postoperative ICU hospitalization as a result of preoperative evaluation and patients who required ICU hospitalisation due to peroperative complications were retrospectively analysed. As a result of this study, it was determined that patients hospitalised in the postoperative ICU were older, ASA3 and above, male patients, and were mostly admitted to the ICU for monitoring and close follow-up in terms of hemodynamic instability.[22] In our study, 78.7% of the patients were hospitalised in the ICU for only 1 day, 14.8% for 2 days, and 6.5% for 3 days or more. It was observed that 57.4% of these patients developed peroperative hypotension. In this respect, our study was found to be compatible with the literature and it was thought that ICU hospitalisation was performed for hemodynamic monitoring and treatment in elderly patients with high ASA scores.[22] Within the framework of the ERAS protocol, it is recommended that elderly patients should be operated under regional anesthesia with opioid-limited anesthesia.[23] In our clinic, regional anesthesia is chosen as much as possible in accordance with this protocol and opioids are not preferred for sedation in elderly patients.

## CONCLUSION

As a result of our study, it was observed that ASA 3-4 patients over 80 years of age who received general anesthesia were more risky group in terms of intensive care requirement.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

The study was carried out with the permission of Keçiören Training and Researches Hospital Clinical Research Ethics Committee (Date: 08.04.2015, Decision No: 784).

### Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

### Referee Evaluation Process

Externally peer-reviewed.

### Conflict of Interest Statement

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

### Financial Disclosure

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### Author Contributions

All of the authors declare that they have all participated in the design, execution and analysis of the paper and that they have approved the final version.

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# The predictive value of first trimester maternal serum pregnancy-associated plasma protein-A (PAPP-A) level in predicting gestational diabetes mellitus

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## ABSTRACT

**Aims**: The aim of this study is to evaluate the predictive value of first trimester biochemical markers in the subsequent development of gestational diabetes mellitus.

**Methods**: Data were retrospectively collected from the file records of 361 pregnant patients, who were admitted to the 1st Obstetrics and Gynecology Clinic at Şişli Etfal Education and Training Hospital for first trimester prenatal screening test between 11-14 weeks of their gestation and who later had undergone 50 gram glucose challenge test at 24-28 weeks of their gestation, between November 2007 and February 2011. Age, patient weight, Crown rump length (CRL), gestational week, Pregnancy-Associated Plasma Protein-A (PAPP-A) concentration, PAPP-A multiple of median (MoM) value, Beta-human koryonik gonadotropin (B-HCG) concentration, B-HCG MoM value, 50 and 100 g oral glucose challange test result were recorded from the files. Gestational diabetes was diagnosed according to National Diabates Data Grup cutt-off values and criteria. The association between first trimester biochemical markers and subsequent development of gestational diabetes was evaluated.

**Results**: In this study low PAPP-A and/or HCG MoM values and increased Nuchal translucency (NT) MoM values were found to be statistically significant for subsequent development of gestational diabetes.

**Conclusion**: GDM is an important health problem that carries many risks of complications for both mother and fetus. Pregnant women with GDM may have high blood sugar levels before diagnosis at 24 weeks of gestation, so fetal growth may be negatively affected by maternal hyperglycemia. Use of first trimester screening maternal serum biomarkers may lead to early diagnosis of GDM and interventions to improve maternal and fetal outcomes.

**Keywords**: Fetal screening tests, pregnancy complications, chromosomal anomalies

## INTRODUCTION

Diabetes mellitus is a chronic metabolic disease in which the organism cannot benefit sufficiently from carbohydrates, fats and proteins due to insulin deficiency or defects in insulin action, requiring constant medical care. Hyperglycemia resulting from uncontrolled diabetes mellitus can lead to death with acute complications, and impairs the quality of life with long-term chronic complications .

Gestational diabetes mellitus (GDM) is called abnormal carbohydrate intolerance that begins during pregnancy or is detected for the first time during pregnancy.[1] Approximately 7% of all pregnancies are complicated by GDM, and more than 200,000 cases are estimated to occur annually worldwide.[2,3] Studies conducted in different regions in Türkiye have found that the prevalence of GDM varies between 3-8%.[4]

Pregnancies complicated by diabetes mellitus are risky pregnancies that require careful monitoring from both maternal and fetal perspectives. It is a metabolic disorder that can cause morbidity and mortality in various spectrums, from congenital malformations and in utero death in the baby, to hypoglycemia, diabetic ketoacidosis, to an increase in retinopathy, neuropathy and nephropathy in the mother, when adequate glycemic control is not achieved.[5]

Thanks to developing screening programs, diagnosis and treatment protocols, maternal-fetal mortality and morbidity in pregnancies with gestational diabetes have decreased significantly. Despite this, some complications are more common in pregnancies with gestational diabetes, and GDM is still an important risk factor for maternal and neonatal morbidity. In this sense, early diagnosis and treatment is important.

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The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO Study) study published in 2008 showed that an increase in plasma glucose level at any time during pregnancy is associated with an increase in adverse obstetric outcomes such as macrosomia, cesarean delivery, hypoglycemia, preterm birth, dystocia, etc. Riskin-Mashiah et al.[6] reported that there is a relationship between high plasma glucose level in the first trimester and the development of GDM and poor obstetric outcomes. In the light of this information, it can be assumed that if markers that can predict the development of GDM in the early weeks of pregnancy, poor obstetric outcomes that may occur due to gestational diabetes can be prevented with early diagnosis and treatment.

For the first time, the working group of the Royal College of Obstetricians and Gynaecologists (RCOG) talked about first trimester serum markers in 1997, which could be as effective as specific serum markers used in Down syndrome screening at 15-22 weeks of gestation. The best known serum markers used in the first trimester are pregnancy-associated plasma protein-A (PAPP-A) and free beta human chorionic gonadotropin. (Sb-HCG). The detection rate of PAPP-A and sb-HCG for Down syndrome at 9-11 weeks of gestation is 60% with 5% false positivity.[7]

It is known that abnormal maternal serum biochemical markers examined in the first trimester are associated with poor obstetric outcomes in the absence of fetal aneuploidy and neural tube defects.[8,9] It has been shown in many studies that especially low pregnancy-associated plasma protein-A (PAPP-A) is associated with poor obstetric outcomes such as spontaneous fetal losses, low birth weight, intrauterine growth restriction (IUGR), and preeclampsia.[10-13]

Whether gestational diabetes, as an important pregnancy complication, has a relationship with abnormal maternal serum biochemical markers in the first trimester has not been adequately examined by studies, and a few studies in the literature have found a significant relationship, especially between low PAPP-A and gestational diabetes.[14,15]

The aim of this study is to investigate the relationship between first trimester abnormal maternal serum biochemical marker levels and the risk of developing gestational diabetes in chromosomally normal pregnant women.

## METHODS

This study is produced from a master thesis in 2011. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Data were retrospectively collected from the file records of 361 pregnant patients, who were admitted to the 1st Obstetrics and Gynecology Clinic at Şişli Etfal Education and Training Hospital for first trimester prenatal screening test between 11-14 weeks of their gestation and who later had undergone 50 gram glucose challenge test at 24-28 weeks of their gestation, between November 2007 and February 2011.

CRL measurement, weeks of gestation based on CRL measurement, PAPP-A concentration, PAPP-A MOM value, β-HCG concentration, β-HCG MOM value, smoking, presence of pregestational diabetes and presence of twin pregnancy were recorded by examining pregnant patient files.

NT was measured in accordance with the Fetal Medicine Foundation criteria using the Siemens model Acusun Antares P.E. (U.S.A) transabdominal CH6-2 probe.

Serum PAPP-A, β -HCG concentrations were obtained by Şişli Etfal Training and Research Hospital Biochemistry Clinic using the Enhanced Chemiluminescent method on the Immulite 2000 autoanalyzer (Siemens Brand Immulite 2000 model Fully automatic immunoassay autoanalyser). Using the Prisca 3.4 screening program, PAPP-A and β-HCG MOM values were calculated by taking the information in the form filled out for the first trimester screening test.

Pregnant women whose 1st hour plasma glucose level was 140 mg/dl and above in the 50-gram oral glucose screening test at 24-28 weeks of gestation were subjected to a 100-gram oral glucose screening test. In 100 g OGTT, after blood was taken for fasting blood sugar, blood sugar levels were measured again at 1, 2 and 3 hours.The threshold value for fasting blood sugar is 105 mg/dl, the threshold value for 1st hour postprandial blood sugar is 190 mg/dl, the threshold value for 2nd hour postprandial blood sugar is 165 mg/dl, the threshold value for 3rd hour postprandial blood sugar is 145 mg/dl received. If two or more of the blood sugar levels measured exceed the threshold values, gestational diabetes mellitus was diagnosed. Plasma glucose levels recommended by the National Diabetes Data group were accepted as the threshold value for the diagnosis of gestational diabetes mellitus.

Pregnancies with multiple pregnancies, pregestational diabetes, fetal chromosomal disease diagnosis, and structural anomalies seen in ultrasonographic examination were not included in the study.

### Statistical Analysis

NCSS (Number Cruncher Statistical System) 2007&PASS (Power Analysis and Sample Size) 2008 Statistical Software (Utah, USA) program was used for statistical analysis.

While evaluating the study data, in addition to descriptive statistical methods (mean, standard deviation, median), Student's t test is used for intergroup comparisons of normally distributed parameters; Mann Whitney U test was used for intergroup comparisons of parameters that did not show normal distribution. Chi-Square test was used to compare qualitative data. Significance was evaluated at $p<0.05$ level.

## RESULTS

The ages of the cases ranged between 18 and 42 years, and the average was 28.45±5.67 years. When looking at weight measurements, it varies between 40 and 112 kg and the average is 65.19±12.54 kg. Pregnancy weeks vary between 11 and 14 weeks, and the average is 12.66±0.67 weeks.

PAPP-A mlU/ml measurements range between 0.26 and 13.70, and the average is 2.05±1.61 mlU/ml. PAPP-A mom measurements also vary between 0.14 and 4.28, and the average is 0.89±0.54 mom.B-HCG ng/ml measurements of the cases ranged between 10 and 200, and the average was 45.82±31.11 ng/ml. B-HCG mom measurements vary between 0.28 and 4.96, and the average is 1.20±0.76 mom. NT mom measurement also varies between 0.47 and 1.91, and the average is 0.96±0.21 mom. The 50 gram oral glucose tolerance test result was high in 42.9% (n=155) of the participants and GDM is seen in 25.5% (n=92) of the participants. Distribution of general features was presented in **Table 1**.

| Table 1. Distribution of general features | | |
|---|---|---|
| (n=361) | Min-Max | Mean±SD |
| Age (year) | 18-42 | 28.45±5.67 |
| Weight (kg) | 40-112 | 65.19±12.54 |
| Week Of Pregnancy | 11.14-14.00 | 12.66±0.67 |
| CRL (mm) | 35.6-82.0 | 63.05±8.99 |
| PAPP-A (mlU /ml) | 0.26-13.70 | 2.05±1.61 |
| PAPP-A (mom) | 0.14-4.28 | 0.89±0.54 |
| B-HCG (ng/ml) | 10-200 | 45.82±31.11 |
| B-HCG (mom) | 0.28-4.96 | 1.20±0.76 |
| FBG | 62-146 | 85.70±9.85 |
| 50 gr OGTT | 66-226 | 137±34.70 |
| Nt (mom) | 0.47-1.91 | 0.96±0.21 |

There is a statistically significant difference between the average ages according to gestational diabetes status (p<0.01). The ages of cases with gestational DM are significantly higher than those without. Also there is a statistically significant difference between weight averages according to gestational diabetes status (p<0.01). The weight of cases with gestational DM is significantly higher than those without. No statistically significant difference between the smoking rates of cases with and without gestational diabetes (p>0.05). Descriptive Characteristics According to Gestational Diabetes was presented in Table 2.

| Table 2. Evaluations of descriptive characteristics according to gestational diabetes mellitus (GDM) | | | |
|---|---|---|---|
| Table | GDM | | p |
| | Yes (n=92) Maen+SD | NO (n=269) Mean+SD | |
| Age (year) | 32.01±5.06 | 27.23±5.35 | 0.001** |
| Weight (kg) | 69.39±11.90 | 63.75±12.45 | 0.001** |
| +Smoking | n (%) | n (%) | |
| Yes<br>No | 12 (13.0%)<br>80 (87.0%) | 41 (15.2%)<br>228 (84.8%) | 0.607 |
| Student t test +Ki kare test | | | |

There is a statistically significant difference between β-HCG ng/ml measurements according to gestational diabetes status (p<0.05). The average β-HCG ng/ml measurement of those with gestational diabetes is significantly lower than those without, and the median is 32.90. Also there is a statistically significant difference between β-HCG mom measurement according to gestational diabetes status (p<0.05). The mean β-HCG mom measurements of those with gestational diabetes are significantly lower than those without, and the median is 0.92. Evaluation of β-HCG measurements according to gestational diabetes status was presented in Table 3.

| Table 3. Evaluation of Beta-human korionik gonadotropin (β-HCG) measurements according to gestational diabetes status | | | | |
|---|---|---|---|---|
| GDM | β -HCG (ng/ml) | | β -HCG (mom) | |
| | Ort±SD | Median | Ort±SD | Median |
| Yes | 39.79±27.94 | 32.90 | 1.07±0.69 | 0.92 |
| No | 47.88±31.91 | 40.80 | 1.25±0.77 | 1.06 |
| P | 0.017* | | 0.032* | |
| Mann-Whitney U test, *p<0,05 | | | | |

There is a statistically significant difference between PAPP-A mlU/ml measurements according to gestational diabetes (p<0.05). The mean PAPP-A of those with gestational diabetes is significantly lower than those without gestational diabetes, with a median of 1.40. Also there is a statistically significant difference between PAPP-A mom measurements according to gestational diabetes (p<0.01). The mean PAPP-A mom of cases with gestational diabetes is significantly lower than those without gestational diabetes and the median is 0.68. PAPP-A Evaluations According to Gestational Diabetes was presented in Table 4.

| Table 4. Pregnancy-associated plasma protein-A PAPP-A evaluations according to gestational diabetes | | | | |
|---|---|---|---|---|
| GDM | PAPP-A mlU/ml | | PAPP-A mom | |
| | Mean±SD | Median | Mean±SD | Median |
| Yes | 1.71±1.10 | 1.40 | 0.76±0.39 | 0.68 |
| No | 2.17±1.74 | 1.68 | 0.93±0.58 | 0.78 |
| p | 0.017* | | 0.009** | |
| Mann-Whitney U test, *p<0,05, **p<0,01 | | | | |

Based on this significance, calculation of the cut-off point for PAPP-A mom was considered. ROC analysis was used to determine the cut-off point for PAPP-A MoM.In cases with a PAPP-A MoM level of 0.70 and below, the sensitivity in detecting gestational diabetes was found to be 53.26%, the specificity was 57.99%, the positive predictive value was 30.25% and the negative predictive value was 78.39%. ROC analysis was given in Figure.

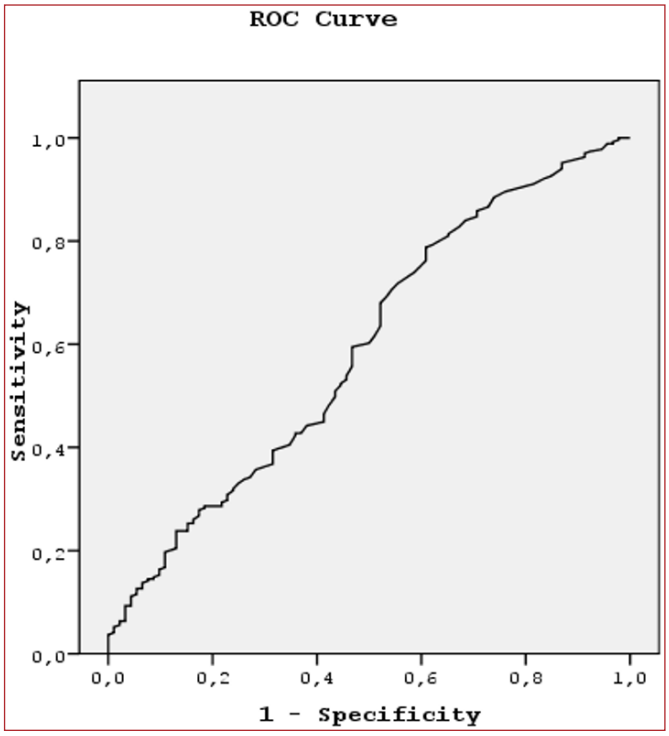


**Figure.** ROC curve obtained for PAPP-A MoM
The area under the ROC curve obtained was found to be 59.2%, with a standard error of 3%.

## DISCUSSION

Gestational diabetes is defined as glucose intolerance that begins and is first detected during pregnancy.[16] It is an important health problem that can cause both maternal and fetal mortality and morbidity if glycemic control is not provided with adequate treatment at the time of diagnosis. Nowadays, screening tests performed in the second trimester of pregnancy are used to diagnose gestational diabetes, but after diagnosis, the time period remaining for clinicians to find the ideal treatment will be narrowed. There are various metabolic changes in the blood of pregnant women who will develop gestational diabetes in the early stages of pregnancy before the diagnosis of gestational diabetes and if these changes are detected, early diagnosis and treatment may be possible.

In the present study, in the light of this information, we investigated whether PAPP-A level, which is known to have an effect on fetal growth and development, is a serum marker that can be used to diagnose gestational diabetes in the early period.

Although the relationship between PAPP-A level and pregnancy complications such as preeclampsia, low birth weight, and preterm birth has been examined by many researchers, its relationship with gestational diabetes has been mentioned in only a few studies.

Spencer et al.[7] investigated the relationship between first trimester maternal serum PAPP-A and sb-HCG and second trimester uterine artery Doppler findings and pregnancy complications. A significant relationship was found between low PAPP-A and preeeclampsia, fetal growth restriction and preterm birth (in case of PAPP-A <0.844, <0.813 and <0.928 MOM, respectively). No relationship was found between Sb-HCG levels and pregnancy complications.

Krantz et al.[17] found that low or high levels of sb-HCG, PAPP-A and NT values carry an increased risk of intrauterine growth retardation, premature birth, preeclampsia and stillbirth.

In a prospective study conducted by Smith et al.[9] on 8839 pregnant women between 8-14 weeks of gestation, it was determined that low PAPP-A levels carried an increased risk of intrauterine growth retardation, premature birth, preeclampsia and stillbirth.

In a retrospective study conducted by Beneventi et al.[13] in 2011 on 456 singleton pregnant women, the relationship between PAPP-A levels measured in the first trimester and the development of gestational diabetes was investigated. The average PAPP-A MOM value in pregnant women who developed gestational diabetes was 0.7, and the average PAPP-A MOM value in the control group was 1.2, which was significantly lower than the control group (P<0.001).

In the retrospective case control study conducted by Xiao et al.[19] on 599 pregnant women with GDM and 986 euglycemic pregnant women, the average PAPP-A MOM value was found to be 0.88 in pregnant women with GDM and 0.97 in euglycemic pregnant women, and it was found to be statistically significant (p<0.001).

In the retrospective case-control study conducted by Cui et al.[20] on 4872 patients, the PAPP-A MOM value was found to be lower in pregnant women with GDM, 0.86, and 0.97 in patients without GDM.

In the study conducted by Ren et al.[21] on 99 patients, PAPP-A value was found to be lower in pregnant women with GDM than in the control group. The average value was 13.84 ng/L in patients with GDM and 16.96 ng/L in the group without GDM (p<005).

In the prospective study conducted by Ramezani et al.[22] on 284 pregnant women, the relative risk of GDM in patients with decreased PAPP-A levels was estimated to be 4.77 times compared to healthy people.

In the retrospective case-control study conducted by Yanachkova et al.[23] on 662 pregnant women, the median PAPP-A adjusted MOM was significantly lower in GDM group compared to the control group (1.2 vs 1.3; p<0.001).

In a retrospective study conducted by Visconti et al.[24] on 2410 pregnant women, they found that there was an increased risk for GDM if the PAPP-A mom value was<1.

In present study, as supports the information in the studuies above, the average PAPP-A MOM level was lower and found to be 0.76 in pregnant women who developed gestational diabetes, and the PAPP-A MOM level was 0.93 in the control group, and the difference is statistically significant (P=0.009).

In a large-scale study conducted by Dugoff et al.[10] on 33,395 pregnant women, the relationship between PAPP-A MOM value and pregnancy complications was investigated. A relationship has been found between IUGR, preeclampsia, gestational hypertension and in utero death. Additionally, in this study, a relationship was found between the development of gestational diabetes when the PAPP-A MOM value was taken <10 percentile (PAPP-A MOM<0.52) (P=0.05).

Ong et al.[14] found a significant relationship between low PAPP-A MOM value (<10 percentile) and spontaneous pregnancy losses, IUGR, preeclampsia, and gestational hypertension. In this study, it was found to be statistically significant when the PAPP-A MOM value was below the 10$^{th}$ percentile in pregnant women with gestational diabetes (P=0.002).

In the studies conducted by Dugoff et al.[10] and Ong et al.[14] PAPP-A MOM values were divided into percentiles, and in both studies, the development of gestational diabetes was found to be significantly higher in cases below the 10th percentile. In our study, the PAPP-A MOM value was not considered as a percentile, and when the cut-off value of the PAPP-A MOM value was taken as 0.7, the sensitivity in detecting gestational diabetes was 53.26%; The specificity was determined as 57.99%.

In the study conducted by Kavak et al.[15] on 490 singleton pregnant women in our country, the relationship between PAPP-A value and low birth weight, hypertensive disease, and gestational diabetes was investigated. In their study, no significant relationship was found between PAPP-A level and gestational diabetes. 18 pregnant women with gestational diabetes were included in the study, and we think that this number is insufficient for sampling.

Another result we found in our research is the existence of a relationship between low β-HCG MOM levels and the development of gestational diabetes. In our study, the β-HCG MOM value was found to be 0.92 in the group that developed gestational diabetes and 1.06 in the control group (P=0.032). In the studies conducted by Beneventi et al.[13] Dugoff et al.[10] and Kavak et al.[15] no relationship was found between low β-HCG MOM level and the development of gestational diabetes. In the study conducted by Ong et al.[14] β-HCG levels were found to be significantly low, supporting our study.

In our study, the average age of pregnant women who developed gestational diabetes was significantly higher than the control group (P=0.001). In addition, the average weight of pregnant women who developed gestational diabetes was found to be significantly higher than the control group (P=0.001). In research conducted in the literature; Ben-Haroush et al.[18] Beneventi et al.[13] Body mass index (BMI) was used instead of weight, and BMI was found to be significantly higher in pregnant women who developed gestational diabetes. In our own research, since the heights of the pregnant women were not included in the forms filled out for the first trimester screening tests, we could only compare their weights.

The Hyperglycemia and Adverse Pregnancy Outcomes (HAPO Study) study published in 2008 showed that an increase in plasma glucose level at any time during pregnancy is associated with an increase in adverse obstetric outcomes such as

macrosomia, cesarean delivery, hypoglycemia, preterm birth, dystocia, etc. Both in our study and in studies reported in the literature, a significant relationship was found between low PAPP-A levels and gestational diabetes. In pregnant women who are found to have low PAPP-A and/or B-HCG MOM levels in the first trimester screening test, we recommend that a direct 75-g OGTT test can be performed to protect the fetus from possible hyperglycemia-related complications in the early period, without undergoing the OGTT screening test between 24-28 weeks. However, this conclusion needs to be supported by large prospective studies.

## CONCLUSION

Maternal and fetal complications may occur in the later weeks of pregnancy in pregnant women whose abnormal value is detected in the first trimester screening test but is found to be chromosomally normal. For this reason, these pregnant women should be carefully monitored during their antenatal follow-up and early diagnosis methods should be used. While counseling families for the first trimester screening test, it is important to note that a positive screening test does not always mean a chromosomally diseased baby, but that a positive result may accompany some pathological conditions related to pregnancy (gestational diabetes, preeclampsia, fetal growth restriction, low birth weight, premature birth, fetal death).

## ETHICAL DECLARATIONS

### Ethics Committee Approval

Since the study is produced from a master thesis in 2011, ethics committee approval is not required.

### Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

### Referee Evaluation Process

Externally peer-reviewed.

### Conflict of Interest Statement

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

### Financial Disclosure

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### Author Contributions

All of the authors declare that they have all participated in the design, execution and analysis of the paper and that they have approved the final version.

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# The contribution of imaging to non-invasive fibrosis biomarkers in the diagnosis and staging of chronic liver disease

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## ABSTRACT

**Aims**: Gold standard technique for determining the stage of fibrosis in cirrhosis is a biopsy. Non-invasive tests are used when a biopsy is contraindicated. However, their specificity and sensitivity still fall short of expectations. Aim of the study is to develop a model capable of determining fibrosis using serum biomarkers and liver ultrasonography.

**Methods**: A retrospective study was designed including patients with chronic hepatitis B and C underwenting liver biopsies between the time frame of 2015 to 2020 years at Trakya University School of Medicine. Epidemilogical data, ultrasonography and pathology reports were noted. Blood values were recorded and used to calculate AST / Platelet Ratio Index (APRI), Fibrosis-4 Index (FIB-4), Gothenburg University Cirrhosis Index (GUCI) noninvasive fibrosis indices. The fibrosis stages of the patients were assessed accoridng to pathology reports into three categories: advanced (F5-F6), moderate (F3-F4), and lower Ishak scores.

**Results**: A total of 259 patients were included in the study. The median age of the patients was 54 (19-90), and 40.9% (106) were female. The median values of APRI, GUCI and FIB-4 scores were respectively: 0.6 (0-21.8), 0.6 (0-26.2) and 1.6 (0.2-8.5). The effects of ultrasonography findings were examined to improve the diagnostic performance of APRI, GUCI and FIB-4 indices. Accompanied by statistical analysis, it was observed that the FIB-4 index and the presence of hepatosteatosis in the liver had a significant effect on the detection of F≥3 (respectively; p<0.001, p=0.033). A new model named FIB4u (ultrasonography) was developed. The AUC values of indices for differentiation of intermediate and advanced stages of fibrosis (≥3) were respectively:FIB4u 0.760; FIB-4 0.753; GUCI 0.676; APRI 0.667 (p<0.001). The FIB4u index demonstrated considerably better performance compared to both APRI and GUCI.

**Conclusion**: The FIB4u index, developed by combining ultrasonography and laboratory data, can be used as a new index for fibrosis assessment in the absence of advanced elastography techniques. It needs to be validated in larger patient cohorts to be used safely in the long term.

**Keywords**: Cirrhosis, FIB4, non-invasive fibrosis indices, ultrasonography

## INTRODUCTION

Worldwide, approximately two million people die each year due to liver diseases. One million of these deaths are due to complications of cirrhosis. Cirrhosis ranks 11th cause of death. Together, cirrhosis and HCC account for 3.5% of all fatalities worldwide. The mortality rate has increased by 0.5% since the year 2000.[1] It has been observed that as fibrosis progresses, cirrhosis development and viral, non-viral liver disease complications increase.[2,3] Therefore, it is important to be able to determine the stage of fibrosis. There are invasive (liver biopsy) and non-invasive (serum markers and imaging) methods for detecting fibrosis. Although liver biopsy is the best method, due to its interventional nature it can cause pain, morbidity and mortality. In addition, the distribution of fibrosis is heterogeneous, and tissue biopsies represent only 1:500000 of the entire organ. The stage of fibrosis can be interpreted variably by pathologists.[4]

There are two major classifications for non-invasive markers. Biological methods consisting of serum biomarkers and imaging techniques measuring liver rigidity. Many indices have been developed by using various combinations of markers and adding clinical parameters such as age, gender, and body mass index to the formulations. Some of these formulas are as follows: AST / Platelet Ratio Index (APRI), Fibrosis-4 Index (FIB-4), GUCI Gothenburg University Cirrhosis Index (GUCI), Hui score, Zeng score, ALT ratio. Ultrasonography

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(US) and magnetic resonance-based elastography are the methods that examine the liver parenchyma structure using a physical approach. The main principle is that the tissue stiffness increases as fibrosis increases.[5] The advantages of biomarkers are easy applicability, safe interlaboratory reproducibility, and widespread availability, especially of non-patent ones.[6,7] However, these markers have disadvantages such as not only reflecting liver specific fibrosis and their values can be affected in different physiological conditions and diseases. Similarly, elastography methods have disadvantages such as availability of special equipment, application problems (obesity, ascites, experience of the performer), failure to reflect intermediate fibrosis values, and false positive results (due to acute hepatitis, extrahepatic cholestasis, liver congestion, post meal).[5] Therefore, there is no ideal marker to predict fibrosis.

The aim of our research is to develop a model that can determine fibrosis with serum biomarkers and liver ultrasound features in patients with chronic liver disease and to predict the prognosis of liver disease without any intervention.

## METHODS

### Patients and Sample Collection

Our retrospective study included 259 patients over the age of 18 as participants, who underwent liver parenchymal biopsy and were monitored in the Gastroenterology department of Trakya University Medical Faculty Hospital between 2015 and 2020 with HBV and HCV diagnoses. The study was approved by the Trakya University Faculty of Medicine Scientific Researches Ethics Committee (Date: 10.08.2020, Decision No: 12/10). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Age, gender, chronic liver disease etiologies, blood sample results (hemoglobin, white blood cells, neutrophil, lymphocyte, platelet, total bilirubin, direct bilirubin, sodium, potassium, urea, creatinine, total protein, albumin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma glutamyl transpeptidase, prothrombin time, international normalized ratio, activated partial thromboplastin clotting time levels) were obtained from medical records of patients. Liver and spleen US was performed using Toshiba Aplio 500 and Esaote MyLab 70 model US device. Fibrosis scores from liver parenchymal biopsy reports were obtained from Pathology Department. ISHAK fibrosis scoring system was used. With laboratory results, APRI ((AST/AST upper limit) x (100/PLT)) score, GUCI score ((AST/AST upper limit) x INR x 100/PLT )) and FIB-4 ((Age x AST/(PLT x$\sqrt{}$ALT)) scores were calculated. Liver size, spleen size, liver heterogeneicty, microlobulation and hepatosteatosis findings were recorded from US reports.

### Statistical Analysis

The normality condition for continuous variables was checked with the Shapiro-Wilk test. The Kruskal-Wallis test (Post-Hoc: Dunn-Bonferroni test) was performed when the data of the three groups did not exhibit normal distribution, and the one-way analysis of variance was performed otherwise. The relationship between two categorical variables was examined with Pearson's Chi-square test and Fisher's Exact test. The development work on the indices was carried out by logistic regression analysis. Receiver Operating Characteristic (ROC) curve analysis was performed and Area Under Curve (AUC) values were compared with DeLong test. Sensitivity, specifity, positive cut-off and negative cut-off values were calculated. Data were expressed as mean, standard deviation, median, minimum and maximum values. Statistical software SPSS version 23 (SPSS Inc., Armonk, NY) was used for all analyzes. R (Version 4.1.0) program ("pROC",Version 1.17.0.1) package was used for ROC analysis. The significance level was determined as $p<0.05$.

## RESULTS

The median age of the patients was 54 (19-90). 40.9% (n=106) were female. Of the viral hepatitis etiology in the patients, 226 (87.3%) were HBV and 33 (12.7%) were HCV.

In the ultrasonography examination, spleen enlargement was detected in 6.2% (n=16), liver heterogenecity in 22.8% (n=59), liver microlobulation in 5% (n=13), liver hepatosteatosis in 12.7% (n=33) of patients (**Table 1**).

**Table 1. Ultrasonography findings of the patients**

| | n | % |
|---|---|---|
| **Spleen size** | | |
| Normal | 243 | 93.8 |
| Increased | 16 | 6.2 |
| **Liver heterogeneity** | | |
| No | 200 | 77.2 |
| Yes | 59 | 22.8 |
| **Liver microlobulation** | | |
| No | 246 | 95.0 |
| Yes | 13 | 5.0 |
| **Liver hepatosteatosis** | | |
| No | 226 | 87.3 |
| Yes | 33 | 12.7 |
| **Liver enlargement** | | |
| No | 217 | 83.8 |
| Yes | 42 | 16.2 |

The median values of the patients' APRI, GUCI and FIB-4 scores were respectively; 0.6 (0-21.8), 0.6 (0-26.2) and 1.6 (0.2-8.5).

The distribution of the patients numbers (n) according to histopathological fibrosis stages (F) was as follows: F0, n=13; F1, n=42; F2, n=86; F3, n=60; F4, n=29; F5,n=28; F6, n=1.

According to the stages of fibrosis, patients were divided into three groups: advanced (F5-F6), intermediate (F3-F4), and lesser levels (F0-F1-F2). And analyses were conducted based on these groupings.

When the characteristics of the patients were examined in terms of the Ishak Fibrosis Score, a significant relationship was found with age. Those with fibrosis stage F5-F6 were significantly older than those with F0-F1-F2 and F3-F4 scores. Those with fibrosis stage F3-F4 were significantly older than those with F0-F1-F2 (KW: $\chi2=25.083$, $p<0.001$, Post-Hoc: respectively, $p=0.006$, $p<0.001$, $p=0.043$) (**Table 2**).

**Table 2. Ishak fibrosis scores according to the characteristics of the patients**

| | Total (n=259) | Ishak Fibrosis Scores | | | Test p |
|---|---|---|---|---|---|
| | | F0-F1-F2 (n=141) | F3-F4 (n=89) | F5-F6 (n=29) | |
| Age | | | | | |
| Mean±sd | 52.4±13.6 | 48.8±14.3 | 55±10.9 | 61.8±11.3 | <0.001* |
| Gender | | | | | |
| Female | 106 (40.9) | 57 (53.8) | 37 (34.9) | 12 (11.3) | 0.984** |
| Male | 153 (59.1) | 84 (54.9) | 52 (34) | 17 (11.1) | |

Sd:standard deviation, Med (Min-Max): Median (Minimum - Maximum), Kruskal Wallis test*, Pearson's chi-square test**

When laboratory values and fibrosis stages were compared, as expected, white blood cells, neutrophil and thrombocyte count, albumin values were significantly decreased in advanced fibrosis stages. Additionally in patients with a high stage of fibrosis, total bilirubin, direct bilirubin, urea, ast, alp, ggt, prothrombin time, and INR values were elevated (Table 3).

**Table 3. Ishak fibrosis scores according to the laboratory values of the patients**

| | Ishak Fibrosis Scores | | | Test p* |
|---|---|---|---|---|
| | F0-F1-F2 (n=141) (mean±sd) | F3-F4 (n=89) (mean±sd) | F5-F6 (n=29) (mean±sd) | |
| Hemoglobin level (gr/dl) | 14.4±1.6 | 14.3±1.5 | 13.9±1.6 | 0.319 |
| White blood cells count | 6.9±2 | 6.7±1.9 | 6±1.9 | 0.036 |
| Neutrophil count | 4±1.4 | 3.7±1.4 | 3.3±1.1 | 0.020 |
| Lymphocyte | 2.2±0.7 | 2.1±0.7 | 2±0.8 | 0.195 |
| Platelet count (x10$^3$) | 229.6±60.7 | 188.5±54.2 | 162±43.6 | <0.001 |
| Total Bilirubin | 0.8±0.5 | 1±0.7 | 1±0.4 | 0.031 |
| Direkt Bilirubin | 0.3±0.3 | 0.3±0.5 | 0.4±0.3 | 0.001 |
| Sodium | 139.3±2.7 | 139±4.4 | 139.2±2.3 | 0.993 |
| Pootassium | 4.5±0.4 | 4.4±0.4 | 4.4±0.3 | 0.277 |
| Urea | 28.6±9.1 | 31.2±17.8 | 32.8±9.3 | 0.031 |
| Creatinin | 0.8±0.3 | 0.8±0.5 | 0.8±0.2 | 0.583 |
| Total Protein | 7.4±0.6 | 7.3±0.9 | 7.3±0.7 | 0.609 |
| Albumin | 4.2±0.4 | 4.1±0.4 | 3.9±0.5 | <0.001 |
| ALT | 131.1±240.3 | 108.7±152.3 | 162.8±167.6 | 0.061 |
| AST | 84.1±153.7 | 75.8±88.4 | 109.9±91.2 | <0.001 |
| ALP | 86.2±37.9 | 97.8±43.8 | 101.5±33.5 | 0.009 |
| GGT | 47.8±61.4 | 84.2±240.1 | 125±132.1 | <0.001 |
| Protrombin time | 13.7±1.3 | 14.2±0.9 | 14.5±1.1 | <0.001 |
| INR | 1±0.1 | 1.1±0.1 | 1.1±0.1 | <0.001 |
| APTT | 28.4±2.7 | 28.9±2.6 | 29.2±2.4 | 0.333 |

Sd:standard deviation, Med (Min-Max): Median (Minimum - Maximum), ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, ALP: Alkaline Phosphatase, GGT: Gamma glutamyl transpeptidase, INR: International Normalized Ratio, APTT: Activated Partial Thromboplastin Time. *Kruskal Wallis test, One-way analysis of variance

Liver ultrasonography findings and fibrosis stage were compared. Liver heterogeneity and microlobulation features were more observed in advanced fibrosis stages (p=0.043; p=0.004) (Table 4).

**Table 4. Ishak fibrosis scores according to the ultrasonographic findings of the patients**

| | Total (n=259) | Ishak Fibrosis scoring | | | Test p* |
|---|---|---|---|---|---|
| | | F0-F1-F2 (n=141) | F3-F4 (n=89) | F5-F6 (n=29) | |
| **Spleen size** | | | | | 0.528 |
| Normal | 16 (6.2) | 7 (43.8) | 6 (37.5) | 3 (18.8) | |
| Enlarged | 243 (93.8) | 134 (55.1) | 83 (34.2) | 26 (10.7) | |
| **Liver heterogeneity** | | | | | 0.043 |
| No | 200 (77.2) | 116 (58) | 66 (33) | 18 (9) | |
| Yes | 59 (22.8) | 25 (42.4) | 23 (39) | 11 (18.6) | |
| **Liver microlobulation** | | | | | 0.004 |
| No | 246 (95) | 139 (56.5) | 82 (33.3) | 25 (10.2) | |
| Yes | 13 (5) | 2 (15.4) | 7 (53.8) | 4 (30.8) | |
| **Liver hepatosteatosis** | | | | | 0.303 |
| No | 226 (87.3) | 127 (56.2) | 74 (32.7) | 25 (11.1) | |
| Yes | 33 (12.7) | 14 (42.4) | 15 (45.5) | 4 (12.1) | |
| **Liver enlargement** | | | | | 0.660 |
| No | 217 (83.8) | 117 (53.9) | 74 (34.1) | 26 (12) | |
| Yes | 42 (16.2) | 24 (57.1) | 15 (35.7) | 3 (7.1) | |

Pearson's chi-square test, Fisher exact test*

When APRI, GUCI, and FIB-4 index values were examined, a significant difference was found between all fibrosis stage groups (Respectively; $\chi2$=31,346, $\chi2$=33,799, $\chi2$=59,460, $\chi2$=40.936, p<0.001) (Table 5).

**Table 5. Ishak fibrosis scores according to fibrosis indices values**

| | Ishak fibrosis scoring | | | Test P* |
|---|---|---|---|---|
| | F0-F1-F2 (n=141) (mean±sd) | F3-F4 (n=89) (mean±sd) | F5-F6 (n=29) (mean±sd) | |
| APRI | 1.2±2.5 | 1.3±1.5 | 2±1.4 | <0.001 |
| GUCI | 1.2±2.8 | 1.4±1.7 | 2.2±1.5 | <0.001 |
| FIB-4 | 1.6±1.4 | 2.3±1.3 | 3.8±1.9 | <0.001 |

Sd:standard deviation, Med (Min-Max): Median (Minimum - Maximum), APRI: AST / Platelet Ratio Index; GUCI: Gothenburg University Cirrhosis Index, FIB-4: Fibrosis 4 Index. *Kruskal Wallis test

## Model Study with Ultrasonography Findings in Fibrosis Indices

The effects of ultrasonography findings were examined with logistic regresion analysis to improve the diagnostic performance of APRI, GUCI and FIB-4 indices for diagnosis of Ishak Fibrosis score ≥3 (F≥3).

As a result it was seen that APRI and GUCI indices were not significant in detecting F≥3 (respectively; p=0.348, p=0.321). Therefore, model development was not carried out.

In the analysis, it was observed that the FIB-4 index and the presence of hepatosteatosis in the liver had a significant effect in the detection of Fibrosis score ≥3 (Respectively; p<0.001, p=0.033) (Table 6).

**Table 6. Logistic regression models for Ishak Fibrosis ≥3 with indices and ultrasonography findings**

| | Ishak Fibrosis score ≥3 | | | p |
|---|---|---|---|---|
| | ß coefficient | SE | Odds | |
| APRI | 0.061 | 0.065 | 1.063 | 0.348 |
| Liver heterogeneity | -0.613 | 0.312 | 0.542 | 0.049 |
| Liver microlobulation | 1.964 | 0.787 | 7.128 | 0.013 |
| Liver hepatosteatosis | -0.758 | 0.384 | 0.468 | 0.048 |
| Constant | 2.163 | 0.975 | 8.701 | 0.026 |
| GUCI | 0.060 | 0.060 | 1.061 | 0.321 |
| Liver heterogeneity | 0.603 | 0.312 | 1.828 | 0.053 |
| Liver microlobulation | 1.961 | 0.787 | 7.105 | 0.013 |
| Liver hepatosteatosis | 0.830 | 0.391 | 2.292 | 0.034 |
| Constant | -0.580 | 0.179 | 0.560 | 0.001 |
| FIB-4 | 0.534 | 0.109 | 1.706 | <0.001 |
| Liver microlobulation | 1.535 | 0.810 | 4.639 | 0.058 |
| Liver hepatosteatosis | 0.897 | 0.396 | 2.452 | 0.024 |
| Constant | -1.456 | 0.263 | 0.233 | <0.001 |

SE: Standard error, APRI: AST / Platelet Ratio Index, GUCI: Gothenburg University Cirrhosis Index, FIB-4: Fibrosis 4 Index.

Although the presence of microlobulation in the liver does not have a statistically significant effect on the model, it is included in the final model due to its positive contribution to the model fit (p=0.058). The model named "FIB4u" is significant and the model related -2 Log Likelihood value of the model: 313.245, Cox & Snell R Square value: 0.155, Nagelkerke R Square value: 0.208, and goodness-of-fit (Hosmer and Lemeshow test) $\chi2$=14,237 and p=0.076 was found (p<0.001). The formula of the developed model is given below.

Formula for the detection of fibrosis ≥3:

$$FIB4u = \frac{1}{1 + e^{-(-1,456 + 0,534xFIB - 4 + 1,535xmicrolobulation\ \ in\ liver + 0,897xhepatosteatosis\ in\ liver)}}$$

The effects of ultrasound findings were examined in order to improve the diagnostic performance of APRI, GUCI and FIB-4 indices also for Ishak Fibrosis score ≥5 (F≥5). Analysis revealed that APRI and GUCI indices were not significant in detecting Fibrosis score ≥5 (Respectively; p=0.082, p=0.087). Therefore, model development was not carried out. FIB-4 index had a significant effect on the detection of Fibrosis score ≥5 (p<0.001), but the microlobulation status in the liver did not have a significant effect on the model (p=0.191). Therefore, a new model could not be developed to improve the performance of the FIB-4 index for fibrosis score ≥5 (Table 7).

**Table 7. Logistic regression models for Ishak Fibrosis ≥ 5 with indices and ultrasonography findings**

| | Ishak Fibrosis score ≥5 | | | p |
|---|---|---|---|---|
| | ß coefficient | SE | Odds | |
| APRI | 0.120 | 0.069 | 1.128 | 0.082 |
| Liver microlobulation | 1.411 | 0.639 | 4.100 | 0.027 |
| Sabit | -2.365 | 0.245 | 0.094 | <0.001 |
| GUCI | 0.105 | 0.062 | 1.111 | 0.087 |
| Liver microlobulation | 1.395 | 0.639 | 4.036 | 0.029 |
| Sabit | -2.349 | 0.242 | 0.095 | <0.001 |
| FIB-4 | 0.561 | 0.112 | 1.753 | <0.001 |
| Liver microlobulation | 0.880 | 0.673 | 2.410 | 0.191 |
| Sabit | -3.647 | 0.416 | 0.026 | <0.001 |

SE: Standart error, APRI: AST / Platelet Ratio Index, GUCI: Göteborg University Cirrhosis Index, FIB-4: Fibrosis 4 Index.

## Roc Curve Analysis Evaluation for Fibrosis

The indices with the highest AUC values for the detection of intermediate and advanced stages of fibrosis (≥3) from higher to lower stages were respectively: FIB4u 0.760 (95% CI: 0.702-0.818), p<0.001; FIB-4 (0.753 (95% CI: 0.694-0.812), p<0.001; GUCI 0.676 (95% CI: 0.611-0.741), p<0.001; and APRI 0.667 (95% CI: 0.601-0.732), p<0.001. FIB-4 and FIB4u indices performed significantly higher AUC values than APRI and GUCI indices (respectively; p=0.001, p=0.003). Threshold values were determined as 0.515 for APRI, 0.365 for GUCI, 1.965 for FIB-4, and 0.456 for FIB4u (Table 8).

The AUC values of indices for detection of advanced stage of fibrosis (≥5) are respectively: FIB-4 0.818 (95% CI: 0.748-0.889), p<0.001; GUCI 0.774 (95% CI: 0.699-0.849), p<0.001; APRI 0.771 (95% CI: 0.696-0.846), p<0.001; and FIB4u 0.770 (95% CI: 0.677-0.862, p<0.001. In the examination, it was seen that the indices were not significantly superior to each other in the diagnosis of advanced stage of fibrosis (p>0.05).

The threshold values for APRI was 0.745, GUCI was 0.905, FIB-4 was 2.080 and FIB4u was 0.459 (Table 8).

The ROC curves of the APRI, GUCI, FIB-4 and FIB4u indices for fibrosis stages ≥3 and ≥5 are shown in Figure 1 and Figure 2.

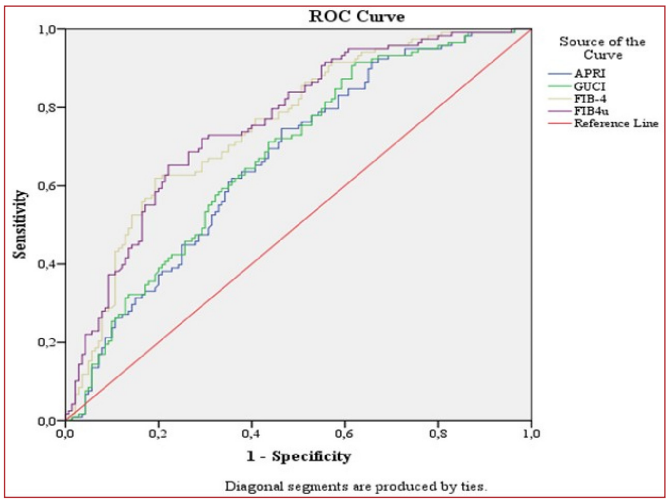


**Figure 1.** ROC curve for differentiation of fibrosis stage<3 and ≥ 3 distinction

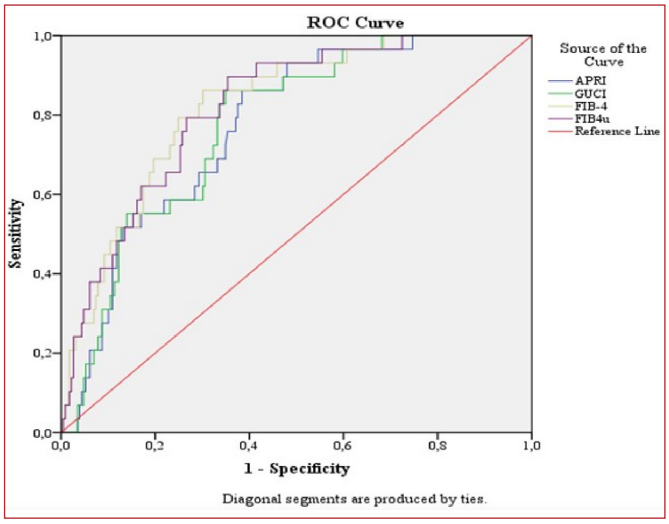


**Figure 2.** ROC curve for differentiation of fibrosis stage<5 and ≥5

The performances of the indices for fibrosis ≥3 and ≥5 distinctions were compared with each other. FIB-4 and FIB4u were found to be superior to other indices in detecting fibrosis ≥3. Compared to each other, they were not superior to each other. None of them were found to be superior to the other in detecting of fibrosis stage≥5 (Table 9).

**Table 8. ROC curve analysis findings of indices for ≥ 3 and ≥ 5 fibrosis distinction**

| | AUC (%95 CI) | Cut-off value | Sensitivity | Specificity | Positive predictive value | Negative predictive value |
|---|---|---|---|---|---|---|
| APRI | | | | | | |
| Fibrosis ≥3 | 0.667 (0.601-0.732) | 0.515 | 0.737 | 0.532 | 0.569 | 0.708 |
| Fibrosis ≥5 | 0.771 (0.696-0.846) | 0.745 | 0.862 | 0.613 | 0.219 | 0.972 |
| GUCI | | | | | | |
| Fibrosis ≥3 | 0.676 (0.611-0.741) | 0.365 | 0.915 | 0.379 | 0.554 | 0.841 |
| Fibrosis ≥5 | 0.774 (0.699-0.849) | 0.905 | 0.862 | 0.646 | 0.236 | 0.974 |
| FIB-4 | | | | | | |
| Fibrosis ≥3 | 0.753 (0.694-0.812) | 1.965 | 0.619 | 0.809 | 0.703 | 0.698 |
| Fibrosis ≥5 | 0.822 (0.752-0.893) | 2.080 | 0.862 | 0.700 | 0.266 | 0.976 |
| FIB4u | | | | | | |
| Fibrosis ≥3 | 0.760 (0.702-0.818) | 0.456 | 0.653 | 0.773 | 0.706 | 0.727 |
| Fibrosis ≥5 | 0.818 (0.748-0.889) | 0.459 | 0.897 | 0.643 | 0.241 | 0.980 |

ROC: receiver operating characteristic, AUC: Area Under Curve, CI: confidence interval; APRI: AST / Platelet Ratio Index, GUCI: Goteborg University Cirrhosis Index, FIB-4: Fibrosis 4 İndex, FIB4u: Fibrosis 4 İndex-Ultrasonography,

**Table 9. Comparison of the performances of the indices for ≥ 3 and ≥ 5 fibrosis distinction**

| | Fibrosis ≥3 (p) | Fibrosis ≥5 (p) |
|---|---|---|
| APRI - GUCI | 0.058 | 0.581 |
| APRI - FIB-4 | 0.001 | 0.159 |
| APRI - FIB4u | 0.001 | 0.280 |
| GUCI - FIB-4 | 0.003 | 0.170 |
| GUCI - FIB4u | 0.003 | 0.306 |
| FIB-4 - FIB4u | 0.672 | 0.852 |

APRI: AST / Platelet Ratio Index, GUCI: Göteborg University Cirrhosis Index, FIB-4: Fibrosis 4 Index, FIB4u: Fibrosis 4 Index-Ultrasonografi.

## DISCUSSION

In our study, a positive correlation was found between the age of the patients and the stage of fibrosis. It was consistent with the literature. We did not find a statistically significant difference between gender and fibrosis when we analyzed their relationship. Similarly, in the study of 304 chronic HBV patients by Saglam et al.8, there was a significant correlation between age and fibrosis, but no correlation between gender and fibrosis.

In our study examining the correlation between Ishak fibrosis scores and laboratory results, we discovered that leukocytes, neutrophils, platelets, and albumin values decreased as the Ishak fibrosis score increased. In contrast, the values for urea, AST, ALP, GGT, PTZ, INR, total and direct bilirubin increase simultaneously.

It is known that ALT and AST rise in the blood in liver damage. Nevertheless, the threshold values for determining the extent of damage are unclear. It has been reported in the literature that as fibrosis progresses, AST clearance decreases, and with concurrent mitochondrial injury, AST levels rise significantly more than ALT levels.[9] Similar to our research, we discovered a positive correlation between the stage of fibrosis and AST in other published study.[10]

Gamma-glutamyl transpeptidase is an enzyme found in the microsomes of hepatocytes and gall bladder epithelium. Elevated levels of GGT are observed in liver, gall bladder, and pancreatic disorders. Eminler et al.[11] in a study conducted with 246 HBV and 151 HCV patients in 2014, stated that GGT was found to be significantly higher in patient groups with significant hepatic fibrosis. Saglam et al.[8] also stated in their study that GGT was higher in patients with significant fibrosis. Similar to the studies we mentioned, we found a statistically significant positive correlation between the increase in fibrosis score and the increase in GGT levels.

Studies have reported that with the increase in fibrosis in the liver, there is a decrease in thrombopoietin production in hepatocytes and as a result thrombocytopenia develops.[12] In a study by Iacobellis et al.[13] in 1143 chronic HCV patients, the platelet level threshold value <140,000/mm3, has a high sensitivity in demonstrating cirrhosis. In a study conducted by Aygün et al.[14] with 140 HBV patients, it was stated that the platelet counts were significantly lower in patients with high fibrosis degree compared to those with low fibrosis. Karasu et al.[15] in a study conducted on 519 HBV and 265 HCV patients, excluded patients with splenomegaly and reported that platelet level was negatively correlated with fibrosis stage in chronic hepatitis patients, independent of splenic sequestration. In our study, we found that platelet level was also negatively correlated with fibrosis.

It is known that alkaline phosphatase is significantly increased in biliary tract diseases. Lun-Gen Lu et al.[16] reported that high ALP levels may also be associated with fibrosis in the liver in their study of 200 patients with chronic liver failure. Aygün et al.[14] on the other hand, stated that there was no significant relationship between ALP level and fibrosis staging. In our investigation, a positive correlation was found between the level of ALP and the stage of fibrosis. Although concurrent biliary tract pathology is not observed on scanned US, we cannot make a meaningful generalization because this has not been investigated with more sensitive techniques.

The mean scores of the APRI, GUCI and FIB-4 indices calculated in our study were significantly higher in the patients with high fibrosis scores. In 2003, Chun-Tao Wai et al.[17] reported that the APRI score, which they devised using liver biopsy data and laboratory results of 192 chronic HCV patients, could predict significant fibrosis (≥F3) in 51% of cases and cirrhosis (≥F5) in 88% of cases. In the study, the AUROC value of the APRI score for predicting substantial fibrosis (≥F3) was 0.88 and for predicting cirrhosis (≥F5) was 0.94. Similar results were found for cirrhosis in patients with chronic HBV infection. The AUROC values for the APRI score in considerable fibrosis and cirrhosis were 0.81 and 0.83, respectively, according to a study by Xia Zhu et al.[18] that examined the relationship between liver biopsies and APRI scores in HBV patients. In our study, the AUROC values of the APRI score were found to be 0.66 for F≥3 and 0.77 for F≥5. The AUROC values of the APRI score in our study were found to be lower in demonstrating fibrosis when compared to other studies.

Another index that can be used to predict fibrosis and cirrhosis is GUCI. Islam et al.[19] created the GUCI as a consequence of a study that was carried out in 2004 with 179 chronic HCV patients. In a 2009 study involving 68 chronic HCV patients, Kandemir et al.[20] found that the GUCI score distinguished between stages 3-4 and 1-2 with a high degree of precision. In our study, the AUROC values of the GUCI score were found to be 0.67 for F≥3 and 0.77 for F≥5.

The Fibrosis-4 Index was developed by Sterling et al.[21] in 2006 to predict liver fibrosis in HCV-HIV co-infected patients. The AUROC of the FIB-4 index was found to be 0.76 in estimating fibrosis stage≥4. In the study of Vallet et al.[22] in which they examined liver biopsy results and FIB-4 indices of 847 HCV patients; AUROC values of the FIB-4 index in patients with significant fibrosis (F3-F4) and cirrhosis were reported as 0.85 and 0.91, respectively. In this study, it was reported that the FIB-4 index accurately predicted 847 liver biopsies with a rate of 72.8%. In the study of Xia Zhu et al.[18] in which HBV patients (n=175) were examined the AUROC values for the FIB-4 score in significant fibrosis and cirrhosis were found to be 0.86 and 0.77, respectively. The World Health Organization also recommends the use of the FIB-4 index in the follow-up of chronic HBV patients.[23] In our study, the AUROC value of the FIB-4 index for F≥5 was found to be 0.82, and AUROC values were similar to the studies in the literature.

FIB-4, GUCI and APRI scores were significantly higher in patients with significant liver fibrosis (F≥3). When we performed logistic regression analysis on patients with F≥3 and added ultrasonography findings to the FIB4 index, we created a new model that substantially predicts fibrosis. Although the presence of microlobulation in the liver did not have a statistically significant contribution to the model, it contributed positively to the model. For this reason, we

included microlobulation together with hepatosteatosis in the new model named FIB4u. For the newly developed FIB4u index in patients with F≥3, the mean AUROC value was 0.76. Although we found the most successful AUROC value for FIB4u in predicting F≥3 fibrosis stage, there was no statistically significant difference between the performances of FIB-4 (0.75). In addition the performances of FIB-4 and FIB4u were significantly superior to APRI and GUCI for F≥3.

## CONCLUSION

Upon analysis of the data obtained from our investigation, it has been determined that the FIB4u index exhibits promising potential for utilization in the prediction of fibrosis. It demonstrates comparable efficacy to other authorized indices now in use. Nevertheless, in order to ensure widespread utilization, it is imperative that further validation of this approach be conducted using cohorts comprising bigger patient populations. The study is limited by its retrospective design and the limited sample size of patients. In conclusion, it is necessary to conduct bigger prospective studies, incorporating elastography, in order to establish more accurate combined noninvasive indices for the identification of fibrosis.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

The study was carried out with the permission of Trakya University Faculty of Medicine Scientific Researches Ethics Committee (Date: 10.08.2020, Decision No: 12/10).

### Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

### Referee Evaluation Process

Externally peer-reviewed.

### Conflict of Interest Statement

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

### Financial Disclosure

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### Author Contributions

All of the authors declare that they have all participated in the design, execution and analysis of the paper and that they have approved the final version.

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Original Article

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# Assessing the impact of internal carotid artery stenosis on choroidal thickness using cirrus optical coherence tomography

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## ABSTRACT

**Aims**: The choroid, one of the body's most highly vascularized tissues, receives its blood supply from the ophthalmic and posterior ciliary arteries, which stem from the internal carotid artery. The utilization of spectral-domain optical coherence tomography (SD-OCT) for both qualitative and quantitative assessment of the retina is increasing. The recent introduction of enhanced depth imaging OCT (EDI-OCT) has offered a novel approach to evaluate the choroid using commercially accessible SD-OCT devices. EDI-OCT enables the in vivo examination and measurement of the choroid. The main objective of our study is to evaluate choroidal thickness using EDI-OCT in patients with unilateral significant carotid stenosis; the secondary objective is to observe whether hemodynamic changes affect choroidal thickness.

**Methods**: The study is prospectively designed as a cross-sectional, controlled, and single-blind study, encompassing patients who underwent neck computed tomographic angiography within a one-year period due to any disease. Included patients had carotid stenosis of 50% or more on one side and less than 50% on the other side. The eyes on the side with higher carotid stenosis constituted the study group, while the other side formed the control group. Anterior and posterior segment examinations of the patients, visual acuity according to Snellen Chart, and choroidal thickness were measured.

**Results**: A total of 30 eyes of 15 patients were evaluated. Of the patients included in the study, 9 were men and 6 were women; the average age was 67.9 years (49-85). In the study group, the average choroidal thickness measurements were 211 µm in the nasal, 221 µm in the central and 209 µm in the temporal; in the control group, they were measured as 223 µm in the nasal, 243 µm in the central, and 231 µm in the temporal, respectively. Despite the choroidal thickness being thinner in the study group, the difference did not reach statistical significance.

**Conclusion**: Additional research is required to pinpoint the factors contributing to the dynamics of choroidal thickness and to delineate its significance in carotid artery stenosis more comprehensively.

**Keywords**: Choroidal thickness, internal carotid artery stenosis, optical coherence tomography.

## INTRODUCTION

The choroid, renowned as one of the body's most extensively vascularized tissues, is nourished by the ophthalmic and posterior ciliary arteries, originating from the internal carotid artery (ICA).[1]

The use of spectral-domain optical coherence tomography (SD-OCT) for assessing the retina, both qualitatively and quantitatively, is increasing. The recent integration of enhanced depth imaging OCT (EDI-OCT) has brought a new approach to evaluating the choroid using SD-OCT devices that are readily available on the market. EDI-OCT enables the live examination and measurement of the choroid.[2,3] The main objective of our study is to evaluate choroidal thickness using OCT in patients with unilateral significant ICA stenosis; the secondary objective is to observe whether hemodynamic changes affect choroidal thickness.

## METHODS

Written informed consent was obtained from all patients included in the study and the study adhered to the tenets of the Declaration of Helsinki. The study was approved by Ankara Numune Training and Research Hospital Ethics Committee (Date: 07.05.2014, Decision number: E-14-177).

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The research is structured as a prospective, cross-sectional, controlled, and single-blind study, involving individuals who underwent neck computed tomographic angiography over a one-year duration for any medical condition. Included participants exhibited ICA stenosis of 50% or greater on one side and less than 50% on the opposite side. The eyes corresponding to the side with higher ICA stenosis comprised the study group, whereas those on the opposite side constituted the control group. Exclusion criteria were:

1. Patients with diabetes mellitus
2. Patients with additional ocular pathologies (Glaucoma, spherical equivalent refractive error greater than 4, uveitis, age-related macular degeneration, central serous chorioretinopathy)
3. Patients with a history of vitrectomy
4. Patients with a history of ocular surgery within the last 3 months
5. Patients who received intraocular injections within the last 3 months
6. Patients with one phakic and one pseudophakic eye
7. Patients with inadequate measurement quality of choroidal thickness

Medical and ophthalmic background information was gathered from all participants enrolled in the research. Subsequently, the individuals underwent a thorough ophthalmic assessment, which involved assessing Snellen visual acuity, measuring intraocular pressure, examining the anterior segment with biomicroscopy, and conducting fundoscopy following.

In all participants, SD–OCT scans were conducted using the Cirrus Spectral Domain OCT (Carl Zeiss Meditec Inc.). The chosen scan pattern was the HRD Single Line Raster with the EDI acquisition mode, facilitating detailed choroidal imaging. Exclusion criteria included images with a signal strength ≤9. To minimize potential diurnal variations in choroidal features, EDI-OCT scans were performed between 9 am and 1 pm. Choroidal thickness was assessed as the vertical distance between two hyperreflective lines: one corresponding to the retinal pigment epithelium and the other to the inner surface of the sclera. Measurements were taken centrally at the subfoveal position and at 1,000 µm nasal and temporal to the fovea, only when the border between the choroid and sclera was clearly discernible. Images where choroidal borders were indistinct were excluded from the study cohort.

### Statistical Analysis

All statistical analyses were performed using SPSS 25.0 program. The distribution of the data will be assessed with the Kolmogorov-Smirnov test. Descriptive statistics will be used for demographic data; for measurements showing normal distribution, Student's t-test will be used, and for measurements not showing normal distribution, the Mann-Whitney U test will be conducted. A p-value of less than 0.05 will be considered significant.

## RESULTS

Totally 30 eyes of 15 patients who underwent computed tomographic angiography and diagnosed as a unilaterally significant ICA stenosis (one-side 50% and >50% stenotic, the other-side <50% stenotic) evaluated in this study. The mean age of the patients was 67.9±11.4. None of the patients had a history of amaurosis fugax. The mean best-corrected visual acuity (BCVA) measured with the Snellen chart was 0.747±0.29 (minimum: 0.3, maximum: 1) for the study group and 0.840±0.22 (minimum: 0.4, maximum: 1) for the control group. For statistical analysis, BCVA measured with the Snellen chart was converted to LogMAR. After conversion, the mean BCVA was 0.16±0.19 for the study group and 0.11±0.14 for the control group. No statistically significant difference was observed between the groups in terms of BCVA (p=0.346). The mean choroidal thickness values of the study and the control groups were 221.27±66.93 µm and 243.07±72.62 µm for the central area; 209.93±65.64 µm and 231.27±66.11 µm for the temporal area; and 211.73±70.44 µm and 223.01±73.77 µm for the nasal area. The values in the study group were lower than those in the control group; however, this difference was statistically nonsignificant (p=0.401 for central, p=0.383 for temporal, p=0.669 for nasal) (**Table**).

**Table. Mean choroidal thickness and best corrected visual acuity values between the control and study groups**

| | Study group Mean±SD | Control group Mean±SD | p |
|---|---|---|---|
| Nasal CT (µm) | 211.73±70.44 | 223.01±73.77 | 0.669 |
| Central CT (µm) | 221.27±66.93 | 243.07±72.62 | 0.401 |
| Temporal CT (µm) | 209.93±65.64 | 231.27±66.11 | 0.383 |
| BCVA (LogMAR) | 0.167±0.19 | 0.107±0.14 | 0.346 |

CT: Choroidal thickness, BCVA: Best corrected visual acuity

## DISCUSSION

The ophthalmic artery, deriving from the ICA, serves as the main source of blood for the long and short posterior ciliary arteries, which are crucial for choroidal perfusion. Therefore, stenosis of the ICA could potentially affect the choroid.[4]

The utilization of SD-OCT for qualitative and quantitative assessment of the retina is on the rise. The recent introduction of EDI-OCT has provided a new avenue for evaluating the choroid using commercially available SD-OCT devices. EDI-OCT allows for the in vivo examination and measurement of the choroid.[2,3]

In this research, individuals who underwent neck computed tomographic angiography and exhibited ICA stenosis of 50% or more on one side and less than 50% on the opposite side were assessed. Despite similar anterior/posterior segment examinations and best-corrected visual acuities determined by Snellen Chart in both eyes of the participants, the study group displayed decreased choroidal thickness values compared to the control group, which is not statistically significant.

Sezgin Akcay et al.[5] investigated 21 patients with over 70% stenosis in the ICA on one side and less than 70% stenosis on the opposite side. They observed a subfoveal choroidal thickness of 231 µm on the stenotic side and 216 µm on the other side. Their hypothesis suggests that the increased subfoveal choroidal thickness on the stenotic side might be a consequence of compensatory dilatation of the choriocapillaris, aiming to mitigate ischemia resulting from reduced blood flow due to ICA stenosis.[5] While it's challenging to elucidate the reasons behind these findings diverging from our study, there are also studies in the literature that corroborate our findings.

Rabina et al.[6] observed no notable distinction in choroidal thickness between patients with ICA stenosis and controls. Sayin et al.[4] in a comparison between the eyes of 25 individuals with ICA stenosis and 25 age- and gender-matched healthy subjects, noted a reduction in choroidal thickness within the study group. In another study, Wang et al.[7] conducted a

retrospective analysis of 219 patients with severe unilateral ICA stenosis, revealing a significantly diminished mean subfoveal choroidal thickness in the ICA stenosis group compared to normal eyes. They proposed that ICA stenosis might impede the blood flow in the posterior ciliary arteries, leading to inadequate perfusion of the choriocapillaris.

Various conditions and illnesses, such as age related macular degeneration and myopia resulting in a thinner choroid, or polypoidal choroidal vasculopathy leading to a thicker choroid, can induce alterations in choroidal thickness.[8-11] Noteworthy factors such as axial length, refractive error, gender, and age can influence choroidal thickness.[12-14]

In this study, the choroidal thickness of the eyes of patients with varying degrees of carotid artery stenosis on both sides was examined. Considering the presence of many physiological factors affecting choroidal thickness, comparing the two eyes of the same patient was thought to largely eliminate these factors and minimize the interaction between the factors thereby enhancing the value of the results.

One of the limitations of the study is being a single-center study with a relatively small sample size might have affected the statistical significance of findings. Secondly, in addition to choroidal structural changes, if there were examinations such as doppler ultrasonography for ocular haemodynamic changes, it could make a more detailed contribution. However, using a very special patient group to eliminate additional factors and having both study and control eyes on the same patient are both advantages of the study and reasons for the low number of cases.

In summary, this study reveals that while the choroidal thickness measured by EDI-OCT was found to be lower on the side with ipsilateral carotid stenosis across all temporal, nasal, and central choroidal thickness measurements compared with contralateral eyes, the difference did not reach statistical significance. Despite the presence of significant ICA stenosis, the choroidal thickness can remain within normal ranges. Comprehensive research is required to ascertain the factors influencing choroidal thickness either directly or via compensatory mechanisms.

## CONCLUSION

Additional research is required to pinpoint the factors contributing to the dynamics of choroidal thickness and to delineate its significance in ICA stenosis more comprehensively.

## ETHICAL DECLARATIONS

### Ethics Committee Approval

The study was carried out with the permission of Ankara Numune Training and Research Hospital Ethics Committee (Date: 07.05.2014, Decision number: E-14-177).

### Informed Consent

All patients signed and free and informed consent form.

### Referee Evaluation Process

Externally peer-reviewed.

### Conflict of Interest Statement

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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### Author Contributions

All of the authors declare that they have all participated in the design, execution and analysis of the paper and that they have approved the final version.

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Review

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# Health follow-up visits of children with autism

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## ABSTRACT

Child health follow-up is the most important of basic health services and should continue at regular intervals until the age of 18 years. Physicians' child health follow-up examinations present the best opportunity to deliver evidence-based preventive health services, such as monitoring the growth and development of the child, conducting age-appropriate screenings, providing vitamin/mineral support according to age and requirements, administering childhood vaccinations, informing the family about home accidents and nutrition, monitoring the child in terms of child neglect and abuse risks, and raising the awareness of the family in this regard. Child health follow-up should encompass not only children without any health problems but also those with mental, physical, visual, or hearing impairments, or special needs such as those with autism. Autism spectrum disorder is a neurodevelopmental disorder characterized by social and communication limitations and repetitive, restricted behaviors. The presence of a child with special needs such as autism can have social, psychological, and economic implications for family members. While there are many difficulties in caring for a healthy child, these difficulties increase exponentially in the care of a child with special needs. Professional assistance is necessary for families to address matters such as monitoring the child's development, providing nourishment, and administering vaccinations. Children with autism constitute a group that needs to be closely followed up for vitamin-mineral deficiencies and growth retardation due to their higher risk of malnutrition. For these reasons, regular health follow-up of children with autism is essential at regular intervals.

**Keywords**: Children, follow-up visit, autism

## INTRODUCTION

The primary objective of health services and the principal responsibility of healthcare personnel is to promote and maintain the well-being of individuals, striving to proactively prevent the occurrence of illnesses. Child health follow-up is the most important of the basic health services and should continue at regular intervals until the age of 18 years. Physicians' child health follow-up examinations encompass evidence-based preventive health services, such as monitoring the growth and development of the child, conducting age-appropriate screenings, initiating vitamin and mineral support according to age and requirements, administering childhood vaccinations, and informing the family about home accidents and nutrition, and monitoring the child in terms of child neglect and abuse risks.[1,2]

The concept of well-child follow-up has seen a transformation in recent years, being replaced by child health follow-up, with the recognition of the utmost importance of regularly monitoring not only healthy children but also those with chronic diseases or disabilities. Child health follow-up is a service that involves the monitoring of the growth and development of all children, evaluating their health and disease status, offering preventive medicine practices such as vaccination, age-appropriate nutrition, and protection from accidents, and aims to make families competent in child care. It is every child's natural right to benefit from this service.[3] Therefore, child health follow-up should include not only completely healthy children without any health problems but also those with mental, physical, visual, hearing impairments, and autism, i.e., children with special needs.[2,4]

Autism spectrum disorder (ASD) is a heterogeneous neuropsychiatric disorder characterized by varying degrees of social impairment, problems in communication and behavior, and delayed cognitive development.[5] ASD is defined as a permanent neurodevelopmental disorder that commonly occurs in the first years of life and presents with deficits in social skills, language impairment, and limited interest and behavior. However, these problems may not be fully recognized until the child's capacity falls behind environmental demands.[6,7] The majority of children with ASD have cognitive and linguistic impairments, and this disorder has been associated with known medical, genetic, and environmental factors. There is no medical or biological marker for the diagnosis of this complex disorder, which is divided into different levels of severity.

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Diagnosis is made clinically based on history, observation, and structured tests used in ASD screening and evaluation.[8] In the literature, the prevalence of ASD varies between 1 in 40 and 1 in 500, depending on the methodology used and the population evaluated in previous studies. In a report published in the USA in 2018, the prevalence of ASD was reported to be 1/59. This prevalence has increased across the world, especially since the late 1990s, primarily due to changes in the case definition and increased awareness.[9,10] In Turkiye, the frequency of ASD in children aged 18-30 months has been found to be 1/1,000.[11,12] ASD has been found to be four to six times more common in boys than in girls in studies conducted with clinical samples and two to three times more common in boys in population studies.[13]

Although there is no treatment method that completely normalizes development or functionality in ASD, it is known that evidence-based treatment and intervention programs enable children diagnosed with ASD to achieve developmental and behavioral gains. An individualized treatment plan is required for individuals with ASD and their families. This intervention may vary depending on the age, condition, and additional physical and mental disorders of the child and requires a multidisciplinary approach. Treatment targets specified in the National Institute for Health and Care Excellence 2013 guidelines include reducing the core symptoms of ASD, enabling individuals to reach their potential, treating simultaneous physical and mental illnesses that disrupt the harmony and functionality of the family or the patient, supporting caregivers, and applying education and certain evidence-based treatment methods to individuals with ASD.[14,15] Families play an important and effective role in this entire treatment and intervention process. However, living with a child with special needs such as autism has social, psychological, and economic implications for family members. Parents experience significant stress in adapting to this challenging condition, which hinders their ability to meet the demands of everyday life. While even caring for a healthy child has many difficulties, these difficulties increase exponentially in caring for a child with special needs. Families with children who have special needs require expert assistance in various areas, including their child's growth, dietary requirements, nutritional supplements, and protection from diseases.[16,17]

## NUTRITIONAL STATUS IN AUTISM SPECTRUM DISORDER

Children with ASD exhibit distinct variations in their eating practices in comparison to their typically developing peers. Feeding problems are more common in these children than in healthy children in the first year of life, from the moment they are introduced to complementary foods. Autistic children have difficulty eating and require a significantly higher level of additional parental involvement than their healthy peers.18 Studies evaluating children with ASD highlight nutritional problems such as food rejection, food selectivity, and excessive consumption of a particular food. In addition, research shows that children with ASD are inclined toward consuming certain food groups based on their texture, color, smell, and temperature, and that they frequently exhibit a preference for particular foods while rejecting others.[19,20] Furthermore, gastrointestinal disorders are one of the most common medical conditions associated with ASD. If left untreated, these comorbidities can exacerbate the symptoms of ASD and lead to other associated clinical findings and a poorer quality of life. Therefore, it is important for clinicians to understand how these gastrointestinal problems occur and apply effective treatments.[21] It is considered that along with these complaints, food selectivity and rejection may put the individual at risk of nutritional deficiency. It has been suggested that children with ASD experience many vitamin and mineral deficiencies as a result of their poor intake of daily energy sources, carbohydrates, fats, and protein, as well as their extremely permeable intestines and highly selective diets.[22,23] Another study found that children with autism have a higher rate of food rejection compared to healthy children, resulting in nutritional inadequacies caused by their limited dietary preferences.[24] In addition, nutritional treatments applied to prevent the symptoms of autism, such as gluten-free and casein-free diets, may cause vitamin and mineral deficiencies.[25,26] Research conducted on children with autism generally indicates low whole blood, serum, and plasma levels of pantothenic acid, folate, biotin, vitamin B12, vitamin D, and vitamin E in this group.[22,25] While vitamin D insufficiency is prevalent among children with ASD, for whom regular prophylaxis is recommended, there are only limited studies on the effect of vitamin D in the treatment of ASD.[27] In a case report by Jia et al.[28] a 32-month-old infant diagnosed with ASD was administered 150,000 IU of vitamin D intramuscularly every month and 400 IU of oral vitamin D daily. The results of the study showed a significant increase in the serum 25(OH) D level and significant improvements in scale scores. Another study evaluated the relationship of vitamin D status and vitamin D deficiency with autism severity. Vitamin D deficiency was observed in 57% of the participants (n=122), and vitamin D insufficiency was detected in 30%. Approximately 81% of children who received vitamin D supplements at the treatment dose for three months exhibited improvement in ASD scales measuring behavior, eye contact, and attention span.[29]

For all the reasons discussed above, children with autism are at risk of malnutrition and constitute a group that needs to be closely followed up in terms of vitamin-mineral deficiencies and growth retardation due to malnutrition. A review of the literature shows that a multitude of treatment approaches have been attempted in relation to nutritional support. These treatment approaches generally include special diets and nutritional supplements. Special diets include the gluten- and casein-free diet, ketogenic diet, specific carbohydrate diet, Feingold diet, and candida body ecology diet. Nutrient supplements include fatty acid supplements (omega-3 fatty acids), multivitamin supplements, mineral supplements (zinc), and probiotics.[30-32] The preference of these special diets and supplements may differ among individuals with ASD, and there is ongoing debate regarding their potential benefits. Therefore, families with children who have autism require more professional support on nutrition and vitamin and mineral supplements, which are key aspects of child health follow-up.

## IMMUNIZATION IN AUTISM SPECTRUM DISORDER

Vaccination is a public health service that saves the lives of millions of individuals in developed countries.[33] According to data from the World Health Organization (WHO), vaccination is a crucial preventive public health service that saves the lives of two to three million children every year, and it is projected that by enhancing global vaccination efforts, an additional 1.5 million children's deaths can be prevented.[34] The success of

vaccination strategies depends on societies' perceptions of the benefits or risks of vaccines and, thus, their trust in vaccination. In this context, one of the major sources of hesitation has been the debate about whether vaccines cause autism. Research published by Wakefield et al.[35] in the Lancet in 1998 suggested a relationship between the measles, mumps, and rubella (MMR) vaccine administered during infancy and autism, resulting in changes in parental behavior regarding MMR vaccination and a decrease in trust in healthcare providers. This publication was later retracted from the Lancet, and Andrew Wakefield, the principal researcher, was banned from practicing medicine due to the methodology problems in the study, such as the inclusion of only 12 non-randomly selected children and the involvement of some families in a lawsuit against vaccine companies, as well as his subsequent attempts to market his own mumps vaccine.[36] A 2014 meta-analysis evaluated 10 observational studies of childhood vaccines, including five cohort studies or five case-control studies. No correlation was detected between the MMR vaccine and autism in any of the two cohort studies and four case-control studies that explicitly investigated the association between the MMR vaccine and autism.[37] Across various international studies investigating the potential link between MMR vaccination and autism, no evidence was found to support a correlation between MMR vaccination and the rise in autistic cases. A nationwide cohort study was conducted in all children born between January 1, 1999, and December 31, 2010, in Denmark to evaluate whether the MMR vaccine increased the risk of autism in children during the post-vaccine period. The study initially included 663,236 children born to Danish mothers who were followed up during this period, but 5,775 children were excluded from follow-up. During follow-up, 6,517 children were diagnosed with autism (incidence: 129.7/100,000 person-years). The risk of autism did not increase in those who received or did not receive the MMR vaccine. In addition, no correlation was found between the time of vaccination and the development of autism in autistic children. Covering 6517 cases, that study is the largest single-center study to date and considerably enhances our knowledge on this subject.[38] In a similar national study conducted in 2003, 467,450 Danish children were vaccinated with the thiomersal-containing pertussis vaccine or a thiomersal-free formulation of the same pertussis vaccine and detected no association between thiomersal content and autism.[39] Thiomersal is widely recognized as the best vaccine preservative, primarily used in multi-dose non-live vaccine vials, due to its antiseptic and antifungal properties.[40] It is metabolized to the compound ethylmercury and is used in concentrations corresponding to 12.5-50 μg per vaccine dose. Concerns about mercury accumulation from childhood vaccination schedules and other sources led to the replacement of thiomersal-containing vaccines with thiomersal-free formulations in many high-income countries in the 1990s and early 2000s. All mercury compounds are neurotoxic when exposed to high doses, but most concerns about thiomersal-containing vaccines are based on experience with methylmercury, a different organic mercury compound with known neurotoxic effects. Humans are commonly exposed to methylmercury through fish consumption, and there is abundant evidence that fetal exposure, particularly through fish consumption during pregnancy, leads to adverse effects on neurodevelopment. Furthermore, ethylmercury has different pharmacokinetic properties than methylmercury. The half-life of ethylmercury (less than 1 week) is shorter than that of methylmercury (1.5 months), meaning that blood exposure to the former is relatively short-term. Ethylmercury is also rapidly excreted through the digestive system.[41,42] Thiomersal has a proven track record of effectiveness and safety. Although thiomersal has been removed from routinely used childhood vaccines in most high-income countries as a precautionary measure, it nevertheless serves a crucial function as a potent preventative agent, guaranteeing millions of individuals across the world access to vaccines that are free from contamination. It is also noteworthy that in countries where thiomersal has been excluded from childhood vaccines, the prevalence of neurodevelopmental disorders such as autism continues to rise.[43]

While concerns about thiomersal have begun to decrease due to the statements made by international authorities and the removal of thiomersal from many vaccines in use, aluminum adjuvanted vaccines have emerged as a fresh subject of debate. Aluminum is widely found in the environment and is a component of many consumer products, including antacids, skin astringents, and antiperspirants. Since the early 20th century, aluminum oxide has been used as an adjuvant to enhance immune responses to vaccines in various forms, including hydroxide and soluble salts.44 The mechanism of action of aluminum is complex and involves the direct stimulation of multiple immune receptors, thereby enhancing the body's innate immune response to the antigen. Concentrations of aluminum vary among vaccines. The diphtheria-tetanus vaccine contains 1.5 mg of aluminum phosphate per dose, although it is not present in the MMR vaccine, which is a live vaccine.[45] Many studies in the literature have shown no risky levels of aluminum compounds in the blood or hair of children who have received vaccines containing aluminum adjuvants.[46,47] The Global Advisory Committee on Vaccine Safety, a scientific advisory body of the WHO, stated in a report published in June 2012 that there is no scientific evidence supporting a relationship between thiomersal-containing and aluminum adjuvant vaccines and autism.[48]

Gaining further insight into concerns surrounding vaccines among families of individuals with autism and the underlying reasons can inform the development of optimal vaccination strategies. Both practitioners and individuals should engage in informative activities that are grounded in scientific data. It is crucial to effectively manage these processes to access accurate information. It is also necessary to base our actions on objective data rather than relying on prejudices or presuppositions.

## AUTISM AND CHILD NEGLECT-ABUSE

According to the WHO, 1/4 of adults are physically abused as children, 1/5 of women and 1/13 of men are exposed to sexual abuse during childhood, and 31,000 children under the age of 15 years die due to child abuse every year across the world.[49] The Child Abuse and Domestic Violence Research in Turkiye showed that in school and family environments, 43% of children aged seven to 18 years were physically abused, 51% were emotionally abused, and 3% were sexually abused, while a total of 681,000 children were victims of some type of neglect or abuse.[50] It is very important that children with autism who cannot protect themselves and cannot clearly explain the incident to others due to their mental and motor development are protected from individuals who may exploit their vulnerability and their possible acts of abuse. The most important basis for preventing this situation and

safeguarding children against these acts is to determine their parents' awareness of abuse.[51] It is considered that determining parents' awareness of abuse will form the basis for understanding their thoughts and attitudes concerning potential abuse before it occurs, as well as their responses following the abuse. Clarifying the relationship between ASD and abuse and parents' views on this issue will form the cornerstone of abuse prevention to be provided for parents. In this regard, increasing parents' awareness of this issue is important in terms of both effectively identifying the situation and intervening at an early stage.[49]

## CONCLUSION

It is important to conduct regular health follow-up visits for children with autism, particularly when there are concerns regarding vaccination, malnutrition, growth retardation, neglect, and abuse. It should not be forgotten that child health follow-up includes not only completely healthy children without any health problems but also those with mental, physical, visual, or hearing impairments and autism, i.e., children with special needs.

## ETHICAL DECLARATIONS

### Referee Evaluation Process

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All of the authors declare that they have all participated in the design, execution and analysis of the paper and that they have approved the final version.

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KASTAMONU MEDICAL JOURNAL

Case Report

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# A rare coronary anomaly: the right coronary artery originating from the left anterior descending artery

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## ABSTRACT

Coronary artery anomalies are structural variations which are usually detected incidentally as a result of coronary angiographies. Clinically, they are usually asymptomatic. The prevalence of the coronary anomalies was detected to be 1.3% in patients undergoing coronary angiography. Among coronary artery anomalies; the anomaly in which all coronary arteries are originating from a single coronary is called the single coronary artery (SCA). Among the single coronary artery anomalies; the right coronary artery (RCA) originating from the left anterior descending artery (LAD) is an even rarer condition with a rate around 0.009%. In this anomaly, while the RCA usually originates from the left main coronary artery (LMCA), it may also rarely be seen as a branch of the LAD.

**Keywords**: Coronary anomaly, right coronary artery, anjiography

## INTRODUCTION

Coronary artery anomalies are structural variations that are usually detected incidentally as a result of coronary angiographies. Clinically, they are generally asymptomatic. The prevalence of coronary anomalies was seen to be 1.3% in patients undergoing coronary angiography.[1,2] Among coronary artery anomalies, the anomaly in which all coronary arteries originate from a single coronary is called the single coronary artery (SCA). Among the single coronary artery anomalies, the right coronary artery (RCA) arising from the left anterior descending artery (LAD) is an even rarer condition with a rate of around 0.009%. In this anomaly, while the RCA usually originates from the left main coronary artery (LMCA), it may also rarely be seen as a branch of the LAD.[3,4]

## CASE

A 46-year-old male patient presented with chest pain and was referred to our hospital due to elevated troponin levels. Chest pain is typical, and the patient applied to the hospital in the 5$^{th}$ hour of the pain. The patient had no known history of chronic disease. The patient had no familial history of coronary artery disease (CAD) or sudden cardiac death. Smoking was the only risk factor for CAD. In the physical examination, the patient's vital signs were typical, with no anomalies in the electrocardiography. In the coronary angiography performed via the left radial artery, the left main coronary artery (LMCA) was observed to be expected, and the right coronary artery (RCA) was observed to originate from the left anterior descending artery after the first septal artery (S1) (**Figure 1**). A 50-60% stenosis was observed in the LAD at the level from which RCA arises, a stenosis of 70% in the distal section of the LAD, and a stenosis of 60% in the first diagonal (D1) artery. A stenosis of 99% was observed at the circumflex artery (CX)-OM1 level. A stenosis of 60% was observed in the RCA trunk. The lesion in the CX artery was considered the culprit lesion. Primary percutaneous coronary intervention (PCI) was decided to be performed for CX and operation for the other coronary arteries. A drug-eluting stent (DES) with a size of 2.25x18 mm was implanted in the lesion in the CX artery. Coronary CT angiography was taken to evaluate the course of the coronary arteries. No artery was originating from the right coronary cusp (**Figure 2**). During the follow-up, the patient had no active complaint with a stable general status and was discharged with recommendations for operation.

## DISCUSSION

The coronary anomaly in which the RCA originates from the LAD is extremely rare. When it does, it is usually from the proximal LAD, which was the case in our patient.[3,4] The RCA has two courses after arising from the LAD. In one of them, it courses through the posterior side of the aorta; in the other, it runs through the anterior side of the pulmonary artery.[3-5] While there have been 2 cases in which the RCA has a retro-aortic course in the literature so far, the RCA courses through the anterior side of the pulmonary artery in the other cases.

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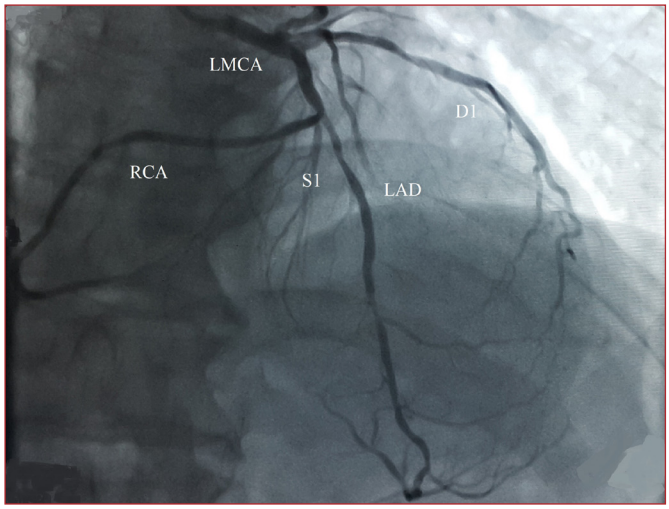


**Figure 1.** RCA originating after the first septal perforating artery in the image taken using anteroposterior projection and cranial angulation.

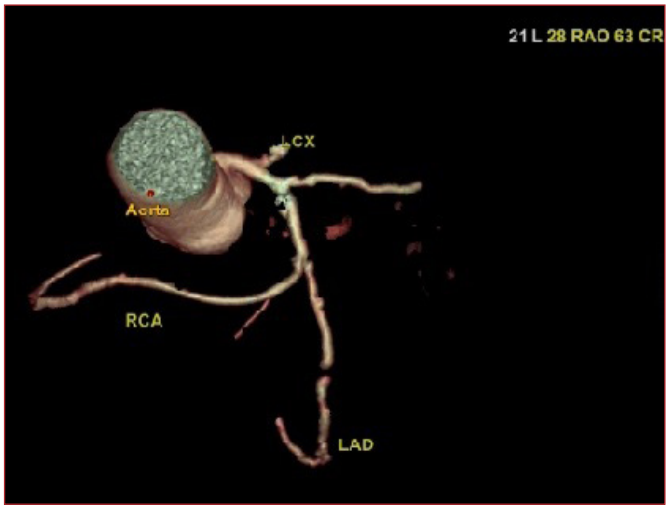


**Figure 2.** RCA originating from LAD in the coronary computerized tomography angiography image.

Since large vessels cause external compression to the coronary artery, the anomalies in which the RCA originates from the LMCA and courses between the aorta and pulmonary arteries might be considered as one of the reasons for sudden cardiac death at a younger age.[6,7] While our patient had no known risk factors except tobacco use, he had generalized atherosclerosis. Although it has been stated that a single coronary artery anomaly is associated with an increased risk of atherosclerosis in several studies in the literature, such an association could not be demonstrated in others.

## CONCLUSION

While coronary artery anomalies are rare, the anomaly in which the RCA originates from the proximal LAD is even more occasional. When it does, it usually stems from the LAD after the first septal perforating artery (S1) and courses through the anterior side of the pulmonary conus, as in our patient.[7,8]

## ETHICAL DECLARATIONS

### Informed Consent
All patients signed and free and informed consent form.

### Referee Evaluation Process
Externally peer-reviewed.

### Conflict of Interest Statement
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### Author Contributions
All of the authors declare that they have all participated in the design, execution and analysis of the paper and that they have approved the final version.

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KASTAMONU MEDICAL JOURNAL

Clinical Image

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# Acute concurrent bilateral internal carotid artery occlusion: a teaching clinical image

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## ABSTRACT

Acute bilateral internal carotid artery (ICA) occlusion is a rare stroke syndrome presenting with acute coma, and patients usually have preserved brainstem function on initial examination. In this clinical image, we report a case of acute concurrent bilateral ICA occlusion. Acute bilateral ICA occlusion is an unusual entity with a poor outcome. It can mimic metabolic encephalopathies and posterior circulation infarcts and can be differentiated by careful evaluation of brainstem functions.

**Keywords**: Coma, bilateral carotid artery occlusion, stroke

## INTRODUCTION

Acute bilateral internal carotid artery (ICA) occlusion is a rare stroke syndrome presenting with acute coma, and patients usually have preserved brainstem function on initial examination.[1,2] In this clinical image, we report a case of acute concurrent bilateral ICA occlusion.

## CLINICAL IMAGE

A 77-year-old male patient with a past medical history of uncontrolled hypertension, previous ischemic stroke, and no ICA agenesis or occlusion was detected in previous examinations, was admitted to the emergency department with sudden onset coma. His last known well time was 16 hours before the admission. The neurological examination of patient at the emergency department showed minimal motor extension response to central pain, Decorticated postur, bilateral Babinski sign, and intact brainstem reflexes. The patient was electively intubated before admission due to vomiting-related aspiration. Electrocardiography (ECG) showed atrial fibrillation. Brain computer tomography (CT) scan revealed bilateral hyperdense middle cerebral arteries (A). Subsequently planned CT angiography demonstrated bilateral internal carotid artery (ICA) occlusion (B) and brain magnetic resonance diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) map showed an area of diffusion restriction in the bilateral ICA territory (C and D). Due to the delayed admission, neither endovascular thrombectomy nor thrombolytic treatment could be planned and the patient was transferred to the intensive care unit for palliative monitoring.

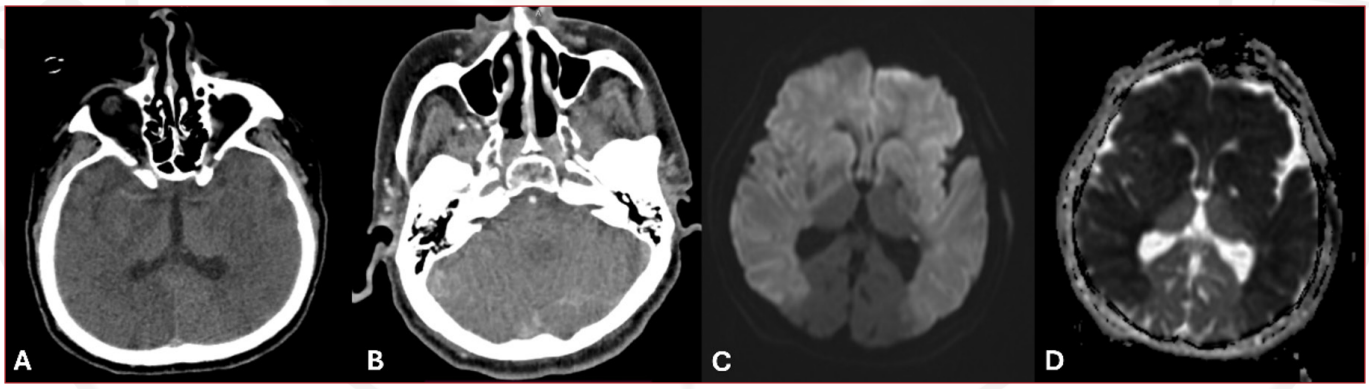


**Figure.** Bilateral hyperdense middle cerebral arteries were shown in brain computer tomography scan (A). Brain computer tomography angiography demonstrated bilateral internal carotid artery occlusion (B). Brain magnetic resonance diffusion-weighted imaging (C) and apparent diffusion coefficient map (D) showed an area of diffusion restriction in the bilateral ICA water supply.

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## DISCUSSION

Acute bilateral ICA occlusion is an unusual entity with a poor outcome.[3] It can mimic metabolic encephalopathies and posterior circulation infarcts and can be differentiated by careful evaluation of brainstem functions.[4] For this purpose, imaging methods are very helpful in supporting the diagnosis. As in our case, clinical imaging and detailed neurological examination are of great importance in making a differential diagnosis and managing the process.

## CONCLUSION

Bilateral simultaneous ICA occlusions are rare.We think that acute bilateral ICA occlusions can be detected with a detailed anamnesis, medical history and clinical imaging.

## ETHICAL DECLARATIONS

### Informed Consent

All patients signed and free and informed consent form.

### Referee Evaluation Process

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### Conflict of Interest Statement

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### Author Contributions

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