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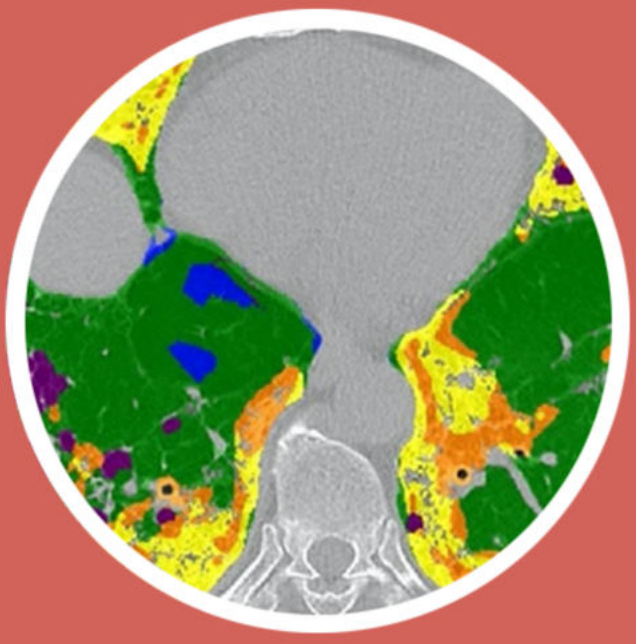

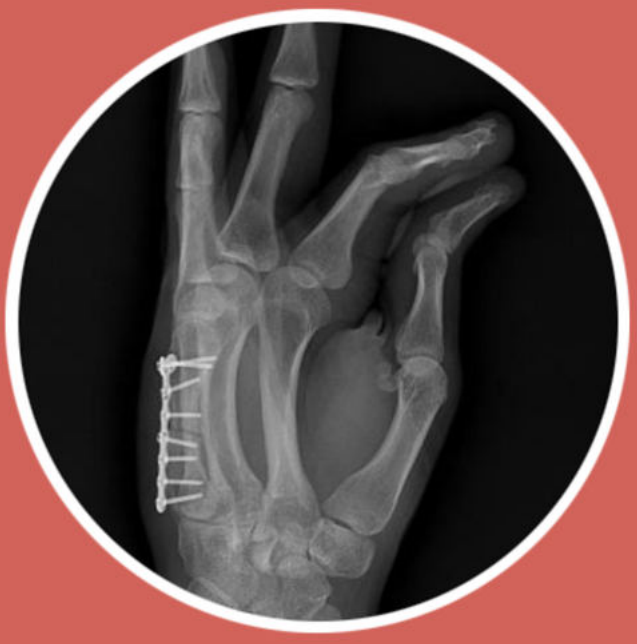

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The European Research Journal 2022;8(4):428-433 Original Article

DOI: 10.18621/eurj.879908 *Orthopaedics and Traumatology*

In situ transverse osteotomy and locked mini plate for the correction of metacarpal rotational deformity

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ABSTRACT

Objectives: We aimed to investigate the radiological and clinical results of transverse osteotomy and fixation applications in rotation deformities due to metacarpal malunion.

Methods: A total of 18 fingers from 18 patients were enrolled in the study (14 males and 4 females). The average age of the patients was 32.8 ± 14.4 years (range: 18-58 years). The average follow-up duration was 19.7 ± 7.9 months (range: 7-36 months). All patients had a scissoring deformity which affected their daily activities or caused cosmetic problems.

Results: In all patients, the scissoring and overlapping deformities improved and in all osteotomies union was achieved. A total range of motion for the DIP, PIP, MP and wrist joints was achieved in all patients. The average DASH score was 5.2 ± 5.6 (range: 0-21.7), and the average VAS score was 0.8 ± 0.9 (range: 0-3). The average grip strength was 40.5 ± 10.2 kg (range: 19-55 kg) and 94% of the healthy side. There was no statistically significant difference in grip strength compared to the healthy side ($p = 0.23$). Fourteen excellent and 4 good scores were obtained based on Büchler criteria.

Conclusions: In situ transverse osteotomy and the locked miniplate method is effective and feasible in the treatment of metacarpal malunions with finger rotational deformities, given their ease of use, allowance of early movement, high union rates, and good results.

Keywords: Finger, rotational deformity, osteotomy, transverse, malunion

Rotation deformity may occur in the fingers due to incorrectly united phalanx and metacarpal fractures, especially spiral and oblique fractures [1]. This can result in the scissoring finding of the fingers, pain and stiffness due to joint line rotation, impaired soft tissue balance, and reduced grip strength [2]. It is necessary to correct the functional and aesthetic problems caused by the deformity with surgical treatment. It is difficult to view the original fracture line in late cases, so an osteotomy is required [3]. A transverse, step-cut, or modified step-cut osteotomy can be performed on the affected bone or metacarpus [3-5]. Osteosynthesis options include intraosseous wires, Kirschner (K) wires, plates, and screws [6].

Treatment of visual and physical defects in metacarpal rotation deformity increases the comfort of life of the patient. We employed a transverse metacarpal osteotomy and a locked miniplate on the affected metacarpal to treat finger rotation deformities caused by metacarpal malunions. In this study evaluated the clinical and radiological results of transverse osteotomy and fixation applications in rotation defor-

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mities due to metacarpal malunion. Compared to studies in the literature evaluating osteotomy only in metacarpal malunions, the number of our cases is higher in this study.

METHODS

Adult patients who received an in-situ transverse metacarpal osteotomy and a locked miniplate to treat a finger rotation deformity caused by metacarpal malunions between 2015 and 2019 were evaluated retrospectively. Patients for whom at least one year of follow-up data were available were spoken to by phone, and those who responded to the last control call were considered for the study. The medical reports of these patients were reviewed, and those with incomplete metacarp callus maturation, additional injuries in the ipsilateral extremity, previously undergone surgery on the same hand, presence metacarpal angulation and shortness were excluded. This study was approved by the institutional review board of Haydarpaşa Numune Training and Research Hospital (HNEAH-KAEK2020/KK/192), verbal and written informed consent was obtained from all patients.

Except for three patients who could not be reached, 18 fingers of 18 patients (14 males and 4 females) who met the criteria were enrolled in the study. The mean age of the patients was 32.8 ± 14.4 years (range: 18-58 years). All patients had a scissoring deformity which affected their daily activities or caused cosmetic problems, thus surgical treatment was employed. In addition, five patients complained of pain. The cause of the rotation deformity in all patients was a malunited metacarpal fracture; 14 patients had been treated with a closed reduction and plaster splint, while 4 patients had received no treatment. The average interval between the injury and surgery was 11.2 ± 7.3 months (range: 4-30 months). The fracture pattern could not be assessed clearly for all patients because the original fracture line could not be completely distinguished. None of the patients had vascular, nerve and tendon injuries before surgery. The fracture line was closed in all patients and there were no pathological fractures. Bone maturation was complete in all patients during injury.

A transverse osteotomy and a locked miniplate were used to treat the metacarpals of the patients. All patients received 1 g of cefazolin sodium prophylactically 1 hour before surgery and then operated under general anesthesia or axillary block.

Surgical Technique

The patients were placed on the operating table in the supine position and then a 250 mmHg pressure pneumatic tourniquet was applied. A longitudinal incision was made over the metacarpal. The skin and subcutaneous tissue were passed and cutaneous nerves preserved. The extensor tendon was retracted to one side while preserving the paratenon. The carpometacarpal joint was identified using a needle. A straight line was drawn parallel to bone with a marker pen and the axis of the bone was determined. The plate was applied to the bone from dorsal side of the metacarpal bone, with one screw from the most proximal hole used as a single cortex. A transverse line was drawn distal to the 3rd or 4th screw hole to determine the osteotomy line and the plate was removed. A transverse osteotomy was performed perpendicular to the bone (from the previously marked transverse line) using an oscillating saw. The plate was fixed to the proximal fragment with three or four screws. The distal fragment was sufficiently rotated, the longitudinal line was checked, and two of the distal screw holes were temporarily fixed with two K-wires as double cortices. The wrist was extended, and the correction of the deformity was checked based on the tenodesis effect of the flexor tendons, in which the proximal interphalangeal phalanx (PIP) joint was flexed to 90° and the affected finger was observed to be parallel to the other fingers. Sufficient improvement was achieved with only a minor rotation. If the correction was appropriate, screws were applied to the distal fragment; if not, the temporary K-wire was removed, and the correction was made again. The correction was checked using a tenodesis test after placing each screw in the distal fragment. Intraoperative fluoroscopy was employed to confirm the plate placement, screw length, and osteotomy line.

No grafts or extra lag screws were used in any patient, and 2.0-mm fixed angle locked miniplates were used for all patients. Only locking screws were used, with three or four screws (at least six cortices) applied to both sides of the osteotomy line. No splint was applied to any patient after the operation. The correction was checked by making fist to patient immediately

postoperative. On the first day after the operation, active hand and wrist joint movements were started. Extremity elevation and cold compress were used for edema control at the first week. Daily activities such as writing with a pencil, button-up, eating and using cutlery were allowed for the first three weeks. After three weeks, the patients referred the physical therapy department of our hospital, and a hand rehabilitation program was initiated for 1 hour/day and 5 days/week, including Transcutaneous Electrical Nerve Stimulation (TENS) and soft tissue stretching exercises. Physical exercise program were initiated when radiographs confirmed osteotomy healing. The sutures were removed at postoperative second week. In the final follow-up, the range of motion (ROM) for the DIP, PIP and MP joints was measured using a finger goniometer and compared with the healthy side. Using posteroanterior, oblique, and lateral radiographs, union was defined as cortical trabeculation, the formation of a bridging callus, and no sensitivity upon palpation of the osteotomy line. The absence of a bridging callus after six months was evaluated as non-union [7]. In addition, the Disabilities of the Arm, Shoulder, and Hand (DASH) questionnaire and the visual analogue scale (VAS) were used for functional evaluation and pain assessment [8, 9]. A Saehan hydraulic hand dynamometer was used to measure the patient's grip strength while sitting with shoulder adduction, an elbow flexion of 90°, and the forearm and wrist in a neutral position. Periodical measurements were made three times and the average was calculated. The grip strength were compared with the healthy side. Büchler criteria were used to evaluate the results (Table 1) [2].

Table 1. Criteria and grading of results [2]

Criteria	
1	Complete correction of preoperative deformity
2	Full bony union
3	Patients experiencing no pain
4	Patients has returned to work
5	Patients satisfaction rating good or above
6	No trophic or sensory problems
7	No tendon adhesions
8	ROM to within 10 degrees of full range in each joint
9	Flexion brings finger tip to within 1 cm of palm
Grading	
Excellent	≥ 8 criteria satisfied
Good	7 criteria satisfied
Fair	5 or 6 criteria satisfied
Poor	< 5 criteria satisfied

Statistical Analysis

The normality of the parameter distributions was evaluated using the Shapiro–Wilk test, while the Mann-Whitney U test was used to compare parameters between the two groups. $P < 0.05$ was considered statistically significant.

RESULTS

The average interval between surgery and contact via phone was 19.7 ± 7.9 months (range: 7-36 months). The average interval between fracture and surgery time was 7.3 months (range: 3-15). In 11 patients the dominant side was affected. The right side was affected in nine patients and the left side in nine patients. The cause of the injury was a fall for 10 patients, injury during sports activities for three patients, a work accident for two patients, a motor vehicle accident for one patient, punch injury for one patient, and an attack for one patient. The index metacarp was affected in four patients, the middle metacarp in three patients, the ring metacarp in five patients, and the small metacarp in six patients.

In all patients, the scissoring and overlapping deformities improved and in all osteotomies union was achieved. Fig.1. A complete ROM for the distal interphalangeal, proximal interphalangeal, metacarpophalangeal and wrist joints were achieved in all patients. The mean DASH score was 5.2 ± 5.6 (range: 0-21.7), and the mean VAS score was 0.8 ± 0.9 (range: 0-3). The average grip strength was 40.5 ± 10.2 kg (range: 19-55 kg) and 94% of the healthy side. Mean surgery time was 50.5 ± 13.7 minutes (range: 30-75 minutes). When compared with the healthy side, no statistical significant difference was found in terms of grip strength ($p = 0.23$). In total, 14 excellent and 4 good scores were obtained based on Büchler criteria.

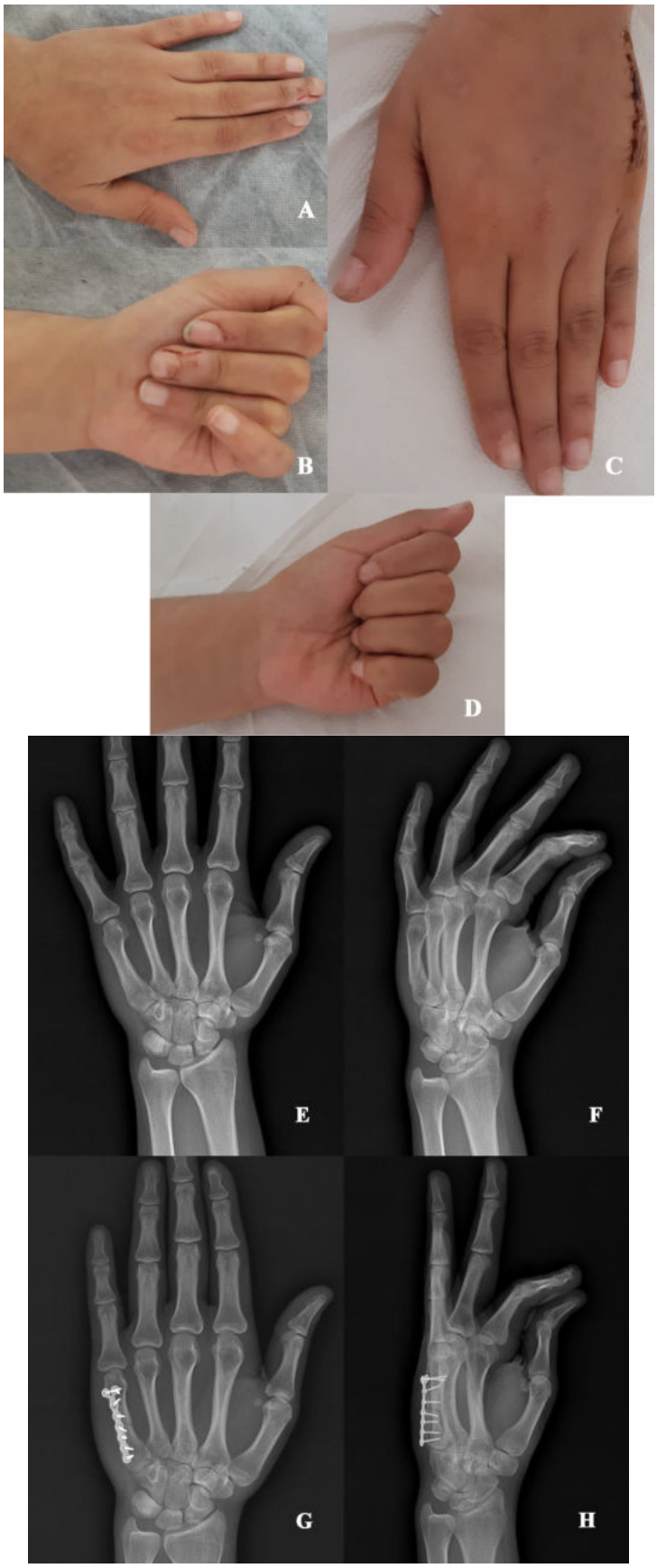

Fig. 1: A-B: Malrotation of the small finger caused scissoring during finger flexion, C-D: postoperative 2. week clinical images after the rotational deformity was corrected, E-F: preoperative and, G-H: postoperative 6. week radiographs of the same patient.

There were no complications such as plate/screw irritation, implant displacement, hardware loosening or loss of correction, and no implant was removed from any patient. In addition, no patient experienced infection, digital nerve injury, or hypertrophic scarring. No secondary surgery was required in any patient. One patient experienced sudeck atrophy syndrome that improved using physical therapy and conservative therapy.

DISCUSSION

While metacarpal and phalangeal fractures are treated conservatively, interphalangeal joints are splinted in extension and the MP joint in flexion. In doing so, any rotation deformity that occurs is not obvious. A scissoring deformity becomes apparent when movement is started and the finger is flexed, and this causes functional and aesthetic problems. If diagnosed late, the fracture will unite and surgical treatment becomes necessary [3].

There is no consensus on the location, type, and fixation method for an osteotomy. There are two osteotomy locations for a finger with rotation deformity; the first is at the site of the malunion and the second is at the metacarpal of the affected ray. Weckesser was the first to report on the treatment of finger rotational deformities in 1965. He described the transverse osteotomy of the metacarpal base for both phalanx and metacarpal malunions and fixation with K-wires, emphasizing the importance of early movement [10].

Gross *et al*. [11] performed basal metacarpal osteotomies on 80 fingers of 40 cadavers, showing that a correction of 18-19° was possible in the index, long, and ring fingers, and a correction of 20-30° was possible in small fingers. It was reported that the deep transverse metacarpal ligament was the limiting factor for rotation. The release of this ligament can cause loss of the transverse palmar arch and instability of the MP joint [11].

Pichora *et al*. [12] performed a step-cut osteotomy on the malunion area of 23 fingers of 18 patients with rotational deformity, of which seven involved the metacarpal and 16 the proximal phalanx. They reported good results and fast union. In the literature review of Lei *et al*. [13], metacarpal corrective osteotomies were performed on nine phalanges and six metacarpals, and complete recovery was achieved in 13 of the 15 patients (87%), while bony union was obtained in all patients.

Menon *et al*. [14] performed a metacarpal osteotomy on 12 fingers with metacarpal and phalangeal malunion-induced rotational deformities and all preoperative deformities were corrected. The metacarpal-based osteotomy described by Bindra *et al*. [3] is simple, allows early movement and has few complications. However, this technique is not suitable for fingers with rotational deformities of more than 20° [3]. Jawa *et al*. [4] performed a step-cut osteotomy at the metacarpal shaft level for 12 fingers with rotational deformities and fixed them with lag screws. Seven of these were metacarpal and five were phalanx malunions. They recommended this method due to the advantage of precise intraoperative control, including selecting the osteotomy site, offering a large surface area with bony healing, and making possible rigid fixation with early digital motion [4].

Limitations

The retrospective nature of our study and the absence of a control group are weaknesses of the present study. We preferred in situ osteotomy because exposure of the malunited area allows for more accurate evaluation, intervention in flexor and extensor tendon adhesion, and the potential for further correction. We preferred transverse osteotomy because it is less complicated. We preferred plate fixation for early rehabilitation; we applied at least three screws on both sides of the osteotomy line and did not apply postoperative splints. We achieved a full ROM in the DIP, PIP and MP joints and achieved union in all patients.

CONCLUSION

We believe that in-situ transverse osteotomy and the locked miniplate method is effective and feasible in the treatment of metacarpal malunions with finger rotational deformities, given their ease of use, allowance of early movement, high union rates, and good results.

Authors' Contribution

Study Conception: BK; Study Design: LA; Supervision: LA, BK; Funding: N/A; Materials: LA, BK; Data Collection and/or Processing LA, BK; Statistical

Analysis and/or Data Interpretation: LA; Literature Review: LA; Manuscript Preparation: LA, BK and Critical Review: LA.

Conflict of interest

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The European Research Journal 2022;8(4):434-441 Original Article

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Selective C5 nerve root block versus combined interscalene block for clavicle surgery

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ABSTRACT

Objectives: The pain sensation of the clavicle is innervated by two separate plexuses. Regional anesthesia techniques for this area are challenging and complicated. Interscalene block, superficial cervical block, or a combination of these two is commonly used for regional anesthesia in clavicle surgery. The aim of this study was to investigate the efficacy of C5 nerve root block for clavicle surgery.

Methods: Patients were divided into two groups: Group C5B (patients who received C5 nerve root block + superficial cervical plexus block) and Group ISB (patients who received interscalene block + superficial cervical plexus block). Motor block was assessed by the Medical Research Council Scale for Muscle Strength, while the sensory block of the areas corresponding to the nerve trace was assessed using the pinprick and cold testing. Furthermore, ultrasound was employed to evaluate phrenic nerve paralysis.

Results: There was no difference between the groups in terms of mean age. The mean age of Group ISB was higher; however, the comparison of comorbidities revealed no significant difference between the groups. This statistically significant difference was clinically insignificant. Group C5B had lower 6-hour pain at rest, lower 0, 2, 4-hour pain on movement, and less postoperative analgesic consumption. Moreover, the time to first analgesic requirement was significantly longer in Group C5B. The motor examination of the peripheral nerves showed a significant difference in Group C5B.

Conclusions: We are of the opinion that C5 nerve root block can be used instead of interscalene block since it does not produce a motor block in hand movements and preserves diaphragmatic functions. C5 nerve root block may therefore be considered an alternative to conventional interscalene block for clavicle surgery.

Keywords: C5 root block, clavicle surgery, selective nerve root block, interscalene block, ultrasound, superficial cervical block

Clavicle fractures are one of the most common fracture types with an incidence of 22.4 per 100,000 people [1]. Clavicle fractures most commonly result from sports injuries and falls [1]. While the most frequent fracture location is the midshaft of the clavicle, medial fractures are the least common type of clavicle fractures [2].

Sclerotomally, the sensation of the clavicle originates from the C4-C5 nerve root. The cervical plexus is formed by the anterior rami of cervical spinal nerves C2-4. It is situated between the musculus longus capitis and musculus scalenus medius and lies underneath the prevertebral fascia. Perforating this fascia and passing through the interfascial region between the musculus sternocleidomastoideus (SCM) and the prevertebral muscles, it is divided into 4 branches at the

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midpoint of the SCM: n. auricularis magnus, n. occipitalis minor, n. transversus colli, and n. supraclavicularis. N. supraclavicularis is a sensory nerve originating from the C3-4 roots of the cervical plexus and provides sensation over the proximal clavicle, anteromedial shoulder, and proximal wall of the chest [3]. The subclavian nerve that arborizes from the upper trunk of the brachial plexus provides sensation over the clavicle region [3].

In clavicle surgery, anesthetic management is often maintained by general anesthesia. Regional anesthesia techniques for the clavicle, which receives sensation from two separate plexuses, are often complicated. Interscalene block, superficial cervical block, or a combination of these two is commonly used for regional anesthesia in clavicle surgery [4, 5].

There are publications reporting the use of selective cervical root blocks as an anesthetic technique for clavicle surgery to avoid the potential serious side effects of interscalene block on the distal clavicle and midshaft fractures [6].

The aim of this study was to retrospectively compare the intraoperative and postoperative efficacy (in terms of pain, movement, and diaphragm paralysis) of the selective C5 nerve root block plus superficial cervical plexus nerve block with interscalene block plus superficial cervical plexus nerve block for anesthesia in clavicle surgery.

METHODS

The approval for the study was obtained from the Clinical Research Ethics Committee of Erzincan Binali Yildirim University, Faculty of Medicine, with the number of 33216249-903.99-E.18831. The study was conducted by retrospectively evaluating patients who underwent open reduction internal fixation surgery for clavicle fractures at Ercis State Hospital between 1 December 2016 and 31 December 2018. The study included a total of 31 patients over 16 years of age with ASA scores of I-II. Patients who did not give written consent, had peripheral nerve disease, respiratory failure, brachial plexus injury, and did not accept to undergo surgery with peripheral block were excluded from the study.

For premedication, patients received 0.01 mg/kg intravenous midazolam in the operation room as a standard protocol. All patients who were placed on the operating table were monitored with standard monitoring methods including ECG, noninvasive blood pressure, peripheral oxygen saturation, end-tidal CO_2 pressure ($ETCO_2$), temperature (tympanic), and bispectral index (BIS, Aspect 1000TM, Aspect Medical Systems, Inc., Natick, MA, USA). The patients were divided into 2 groups: Group C5B and Group ISB. Group C5B included patients who received C5 nerve root block + superficial cervical plexus block (SCPB), while Group ISB included patients who received interscalene block + SCPB. Both peripheral block techniques were explained to patients. After establishing vascular access in all patients, the fluid infusion was administered by calculating the fluid deficit. The fluid requirement of patients was met with crystalloid by calculating fasting (with the 4/2/1 rule), maintenance (with the 4/2/1 rule), and insensible loss (4 mL/kg/h). A BIS probe was placed on the forehead of patients. An ultrasound-guided peripheral nerve block was performed in both groups for intraoperative analgesia and postoperative analgesia. To assess the location of the block and prevent intraneural injection, the block needle was connected to a nerve stimulator (Braun Stiumplex HNS11, Melsungen, Germany) delivering stimulation at a current of 1 mA with a frequency of 2Hz and 0.1 ms interval period. When the contraction of the musculus deltoideus indicated the correct location, the current was reduced to 0.3 mA. In both groups, 10 ml of 0.25% bupivacaine was administered under the SCM muscle at the C6 thyroid cartilage level

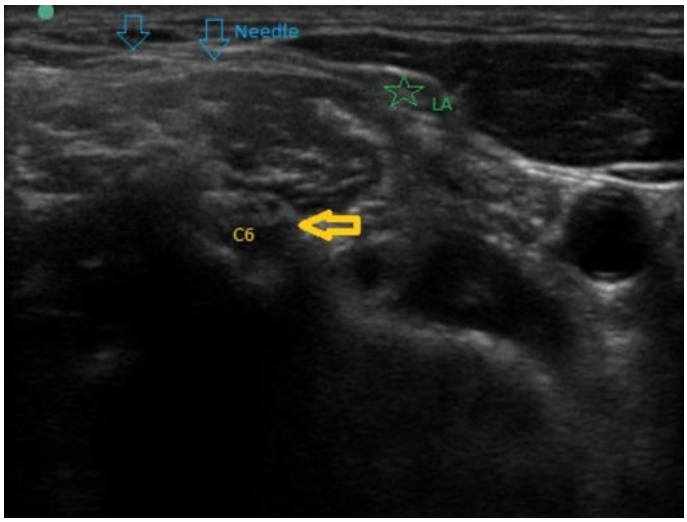

Fig. 1. Ultrasound-guided superficial cervical plexus block. LA = local anesthetic, C6 = C6 cervical nerve root.

using a linear USG probe, with the patient's head positioned straight upward at 30 degrees opposite to the block side to perform a superficial cervical plexus block (Fig. 1).

In Group C5B, the subclavian artery and the surrounding brachial plexus were identified in the supraclavicular region. The probe was moved cranially to distinguish the prominent posterior process of the C7, prominent anterior process of the C6, and double-edged tubercles of the C5. After identifying the C5 root, the block needle was guided using an in-plane technique and 4 ml of 0.25% bupivacaine was administered (Fig. 2). In Group ISB, the patient's head was positioned straight upward opposite to the block side. The sternocleidomastoid muscle was scanned laterally at the C6 cricoid cartilage level to visualize the carotid artery, internal jugular vein, anterior and middle interscalene muscles at the end of the SCM, and interscalene groove between them. After visualizing the typical "stoplight sign" of the C5-6-7 roots in the interscalene groove, 15 ml of 0.25% bupivacaine was administered.

Following the block, the sensory block of patients was assessed with pinprick and cold testing in the C5-T1 dermatomes. Those who could not abduct their shoulders and achieved sensory block were considered to have adequate anesthesia, thus surgical procedure was initiated. All patients received midazolam at a level to respond to verbal stimuli during surgery.

Age and body mass index values of patients were recorded. Patients postoperatively underwent a digital examination for the motor examination of the radial, ulnar, and median nerves. Motor block was assessed by the Medical Research Council (MRC) Scale for Muscle Strength [7], while the sensory block of the areas corresponding to the nerve trace was assessed using the pinprick and cold testing (0: no block, 1: analgesia (no sensation of warmth, feel sensation of touch), 2: complete sensory block (no sensation of warmth, no sensation of touch). The Numeric Pain Rating Scale (NPRS) (0=no pain, 10=unbearable pain) was used to assess the 0, 2, 6, 24-hour pain of patients at rest and on movement. In the early postoperative rehabilitation phase, patients performed shoulder abduction up to 90 degrees. Postoperative analgesia was provided by intravenous 1mg\kg tramadol when the NPRS was >4. In the postoperative period, patients routinely received 50 mg intravenous dexketoprofen twice a day. The time to first analgesic requirement, analgesic consumption, duration of motor block (the time until the patients moved their shoulders for the first time) were recorded.

We also evaluated phrenic nerve paralysis after the block. We ruled out phrenic nerve paralysis with the M-mode ultrasound measurement of diaphragmatic movement using a convex probe during normal and deep breathing. Following the technique described by Boussuges *et al*., we started the evaluation in the 2-dimensional mode, placed the probe in the subcostal area between the midclavicular and anterior axillary lines, and directed the beam cranially to reach the posterior third of the hemidiaphragm on the block side. After switching to the M-mode, we identified the echoic line of the diaphragm and measured the inspiratory amplitudes from the base to the apex of the inspiration slope [8]. These measurements were performed when the patient arrived in the holding area, 15 minutes after the performance of the block, and immediately after surgery.

Statistical Analysis

Statistical analyses were performed using the SPSS version 25.0 software (SPSS Inc., IBM, NY, USA). Numerical variables were presented as mean and standard deviation, while categorical variables were given as frequency and percentage. The t-test or

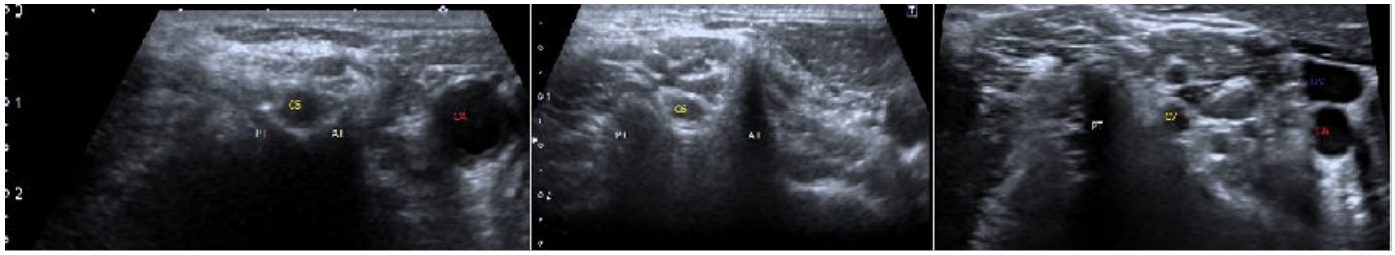

Fig. 2. Ultrasound-guided C5 nerve root block. AT = Anterior tubercle, PT = posterior tubercle, C5 = C5 cervical nerve root, C6 = C6 cervical nerve root, C7 = C7 cervical nerve root, CA = Carotis arteria, IJV = internal jugular vein.

Mann-Whitney U test was used to compare the means based on the results of the Kolmogorov-Smirnov normality test. The chi-square test was used to compare frequencies. A p - value of < 0.005 was considered statistically significant.

RESULTS

The comparison of the groups for homogeneity showed no statistically significant difference in terms of gender, male to female ratio, and body mass index. The mean age of Group C5B was lower than that of the Group ISB ($p < 0.001$) (Table 1). There was no statistically significant difference between the two groups in terms of operative time and anesthesia duration ($p > 0.05$).

There was no statistically significant difference between the groups in terms of postoperative 0, 2, and 24-hour pain scores at rest. There was a statistically significant difference between the groups in terms of 6-hour pain scores. Group C5B had lower pain at rest compared to Group ISB.

There was statistically significant difference between the groups in terms of 0, 2, and 6-hour postoperative pain scores on movement ($p < 0.001$, $p = 0.012$, $p = 0.001$). Group C5B had lower pain on movement compared to Group ISB.

The sensory examination of the radial nerve revealed a significant difference between the two groups. No sensory block was observed in Group C5B. The evaluation of the radial nerve motor muscle strength showed a statistically significant difference between the two groups in favor of Group C5B ($p < 0.001$). The sensory examination of the median nerve revealed a significant difference between the two groups. No sensory block was observed in Group C5B. The evaluation of the median nerve motor mus-

Table 1. Baseline characteristics and comparison of groups

	Group C5B (n = 16)	Group ISB (n = 15)	*p* value
Gender, n (%)			
Female	1 (6)	1 (6)	0.919
Male	15 (94)	14 (94)	
BMI (kg/m^2)	24.10 ± 1.77	24.85± 1.25	0.184
Age (years)	24.1 ± 6.7	46.8 ± 21.2	**< 0.001***
Operative time (min)	75.19 ±6.32	76.33 ±5.36	0.590
Anesthesia duration (min)	186.0 ± 26.8	199.2 ± 7.1	0.077
Analgesic duration (min)	418.63 ± 12.08	392.40 ± 7.93	**< 0.000***
Analgesic consumption	31.25 ± 34.79	73.33 ± 30.91	**< 0.001***
NPRS static (at rest)			
0 hour	0.25 ± 044	0.26 ± 0.45	0.919
2 hours	1.25 ± 0.44	1.26 ± 0.45	0.919
6 hours	3.81 ± 0.65	4.46 ± 0.51	**0.004***
24 hours	2.25 ± 0.93	2.66 ±0.89	0.215
NPRS dynamic (on movement)			
0 hour	2.5 ± 0.51	3.06 ± 0.59	**< 0.001***
2 hours	3.31 ± 0.60	3.93 ± 0.45	**0.012***
6 hours	4.62 ± 0.61	5.33 ± 0.48	**0.001***
24 hours	3 ± 0.81	3.33 ± 0.72	0.23

Data are shown as mean±standard deviation. BMI = body mass index, NPRS = Numeric Pain Rating Scale
**p* values according to t-test or Mann-Whitney U test

Table 2. The effect of the block on hand movements

	Group C5B (n = 16)	Group ISB (n = 15)	*p* value
Radial Nerve Sensory Block			
No block	16	1	
Analgesia	0	13	**< 0.001****
Complete sensory block	0	1	
Median Nerve Sensory Block			
No block	16	7	
Analgesia	0	6	**0.003****
Complete sensorial block	0	2	
Ulnar Nerve Sensory Block			
No block	16	6	
Analgesia	0	9	**< 0.001****
Complete sensorial block	0	0	
Radial Nerve Motor Block			
0/5			
1/5	0	0	
2/5	0	0	
3/5	16	0	**< 0.001****
4/5	0	15	
5/5	0	0	
Median Nerve Motor Block			
0/5			
1/5	0	0	
2/5	0	1	
3/5	0	13	**< 0.001****
4/5	6	0	
5/5	10	1	
Ulnar Nerve Motor Block			
0/5			
1/5	0	0	
2/5	0	0	
3/5	0	2	**< 0.001****
4/5	0	10	
5/5	16	3	

BMI = body mass index, VAS = visual analog scale

**p* values according to Chi-Square test

cle strength showed a statistically significant difference between the two groups in favor of Group C5B ($p = 0.003$). The sensory examination of the ulnar nerve revealed a significant difference between the two groups. No sensory block was observed in Group C5B. The evaluation of the ulnar nerve motor muscle strength showed a statistically significant difference between the two groups in favor of Group C5B ($p < 0.001$) (Table 2).

Furthermore, the comparison of the groups for time to first postoperative analgesic requirement and analgesic consumption showed that Group C5B had a significantly longer time to first analgesic requirement compared to Group ISB and less postoperative analgesic consumption ($p < 0.001$). Diaphragm paralysis was not observed in Group C5B. All patients in Group ISB had diaphragm paralysis. None of the patients developed intraoperative intraneural injection or local anesthetic toxicity. Moreover, none of the patients developed postoperative neurological complications associated with the block. Patients did not require additional opioid analgesic or sedation intraoperatively.

DISCUSSION

The innervation of the clavicular nerve is complex and has not been fully elucidated. A group of nerves originates from the cervical plexus, while a group of nerves originates from the brachial plexus. Combinations of interscalene block are commonly used as regional anesthesia techniques. In this study comparing interscalene block with C5 nerve root block, there was no difference between the groups in terms of mean age. The mean age of Group ISB was higher; however, the comparison of comorbidities revealed no significant difference between the groups. This statistically significant difference was clinically insignificant. Group C5B had lower 6-hour pain at rest, lower 0, 2, 4-hour pain on movement, and less postoperative analgesic consumption. Moreover, the time to first analgesic requirement was significantly longer in Group C5B. The motor examination of the peripheral nerves showed a significant difference in Group C5B.

It has been shown that the use of superficial cervical block alone can be effective in relieving acute pain in midshaft clavicle fractures [9]. In clavicle fractures, superficial cervical block and interscalene block are combined to relieve postoperative pain and to provide intraoperative anesthesia [4, 5]. The postoperative analgesic efficacy of interscalene block has been demonstrated in distal clavicle and shoulder surgeries [10].

Interscalene block blocks the C5-8 nerve roots, making patients experience weakness in hand movements. In this case, it may be difficult to evaluate early postoperative neurological damage that may result from surgery. A study by Dobbie *et al*. [10] showed that interscalene block performed at the level C5-6 nerve root did not cause a motor block in hand movements. A study by Deng *et al*. [11] comparing conventional interscalene block with interscalene block performed at the level of the C5 nerve root showed similar postoperative analgesia. A study by Shin *et al*. [12] showed that interscalene block with the C5 approach provided equivalent motor postoperative analgesia to the conventional approach with a minimal motor block. In our study, no motor block was observed in the radial, median, and ulnar nerves of Group C5B postoperatively. Group C5B had a difference in postoperative 6-hour pain scores at rest, but it was clinically insignificant. We are of the opinion that the reason for higher pain on movement in Group ISB is the excessive load on the distal clavicle due to the absence of a motor block.

Patients at risk of undergoing general anesthesia can be operated using the regional anesthesia techniques with the combination of interscalene block and superficial cervical block. Valdepitte *et al*. provided successful intraoperative anesthetic management in a case where they performed combined interscalene and superficial cervical block on a 15-week pregnant woman [13]. Interscalene block causes phrenic nerve paralysis. C5 nerve root block can be performed in cases where general anesthesia poses a risk and interscalene block is contraindicated due to phrenic nerve paralysis. There is a publication by Shanthanna [14] showing that a patient with severe emphysema and respiratory failure was successfully operated with a selective C5 nerve root block and superficial cervical block. Kline *et al*. [15] used 2 separate perineural catheters to perform a selective C5 nerve root block and superficial cervical block on their patient who refused to undergo general anesthesia and demonstrated its efficacy for pain relief. Salvatores *et al*. [16] suc-

cessfully performed clavicle midshaft fracture surgery with C5 nerve root block and superficial cervical block on a high-risk patient with morbid obesity, heart failure, diabetes, and COPD. In our study, diaphragmatic functions on the block side were preserved in Group C5B.

It is known that postoperative opioid consumption is significantly less in patients undergoing ISB for clavicle surgery compared to general anesthesia [5]. It has been shown that patients undergoing C5 block for shoulder surgery with arthroscopic distal clavicle resection had less opioid consumption compared to the ISB group [17]. Our study also demonstrated that postoperative opioid consumption was less in the C5B group.

The most commonly used regional anesthesia technique as an alternative to general anesthesia for clavicle surgery is combinations of interscalene block. We are of the opinion that C5 nerve root block can be used instead of interscalene block since it does not produce a motor block in hand movements and preserves diaphragmatic functions. C5 nerve root block may therefore be considered an alternative to conventional interscalene block for clavicle surgery. There is a need for larger-scale prospective randomized controlled studies to determine the difference in functional outcomes of these two anesthesia techniques.

CONCLUSION

We are of the opinion that C5 nerve root block can be used instead of interscalene block since it does not produce a motor block in hand movements and preserves diaphragmatic functions. C5 nerve root block may therefore be considered an alternative to conventional interscalene block for clavicle surgery.

Authors' Contribution

Study Conception: EÇ, FY; Study Design: EÇ; Supervision: FY; Funding: EÇ, FY; Materials: EÇ, FY; Data Collection and/or Processing: EÇ, FY; Statistical Analysis and/or Data Interpretation: EÇ, FY; Literature Review: EÇ; Manuscript Preparation: EÇ, FY and Critical Review: EÇ.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

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The European Research Journal 2022;8(4):442-449 Original Article

DOI: 10.18621/eurj.1083732 *Radiology*

Comparison of quantitative lung computed tomographic findings between idiopathic pulmonary fibrosis patients diagnosed by biopsy and by multidisciplinary discussion without biopsy

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ABSTRACT

Objectives: We aimed to investigate the objective quantitative differences between the parenchymal computed tomography (CT) findings of idiopathic pulmonary fibrosis (IPF) patients diagnosed by surgical lung biopsy and by multidisciplinary discussion without biopsy.

Methods: We performed parenchymal texture analyses in lung CT images of 116 IPF patients, 42 diagnosed by surgical lung biopsy, and 74 by multidisciplinary discussion without biopsy. The relative volumes of the ground-glass, reticular, honeycomb, hyperlucent, and normal parenchymal patterns were measured in six predefined sections of each lung by an automatic texture analysis software (CALIPER: Computer-Aided Lung Informatics for Pathology Evaluation and Rating). The results were compared between the two patient groups.

Results: When the relative volumes of the parenchymal patterns were compared between the biopsied and non-biopsied groups in a total lung-based manner, the mean percentage of only the ground-glass pattern was significantly higher in the biopsied group. When compared between the corresponding lung sections, the percentages of the ground-glass pattern were higher in the biopsied group than those in the non-biopsied group at the bilateral central sections of the upper, middle, and lower lung zones. At the bilateral peripheral sections of the middle and lower lung zones, the sectional reticular pattern percentages were lower in the biopsied group than those in the non-biopsied group.

Conclusions: CALIPER's quantitative CT measurements revealed that the sectional relative volumes of the ground-glass and reticular patterns, but not of the honeycomb, normal, and hyperlucent parenchyma, were significantly different between some of the corresponding lung sections of the biopsied and non-biopsied IPF patients. This information may help a better understanding of the role of the CT findings in biopsy decisions and avoiding some of the unnecessary biopsies in suspected IPF patients.

Keywords: idiopathic pulmonary fibrosis, quantitative computed tomography, texture analysis, surgical lung biopsy, usual interstitial pneumonia

Idiopathic pulmonary fibrosis (IPF) is the most common and most fatal pulmonary fibrotic disease. The American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association (ATS/ERS/JRS/ALAT) guideline recommends a multidisciplinary discussion when IPF is suspected [1]. Surgical lung biopsy is suggested to make a definitive diagnosis in patients without the

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usual interstitial pneumonia (UIP) pattern on high resolution computed tomography (HRCT). It was reported that biopsy may be needed in up to one-third of patients for an accurate diagnosis, and the morbidity and mortality associated with biopsies are as high as 3-4% [2].

HRCT is essential in diagnosis and in biopsy decision. Unfortunately, there is interobserver variability in the identification and interpretation of HRCT features of UIP. Besides, conditions that mimic honeycombing, such as bronchiectasis and emphysema, can cause interobserver disagreement about the presence of honeycombing [3]. Furthermore, some commonly used adjectives in guidelines such as 'mild' and 'predominant' (e.g. 'mild ground-glass opacity (GGO)' and 'predominant GGO') are prone to subjectivity and may increase interobserver variability. Quantification of CT findings decreases interobserver variations.

ATS/ERS/JRS/ALAT guideline has pointed out some research questions and future directions about the potential value of the quantification of parenchymal patterns in IPF diagnosis [1].

Quantitative CT (qCT) has been increasingly used for lung diseases due to its objective and reproducible results. Thanks to advances in hardware and software technologies, computers gained the ability to 'recognize' and quantify parenchymal patterns. CALIPER (Computer-Aided Lung Informatics for Pathology Evaluation and Rating) is a software algorithm created at the Biomedical Imaging Resource of the Mayo Clinic and has the ability to detect and quantify parenchymal patterns [4, 5].

In this study, we aimed to determine the differences that can be 'seen by the objective eye of the CALIPER', between the CT findings of biopsied and non-biopsied IPF patients.

METHODS

We performed a retrospective qCT analysis of lung parenchyma in 116 IPF patients, 42 diagnosed by surgical lung biopsies (biopsied group) and 74 by multidisciplinary discussion without biopsy (non-biopsied group), in our hospital between 2013-2020. Biopsy decisions and non-biopsy IPF diagnoses were made by our hospital's Institutional Council of Interstitial Lung Diseases (consisted of a radiologist, a pathologist, and at least three respiratory clinicians).

We included only those patients who had volumetric, non-contrast CT scans, performed in our own institution within the 3-month period before the time of diagnosis by using the same acquisition technique (by

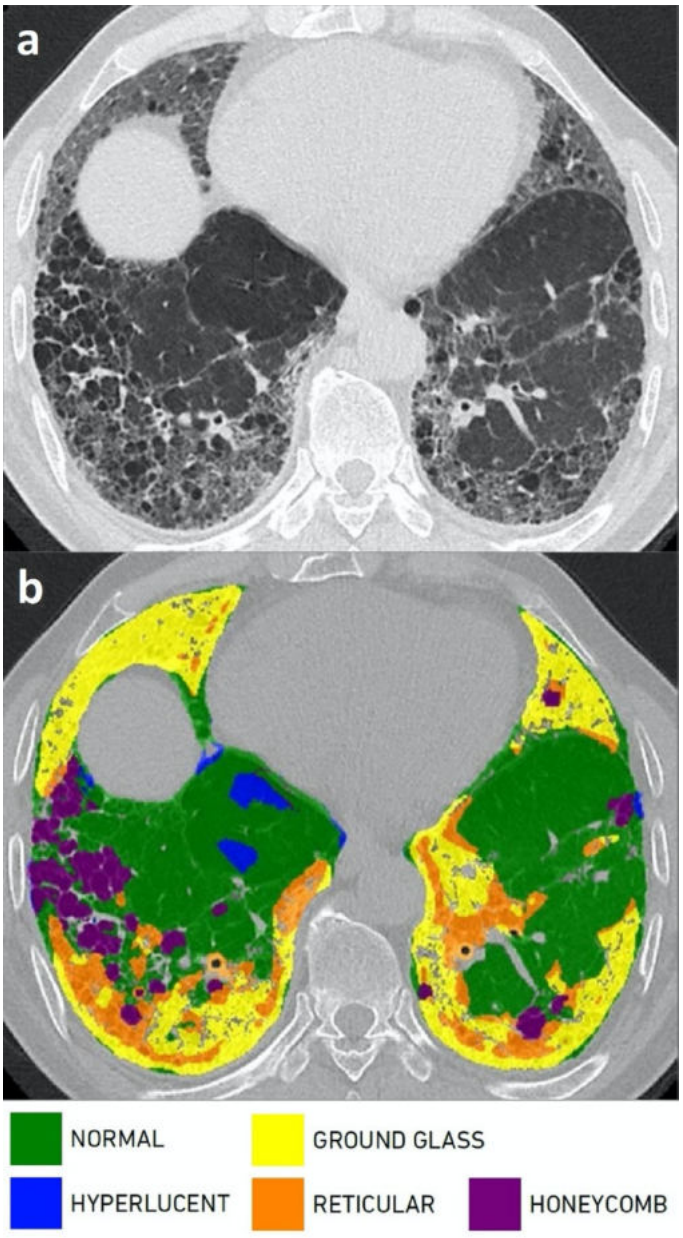

Fig. 1. Axial CT slice (a) and its color overlay (b) representing the mapping of lung texture detection. Five different parenchymal patterns (normal parenchyma, ground glass pattern, hyperlucent parenchyma, reticular pattern, and honeycombing) were automatically detected by the computer. The computer assigned five different colors for these five different parenchymal patterns, as listed below the image (b). The lung parenchyma was then colored regionally by the computer in accordance to the dominant parenchymal pattern in that region.

using Philips Ingenuity 128 slice CT scanner, with a tube voltage of 120 kV, a pitch of 1, a rotation time of 0.4 second, and a reconstruction thickness of 1 mm with filter B).

For quantification, we used Lung Texture Analysis software (Imbio, Minneapolis, Minnesota, USA) based on CALIPER technology developed by the Mayo Clinic (Rochester, Minnesota, USA) (This is an 'investigational use only' software in the USA). This software associated a certain group of neighboring voxels to one of the five basic parenchymal patterns (normal, hyperlucent, ground-glass, reticular, and honeycombing) (Fig. 1), and measured the absolute and relative volumes of each pattern in six predefined lung sections (obtained by dividing each lung's upper, middle, and lower thirds into central 'core' and peripheral 'rind' areas that comprise about half of the lung parenchyma) [5]. The relative volume of a parenchymal pattern was calculated as the percentage of the volume of that pattern in the concerned parenchymal volume. We obtained the sectional relative volumes of five different parenchymal patterns as a tabular data of percentages, in addition to a graphical report illustrating these percentages for each patient (Fig. 2).

This study was approved by our Institutional Review Board and written informed consent was waived because of its retrospective nature.

Statistical Analysis

SPSS Statistics software (version 26) was used to perform two-tailed Student's t-tests.

RESULTS

There were 42 patients in the biopsied and 74 in the non-biopsied group. The mean age was 60.9 ± 8.9 years (55.3 ± 7.3 years in the biopsied group and 64.0 ± 8.9 years in the non-biopsied group). There were 92 male and 24 female patients (in the biopsied group 28 male and 14 females, in the non-biopsied group 64 male and 10 females).

The mean volume percentages of the parenchymal patterns measured by CALIPER in the biopsied and in the non-biopsied patient groups and the results of the comparisons between these two groups are listed in Table 1.

When we compared the volume percentages of the

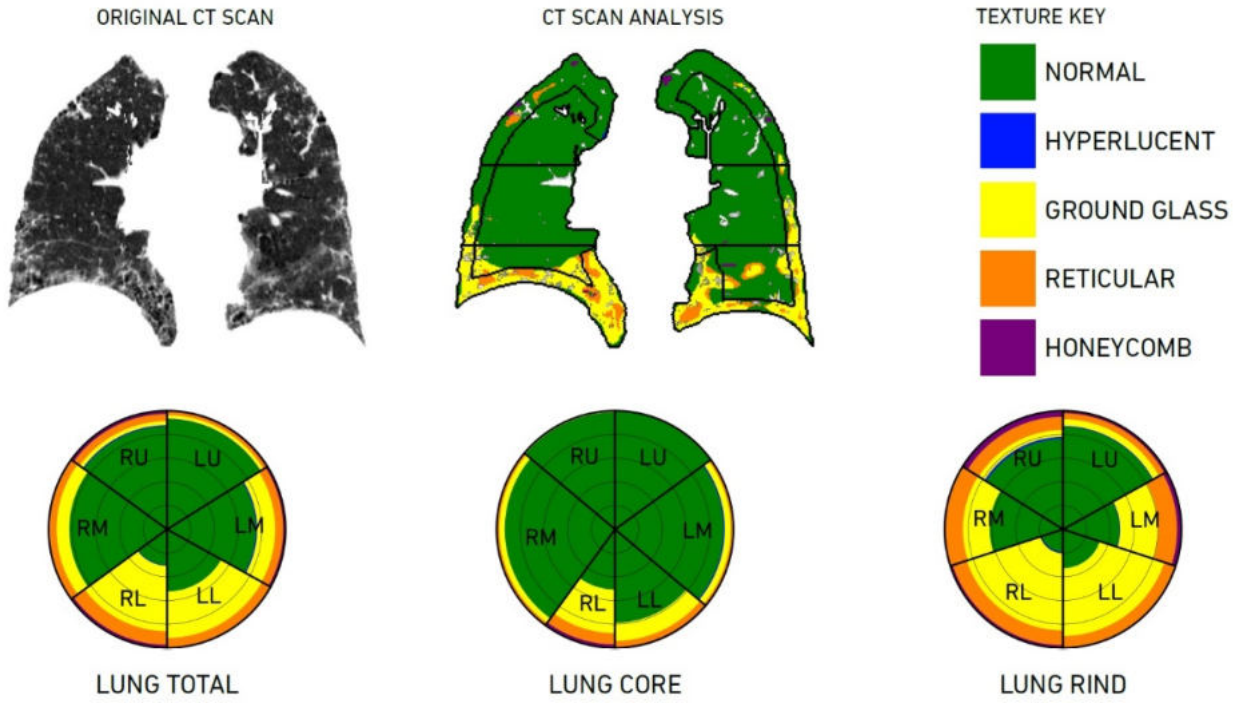

Fig. 2. An example of the graphical report of the quantitative CT analysis of IPF patients. Five different parenchymal patterns were masked by different colors on a mid-coronal CT slice, and the relative volume of each pattern was represented with the same color on circular glyphs. (RU = Right Upper, RM = Right Middle, RL = Right Lower, LU = Left Upper, LM = Left Middle, LL = Left Lower). The 'lung core' and the 'lung rind' glyphs represent the central and peripheral half volumes of the lungs, respectively.

Table 1. **Mean relative volumes (%) of parenchymal patterns in biopsied and non-biopsied groups**

	Normal parenchyma		Hyperlucent		Ground glass			Reticular			Honeycomb	
Lung Section	Biopsied	Non-biopsied	Biopsied	Non-biopsied	Biopsied		Non-biopsied	Biopsied		Non-biopsied	Biopsied	Non-biopsied
RL upper-central	77.0 ± 29.7	84.8 ± 20.0	0.4 ± 1.0	0.8 ± 2.7	15.7 ± 26.9	>	6.2 ± 13.1	5.2 ± 9.8		6.4 ± 11.8	1.7 ± 2.9	1.8 ± 4.1
LL upper-central	81.1 ± 26.9	87.7 ± 18.6	0.5 ± 1.3	1.6 ± 8.0	14.1 ± 26.5	>	4.4 ± 11.9	2.6 ± 4.5		4.6 ± 9.7	1.7 ± 3.0	1.6 ± 5.4
RL middle-central	73.8 ± 27.6	80.0±19.2	0.5 ± 1.3	0.7 ± 1.6	19.1 ± 28.2	>	9.0 ± 12.8	5.2 ± 7.6		8.8 ± 11.9	1.4 ± 2.5	1.5 ± 3.0
LL middle-central	69.5 ± 28.2	79.8 ± 21.1	0.35 ± 0.6	0.6 ± 2.8	24.3 ± 28.7	>	11.5 ± 16.6	4.6 ± 6.6		6.9 ± 9.6	1.2 ± 2.6	1.2 ± 3.0
RL lower-central	47.9 ± 28.3	55.9 ± 30.4	1.25 ± 7.2	0.9 ± 5.7	30.4 ± 29.6	>	14.6 ± 18.5	17.8 ± 20.3		25.6 ± 24.7	2.7 ± 4.7	3.0 ± 5.5
LL lower-central	48.7 ± 35.0	57.8 ± 31.2	0.35 ± 1.4	0.9 ± 3.6	32.0 ± 34.6	>	16.3 ± 20.1	16.9 ± 21.3		22.1 ± 23.3	2.1 ± 4.0	2.8 ± 5.4
RL upper-peripheral	66.9 ± 29.3	70.3 ± 25.4	2.55 ± 3.8	2.9 ± 4.4	17.4 ± 24.5		10.8 ± 15.1	11.6 ± 16.1		14.0 ± 16.2	1.6 ± 2.1	2.1 ± 3.3
LL upper-peripheral	71.5 ± 26.5	76.8 ± 21.4	3.15 ± 5.5	3.5 ± 5.5	15.8 ± 24.5		7.7 ± 13.0	8.1 ± 11.2		10.2 ± 13.6	1.4 ± 1.9	1.7 ± 3.0
RL middle-peripheral	57.3 ± 26.8	57.0 ± 23.5	2.15 ± 2.9	1.8 ± 2.5	26.0 ± 26.7		16.8 ± 16.2	13.2±14.1	<	22.5 ± 16.7	1.4 ± 2.3	2.0 ± 4.0
LL middle-peripheral	51.4 ± 29.0	56.5 ± 28.9	1.3 ± 2.0	1.2 ± 2.1	32.0 ± 29.1	>	19.2 ± 19.4	14.0 ± 15.6	<	21.5 ± 19.4	1.3 ± 2.1	1.7 ± 2.8
RL lower-peripheral	41.0 ± 23.2	41.0 ± 22.6	2.5 ± 5.4	1.7 ± 4.0	34.6 ± 26.0		26.5 ± 19.6	20.4 ± 17.5	<	28.8 ± 18.8	1.5 ± 2.4	2.0 ± 4.0
LL lower-peripheral	41.0 ± 27.9	40.9 ± 25.7	1.8 ± 3.1	1.8 ± 4.9	37.0 ± 29.3		28.5 ± 21.7	18.9 ± 19.0	<	26.8 ± 19.7	1.2 ± 2.0	2.0 ± 3.7
RL total	63.3 ± 25.5	68.1 ± 20.2	1.6 ± 3.1	1.5 ± 2.8	22.8 ± 25.3	>	13.1 ± 12.9	10.7 ±10.8		15.4 ± 13.8	1.6 ± 2.3	1.9 ± 3.2
LL total	63.1 ± 25.3	69.7 ± 20.0	1.4 ± 2.1	1.8 ± 3.3	24.4 ± 25.4	>	13.4 ± 13.2	9.7 ± 10.7		13.3 ± 12.8	1.4 ± 2.0	1.8 ± 2.9
Total lung	64.0 ± 24.3	69.9 ± 19.0	1.4 ± 2.4	1.7 ± 2.9	23.3 ± 24.2	>	13.3 ± 12.8	9.8 ± 10.5		13.2 ± 12.6	1.5 ± 2.1	1.8 ± 2.8

RL = right lung, LL = left lung. The mean relative volumes are given as the means of the relative volume percentages ± standard deviations.

The boxed values with blue backgrounds, with a greater (>) or lesser (<) sign in between, are those that are significantly different in the biopsied and non-biopsied groups with a $p < 0.05$. Note that the ground glass pattern percentages were significantly higher in the biopsied patients than in the non-biopsied ones mainly in the central lung sections. The reticular pattern percentages were significantly lower in the biopsied patients than in the non-biopsied ones only in the peripheral sections of the middle and lower lung zones

parenchymal patterns in the biopsied group with those in the non-biopsied group, in a total lung-based manner, only the ground-glass pattern showed a significant difference (it was higher in the biopsied [23.3%] than in the non-biopsied group [13.3%]) ($p < 0.01$).

When we compared the sectional volume percentages of the parenchymal patterns between the corresponding lung sections of the biopsied and non-biopsied groups for each of the twelve lung sections (six in each lung), we found that the mean percentages of the ground-glass pattern were significantly higher in seven of the lung sections of the biopsied group than those in the corresponding sections of the non-biopsied one (six of these sections were symmetric including the bilateral central sections of the upper, middle, and lower lung zones, and an additional one was asymmetric, the middle-peripheral section of the left lung) (Table 2).

On the other hand, the reticular pattern percentages were significantly lower in the middle and lower peripheral sections of both lungs of the biopsied group than those in the corresponding sections of the non-biopsied group (Table 3).

The relative volumes of the honeycomb, hyperlucent, and normal lung patterns showed no significant difference between the corresponding lung sections of the two patient groups.

DISCUSSION

In our study, CALIPER has detected that, compared to the non-biopsied patients the biopsied patients have significantly higher percentages of the ground-glass volume in the central sections, and lower percentages of the reticular pattern in the peripheral sections of the lungs.

IPF is the most common fibrotic disease of the lung. It is more common in older ages and in males [6, 7]. There was an elder-male dominance in our patient population and this was compatible with the literature.

According to the ATS/ERS/JRS/ALAT guideline, in patients with a definite UIP pattern on lung CT, in the absence of a detectable etiology, surgical lung biopsy is not necessary for an IPF diagnosis. However, biopsy should be considered in patients with CT findings of 'probable UIP' or 'indeterminate for UIP', especially when an alternative diagnosis is not achievable [1, 8, 9]. Radiologically, the main difference between 'definite UIP' and 'probable UIP' is the presence or absence of honeycombing, respectively, and this difference may change a decision from 'no need to biopsy' into 'biopsy'. However, visual evaluation of CT images is subjective and prone to interobserver discrepancies. Sometimes it may be difficult to differentiate honeycombing from bronchiectasis and

Table 2. Comparison of relative volumes of ground-glass pattern (%) in corresponding lung sections of biopsied and non-biopsied IPF groups

	Right Lung		Left Lung	
	Peripheral	**Central**	**Central**	**Peripheral**
Upper	B: 17.4 ± 24.5	B: 15.7 ± 26.9	B: 14.1 ± 26.5	B: 15.8 ± 24.5
	NB: 10.8 ± 15.1	NB: 6.2 ± 13.1	NB: 4.4 ± 11.9	NB: 7.7 ± 13.0
	$p = 0.13$	**$p = 0.04$**	**$p = 0.03$**	$p = 0.60$
Middle	B: 26.0 ± 26.7	B: 19.1 ± 28.2	B: 24.3 ± 28.7	B: 32.0 ± 29.1
	NB: 16.8 ± 16.2	NB: 9.0 ± 12.8	NB: 11.5 ± 16.6	NB: 19.2 ± 19.4
	$p = 0.50$	**$p = 0.04$**	**$p = 0.01$**	**$p = 0.02$**
Lower	B: 34.6 ± 26.0	B: 30.4 ± 29.6	B: 32.0 ± 34.6	B: 37.0 ± 29.3
	NB: 26.5 ± 19.6	NB: 14.6 ± 18.5	NB: 16.3 ± 20.1	NB: 28.5 ± 21.7
	$p = 0.07$	**$p = 0.004$**	**$p = 0.01$**	$p = 0.12$

B = Biopsied IPF group, NB = Non-biopsied IPF group. Values are means ± standard deviations.

Each table cell represents one of the twelve lung sections and positioned on this table in accordance to the position of the corresponding lung section on a postero-anterior chest x-ray. The table cells with blue background represent those lung sections in which a significantly higher percentage of the ground-glass pattern were measured in the biopsied group than in the non-biopsied group with a $p < 0.05$.

Table 3. Comparison of Relative Volumes of Reticular Pattern (%) in Corresponding Lung Sections of Biopsied and Non-Biopsied IPF Groups

	Right Lung		Left Lung	
	Peripheral	**Central**	**Central**	**Peripheral**
Upper	B: 11.6 ± 16.1	B: 5.2 ± 9.8	B: 2.6 ± 4.5	B: 8.1 ± 11.2
	NB: 14.0 ± 16.2	NB: 6.4 ± 11.8	NB: 4.6 ± 9.7	NB: 10.2 ± 13.6
	$p = 0.47$	$p = 0.60$	$p = 0.17$	$p = 0.42$
Middle	B: 13.2 ± 14.1	B: 5.2 ± 7.6	B: 4.6 ± 6.6	B: 14.0 ± 15.6
	NB: 22.5 ± 16.7	NB: 8.8 ± 11.9	NB: 6.9 ± 9.6	NB: 21.5 ± 19.4
	$p = 0.004$	$p = 0.06$	$p = 0.14$	**$p = 0.04$**
Lower	B: 20.4 ± 17.5	B: 17.8 ± 20.3	B: 16.9 ± 21.3	B: 18.9 ± 19.0
	NB: 28.8 ± 18.8	NB: 25.6 ± 24.7	NB: 22.1 ± 23.3	NB: 26.8 ± 19.7
	$p = 0.02$	$p = 0.09$	$p = 0.26$	**$p = 0.04$**

B = Biopsied IPF group, NB = Non-biopsied IPF group. Values are means ± standard deviations.

Each table cell represents one of the twelve lung sections and positioned on this table in accordance to the position of the corresponding lung section on a postero-anterior chest x-ray. The table cells with blue background represent those lung sections in which a significantly lower percentage of the reticular pattern were measured in the biopsied group than in the non-biopsied group with a $p < 0.05$.

emphysema and this may cause interobserver disagreement about the presence of honeycombing [3].

In the ATS/ERS/JRS/ALAT guideline, it is emphasized that 'mild' ground-glass opacities can be seen in 'probable UIP' and, if ground-glass is a 'prominent' feature on CT, then this is suggestive of an alternative diagnosis other than UIP [1]. These 'mild' and 'prominent' adjectives seem to be a little subjective and may cause interobserver discrepancies, especially when there is a lack of experience. Guideline authors pointed out the potential role of quantification of parenchymal patterns and directed future researchers to conduct quantitative studies with automated methods.

Quantitative CT techniques can help us to decrease subjectivity. CALIPER, a computer technology pioneered at the Mayo Clinic, has the ability to detect five parenchymal patterns (normal, ground-glass, reticular, honeycomb, and emphysema). It was reported that interstitial findings measured by CALIPER were predictive of survival, helpful in evaluating the response to pirfenidone, and correlated with the findings of pulmonary function tests in IPF patients [10-12]. CALIPER was shown to produce classification results comparable to expert radiologic judgment [4].

Jacob *et al*. [13] reported that a large proportion of the areas visually labeled as reticular pattern were characterized as ground-glass opacities by CALIPER]. Therefore, in their study, the ground-glass pattern was reported to be the abnormal parenchymal pattern with the highest volume percentage measured by CALIPER in 283 IPF patients, whereas the reticular pattern had the highest percentage measured by visual scoring. In our study, CALIPER's findings were similar and the percentages of ground-glass were higher than those of the reticular pattern in both biopsied and non-biopsied IPF groups.

We used CALIPER's measurements to compare the relative volumes of parenchymal patterns between the biopsied and non-biopsied IPF groups, in a total lung-based manner and then in a section-based manner. To our knowledge, this is the first study doing such a comparison.

When compared in a total lung-based manner, we found that only the ground-glass pattern percentages were significantly different between the two patient groups and it was higher in the biopsied group ($p < 0.01$).

Section-based comparisons revealed that the ground-glass volume percentages were higher in the central sections of the lungs in the biopsied patients than those in the corresponding central sections of the non-biopsied ones (Table 2). Since the ground-glass pattern seen in IPF usually happens in areas of periph-

eral reticulation or honeycombing, it may be thought that the presence of ground-glass in the central lung sections possibly acted in favor of the biopsy decisions in our biopsied patient group.

Reticular pattern percentages were not significantly different in the two groups when compared cumulatively. However, section-based comparisons revealed significantly lower reticular pattern percentages in bilateral middle and lower peripheral lung sections of the biopsied group than those in the corresponding sections of the non-biopsied group (Table 3). In IPF patients, the reticular parenchymal pattern is expected to be observed prominently in bilateral lower peripheral areas of the lungs, and therefore, the relatively lower reticular pattern percentages at the bilateral middle and lower peripheral regions in our biopsied patient group, compared to those in the non-biopsied, may be interpreted as a factor that possibly acted in favor of the biopsy decisions in our biopsied patients.

Interestingly, the relative volumes of the honeycomb pattern were not significantly different in the two groups, neither in total lung-based nor in section-based comparisons, contrary to what might be expected. Since the presence of honeycombing, especially when it is in a bilateral and bibasilar distribution, is in favor of a 'no need to biopsy' decision, we expected that the honeycomb pattern might have a higher percentage in the non-biopsied group. However, CALIPER found similar percentages in the two groups. Jacob *et al*. reported that a substantial proportion of the areas visually labeled as honeycombing were characterized as reticular and/or ground-glass patterns by CALIPER [13]. This was the same in our study and in both of our patient groups CALIPER 'recognized' only some portions of the honeycomb pattern and the percentages of these portions happened to be similar in our two patient groups.

The percentages of normal and hyperlucent parenchyma were not significantly different in the two patient groups, neither cumulatively nor sectionally.

Limitations

Our study has limitations: i) We think that other texture analysis algorithms may have different measurement results from those of CALIPER's. Hence, our findings cannot be generalized to all qCT methods. ii) CALIPER characterizes some portions of the parenchymal patterns different from those of visual labeling. For this reason, our measurement findings cannot be directly translated into routine radiological practice that is mainly dependent on visual labeling. iii) We focused only on the qCT findings of our patients and did not collect and compare the detailed clinical and laboratory findings of the two groups. Therefore, we cannot claim about the independent role of the qCT findings on biopsy decisions.

We think that qCT is a promising tool in the diagnosis and follow-up of interstitial lung diseases, and we hope to inspire future studies that analyze qCT findings in large series to develop quantitative methods that can help to avoid at least some of the unnecessary surgical lung biopsies.

CONCLUSION

Comparison of the CALIPER's measurements between the corresponding lung sections of the biopsied and the non-biopsied IPF patients revealed that the biopsied patients have significantly higher percentages of the ground-glass volume in the central sections of the upper, middle, and lower lung zones, and lower percentages of the reticular pattern in the peripheral sections of the middle and lower lung zones, compared to the non-biopsied patients. Regarding the relative volumes of the honeycomb, hyperlucent and normal parenchyma patterns, CALIPER detected no significant difference between the biopsied and non-biopsied patients. We think that quantification may facilitate a better understanding of the role of CT findings in biopsy decisions and may help to avoid from at least some of the unnecessary biopsies in suspected IPF patients.

Authors' Contribution

Study Conception: AG; Study Design: AG; Supervision: AG; Funding: AG; Materials: AG; Data Collection and/or Processing: AG; Statistical Analysis and/or Data Interpretation: AG; Literature Review: AG; Manuscript Preparation: AG and Critical Review: AG.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Determinants of clinical course and mortality in COVID-19 patients with hematological disorders: real life data from a single center

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ABSTRACT

Objectives: Patients with hematological disorders are often immunosuppressive due to underlying diseases, immunosuppressive therapies or cytotoxic chemotherapeutics. In the case of coronavirus disease 2019 (COVID-19), they are at high risk of poor prognosis. Therefore, the present study aimed to evaluate the determinants of clinical course and mortality in COVID-19 patients with hematological disorders.

Methods: Sixty-two hospitalized patients older than 18 years with documented COVID-19 and hematological disorders were included in the study. The clinical and laboratory data of the patients were recorded. Age, gender, overall follow-up time, duration of hospitalization, neutropenia, D-dimer levels, disease status, presence of underlying diseases, prior autologous and allogeneic stem cell transplant, immunosuppressive drug use, chemotherapy within 28 days, pneumonia, secondary bacterial infection, intubation, survival and mortality of the patients were evaluated.

Results: Twenty-eight (45.2%) of 62 patients died due to COVID-19 and its complications. It was observed that presence of pneumonia, secondary bacterial infection, intubation, neutropenia developed after the diagnosis of COVID-19, and elevated D-dimer levels were associated with significant mortality. A D-dimer level of > 1.2 µg/dL was found to be associated with 5.02 fold increase in the risk of death, with 60.7% sensitivity and 76.5% specificity. Presence of rheumatologic diseases also affected survival negatively.

Conclusions: D-dimer levels have high predictive value for mortality. Considering the identified risk factors, it can be concluded that broad spectrum antibiotics can be administered earlier for prevention of high mortality rates in COVID-19 patients with underlying hematological disorders. These observations can give confidence to clinicians that delivery of effective anticancer regimens should continue during this difficult pandemic.

Keywords: COVID-19, hematological disorders, mortality

Novel coronavirus (severe acute respiratory syndrome coronavirus 2, SARS Cov-2) disease (coronavirus disease 2019, COVID-19) has been the most important global health problem since the end of

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2019 [1]. According to the current World Health Organization (WHO) data, approximately 150 million people have been infected with the virus to date, and more than 3 million have died due to COVID-19 and/or its complications [2]. Characteristics of COVID-19 symptoms in hematological patients share similarities with the general population with fever, dry cough, fatigue and diarrhea being the most common initial signs/symptoms of infection [3]. Some special patient groups such as diabetics, older patients and especially immunosuppressive patients have poor outcome [4]. Patients with hematological disorders are often immunosuppressive due to underlying diseases, immunosuppressive therapies or cytotoxic chemotherapeutics [5]. Therefore, assessment and determination of the best therapeutic needs of the immunosuppressed patient with COVID-19 is critical. However, there are few published data on the consequences of COVID-19 in hematological patients so far [5-9]. Based on available information, patients with hematological malignancies and bone marrow transplants are at high risk of poor prognosis in case of COVID-19 [10]. Furthermore, patients with hematological malignancies have worse outcomes than patients with solid tumors [11]. During COVID-19 outbreak, it is of extreme importance to understand that cancer patients should be considered as a special population due to their higher risk of acquiring secondary infections and faster decline rate. Therefore patients with hematological disorders, both benign and malignant need special attention during this crisis time [12]. Mortality reports have shown a higher mortality rate in cancer patients with COVID-19 compared to the general population [13]. COVID-19 is a respiratory infection with a significant impact on the hematopoietic system and hemostasis leading to several cardiovascular complications. A better understanding of COVID-19 in particular hematological disorders will help to choose appropriate treatment strategies in the future [14]. COVID-19 infection is associated with a coagulopathy characterized by an increase in procoagulant factors such as fibrinogen, together with a strong increase of D-dimers that have been associated with a higher mortality [15, 16]. Accordingly, the present study aimed to evaluate the determinants of clinical course and mortality in COVID-19 patients with hematological disorders.

METHODS

Patients

Patients with documented COVID-19 and hematological disorders older than 18 years were included in the study. Diagnostic analysis, survival data, predictors of death and laboratory results of those patients were evaluated. Only hospitalized patients were accepted. The endpoint of the study was hospital discharge with clinical recovery or death. The clinical and laboratory data of the patients were recorded. D-dimer levels were recorded at the time of admission. Written informed consent was obtained from all patients. This study was conducted in accordance with the World Medical Association Declaration of Helsinki and reviewed and approved by the Ethics Committee of Memorial Hospitals Group after obtaining permission of the Turkish Ministry of Health Ethics Committee.

Laboratory Assay

D-dimer was determined on Cobas C501 automatic biochemistry analyzer (Roche Diagnostics, Tokyo, Japan) via immunoturbidimetric assay. The laboratory reference range was 0-0.5 µg/mL. The D-dimer result was expressed in µg/mL FEU (Fibrinogen Equivalent Unit). All measurements were performed within 2 hours after blood sampling. Confirmed COVID-19 infection was defined as a positive result on a SARS-CoV-2 reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay of a nasopharyngeal swab specimen.

Statistical Analysis

Data analyses were performed using the IBM SPSS Statistics for Windows, Version 27.0 (IBM Corp., Armonk, NY, USA) software. Normality of the univariate data was assessed using the Shapiro-Wilk and Shapiro-Francia tests, while Levene's test was used to assess the homogeneity of variances. For the comparison of two independent groups of quantitative data, independent samples t-test was used together with Bootstrap results, and Mann-Whitney U test. For the comparison between categorical variables, Pearsons chi-square and Fisher's exact tests were used with the Monte Carlo Simulation technique. Odds ratio was used to demonstrate the relative risk of death in patients with a risk factor compared to those without. Receiver Operating Curve (ROC) analysis was used to

show the relationship between sensitivity and specificity for every possible cut-off value calculated according to the variables of the groups and the actual classification. Kaplan-Meier (product limit method) - Log-Rank (Mantel-Cox) analysis was used to examine the effects of the factors on mortality and lifespan. Quantitative variables are expressed as mean (standard deviation) and median (25th Percentile [Q1]/75th percentile [Q3]) in the tables, while categorical variables are shown as number (percentage, %). Variables were analyzed at a 95% confidence level and a p value of less than 0.05 was considered significant.

RESULTS

Sixty-two hospitalized patients with documented COVID-19 and hematological disorders older than 18 years were enrolled in the study. Nineteen patients had acute myeloid leukemia (AML) and 17 patients had non-Hodgkin's lymphoma (NHL) with a mortality rate of 57.9% and 29.4%, respectively. Of 62 patients, 28 (45.2%) died due to COVID-19 and its complications (Table 1). Patients had an average age of 60.9 years and the average duration of hospitalization was 14 days. When clinical and demographic data were evaluated, it was found that age, gender, overall follow-up time, duration of hospitalization, presence of neutropenia at the diagnosis of COVID-19, underlying diseases and disease status were not associated with mortality; however, the presence of pneumonia, secondary bacterial infection, intubation, neutropenia developed after the diagnosis of COVID-19, and D-dimer levels were associated with a statistically significant mortality ($p < 0.05$) (Fig. 1). A D-dimer level over 1.2 µg/dL is the percentile 75 value of the alive group; therefore it is accepted as a cut off value in this patient group to predict the risk of death. A D-dimer level greater than 1.2 µg/dL was found to be associated with a 5.02 fold increase in the risk of death with 60.7% sensitivity and 76.5% specificity (Table 2). Similarly presence of pneumonia, secondary bacterial infection, intubation, neutropenia after the diagnosis of COVID-19, a D-dimer levels > 1.2 µg/dL had a negative effect on the survival of the patients. Presence of rheumatologic diseases also affected survival negatively ($p < 0.05$) (Table 3).

DISCUSSION

The relationship between COVID-19 and pre-existing diseases is poorly described and based on small retrospective studies [17]. The current pandemic coronavirus, SARS-CoV-2, is known to cause severe infection in patients with comorbidities, particularly cancer or immunosuppression [18]. Patients suffering from cancer are vulnerable to the effects of COVID-19, and they have been postulated to be at increased risk of mortality [19]. In addition, male sex, older age, hypertension, diabetes, and obesity have been shown to be associated with higher COVID-19 mortality [20]. In general population, data from different countries suggest a case-fatality of 2.3% in patients with COVID-19, with more than 50% of the fatalities occurring in patients 50 years of age or older [21]. In our

Table 1. Mortality rates of the study patients according to the type of hematological disorder

Diagnosis	n (%)	Alive	Dead	Mortality (%)
Acute myeloid leukemia	19 (27.4)	8	11	57.9
Non-Hodgkin's lymphoma	17 (27.4)	12	5	29.4
Multiple myeloma	8 (12.9)	6	2	25.0
Chronic lymphocytic leukemia	4 (6.5)	2	2	50.0
Chronic myeloid leukemia	3 (4.8)	2	1	33.3
Myelodisplastic syndrome	3 (4.8)	2	1	33.3
Hodgkin's lymphoma	3 (4.8)	1	2	66.6
Idiopathic thrombocytopenic purpura	2 (3.2)	0	2	100.0
Chronic myelomonocytic leukemia	2 (3.2)	1	1	50.0
Myelofibrosis	1 (1.6)	0	1	100

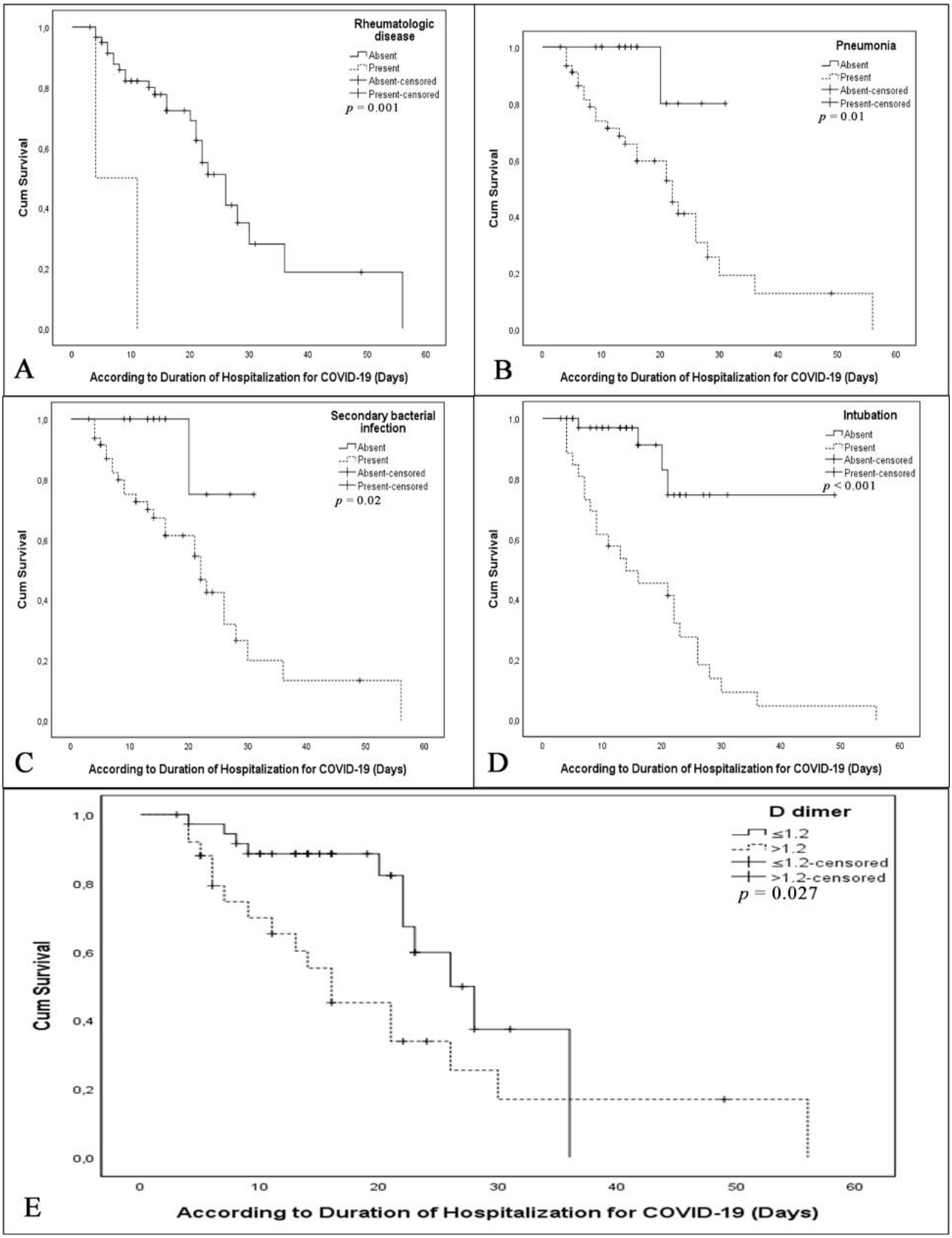

Fig. 1. Significant predictors of mortality. (A) Rheumatologic disease, (B) Pneumonia, (C) Secondary bacterial infection, (D) Intubation and (E) D-Dimer level.

Table 2. Comparison of alive and dead patients in terms of clinical and demographic data

	Total	Alive	Dead	*p* value	OR (95% CI) or AUC (SE)
	(n = 62)	(n = 34)	(n = 28)		
Age, years, mean (SD)	60.9 (14.6)	58.0 (15.3)	64.3 (13.1)	0.106	-
Age, n (%)					
< 65	33 (53.2)	21 (61.8)	12 (42.9)	0.201	-
≥ 65	29 (46.8)	13 (38.2)	16 (57.1)		
Sex					
Female	28 (45.2)	13 (38.2)	15 (53.6)	0.306	-
Male	34 (54.8)	21 (61.8)	13 (46.4)		
Overall follow-up time, median (Q1/Q3)	478 (159/1477)	697 (148 / 1513)	404 (160/888.5)	0.563	
Duration of hospitalization for COVID-19, days, median (Q1/Q3)	14 (9/22)	14 (10/21)	15 (7/22.5)	0.959	-
Neutropenia at COVID-19 diagnosis, n (%)					
Absent	45 (72.6)	28 (82.4)	17 (60.7)	0.086	-
Present	17 (27.4)	6 (17.6)	11 (39.3)		
Neutropenia after COVID-19 diagnosis, n (%)					
Absent	36 (58.1)	25 (73.5)	11 (39.3)	**0.010**	**4.3 (1.5-12.6)** OR
Present	26 (41.9)	9 (26.5)	17 (60.7)		
Disease status, n (%)					
Active	34 (54.8)	17 (50.0)	17 (60.7)	0.450	-
Remission	28 (45.2)	17 (50.0)	11 (39.3)		
Diabetes, n (%)					
Absent	50 (80.6)	29 (85.3)	21 (75.0)	0.349	-
Present	12 (19.4)	5 (14.7)	7 (25.0)		
Hypertension, n (%)					
Absent	35 (56.5)	21 (61.8)	14 (50.0)	0.443	-
Present	27 (43.5)	13 (38.2)	14 (50.0)		
Coronary disease, n (%)					
Absent	48 (77.4)	29 (85.3)	19 (67.9)	0.132	-
Present	14 (22.6)	5 (14.7)	9 (32.1)		
Rheumatologic disease, n (%)					
Absent	60 (96.8)	34 (100.0)	26 (92.9)	0.200	-
Present	2 (3.2)	0 (0.0)	2 (7.1)		
Chronic obstrucive lung disease/asthma, n (%)					
Absent	59 (95.2)	34 (100.0)	25 (89.3)	0.087	-
Present	3 (4.8)	0 (0.0)	3 (10.7)		
Prior autologus stem cell transplant, n (%)					

Table 2 contunied. Comparison of alive and dead patients in terms of clinical and demographic data

	Total	Alive	Dead	*p* value	OR (95% CI) or AUC (SE)
	(n = 62)	(n = 34)	(n = 28)		
Absent	53 (85.5)	28 (82.4)	25 (89.3)	0.494	-
Present	9 (14.5)	6 (17.6)	3 (10.7)		
Prior allogeneic stem cell transplant, n (%)					
Absent	54 (87.1)	30 (88.2)	24 (85.7)	0.999	-
Present	8 (12.9)	4 (11.8)	4 (14.3)		
Immunosuppressive drug use, n (%)					
Absent	51 (82.3)	31 (91.2)	20 (71.4)	0.092	-
Present	11 (17.7)	3 (8.8)	8 (28.6)		
Chemotherapy within 28 days, n (%)					
Absent	29 (46.8)	14 (41.2)	15 (53.6)	0.444	-
Present	33 (53.2)	20 (58.8)	13 (46.4)		
Pneumonia, n (%)					
Absent	17 (27.4)	16 (47.1)	1 (3.6)	**< 0.001**	**24 (2.9-197.3) OR**
Present	45 (72.6)	18 (52.9)	27 (96.4)		
Secondary bacterial infection, n (%)					
Absent	15 (24.2)	14 (41.2)	1 (3.6)	**0.001**	**18.9 (2.3-155.8) OR**
Present	47 (75.8)	20 (58.8)	27 (96.4)		
Intubation					
Absent	36 (58.1)	32 (94.1)	4 (14.3)	**< 0.001**	**96 (16.2-568.1) OR**
Present	26 (41.9)	2 (5.9)	24 (85.7)		
D-dimer, median (Q1/Q3), µg/dL	1.03 (0.37 / 2.22)	0.765 (0.28 / 1.2)	1.49 (0.765 / 2.925)	**0.001**	
D-dimer, n (%)					
≤ 1.2	37 (59.7)	**26 (76.5) sp**	11 (39.3)	**0.002 rc**	**0.709 (0.067) AUC (SE) 5.02 (1.7-15.04) OR**
> 1.2	25 (40.3)	8 (23.5)	**17 (60.7) ss**		

OR = Odds Ratio; CI = Confidence interval, rc Roc (Receiver Operating Curve) Analysis (Honley&Mc Nell - Youden index J), AUC = Area under the ROC curve; SE = Standard Error.

ss Sensitivity; sp Specificity; SD = standard deviation, Q1, 25th percentile; Q3, 75th percentile; Q1/Q3, 25th percentile / 75th percentile.

study, the mortality rate of COVID-19 in hematological disorders was 45.2% showing a range of 25% to 100% according to the type of the hematological disorder. This shows that mortality rates and clinical course of COVID-19 in specific underlying diseases and conditions can be very different compared to general population. The highest mortality rates were observed in ITP, AML and NHL with 100%, 57.9% and 29.4% of the patients respectively. The findings of our study support the data published in the literature on the expected high mortality of COVID-19 in cancer patients.

Our study is important for showing the results of 62 patients with co-occurrence of COVID-19 and hematological disorders in a single center, while individual health-care centers and physicians only see a

Table 3. Survival estimates in dead and alive patients in terms of clinical and demographic data

	Dead	Alive	According to Duration of Hospitalization for COVID-19 (Days)		
			Estimate Survival	Estimate Proportion Surviving at	*p*
	n (%)	n (%)	Mean ± SE	7 / 14 / 28 days (SE)	
Overall	28 (45.2)	34 (54.8)	26.7 (3.17)	86.4 (4.5) / 90.0 (3.9) / 79.1 (5.4)	
Age					
< 65	12 (36.4)	21 (63.6)	26 (3.72)	93.4 (4.5) / 72.4 (9.1) / 44.7 (14.2)	0.779
≥ 65	16 (55.2)	13 (44.8)	26.8 (4.52)	78.9 (7.7) / 75.3 (8.1) / 22.9 (12.4)	
Gender					
Female	15 (53.6)	13 (46.4)	25.4 (4.89)	82.0 (7.3) / 85.7 (6.6) / 74.1 (8.5)	0.466
Male	13 (38.2)	21 (61.8)	26.9 (3.45)	90.0 (5.5) / 93.3 (4.6) / 83.1 (6.9)	
Neutropenia at COVID-19 Diagnosis					
Absent	17 (37.8)	28 (62.2)	27 (3.12)	88.4 (4.9) / 93.2 (3.8) / 80.9 (6.1)	0.229
Present	11 (64.7)	6 (35.3)	22.4 (5.04)	80.4 (10.2) / 80.4 (10.2) / 73.7 (11.3)	
Neutropenia after COVID-19 diagnosis					
Absent	11 (30.6)	25 (69.4)	32.8 (3.87)	85.7(5.9) / 91.6 (4.7) / 79.6 (6.9)	0.210
Present	17 (65.4)	9 (34.6)	23 (3.18)	87.5 (6.8) / 87.5 (6.8) / 78.7 (8.5)	
Disease status					
Active	17 (50.0)	17 (50.0)	27.6 (4.41)	84.4 (6.4) / 87.7 (5.8) / 81.2 (6.9)	0.991
Remission	11 (39.3)	17 (60.7)	23.7 (2.69)	88.9 (6.1) / 92.7 (5.0) / 76.5 (8.4)	
Diabetes					
Absent	21 (42.0)	29 (58.0)	29 (3.95)	89.5 (4.5) / 91.7 (4.0) / 80.4 (5.9)	0.481
Present	7 (58.3)	5 (41.7)	21.8 (3.9)	74.1 (12.9) / 83.3 (10.8) / 74.1 (12.9)	
Hypertension					
Absent	14 (40.0)	21 (60.0)	29.4 (5.12)	88.0 (5.6) / 91.2 (4.9) / 81.2 (6.9)	0.624
Present	14 (51.9)	13 (48.1)	22.7 (2.44)	84.3 (7.2) / 88.3 (6.4) / 76.2 (8.5)	
Coronary disease					
Absent	19 (39.6)	29 (60.4)	29 (4.41)	91.2 (4.2) / 93.5 (3.6) / 81.7 (5.9)	0.414
Present	9 (64.3)	5 (35.7)	21.3 (3.53)	70.1 (12.6) / 77.9 (11.3) / 70.1(12.6)	
Rheumatologic disease					
Absent	26 (43.3)	34(56.7)	27.4 (3.25)	87.7 (4.4) / 91.3 (3.7) / 82.1 (5.1)	**0.001**
Present	2 (100.0)	0(0.0)	7.5 (3.5)	50.0 (35.4) / 50.0 (35.4) / 0.0 (0.0)	
Chronic obstrucive lung disease/asthma					
Absent	25 (42.4)	34 (57.6)	27.9 (3.41)	89.4 (4.1) / 91.2 (3.7) / 81.7 (5.3)	0.065
Present	3 (100.0)	0 (0.0)	13 (6.51)	33.3 (27.2) / 66.7 (27.2) / 33.3 (27.2)	
Prior autologous stem cell transplant					
Absent	25 (47.2)	28(52.8)	27 (3.32)	88.1 (4.6) / 92.2 (3.8) / 79.6 (5.8)	0.784
Present	3 (33.3)	6 (66.7)	18.7 (3.24)	76.2 (14.8) / 76.2 (14.8) / 76.2 (14.8)	

Table 3 contunied. Survival estimates in dead and alive patients in terms of clinical and demographic data

	Dead	Alive	According to Duration of Hospitalization for COVID-19 (Days)		
			Estimate Survival	Estimate Proportion Surviving at	*p*
	n (%)	n (%)	Mean ± SE	7 / 14 / 28 days (SE)	
Prior allogeneic stem cell transplant					
Absent	24 (44.4)	30 (55.6)	27.9 (3.65)	84.3(5.1)/88.4(4.5)/77.9(5.9)	0.867
Present	4 (50.0)	4 (50.0)	23.7 (5.36)	84.3(5.1)/88.4(4.5)/85.7(13.2)	
Immunosuppressive drug use					
Absent	20 (39.2)	31 (60.8)	29.8 (3.92)	85.5 (5.1) / 87.7(4.7) / 83.3 (5.4)	0.054
Present	8 (72.7)	3 (27.3)	17.8 (3.68)	90.9 (8.7) /87.7 (4.7) /60.6 (15.4)	
Chemotherapy within 28 days					
Absent	15 (51.7)	14 (48.3)	20.4 (2.18)	89.1 (5.9) / 96.6 (3.4) /77.1 (8.3)	0.107
Present	13 (39.4)	20 (60.6)	32.7 (5.01)	83.9 (6.6)/ 83.9 (6.6)/ 80.6 (7.1)	
Pneumonia					
Absent	1 (5.9)	16 (94.1)	28.8 (1.97)	100 (0) / 100 (0) / 100 (0)	**0.010**
Present	27 (60.0)	18 (40.0)	23.2 (2.99)	81.3 (6.0) / 86.3 (5.2) / 71.2 (7.0)	
Secondary bacterial infection					
Absent	1 (6.7)	14(93.3)	28.3 (2.38)	100 (0) / 100 (0) / 100 (0)	**0.020**
Present	27 (57.4)	20 (42.6)	23.7 (3.02)	82.2 (5.7) / 86.9 (5.0) / 72.6 (6.8)	
Intubation					
Absent	4 (11.1)	32 (88.9)	41.1 (3.57)	96.9 (3.1) /96.9 (3.1) / 96.9 (3.1)	**< 0.001**
Present	24 (92.3)	2 (7.7)	17.8 (2.6)	73.1 (8.7) /80.8 (7.7) / 57.7 (9.7)	
D-dimer					
≤ 1.2	11 (29.7)	26 (70.3)	26.6 (2.19)	94.4(3.9) / 97.2(2.7) / 88.6 (5.4)	**0.027**
> 1.2	17 (68.0)	8 (32.0)	21.9 (4.21)	74.5(9.0) / 79.2 (8.3) / 65.2 (10.0)	

Kaplan Meier Test- Log Rank (Mantel-Cox), SE = Standard Error

few patients with both diseases. Lee *et al*. [17] studied mortality patterns from COVID-19 in cancer patients (8% and 14% had lymphomas and hematological malignancies, respectively) and found no increased risk of death. On the other hand, He *et al*. [8] studied 13 patients with hematological cancers (acute myeloid leukemia, acute lymphoblastic leukemia, plasma cell myeloma, and myelodysplastic syndromes) who developed COVID-19, and found more severe disease and a higher case fatality rate than other hospitalized patients. The higher case fatality rates may be attributed to the therapy they were receiving or due to other comorbid conditions such as diabetes, which is common in this group of patients. There was no association between the type of cancer and risk of developing COVID-19 [8]. In another study on cancer patients (8.6% had hematological cancers-leukemia, myeloma, and lymphoma) with SARS-CoV-2 infection, those with hematological cancers had the highest severity and death rate (33%). This may be because patients with hematological cancers receive more immunosuppression than those with solid tumors [22]. In our study it was observed that the presence of prior autologous or allogeneic stem cell transplantation or

chemotherapy within 28 days had no effect on mortality in patients with hematological disorders with COVID-19 infection. Immunosuppressive drug use and neutropenia at diagnosis of COVID-19 infection increased mortality, although not significantly. In some studies in the literature, it was observed that COVID-19 mortality in patients with cancer was principally driven by advancing age and the presence of other non-cancer comorbidities. Chemotherapy or anticancer treatments did not necessarily increase the risk of mortality from COVID-19 [17, 19]. These observations can give confidence to oncologists and other clinicians that delivery of effective anticancer regimens should continue during this difficult time. Although male sex and older age are risk factors for increased mortality in general population [20], we observed in our study that age and gender did not affect the mortality and clinical course of COVID-19 in patients with hematological disorders. Duration of hospitalization also was not related to mortality in our patients. In order to obtain more definite results, larger group of patients are needed.

SARS-CoV-2 infection can cause several hematological abnormalities. Some cases of autoimmune cytopenias such as thrombocytopenia and hemolytic anemia have been described [23, 24]. Lymphopenia is the most common laboratory finding in patients with COVID-19. Neutrophilia predicts poor outcome and severe respiratory failure [25]. There are also cases of COVID-19 with severe neutropenia [26]. Other viral infections associated with the development of transient neutropenia are herpesvirus 6, parvovirus, EBV, adenovirus, influenza A, HIV, hepatitis C virus, and cytomegalovirus. These viruses can cause direct damage to bone marrow progenitors and trigger autoimmune destruction [27]. Neutropenia arising as a result of underlying hematologic disorders is far more significant. Such patients are at risk for infectious complications [28]. Although in our study the presence of neutropenia at the diagnosis of COVID-19 was not associated with mortality, neutropenia developed after the diagnosis of COVID-19 led to a statistically significant increase in the mortality rates. This can be due to the co-occurrence of hematological disorders and COVID-19, which is an important observation for predicting high mortality in these patients.

Presence of underlying diseases such as diabetes, hypertension, coronary diseases and asthma had no effect on mortality in our study. Disease status either active disease or remission did not affect clinical course and mortality in our patients as well. In general population, it was observed that diabetes in patients with COVID-19 was associated with a two-fold increase in mortality as well as severity of COVID-19, as compared to non-diabetics [29]. It was also found that hypertension is associated with a 2.5 fold increased risk of both increased severity and mortality in COVID-19. In a meta-regression, it was observed that this effect is mainly attributed to those over the age of 60 [30]. Also underlying cardiovascular disease is associated with an increased risk of in-hospital death among patients hospitalized with COVID-19 [31]. Studies show that asthma as a concomitant disease may not increase COVID-19 mortality [32]. Again, in some studies, the results show that there is no statistically significant relationship between asthma history and mortality, regardless of COVID-19 status (33). In the case of specific underlying diseases like hematological disorders in our study, the determinants of the clinical course of COVID-19 and mortality are affected by some different parameters like neutropenia developed after diagnosis of COVID-19 apart from the general risk factors. Additionally the presence of pneumonia, intubation, secondary bacterial infection, and a D-dimer level of >1.2 µg/dL were associated with a statistically significant mortality in our study. Studies suggested that older age and underlying comorbidities were associated with disease severity or death of COVID-19 pneumonia patients. Pneumonia itself is one of the most important factors leading to mortality [34]. COVID-19 pneumonia is a specific disease of which the main characteristic is the dissociation between the severity of hypoxemia and the maintenance of relatively good respiratory mechanics [35]. In our study, presence of pneumonia and intubation increased mortality precisely in COVID-19 patients with hematological disorders. Intubation is a risk factor for hospital-acquired infections and also indicates the severity of clinical manifestations. Therefore, its presence increased mortality and adversely affected the clinical course. Secondary bacterial infection was also related to mortality in our study. Although low rates of pulmonary bacterial coinfection was reported in some studies in patients with COVID-19, the low rate of coinfection described seems to be underestimated [36-38].

Infection induced coagulopathy and secondary hyper-fibrinolysis has been identified in severe cases of COVID-19. As well, higher D-dimer level on admission was related to a worse prognosis [16, 39]. Anticoagulant treatment may benefit severe COVID-19 patients, especially those without cardiovascular diseases [40]. D-dimer is commonly elevated in patients with COVID-19. D-dimer level correlates with disease severity and is a reliable prognostic marker for in-hospital mortality in patients admitted for COVID-19 [41]. Coagulopathy was reported, and D-dimer elevations were seen in 3.75-68.0% of the COVID-19 patients in previous studies [16]. In a previous study, it was found that D-dimer on admission greater than 2.0 ④g/mL could effectively predict mortality in patients with COVID-19, which indicates that D-dimer can be an early and helpful marker to improve management of COVID-19 patients [42]. In our study, D-dimer level greater than 1.2 µg/dL was found to be associated with 5.02 fold increase in the risk of death in COVID-19 patients with hematological disorders. In our study, results parallel to the literature were obtained. When estimated survival in terms of clinical and demographic data were analyzed on the basis of duration of hospitalization for COVID-19, it was observed that presence of pneumonia, secondary bacterial infection, intubation, neutropenia after the diagnosis of COVID-19 and a D-dimer level of > 1.2 had a negative effect on the estimated survival of the patients. Besides other risk factors identified, it was observed that presence of rheumatologic disease as an underlying condition also affected survival negatively in COVID-19 patients with hematological disorders. In a previous study, it was reported that rheumatic disease activity might be associated with mortality. Inflammation was closely related to severity of COVID-19 [43].

CONCLUSION

Although the clinical course and determinants of mortality in COVID-19 patients with hematological disorders are parallel to the literature to a certain extent, they have some distinctive features. In our study, mortality rate of COVID-19 in hematological disorders was 45.2% which is very high compared to general patients showing a range of 25 to 100 % according to diagnosis. This shows that mortality rate and clinical course of COVID-19 in specific underlying diseases and conditions can be very different compared to general population. Age, sex, disease status, duration of hospitalization, presence of hypertension, diabetes and coronary disease were not associated with mortality. Immunosuppressive drug use and neutropenia at diagnosis of COVID-19 infection somewhat increased mortality although not statistically significant. D-dimer level above 1.2 µg/mL has a high predictive value for mortality. In our study, it was observed that presence of prior autologous or allogeneic stem cell transplantation, chemotherapy within 28 days and immunosuppressive therapy had no effect on mortality in patients with hematological disorders with COVID-19 infection. These observations can give confidence to clinicians that delivery of effective anticancer regimens should continue during this difficult pandemic. The presence of pneumonia, secondary bacterial infection, intubation and neutropenia developed after the diagnosis of COVID-19 were associated with a statistically significant mortality.

Authors' Contribution

Study Conception: BD, RS; Study Design: BD, RS; Supervision: RS, LD; Funding: N/A; Materials: MYT; Data Collection and/or Processing: AA, GA, BÜ, MYA; Statistical Analysis and/or Data Interpretation: TT; Literature Review: BD; Manuscript Preparation: BD and Critical Review: BD, RS.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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The European Research Journal 2022;8(4):462-467 Original Article

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Does serum prostate specific antigen levels correlate with the prostatic inflammation in elderly patients without clinically proven prostate cancer?

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ABSTRACT

Objectives: To determine the whether histological prostatic inflammation correlates with serum prostate specific antigen (PSA), free PSA (fPSA) and percent of fPSA (%fPSA) levels in elderly patients without clinically proven prostate cancer.

Methods: A total of 115 patients without clinically proven prostate cancer with transrectal prostate biopsy were included in this retrospective study. Patients were divided two main groups as patients with and without histologic prostatic inflammation. A grading of the histological prostatic inflammation was performed and patients with prostatic inflammation were divided into three subgroups. The age, prostate volume, serum PSA, fPSA and %fPSA levels were compared between patients with and without prostatic inflammation. Correlation between the parameters and grade of prostatic inflammation was also investigated.

Results: Serum PSA and %fPSA levels were significantly higher in men with histologically proven prostatic inflammation (15.47 ± 15.28 ng/mL vs. 11.67 ± 8.12 ng/mL; $p = 0.002$ and 19.8 ± 0.7 vs. 15.79 ± 0.9; $p = 0.01$, respectively). The mean serum PSA levels were significantly different among the subgroups ($p = 0.02$) and prostatic inflammation correlated positively with the PSA levels ($r = 0.320$, $p < 0.001$).

Conclusions: Our findings suggested that reporting the grade of prostatic inflammation in elderly patients may help avoiding unnecessary repeat biopsies if elevated serum PSA level is the only indication for initial prostate biopsy.

Keywords: Inflammation, prostate, prostate specific antigen, elderly, men

The serum prostate-specific antigen (PSA) is the most important and widely used marker in the screening, detection, and monitoring of prostate cancer (PCa) [1]. Millions of prostate biopsies are performed annually, most commonly due to an elevated PSA level. In addition to PCa, benign conditions such as benign prostatic hyperplasia (BPH) and prostatic inflammation can also increase the serum PSA levels [1, 2]. Histological findings of the prostatic inflammation in prostate biopsy or prostatectomy specimens are common in asymptomatic patients, as well as those with BPH [2]. Several studies have investigated the relationship between serum PSA level and histological prostatic inflammation in asymptomatic males; how-

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ever, the results have been controversial [3-5]. The previous studies were performed using either the intensity or the extent of neutrophilic infiltration in the prostate for grading the inflammation with a relatively lower number of specimens.

In the present study, we aimed to determine whether the histological prostatic inflammation correlates with serum PSA, free PSA (fPSA) and percent of fPSA (%fPSA) levels in elderly patients without clinically proven prostate cancer.

METHODS

The institutional ethical board approved the study (Approval ID: 2017/565). Data of the patients who underwent transrectal ultrasound guided 12-core prostate biopsy between January 2004 and January 2006 due to elevated serum PSA levels or abnormal digital rectal examination findings were collected retrospectively. A total of 260 patients were identified and patients with a history of documented acute/chronic prostatitis, symptoms related to acute/chronic prostatitis, urinary tract infection and abnormal digital rectal examination findings were excluded. Previous prostate biopsy and/or surgery, radiotherapy, 5-alpha reductase inhibitor treatment, and a history of urethral catheterization and non-steroidal antiinflammatory drug usage 2 weeks before the prostate biopsy were other exclusion criteria. Moreover, patients with diagnosis of PCa or high grade prostatic intraepithelial neoplasia on the current biopsy were also excluded.

All serum PSA and fPSA levels were measured in the same institute and device (Immulite 2000, DPC, Los Angeles, CA, USA). The %fPSA was calculated as the free/total serum PSA ratio . A urine analysis was performed just before the biopsy to rule out the evidence of urinary tract infection. Transrectal ultrasonography (Logic 400 machine, GE, Milwaukee, WI) with a 7.5-MHz endorectal probe was used to determine the prostate volume and to guide the needle biopsy. The total of 12-core prostate sampling was performed during the transrectal ultrasound guided prostate biopsy (TRUS-Bx) for each man in the lateral decubitus position, using an 18-gauge needle and an automatic biopsy gun. All patients received oral ciprofloxacin (500mg twice daily) for 7 days starting from the night before the biopsy and an enema at the morning of the procedure.

The pathological specimens of the patients diagnosed with benign prostatic pathologies were underwent further histological evaluation to determine the degree of inflammation by a single uropathologist (CB). The newly designed grading system based on the intensity and the extent of the prostatic tissue neutrophilic infiltration and tissue destruction to categorize and determine the grade of prostatic inflammation was used (Table 1 and Fig. 1). The degree of prostatic inflammation was evaluated in all 12 biopsy cores and grades of the inflammation were scored from 1 to 3.

Finally, men were classified to patients with and without prostatic inflammation and the parameters were statistically compared between patients with and without prostatic inflammation. Patients with prostatic inflammation were also classified to 3 subgroups according to grade of prostatic inflammation and correlation between the parameters and grade of prostatic inflammation was also investigated.

Statistical Analysis

Data were analyzed using SPSS-16 for Windows (SPSS Inc., Chicago, IL). Test of normality was determined with Shapiro-Wilk test. Kruskal Wallis Test, Mann Whitney U Test and Spearman correlation test were used to analyze the statistical differences. The results are expressed as mean ± SD while $p < 0.05$ was

Table 1. Classification of the prostatic inflammation according to intensity and the extent of the neutrophilic infiltration

Grade of inflammation	Description
Grade 1	Scattered neutrophilic infiltrate in < 6 biopsy cores (Fig. 1A).
Grade 2	Scattered neutrophilic infiltrate in ≥ 6 biopsy cores or scattered neutrophilic infiltrate in <6 biopsy cores with intensifying in some focal areas (Fig. 1B).
Grade 3	Heavy neutrophilic infiltrate intensifying in some focal areas in ≥ 6 biopsy cores and/or destruction of glands in any cores (Fig. 1C).

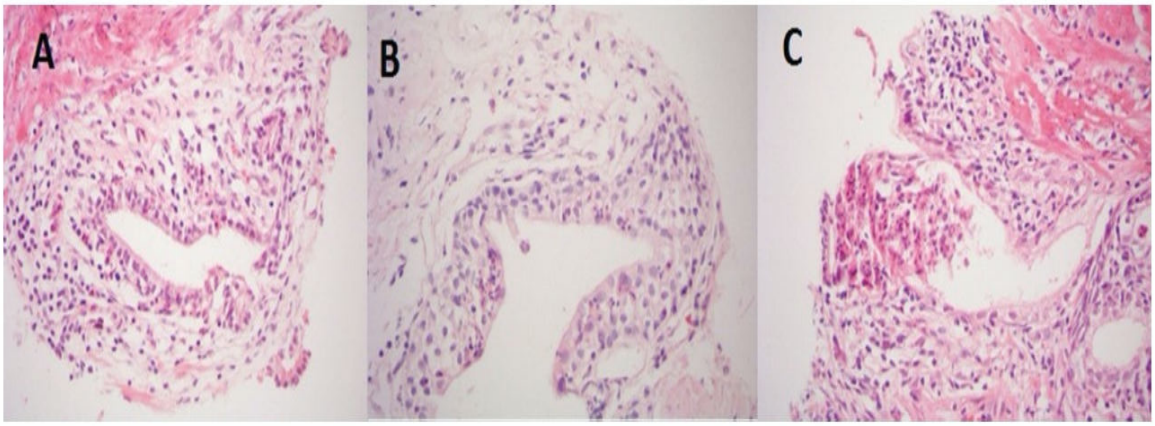

Fig. 1. (a) Scattered neutrophilic infiltrate in stroma, and in gland epithelia. Hematoxylineosin stain, orginal magnification ×400. (b) Conspicuous neutrophilic infiltrate in gland epithelia. Hematoxylin-eosin stain, orginal magnification ×400. (c) Destructed gland with heavy neutrophilic infiltrate. Hematoxylin-eosin stain, orginal magnification ×400.

considered as statististically significant.

RESULTS

Of the 260 men 115 met the inclusion criteria. The mean age, prostate volume, serum PSA and fPSA levels and %fPSA levels were 64.7 ± 7.56 years, 51.4 ± 24.7 cm 3, 12.66 ± 10.73 ng/mL and 17.52 ± 1.2, respectively. Prostatic inflammation was diagnosed in 50 (43.47%) patients. Mean serum PSA and %fPSA levels were significantly higher in men with histologically proven prostatic inflammation (15.47 ± 15.28 ng/mL vs. 11.67 ± 8.12 ng/mL; $p = 0.002$ and 19.8 ± 0.7 vs. 15.79 ± 0.9; $p = 0.01$, respectively). However, the mean age (65.4 ± 7.0 vs. 63.3 ± 9.8 years), serum fPSA level (2.09 ± 1.44 vs. 2.67 ± 4.2 ng/mL) and prostate volume (51.7 ± 24.0 vs. 51.86 ± 27.1 cm3) were similar in patients with and without prostatic inflammation ($p = 0.32$, $p = 0.08$ and $p = 0.42$, respectively).

Table 2 summarizes the demographics and characteristics of the patients among the prostatic inflammation subgroups. Mean age and prostate volume were similar between the subgroups ($p = 0.27$ and p = 0.64, respectively). In the subgroup analysis, the grade of prostatic inflammation was significantly correlated with the serum PSA levels (r = 0.320, $p < 0.001$). The mean PSA level of the patients with grade 3 prostatic inflammation was significantly higher than those of with grade 1 inflammation ($p = 0.001$). Serum fPSA levels, on the other hand, were similar among different groups ($p = 0.07$). However, percent of fPSA was correlated negatively with the grade of prostatic inflam-

Table 2. Patient characteristics and the parameters according to inflammation subgroups

Characteristics	Inflammation severity within the prostate gland			*p* and r value	*p* value
	Grade 1	Grade 2	Grade 3		
Patients (n)	30	11	9		
Age (year)	65.0 ± 8.9	61.3 ± 5.9	60. 2 ± 6.1		0.27*
Prostate volume (cm3)	47.5 ± 23.2	56.3 ± 30.4	61.0 ± 34.0		0.64*
PSA (ng/ml)	13.8 ± 10.3	13.3 ± 10.8	29.0± 29.7	**< 0.001†** r = 0.320	**0.02***
fPSA (ng/ml)	2.09 ±1.8	2.05 ±2.5	5.4 ± 8.3		0.07*
%fPSA	16.2 ± 0.7	15.6 ± 1.2	13 ± 1.9	**0. 01†** r = - 0.286	0.06*

Data presented as mean ± standard deviation. PSA = prostate-specific antigen, fPSA = free prostate-specific antigen. *Kruskal Wallis Test, †Spearman correlation test.

mation (r = -0.286, p = 0.01).

DISCUSSION

With the widespread application of PSA based screening, most of the current prostate biopsies are performed due to elevated PSA levels [1]. However, an important percentage of these patients do not have PCa as other factors such as BPH, prostate volume, and the age of the patients can also result in increased PSA levels [1]. On the other hand, TRUS-Bx may fail to detect cancer in up to 30% of patients [6], making the faith of the patients with negative biopsies more challenging. However, excluding the patients with elevated PSA levels because of benign conditions may decrease the necessity of repeated prostate biopsies. In the present study, we found that serum PSA level were significantly higher in men with prostatic inflammation. Moreover, we determined a significant correlation between serum PSA level and prostatic inflammation, graded on a 3-point scale. Approximately 70 to 90% of PSA is bound to alpha-1-antichymotripsin in serum and called total PSA. The remaining 10 to 30% of the PSA which is not bound to serum proteins represents the fPSA. As such in PSA, there are controversial results about the correlation between prostatic inflammation and serum fPSA and %fPSA levels [3, 4]. Our findings revealed that despite fPSA levels were comparable among the groups, %fPSA was significantly lower in patients with prostatic inflammation. A negative correlation with %fPSA and prostatic inflammation were also determined. We thought that it could be explained by the increased serum total PSA levels with prostatic inflammation, while the fPSA was stable. In our opinion, according to our results, unnecessary repeat biopsies may be avoided in elderly patients with elevated serum PSA levels who have high grade prostatic inflammation and normal digital rectal examination findings. In this group of men, the only determinant of elevated serum PSA levels seems to be prostatic inflammation without histologic PCa and its indicator abnormal digital examination findings. Therefore, detailed intensity and extent of neutrophilic infiltration within the prostate gland should be provided in the pathology reports of the biopsies. However, the possibility of PCa should always be kept in mind, and these patients should be closely followed up with serial digital rectal examination and serum PSA measurements. Or, as such in recent years, the use of various imaging techniques such as contrast-enhanced ultrasound, sonoelastography, and multiparametric prostate magnetic resonance imaging (mpMRI) may be rationale [7-9].

Two possible mechanisms exist explaining why prostatic inflammation increases the serum PSA levels. One of them is, the epithelial cells surrounding the affected area may be stimulated to produce PSA through unknown substances released in association with the inflammatory processes [10]. The other possible mechanism is that the disturbance of the prostate duct integrity by the inflammation causes leakage of PSA from the acini and ductal lumina to the interstitium [11]. It seems that our findings may support both of the mechanisms. However, higher serum PSA levels with higher grade which exhibits significant destruction of the prostate tissue clearly supported the second mechanism. In the literature, whereas some previous reports have not showed an association between the serum PSA level and prostatic inflammation, several studies have successfully demonstrated clear evidences about the association between them [3, 5, 12-14]. Hasui *et al*. [14] investigated a total of 42 patients who underwent transurethral resection of the prostate (TURP) and demonstrated a statistically significant positive correlation between histological acute prostatitis and serum PSA levels with a 0.765 correlation coefficient. However, the authors reported that the correlation between serum PSA and the extent of chronic-inactive prostatitis was not significant [14]. Okada *et al*. [5] also confirmed the findings of Hasui *et al* using TRUS-Bx specimens. The authors investigated the correlation between histological prostatic inflammation and serum PSA level in 93 patients and found that the degree of acute inflammation was the only parameter correlating significantly with serum PSA levels in patients with a prostate volume smaller than 25 mL [5]. In 2012, Man *et al*. [15] reported that the aggressiveness and extent of prostatic inflammation in 120 asymptomatic prostatitis patients were significantly correlated with level of serum PSA. The other study published by Stimac *et al*. [4] in 2014 reported a significant negative correlation of inflammation aggressiveness with fPSA (r = -0.31, p = 0.001) and %fPSA (r = -0.43, p < 0.001), but not with PSA, in 106 patients with lower than 10 ng/mL PSA levels.

In a large sample study investigated 6238 men aged 50 years to 75 years with PSA levels between 2.5 ng/mL and 10 ng/mL, it has been reported that prostatic inflammation upon first biopsy reduces the odds of PCa in repeat biopsies, presumably reflecting an elevated PSA as a result of inflammation (16]. A most recent study published by Kato *et al*. [17] in 2016 which attempted to clarify the association between PCa detection and various risk factors in 24-core repeat saturation biopsies has revealed that patients with asymptomatic inflammation appear to have a lower risk of PCa. The authors concluded that it should be considered that inflammation may cause persistent elevated PSA in patients with a negative initial biopsy, leading to unnecessary repeat biopsy [17]. Almost all previous papers used grading systems relying either on the intensity or extent of inflammation [5, 18]. In the present study, the inflammation was categorized more profoundly, using both the intensity and the extent of inflammation. We evaluated all the 12 specimens, as well, for each patient which may predict the extent of the inflammation more precisely. We took into consideration the age, prostate volume and digital rectal examination findings of the patients, three parameters with proven effects on PSA levels, as well. In our opinion, the most important superiority of the current study was the exclusion of patients with positive digital rectal examination findings even if they had no PCa diagnosis on TRUS-Bx. Therefore, the exclusion of PCa diagnosis was performed optimally in our study cohort and strengthened our results. In 2015, Umbehr *et al*. [19] investigated the association of intraprostatic inflammation and serum PSA in 224 men excluding the patients with abnormal digital rectal examination findings and histologically diagnosed PCa. Nevertheless, they considered only patients with serum PSA levels < 4 ng/mL. The authors found that prostatic inflammation was associated with higher serum PSA. Our findings were comparable with Umbehr *et al*.'s results [19] and we confirmed their report in men with any PSA levels. Finally, a recent systematic literature review published in 2018 and investigated two randomized trials and nine cohort studies with a total 1011 patients have demonstrated that antibiotic treatment exhibit a decrease in serum PSA levels of the patients with asymptomatic prostatitis [20]. Result of that systematic literature review can be accepted as a clear evidence of the elevated serum PSA levels with chronic inflammation. And, our findings were coherent with this hypothesis.

Limitations

The present study had some limitations. First the efficacy and reproducibility of the grading system has not been validated. Secondly, the inflammatory cells were only visually determined based on hematoxylin-eosin staining and morphology. We did not stain for immune cell surface markers and did not use image analysis. Thirdly, we could have performed mpMRI to exclude the diagnosis of PCa more successfully. We think that it can be an interesting topic for future researches. Beyond the limitations, the exclusion of patients with suspicious digital rectal examination findings even if they had no PCa diagnosis on TRUS-Bx provided an optimal exclusion of PCa diagnosis and strengthened our findings.

CONCLUSION

In conclusion, prostatic inflammation was correlated with serum PSA and %fPSA levels. We concluded that histologically proven prostatic inflammation may be used to prevent unnecessary repeat prostate biopsies in elderly patients who underwent TRUS-BX and diagnosed with benign pathologies. However, more investigations are needed and furtherstudies are awaited. Moreover, the possibility of PCa should be kept in mind, and these patients should be followed periodically.

Authors' Contribution

Study Conception: EK, AÇ; Study Design: MZT, ÇB; Supervision: EK; Funding: EK; Materials: ÇB, YB; Data Collection and/or Processing: AÇ, YB; Statistical Analysis and/or Data Interpretation: MZT, ÇB; Literature Review: AÇ, YB; Manuscript Preparation: AÇ, MZT and Critical Review: ÇB, EK.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Evaluation of central neuropathic pain and its relationship with quality of life in patients with stroke: a cross-sectional study

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ABSTRACT

Objectives: Unlike other complications in stroke patients, central post-stroke pain (CPSP) can sometimes be underestimated and overlooked. Considering the morbidities caused by CPSP in patients, it is clear that it is actually a very important problem. The aim of this study is to investigate the frequency of CPSP, the factors that cause CPSP, and the relationship between CPSP and individuals' quality of life and ambulation.

Methods: A cross-sectional study was conducted on a group of patients with stroke. 140 stroke patients were included in the study. The neuropathic pain was assessed with The Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) pain scale, quality of life was assessed with Short Form 36 (SF-36) Questionnaire, and ambulation was evaluated according to the Functional Ambulation Classification (FAC). In addition, a special evaluation form was created for this study. With this form, the demographic characteristics of the patients, the type of stroke, the brain region affected by the stroke and the affected hemisphere were recorded. The patients were divided into two groups. Group 1 included patients with CPSP, and group 2 included patients who could not meet the diagnosis of neuropathic pain according to the LANSS pain scale, regardless of other pain types.

Results: CPSP was detected in 23 (16.5%) of 140 patients. CPSP was statistically significantly higher in female patients ($p = 0.006$). There was no statistically significant difference between the two groups in terms of other demographic characteristics ($p < 0.05$). There was no significant difference between the two groups in terms of affected cerebral region and stroke type ($p < 0.05$), but CPSP was found to be statistically significantly higher in patients with left hemispheric involvement ($p = 0.003$). Emotional role restriction, body pain, social function, general health and mental health subcategory scores of SF-36 were found to be significantly lower in group 1 than in group 2 ($p > 0.05$). In addition, when the two groups were compared in terms of ambulation levels, the rate of patients with FAC 2 and below was 73% in group 1, while this rate was 34.1% in group 2.

Conclusions: It was concluded that CPSP is a common problem and negatively affects the quality of life. Therefore, CPSP should be recognized in the early period after stroke and treatments should be arranged accordingly.

Keywords: Neuropathic pain, stroke, quality of life

According to the International Association for the Study of Pain (IASP), central post-stroke pain (CPSP) is a central neuropathic pain condition in which pain arises as a direct result of a cerebrovascular lesion in the central somatosensory nervous system [1]. The prevalence of CPSP has been reported to be

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11% [2]. Many complications can occur after stroke. One of these complications is the formation of CPSP. Although about 50% of stroke patients suffer from chronic pain, this can be overlooked [3].

There is an inversely proportional relationship between stroke severity and disability and quality of life [4]. The decrease in quality of life after stroke is not just related to stroke. Complications that occur after stroke can also negatively affect the quality of life of individuals. Depression, low socioeconomic status, fatigue, physical disability, female gender, residence in a nursing home, situations requiring social assistance, presence of pain in the affected limbs, situations requiring soft diet or tube feeding, and lack of physical exercise adversely affect the quality of life in post-stroke patients [5-7]. One of the complications that negatively affect the quality of life is the occurrence of CPSP. CPSP can adversely affect the quality of life by disrupting sleep quality and causing depression [8]. Also, neuropathic pain severity may be associated with decreased quality of life [9]. Therefore, CPSP should not be considered as a simple pain syndrome.

The aim of this study is to evaluate the frequency of CPSP, the effects of CPSP on quality of life and ambulation in stroke patients, and to determine the factors that may cause CPSP formation.

METHODS

Study Design

This study was conducted as a cross-sectional study between May 2016 and January 2018. The ethics committee approval for this study was made by Bursa Uludag University Faculty of Medicine Clinical Research Ethics Committee (decision no: 2016-8/20, date: April 26, 2016).

One hundred fourty patients diagnosed with stroke who were evaluated in an outpatient clinic or clinic were included in the study. Patients were divided into two groups. Group 1 included patients with CPSP and Group 2 patients without CPSP (Fig. 1). The patients included in Group 2 were selected from patients who could not meet the neuropathic pain criteria according to The Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) pain scale, regardless of other pain types. Demographic data including age, gender, education level, and marital status were recorded. In addition, stroke type, number of previous strokes, time to post-stroke evaluation, affected brain region and hemisphere were recorded.

Patients older than 18 years of age and with sufficient cognitive level to answer the survey questions were included in the study. Patients who applied to the hospital or received treatment due to neuropathic pain complaints and patients with other conditions that may cause neuropathic pain (polyneuropathy, carpar tunnel syndrome, etc.) were not included in the study.

All patients who met the study criteria were informed of the study and a written consent was obtained.

Measures

Pain Assessment Tools - LANSS Pain Scale

Central neuropathic pain was evaluated with the LANSS pain scale. The total score on this scale is 24. Pain with scores of 12 and above is considered to be neuropathic pain. The LANSS pain scale was first used clinically by Bennett [10] to distinguish neuropathic pain from nociceptive pain . The Turkish validity and reliability of the LANSS pain scale was made by Yücel *et al*. [11] in 2004.

Assessment of Health-Related Quality of Life - Short Form 36 Questionnaire (SF-36)

SF-36 is a scale that evaluates the general health

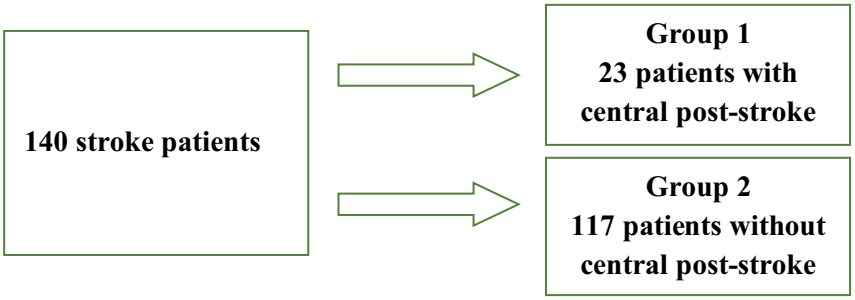

Fig. 1. Study flow diagram.

status with 36 questions in 8 subcategories including physical function, physical role restriction, emotional role restriction, body pain, social function, mental health, vitality and general health [12]. The Turkish validity and reliability of the SF-36 was made by Koçyiğit *et al*. [13] in 1999.

Assessment of Functional Level - Functional Ambulation Classification (FAC)

This scale was used to determine the level of functional ambulation. Patients with FAC 2 and below require varying degrees of manual support for ambulation, depending on their level [14].

Statistical Analysis

All data were analyzed using SPSS 23 for Windows (IBM Corp., Armonk, NY, USA). Whether the data showed normal distribution was examined by Shapiro-Wilk test. In descriptive statistics for continuous data, it was stated as mean ± standard deviation for variables with normal distribution and as median (minimum-maximum) for variables not showing normal distribution. Dependent sample t-tests and Mann–Whitney U tests were used to examine and compare the relationship between the characteristics of the sample. $P < 0.05$ was considered statistically significant.

RESULTS

Study Population

A total of 140 patients (66 female and 74 male) were enrolled in this study. The mean age of the patients was 62.4 ± 9.9 years. One hundred thirty of the patients were married and 10 were single. Fourty-two patients were illiterate, 70 patients were primary school graduates, 11 patients were high school graduates, and 17 patients were university graduates (Table 1).

Stroke Characteristics

The mean evaluation period of the patients with the occurrence of stroke was 7.2 ± 2.2 months. 43 of the patients (30.7%) had right hemiplegia, 97 (69.3%) patients had left hemiplegia; while the lesion site was in the extra-thalamic area in 99 (71.4%) patients, the lesion site was in the thalamic area in 41 (28.6%) patients. 30 (21.4%) of the patients had hemorrhagic stroke, and 110 (78.6%) had ischemic stroke (Table 1).

CPSP

While CPSP was observed in 23 (16.5%) patients, it was not observed in 117 (83.5%) patients. In cases

Table 1. Demographic and clinical characteristics of the participants

		n	%
Marital status	Maried	130	92.8
	Single	10	7.2
Education status	İlliterate	42	30.0
	Primary school	70	50.0
	High school	11	7.8
	University	17	12.2
Gender	Female	66	47.1
	Male	74	52.9
Affected hemisphere	Right hemisphere	111	79.3
	Left hemisphere	29	20.7
Affected cerebral localization	Thalamic	41	28.6
	Extra-thalamic	99	71.4
Stroke type	Hemorrhagic	30	21.4
	Ischemic	110	78.6

n = number of patients, % = percentage of patients

Table 2. Central post-stroke pain and related factors

	Group 1 (n = 23)	Group 2 (n = 117)	*p* value
Gender Female/male, n (%)	17/6 (73.9/26.1)	49/68 (41.9/58.1)	**0.006**
Age (years) (mean ± SD)	61.18 ± 9.86	64.15 ± 7.65	0.530
Affected hemisphere Right/left, n (%)	8/15 (34.8/65.2)	89/28 (76.1/23.9)	**0.003**
Affected cerebral region Thalamic/extra-thalamic, n (%)	5/18 (21.7/78.3)	36/81 (30.8/69.2)	0.384
Stroke type Hemorrhagic/ischemic, n (%)	3/20 (12.0/87.0)	27/90 (23.1/76.9)	0.407

n = number of patients, % = percentage of patients, SD = standard deviation, Group 1 = patients with central post-stroke pain, Group 2 = patients without central post-stroke pain.

with CPSP, the median time from the time of stroke to the onset of neuropathic pain was 2 (0-12) months.

CPSP and Demographic Data

Seventeen (73.9%) of 23 patients with CPSP were female. Statistically, the frequency of CPSP in female patients was found to be significantly higher than in male patients ($p = 0.006$). There was no statistically significant relationship between CPSP and age ($p = 0.530$) (Table 2).

CPSP and Stroke Characteristics

There was no significant difference between the two groups in terms of the affected cerebral region and stroke type ($p > 0.05$). But CPSP was significantly more common in patients with left hemispheric involvement ($p = 0.003$) (Table 2).

CPSP and Quality of Life

Emotional role restriction, body pain, social function, general health and mental health subcategories of the SF-36 were found to be significantly lower in group 1 compared to group 2 ($p < 0.05$). There was no statistically significant difference between the two groups between other SF-36 subcategories ($p > 0.05$) (Table 3).

CPSP and Ambulation

Table 3. The relationship between central post-stroke pain and quality of life

SF-36 subcategories	Group 1 (n = 23)	Group 2 (n = 117)	*p* value
Physical function	70.0 (10-90)	67.5 (10-95)	0.442
Physical role restriction	25.0 (0-100)	25.0 (0-100)	0.160
Emotional role restriction	0.0 (0-33)	33.0 (0-100)	**< 0.001**
Body pain	30.0 (0-50)	80.0 (40-100)	**< 0.001**
Social funtion	30.0 (0-60)	50.0 (20-90)	**< 0.001**
Mental health	20.0 (0-60)	40.0 (0-80)	**< 0.001**
Viality	0.0 (0-20)	0.0 (0-60)	0.780
General health	25.0 (0-50)	50.0 (0-100)	**< 0.001**

Variables are presented as median (min-max). Group 1 = patients with central post-stroke pain, Group 2 = patients without central post-stroke pain.

Patients with FAC 2 and below require varying degrees of manual support for ambulation, depending on their level. That's why we divided the patients according to whether they need manual support or not. While the rate of patients with FAC 2 and below was 73% in group 1, this rate was 34.1% in group 2 (Fig. 2).

DISCUSSION

In our study, the prevalence of CPSP was found to be 16.5%. Liampas *et al*. reported the prevalence of CPSP as 11% [2]. In one study, the minimum prevalence of absolute or probable CPSP was 7.3%, and the prevalence of CPSP-like dysesthesia or pain was 8.6% [15]. In another study, CPSP was detected in 8% of 166 stroke patients [16]. In a study conducted in Nigeria, the prevalence of CPSP was found to be 5% [17]. This variation in the literature may be due to selection criteria, evaluation time of patients, and the different ethnic populations studied.

There are studies in the literature showing that CPSP may be related to demographic characteristics of patients. Post-stroke pain found to be associated with female gender [18]. No relationship was found between CPSP and gender in another study [19]. In the study of Osama *et al*., the mean age of patients with CPSP was significantly lower than for patients without CPSP [20]. Kılıç *et al*. [19] found no relationship between age and CPSP . In our study, CPSP was significantly more common in women than in men ($p = 0.006$). Considering that pain syndromes are more common in female gender, we can say that our study is similar to the literature. Conversely, we found no relationship between age and CPSP.

In our study, there was no significant difference between the two groups in terms of affected cerebral region and stroke type, but CPSP was significantly more common in patients with left hemisphere involvement. We found that among stroke features, only the affected hemisphere was associated with CPSP. However, many studies show that the affected cerebral region is associated with CPSP. One study found that CPSP formation was associated with the cortical or thalamic location of stroke [21]. In another study, the brain regions most associated with CPSP risk were the anterior/middle cingulate cortex, insula, thalamus, and lower parietal lobe [22]. Harno *et al*. [23] found that the area affected in stroke was not associated with CPSP. There are different results in the literature regarding the relationship between CPSP and stroke characteristics. However, in general, we can say that CPSP is more common in strokes with thalamic involvement. Contrary to the literature, in the current study, no relationship was found between the affected brain region and CPSP. We think that this difference may be due to the different time of questioning the patients in terms of neuropathic pain.

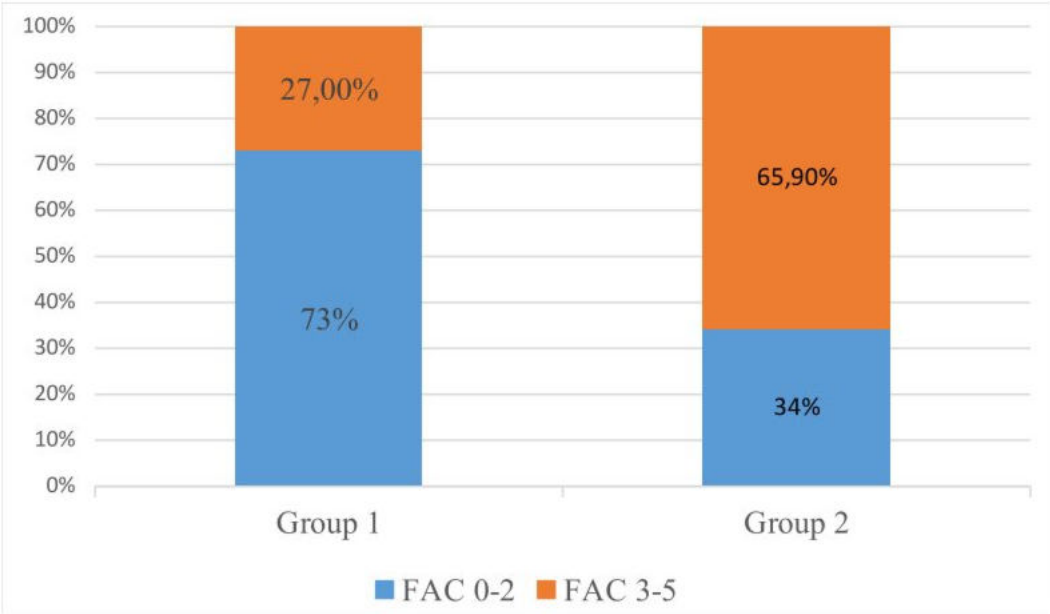

Fig. 2. Central post-stroke pain and ambulation.

In our study, some subcategories of SF-36 were lower in patients with CPSP than in patients without CPSP. In the study of Şahin *et al*. [24], some subcategories of SF-36 (emotional role restriction, social function, mental health, vitality and general health) were found to be significantly lower in patients with CPSP. In another study, CPSP was found to be associated with quality of life [25]. In the study of Gökkaya *et al*. [26], it was determined that quality of life in stroke patients was related to functional status, gender, education, presence of comorbidity and psychological factors. Gorst *et al*. [27] found that foot and ankle disorders such as pain, altered somatosensory input, and weakness contributed significantly to ambulation, balance, and fear of falling problems in stroke patients. In another study, neurological symptoms, cognitive function, and initial neuroimaging findings were found to be useful in predicting independent walking in patients with thalamic hemorrhage [28]. There are many studies showing that pain in stroke, and especially CPSP, affects quality of life. In our study, it was found that the quality of life was negatively affected in the presence of CPSP, which was consistent with the literature. There is not enough data in the literature showing the relationship between ambulation and CPSP. In our study, the presence of CPSP caused poor ambulation results. We think that this may be due to both the negative effects of pain on patients' ambulation and the higher incidence of CPSP in severe and widespread strokes, which cause worse functional outcomes.

Limitations

The missing aspects of our study; The fact that the included patients were not distributed homogeneously in terms of age and involved lesion location made it difficult to evaluate the effect of the involved hemispheric area on the development of CPSP. In addition, since we grouped patients only as thalamic and extrathalamic according to the lesion location, widespread or limited infarcts, affected brain structure and other extra factors were not taken into account. Apart from this, evaluation of patients at different times may have affected the prevalence of CPSP. In addition, the fact that the spasticity of the cases was not evaluated and more sensitive scales were not used to evaluate the ambulation are the weaknesses of our study.

CONCLUSION

In conclusion, due to the increase in diagnosis, treatment opportunities and survival rates, the incidence of stroke patients is increasing day by day and it becomes a more important public health problem. This shows the importance of follow-up and complications of stroke patients for the individual and society. As with other complications after stroke, CPSP causes a decrease in functional capacity and loss of quality of life. Although CPSP is such an important problem, it is neglected compared to other complications. CPSP should be recognized in the early period after stroke and treatments should be arranged accordingly.

Authors' Contribution

Study Conception: UE, Jİ; Study Design: UE, Jİ; Supervision: UE, Jİ; Funding: N/A; Materials: N/A; Data Collection and/or Processing: UE, Jİ; Statistical Analysis and/or Data Interpretation: UE, Jİ; Literature Review: UE, Jİ; Manuscript Preparation: UE, Jİ and Critical Review: UE, Jİ.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

The authors disclosed that they did not receive any grant during conduction or writing of this study.

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It was presented only in Turkish as an oral presentation in a congress in our country.

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The European Research Journal 2022;8(4):475-481 Original Article

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The relationship between the time factor and in-hospital mortality in the hospitalized patients

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ABSTRACT

Objectives: As in-hospital deaths are encountered by all healthcare professionals, investigating the factors affecting in-hospital mortality may help to reduce the number of deaths. In this study; the relationship between time factor and in-hospital deaths is examined.

Methods: The study included all hospitalized patients who died at Balikesir State Hospital between January 01, 2014 and December 31, 2014. Time of death, workdays, and holidays were examined on a monthly and seasonal basis and at shift change times. In calculating in-hospital mortality, 'Crude Death Rate (CDR)' was used.

Results: The number of in-hospital deaths during the study period was found to be 1418. It was discovered that the number of patients hospitalized per day was 314.6 ± 46.95, the number of hospitalized patients who died per day was 3.88 ± 2.16, and the mean daily CDR was 12.77 ± 7.5. Additionally, CDR was found to be as 7.56 ± 5.5 in males, while it was 5.21 ± 4.55 in females. Moreover, CDR was 13.07 ± 7.52 on workdays, whereas it was 12.07 ± 7.43 on holidays. As for seasons, CDR was found to be as 14.35 ±8.63 in summer, while it was 11.43 ± 7.84 in winter.

Conclusions: In-hospital mortality, the death rate of males was higher than females while their average age was found to be less than females. No change was observed at shift change hours. The mortality rate increased in summer. However, no difference was found between workdays and holidays in terms of mortality rate.

Keywords: Emergency department, mortality rate, crude death rate

Hospital mortality rates are relatively easy to calculate. Administrative data with a high mortality rate are seen as a critical indicator of poor care. It is widely used to highlight clinical failures and thus to encourage hospitals to research and improve the quality of care. Although it has some imperfections, it is believed to be useful measures of hospital performance and is used in the USA, Canada, the Netherlands, Sweden and the UK [1, 2].

Approximately, 370.000-390.000 deaths occur in Turkey per year. While 60% of deaths are determined by hospitals and health centers, 40% of them are identified by the municipal medical offices, community health centers, and family physicians. The majority of deaths are non-judicial 'natural' deaths [3, 4]. In-hospital deaths are problems faced by all healthcare professionals. Although it is impossible to eliminate all these deaths, we may have a chance to reduce them.

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For this purpose, to reveal the cause of death and try to prevent should be the primary target at the hospitals [5]. In addition, investigating all of the factors affecting in-hospital deaths may help reduce these deaths.

In this study, the relationship between the time factor and in-hospital deaths is questioned. Additionally, whether there were time periods in which the rate of deaths increased is investigated and possible solutions are discussed.

METHODS

Study Design and Setting

This study is observational and descriptive. All patients who died in Balikesir State Hospital (BSH) while hospitalized between January 01, 2014 and December 31, 2014 were included in this study. Throughout 2014, the number of deaths at BSH was 1418. The list and information of all patients were obtained from data processing center of BSH. During the planning phase, the date of death, demographic data, service in which they died, and the number of patients on a daily basis was recorded. In calculating in-hospital mortality, mainly "crude death rate" was used. To calculate the crude death rate, the formula; the crude death rate (CDR) = (number of died patients /number of hospitalized patients) × 1000 was used.

To examine the relationship between hospital mortality and time factors, a detailed classification on the basis of death dates, months, and seasons were made. When calculating the difference of mortality in working hours and holidays, all holidays in the country over 2014 (weekend holidays, religious holidays, public holidays) were considered. For the analysis of daily hours, a day was divided into three periods as 08: 00-16: 00, 16: 00-00: 00 and 00: 00-08: 00. In addition, to investigate whether there was a difference in shift changes, mortality was calculated in the form of 2 hour periods; 07: 00-09: 00, 09: 00-11: 00 and so on.

Sample Size Estimation

In this study; no sample size estimation test was used as all patients who died in BSH in 2014 were included in study.

Selection of Participants

All the data regarding patients who died while hospitalized in BSH between January 01, 2014 and December 31, 2014 were obtained from data processing center. All the data related to patients was reached.

Interventions

As it is an observational-descriptive study, no intervention was made by researchers.

Methods and Measurements

Researchers recorded patients' data and tried to examine the time of death, workdays, and holidays on a monthly and seasonally basis and on shift changes.

Outcomes

Patients who died in BSH in 2014 were analyzed in terms of demographic information, the service and the time of death.

Power of the Study

As the study was observational and descriptive, no power analysis was conducted.

Ethics Committee

Approval from the Ethics Committee of Balıkesir University School of Medicine was obtained.

Statistical Analysis

The data were analyzed with IBM Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) in Version 22.0 software package with 95% reliability. Pearson product-moment correlation coefficient was conducted to assess the change of the number of studies according to years. $P < 0.05$ was considered statistically significant.

RESULTS

The number of patients who died in BSH during the study period was found as 1418. It was discovered that 314.6 ± 46.95 patients were hospitalized, 3.88 ± 2.16 patients died per day, and the daily average CDR was 12.77 ± 7.5. On the other hand, 59.4% (n = 843) of the patients were male while 40.6% (n = 575) were female. The average age of all patients was 70.36 ± 13.73 (range; 14-102) years. To be more specific, the average age of males was 68.97 ± 13.75 years, while the average age of females was 72.39 ± 13.46 years (*p*

Table 1. The average distribution of CDR and patients died according to the time of death

	Hours	Mean ± SD	Min. - Max.	*p value**
The number of patients died	00:00-08:00	1 ± 1.05	0-4	**< 0.001**
	08:00-16:00	1.6 ± 1.3	0-6	
	16:00-24:00	1.28 ± 1.18	0-7	
CDR	00:00-08:00	3.32 ± 3.67	0-23.95	**< 0.001**
	08:00-16:00	5.22 ± 4.35	0-18.73	
	16:00-24:00	4.23 ± 4.03	0-21.74	

CDR = Crude death rate, SD = standard deviation, *Mann Whitney U

< 0.001). As for CDR, it was found as 7.56 ± 5.5 for males while it was calculated as 5.21 ± 4.55 (p < 0.001) for females. In addition, CDR was found as 8.85 ± 5.93 in patients over the age of 65 while it was 3.92 ± 4.07 in patients under 65 (p < 0.001). 76.23% of the cases (n = 1081) died in intensive care, 10:22% (n = 145) died in oncology services, and 5.21% (n = 74) died in internal services. CDR was found as 9.79 ± 6.54 in intensive care, while it was 2.97 ± 3.14 in services (p < 0.001).

During the examination in which a day was divided into three periods, 25.6% (n = 366) of the cases died between 00: 00-08, 40.9% (n = 585) of the patients died between 08: 00-16, and 32.6% (n: 467) died between 16:00-00:00, respectively. When the number of died patients and CDR according to the time of deaths were investigated, statistically significant difference was found between groups (p < 0.001). In the analysis which investigated the reasons of the difference, it was discovered that all dual pairings were statistically significant (p < 0.0167) (Table 1). In the analysis conducted in 2 hour periods; the highest number of deaths occurred between 23:00-01:00 (11.2%, n = 160) and 13:00-15:00 (10.8%, n = 154). Moreover, between 07:00-09:00 which was the shift change hours, 8.2% (n = 118) of the patients died and of 9.9% (n: 142) of the patients died between 15:00-17:00. However, no statistically significant difference was found in 2 hour periods between groups (p > 0.05).

Table 2. The average distribution of CDR according to months

Crude death rate (per thousand)		
Months	**Mean ± SD**	**Min. - Max.**
January	13.64 ± 6.84	0-26.32
February	9.64 ± 5.27	0-21.98
March	11.49 ± 7.61	0-37.45
April	12.65 ± 6.11	0-27.36
May	12.4 ± 5.9	2.77-28.13
June	12.78 ± 8.53	0-30.72
July	16.33 ± 9.17	2.9-41.92
August	13.91 ± 8.03	0-32.71
September	10.84 ± 6.12	0-21.41
October	15.29 ± 7.31	5.76-40.82
November	13.02 ± 5.64	0-21.9
December	10.85 ± 10.11	0-39.22

CDR = Crude death rate, SD = standard deviation

In July, CDR was found to be as 16.33 ± 9.17. It was found as 15.29 ± 7.31 in October, and in August, it was 13.91 ± 8.03 (Table 2). In summer, CDR was 14.35 ± 8.63, while it was 11.43 ± 7.84 in the winter. A statistically significant difference was found between the groups in terms of number of patients hospitalized and CDR according to the seasons (p < 0.05) (Table 3).

On workdays, CDR was found as 13.07 ± 7.52 while it was 12.07 ± 7.43 on holidays. The number of patients hospitalized on workdays was statistically lower than the number of patients hospitalized on holidays (p < 0.001). There was no statistically significant difference found between the groups in terms of number of patients and CDR (p > 0.05) (Table 4).

DISCUSSION

In health systems, information about mortality is needed for identifying needs, planning, financing, and evaluating the effect of services, calculating life ex-

Table 3. The average distribution of inpatients and patients died and CDR according to seasons

	Seasonal (depending on climate)	Mean ± SD	Min. - Max.	*p value*
The number of inpatients	Winter	340.52 ± 38.62	260-418	*< 0.001*
	Spring	319.46 ± 33.36	245-380	
	Summer	295.27 ± 51.03	154-381	
	Autumn	303.6 ± 49.82	161-373	
The number of patients died	Winter	3.84 ± 2.6	0-14	0.730
	Spring	3.83 ± 1.96	0-10	
	Summer	4.04 ± 2.27	0-9	
	Autumn	3.82 ± 1.72	0-8	
Crude death rate (per thousand)	Winter	11.43 ± 7.84	0-39.22	*0.034*
	Spring	12.17 ± 6.54	0-37.45	
	Summer	14.35 ± 8.63	0-41.92	
	Autumn	13.07 ± 6.6	0-40.82	

CDR = Crude death rate, SD = standard deviation

Table 4. The average distribution patients hospitalized and the patients died and on weekdays and holidays

		Mean ± SD	Min. - Max.	*p value**
The number of inpatients	Workdays	304.97 ± 40.1	154-418	**< 0.001**
	Holidays	336.36 ± 53.75	167-411	
The number of patients died	Workdays	3.91 ± 2.24	0-14	0.896
	Holidays	3.84 ± 1.96	0-9	
Crude death rate (per thousand)	Workdays	13.07 ± 7.52	0-39.22	0.089
	Holidays	12.07 ± 7.43	0-41.92	

SD = standard deviation

pectancy, and comparison between settlements, regions and countries [6]. Thus, studies related to in-hospital mortality may guide the hospital staff and provide recommendations for a better health care.

In the study conducted by Cilingiroglu *et al*. [6], 659 patients who died in hospital were examined. They found the mean age of the patients as 60.64 ± 8.17. In addition, the mortality rate was 56.6% in patients over 60 years old. This rate was 1.3% in patients between 30-39 years of age, whereas it was found as 6.9% in patients in the range of 70-104. The rate of males was 53.4%. 37.3% of deaths occurred in the intensive care unit, whereas 35.5% happened in the internal services. As for the death rates according to seasons, 24.4% of deaths occurred in spring, 24.2% happened in summer, 25.6% were in fall and 25.8% were in winter. 35.1%, of deaths occurred in the range of 08: 00-16: 00, 32.8%, occurred in the range of 16:00-00:00, and 31.8% were in the range of 00:00-08:00. No difference was found between weekend and weekdays death rates [6]. In a study conducted with 351 patients, Korkmaz *et al*. [7] found the mean age of the patients as 67.1 ± 0.7 and the rate of males as 62.1%. In addition, they found that 87.5% of in-hospital mortality was over 60 years old. The most frequent deaths occurred in intensive care units (28%). Seventeen percent of deaths occurred in the internal medicine service, 16% occurred in cardiology departments [7].

In another study conducted by Mohammed *et al*. [8], the difference of mortality rate of the patients admitted to the hospital over the weekend and on week-

days was investigated. The authors found that the mortality was higher in patients admitted to the hospital over the weekend. Barba *et al*. [9] examined 'first 48 hours mortality difference' in patients admitted to emergency service during weekdays and weekend. Similar results were obtained in this study. That is to say, the mortality rate was higher in patients admitted to emergency service at weekend [9]. In addition, in both of the studies, it was noted that the number of hospital staff working at weekend was less, and those staff were less experienced, which affected the quality of patient care.

Aylin *et al*. [10] investigated patients admitted to emergency services and died in England between 2005 and 2006. They found that the mortality rate was 10% higher in patients admitted to emergency services and died in hospital at weekend than on weekdays. In a study conducted at the Mayo Clinic; the mortality rate of the patients admitted to intensive care unit (ICU) on weekdays and over the weekend were compared. No significant difference was found between the mortality of patients admitted over the weekend and on weekdays. It was indicated that the number of beds in the hospital, the location of hospital and academic status, clinical severity in patients, and the number of employees had an effect on in-hospital mortality [11].

In our study, the mean age of the patients who died was found as 70.36 ± 13.73. The mean age of males was lower than females. The number of male patients who died was higher than females. Those results were highly compatible with other studies [6,7]. In addition, the results which demonstrated CDR was higher in males than females may be related with the fact that male patients may have been admitted to the hospital due to more serious health problems compared to females. Additionally, in patients over the age of 65, CDR was two times higher than in patients below 65. This data confirmed that the patients over 65 struggle with serious chronic and mortal problems at the hospital.

As more critically ill patients are followed in the intensive care units, higher death rates in these services may be accepted as normal. Monitoring critically ill patients in intensive care not in the internal or surgical services is medically and maybe legally correct. In this case; the mortality rate is expected to be higher in intensive care units than any other services. The mortality rate of intensive care of BSH was found as 76.23%. Compared to other studies conducted in Turkey, our intensive care mortality rate was higher than other services [6, 7].

In the part of the study in which the day was divided into three and mortality rate was calculated, we encountered some interesting results beyond our expectations. In our preliminary estimation; we thought that the mortality rate might have increased in evening and especially at night. Because; we thought that the number of employees in most units was higher and health care workers might be more dynamic during the daytime [8, 9]. In addition, as the study was conducted in a state hospital; doctors were less accessible in the evening or at night. However, the results obtained were contradictory with our expectations. In our study, the death rate and CDR were statistically higher in the range of 08:00-16:00 than the other two periods. In the study conducted by Çilingiroglu *et al*. based on the same time interval, no significant difference was found among the three time intervals. In this case; it is clear that health workers carefully monitor the patients in intensive care services during day and night. The results obtained from the three time period of the day confirmed those results.

Shift change hours are important for health care workers. When the shift is changed, the treatment and monitoring of the patients should be carefully carried out at the same time. We investigated whether shift change had an effect on in-hospital mortality by conducting 2-hour analysis. In most of the hospitals, 15:00-17:00 and 07:00-09:00 are the shift change times. Fortunately, we found that the mortality rate did not increase in those two time intervals. Moreover, in our study, we discovered that the most frequent deaths occurred in the range of 23:00-01:00.

Whether months and seasons have an effect on mortality rates was examined. For instance; we investigated whether the death rates increase in cold weather in winter or increased use of motor vehicle in summer affects the mortality. We found that CDR was significantly higher in summer than the other seasons. As for months, the death rate and CRD were significantly higher in July, August and October. Çilingiroğlu *et al*. [6] did not find a difference in terms of seasons. In our study, the reason why summer was higher than other seasons can be related to the factor that Balıkesir is located on the İstanbul-Bursa-Izmir traffic route and is also a popular host to many tourist districts. That is

to say, the high intensity of vehicles and traffic causes many accidents in summer. Another data supporting this information is that the death rate was higher in July, August and October. Thus; these months are round-trip months for people who are on vacation. Nevertheless; in this study, if we had obtained the data including the causes of deaths, we might have had better estimations in seasonal and monthly analysis. We also examined whether there was a difference between workdays and holidays in terms of mortality rates. This time parameter has actually attracted the attention of many researchers, and many studies conducted on it. However, some researchers compared the mortality rates of the patients admitted to hospital on holidays with workdays; while some others investigated the mortality rates of in-patients in terms of workdays and holidays [8-10]. In this study, we examined the mortality rates of in-patients on workdays and holidays. However, contrary to our expectations (the number of the staff working at weekend was less, and those staff were less experienced), no statistically significant difference was found between workdays and holidays. In some studies the number of the patients admitted to the hospital during the holidays was generally higher than those admitted on working days [8-10]. In a study conducted at the Mayo Clinic; the mortality rate of the patients admitted to intensive care units on weekdays and weekend was compared, and no statistically significant difference was found [11].

Limitations

If we had been able to investigate the data including the causes of deaths, we might have better questioned the relationship between the mortality rates and time factor. Another limitation is that the study is retrospective. A third limitation is that the study was single-centered.

CONCLUSION

In-hospital mortality, the mortality rate was higher in males, and their mean age was found to be less than women. Moreover, the mortality rate was higher between 08:00-16:00. No increase or decrease was observed at shift change times. The mortality rate increased in summer. No statistically significant difference was found between workdays and holidays in terms of mortality rate. In future studies; better results can be obtained if in-hospital causes of death, emergency service waiting times and additional diseases of the deceased can be examined. Multicenter studies are needed on this subject.

Authors' Contribution

Study Conception: VE, MY, MEE, UK; Study Design: VE, MY, MEE, UK; Supervision: VE, MY, MEE, UK; Funding: MEE, UK; Materials: VE, MY; Data Collection and/or Processing: VE, MY, MEE; Statistical Analysis and/or Data Interpretation: VE, MY, MEE, UK; Literature Review: VE, MY; Manuscript Preparation: VE, MY, MEE, UK and Critical Review: VE, MY.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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The European Research Journal 2022;8(4):482-490 Original Article

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The effect of personality traits and parental attitudes on treatment in children and adolescents: a 6-month follow-up study

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ABSTRACT

Objectives: This study aims to examine the effects of personality traits and parental attitudes on the change of emotional and behavioral problems in children and adolescents with mental disorders receiving outpatient treatment during the six months.

Methods: In the study, 233 individuals between the ages of 7-17 who applied to the Child Psychiatry Outpatient Clinic of a private hospital in Istanbul between September 2015 and September 2017 and who had psychiatric disorders regarding DSM-V diagnostic criteria were evaluated before treatment with the Sociodemographic Data Form, Strengths and Difficulties Questionnaire (SDQ), Quick Big Five Personality Test (QBFPT), and Parental Attitude Scale (PAS). Emotional and behavioral problems of children and adolescents who were followed up for psychiatric treatment were evaluated by SDQ at the first, third, and sixth months.

Results: According to the Pearson Correlation Analysis, it was found that the SDQ total scores of children and adolescents in the pre-treatment period were statistically significantly positively correlated with the Democratic Attitude subscale scores ($r = 0.129$, $p = 0.049$). Considering the QBFPT and PAS sub-dimension scores in ANCOVA analyzes, the change in the SDQ total scores before and after treatment was statistically significant ($p < 0.05$), and Democratic Attitude subscale scores ($F = 2.70$, $p = 0.048$) and Emotional Stability subscale scores ($F = 3.27$, $p = 0.023$) had statistically significant effects on this change.

Conclusions: In children and adolescents with mental disorders, focusing on democratic attitudes and personality traits associated with emotional stability may help reduce emotional and behavioral problems during treatment.

Keywords: Emotional and behavioral problems, personality traits, parental attitudes

Psychopathological features in children and adolescents often manifest themselves with emotional and behavioral problems. It has been evaluated that emotional and behavioral problems are common starting from infancy, 6% of toddlers (1-2 age range) have behavioral problems and 32% of these children have delayed social-emotional competence [1]. Regarding the interviews with parents of preschool children, the frequency of emotional and behavioral problems was found to be 7.1% [2]. In a study examining men between 6-18 years, 8.3% of the participants were found to have emotional and behavioral problems [3]. In a

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study in which adolescents (10-18 years old) were evaluated, the prevalence of emotional and behavioral problems was 16.5% as a result of detailed interviews with these people, 12.7% of the adolescents had a sub threshold psychiatric disorder, and 92.5% of those has been evaluated not to receive any mental assistance yet [4]. It has been reported that emotional and behavioral problems seen in children and adolescents are affected by the severity of mental illness, additional medical problems, and the mental state of family members [5-7].

Emotional and behavioral problems are good predictors of mental disorders. Temperament and character traits are the leading factors that cause the emergence of emotional and behavioral problems. Emotional and behavioral problems were found to be lower in adolescents with healthy characters compared to adolescents with inconsistent character traits [8]. It has been evaluated that emotional and behavioral problems seen in adolescents are significantly affected by personality and family characteristics and that emotional and behavioral problems in adolescents may change according to age [9]. In a nine- year follow-up study, according to the mothers' views, it was found that agreeableness and conscientiousness, among the personality traits determined in 3.5-year-old children, were associated with good self-control in the following years, in addition to this, conscientiousness was associated with high academic performance. On the other hand, neurotic features, anxiety, and extraversion features were found to be associated with difficulty in inhibiting behavior [10].

Emotional and behavioral problems in children and adolescents are affected by family characteristics. It was observed that emotional and behavioral problems in children of mothers who refused positive attitudes towards family life and child-rearing styles increased in the preschool period [11]. The interpersonal relationship style between family members, personal development tasks emphasized in the family, and the structure of the family was found to be related to emotional and behavioral problems observed in adolescents [9]. It was found that both parents' having an authoritarian attitude was negatively related to problematic behaviors in children. However; differences of attitudes observed in parents were positively associated with problematic behaviors, authoritarian parenting, therefore, predicted less problematic behaviors, and permissive attitude predicted high levels of emotional and behavioral problems [12].

It is known that personality traits and parental attitudes affect the emotional and behavioral problems of children and adolescents with mental disorders. Despite this, the number of studies investigating the effects of parental attitudes and personality traits on changes in emotional and behavioral problems in children and adolescents receiving mental treatment is limited. Thus, the aim of this study is to investigate the effects of parental attitudes and personality traits on the change in emotional and behavioral problems in children and adolescents who received outpatient psychiatric treatment for six months.

METHODS

In the study, individuals between the ages of 7-17 who applied to the Child Psychiatry Outpatient Clinic of a private hospital in Istanbul between September 2015 and September 2017 and who have psychiatric disorders regarding DSM-V diagnostic criteria were evaluated. Participation in the study was determined voluntarily, and signed-consent was obtained from the children, adolescents, and families that they volunteered to participate in the study. The cases were included in the study randomly and the research was carried out in accordance with the Helsinki Declaration. Acceptance criteria for the study were volunteering to participate in the study, having a psychiatric disorder according to DSM V diagnostic criteria, and being in the age range of 9-17. The exclusion criteria from the study were unclear psychiatric diagnosis process, not being willing to participate in the study, the presence of a physical disability that prevents taking measurements, and the presence of a comorbid mental disorder (manic period, active psychotic period, etc.) Ethical approval for the study was obtained from the Ethical Committee (IRB Date/Number: 04.08.2017 / 1052).

In the study, 233 children and adolescents who met the inclusion and exclusion criteria and received outpatient psychiatric treatment and mental disorders, were evaluated at the beginning of the treatment with the socio-demographic data form and psychometric measurement tools (Strengths and Difficulties Questionnaire, Quick Big Five Personality Test and

Parental Attitude Scale). Later, children and adolescents who continued treatment outpatient were re-evaluated with the Strengths and Difficulties Questionnaire in the first, third, and sixth months of treatment.

Assessment Tools

Sociodemographic Question Form

This form was created by researchers to evaluate the demographic and clinical characteristics of children and adolescents such as age, gender, mental illness, and treatment history.

Strengths and Difficulties Questionnaire (SDQ)

It is a measurement tool developed to measure emotional and behavioral problems in children and adolescents and includes 25 Likert items that evaluate peer problems, hyperactivity, and emotional and behavioral problems in individuals [13]. In the adaptation study of the scale into Turkish, it was found that the Cronbach's Alpha value of the SDQ was 0.84 for the parent form, 0.73 for the adolescent form. Thus, the SDQ was considered a valid and reliable measurement tool for measuring emotional and behavioral problems in children and adolescents [14].

Quick Big Five Personality Test (QBFPT)

QBFPT is a 30-item Likert measurement tool that measures basic personality traits in children and adolescents, including agreeableness, extraversion, conscientiousness, emotional stability, and openness to experience [15]. In the adaptation study of the scale into Turkish, it was found that the Cronbach's Alpha values of the sub-dimensions ranged from 0.73 to 0.81 and the validity and reliability level of the measurement tool was sufficient [16].

Parental Attitude Scale (PAS)

PAS has been developed in Turkish and consists of 62 questions and four sub-dimensions are Democratic Attitude, Authoritarian Attitude, Overprotective Attitude, and Permissive Attitude [17]. As a result of Principal Components and Varimax Rotation analyzes conducted within the framework of validity studies, 16 items were removed from the scale. In this way, the scale took its final form with 46 items. In the reliability analysis of the scale, it was found that the Cronbach's Alpha values for its sub-dimensions ranged from 0.74 to 0.83. High scores in PAS subscales indicate that parental attitudes increase.

Statistical Analysis

The demographic and clinical characteristics of children and adolescents receiving outpatient psychiatric treatment were evaluated by descriptive statistical analyzes such as number, ratio, mean, and standard deviation. Relationships between pre-treatment children and adolescents' SDQ total scores, QBFPT, and PAS scores were analyzed using the Pearson Correlation Analysis. Changes in pre-treatment, first month, third month, and sixth-month SDQ total scores were evaluated by One-Way ANOVA for Repeated Measures. Greenhouse-Geisser'sresult was used in the study when the sphericity assumption was not met in the ANOVA analyzes for repeated measurements. Whether there was a significant difference between pre- and post-treatment SDQ measurements was tested by Bonferroni Analysis. Besides, the effectiveness of the QBFPT and PAS subscale scores on the SDQ total scores was evaluated by ANCOVA analysis, and the effect size of the covariants on the variable was determined using Partial Eta Squared. The change in the SDQ scores according to past treatment history, drug use status, and mental disorders was analyzed by Two-Way ANOVA for Repeated Measures. Normality assumption was met for Pearson Correlation Analysis and ANOVA analyzes. The significance level for all analyzes was set as $p < 0.05$. IBM SPSS 22.0 program was used in the application of the analyzes.

RESULTS

The age mean of children and adolescents evaluated in the study was found to be 10.73 ± 4.09 and 127 of the participants (54.5%) were male. It was examined the presence of adjustment disorder in 23 (9.9%) of the outpatients, ADHD in 59 (25.3%), Obsessive-Compulsive and Related Disorders in 14 (6%), Oppositional Defiant Disorder in 25 (10.7%), Autism Spectrum Disorder in 22 (9.5%), Anxiety Disorder in 14 (6%), Separation Anxiety Disorder in 9 (3.9%), and one of the other mental disorders in 67 (28.8%). It was found that 167 of the cases (71.7%) had received mental treatment and used medication in the past, 38 (16.3%) had physical disabilities, and 78 (33.5%) had

a family history of mental disorder.

According to the Pearson Correlation Analysis, it was found that the SDQ total scores of children and adolescents receiving outpatient psychiatric treatment were statistically significantly correlated with the Democratic Attitude subscale scores (r = 0.129, p = 0.049). Besides, it was found that there was no statistically significant correlation ($p > 0.05$) between SDQ total scores and PAS and QBFPT sub-scales (Table 1). The mean SDQ total scores of the participants evaluated in the study before and after the treatment (1st, 3rd, and 6th months) were 36.76 ± 5.66, 36.12 ± 5.62, 36.08 ± 5.65, and 35.73±5.56, respectively and the mean SDQ total score did not show statistically significant change before and after treatment (F = 1.44, $p = 0.233$). According to the Bonferroni Analysis comparisons between pre-treatment and months, it was found that the SDQ scores did not show a statistically significant change ($p > 0.05$) (Fig. 1).

In ANCOVA for Repeated Measures analysis, when personality scale sub-dimension scores in the change in SDQ total scores were included inthe analysis as covariates, the change in SDQ scores was found to be statistically significant (F = 3.10, $p = 0.026$). In this analysis, it was evaluated that only Emotional Stability sub-dimension scores were statistically significantly effective (F = 3.27, $p = 0.023$), but the level of this effect was low (Partial Eta Squared = 0.014) in the change of SDQ total scores. Additionally, in the change in SDQ total scores, Agreeableness (F = 1.21, $p = 0.307$), Extroversion (F = 2.05, $p = 0.109$), Conscientiousness (F = 1.87, $p = 0.136$), and Openness to Experience (F = 1.87, $p = 0.136$) sub-dimension scores were found to have no statistically significant effect (Table 2).

In ANCOVA for Repeated Measures analysis, when the parental attitudes scale's sub- dimension scores in the change in SDQ total scores were included in the analysis as covariates, the change in the SDQ scores was found to be statistically significant (F =

Table 1. Relationships between psychometric measurements of pre-treatment participants (n = 233)

		1	2	3	4	5	6	7	8	9
1-SDQ Total	r	-								
	p	-								
2-Aggreeableness	r	0.078								
	p	0.238								
3-Extraversion	r	-0.005	**-0.492**							
	p	0.941	**<0.001**							
4-Conscientiousness	r	0.012	**0.500**	**0.230**						
	p	0.858	**< 0.001**	**< 0.001**						
5-Emotional Stability	r	0.108	**0.616**	-0.078	**0.823**					
	p	0.100	**<0.001**	0.236	**< 0.001**					
6-Opennes to Experience	r	-0.008	**0.289**	**0.412**	**0.909**	**0.617**				
	p	0.909	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**				
7-Democratic Attitude	r	**0.129**	0.029	0.060	0.106	0.052	**0.100**			
	p	**0.049**	0.662	0.360	0.106	0.427	**0.130**			
8- Autoritarian Attitude	r	0.111	0.016	0.085	0.080	0.033	**0.094**	**0.824**		
	p	0.090	0.808	0.196	0.223	0.612	**0.151**	**< 0.001**		
9-Protective Attitude	r	0.107	0.005	-0.035	0.026	-0.005	**0.035**	**0.516**	**0.383**	
	p	0.104	0.935	0.592	0.689	0.943	**0.591**	**< 0.001**	**<0.001**	
10-Permissive Attitude	r	0.071	0.056	-0.024	0.047	0.039	**0.005**	**0.782**	**0.512**	**0.271**
	p	0.278	0.396	0.715	0.479	0.555	**0.937**	**< 0.001**	**< 0.001**	**< 0.001**

Results of Pearson Correlation Analysis, SDQ = Strength and Difficulties Questionnaire

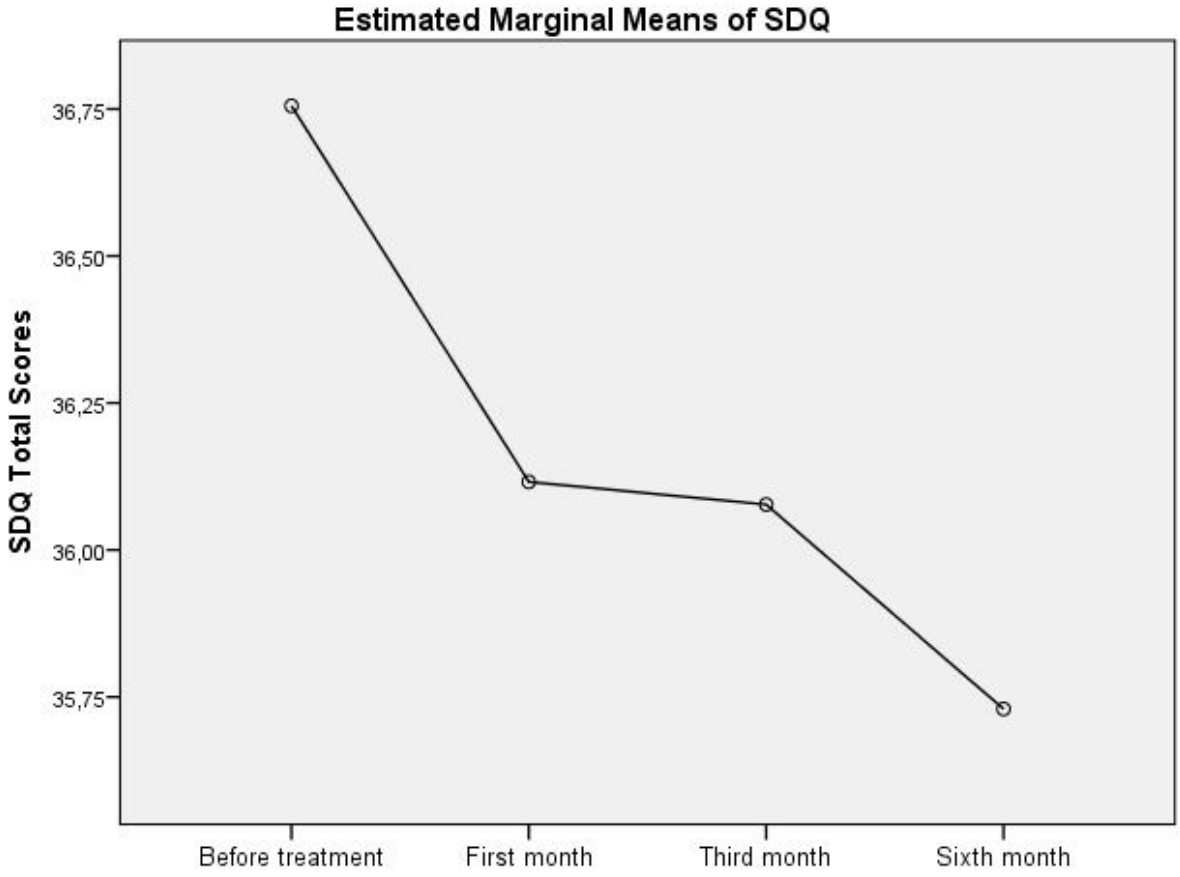

Fig. 1. The change in the mean SDQ scores of the participants (n = 233) before and after treatment.

4.42, $p = 0.005$). In this analysis, it was evaluated that the Democratic Attitude sub-dimension scores were statistically significantly effective (F = 2.70, $p = 0.048$) in the change of SDQ total scores, but the level of this effect was low (Partial Eta Squared = 0.012). Besides, sub- dimension scores of Authoritarian Attitude (F = 0.91, $p = 0.434$), Protective Attitude (F = 0.20, $p = 0.887$), and Permissive Attitude (F = 2.11, p

Table 2. Psychometric properties affecting the change in SDQ scores before and after treatment

	Covariates	Mean Square	df	F	*p* value	Partial Eta Squared
Treatment Affect		95.51	2.85	3.10	**0.026**	0.013
	Agreeableness	37.13		1.21	0.307	0.005
	Extraversion	63.12		2.05	0.109	0.009
	Conscientiousness	57.66		1.87	0.136	0.008
	Emotional stability	100.59		3.27	**0.023**	0.014
	Openness to Experience	57.70		1.87	0.136	0.008
Treatment Affect		136.62	2.85	4.42	**0.005**	0.019
	DemocraticAttitude	83.36		2.70	**0.048**	0.012
	Authoritarian Attitude	28.02		0.91	0.434	0.004
	Protective Attitude	6.19		0.20	0.887	0.001
	Permissive Attitude	65.07		2.11	0.102	0.009

One-way ANCOVA analysis result for Repetitive Measurements, SDQ = Strength and Difficulties Questionnaire

= 0.102) were found to have no statistically significant effect (Table 2).

In the Two-Way ANOVA for Repetitive Measures analysis, based on the examination of the effects of demographic and clinical characteristics that may have effects on the change in SDQ total scores, only the diagnosis of Separation Anxiety was a statistically significant factor (F = 2.86, p = 0.039), also, the effect size of this diagnosis on the change on the scores (Partial Eta Squared = 0.012) was evaluated as low (Table 3).

DISCUSSION

In the study, it was found that emotional and behavioral problems of children and adolescents who applied for mental treatment were positively associated with democratic parental attitudes, emotional and behavioral problems decreased in these individuals before and after treatment, but this decrease was not statistically significant. Moreover, it was detected that emotional stability, which is one of the personality traits, the democratic attitude of the parents, and the

Table 3. Demographic and clinical characteristics affecting the change in SSQ scores before and after treatment

	Between Subjects Factors	Mean Square	df	F	*p* value	Partial Eta Squared
Treatment Affect		43.19	2.85	1.37	0.248	0.006
	Gender	38.79		1.24	0.294	0.005
Treatment Affect		47.78	2.85	1.52	0.209	0.007
	Treatment history	10.00		0.32	0.801	0.001
Treatment Affect		26.13	2.85	0.84	0.469	0.004
	Use of Medication	23.05		0.74	0.524	0.003
Treatment Affect		46.96	2.85	1.50	0.214	0.006
	Family History	27.22		0.87	0.451	0.004
Treatment Affect		35.17	2.85	1.12	0.337	0.005
	Physical Disability	17.88		0.57	0.625	0.002
Treatment Affect		45.32	2.85	1.45	0.230	0.006
	Adjustment Disorder	17.34		0.55	0.637	0.002
Treatment Affect		42.45	2.85	1.35	0.257	0.006
	ADHD	10.01		0.32	0.801	0.001
Treatment Affect		28.08	2.85	0.90	0.437	0.004
	OCD	34.82		1.12	0.341	0.005
Treatment Affect		16.86	2.85	0.54	0.647	0.002
	Oppositional Defiant Disorder	20.85		0.67	0.566	0.003
Treatment Affect		32.59	2.85	1.04	0.370	0.004
	Autism	34.12		1.09	0.350	0.005
Treatment Affect		41.92	2.85	1.34	0.260	0.006
	Anxiety	34.28		1.10	0.348	0.005
Treatment Affect		71.12	2.86	2.30	0.079	0.010
	Separation Anxiety	88.36		2.86	0.039	0.012
Treatment Affect		42.78	2.85	1.37	0.253	0.006
	OTHER	11.91		0.38	0.757	0.002

Two-way ANOVA analysis result for Repetitive Measurements, SDQ = Strength and Difficulties Questionnaire

diagnosis of separation anxiety, which is a mental illness, are partially effective factors in the change in emotional and behavioral problems in the participants. In the literature, it has been shown in different studies that psychopathological characteristics in children and adolescents have been associated with personality traits [18-20], and it has been stated that different parental attitudes can increase emotional and behavioral problems in children and adolescents [11,12].

Democratic attitude shows that mothers and fathers have a reassuring and tolerant attitude in their approach to children. Democratic attitude is, therefore, accepted as a positive approach in parents and it has been reported that it is associated with the development of healthy personality traits in children [21]. Thus, it can be considered unexpected that the democratic attitude characteristics of parents are positively associated with behavioral and mental problems in this study. In a study conducted on adolescents, Rizvi and Najam [12] stated that similar attitudes between parents can reduce emotional and behavioral problems, and similarly, the difference between different authoritarian or permissive attitudes in the mother or father may increase mental problems in adolescents. In this study, the differences between mothers' and fathers' attitudes were not compared. Also, the study examined the data of the parents of children who needed psychological treatment, not data from the normal population. For this reason, keeping in mind that democratic attitudes may also contribute to the increase of emotional and behavioral problems in children and adolescents, making new researches in this area may contribute to the literature. It was also found in the current study that democratic attitudes had a statistically significant effect on the change in emotional and behavioral problems of children and adolescents before and after treatment, and democratic attitudes had a limited effect. Researchers have stated that parental attitudes may differ according to cultural characteristics, which can change the way children perceive behaviors, however, parental attitudes that combine authoritarian attitude with expressing emotional warmth are the most advantageous method for the development of the child [21, 22]. Schofield *et al*. [23] stated that parents learned by experimenting which behavior worked or not overtime, and as a result, their beliefs about parenting could change over time. In the present study, the parenting attitudes of children and adolescents who applied for mental treatment were evaluated. For this reason, it should be kept in mind that the attitudes of parents who often see emotional and behavioral problems in their children may be variable, and thus democratic attitudes can have effects on the change of mental problems.

Emotional stability includes personality traits such as openness to criticism, calmness, and comfort in a positive sense, and personality traits that are aggressive, nervous, sensitive, anxious, and timid [16]. Personality traits were found to be an effective confounding factor in the change of emotional and behavioral problems in children and adolescents evaluated in the study, and when the personality sub-dimensions were examined, the emotional stability was found to be a partial but statistically significant factor. Similarly, studies in the literature have shown that neuroticism characteristics in children are one of the effective factors in the emergence of mental problems, and emotional instability is associated with problematic behaviors [10, 24]. Therefore, it can be said that the results obtained from this study were compatible with the literature. It may be useful to keep in mind that emotional and behavioral problems are high in adolescents with high problematic personality traits, and psychopathological characteristics observed in adolescents are shaped by personality and family characteristics [8, 9].

In the study, it was found that only the diagnosis of separation anxiety was a statistically significant factor in the change of emotional and behavioral problems in children and adolescents receiving treatment. Separation anxiety is a mental disorder (DSM-V) that describes the state of anxiety and fear that is not compatible with the development of the person and is related to separation from the people they are attached to. It has been stated that separation anxiety disorder that begins in childhood creates a great vulnerability for the emergence of mental disorders in young adulthood, and being sensitive to the diagnosis of separation anxiety for clinicians may mediate the reduction of psychopathological problems in the following years [25]. Prioritizing the diagnosis of separation anxiety to reduce emotional and behavioral problems in children and adolescents receiving mental treatment may be, therefore, beneficial in terms of treatment.

In the literature, it has been shown that emotional and behavioral problems in children and adolescents are

associated with parental attitudes and personality traits, but the effects of these characteristics on the change of psychopathological problems in outpatients have not been adequately studied.

Limitations

The important limitations of the study firstly is the evaluation of emotional and behavioral problems, parental attitudes, and personality traits in children and adolescents with self-report scales. Secondly, the study is that children and adolescents receiving psychiatric treatment consist of people who are followed up from a single-center and the number of participants in some diagnostic groups is low. Thirdly, the study is that the effects of age events that may affect emotional and behavioral problems in adolescents during treatment were not controlled. The psychopathological characteristics of the parents were not evaluated in the study.

CONCLUSION

Considering the result of this study, it should be kept in mind that parental attitudes and personality traits are effective factors on the six-month change in emotional and behavioral problems in children and adolescents receiving outpatient treatment. It may be beneficial to focus on democratic parental attitudes and personality traits associated with the emotional stability to improve the quality of mental treatment, especially in these people's treatment processes.

Authors' Contribution

Study Conception: Mİ; Study Design: Mİ; Supervision: Mİ; Funding: Mİ; Materials: Mİ; Data Collection and/or Processing: Mİ; Statistical Analysis and/or Data Interpretation: Mİ; Literature Review: Mİ; Manuscript Preparation: Mİ and Critical Review: Mİ.

Conflict of interest

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Short-term treatment results of endometrial hyperplasia without atypia

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ABSTRACT

Objectives: Endometrial hyperplasia is a pathology that often represents with abnormal uterine bleeding and develops under the influence of unopposed estrogen. In this study, the response to cyclic medroxyprogesterone acetate (MPA) treatment in endometrial hyperplasia without atypia, which is known to have a good response to progestagen agents, was retrospectively evaluated.

Methods: Control endometrial biopsy results of 111 patients who were initiated cyclic MPA treatment due to endometrial biopsy results of endometrial hyperplasia without atypia were evaluated after 3 months of treatment. Endometrial hyperplasia free biopsy results after treatment were accepted as a successful treatment in those patient.

Results: Control biopsies revealed proliferative endometrium in 37 (33.3%) patients, secretory endometrium in 34 (30.6%) patients, inactive endometrium in 9 (8.1%) patients, endometritis in 4 (3.6%) patients, endometrial hyperplasia without atypia in 26 (23,4%) patients, and endometrial hyperplasia with atypia in 1 (0.9%) patient. Our response rate to treatment was 75.7% (84/111) and the persistence was found to be 23.4% (26/111). In patients with a positive response to treatment (n = 84), the mean age was 45.15 ± 5.19 years and in patients with no response to treatment (n = 27) the mean age was 45.56 ± 6.41 years, and there was no difference between the two groups in terms of average age.

Conclusions: Although the use of cyclic MPA in the treatment of endometrial hyperplasia without atypia is an effective treatment method, we believe that better results will be achieved in the use of more than 3 months duration.

Keywords: Endometrial hyperplasia, medroxyprogesterone acetate, cyclic

Endometrial hyperplasia is a pathology characterized by an increase in the gland / stroma ratio in the endometrium tissue lining the uterine cavity [1]. Proliferative glandular changes occurs as a result of prolonged estrogenic stimulation unmet with progesterone, and this unopposed estrogenic stimulus induces the sporadic mutations in the endometrial glands. Proliferating glands can differ in shape and size and may include cytological atypia [2].

Patients often present with complaints of abnormal uterine bleeding. Every year, 1/20 of women between the ages of 30-49 apply to gynecology outpatient clinics with the complaint of abnormal uterine bleeding [3]. Endometrial biopsy is recommended for patients over the age of 40 who present with abnormal uterine bleeding, and who do not respond to medical treatment, or who have endometrial cancer risk factors even though younger than 40 [4].

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To date, three main classification systems have been developed in endometrial hyperplasia, considering the histopathological findings that will affect the progression to endometrial cancer [5]. Following the widely used classification system (WHO94) which was adopted by the World Health Organization (WHO) in 1994, endometrial interepithelial neoplasia (EIN) classification system was proposed in the early 2000s. According to this classification system, endometrial hyperplasia includes two different conditions; benign endometrial hyperplasia (BEH) caused by unopposed estrogenic stimulation and atypical endometrial hyperplasia / endometrial intraepithelial neoplasia (AEH/EIN) which is a precancerous lesion [6, 7]. However, since the tests used for the objective diagnosis of EIN are expensive, inconvenient and cannot be applied in every center, this classification system has not been widely used and the search for a new classification system has continued. Today, it is recommended to use the classification system, which was established by the WHO in 2014 on the basis of cytological atypia [8, 9]. According to this classification system, endometrial hyperplasia is divided into two groups as with atypia and without atypia. It is thought that this new classification system is more successful in predicting precancerous lesions [10]. In our patients, histopathological diagnosis was made according to the classification system accepted by WHO in 2014.

Follow-up, medical and surgical treatment options are available in management of endometrial hyperplasia cases without atypia. Progestagen agents are used in medical treatment. Progesterone treatment has been shown to decrease proliferative activity in the endometrium [11]. We included patients who received cyclic medroxyprogesterone acetate (MPA) treatment for the diagnosis of endometrial hyperplasia without atypia.

We aimed in this study to find out the effectiveness of the treatment modality in our patient population and to be a guide to determine the most appropriate treatment option and treatment period.

METHODS

We aimed to retrospectively evaluate the response to 10 mg/day oral MPA treatment for 3 months in patients who applied to Bursa Çekirge State Hospital and Bursa City Hospital with the complaint of abnormal uterine bleeding and were diagnosed with endometrial hyperplasia without atypia.

The collection of patients information started after the approval of the Uludag University Ethics Committee (ethic approval no: 2020-5/30). 111 patients who were diagnosed with endometrial hyperplasia without atypia between January 2018 and June 2020 and who were started on the 14th day of the cycle with MPA treatment and administered 10 mg/day treatment dose for 12 days were included in the study. Diagnoses other than endometrial hyperplasia were evaluated as response to treatment in control endometrial biopsies taken after 3 months of treatment.

Statistical Analysis

The comparison of the age variable to normal distribution was examined with the Shapiro-Wilk test and expressed as mean ± standard deviation (minimum: maximum) values as an indicative statistic. In terms of age variable, independent double sample t-test was used for the comparison made between patient groups with and without response to treatment. The ANOVA test was used in the comparison of the patient groups who were implanted with levonorgestrel-releasing intrauterine device (LNG-IUD), who had hysterectomy, and whose treatment was extended to 6 months, in terms of age variable. Categorical variables in the study were expressed in terms of frequency and related percentage values. In the comparison of the age variable between groups, the type I error level was accepted as 5%, and the statistical analysis of the study was performed using the SPSS (IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.) program.

RESULTS

The mean age of the study participants was 45.25 ± 5.48 years (min: 29 years - max: 58 years). In patients with a positive response to treatment (n = 84), the mean age was 45.15 ± 5.19 years (min: 33 years – max: 58 years) and in patients with no response to treatment (n = 27) the mean age was 45.56 ± 6.41 years (min: 29 years - max: 56 years), and there was no difference between the two groups in terms of av-

erage age ($p = 0.743$).

The distribution of control biopsy results after 3 months of treatment in the groups with and without response to treatment is given in Table 1.

In 27 patients who did not respond to treatment after three months; LNG-IUD was applied to 22.20% (n = 6), and hysterectomy and bilateral salpingo-oophorectomy were applied to 44.40% (n = 12), considering that they did not have fertility desires. In 33.30% of the patients (n = 9) with no response, the medical treatment duration was extended to 6 months. The mean age was found to be 39.83 ± 7.03 (min: 29 years - max: 50 years) in patients with LNG-IUD group (n = 6), 49.83 ± 3.74 years (min: 46 years - max: 56 years) in patients with hysterectomy group (n = 12) and 43.67 ± 5.22 years (min: 35 years - max: 51 years) in patients with 6-month treatment group (n = 9). It was determined that there was a difference according to age between the groups ($p = 0.001$). In subgroup analyzes, it was determined that the average age of patients with hysterectomy and bilateral salpingo-oophorectomy and whose treatment was extended to 6 months was higher than the group with LNG-IUD ($p = 0.002$ and $p = 0.002$, respectively), while there was no difference in terms of age between the groups with hysterectomy and bilateral salpingo-oophorectomy and whose treatment duration was 6 months.

After 3 month of MPA treatment control biopsies revealed proliferative endometrium in 37 (33.3%) patients, secretory endometrium in 34 (30.6%) patients, inactive endometrium in 9 (8.1%) patients, endometritis in 4 (3.6%) patients, endometrial hyperplasia without atypia in 26 (23.4%) patients, and endometrial hyperplasia with atypia in 1 (0.9%) patient.

Treatment response parameters vary in different studies. At the stage of evaluating the response to cyclic MPA treatment, if the histopathological diagnoses of control endometrial biopsy were evaluated as resolution, regression, persistence and progression, as in some studies, these parameters were found to be 42.3%; 33.3%; 23.4%; and 0.9%; respectively [12-14]. If histopathological diagnoses other than endometrial hyperplasia were accepted as a response to treatment in control endometrial biopsy, we found the rate of response to treatment 75.7% and the persistence 23.4% in our study.

DISCUSSION

Endometrial hyperplasia is more common in women between the ages of 50-54, with an average age of 52, which is ten years younger than the age of incidence of endometrial cancer [10, 15]. Patients who are diagnosed with endometrial hyperplasia without atypia should be informed that the probability of developing endometrial cancer in the following 20 years is less than 5% and that some of them may regress spontaneously [8]. The chance of spontaneous resolution will be higher by preventing obesity and changing or discontinuing estrogen-containing hormone replacement therapies so as to eliminate the hyperestrogenic state [16]. In a study where 51 cases of endometrial hyperplasia were followed up for 6 months, investigating the natural course of endometrial hyperplasia, spontaneous regression was reported as 74.2% and persistence as 17% in the simple endometrial hyperplasia without atypia group [17].

Table 1. Distribution of control biopsy results

	Response to Treatment	
	Positive (n = 84)	**Negative (n = 27)**
Proliferative endometrium	37 (44%)	0
Secretory endometrium	34 (40.50%)	0
Hyperplasia without atypia	0	26 (96.30%)
Inactive endometrium	9 (10.70%)	0
Endometritis	4 (4.80%)	0
Hyperplasia with atypia	0	1 (3.70%)

Data are expressed as n%

The aim of the treatment of endometrial hyperplasia is to treat the severe menstrual bleeding it causes, to identify a possible accompanying endometrial cancer and to prevent the progression to endometrial cancer [18].

Progesterone treatment is applied in patients who do not have regression during follow-up or who have ongoing complaints such as heavy menstrual bleeding. Regression rates with progesterone treatment have been reported as 89-96% in the literature [19]. The main progestagen agents used in the treatment of endometrial hyperplasia are megestrol acetate, MPA, norethisterone acetate and LNG-IUD [19]. It is recommended to start cyclic use of MPA, which is one of the medical treatment options and was used in our study, on the 14th day of menstruation. Treatment is applied by using 10-20mg / day MPA for 11-14 days each month [20].

Ferenczy *et al*. [21] evaluated the response to cyclic oral MPA treatment in endometrial hyperplasia, and in this study, they found that there was 20% persistence and 80% regression after 6 months of treatment. We achieved similar results after 3 months of treatment in a larger study group. However, it should be kept in mind that it carries a 10% risk of recurrence after treatment, together with high regression rates [22].

Emarh *et al*. [23] compared the effectiveness of cyclic and continuous use of MPA in patients with endometrial hyperplasia without atypia and found that the use of cyclic MPA was effective and safe. Unlike our study, the duration of treatment was 6 months in this study, and regression rates in cyclic and continuous MPA groups were reported as 90% and 82.5%, respectively. Again, in this study, side effects such as acne, nausea, and menstrual cycle changes were more common in the continuous MPA group. In our study, similar to this study, when histopathological diagnoses other than hyperplasia in control endometrial biopsies are accepted as regression, our response rate after 3 months of treatment was 75.7%. Also we did not record any evidence of side effects of MPA in our study group. In another study in which cyclic 10 mg/day MPA was applied for 3 months as in our study in the treatment of endometrial hyperplasia that developed after unopposed estrogen replacement therapy, response rates to treatment were reported above 90% [24].

Ozdegirmenci *et al*. [13] compared the efficacy of MPA, linestrenol, and norethisterone in simple endometrial hyperplasia without atypia. In this study, 3-month cyclic use results were evaluated prospectively and no difference was observed in terms of the efficacy of all three preparations. Control biopsy results were evaluated as resolution, regression, persistence and progression. As a result of this study, it was observed that there was 60% regression, 36.7% resolution and 3.3% persistence in the MPA group [13]. In another study comparing the MPA, norethisterone and LNG-IUD activities, similar results were obtained in the MPA group [14]. In our study, the resolution rate after 3 months of treatment was found to be 42.3%, but the persistence was found to be 23.4%. In the data we obtained retrospectively, we think that the high number of patients in our study group was a factor in these results. In addition, the main complaint of our patients was heavy menstrual bleeding.

The studies comparing the efficacy of MPA and LNG-IUD in patients with endometrial hyperplasia without atypia reported a regression rate 54,8- 100% in the MPA group [25, 26, 27]. In these studies, treatment response rates were evaluated as remission and persistence, and when evaluated in this way, being the number of patients was higher in our study, the rates of remission and persistence were 75.7% and 23.4%, respectively.

Our study was designed retrospectively and the effectiveness of MPA treatment, which was applied cyclically for 3 months in order to avoid the side effects of progesterone, was evaluated. Control endometrial biopsy results are shown in Table 1. Patients who did not respond to treatment were offered options to continue MPA treatment for 6 months or to insert LNG-IUD. Hysterectomy option was provided for patients who did not want to come for medical monitoring and did not desire fertility preservation. The high persistence rate in control endometrial biopsy after 3 months of treatment in our study can be explained by the high number of cases and all of our patients having severe menstrual bleeding complaint compared to other studies in the literature. Progression to endometrial cancer has been reported as 1% in the hyperplasia group without atypia among endometrial hyperplasia cases with an average follow-up period of 13.4 years [16]. In our study, in the patient whose control endometrial biopsy result was endometrial hyperplasia

with atypia, we think that this situation was caused by the failure of sampling the entire endometrial cavity in the first biopsy rather than progression during the 3-month follow-up. As a matter of fact, studies have shown that endometrial sampling methods can sample less than 50% of the entire endometrial cavity [28].

In line with current data, it is recommended to continue progesterone (MPA 10-20 mg/day or norethisterone 10-15 mg/day) treatment or LNG-IUD usage for at least 6 months, and unresponsiveness to medical treatment is accepted as no regression observed after 12 months of therapy [9]. In monitoring the treatment, it is recommended to perform endometrial biopsy at 6-month intervals and follow-up the patient until two negative biopsy results are obtained.

Limitations

The limitation of our study is that we evaluated our own treatment method in a limited patient population in the short term, without the possibility of comparison with different treatment options.

CONCLUSION

Progestagens are first-line treatment options in the management of endometrial hyperplasia without atypia. As a result of this study, we have seen that the cyclic 3-month treatment protocol we have applied in our clinical practice in order to avoid the side effects of progestagens due to long-term use is effective. However, we think that long-term uninterrupted treatment would be more beneficial for maximal efficiency.

Authors' Contribution

Study Conception: ZA, SRO; Study Design: ZA, SRO, AE, GO; Supervision: ZA, SRO, AE, GO; Funding: ZA; Materials: ZA, AE; Data Collection and/or Processing: ZA, AE; Statistical Analysis and/or Data Interpretation: GO, SRO; Literature Review: ZA, SRO; Manuscript Preparation: ZA and Critical Review: GO, ZA.

Conflict of interest

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Diagnostic importance of hepatocyte nuclear factor 1 beta (HNF1ß) in testicular tumors and its sensitivity for the detection of yolk sac tumors: an immunohistochemical analysis

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ABSTRACT

Objectives: Testicular tumors are common solid malignancies in young fertile men, and most are germ cell tumors. In general, they originate from a single germ cell and transform into different tumor types or present with the coexistence of different morphological patterns. Due to the heterogeneity of these tumors, immunohistochemical markers are frequently used in their differential diagnosis. In recent years, some studies have indicated hepatocyte nuclear factor 1 beta (HNF1β) can be used in the differential diagnosis of testicular tumors, especially yolk sac tumors (YSTs). In this study, we aimed to investigate the general expression status of HNF1β in all testicular tumors and determine its importance in YST detection.

Methods: A total of 144 testicular tumors treated with orchiectomy between 2011 and 2020 were included in our study. The pathological diagnosis reports of these cases were retrospectively reviewed and their general prognostic features were determined. HNF1β immunohistochemical staining was applied to the characteristic paraffin blocks representing the lesions. Staining was evaluated in terms of severity and prevalence.

Results: Most cases (38.2%) were seminomas, followed by mixed germ cell tumors (34.0%, 49/144), embryonic carcinomas (7.6%), pure YSTs (4.9%), and others (Leydig cell tumors, mesenchymal tumors, lymphomas, etc.). No HNF1β immunostaining was observed in any of the seminomatous lesions. A high level of staining was present in almost all the pure YSTs and tumor areas with the YST component. HNF1β had a specificity of 95.1% and sensitivity of 87.1% in the detection of YSTs.

Conclusions: HNF1β has high specificity and sensitivity in detecting YSTs among testicular tumors, and therefore we consider that it can be routinely used to detect the presence of YSTs, especially in patients with mixed germ cell tumors.

Keywords: Testicular germ cell tumor, seminoma, yolk sac tumor, hepatocyte nuclear factor 1 beta (HNF1β)

Testicular cancer is a solid malignancy with an increased global incidence in recent years and is commonly seen in young men [1]. Approximately 95% of these cancer cases are germ cell tumors, constituting 1% of all cancers [2, 3]. According to the 2016 classification of the World Health Organization (WHO), testicular germ cell tumors (TGCTs) are divided into two main groups as those associated and non-associated with intratubular germ cell neoplasia (ITGCN) [4]. TGCTs that are not associated with ITGCN include prepubertal teratomas, prepubertal yolk sac tumors (YSTs), and spermatocytic seminoma,

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while ITGCN-associated TGCTs cause seminomatous and non-seminomatous tumors (Embryonic carcinoma, YST, teratoma, and choriocarcinoma) [5]. In brief, these tumors can originate from a single stem cell and develop into other tumors, leading to the coexistence of different tumor types. There are difficulties in the histopathological differential diagnosis due to the combination of very different histological and morphological patterns and tumor heterogeneity. Therefore, immunohistochemical biomarkers, such as Pan CK, PLAP, CD30, AFP, and OCT3 are widely used to assist differential diagnosis. However, more biomarkers are needed for definitive typing.

The hepatocyte nuclear factor 1 beta (HNF1β) gene was first identified as the factor that regulates the active transcription of liver-specific genes [6]. This gene is localized on the 17q12 chromosome and is also called TCF2 [7]. Four important subtypes of hepatocyte nuclear factor have been defined, among which the HNF1β family is reported to be more closely related to cellular development and tumorigenesis [8]. It has been reported that mutations in this gene cause diabetes, kidney cysts, genital malformations, and benign lesions such as pancreatic atrophy, as well as some malignancies of organs such as the liver, kidney, and ovary [9]. Many genetic and epigenetic changes of the HNF1β gene are considered to play a role in the development and progression of a tumor. It has been reported that the CpG island on the HNF1β' gene is overexpressed in ovarian clear cell carcinomas due to hypomethylation, and this has a diagnostic feature. It has also been suggested that changes in the gene family affect the prognosis of some tumors and the survival of the patient [10].

In recent years, some studies have indicated that HNF1β may be useful in differentiating YSTs from other germ cell tumors [11, 12]. In our study, we aimed to determine the role of the HNF1β immunomarker in the differentiation of different histological types through its expression profile in testicular tumors, and especially in pure YSTs and mixed germ cell tumors (MGCTs). In addition, the relationship of this marker with some prognostic parameters was investigated.

METHODS

Various testicular tumors of 144 cases who underwent partial/total orchiectomy at Atatürk University Medical Faculty Hospital between 2011 and 2021 and were diagnosed at the Department of Pathology were included in the study. The pathology reports of the cases were retrospectively reviewed from the hospital information system. Tumor type, patient age, tumor side, necrosis, bleeding, lymphovascular, perineural, rete testis, epididymis, tunica albuginea, tunica vaginalis, perihilar adipose tissue, spermatic cord invasion, presence of tumor at the surgical margin, lymph node involvement, pathological stage, metastasis, and survival prognostic features were determined. HNF1β immunohistochemical staining was applied to the most suitable samples obtained from paraffin blocks containing tumors. Staining was evaluated in terms of prevalence and intensity. Findings were compared according to tumor types and some prognostic parameters.

This research was ethically approved by the ethics committee of Atatürk University School of Medicine with the decision number 17.06.2020/16.

Immunohistochemical Staining and Interpretation

Sections of 4-micron thickness were taken from the most suitable samples from paraffin tissue blocks fixed with formalin. Immunohistochemical staining was performed using the Ventana BenchMark ULTRA automated stainer (Roche, Basel, Switzerland) according to the manufacturer's protocol. The tissues were stained with a mouse antibody against the HNF1β protein (mouse monoclonal, anti-HNF1β antibody (CLO0374) ab236759, dilution 1:100, ABCAM) with the Ventana BenchMark ULTRA automated stainer. A citrate buffer (pH 6.0) was used for heat-induced epitope recruitment. The primary antibody was visualized with the OptiView DAB IHC Detection Kit (Ventana, Roche). Only nuclear staining was considered positive in HNF1β immunohistochemistry. The presence of staining greater than 1% in the tumoral area was considered positive. Staining was scored from 0 to 3 as follows: negative or 0, no staining; 1+ = weak, 2+ = intermediate and 3+ = strong positive. The expression of HNF1β was evaluated by two independent pathologists [13].

Statistical Analysis

The Pearson/Spearman correlation test was used to determine the correlation between HNF1B staining

and prognostic parameters. A p value of < 0.05 was accepted to indicate significant differences. Data analysis was performed using IBM SPSS statistics v. 20

RESULTS

Orchiectomy materials belonging to 144 individuals in total were included in the study. The mean age of the patients was 33.46 years. Seventy-three tumors were localized in the left testis and 71 in the right testis. Seminomas constituted the majority of cases at a rate of 38.2% (55/144), followed by MGCTs (34.0%, 49/144), embryonic carcinomas (7.6%, 11/144), YSTs (4.9%, 7/144), Leydig cell tumors (3.5%, 5/144), different types of lymphoma (5.5%, 8/144), pure teratomas (4.1%, 6/144), and mesenchymal tumors (2.0%, 3/144; one osteosarcoma, one liposarcoma, and one leiomyoma). Of the cases diagnosed with MGCTs,

Table 1. Distribution of cases according to tumor types and prognostic features

		Seminoma (n = 55)	MGCT (n = 49)	EC (n = 11)	YST (n = 7)	TeRT (n =6)	Leydig (n = 5)	Total (n = 144)
Side, n (%)	Right	27 (49.)	25 (51.)	5 (45.4)	3 (42.8)	2 (33.3)	2 (40)	71 (49.3)
	Left	28 (51.0)	24 (48.)	6 (54.6)	4 (57.2)	4 (66.6)	3 (60)	73 (51.7)
Metastasis, n (%)	Present	10 (18.1)	16 (32.)	2 (18.1)	3 (42.8)	0	0	41 (28.5)
	Absent	45 (81.2)	34 (69.)	9 (91.8)	4 (57.2)	6 (100)	5(%100	103 (71.9
Size, n (%)	≤ 3 cm	16 (29.1)	13 (26.)	6 (54.6)	4 (57.2)	1 (16.6)	1(%20)	43 (29.8)
	> 3 cm	39 (70.9)	36 (73)	5 (45.4)	3 (42.8)	5 (83.4)	4(%40)	101 (70.2
Necrosis, n (%)	Present	31 (56.3)	42 (85.79	2 (18.1)	2 (28.5)	0	1 (20)	85 (59.0)
	Absent	24 (43.7)	7 (14.2)	9 (91.8)	5 (71.5)	6 (100)	4 (80)	59 (410.)
Bleeding, n (%)	Present	8 (14.5)	36 (73.4)	9 (91.8)	2 (28.5)	0	1 (20)	58 (40.2)
	Absent	47 (85.5)	13 (26.6)	2 (18.1)	5 (71.5)	6 (100)	4 (80)	86 (59.39
LVI, n (%)	Present	30 (54.5)	35 (71.59	8 (72.8)	3 (42.8)	0	1 (20)	83 (57.6)
	Absent	25 (45.5)	14 (28.5)	3 (27.2)	4 (57.2)	6 (100)	4 (80)	61 (42.3)
Rete, n (%)	Present	23 (41.8)	17 (34.6)	8 (72.8)	2 (28.5)	0	0	60 (41.79
	Absent	32 (58.2)	32 (65.3)	3 (27.2)	5 (71.5)	6 (100)	5 (100	84 (58.39
Vaginalis, n (%)	Present	8 (14.5)	4 (58.1)	1 (9)	0	0	0	16 (11.1)
	Absent	47 (85.5)	45 (91.9)	10 (91	7 (100)	6 (100)	5 (100)	128 (88.9
Epididymis, n (%)	Present	7 (12.7)	6 (12.2)	0	0	0	0	16 (11.1)
	Absent	48 (87.3)	43 (87.8)	11 (100	7 (100)	6 (100)	5 (100)	128 (88.9
Perihilar, n (%)	Present	7 (12.7)	6 (12.2)	0	0	0	0	14 (9.8)
	Absent	48 (87.3)	43 (87.8)	11 (100	7 (100)	6 (100)	5 (100)	130 (90.2
Spermatic cord, n (%)	Present	2 (3.6)	3 (6.1)	1 (9)	0	0	1 (20)	9 (6.2)
	Absent	53 (96.4)	46 (93.9)	10 (91)	7 (100)	6 (100)	4 (80)	135 (93.8
Surgical margin, n (%)	Present	1 (1.8)	0	0	0	0	0	1 (0.6)
	Absent	54 (98.2)	49 (100)	11 (100	7 (100)	6 (100)	5 (100)	141 (98)
pT, n (%)	1	23 (41.8)	15 (30.6)	4 (36.6)	3 (42.8)	6 (100)	4 (80)	63 (43.7)
	2	28 (50.9)	31 (63.2)	7 (63.4)	4 (57.2)	0	1 (20)	71 (49.3)
	3	4 (7.2)	3 (6.1)	0	0	0	0	10 (7)
In situ component, n (%)	Present	42 (76.4)	42 (85.7)	10 (91)	3 (42.8)	0	0	97 (67.3)
	Absent	135 (23.6)	7 (14.3)	1 (9)	4 (52.2)	6 (100)	5 (100)	47 (32.6)
Mortality status, n (%)	Survive	2 (3.6)	2 (4.0)	0	0	0	1 (20)	12 (8.3)
	Died	53 (96.4)	47 (96)	11 (100	7 (100)	6 (100)	4 (80)	132 (91.7

MGCT = Mixt Germ Cell Tumor, EC = Embrional Carcinoma, YST = Yolk Sac Tumor, TeRT = Teratoma, Leydig = leydig cel tumor, LVI = Lymphovascular invasion, pT =Patholojic stage

39 had embryonal carcinomas, 34 had seminomas, 31 had YSTs, and 13 had teratoma components. The choriocarcinoma component was observed in four cases.

Tumor size was below 3 cm in 43 (29.9%) cases and over 3 cm in 101 (70.1%). While metastasis was observed in 41 (28.6%) cases, the tumor was limited to the testis in 103 (71.5%) patients. Most of the metastases were those of MGCTs. Lymphovascular invasion was observed in 88% (127/144) of the cases. The highest pathological stage was seen in the pT2 group including 71 (49.3%) cases. The presence of carcinoma in situ was detected in 102 (70.8%) cases. A total of 132 of the cases are still alive, while the remaining 12 died. Of the patients that died, six had lymphomas, two had MGCTs, two had seminomas, and two had sarcomas. Other findings are summarized in Table 1.

Immunohistochemical distribution with HNF1β

Staining was graded as 3+ in 32 of these cases, 2+ in five, and 1+ in two (Figs. 1 and 2). Of the cases diagnosed with MGCTs, two were interpreted as YSTs but did not present with HNF1β staining. On the other hand, 1+ HNF1β staining was observed in the embryonal carcinoma areas in five cases with MGCTs (Figs. 1 to 3). HNF1β staining was not observed in any of the seminomas and seminomatous areas of the MGCTs (Figs. 1D and 3B). Lymphomas, mesenchymal tumors, and Leydig cell tumors included in the study, while it was present in almost all the pure YSTs and YST components of the MGCTs (39/41). More than 70% of the cases diagnosed with pure YSTs and the YST areas in cases diagnosed with MGCTs had HNF1β staining. HNF1β staining was graded as 3+ in all the teratomatous areas. No staining was observed in the lymphomas (Fig. 3D) or the choriocarcinomatous areas (Fig. 3E). The main immunohistochemical findings and their comparison according to other YST markers are summarized in Table 2. In our study, the sensitivity of HNF1B in terms of detecting the YST component was 87.1%, and the specificity was 95.1%.

No significant correlation was found between HNF1B staining and histopathological and clinical prognostic parameters such as necrosis, lymphovascular invasion, perineural invasion, rete testis invasion, perihilar adipose tissue invasion, spermatic cord invasion, lymph node involvement, pathological stage, metastasis and survival etc. ($p > 0.005$). No significant correlation was found between HNF1B staining and

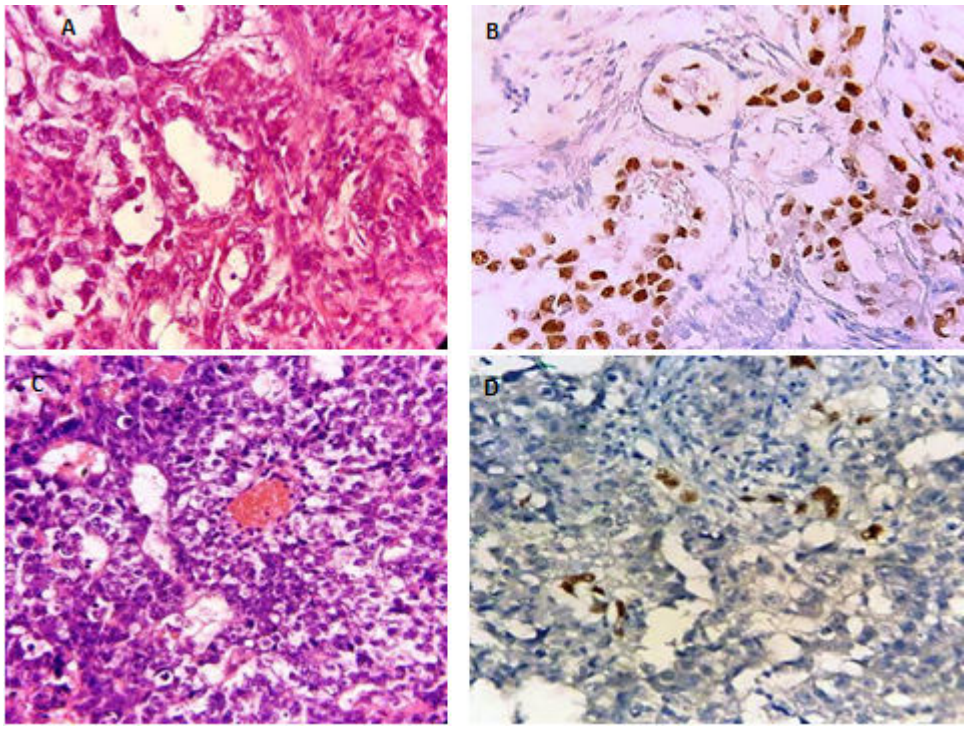

Fig. 1. HNF1B expression in MGCT component YST and Pure YST. (A) Pure YST with the microcystic pattern (HE ×20), (B) Strong nuclear positivity for HNF1β in YST (HNF1β ×20), (C) Mixed germ cell tumor with YST component (HE ×20), and (D) Nuclear positivity for HNF1β in the YST component of MGCT (HNF1β ×20).

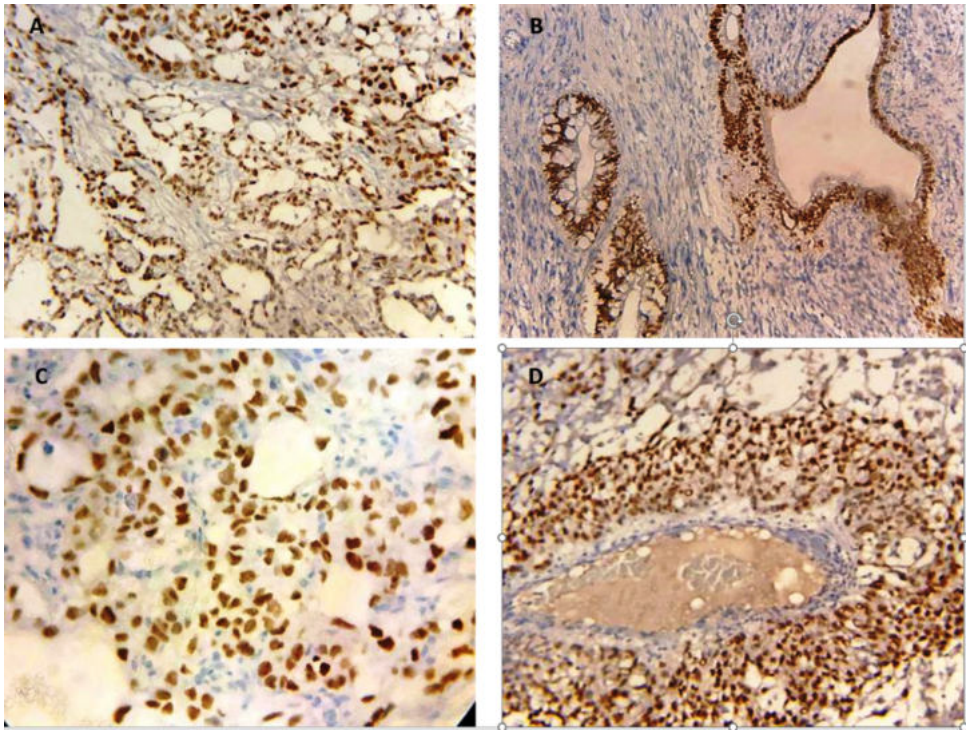

Fig. 2. HNF1β expression in different patterns of YST. (A) Diffuse nuclear positivity for HNF1β in YST with the microcystic pattern (HNF1B ×20), (B) Glandular pattern YST (HNF1β ×20), (C) Solid pattern YST (HNF1β ×20), and (D) Mixed pattern YST (HNF1β ×20).

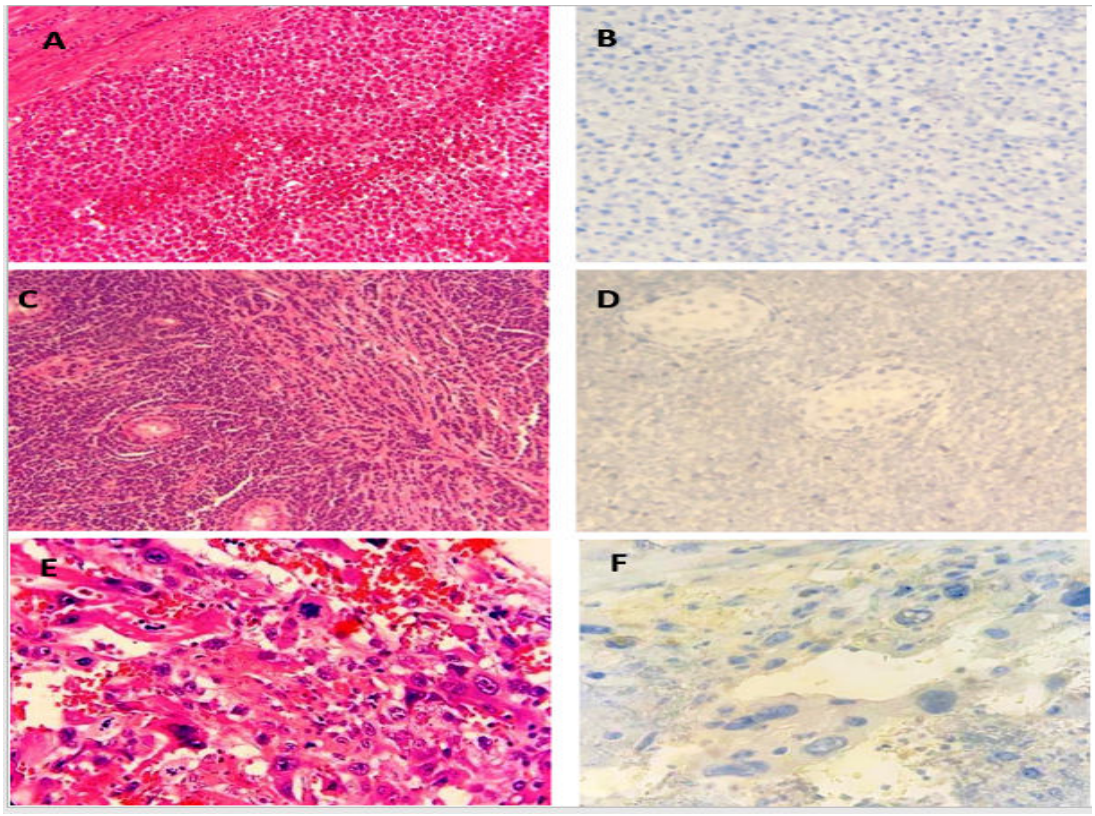

Fig. 3. HNF1β expression profile in different tumor types and areas. (A) Seminoma (HE ×20), B-Negative HNF1β staining in seminoma (×20), (C) Intratesticular lymphoma (HEx20), (D) Negative HNF1β staining in intratesticular lymphoma (×20), (E) Choriocarcinomatous area in MGCT (HEx40), and (F) Negative HNF1β staining in the choriocarcinomatous area of MGCT (×40)

histopathological and clinical prognostic parameters such as necrosis, lymphovascular invasion, perineural invasion, rete testis invasion, perihilar adipose tissue invasion, spermatic cord invasion, lymph node involvement, pathological stage, metastasis and survival etc. ($p > 0.005$). A significant difference was observed between YST and other histological types with the Chi-square test, which supports the specificity and sensitivity tests, with HNF1B ($p < 0.001$). When histological types were examined separately, a significant difference was observed between embryonal carcinoma ($p < 0.001$) and seminoma ($p < 0.001$).

DISCUSSION

Although testicular germ cell tumors constitute less than 1% of all tumors in men, they are the most common tumors of the testis. Their prevalence in young fertile men makes them particularly important. Depending on their development from intratubular germ cell neoplasia, they may contain seminomatous and non-seminomatous, or embryonal and extra-embryonal differentiation areas, or all these areas together. Due to their heterogeneity, it is difficult to make an accurate diagnosis of testicular germ cell tumors. The accuracy of diagnosis is very important in terms of case management and treatment [14].

MGCTs and especially YSTs have many morphological patterns, making the diagnosis very difficult. Numerous immunohistochemical markers are used to distinguish tumor types and patterns. Alpha-fetoprotein (AFP) and glypican-3 are the most well-known examples of these markers. Some studies conducted in recent years state that HNF1β is an important YST marker [11, 12].

HNF1β was identified as a liver-specific transcription factor. It has been suggested to play a role in liver, pancreas, and kidney organogenesis, and mutations in this gene have been associated with diabetes, kidney cysts, genital malformations, and benign lesions such as pancreatic atrophy [9], as well as cancer risk in various tumors, including hepatocellular carcinoma, pancreatic, renal, ovarian, endometrial, and prostatic cancers [15, 16].

Many genetic and epigenetic changes of the HNF1β gene are considered to play a role in the development and progression of a tumor. In humans, one of the epigenetic mechanisms regulating the expression of genes is the methylation of CpG dinucleotide

Table 2. Distribution of HNF1β expression according to tumor types (n = 144)

Tumor type		HNF1β			
		0	1+	2+	3+
Seminoma, n (%)	**n = 55**	55 (100)	0	0	0
MGCT, n (%)	**n = 49**				
YST	34 (69.3)	2 (5.8)	2 (5.8)	4 (11.7)	26 (76.7)
EC	39 (79.5)	34 (87.1)	5 (12.8)	0	0
Seminoma	31 (63.2)	31 (100)	0	0	0
Teratoma	13 (26.5)	2 (15.4)	2 (15.4)	3 (23)	6 (46.2)
Choriocarcino	4 (8.1)	4 (100)	0	0	0
Pure YST, n (%)	**n = 7**	0	0	1 (14.29	6 (85.8)
EC, n (%)	**n = 11**	9 (81.8)	2 (18.2)	0	0
Teratoma, n (%)	**n = 6**	0	0	1 (16.7)	5 (83.3)
Lymphoma, n (%)	**n = 8**	8 (100)	0	0	0
Leydig cell tumor, n (%)	**n = 5**	5 (100)	0	0	0
Mesenchymal tumor, n (%)	**n = 3**	3 (100)	0	0	0
Total	**144**				

HNF1β = hepatocyte nuclear factor 1 beta, MGCT = mixed germ cell tumor, YST = yolk sac tumor, EC = embryonal carcinoma

clusters. It is stated that HNF1β is overexpressed in clear cell carcinomas of the ovary due to the hypomethylation of the CpG island on the HNF1β' gene [1]). It has been suggested that the epigenetic inactivation of HNF1β is involved in tumorigenesis [17]. Some studies have reported that HNF1β plays a role in the expression of genes closely related to stem/progenitor cells [18]. However, the potential pathogenic mechanisms of HNF1β in cancer and regulatory mechanisms in stem cells are not yet fully understood. Therefore, further studies are still needed to elucidate the relationship between tumor and stem cell and HNF1β [19].

In a study by Shim *et al*. [20], the members of the HNF1 family were reported to regulate the activity of the AFP promoter during hepatic development and carcinogenesis process, and therefore a high HNF1β expression in hepatocellular carcinomas was associated with a high serum AFP level and AFP expression.

HNF1β has been identified as an important biomarker in clear cell carcinomas of the uterus and ovary in many gene expression studies. It has been reported that while HNF1β is highly expressed in ovarian clear cell carcinomas (CCC), non-CCCs do not express this protein [21]. Yamamoto *et al*. [22]suggested that the prevalence of HNF1β immunoreactivity in both the ovary and the endometrium would be an excellent marker for differentiating CCCs from other tumors. Kao *et al*. [23] stated that the overexpression of HNF1β was specific to ovarian CCC among ovarian carcinomas. In the pancreas, Kim *et al*. [24] showed that clear cell carcinomas and ductal carcinomas with clear cell features were overexpressed in clear cell components and were associated with worse survival. In another study, Silva *et al*. [25] showed HNF1β to be among five important genes that played an epigenetic role in colorectal cancer. They stated that HNF1β could be used as a useful biomarker in this cancer [25].

Buchner *et al*. [26] reported that HNF1β had a high expression in normal kidney tissue than in tumor tissue, and its loss was associated with renal cell carcinoma. They also suggested that HNF1β might be a tumor suppressor prognostic factor and therapeutic target [26]. In a study by Nogales *et al*. [27], it was determined that HNF1β was highly expressed in ovarian clear cell carcinoma and germ cell tumors with the glandular yolk sac pattern. Fadare *et al*. [28] reported that while HNF1β showed nuclear expression in 92% of ovarian clear cell carcinomas and 100% in YSTs, it was not stained in granulosa cell tumors or dysgerminomas. In a study by Rougemont *et al*. [11] evaluating 45 germ cell tumors, HNF1β staining was present in all the pure YSTs and YST components of the tumoral areas, and it was graded as 3+ in 93.9% of the cases. The authors stated that HNF1β had 100% sensitivity and 80% specificity for the detection of YSTs. In the same study, there was no staining in the seminomas or ECs, but staining was noted in the enteric type glandular areas of the teratomas [11].

Gallo *et al*. [12], comparing the expression of AFP, glypican-3 and HNF1β in 601 testicular germ cell tumors, determined their specificity as 97.7%, 90.3%, and 96.5%, respectively and their sensitivity as 62.5%, 83.3%, and 85.4%, respectively in the detection of YSTs. Accordingly, HNF1β had a higher rate of YST detection than the other two markers. Thus, the authors suggested that HNF1β could be a very important and reliable biomarker for distinguishing tumors. They also noted that there was no HNF1β staining among the seminomatous tumors [12].

Similarly, in our study, HNF1β expression was not observed in any of the seminomatous tumors. HNF1β staining was also not observed among the lymphomas, mesenchymal tumors, and Leydig cell tumors in our series. In contrast, significant nuclear positive staining was present in almost all (39/41) the YST components of the non-seminomatous tumors and MGCTs. There was no staining in the majority of the embryonal carcinoma areas. Weak (1+) staining being observed in only five cases suggests that these might be possible YST areas but were misinterpreted as embryonal carcinomas. The staining pattern in the teratomatous areas was consistent with previous studies, and a high level of staining was observed especially in areas with intestinal differentiation.

In our study, HNF1β immunostaining has very high sensitivity (87.1%) and specificity (97.1%) in terms of detecting areas in pure YST and MGCTs containing YST component, which is consistent with the Rougement and Gallo research.

Limitations

Our study has several limitations. Among these, the HNF1β application was applied only to the pri-

mary tumor in the testis and did not include the expression status in metastatic or recurrent tumors. Therefore, further research including our limitations is needed.

CONCLUSION

It is clear that HNF1β plays an important role in the tumorigenesis of various organs. It is an important biomarker used in the differential diagnosis of tumors of some organs, such as clear cell carcinoma of the ovary. A high HNF1β expression is known to be associated with poor prognosis and poor survival in patients with tumors of the liver and pancreas. On the other hand, it is stated that HNF1β is expressed at a lower rate in renal cell carcinomas than in normal kidney tissue. In the literature, the number of studies on HNF1β expression in testicular tumors is very limited. In our study, we tried to reveal the expression profile of HNF1β in all testicular tumors. Therefore, our study is very special in terms of detecting the YST component, especially in germ cell tumors, and the data obtained had high sensitivity and specificity. In light of our findings, we consider that HNF1β can be used as a sensitive and reliable marker in the detection of these tumors. Although HNF1β has high sensitivity and specificity for the diagnosis of YSTs, it is very important to support the diagnosis with tumor morphology and genetic and epigenetic changes.

Author' Contribution

Study Conception: RA; Study Design: RA; Supervision: RA; Funding: RA; Materials: RA; Data Collection and/or Processing: RA; Statistical Analysis and/or Data Interpretation: RA; Literature Review: RA; Manuscript Preparation: RA and Critical Review: RA.

Conflict of interest

The author disclosed no conflict of interest during the preparation or publication of this manuscript.

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The European Research Journal 2022;8(4):506-520 Original Article

DOI: 10.18621/eurj.981861 *Cardiology*

Opinions of cardiologists on class II recommendations in current European Society of Cardiology 2018-2020 guidelines: YELLOW BOX

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ABSTRACT

Objectives: We planned our survey study to evaluate the opinion of cardiologists about the class II recommendations on levels of evidence in the current European Society of Cardiology Guidelines (ESC). Our aim is to determine which diagnosis or treatment option most prefer by cardiologist when guidelines do not make clear recommendations.

Methods: The survey was conducted on September 2020 with the participation of cardiologists (n = 102). Our survey covers ESC's guidelines published in 2018-2020 on diagnosis and treatment strategies in coronary artery disease, diabetes, heart valve disease, arrhythmia, dyslipidemia and heart failure. Our survey consisting of 40 questions was shared with the cardiologists via e-mail.

Results: Participants answered all of the survey questions. The majority of the participants (79.41%) did not consider the addition of a second long-term antithrombotic medication in addition to aspirin for secondary prevention in diabetes mellitus (DM) and coronary artery disease (CAD) patients who are not at high risk of bleeding. The lowest low density lipoprotein (LDL) value achieved by the participant physicians with treatment in their practices was < 40 mg/dl in 32 (31.37%) participants. One of the striking results of the survey was that 51.96% of the participants stated that it was not possible to measure the lipoprotein a (Lp(a)) level in the center where they were carrying out their practices, and 34.31% did not consider the Lp(a) level in the treatment of dyslipidemia in terms of directing the treatment. As for patients with asymptomatic Wolff-Parkinson-White (WPW) syndrome, 58.82% of the participants considered catheter ablation therapy.

Conclusions: Although there were different opinions on some recommendations, the participants were mostly in agreement. We think that these survey results, which were mostly based on expert opinions, may contribute to the guidelines to be published in the future with the increase of survey studies on these issues.

Keywords: ESC guidelines, class II, cardiovascular disease.

Cardiovascular diseases (CVD) are still the main preventable cause of morbidity and all-cause mortality worldwide and in our country [1]. The risk of developing CVD increases with other risk factors such as older age, obesity, smoking, hypertension (HT), hypercholesterolemia, and diabetes mellitus (DM) [2]. First and foremost, these diseases should be prevented and risk factors controlled. There is multi-

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tude of evidence suggesting that early treatment with recommended therapies can significantly reduce morbidity and mortality [3, 4]. For this reason, the awareness, advice and consensus of cardiologists on coronary artery disease (CAD), HT, dyslipidemia and DM are important in the prevention and treatment of the disease.

Trials and guidelines are needed to guide for cardiologists on these issues. In the recent years, substantial progress has been made in the diagnosis and treatment of CVD. The European Society of Cardiology (ESC) guidelines provide many recommendations for the prevention, diagnosis and treatment of CVD. The guidelines describe Class I, II and III recommendations. Class II recommendations cover conditions which there is conflicting evidence and/or divergence of opinion about the usefulness, and efficacy of a given treatment or procedure [1-6]. Class recommendations of the guidelines are changing and are revised in line with the developments of diagnosis and treatment, also with new studies. The consensus of cardiologists about class II recommendations of ESC guidelines on levels of evidence regarding CAD, HT, DM and dyslipidemia is important. Surveys help us verify that diagnostic and treatment practices for CVD comply with the guidelines recommended. Therefore, we planned our survey to evaluate approach of cardiologists in their clinical practice on the class II recommendations in the current ESC guidelines.

METHODS

Our study targeted cardiologists working at university hospitals, state hospitals, education and research hospitals, private hospitals and medical centers in the seven geographical regions of Turkey. This study was targeted out on September 2020 with the participation of cardiologists (n = 102).

The survey was shared with the cardiologists via e-mail. 103 cardiologist received our survey and 102 (99.03%) cardiologist answered all the questions of the survey. The survey, consisting of 40 questions, was conducted to evaluate the awareness of cardiologists on approaches to cardiovascular diseases in class II recommendations in the ESC guidelines. Questions were selected based on the guideline recommendations that are frequently discussed in daily practice. Our survey covers topic regarding the diagnosis and treatment strategies in CAD, DM, valvular heart disease, arrhythmia, dyslipidemia and heart failure (HF). In our survey, questions were prepared by taking into account class II recommendations in the 2019 ESC dyslipidemia guidelines [3], 2019 ESC diabetes, prediabetes and cardiovascular diseases guidelines [4], 2019 ESC supraventricular tachycardia guidelines [5], 2019 chronic coronary syndrome (CCS) guidelines [6] and class II recommendations in the 2020 ESC sports cardiology guidelines [7], 2020 ESC atrial fibrillation guidelines [8], 2020 ESC adult congenital heart disease guidelines [9], and 2020 ESC Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation Guidelines [10]. Survey questions were answered online by the participants.

Ethics committee approval of our study was received from Ufuk University School of Medicine Non-Interventional Clinical Research Commission with date and number 20200521/3.

The study period was determined as 3 (three) months, and at the end of this period, survey data were collected through the Survey Monkey survey research site which uses an internet database from physicians who voluntarily completed the questionnaire. The answers of a cardiologist who completed the questionnaire, but did not approve the use of the data for scientific purposes, was excluded from the analysis. Survey data from the other 102 (99.03%) cardiologists who gave their consent were included in the analysis.

Statistical Analysis

IBM SPSS Statistics 25.0 Program was used. Categorical variables are given as numbers (n) and percentages (%). G Power 3.1.9.7 programme was done for the sample size calculation. Estimated sample size was calculated using Student's-t test with 80% power, $\alpha = 0.05$ error level and Cohen (d) effect size = 0.3. Accordingly, it was found appropriate to complete the study with at least 100 participants.

RESULTS

Of the participants, 13 (12.75%) were under the age of 30, 81 (79.41) were between the ages of 30-45, and 8 (7.84%) between the ages of 46-65. There were no participants over the age of 65. The male gender was

dominant in our survey (male: 84.31%, female: 15.69%). There were 29 (28.43%) participants who worked as a cardiologist for less than 5 years and 46 (45.10%) participants who worked as a cardiologist for 5 to 10 years. When look at the institutions where participants work, state hospitals ranked first with 55.88%, whereas university hospitals ranked second with 36.27%. The percentage of cardiologists who examined 60 or more out-patients daily was 35.29%, and the proportion of cardiologists who examined 41-60 - out-patients daily was 32.35%. The proportion of cardiologists who examined 20 out-patients or less was 12.75% (Figs. 1 and 2).

We grouped the results of our survey under the headings of diabetes and cardiovascular system, cardiovascular prevention and diagnosis, CAD, dyslipidemia, arrhythmia, valvular heart disease, and HF. We specified the responses to the survey questions in the relevant subject field within the results of our survey.

Diabetes and Cardiovascular System

Participants stated that they mostly preferred coronary artery calcium scoring with computed tomography (CT) (50.0%) for cardiovascular (CV) risk assessment in asymptomatic patients with DM. In these patients, carotid ultrasonography (USG) and ankle brachial index (ABI) are preferred at a rate of 33.3%, and 13.73%, respectively. Interestingly, 33 (32.35%) cardiologists stated that they did not prefer any of the carotid USG, coronary artery calcium scoring with CT or ABI in the assessment of CV risk in asymptomatic patients with DM. In asymptomatic patients with DM, 62 (60.78%) participants considered CT coronary angiography or functional imaging in CAD screening, 7.84% of the participants were not sure. Sixty-three (60%) participants thought there was enough evidence to recommend a Mediterranean diet rich in poly- and mono-unsaturated fats to reduce CV events in pre-diabetic patients. 59.80% of the participants held the opinion that there is sufficient evidence for the hemoglobin A1c (HbA1c) < 7% to prevent macrovascular complications in diabetic patients. In addition, 72.55% of the participants held that systolic blood pressure target should be < 130 mmHg in this group. Sixty-one (65.69%) participants gave the answer yes to the question about low-dose aspirin prescription rate for primary prevention in high-risk patients with DM. Interestingly, 55 (53.92%) cardiologists did not agree with the recommendation classifying beta-blockers in class IIB in the ESC 2020 diabetes guideline for patients with DM and CAD. When we identified three-vessel disease with a SYNTAX score of 15 in the diabetic patient with CCS, 53.92% of the cardiologists considered percutaneous

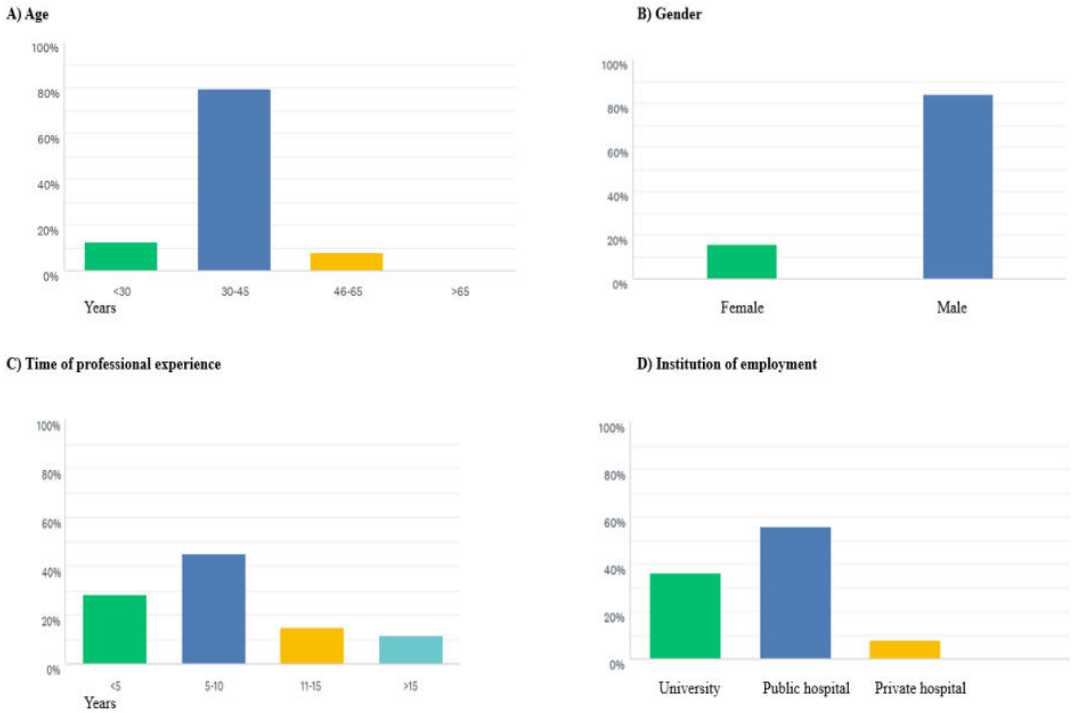

Fig. 1. Demographic data of participants.

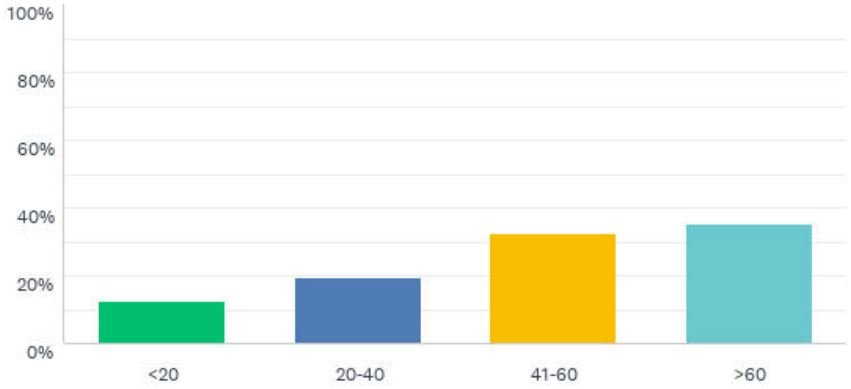

Fig. 2. The number of out-patients dealt with by the participants daily.

coronary intervention (PCI) and 43.14% did not consider PCI despite low surgical risk (Table 1).

Cardiovascular Prevention and Diagnosis

The participants stated that they frequently preferred the treadmill exercise test (38.24%) to determine CAD in asymptomatic patients aged over 50 years, with HT and hyperlipidemia. Interestingly, the total consideration for myocardial perfusion scintigraphy (MPS) alone, and treadmill exercise test in men, and MPS in women (23.53%) was lower than the consideration for coronary CT angiography alone (25.49%). Importantly, the addition of a long-term second antithrombotic drug to aspirin for secondary prevention was not predominantly considered (79.41%) in patients with DM and CAD at high risk of bleeding.

Coronary Artery Disease

In patients who did not have major bleeding complications after acute coronary syndrome (ACS) and who tolerated dual antiplatelet treatment (DAPT), the proportion of participants who recommended DAPT for a period longer than a year was 49 (48.04%), and who did not was 43 (42.16%). It is interesting to note that no participant considered triple antithrombotic therapy more than 6 months in patients with atrial fibrillation (AF) at high risk of stent thrombosis, whereas the proportion of participants who said they would not consider it at all was 2.94%.

To a survey question involving a patient with CCS and angina with accompanying hypertension and hyperlipidemia, who presented a ST segment depression of 1.5 mm in inferior leads in treadmill exercise testing and 55% ejection fraction (EF) in echocardiography, 71.57% of the participants considered revascularization following coronary angiography, and 28.43% considered medical treatment alone. When we asked the participants whether patients undergoing PCI for ACS or elective PCI should be routinely subject to high-dose statin loading before the procedure, 55 (53.92%) participants agreed, 17 (16.67%) participants were not sure.

In patients with non-ST-elevation myocardial infarction (NSTEMI), the majority of the participants (91.18%) considered glycoprotein IIb/IIIa (GPIIb / IIIa) antagonists in no-reflow condition during PCI. In patients who underwent stent implantation after NSTEMI, also at high risk of bleeding, 53 (51.96%) participants stated that they continued P2Y12 receptor inhibitors for 6 months, 30 (29.41%) for 3 months and 17 (16.67%) for 1 month. Most of the participants (68.63%) stated that they did not consider complete revascularization in the same session in patients with NSTEMI-ACS with multi-vessel CAD and without cardiogenic shock. Ninety-nine (97.06%) participants stated that a short-term mechanical support device or inotropic agents can be used in cardiogenic shock after ST-elevation myocardial infarction (STEMI) if possible. Ninety-four (92.16%) participants stated that in patients with chronic renal failure, they applied hydration with isotonic saline before and after the procedure if the expected contrast volume in invasive strategies was > 100 mL (Table 2).

Dyslipidemia

The lowest low density lipoprotein (LDL) value reached in practice with treatment by the cardiologists participating in the study was 40-70 mg/dl for 56 (54.90%) participants and < 40 mg/dl for 32 (31.37%) participants. One of the striking results of the survey

Table 1. Diabetes and cardiovascular system

Question	Answers	n (%)
Which of the following risk modifier would you consider for cardiovascular assessment in asymptomatic patients with DM?	Carotid USG	34 (33.3)
	Coronary artery calcium score by CT	51 (50%)
	ABI	14 (13.73)
	No idea	2 (1.96)
	None	33 (32.35)
Would you consider CT coronary angiography or functional imaging (radionuclide myocardial perfusion imaging, stress cardiac MRI, or exercise / pharmacological stress echocardiography) screening for CAD asymptomatic patients with DM?	Yes	62 (60.78)
	No	32 (31.37)
	Not sure	8 (7.84)
	No idea	0 (0)
Do you think we have enough evidence to recommend a Mediterranean diet, rich in polyunsaturated and monounsaturated fats, for pre-diabetic patients to reduce CV events?	Yes	63 (61.76)
	No	19 (18.63)
	Not sure	17 (16.67)
	No idea	3 (2.94)
Do you think opinions and evidence are sufficient for the target of HbA1C < 7% in diabetic patients to avoid macrovascular complications?	Yes	61 (59.80)
	No	25 (24.51)
	Not sure	15 (14.71)
	No idea	1 (0.98)
In which of the diabetic patient groups would you target SBP < 130 mmHg?	High risk group	74 (72.55)
	Very high risk group	21 (20.59)
	None	7 (6.86)
	No idea	0 (0)
Would you prescribe low-dose aspirin (75 - 100 mg / day) for primary prevention in diabetic patients with a very high CV risk (in the absence of significant contraindications)?	Yes	67 (65.69)
	No	32 (31.37)
	Not sure	3 (2.94)
	No idea	0 (0)
The ESC 2019 diabetes guideline recommends treatment with beta blockers as class IIb in patients with DM and CAD	Agree	44 (43.14)
	Disagree	55 (53.92)
	No idea	3 (2.94)
When you detect a three-vessel disease with a SYNTAX score of 15 in your diabetic patient with CCS, would you consider PCI despite the low surgical risk?	Yes	55 (53.92)
	No	44 (43.14)
	Not sure	3 (2.94)
	No idea	0 (0)
Would you consider the addition of a second long-term antithrombotic drug in addition to aspirin for secondary prevention in patients with DM and CAD without high risk of bleeding?	Yes	18 (17.65)
	No	81 (79.41)
	Not sure	3 (2.94)
	No idea	0 (0)
Would you consider DAPT for longer than 1 year in diabetic patients who do not have major bleeding complications after acute coronary syndrome and who tolerate DAPT?	Yes	49 (48.04)
	No	43 (42.16)
	Not sure	10 (9.80)
	No idea	0 (0)

The questions in this table were prepared based on 2019 Guidelines on Diabetes, Pre-Diabetes and Cardiovascular Diseases [4]. ABI = ankle brachial index, CAD = coronary artery disease, CCS = chronic coronary syndrome, CT = computed tomography, CV = cardiovascular, DM = diabetes mellitus, HbA1c = hemoglobin A1c, MRI = magnetic resonance imaging, PCI = percutaneous coronary intervention, SBP = systolic blood pressure, USG = ultrasonography

Table 2. Chronic coronary syndrome, ACS without persistent ST segment elevation and dyslipidemia

Question	Answers	n (%)
How long would you continue triple therapy with aspirin, clopidogrel and an OAC after PCI in your patients who had AF and high risk of stent thrombosis?	1-2 week	11 (10.78)
	4 week	44 (43.14)
	3 months	15 (14.71)
	3-6 months	29 (28.43)
	> 6 months	0 (0)
	Ever	3 (2.94)
What would be your primary anti-anginal treatment considered in 58-year-old male patient with CCS? In addition he had HT, Hyperlipidemia, 1.5 mm ST depression in DII, DIII and aVF derivations in the treadmill exercise test and 55% EF in echo, and had no previous ACS?	Drug therapy	29 (28.43)
	Revascularization following coronary angiography	73 (71.57)
Which of the following tests would you usually consider for the detection of coronary artery disease in asymptomatic patients over 50 years of age with HT and Hyperlipidemia?	Myocardial perfusion scintigraphy	10 (9.80)
	Treadmill effort test	39 (38.24)
	CT angiography	26 (25.49)
	Treadmill exercise test in men, myocardial perfusion scintigraphy in women	14 (13.73)
	None	13 (12.75)
Should routine high-dose statin loading be performed before the procedure in patients undergoing PCI for ACS or elective PCI?	Yes	55 (53.92)
	No	29 (28.43)
	Not sure	17 (16.67)
	No idea	1 (0.98)
Do you prefer GP IIb / IIIa antagonists in case of no-reflow during percutaneous coronary intervention in NSTEMI patients?	Yes	93 (91.18)
	No	4 (3.92)
	Not sure	3 (2.94)
	No idea	2 (1.96)
When do you consider discontinuing P2Y12 receptor inhibitör treatment in patients with high risk of bleeding undergoing stent implantation after NSTEMI?	1 month	17 (16.67)
	3 months	30 (29.41)
	6 months	53 (51.96)
	No idea	2 (1.96)
Do you perform complete revascularization in the same session in NSTEMI-ACS patients with multi-vessel CAD without cardiogenic shock?	Yes	26 (25.49)
	No	70 (68.63)
	Not sure	4 (3.92)
	No idea	2 (1.96)
If the expected contrast volume in myocardial revascularization is > 100 mL in patients with chronic kidney failure, do you hydrate before and after the procedure with isotonic saline?	Yes	94 (92.16)
	No	6 (5.88)
	No idea	2 (1.96)
What is the lowest LDL range value you have reached with treatment in practice?	> 100	2 (1.96)
	70-100	12 (11.76)
	40-70	56 (54.90)
	< 40	32 (31.37)

Table 2 contunied. Chronic coronary syndrome, ACS without persistent ST segment elevation and dyslipidemia

Question	Answers	n (%)
Do you also consider Lp(a) values in the treatment plan of your patients with dyslipidemia?	Yes	7 (6.86)
	No	35 (34.31)
	Sometimes	7 (6.86)
	There is no possibility to measure Lp(a) level in my center	53 (51.96)
Would you consider statin + fenofibrate treatment for primary prevention or high-risk patients if the LDL-C target is achieved and TG levels are > 200 mg/dL?	Very rare	28 (27.45)
	Rare	47 (46.08)
	Sometimes	22 (21.57)
	Often	2 (1.96)
	Ever	3 (2.94)
How often do you prescribe the Ezetimib + Statine combination?	Very rare	43 (42.16)
	Rare	37 (36.27)
	Sometimes	16 (15.69)
	Often	4 (3.92)
	Ever	2 (1.96)

The questions in this table were prepared based on 2020 ESC Guidelines for the management of acute coronary syndromes, 2019 ESC/EAS Guidelines for the management of dyslipidaemias, 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes [3, 6, 10]. ACS = acute coronary syndrome, AF = atrial fibrillation, CCS = chronic coronary syndrome, CT = computed tomography, DAPT = dual antiplatelet treatment, EF = ejection fraction, GP Iib/IIIa = glycoprotein Iib/IIIa, HT = hypertension, LDL = low density lipoprotein, Lp(a) = lipoprotein a, NSTEMI = non-ST-elevation myocardial infarction, PCI = percutaneous coronary intervention, STEMI = ST-elevation myocardial infarction

was the answer given to the question whether Lp(a) levels were taken into account in order to guide the treatment in patients with dyslipidemia. Fifty-three (51.96%) participants stated that they did not have the capability to measure the Lp(a) level at their center, and 34.31% said they did not consider it. Fenofibrate + statin combination (very rare: 27.45%, rare 46.06%) and ezetimibe + statin combination (very rare: 42.16%, rarely 36.27%) were rarely considered in the treatment of dyslipidemia (see Table 2).

Arrhythmia

One of the important points is that the majority of the participants (77.45%) said they would not recommend an oral anticoagulant to a 60-year-old male patient with AF and a CHA2DS2-VASc score < 1. Forty-five (44.12%) participants said they frequently used the HAS-BLED score in clinical practice to evaluate the bleeding risk of patients with AF, whereas 35 (34.31%) said they used it sometimes and 5 (4.9%) said they never used it. 48 (47.06%) cardiologists said they frequently used amiodarone or propafenone before elective electrical cardioversion in atrial fibrillation, 24 (23.53%) said they used it sometimes and 10 (9.80%) said they never used it.

Ninety-one (%89.22) of cardiologists said they considered closure of the appendix in patients with AF who are at higher risk of stroke and in whom long-term oral anticoagulants are contraindicated. The proportion of considering catheter ablation treatment to asymptomatic Wolff-Parkinson-White (WPW) patients was 58.82%, whereas the proportion of those who had no idea was 5.88%. In stable acute wide QRS tachycardia, 67.65% of the participants considered amiodarone. 83 participants (82.18%) considered catheter ablation in athletes with paroxysmal supraventricular tachycardia (PSVT) without pre-excitation (Table-3).

Valvular Heart Disease and Adult Congenital Heart Disease

In the treatment planning of patients with asymptomatic severe aortic stenosis, 36.27% of the participants recommended exercise test, and 36.27% of the participants did not. One of the striking results of the questionnaire was that 84 (83.17%) cardiologists said

Table 3. Adult congenital heart disease, atrial fibrillation and sports cardiology

Question	Answers	n (%)
Would you consider the use of oral anticoagulation in a 60-year-old male patient with AF and a CHA2DS2-VASc score <1?	Yes	18 (17.65)
	No	79 (77.45)
	Not sure	5 (4.90)
	No idea	0 (0)
Do you use the HAS-BLED risk score to evaluate the bleeding risk of patients with atrial fibrillation in your clinical practice?	Very rare	8 (7.84)
	Rare	9 (8.82)
	Sometimes	35 (34.31)
	Often	45 (44.12)
	Ever	5 (4.90)
Do you use amiodarone or propafenone beforehand to facilitate the success of elective electrical cardioversion in your patients with AF?	Very rare	7 (6.86)
	Rare	13 (12.75)
	Sometimes	24 (23.53)
	Often	48 (47.06)
	Ever	10 (9.80)
Appendix closure in patients with AF who have a high risk of stroke and in whom long-term oral anticoagulants are contraindicated	Recommend	91 (89.22)
	Do not recommend	7 (6.86)
	No idea	4 (3.92)
In patients with suspected paradoxical embolism (after excluding other causes), ASD should be closed regardless of size in the absence of PAH and left ventricular disease	I definitely think	46 (45.10)
	I think	44 (43.14)
	I don't think	10 (9.80)
	I definitely don't think	0 (0)
	No idea	2 (1.96)
Would you consider catheter ablation therapy to your asymptomatic WPW patient?	Yes	60 (58.52)
	No	36 (35.29)
	No idea	6 (5.88)
Is Amiodarone your first choice in stable acute wide QRS tachycardia?	Yes	69 (67.65)
	No	32 (31.37)
	No idea	1 (0.98)
Would you consider catheter ablation in competitive athletes who have paroxysmal supraventricular tachycardia (PSVT) without pre-excitation?	Yes	83 (82.18)
	No	18 (17.82)
	No idea	0 (0)
Would you consider an exercise treadmil test to plan treatment for your patient with asymptomatic severe aortic stenosis?	Yes	37 (36.27)
	No	37 (36.27)
	Sometimes	28 (27.45)
	No idea	0 (0)
Would you consider that additional aortic valve replacement to the patients with moderate aortic stenosis who are scheduled for CABG?	Yes	84 (83.17%)
	No	9 (8.91%)
	I leave the decision to the heart surgeon	8 (7.92%)
Bromocriptine treatment in peripartum cardiomyopathy	Use in all cases	14 (13.73)
	Use if there is no cardiogenic shock	14 (13.73)
	Use in cases with high prolactin levels	31 (30.39)
	Use if there is RV failure and / or cardiogenic shock	23 (22.55)
	Never use	20 (19.61)

The questions in this table were prepared based on 2020 ESC Guidelines for the management of Adult Congenital Heart Disease, 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation,2020 ESC Guidelines on sports cardiology and exercise in patients with cardiovascular disease, 2019 ESC Guidelines for the management of patients with supraventricular tachycardia [5, 7-9]. AF = atrial fibrillation, ASD = atrial septal defect, CABG = coronary artery bypass graft, RV = right ventricul, PAH = pulmonary arterial hypertension, PSVT = paroxysmal supraventricular tachycardia, WPW = Wolff-Parkinson-White

that aortic valve replacement should be performed during the procedure in patients with moderate aortic stenosis who were scheduled for coronary artery bypass graft (CABG), and 9 (8.91%) said it should not be performed. The number of cardiologists who said he or she would leave the decision to the heart surgeon was 8 (7.92%) (see Table-3).

The proportion of those who definitely recommend atrial septal defect (ASD) closure regardless of its size in patients with suspected paradoxical embolism (who do not have pulmonary arterial hypertension (PAH) and left ventricular disease) was 45.10%.

Heart Failure

We asked the participants about the conditions in which they would prefer bromocriptine treatment in peripartum cardiomyopathy, a recent topic of discussion, 13.37% of the participants stated that they would use it in all cases and 19.61% said they did not use it at all. Fourteen (13.37%) participants said they would use it if there was no cardiogenic shock, 30.39% said they would use it in cases with high prolactin level, and 22.55% said they would use it in the absence of right ventricular failure and cardiogenic shock (Table3).

DISCUSSION

In this survey study, we aimed to assess the perspective of cardiologists on ESC class-II recommendations and to raise awareness.

In the assessment of cardiovascular risk in asymptomatic patients with diabetes mellitus, 33 (32.35%) cardiologists stated that they did not prefer either carotid USG, coronary calcium scoring with CT, or ABI, a finding suggesting that there is a difference of opinion regarding the class II recommendations. We think that cost, difficulties in accessing diagnostic tests, and patient-related reasons may be effective in this situation.

In addition, the fact that the participants stated they mostly preferred coronary artery calcium scoring by CT (50.0%), and to a large extent (60.78%), recommended CT coronary angiography or functional imaging for CAD screening shows that a significant number of participants favor selective or nonselective coronary artery imaging. We estimate that the availability of coronary angiography units in many centers was effective in forming such a consensus.

Although beta blockers were classified in class IIB recommendation in patients with DM and CAD in the ESC 2020 diabetes guidelines, 55 (53.92%) cardiologists did not agree with this recommendation. We think that the reason for the high rate of disagreement with this recommendation is that beta blockers may cause glucose irregularity and do not have a sufficient effect on survival in symptomatic patients.

The predominance of those who did not recommend the addition of a second long-term antithrombotic drug to aspirin for secondary protection (79.41%) in patients with DM and CAD without high risk of bleeding suggests that the concerns over the risk of bleeding still outweigh administration of DAPT. However, according to EUROASPIRE IV Turkey data, antiplatelet drugs, beta blockers, ACEI/ARB and statins were used more frequently than EUROASPIRE III Turkey data. This may suggest that patients' awareness has increased and they have started to use their medications more regularly. EUROASPIRE-IV Turkey data revealed that second-ary prevention was unsatisfactory and had progressed unfavorably compared with last EUROASPIRE study, some risk factors were more uncontrolled than overall European average, and coronary artery events at young age remain an important problem [11]. In this respect, it may be necessary to apply additional diagnostic tests to patients with risk factors.

In patients with CCS, angina and accompanying comorbid diseases, with ischemia findings on treadmill exercise testing and echocardiography, 71.57% of the cardiologists said they could consider revascularization with coronary angiography for anti-anginal treatment. We think that the reason behind this opinion is the relative ease of access to coronary angiography units, low complication rates, the perceived difficulty in the application and follow-up of maximal medical treatment. The TURKMI registry demonstrated that PCI was performed in Turkey with a low risk of complication in acute MI. This study also showed that the risk of in-hospital mortality decreased by 50% during 20 years probably due to an increased number of PCI

and high level of guideline implementation [12].

A significant percentage of the participants stated that they could not measure Lp(a) levels in terms of guiding the treatment in dyslipidemia patients, and some of them stated that they did not take it into account. Most likely, the fact that parameters such as LDL, HDL and triglycerides are more easily accessible in many health centers contributed to this result. In addition, more frequent studies have been reported on parameters such as LDL, HDL and triglycerides rather than Lp(a) level in the planning of hyperlipidemia treatment and follow-up.

The fact that the majority of the participants (77.45%) would not give oral anticoagulants to patients AF and a CHA2DS2-VASc score < 1 indicates that the worries about bleeding prevail. According to GARFIELD-AF TURKEY data; AF patients in Turkey were mostly seen in young women. However, despite being younger, patients had a significant burden of comorbidity. Stroke risk by CHADS2 score and CHA2DS2-VASc score compared with world data. The average of the risk score values, including the HAS-BLED score, was lower in Turkey than in the world data. FXa inhibitors alone or in combination with antiplatelets have been prescribed more frequently in low- and high-risk patients in Turkey. New oral anticoagulant (NOAC) therapy was replaced with antiplatelets when the bleeding risk was higher. All-cause mortality was higher in Turkey [13]. In addition RAMSES study showed that the awareness of stroke preventions strategies for NVAF has increased in Turkey and that more than two-thirds of NVAF patients were on OAC therapy. However, the proportion of antiplatelet use was still high among NVAF patients. The findings also showed that NOACs are preferred over VKAs for anticoagulation in a representative clinical population of NVAF patients [14]. The recommendation of catheter ablation in athletes with paroxysmal supraventricular tachycardia without pre-excitation by 83 (82.18%) participants may be associated with the belief that chances of success are high in interventional procedures.

There was consensus among the participants given that 83.17% of the participants said aortic valve replacement should be performed during the procedure in patients who were scheduled for CABG and who had moderate aortic stenosis.

We concluded that there was no clear consensus among participants on the conditions in which they would prefer bromocriptine treatment in peripartum cardiomyopathy, a recent topic of discussion. We think that meta-analyses and larger studies are needed on this subject.

Limitations

In this survey study, class-II recommendations were not evaluated separately as IIa and IIb. Equal distribution was not made from the seven geographical regions of Turkey. Also, the sample size was relatively small. It is inevitable that the cardiologists participating in the survey affected the answers given due to the different service quality of the study centers.

CONCLUSION

Health services in Turkey can contribute to the implementation of some ESC class-II recommendations by increasing access to services in diagnosis and treatment. In online or live training meetings; awareness can be created by literature studies, experience sharing and national multicenter studies on ESC class-II recommendations. At the same time, Turkey's data on this subject can be obtained and contributed to real-life results.

Authors' Contribution

Study Conception: MK, BE; Study Design: MZ, MK; Supervision: BE, TG; Funding: MK, TG; Materials: MK, TG; Data Collection and/or Processing: MK, TG; Statistical Analysis and/or Data Interpretation: TG, MK; Literature Review: MK, BE, TG; Manuscript Preparation: KÇ and Critical Review: MZ, TG.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Table Appendix: Supplementary data

Questions	Options
What is your age range?	< 30 30-45 46-65 > 65
Your Gender?	Female Male
How long have you been working as a cardiologist?	< 5 year 5-10 year 11-15 year > 15 year
What is your practice setting?	University Public Hospital Private Hospital Private Practice
Number of patients you care for per day in the outpatient clinics?	< 20 20-40 41-60 > 60
Which of the following methods would you consider for cardiovascular risk assessment in asymptomatic DM patients? (you can choose more than one option)	Carotid USG Coronary artery calcium score by CT ABI (ankle brachial index) I have no idea. None.
Would you consider CT coronary angiography or functional imaging (radionuclide myocardial perfusion imaging, stress cardiac MRI, or exercise / pharmacological stress echocardiography) for asymptomatic DM patients?	Yes No I am indecisive. I have no idea.
Do you think we have enough evidence to recommend a Mediterranean diet rich in polyunsaturated and monounsaturated fats for pre-diabetic patients to reduce cardiovascular events?	Yes No I am indecisive. I have no idea.
Do you think opinions and evidence are sufficient enough for the HbA1C <7% target to prevent macrovascular complications in diabetic patients?	Yes No I am indecisive. I have no idea.
For which of the following diabetic patient groups would you target SBP <130 mmHg?	High risk group Very high risk group None. I have no idea.
Would you prescribe low dose aspirin (75 - 100 mg / day) for primary prevention in diabetic patients with very high CV risk (in cases where there are no obvious contraindications)?	Yes No I am indecisive. I have no idea.
The ESC 2019 diabetes guideline recommends beta-blockers class IIb for DM and CAD patients.	I agree. I do not agree. I have no idea.
If you detect a three-vessel disease with a SYNTAX score of 15 in your diabetic chronic coronary artery patient, would you recommend PCI despite the low surgical risk?	Yes No I am indecisive. I have no idea.

Table Appendix Continued: Supplementary data

Questions	Options
Which of the following tests do you usually prefer for the detection of coronary artery disease in patients over 50 with asymptomatic, HT and Hyperlipidemia?	Myocardial perfusion scintigraphy Treadmill Effort Test CT angiography Treadmill Effort Test in men, myocardial perfusion scintigraphy in women None.
Would you consider the addition of a second long-term antithrombotic medication in addition to aspirin for secondary prevention in DM and CAD patients who are not at high risk of bleeding?	Yes No I am indecisive. I have no idea.
Would you consider dual antiplatelet therapy for longer than 1 year in diabetic patients who do not have major bleeding complications after acute coronary syndrome and who tolerate DAPT?	Yes No I am indecisive. I have no idea.
Would you consider the use of oral anticoagulation in a patient with AF, Male, 60 years old, with CHA2DS2-VASc score < 1?	Yes No I am indecisive. I have no idea.
What is the lowest LDL range value you have achieved with treatment in your practice?	> 100 mg/dL 70-100 mg/dL 40-70 mg/dL < 40 mg/dL
For how long would you consider triple antiplatelet therapy after PCI in your patients with AF for whom you think the risk of stent thrombosis is high?	1-2 weeks 4 weeks 3 months 3 to 6 months Never
Do you also consider the lipoprotein (Lp(a)) values in the treatment plan of your dyslipidemia patients?	Yes No Sometimes It is not possible to measure Lp(a) level in the center where I carry out my practices.
How often do you prescribe the Fenofibrate + Statin combination?	Very rarely Rarely Sometimes Often Never

Table Appendix Continued: Supplementary data

Questions	Options
What would be your primary anti-anginal treatment preference in your chronic coronary syndrome patient, who is 58 years old, male, suffering from angina, with HT, Hyperlipidemia, 1.5 mm ST depression in DII, DIII and aVF derivations in exercise treadmill test and with an EF of 55% in echo?	Medical treatment Revascularization following coronary angiography
How often do you prescribe the Ezetimibe + Statin combination?	Very rarely Rarely Sometimes Often Never
Should routine loading with high-dose statin be performed before the procedure in patients undergoing PCI with ACS or elective PCI plan?	Yes No I am indecisive. I have no idea.
Would you consider catheter ablation therapy to your asymptomatic WPW patient?	Yes No I have no idea.
Is Amiodarone your first choice in stable acute wide QRS tachycardia?	Yes No I have no idea.
Would you consider Appendix Closure in AF patients with high risk of stroke and contraindicated use of long-term oral anticoagulants?	I would recommend. I would not recommend. I have no idea.
Would you use short-term mechanical assist devices or inotropic agents if possible in cardiogenic shock after STEMI?	I would use. I would not use. I have no idea.
Do you use Bromocriptine treatment in peripartum cardiomyopathy?	I use it in all cases. I use it if there is no cardiogenic shock. I use it in cases with high prolactin levels. I use it if there is RV failure and/or cardiogenic shock. I never use it.
Do you use the HAS-BLED risk score to evaluate the bleeding risk of atrial fibrillation patients in your clinical practice?	Very rarely Rarely Sometimes Never Often
Do you use amiodarone or propafenone in advance to facilitate the success of elective electrical cardioversion in your AF patients?	Very rarely Rarely Sometimes Never Often

Table Appendix Continued: Supplementary data

Questions	Options
Do you consider using GP IIb/IIIa antagonists in case of no-reflow during percutaneous coronary intervention in NSTEMI patients?	Yes No I am indecisive. I have no idea.
How long do you continue P2Y12 receptor inhibitor therapy in patients with high risk of bleeding who underwent stent implantation after NSTEMI?	1 month 3 months 6 months I have no idea.
Do you consider full revascularization in the same session in NSTEMI-ACS patients with multivessel CAD without cardiogenic shock?	Yes No I am indecisive. I have no idea.
Do you hydrate with isotonic saline before and after treatment if the expected contrast volume in invasive strategies in patients with chronic renal failure is> 100 mL?	Yes No I have no idea.
Would you consider catheter ablation for athletes with paroxysmal supraventricular tachycardia (PSVT) without pre-excision?	Yes No I have no idea.
Would you consider ASD closure regardless of size in patients with suspected paradoxical embolism (after excluding other causes) unless they have PAH and left ventricular disease?	I would definitely consider. I would consider. I would not consider. I would definitely not consider. I have no idea.
Would you consider an exercise test to plan the treatment of your patient with asymptomatic severe aortic stenosis?	Yes No Sometimes I have no idea.
Do you think aortic valve replacement should be performed in patients with moderate aortic stenosis in addition to the planned CABG?	Yes No I leave the decision to the heart surgeon.
Do you consent to the use of the answers you provided within the scope of the current survey in scientific processes (provided that your information remains anonymous)?	I consent. I do not consent.

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Quipazine treatment exacerbates oxidative stress in glutamate-induced HT-22 neuronal cells

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ABSTRACT

Objectives: Quipazine is a serotonin agonist. It is known that serotonin, an important neurotransmitter, contributes to the etiology of psychiatric and many neurodegenerative diseases. However, the effect of the serotonin agonist quipazine on HT-22 cells in glutamate-induced cytotoxicity is unknown. This study aims to investigate the effect of quipazine on increased oxidative stress (OS) as a result of glutamate-induced cytotoxicity in HT-22 cells.

Methods: The cells were divided into 4 groups, Control group: no treatment was applied, Glutamate group: glutamate was incubated at 10 mM for 24 h, Quipazine group: incubated with different doses of quipazine for 24 h, Quipazine+Glutamate group were pre-treated with various concentrations (25, 50, 100 and 200 µM) of quipazine for 1 h and then exposed to 10 mM glutamate for 24 h. Cell viability rate between groups was measured by the XTT assay. OS and antioxidant levels were measured with the Total Oxidant Status (TOS) and Total Antioxidant Status (TAS) Elisa kits, and Caspase-3 levels were also examined in caspase activity.

Results: Quipazine at different concentrations showed significant differences in cell viability in HT-22 cells. An appropriate dose of 25 µM was accepted for quipazine in the study. Quipazine treatment with glutamate-toxicity in the cells further reduced TAS levels and significantly increased TOS levels. It was also observed that the Caspase-3 level increased more in the Quipazine + Glutamate group according to the Glutamate group.

Conclusions: The results determined that the use of quipazine is an agent that will further increase the neurodegeneration caused by glutamate toxicity.

Keywords: Quipazine, glutamate-toxicity, oxidative stress, HT-22 cell, cell viability

It is now accepted that excitotoxicity has an important role in the etiology of neurodegenerative diseases. However, the mechanisms of excitotoxicity in the neurodegeneration process are still not fully understood and need further research [1]. Excitotoxicity was first introduced in the 1960s and describes neurodegeneration that occurs as a result of excessive or prolonged activation of amino acid receptors responsible for stimulation [2]. From this overstimulation; more than normal neurotransmitters release into the synaptic gap, failure of the pumps that take neurotransmitters back from the synapse, or overexpression of the receptors in the post-synaptic neuron may be responsible [3]. Oxidative stress (OS) has been reported as the most important damage mechanism in glutamate excitotoxicity [4]. Especially in neuronal cells, receptor activation due to glutamate density causes calcium ion entry into the cell, causing mitochondrial dysfunction and excessive reactive oxygen species (ROS) formation. An excessive increase in intracellu-

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lar ROS also results in neurodegeneration [5, 6].

Glutamate is a neurotransmitter that is important for maintaining the balance of excitatory and inhibitory neurons in the central nervous system [7]. In general, it is responsible for cognitive, motor, sensory, and autonomic activity with its stimulating function. Many physiological cases as diversification, cell migration, synapse induction, and death also play an essential role. Because of these important tasks, it is very important to keep the glutamate level at a certain level. Studies have shown that abnormalities in glutamate levels have been associated with many neurodegenerative diseases [8, 9]. However, there is no established mechanism for toxicity from glutamate overdose, and some believe this process may be mediated through differential activation and inhibition of certain receptors in the cell [10].

Serotonin plays an important role in the initiation and modulation of locomotor behaviour in mammals [11]. In some studies, it has been stated that serotonin activates some cell signaling pathways and decreases intracellular OS damage [12-14]. Quipazine is a serotonin (5-HT) agonist [15]. It has been reported that it has a potential agonist activity for 5-HTR1b [16]. However, quipazine also acts as a potent antagonist on peripheral 5-HT3 receptors [17].

It is known that glutamate-induced cytotoxicity causes neuronal damage in brain cells. Therefore, important to develop a protective therapeutic approach against glutamate-induced excitotoxicity of cells, as well as to investigate the events that will trigger this damage. In our study, we examined the effect of quipazine-mediated serotonin activation on intracellular oxidative stress and caspase activation in a glutamate toxicity model in the HT-22 neuronal cell line.

METHODS

Cell Culture

The HT-22 cell line (SCC129) was selected in this investigation [18]. The Merck provided HT-22 mouse

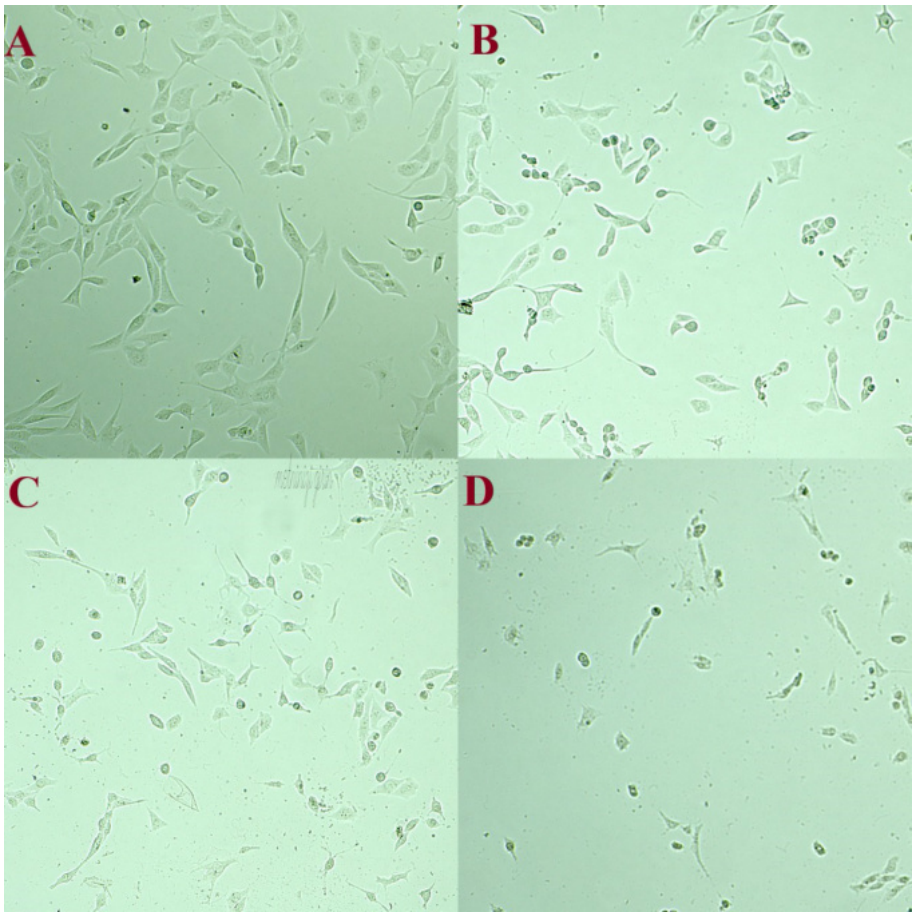

Fig. 1. Images of cells in groups under the microscope. A) Control, B) Quipazine (25 µM), C) Glutamate (10 mM), and D) Quipazine + Glutamate.

hippocampal neuronal cell lines. The cells were cultured in DMEM (Thermo Fisher Scientific, Altrincham, UK) containing 10% Fetal Bovine Serum and 1% L-glutamine and 1% penicillin-streptomycin (Sigma-Aldrich Co., USA). The HT-22 cells were incubated at 37° C and 5% CO_2.

Study Groups

The cells were divided into 4 groups and were prepared to evaluate the effect of quipazine on glutamate-induced cytotoxicity: 1)-Control group: no application has been made. 2)- Glutamate group: glutamate was incubated at 10 mM for 24 h [19]. 3)-Quipazine group: incubated with different doses of quipazine for 24 h. 4)-Quipazine+Glutamate group were pre-treated with different concentrations (25, 50, 100 and 200 µM) of quipazine for 1 h and then exposed to 10 mM glutamate for 24 h (Fig. 1).

Drug Administration

Quipazine dimaleate (Cat no:0629, Tocris) and glutamate (Sigma-Aldrich Co., USA) were dissolved in the cell medium.

Cell Viability Assay

After the doses and duration that we specified for the study are completed, XTT (Abcam, UK) analysis was performed to determine cell viability in the cells. HT-22 mouse hippocampal (SCC129) cells were seeded in 96 wells at 1 x 10^4 cell density in 0.1 mL of DMEM. Different dose ranges (25, 50, 100 and 200 µM) for Quipazine were added to the plate wells. After 1 hour, when the incubation period expired, 10 mM glutamate was added to each well and incubated for a total of 24 h. At the end of the total time (24 h), the XTT (50 µL) reagent mixture was added to the HT-22 cells in the plate wells. In the XTT incubation, the cells were incubated for 4 h in the incubator (37°C and 5% CO2). The absorbance value for XTT analysis was gauged at 450 nm using a microplate reader (Multiskan PLUS, Thermo Scientific For all tests, three replicate readings were made. XTT analysis results are shown as the percentage of viable cells in comparison with the Control group, which did not receive any chemicals.

Preparation of Cells Homogenates

When the indicated incubation times expired, the cells in the plate were transferred to sterile Eppendorf tubes. Cells in the eppendorf tubes were centrifuged at 2000 rpm for 10 min. Supernatants were carefully removed from Eppendorf tubes in laminar flow. Cell pellets under Eppendorf were diluted through phosphate buffered saline (pH: 7.4) to a concentration of 1 million/ml. The cell structure was lysed by repeated freeze-thaw and the intracellular components were permitted to recede. The resulting mixture was centrifuged at 4000 rpm for 10 min. The supernatant remaining in the upper part of the tubes was taken with the help of sterile pipettes and transferred to different sterile tubes for biochemical analysis. Total protein levels for each group were measured with the Bradford assay kit. (Merck, Germany).

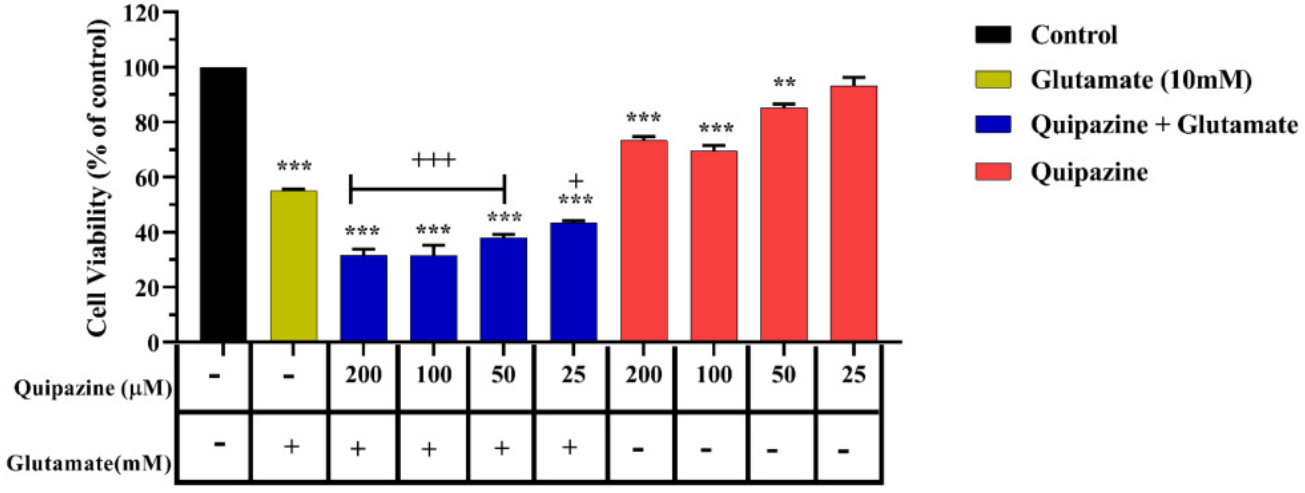

Fig. 2. Effect of Quipazine on glutamate-induced HT-22 cells. (Data are expressed as mean ± mean standard error). (* $p < 0.001$, ** $p < 0.01$, * $p < 0.05$ compared to the control group; +++ $p < 0.001$ and + $p < 0.01$ compared with glutamate group).**

Measurement of Total Antioxidant Status (TAS), Total Oxidant Status (TOS) and Caspase-3 Levels in the HT-22 Cells

TAS, TOS, and Caspase-3 levels in the resulting supernatant of glutamate toxicity induced by HT-22 cells were determined using ELISA commercial kits (BT Lab, China). For the analysis, the protocols determined by the company for commercial kits were performed. Read at 450 nm in an microplate reader (Thermo-Fisher Scientifc, UK).

Statistical Analysis

The results were expressed as mean ± standard error (SEM). SPSS Version 23.0 for Windows was used to analyze the data. ANOVA was used to analyze the data, and the post-hoc Tukey test was used to determine the differences between the groups. A statistically significant result of $p < 0.05$ was accepted.

RESULTS

Effect of Quipazine on Cell Survival in Glutamate-Induced HT-22 Cells

The cell viability was investigated in groups by incubating HT-22 cells with significant doses. XTT assay kit was used to determine cell viability. Cell viability for quipazine was determined in HT-22 cells treated with both control and glutamate at various doses (25, 50, 100, and 200 M). The cells were pretreated with increasing doses of Quipazine (25-200 µM) for 1 hour at first, and then they were incubated with or without glutamate (10 mM) for the next 24 h. As shown in Fig. 2, the 25 µM dose for quipazine did not appear to affect cell viability compared to the control group, and this dose was determined as the appropriate dose for the study. It was observed that the administration of a 25 µM Quipazine dose in the glutamate toxicity groups significantly decreased the cell viability rate ($p < 0.01$). In the Quipazine+Glutamate groups, it was observed that the cell viability rate decreased as the dose of Quipazine increased ($p < 0.001$) (Fig. 2).

Effect of Quipazine on TAS Level in Glutamate-Induced HT-22 Cells

In the groups formed, the effect of quipazine was measured against glutamate cytotoxicity with the TAS Elisa kit in the cells. Compared to the control group, the TAS level of the Glutamate group was significantly lower ($p < 0.01$). Compared to the control group, the TAS level of the Quipazine group was considerably lower ($p < 0.05$). In the Quipazine+Glutamate group, the TAS level was determined that it is dramatically lower than both the Control group and the Glutamate group ($p < 0.01$, $p < 0.001$) (Fig. 3).

Effect of Quipazine on TOS Level in Glutamate-Induced HT-22 Cells

In the groups formed, the effect of quipazine was measured against glutamate cytotoxicity with the TOS Elisa kit in the cells It was observed that the TOS level of the Glutamate group increased considerably com-

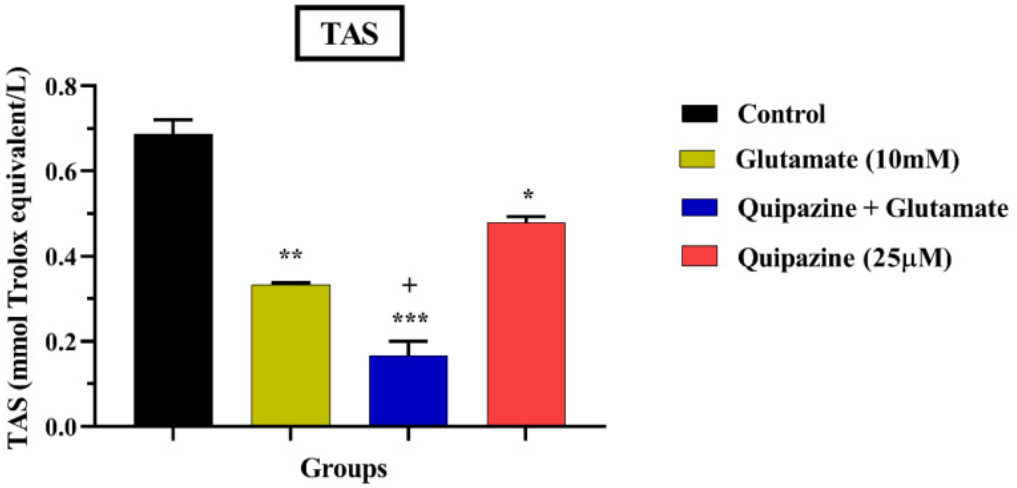

Fig. 3. Effect of Quipazine on TAS level in HT-22 cells. (Data are expressed as mean ± mean standard error). (* $p < 0.001$, ** $p < 0.01$, * $p < 0.05$ compared to the control group; + $p < 0.01$ compared with glutamate group). TAS = Total Antioxidant Status**

pared to the control group ($p < 0.01$). In the Quipazine+Glutamate group, the TOS level was found to be significantly higher than in both the Control group and the Glutamate group ($p < 0.001$, $p < 0.01$) (Fig. 4).

Effect of Quipazine on Caspase-3 Level in Glutamate-Induced HT-22 Cells

ELISA commercial kits were used to investigate the effect of quipazine on Caspase-3 levels in glutamate-induced HT-22 cells. The Caspase-3 level was significantly increased between the groups when the Quipazine+Glutamate group was compared to the control and Quipazine groups ($p < 0.001$). There was no statistically significant difference between the control group and the Quipazine group ($p > 0.05$). When the Quipazine+Glutamate group was compared to the Quipazine group between the groups, it was observed that the Caspase-3 level increased significantly in the Quipazine+Glutamate group ($p < 0.001$) (Fig. 5).

DISCUSSION

In this study, the effect of pretreatment of different doses of quipazine against glutamate-induced toxicity was investigated. It was observed that pretreatment with quipazine further increased oxidative stress and reduced antioxidant level against glutamate-induced cytotoxicity in HT-22 cells. We also determined that it increased the activation of Caspase-3, which is an important marker in the apoptotic pathway.

Studies have shown that administration of the nighttime serotonin agonist quipazine to rats delays the rhythms of melatonin metabolite excretion and activity similar to light [20, 21]. Serotonin has a crucial effect on the initiation and modulation of locomotor behaviour in mammals [11]. In a study, it was stated that serotonin does not protect C6 cells from glutathione depletion by glutamate. Incubation of serotonin and glutamate together depletes the cellular glutathione level. Serotonin caused a significant inhibition of lipid peroxide accumulation in C6 glioma cells against glutamate exposure and controlled a low lipid peroxide accumulation rate [22]. A study using a serotonergic derivative of quipazine found promising results against skin cancer. It has been shown that the quipazine derivative can inhibit cellular growth by inducing S-phase cell cycle delay, ROS generation and apoptosis in cells [23]. In a study investigating the suppressive effect of N-palmitoyl serotonin on glutamate-induced apoptosis in HT-22 cells. It has been stated that N-palmitoyl serotonin promotes BDNF formation and secretion and then protects neuronal cells against oxidative stress-induced apoptosis through activation of the TrkB/CREB pathway [24]. In a previous study, we observed that TAS levels decreased and TOS, NO, and TNF-a levels increased in C6 cells after glutamate treatment in the cytotoxicity model we studied in Glutamate-induced C6 glia cells [25]. We hoped that the quipazine we used would reduce glutamate-induced cytotoxicity. However, in our study, after choosing the appropriate dose (25 µM) for quipazine, it was observed how it would affect glutamate toxicity. The re-

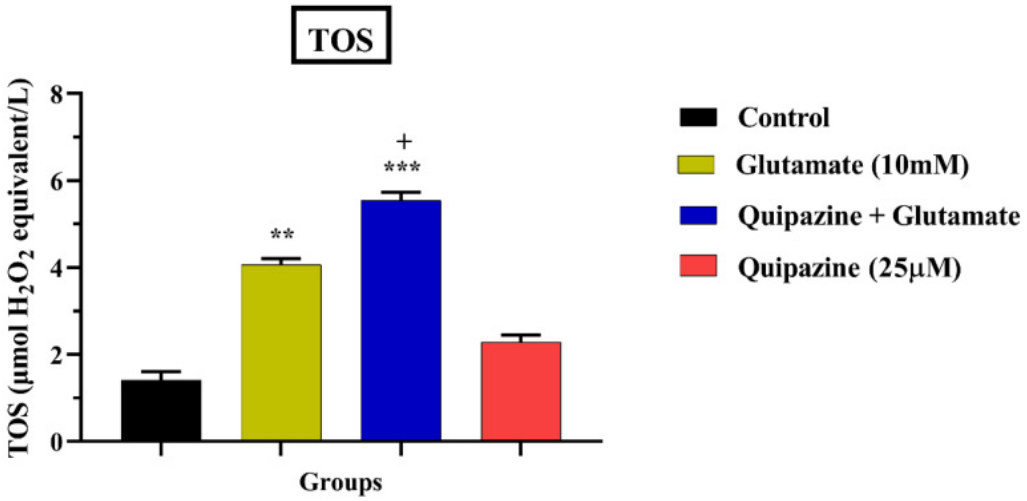

Fig. 4. Effect of Quipazine on TOS level in HT-22 cells. (Data are expressed as mean ± mean standard error). (* $p < 0.001$ and ** $p < 0.01$ compared to the control group; +$p < 0.01$ compared with glutamate group). TOS = Total Oxidant Status**

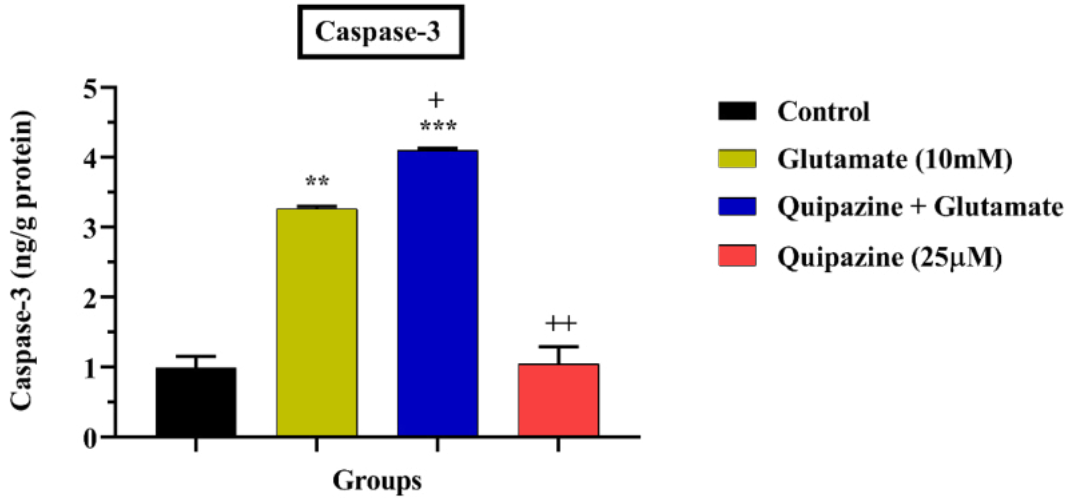

Fig. 5. Effect of Quipazine on Caspase-3 level in HT-22 cells after glutamate-induced cytotoxicity. (Data are expressed as mean ± mean standard error). (* $p < 0.001$, ** $p < 0.01$ compared to the control group; ++ $p < 0.001$ and + $p < 0.01$ compared with glutamate group).**

sults showed that even the use of an appropriate dose of quipazine decreases intracellular antioxidant capacity in HT-22 cells and increases intracellular oxidative stress and Caspase-3 activation (Figs. 3-5).

Glutamate is the most abundant excitatory neurotransmitter in the mammalian CNS. In the CNS, glutamate is found in many cell types and intracellular organelles [26]. Considering the etiology of neurodegenerative diseases, it is seen that neuronal damage follows a progressive process and first results in loss of function and finally death of the neuron [27]. At present, the damage mechanism of many neurodegenerative diseases is still elucidated, but there is increasing evidence that the pathogenesis of neurodegenerative diseases is associated with excitotoxin and oxidative stress [28, 29]. Glutamate is a substantial cause of nerve cell damage and is known to mediate oxidative and excitatory toxicity [30, 31]. For these reasons, it is important to find sources of oxidative stress and stimulant toxicity from glutamate toxicity. A recent study showed that "Kaempferia parviflora" extract, as a pharmacological agent against glutamate-induced cytotoxicity of HT-22 neuronal cells, regulates the increased level of oxidative stress in cells and therefore reduces apoptotic cell death [32]. In our study, we investigated the effects of glutamate toxicity and serotonin activation on HT-22 cells. Glutamate-induced excitotoxicity has an important role in the etiology of neurodegenerative diseases. Currently, there is no safe and effective drug to prevent glutamate-induced excitotoxicity [26]. OS have the most important role in the biochemical processes that lead to cell death in glutamate-induced excitotoxicity. In fact, cells can prevent OS damage thanks to the presence of various molecules that work as antioxidants. However, sometimes oxidative stress is observed in cells that do not have enough antioxidant capacity [7]. It has been emphasised that OS, which occurs with glutamate increase, is an important trigger for neurodegeneration [19, 33]. In addition, it is an important damage factor not only in Alzheimer's and Parkinson's disease, but also in neurodegenerative diseases that occur in living things. Studies have shown that the damage mechanisms of neuronal cells are associated with an increase in OS [19, 33, 34]. In a study, it was reported that melatonin and serotonin have effective DMPD radical scavenging activity and the ability to reduce copper ions. Serotonin has a phenolic hydroxyl group, so it has been emphasized that serotonin has higher radical scavenging and reducing activity than melatonin [35]. Unfortunately, with the results of this study (Figs. 3-5), we observed that serotonin activation, via the quipazine agonist, increased oxidative stress caused by glutamate toxicity.

CONCLUSION

The findings of this research showed that the use of an appropriate dose of quipazine increased cellular damage resistance to glutamate-induced cytotoxicity in HT-22 cells. We think that this damaging impact of

quipazine occurs with the activation of oxidative stress pathways, but more studies should be done to make this determination. Therefore, we determined that the use of appropriate doses of quipazine exacerbates glutamate toxicity that may occur in CNS disorders and causes more damage in neurodegeneration due to neuronal damage. However, further in vitro and in vivo studies are needed to answer questions about the possible mechanisms of action of quipazine in glutamate toxicity.

Authors' Contribution

Study Conception: KY; Study Design: KY, AO; Supervision: KY; Funding: KY, AO; Materials: N/A; Data Collection and/or Processing: AO; Statistical Analysis and/or Data Interpretation: KY, AO; Literature Review: KY, AO; Manuscript Preparation: KY and Critical Review: KY.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

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The European Research Journal 2022;8(4):529-535 Original Article

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Right and left coronary artery angiography with single Judkins left catheter via right radial artery

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ABSTRACT

Objectives: The aim of this study was to assess the safety and efficacy of single Judkins left (JL) catheter to view right and left coronary artery in right transradial coronary angiography.

Methods: A total of 266 patients underwent coronary angiography from the right radial artery were studied prospectively. Patients with ad-hoc percutaneous coronary intervention (PCI), peripheral angiography, ventriculography or aortography procedures (67 patients) were excluded from the study. Coronary angiography was performed with the JL catheter as single catheter group in 171 of the remaining 199 patients, and with the Judkins right and left catheters as the control group in the other 28 patients. Complications, procedure success, procedure time and fluoroscopy time were evaluated between the two groups.

Results: Procedure success were 93% (159/171) in patients with a single catheter group and 96.4% (27/28) in patients with two catheter (Judkins right and left) group (control group) ($p = 0.49$). Complications (spasm) are the same between the two groups (8 of 171 [4.7%] patients in study group and 1 of 28 [3.6%] patients in control group, $p = 0.79$). Fluroscopy time in single JL catheter group was significantly higher (6.20 ± 4.97 min vs 3.76 ± 2.78 min, $p = 0.01$).

Conclusions: Single JL catheter using to view right and left coronary artery in right transradial coronary angiography was safe and effective. In our study, the success rate of getting left and right coronary artery images with a single JL catheter as high as 93%. However, insisting on imaging with a single catheter extends the duration of fluoroscopy time.

Keywords: Right radial angiography, Judkins left catheter, fluoroscopy time, complication

Cardiac catheterization via the radial artery was first applied in 1989 [1]. Later, it started to be used for coronary interventional procedures [2]. Intervention via the radial artery has started to be preferred more because it provides early movement of the patient, fewer bleeding complications, and higher patient comfort [3]. Current guidelines recommend radial angiography instead of femoral angiography for coronary angiography and percutaneous coronary intervention [4]. However, the radial artery diameter is small and contains various congenital differences. In addition, the radial artery is very prone to spasm with manipulation. Again, repeated catheter insertion through the radial artery increases radial spasm. In addition, repeated catheter insertion due to tortuosity in the brachial, subclavian and brachiocephalic arteries may increase embolic and vascular complications. In order to prevent such problems, various catheters have

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been developed to prevent repeated catheter insertion and to visualize both coronary systems (right and left systems) with a single catheter [5]. However, these catheters increase the cost of the procedure. In addition, recent studies investigating the dual versus single catheter strategy for transradial coronary angiography have produced inconsistent results [6, 7], and the double-catheter strategy still represents the standard approach among approximately 40% of operators [8].

In this study, we evaluated the feasibility and safety of imaging the right and left coronary systems with right radial access and single Judkins left (JL) catheter.

METHODS

Study Population

The ethics committee of Bursa Yüksek İhtisas Training and Research Hospital was approved for the study. A total of 266 consecutive patients aged 18 years and older who underwent coronary angiography via the right radial artery were included in the study. Patients who continued percutaneous coronary intervention after coronary angiography, underwent peripheral angiography, or had an imaging other than coronary imaging were excluded from the study (Fig. 1). Of the remaining 199 patients, 171 were included in the single JL catheter group, while 28 were included in the standard right and JL catheter group. Basal and procedural characteristics of the patients were recorded.

Procedure

In patients with palpable right radial artery, a 7 cm, hydrophilic coated, 6F sheath was introduced with a 21G needle and a 40 cm 0.018 guidewire followed by intra-arterial application of nitroglycerine (200 mcg) and unfractioned heparin (7500 IU). In the study, JL 4 catheter was used as a single catheter for right and left coronary angiography. First, the left coronary was visualized with the JL 4 catheter, then 0.038 guide wire was advanced through the JL 4 catheter, which was

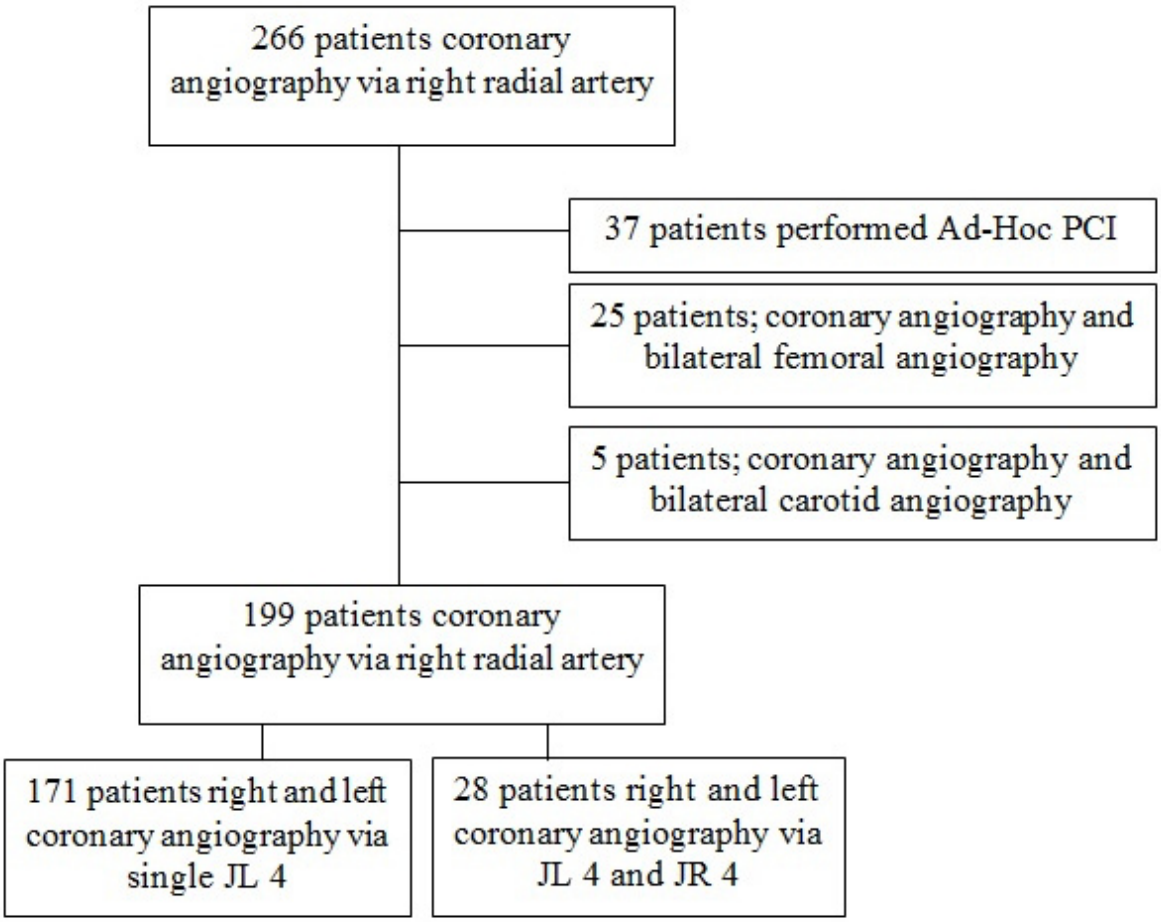

Fig. 1. Study diagram.

pulled back from the LMCA to the aorta, the tip of the JL 4 catheter was straightened, and the right coronary was seated with clockwise rotation, and the right coronary was imaged (Fig. 2). Successful imaging was defined as the JL 4 catheter seating in the right coronary ostium and obtaining clear images (Fig. 2). If the right coronary artery could not be seated with a maximum of 4 attempts, the attempt with a single catheter was considered unsuccessful and the right coronary artery was visualized with a standard JR 4 or another suitable catheter. JR 4 and JL 4 catheters were used for right and left coronary angiography with double catheters. The exchange of the two catheters was made over the 0.038 guidewire, which was sent through the JL 4 catheter to the ascending aorta. Failure to visualize the right coronary with a standard JR 4 catheter and the need for another catheter was defined as a failure for right coronary imaging with a double catheter.

After the radial sheat was entered, imaging was performed first by entering the JL 4 catheter in both groups. The time elapsed from the radial sheath entry of the JL 4 catheter to its exit after imaging of both coronary arteries was defined as the procedure time in single catheter group and recorded. The time elapsed from the radial sheath entry of the JL 4 catheter to the JR 4 exit after imaging of both coronary arteries was defined as the procedure time in control group and recorded. The duration of fluoroscopy used during imaging of the right and left coronary arteries was recorded. The number of exposures taken to view the right and left coronaries was recorded. The amount of contrast used was recorded. The amount of radiation exposed during the procedure was recorded.

Radial spasm was demonstrated by arteriography in case of difficulty in catheter manipulation and pain in the right arm. Routine radial arteriography was not performed. After the procedure, hemostasis at the radial entry site was achieved with a compression band.

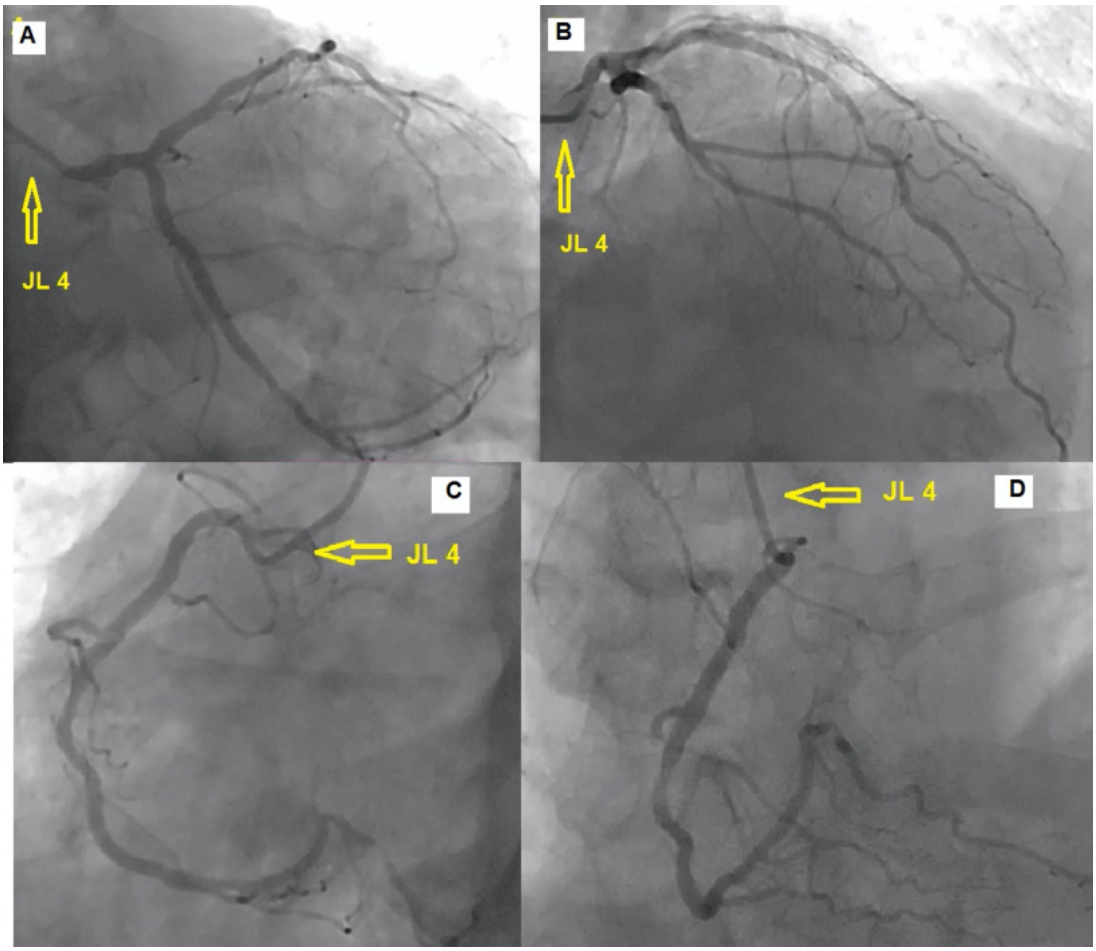

Fig. 2. A: Left system coronary angiography via JL 4 catheter, left caudal view, B: Left system coronary angiography via JL 4 catheter, right anterior oblique view. C: Right coronary angiography via JL 4 catheter, left anterior oblique view, D: Right coronary angiography via JL 4 catheter, anteroposterior cranial view.

Compression was gradually reduced 2 hours after the procedure, and the compression band was removed after bleeding control was achieved.

Coronary artery disease was defined as having stenosis of 50% or more in the coronary arteries. Coronary angiography procedures were performed by 3 different operators experienced in radial angiography.

Statistical Analysis

Statistical analysis was performed using the SPSS computer program (Statistical Package for the Social Sciences ver. 22., SPSS Inc, Chicago, Illinois, USA). Continuous variables were reported as mean ± standard deviation, and categorical variables as percentages. Student's t test was used to compare the normally distributed variables, and the Mann Whitney U test was used to compare the non-normally distributed variables. Categorical variables were compared with the Chi-square test or Fisher's exact test as appropriate. A value of $p < 0.05$ was considered significant.

RESULTS

After 67 of the 266 patients evaluated for the study were excluded due to exclusion criteria, 199 patients were included in the study. 171 patients were included in the single catheter group and 28 patients were included in the double catheter group. There was no difference between the groups in terms of demographic characteristics of the single catheter group and the two-catheter (control) group (Table 1). In the single-catheter group, 36.8% of the patients and in the double catheter group, 17.9% were female ($p = 0.06$). The groups were similar in terms of diabetes, hypertension, peripheral arterial disease and percutaneous coronary

Table 1. Demographic characteristics of the study groups

Variables	Study group (n = 171) (single JL 4)	Control group (n = 28) (JL 4 and JR 4)	*p* value
Age (years) (mean ± SD)	59.77 ± 11.11	57.64 ± 13.48	0.52
Sex			0.06
Male, n (%)	108 (63.2)	23 (82.1)	
Female, n (%)	63 (36.8)	5 (17.9)	
BMI (kg/m^2) (mean ± SD)	28.73 ± 4.51	28.26 ± 4.75	0.97
Diabetes mellitus, n (%)	38 (22.2)	6 (21.4)	0.92
Hypertension, n (%)	132 (77.2)	17 (60.7)	0.06
Peripheral artery disease, n (%)	10 (5.8)	2 (7.1)	0.79
Previous PCI, n (%)	42 (24.6)	7 (25)	0.96
Medication, n (%)			
Aspirin	137 (80.1)	19 (67.9)	0.14
ACEI	121 (70.7)	17 (60.7)	0.32
Beta blocker	103 (60.2)	14 (50)	0.30
CCB	36 (21.1)	3 (10.7)	0.20
Nitrate	26 (15.2)	3 (10.7)	0.53
Statin	76 (44.4)	9 (32.1)	0.22
SBP (mmHg) (mean ± SD)	134.77 ± 15.51	137.18 ± 22.71	0.65
DBP (mmHg) (mean ± SD)	79.32 ± 11.68	79.50 ± 7.91	0.96
HR (beats per minute) (mean ± SD)	86.82 ± 11.23	91.30 ± 12.80	0.26

JL = Judkins left, JR = Judkins right, BMI = Body mass index, PCI = Percutaneous coronary intervention, ACEI = Angiotensin converting enzyme inhibitor, CCB = Calcium channel blocker, SBP = Systolic blood pressure, DBP = Diastolic blood pressure, HR: Heart rate

intervention (PCI) history. There was no difference between the two groups in terms of drugs used by the groups, blood pressures and heart rates (Table 1).

According to the evaluation related to the procedure, an extra catheter was needed in 12 patients in the single catheter group and 1 patient in the double catheter group ($p = 0.49$) (Table 2). The number of lesioned coronary arteries, the contrast volume used, the number of imaging performed on the right and left coronary arteries, and the duration of the procedure were similar in both groups (Table 2). The fluoroscopy time of the single catheter group (6.20 ± 4.97 min) was significantly longer than the double catheter group (3.76 ± 2.78 min) ($p = 0.01$) (Table 2). Although the radiation dose exposed during the procedure was higher in the single catheter group (1089.18 ± 620.42 uGycm2) compared to the double catheter group (855.83 ± 469.46 uGycm^2), it was not significant (p = 0.23) (Table 2). Right coronary artery was visualized with the first movement of JL catheter in 70 of 171 (40.9%) study group patients. Radial spasm was similar in both groups (Table 2).

DISCUSSION

The main results of our study can be listed as follows; i) right and left systems can be safely and successfully visualized by entering through the right radial artery with a single JL catheter, ii) fluoroscopy time during imaging with a single catheter is longer than in the double catheter group, iii) radial artery spasm is similar in the single and double catheter groups.

In recent years, the radial artery has been used with increasing frequency compared to the femoral artery for coronary angiography and PCI, and it has started to replace as a standard approach in the guidelines [4]. In daily practice, the right radial artery is used more frequently because of easy access. With the standard catheters generally used for femoral angiography, intervention is made from the radial artery, which has a much lower profile. As the number of manipulations increases, the risk of complications such as spasm, bleeding and thrombosis increases [9]. For this reason, researches are continuing intensively to terminate the procedure as soon as possible and with the least number of catheter manipulations.

Numerous studies have been conducted to investigate the dual versus single catheter strategy in transradial coronary angiography [10]. The common goal of these studies was to show that a single catheter is at least as effective as a double catheter and less complications occur. Achieving the intended outcomes in a single catheter strategy will provide significant clin-

Table 2. Procedural data of the study groups

Variables	Study group (n = 171) (single JL 4)	Control group (n = 28) (JL 4 and JR 4)	*p* value
Need for additional catheter, n (%)	12 (7)	1 (3.6)	0.49
Coronary disease, n (%)			0.067
1 vessel disease	39 (22.8)	3 (10.3)	
2 vessel disease	27 (15.8)	1 (3.6)	
3 vessel disease	33 (19.3)	10 (35.7)	
Contrast volume (ml) (mean ± SD)	77.84 ± 15.76	72.42 ± 13.35	0.23
Number of right coronary image (mean ± SD)	2.15 ± 0.80	2.22 ± 0.84	0.68
Number of left coronary image (mean ± SD)	4.33 ± 1.17	4.77 ± 0.94	0.07
Procedure time (min) (mean ± SD)	9.83 ± 6.25	9.57 ± 6.26	0.87
Fluoroscopy time (min) (mean ± SD)	6.20 ± 4.97	3.76 ± 2.78	0.01
DAP (uGycm^2) (mean ± SD)	1089.18 ± 620.42	855.83 ± 469.46	0.23
Radial spasm, n (%)	8 (4.7)	1 (3.6)	0.79

DAP = Dose area product

ical and cost benefits.

Catheters with a variety of specific curves, such as Kimny (Boston Scientific, Natick, MA), Barbeau (Cordis Bridgewater, NJ), Jacky (Terumo, Sommerset, NJ), and Tiger (Terumo, Somerset, NJ) were developed for performing single catheter coronary angiography through the radial artery. In addition, many catheters have been tried as multipurpose catheters in transradial interventions [5, 6, 11, 12]. The Tiger catheter is the most well-known of these. In the study performed by Kim *et al*. [5] in 2006, a single Tiger II (Terumo Corporation, Tokyo, Japan) catheter specific for the radial artery and a standard dual Judkins (5F R4, L4; Cordis Corporation, Miami, FL) catheter were compared. The procedure time and fluoroscopy time were shorter in the Tiger II catheter group. While it had the same success in left coronary angiograms, Tiger II catheter was found to be more successful in right coronary angiogram. No angiographic or clinical complications were detected in either group. In 2016, Chen *et al*. [13] compared the radial artery-specific Tiger catheter (5F, Terumo Interventional Systems, Somerset, NJ) with standard JL and JR (5F R4, L4; Cordis Corporation, Miami, FL) catheters. Fluoroscopy time was significantly lower in a single catheter. However, the success of the procedure was found to be higher with dual catheters. In the study of Xanthopoluo *et al*. [7], Tiger II (Tiger II (Terumo Corporation, Tokyo, Japan) catheter and standard dual Judkins (R4, L3.5; Medtronic, Minneapolis, MN) catheter) catheters were compared. The amount of contrast material used, fluoroscopy time, procedure time and spasm rate were found to be less in the Tiger II group. While it was better in RCA imaging, Judkins group was better in left system imaging. In the study of Schneider *et al*. [6], a single catheter group using Tiger II (Terumo Interventional Systems, Somerset, NJ) and BLK (Terumo Interventional Systems, Somerset, NJ) catheters and dual catheter group using standard Judkins (Terumo Interventional Systems, Somerset, NJ) catheters were compared. Coronary angiography with a single catheter does not reduce the procedure time, but also increases the fluoroscopy time and the amount of contrast used.

It is not always possible to reach specific catheters for radial coronary imaging. For this reason, in some studies, instead of special catheters, JL catheters used in standard coronary angiography for both coronary imaging were used. In the study of Turan *et al*. [14], JL 3.5 catheter was used as multipurpose catheter, and JL 3.5 and Judkins right (JR) 4 catheters were used in the dual catheter group. Success was achieved with a single catheter in 66% of cases, and additional catheter use was more necessary than in the dual catheter group. Although the procedure time was shortened in the single catheter group, there was an increase in fluoroscopy time. More spasm occurred in the dual catheter group. In the study of Erden *et al*. [15], JL 3.5 catheter shaped like a Jacky catheter was used in the single catheter group, and standard JL 3.5 and JR 4 catheters were used in the dual catheter group. The need for additional catheters was higher in the single catheter group. Fluoroscopy time was less in the single catheter group. The procedure time was also significantly less when the time used to shape the single catheter was not included. Radial artery spasm was also detected more frequently in the dual catheter group. In a meta-analysis investigating the performance of standard shaped-JL or custom catheters for transradial coronary angiography, less spasm was detected in the single catheter group [10]. However, more crossovers were made compared to the dual catheter strategy.

In our study, we compared a single JL 4 catheter and a standard dual catheter for right and left coronary angiography by entering through the right radial artery. Procedural success, complication rate and procedure time were similar between the two groups. However, the duration of fluoroscopy was found to be longer in the single catheter group. The reason for this is that the operator had the right to make 4 attempts to complete the procedure with a single catheter and the operator's insistence on completing the procedure with a single catheter. Again, in the single catheter group, the amount of radiation exposed due to the length of the fluoroscopy period was higher in the single catheter group, but this value did not reach significance. However, it is obvious that the use of a single catheter is less costly than the use of two catheters.

Limitations

The limitations of our study can be listed as follows: i) the small number of patients, ii) the absence of a group consisting of a special single catheter used for the right and left systems, iii) the procedure being performed by experienced operators (this may in-

crease the possibility of the procedure being subjective), iv) only the right radial artery use for the procedure.

CONCLUSION

In our study, in which a single JL catheter and a standard dual catheter were used for right radial coronary angiography, the duration of fluoroscopy was found to be longer in the single catheter group. Other procedural outcomes such as procedural success and complication rate were similar. Randomized, large-scale studies are needed on the use of the left JL 4 catheter in imaging the left and right systems with a single catheter.

Authors' Contribution
Study Conception: HA, SÇ, TB; Study Design: HA, TB, BU, MM; Supervision: TB, MM, HA; Funding: SÇ, BU, MK, GÖ; Materials: BU, BÇ, AT, MK; Data Collection and/or Processing: BU, BÇ, AT, MK, SÇ; Statistical Analysis and/or Data Interpretation: HA, MM, SÇ; Literature Review: SÇ, BÇ, AT, MK, GÖ, SA; Manuscript Preparation: HA, SÇ and Critical Review: TB, MM, GÖ.

Conflict of interest

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The European Research Journal 2022;8(4):536-540 Original Article

DOI: 10.18621/eurj.945752 *Physiology*

Effect of metaclopramide on urinary bladder smooth muscle contraction-relaxation mechanism

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ABSTRACT

Objectives: Metoclopramide, a dopamine receptor antagonist, a benzamide, is a commonly used antiemetic drug in many diseases with nausea and vomiting. The aim of this study is to examine the effects of metoclopramide, which is also used in urinary system infections, on the urinary bladder contraction-relaxation mechanism.

Methods: In the study, bladder tissue strips obtained from adult female Wistar rats in diestrus were placed in an isolated organ bath containing Krebs solution. The effect of metoclopramide at concentrations of 10 µM and 20 µM on sections where spontaneous contractions were observed under 1.5 g of tension was investigated.

Results: Metaclopramide caused a statistically significant increase in the area under the contraction curve (AUC) and peak to peak (p-p) parameters of spontaneous bladder contractions at concentrations of 10 and 20 µM ($p < 0.01$).

Conclusions: Metaclopramide has an activator effect on spontaneous bladder contractions. This effect should be taken into consideration in clinical use, especially when used in urinary system infections.

Keywords: Metoclopramide, urinary bladder, isometric contraction, rat

Metoclopramide (MCP) is an antiemetic with central and peripheral effects that increases the motility of the gastrointestinal system and accelerates gastric emptying [1, 2]. It is an antiemetic agent used in the prevention and treatment of nausea and vomiting due to acute migraine or urinary tract infections and after chemotherapy and radiotherapy. It may also cause side effects such as movement disorders of the extrapyramidal system [2]. MCP has a peripheral effect in accelerating gastric emptying and a central effect in reducing nausea and vomiting. MCP acts as a dopamine 2 and serotonin (5HT-3) receptor antagonist. It acts by blocking the dopamine receptor and stimulating the acetylcholine receptors in the stomach muscles [3]. MCP is widely used as a motility agent due to its contractile effects on gastrointestinal (GI) smooth muscle. MCP is widely used as an antiemetic agent, especially in patients receiving chemotherapy. Cholinergic reactions on smooth muscles are dominant in the periphery [4]. Its main antiemetic effect is through central dopaminergic antagonism [4].

This agent also has important effects on the urinary system. The effects of MCP on detrusor smooth muscle were studied using a canine model. Data from this animal model have been demonstrated by metoclopramide, a decrease in bladder capacity, an increase in

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detrusor micturition pressure, and a decrease in post-void residual volume [5]. Since urethral relaxation is an important factor in vesical micturition, the effect of metoclopramide on urethral pressure has also been studied and it has been shown to reduce urethral closing pressure [6]. One of the most common cases of emesis is urinary tract infections. In this case, the most preferred anti-emetic drug is MCP. Although it is frequently used in urinary system infections, its effectiveness on bladder activation is unknown. Therefore, in this study, it was aimed to investigate the effects of MCP on the contraction-relaxation of the bladder smooth muscle.

METHODS

Animals

In the study, 8 intact female Wistar rats, weighing 180-200 g, obtained from Fırat University Experimental Research Center were used. Rats were kept in plastic cages at 21°C room temperature, 12 hours light and 12 hours dark period. They were fed with tap water in glass bottles and special rat food in the form of pellets.

In Vitro Bladder Contraction Test

The rats decapitated on the day of the experiment and pelvic cavities were opened by cutting from the midline. The bladder tissues were rapidly excised and carefully separated from the surrounding tissues. The sections obtained from the bladder were opened by cutting vertically. Strips of 1.5×5 mm were obtained from the bladder tissue and placed in an organ bath pre-filled with crebs solution given the electrolyte composition: (118 mM NaCl, 4.7 mM KCl, 1.2 mM MgSO4, 15.8 mM NaHCO3, 1.18 mM KH2PO4, 11.5 mM glucose and 2.4 mM CaCl2, 0.016 mM EDTA). The temperature of the organ bath was kept at 37 °C. 95% O_2 and 5% CO_2 were continuously supplied to the bath solution. Each bladder strip was placed in the organ bath under the optimum resting force of 1.5 g and allowed to equilibrate for 90 minutes prior to drug administration.

Spontaneous contractions were obtained depending on the tension. The strain level in the suspended sections below 1.5 g remained constant throughout the experimental period. During this time, the bladder strips were washed every 15 minutes with fresh physiological solution. Each experiment was repeated using fresh bladder strips from different rats. The contractile forces were recorded isometrically using a force transducer connected to an amplifier and then to the data acquisition system. After the regulation period, 2 separate doses of MCP at concentrations of 10 µM and 20 µM were administered non-cumulatively. The effects of MCP on spontaneous bladder contractions were measured by changes in mean peak to peak (p-p) and area under the contraction curve (AUC). During the control period, contraction activity (mean p-p and AUC) was taken as 100%. AUC and p-p values of contractions before and after the application were normalized as % change.

Statistical Analysis

Statistical analysis of the data were evaluated using the Paired T test in the SPSS 22.0 program. All values were determined as mean ± standard deviation (mean ± SD). For all analysis, $p < 0.05$ was considered statistically significant.

RESULTS

MCP caused a statistically significant increase in p-p and AUC values of spontaneous bladder contractions at 10 and 20 µM doses (Figs.1 and 2). After the 10 µM dose was applied, the p-p values of contractions were calculated as 288 ± 134 and AUC values as 248 ± 94. The p-p values of contractions after MCP applied at 20 µM concentrations were calculated as 236 ± 90 and AUC values as 243 ± 126. It was observed that the p-p ($p = 0.005$ and $p = 0.004$) and AUC values significantly increased ($p = 0.003$ and $p = 0.01$) compared to the pre-administration values of MCP applied at concentrations of 10 and 20 µM. The original traces obtained at 10 and 20 µM doses in isolated organ bath are shown in Figs. 3 and 4, respectively.

DISCUSSION

MCP has an activator effect on spontaneous bladder contractions. In the study, it was shown that after MCP was applied to the bladder sections showing spontaneous contraction, there was a significant increase in the p-p and AUC values of contractions. MCP has

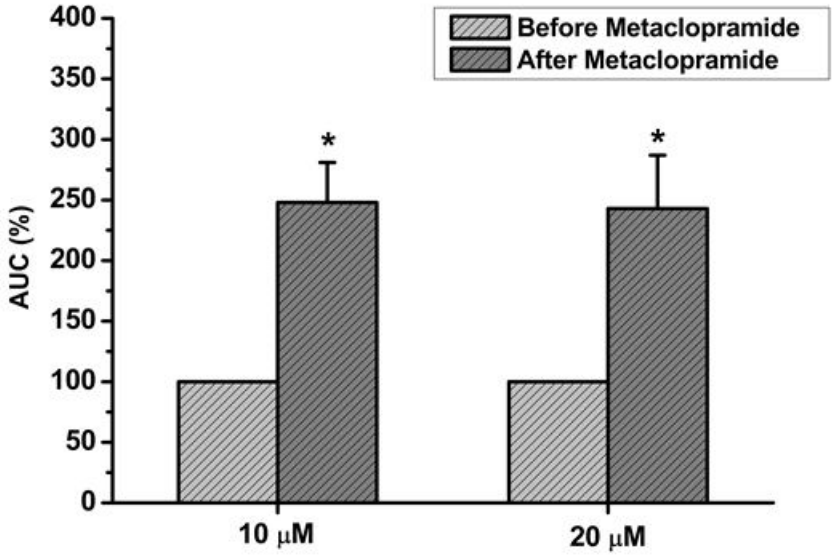

Fig. 1. **Effects of metoclopramide on AUC measurements in bladder contractions. * $p < 0.001$.**

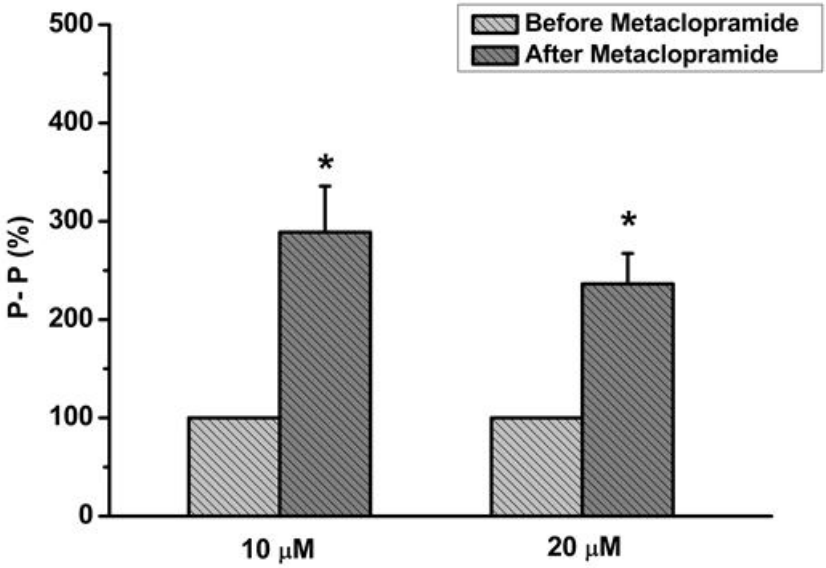

Fig. 2. **Effects of metoclopramide on peak-to-peak (p-p) measurements in bladder contractions. * $p < 0.001$.**

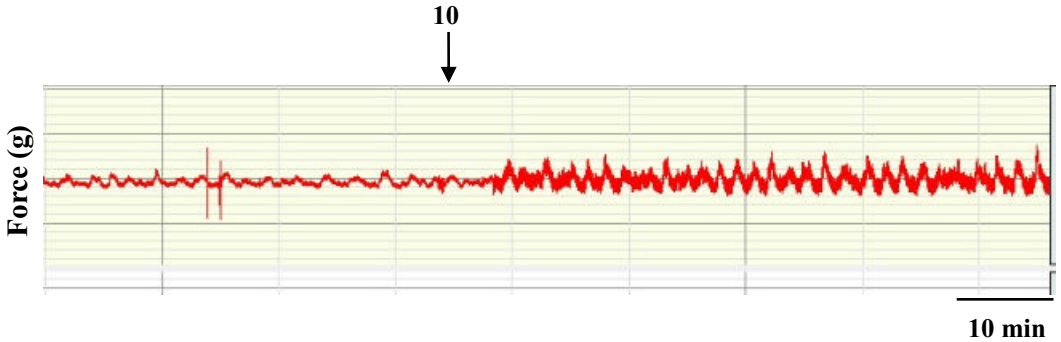

Fig. 3. **Original trace obtained when a 10 µM dose of metoclopramide was administered in an isolated organ bath.**

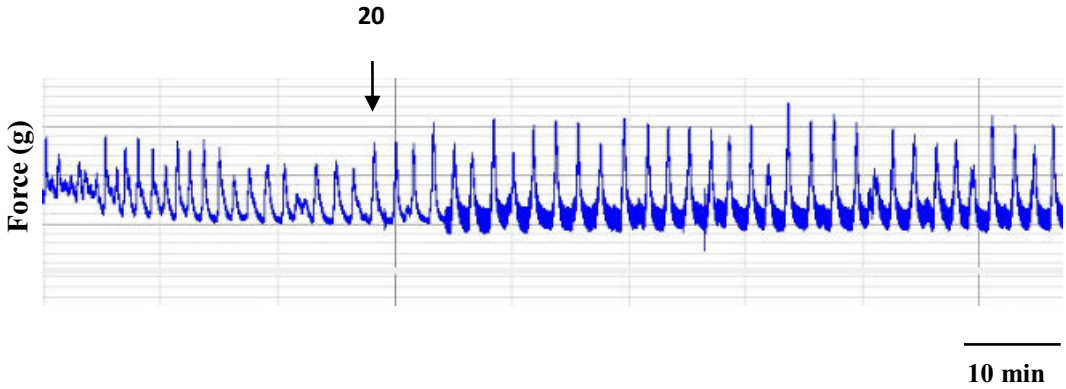

Fig. 4. Original trace obtained when 20 µM dose of metoclopramide was administered in isolated organ bath.

proven useful as a motility agent due to its ability to induce smooth muscle contraction in the gastrointestinal tract. Previous research had characterized the contractile effects on various parts of the urinary tract. In a study, the effect of MCP on detrusor smooth muscle was investigated using an in-vitro guinea pig bladder strip model. In the study, the effects of MCP were compared with those obtained in combination with atropine and acetylcholine.

MCP has been shown to exhibit inhibitory activity on guinea pig detrusor strips at low doses and stimulatory activity at higher doses. Acetylcholine has been observed to attenuate the contraction effect at low doses, but increase this effect at higher doses. Atropine reduces the contraction effect of MCP but increases the relaxation effect. Analysis of these interactions shows that MCP exerts a direct effect on bladder smooth muscle [7]. Nestler *et al*. [8] published a case report showing improvement in bladder function with spontaneous micturition after treatment with MCP in a diabetic man who needed intermittent catheterization with diabetic gastroparesis.

Reports on the possible effects of MCP treatment on the urinary tract are limited. In a clinical study conducted in ten patients with chronic neurological disorders, Vaidyanathan *et al*. [9] noted that administration of MCP in one third of these patients showed a return of detrusor reflex activity within minutes. However, the effects of MCP, a commonly used agent in lower urinary tract infections, on the bladder contraction relaxation mechanism are unknown. Therefore, in our study, we examined the possible effects of MCP on bladder contractions and found that MCP has an activator effect on bladder contractions. It can be said that this effect may be effective in reversing bladder smooth muscle reflex activity in patients with various chronic nervous system disorders characterized by a clinically seen neurogenic bladder.

CONCLUSION

It is clear that an effective and safe agent in the medical treatment of neurogenic bladder will have significant benefits in treatment. In this study, it is thought that MCP is effective in inducing bladder contractions and may have beneficial effects in such patients. This effect should be taken into account in clinical use.

Authors' Contribution

Study Conception: ZE, GZ, OB, IS, AY, EK; Study Design: ZE, GZ, OB, IS, AY, EK; Supervision: ZE, GZ, OB, IS, AY, EK; Funding: N/A; Materials: GZ, OB, IS, AY; Data Collection and/or Processing: ZE, EK, GZ, IS; Statistical Analysis and/or Data Interpretation: ZE, IS, OB, EK; Literature Review: ZE, EK; Manuscript Preparation: ZE, EK and Critical Review: ZE, IS, OB, AY, GZ, EK.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

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The European Research Journal 2022;8(4):541-549 Review

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Cardiovascular diseases and diabetes mellitus

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ABSTRACT

Cardiovascular diseases are among the leading causes of death worldwide. Atherosclerotic cardiovascular diseases consist of a broad spectrum of diseases such as coronary artery disease, carotid artery disease, peripheral artery diseases, cerebral vascular diseases and visceral artery diseases. Although atherosclerosis occurs over time due to age; hypertension, hyperlipidemia, smoking, and diabetes mellitus are important factors that play a role in the emergence of atherosclerosis. Diabetes mellitus has an active role in the development of atherosclerotic cardiovascular disease. It is expected that there will be a significant increase in the incidence of diabetes-related cardiovascular diseases in the future. In this review, it is aimed to review the coexistence of diabetes with different cardiovascular diseases and its menanisms.

Keywords: Diabetes mellitus, hyperglisemia, heart, vascular disease

Cardiovascular diseases are among the leading causes of death worldwide. More than 30% of deaths worldwide are of cardiovascular origin. The main factor in these deaths is atherosclerosis. Atherosclerotic cardiovascular diseases consist of a broad spectrum of diseases such as coronary artery disease, carotid artery disease, peripheral artery diseases, cerebral vascular diseases and visceral artery diseases [1, 2]. Since atherosclerosis is a systemic disease, it usually affects more than one system. Although atherosclerosis occurs over time due to age, hypertension, hyperlipidemia, smoking, and diabetes mellitus (DM) are important factors that play a role in the emergence of atherosclerosis.

DM has an active role in the development of atherosclerotic cardiovascular disease. It is reported that by 2025, approximately 380 million people worldwide will have type 2 DM [3]. Thus, there will be a significant increase in the incidence of diabetes-related cardiovascular diseases.

In this review, it is aimed to review the coexistence of diabetes with different cardiovascular diseases and its mechanisms.

The Relationship Between Diabetes Mellitus and Vascular Diseases

The relationship between hyperglycemia and vascular diseases has a complex structure. Hyperglycemia causes Nuclear Factor-Kappa B (NF-KB) activation. NF-KB is a key mediator that regulates proinflammatory and proatherosclerotic target genes in endothelium, vascular smooth muscle cells and macrophages. This activation is known to increase oxidative stress. Hyperglycemia also causes a decrease in nitric oxide synthesis in platelets and an increase in free radical formation. In addition, it has been shown in experi-

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mental studies that with an increase in plasminogen activator inhibitor-1 level, it causes a decrease in fibrinolysis, plaque instability and dysfunctional arterial remodeling [2].

Effect of Diabetes Mellitus on Cardiovascular Risk Factors

Dyslipidemia plays an important role in the pathogenesis and progression of cardiovascular diseases. The essential feature of the lipid disorder in patients with DM is the presence of high plasma triglyceride levels, decreased high-density lipoprotein cholesterol (HDL-C) concentration, and increased concentration of small-density low-density lipoprotein cholesterol (LDL-C) particles in patients. This occurs due to increased plasma free fatty acid ratios due to increased insulin resistance [4].

In the presence of adequate glycogen stores in the liver, high free fatty acid values stimulate triglyceride production. Failure to provide "up" regulation of Apolipoprotein A-I (ApoA-I) production due to insulin resistance contributes to the formation of decreased HDL-C levels. Tumor Necrosis Factor-α (TNF-α) plays a role in insulin resistance in obese patients and leads to a decrease in HDL-C. Apart from these, many key enzymes that affect HDL-C metabolism undergo changes in patients with insulin resistance. In some people, insulin resistance results in decreased conversion of lipoprotein lipase to hepatic lipase, which contributes to HDL-C reduction. While

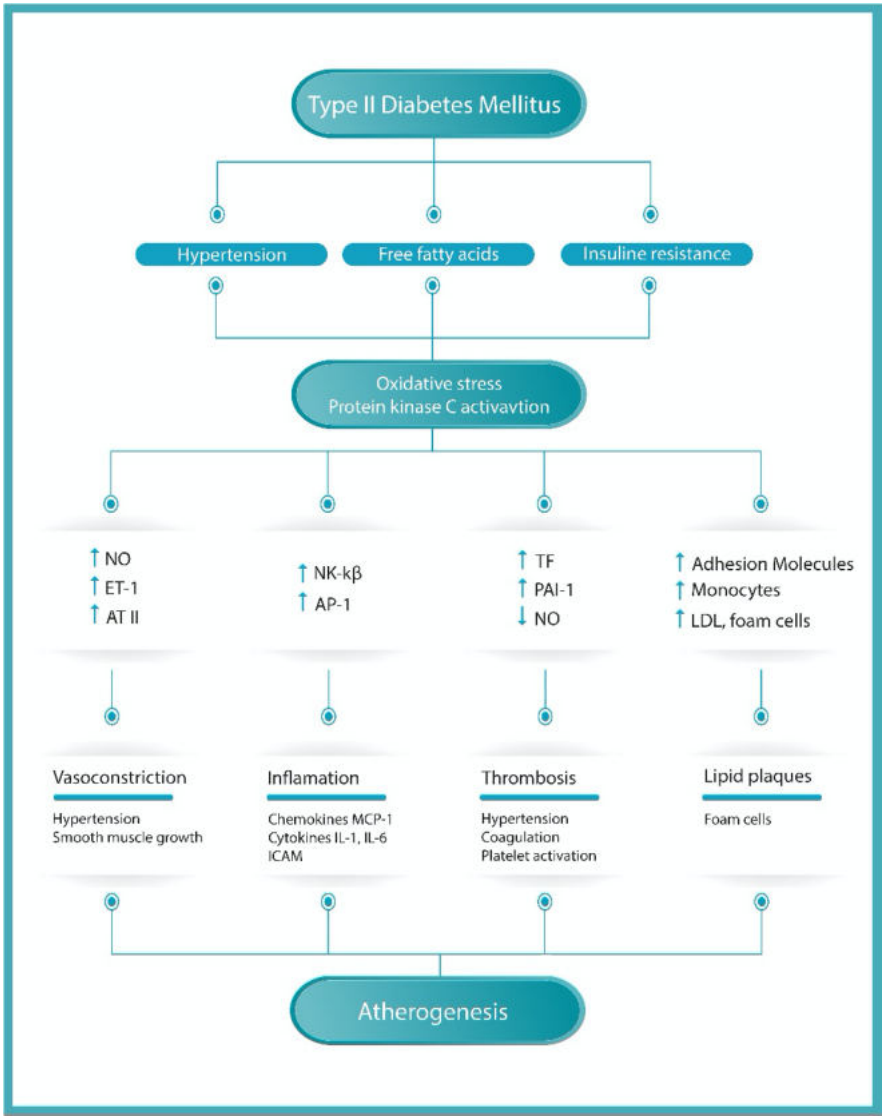

Fig. 1. Pathophysiological mechanisms leading to atherosclerotic vascular disease in Type 2 diabetes mellitus. AP-1 = Activator protein 1, AT II = Angiotensin II, ET-1 =: Endothelin-1, ICAM = Intercellular adhesion molecule, MCP = Monocyte chemoattractant protein, NF-κβ = Nuclear factor-κβ, NO = Nitric oxide, PAI-1 = Plasminogen activator inhibitor-1, TF = Tissue factor.

insulin resistance does not cause an increase or no change in cholesterol esterification provided by cholesterol acyltransferase, it causes an increase in Cholesteryl Ester Transfer Protein (CETP) activity. CETP activity causes a decrease in HDL-C esters [5].

Hypertension is an important risk factor that can develop in patients with DM. The most well-known feature of DM is the deterioration of the autonomic balance in the form of a significant decrease in parasympathetic tone and a relative increase in sympathetic tone. In particular, an increase in sympathetic tone occurs in cerebral centers that provide autonomic control due to high blood sugar [6]. This increase in tone in diabetic patients affects cardiac and vascular functions and leads to hypertension [7]. The mechanism of atherogenesis due to DM is shown in Fig. 1 [8, 9].

Diabetes Mellitus and Coronary Artery Disease

Atherosclerosis, which develops due to diabetes, affects the coronary arteries and leads to the formation of coronary artery disease (CAD). In diabetic patients, atherscleroticprocess progresses, nitric oxide release decreases, inflammation and platelet activation increase, leading to coronary events [10]. In a study in which data were collected from 52 countries, it was revealed that the presence of DM increased the risk of CAD by 10% [11]. In addition, the prevalence of hypertension and hyperlipidemia, which are known as risk factors for CAD, has been reported up to 70% in patients with DM [12]. In the WHO study on Prevention of REcurrences of Myocardial Infarction and StrokE (WHO-PREMISE), patients from 10 countries were examined and the prevalence of DM was found to be 31.5% [13].

In addition to causing CAD, diabetes also affects mortality and long-term prognosis after myocardial infarction [14]. In fact, the presence of DM in patients with CAD also affects treatment strategies. Although percutaneous coronary interventions (PCIs) have come to the forefront today, the presence of DM highlights coronary artery bypass grafting (CABG) surgery as a treatment option, especially in multi-vessel patients. In a study conducted in this direction, the results of PCI (n =1.556) and CABG (n =1.281) in patients with DM with impaired left ventricular function were compared. At 5-year follow-up after treatment, major adverse cardiovascular and cerebral event development rates were approximately twice as high in the PCI group [15].

Apart from this, long-term patency after coronary stent procedure in CAD patients is very important in terms of both patient comfort and treatment costs. Mechanisms similar to atherosclerosis play a very important role in the obstruction here. In a study involving 18,910 patients who underwent coronary stenting, they were divided into two groups as those with DM (n =5123) and those without (n =13.787). At the end of the study, the risk of late-stage stent thrombosis was found to be significantly higher in patients with DM (odds ratio [OR]: 1.95, 95%confidence interval [CI] 1.35-2.81; p=0.0004, I2=0%) [16]. Similarly long-term graft patency rates decrease after CABG surgery in patients with DM [17].

Diabetes Mellitus and Heart Failure

Although ischemic heart diseases are an important cause of heart failure, DM is an independent risk factor for the development of heart failure. The reason here is ‘‘diabetic cardiomyopathy’’, which is caused by diabetes by causing damage to cardiac myocytes. The term ‘‘diabetic cardiomyopathy’’ was coined after histopathological examination of the heart structures of four heart failure patients who died without initial CAD [18]. In conclusion, cardiomyopathy in patients with DM was evaluated in relation to hyperinsulinemia, autonomic neuropathy, activation of the renin-angiotensin system and microvascular ischemia.

In these patients, heart failure usually develops due to diastolic dysfunction and systolic functions may be normal. Studies using tissue flow Doppler methods in diabetic patients have found 40-75% of diastolic dysfunction without CAD [19]. In a follow-up study of 150,000 diabetic patients, the study baseline heart failure rate was 22.3%. In the following years, its annual incidence was determined as 12.6%. Dyslipidemia, insulin use, microalbuminuria, and poor glycemic control, especially the age of the patient and diabetes, have been shown as risk factors for the development of heart failure [20]. It has also been found that left ventricular hypertrophy can occur without hypertension in diabetic patients [21].

Techniques such as heart transplantation, heart support devices and artificial heart can be used in the treatment of advanced heart failure. The presence of DM may also affect the results of these treatments. In

a retrospective study involving 341 heart failure patients, the effect of DM on clinical outcomes after left ventricular assist device application was investigated. The patients were followed for an average of 16.1 months, and DM was found to be associated with all-cause mortality (hazard ratio [HR]: 1.73; 95% CI 1.18-2.53; p=0.005). In addition, complications such as device-related thrombosis and pump infection were found to be associated with DM (HR: 2.1; 95% CI 1.35-3.18; p=0.001). At the end of their study, the authors emphasized that despite optimal post-operative blood glucose regulation, all-cause mortality increased after left ventricular assist device operation in DM patients [22].

Diabetes Mellitus and Atrial Fibrillation

Atrial fibrillation (AF) is the most common cardiac arrhythmia in the population and increases cardiovascular mortality and morbidity [23]. The Framingham Heart study demonstrated that the presence of DM and poor glycemic control are characterized by new-onset AF [24]. It is known that diabetes increases interstitial fibrosis in atrial structures. As a result of obesity-related DM, lipomatous metaplasia develops in the heart and this process ends with fibrosis [25]. Angiotensin II, transforming growth factor-β (TGF-β) signaling and reactive-oxygen species levels increase due to hyperglycemia in diabetic patients. All these substances have cardiac fibrosis stimulating effects [26]. Another factor causing atrial fibrosis is adipokines (Leptin and adiponectin) secreted from epicardial adipose tissue. Angiotensin II increases leptin secretion from wild-type atrial fibroblasts, and leptin triggers TGF-β signaling. Thus, cardiac fibrosis occurs [27]. In addition, the relationship between AF and adiponectin, which has anti-inflammatory and insulin-sensitizing effects, is not clear. Decreased adiponectin levels are associated with increased obesity [28]. However, interestingly, higher circulating adiponectin levels have been associated with increased rates of AF [29].

In addition to being an important factor that increases the incidence of AF in the normal population, DM also affects AF recurrences after treatment. The effect of DM on AF recurrence was investigated in 531 consecutive patients with AF who underwent cryoablation. At the end of the study, the authors identified the presence of DM as an independent predictor for the developmentof AF recurrence [30]. In addition, the incidence of newly emerging AF after surgical operations is affected by the presence of DM [31-34].

Diabetes Mellitus and Carotid Artery Disease

Carotid artery disease is the most important risk factor for stroke in diabetic patients. In patients with carotid artery stenosis (CAS), distal embolisms from plaque are the most important cause of ischemic stroke. In anatomical studies, it has been shown that diabetes leads to a more unstable and vulnerable structure in the carotid artery plaque structure [35]. The pathogenesis of CAS in diabetic patients is based on insulin resistance, obesity, hyperlipidemia and hypertension.

Carotid intima-media thickness is an important predisposing indicator for CAS and cerebrovascular events. Studies have shown that this thickness is increased in diabetic patients compared to non-diabetic patients. In addition, it has been shown that high blood sugar values in diabetic patients are an important factor for intima-media thickness [36].

In addition to affecting the development of CAS, DM also affects clinical outcomes after CAS treatment, as in other vascular diseases. The results of patients with CAS over 70% who were given the best medical treatment and who underwent carotid endarterectomy with this treatment were compared. During this period, the patients were followed up for an average of 60.7±37.5 months. In this study, the presence of DM increased the risk of stroke in both groups, but it also affected restenosis rates in patients who underwent surgery [37]. A meta-analysis including 18 studies and 17,106 patients also showed that the rates of restenosis after surgical carotid revascularization are increased in patients with DM [38]. In another study involving a large cohort of patients who underwent carotid artery stenting, post-procedure stroke and mortality were also found to be higher in patients with DM [39].

Diabetes Mellitus and Peripheral Artery Disease

The clinical condition that occurs when atherosclerosis especially affects the peripheral vessels of the lower extremities is known as Peripheral Arterial Disease (PAD). Less commonly, upper extremity arteries may also be affected. PAD is an important cause of mortality as well as creating an important morbid con-

dition by causing extremity loss. Although PAD occurring in diabetic patients is similar to the normal population, it mostly affects the distal vascular structures [40]. In the Rochester study, the rate of PAD was found to be 15% in 10 years after the diagnosis of DM, and 45% after 20 years [41].

DM negatively affects the development of PAD as well as post-treatment outcomes. In the study in which the revascularization results of 26,799 PAD patients from the Veterans Affairs data set were investigated, 59.9% of the patients had DM. At the end of the study, it was shown that patients with DM and patients with poor blood glucose control had significantly more poor clinical outcomes [42].

Approximately 100,000 major leg amputations are performed each year in the United States, half of which are due to DM and PAD. In patients with critical leg ischemia, the DM rate is given in the range of 27-76%. The coexistence of DM and PAD can increase amputation rates up to 4 times [43, 44].

Ulcers occurring on the feet due to DM is a clinical condition characterized by motor-sensory loss and impaired wound healing, which poses a risk of amputation. PAD accompanies 50% of this patient group [45]. In addition, a 1-year mortality rate was reported as 40.4% in patients undergoing amputation due to critical limb ischemia [46]. The severity of the situation becomes evident when it is considered that the 5-year mortality is 10% in breast cancer patients, 35% in colon cancer and 50% in myeloma [47].

Diabetic Foot

About one-quarter of patients with DM develop diabetic foot once in their lifetime [48]. This condition occurs with the combination of peripheral neuropathy and arteriopathy due to uncontrolled blood sugar. Depending on the loss of sensitivity due to neuropathy, there may be uncontrolled contacts with external surfaces. As a result of peripheral arteriopathy accompanying this condition, healing is impaired and infection may be added to it [49] (Fig. 2). It also plays a role in Charcot arthropathy, which includes progressive destruction of bones, joints and soft tissues, especially the feet, in diabetic patients [50]. All these situations lead to serious socioeconomic problems.

In these patients, glycemic control should be done well in order to prevent the progression of peripheral neuropathy. Close dialogue should be established in order to achieve target hemoglobin (HbA1c) values in patients [51]. A Cochrane review analysis of 11 randomized controlled trials showed that educating patients on this issue may reduce the risk of diabetic foot [52]. Footwear is also one of the important factors that play a role in the development of diabetic foot. Tight clothing, which is uncomfortable for the feet, may cause foot wounds, as well as a predisposing factor for fungal infections [53].

Diabetes Mellitus and Aortic Aneurysm

Although DM is known to increase cardiovascular diseases, it is negatively associated with the develop-

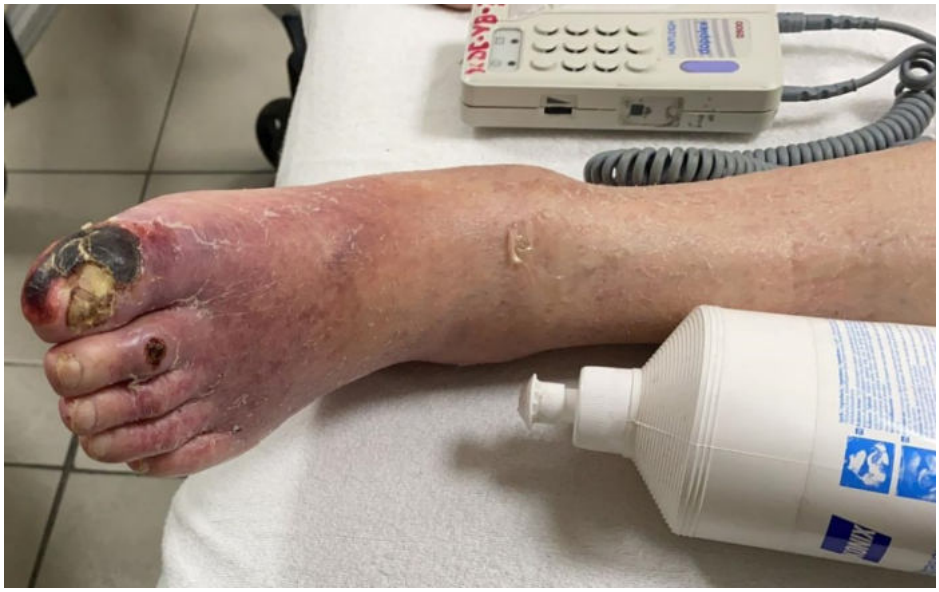

Fig. 2. Imaging of the diabetic foot.

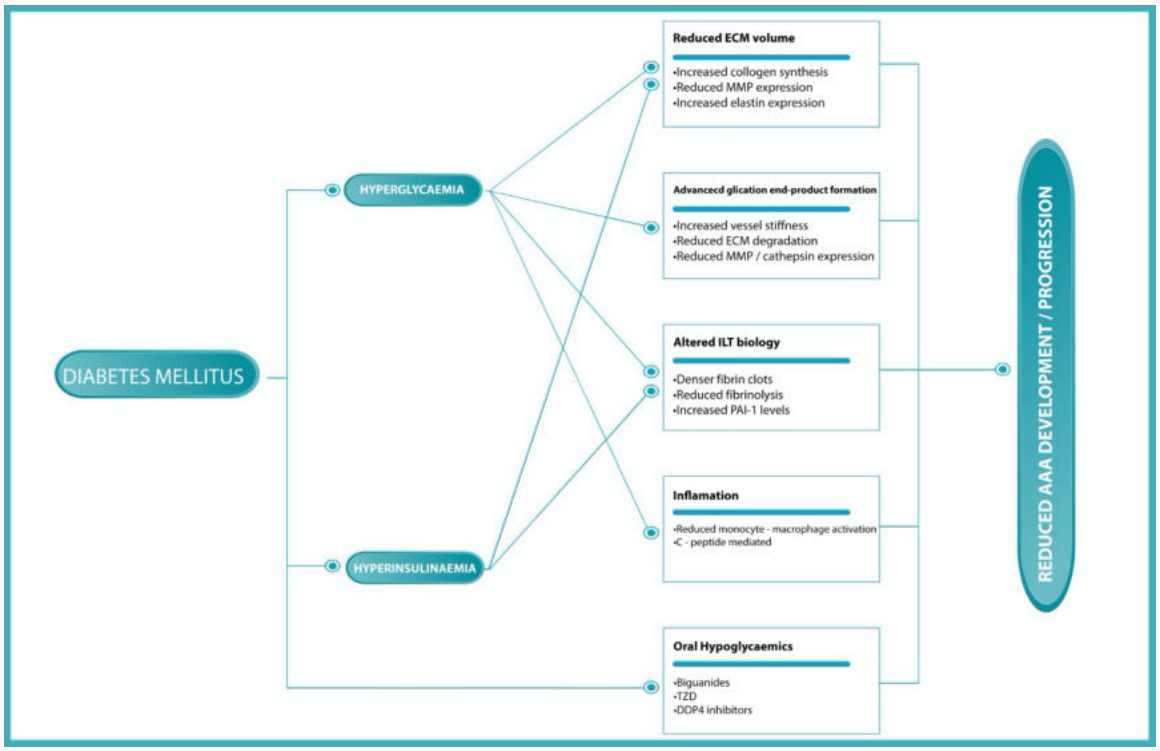

Fig. 3. Potential mechanisms by which diabetes mellitus protects against abdominal aortic aneurysm development and progression. DPP4 = dipeptidyl peptidase-4, ECM = extracellular matrix; ILT = intraluminal thrombus, MMP = matrix metalloproteinase, PAI = plasminogen activator inhibitor, TZD = thiazolidinedione.

ment of abdominal aortic aneurysm (AAA). Although patients with DM have increased arterial calcifications compared to patients without DM, this is not sufficient to explain the reduced aortic dilatation in patients with DM [54, 55]. The explanation of this inverse relationship is basically made in four biological ways. These basic pathways can be listed as follows (Fig. 3) [56]: (1) Extracellular matrix volume, (2) Extracellular matrix glycation and advanced glycation end-product formation, (3) Inflammation and oxidative stress, and (4) Intraluminal thrombus biology.

CONCLUSION

2019 European Society of Cardiology (ESC) Guideline Recommendations for Diabetes Mellitus and Cardiovascular Diseases [57]

(1) DM increases approximately three-fold risk of developing cardiovascular disease. This risk increases with the duration of diabetes and comorbidities (Other previous vascular disease, kidney disease, etc.).

(2) Despite all medical, interventional and surgical treatments for cardiovascular diseases, the prognosis in patients with DM is worse than those without DM. This situation defined as residual risk.

(3) Fasting blood glucose and HbA1c values should be measured in patients presenting with signs of cardiovascular disease and the patient should be examined for DM. If results cannot be obtained with these evaluations, an oral glucose tolerance test should be used.

(4) In patients with DM, management of blood glucose, blood pressure, blood lipids and antiplatelet therapy should be done carefully. This treatment should be planned appropriately for each patient.

(5) Since cardiovascular risk management in patients with DM is complex and difficult, new algorithms should be developed for treatment decisions.

(6) Blood pressure targets should be updated in patients with DM.

(7) LDL-C target should be set below 55 mg/dL in very high risk patient groups, with the use of proproteinconvertase subtilisin/kexin type 9 inhibitors if unachievable with intensive statin therapy plus ezetimibe.

(8) Aspirin therapy should be considered in high and very high risk patient groups. In addition to aspirin

therapy, low-dose novel oral anticoagulant therapy may be considered in patients with coronary syndrome or peripheral artery disease.

(9) The new glucose lowering agents, sodium-glucose co-transporter-2 inhibitors and Glucagon-like peptide-1 receptor agonistsare recommended as first-line therapy in type 2 DM with established cardiovascular disease or high/ very high cardiovascular risk.

(10) Ideas should be generated about DM!

Authors' Contribution

Study Conception: ŞY, AKA, ME; Study Design: ŞY, AKA, ME; Supervision: ŞY, ME, NK, SC; Funding: ŞY, AKA, ME; Materials: ŞY, AKA, ME; Data Collection and/or Processing: ŞY, AKA, ME; Statistical Analysis and/or Data Interpretation: ŞY, ME, NK, SC; Literature Review: ŞY, ME, NK, SC; Manuscript Preparation: ŞY, ME, NK, SC and Critical Review: ŞY, ME, NK, SC.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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The European Research Journal 2022;8(4):550-553 Case Report

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Neuroendocrine carcinoma of the breast: a case report and review of the literature

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ABSTRACT

Objectives: Neuroendocrine carcinoma (NEC) is a very rare condition among other types of invasive cancer of breast. Whole-body screening should be performed in order to detect any metastatic or primary disease localization. A 58-year-old patient admitted to hospital with palpable mass on the right retro areolar region and with bloody nipple discharge. Due to axillary positivity with a diagnosis of neuroendocrine carcinoma neoadjuvant chemotherapy was performed. The pathological stage was reported T2N2 with a 2 cm tumor and 5 of 11 lymph node positivity after modified radical mastectomy following neoadjuvant therapy. Tumor cells were stained with positive for neuroendocrine markers. She received adjuvant hormonal treatment with aromatase inhibitors and on regular follow-up with a free of disease to date. The neuroendocrine tumor of the breast is a diagnosis of exclusion. Primary or metastasis distinction is compulsory for the planning of appropriate treatment. There is still a debate on how neuroendocrine differentiation affects the clinical outcome.

Keywords: Neuroendocrine carcinoma, breast cancer, immunohistochemistry

The term neuroendocrine tumor was first described by Cubilla *et al*. [1] in the late 70's which reports 'neurosecretory' granules were seen under electron microscopy. Neuroendocrine tumors (NET) arise from the neuroendocrine cells. The gastrointestinal tract and the lungs are the most commonly observed locations of neuroendocrine tumors [2]. Pure neuroendocrine tumors of breast are very rare among all types of breast cancer (0.1% of all breast cancers), but neuroendocrine cells can be detected much more in other types of breast cancers [3, 4]. Here we would like to present a 58-year-old patient's management of treatment and review of the literature with a diagnosis of a neuroendocrine differentiating tumor of the breast.

CASE PRESENTATION

A 58-year-old generally in good health condition woman was admitted to policlinic with a palpable mass on her right breast. The patient has only mild hypertension. A palpable 3×2 cm mass examined on the right upper retro areolar region. Ultrasonography and bilateral mammography performed. A BIRADS category 4c was reported by both sonographic and mammographic examination. Enlarged lymph nodes were detected in the axilla. A tru-cut biopsy was performed from the palpable mass under sonographic guidance. Pathology has resulted in a suspicious neuroendocrine tumor whether primary or metastatic. Immunohisto-

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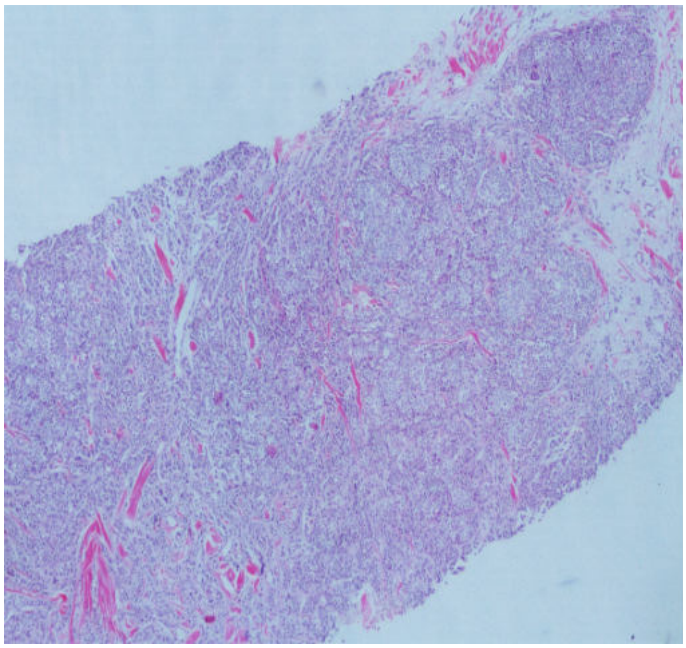

Fig. 1. Tumor as solid nests, H&E X 40

chemical receptor status of the pathology was as follows: Estrogen receptor: (+), progesterone receptor (-), HER2 (human epidermal growth factor receptor): (-), Ki67 proliferation index: 40%. Fig. 1 shows tumor deposits as solid nests; positive synaptophysin and neuron-specific enolase staining of tumor cells were observed in Fig. 2 and Fig. 3, estrogen receptor expressivity was shown in Figure 4. Since primary NETs of the breast are very rare, systemic studies have been conducted for suspected primary focus or metastasis.

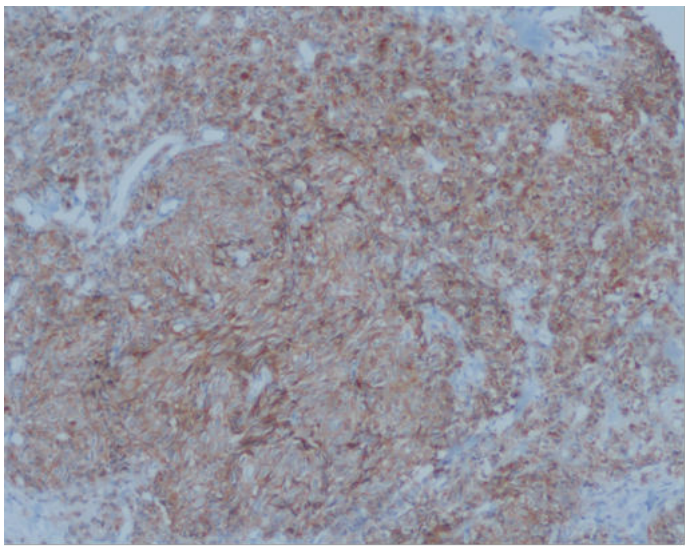

Fig. 2. Immunohistochemical positivitiy in the tumour cells, Synaptophysin, - Immunohistochemical staining X 100

There was no additional focus observed except axillary involvement. Due to the locally advanced stage, neoadjuvant chemotherapy was planned by the oncosurgical tumor board.

After neoadjuvant therapy control positron emission tomography revealed partial response and persistent axillary status. Modified radical mastectomy performed to avoid locoregional relapse. The final pathology result was invasive carcinoma of the breast with neuroendocrine differentiation. Five positive lymph nodes out of 15 were detected. Pathologic grade was T1N2Mx. Adjuvant hormonotherapy with aromatase inhibitors and taxane based treatment was given. She is still on regular follow-up at our clinic.

DISCUSSION

Neuroendocrine carcinoma (NEC) of the breast is a rare condition that represents 0.1 % of breast cancers and less than 1% of other neuroendocrine tumors. Mainly, neuroendocrine tumors observed in the gastrointestinal system and pulmonary system [3]. It was also reported in a retrospective study reported by Wang *et al*. [5] a total of more than 380 thousand invasive carcinomas of the breast only 142 of them were diagnosed as neuroendocrine carcinoma which refers to 0,1 % of invasive carcinoma of the breast, and also was observed relatively older ages (mean age was 64). NEC of breast could also be observed younger ages and among men [6, 7]. Palpable mass, bloody nipple discharge can be the s first signs observed on admission to hospital [7]. Almost there were no specific or pathognomonic sign presents in breast ultrasonography and mammography but Park *et al*. mentioned that some radiological characteristics such as high-density round, oval, or lobular noncalcified mass with non-spiculated margins suggest neuroendocrine tumor of the breast [8, 9]. Chromogranin and synaptophysin and neuron-specific enolase are known as specific immunohistochemical markers of neuroendocrine differentiation. They could be stained with argentaffin histochemically and neurosecretory granules of the tumor could be observed under electron microscopy. NEC diagnosis could be made whether these marker occupy more than 50% of tumor cells [10-12].

Estrogen receptor (ER) and progestron receptor (PR) positivity and human epidermal growth factor re-

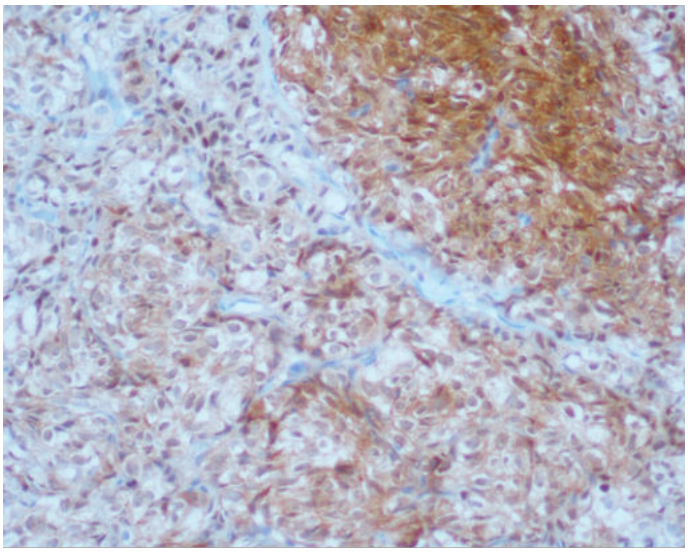

Fig. 3. Immunohistochemical positivitiy in the tumour cells, Neuron Spesific Enolase (NSE)- Immunohistochemical staining X 200

ceptor 2 (HER-2) negativity mostly observed in neuroendocrine tumors of breast [13-15]. Positive ER status may not contribute positive prognostic benefit as it does in other types of invasive carcinomas of breast [5].

Ki 67 protein is a proliferation antigen, which is present in the different phases of the cell cycle and accepted as a poor prognostic factor and high Ki 67 index observed in poorly differentiated tumors [15, 16]. Although neuroencocrine carcinoma is a rare condition observed in the breast, routine systemic work-up should be performed to rule out any other primary or metastatic focus with positron emission tomography and bone scintigraphy [17, 18].

Surgical approach to neuroendocrine carcinoma of the breast is not different in any other type of invasive carcinoma of breast. The location of the tumor and the clinical stage are the main determinants of the surgical procedure [19, 20]. Neo-adjuvant chemotherapy is indicated in case of locally advanced disease or malignity which is not suitable for surgery. Adjuvant therapy regimens including anthracyclines and/or taxanes, hormonal and HER-2 status should be evaluated for endocrine and anti HER-2 treatment [19].

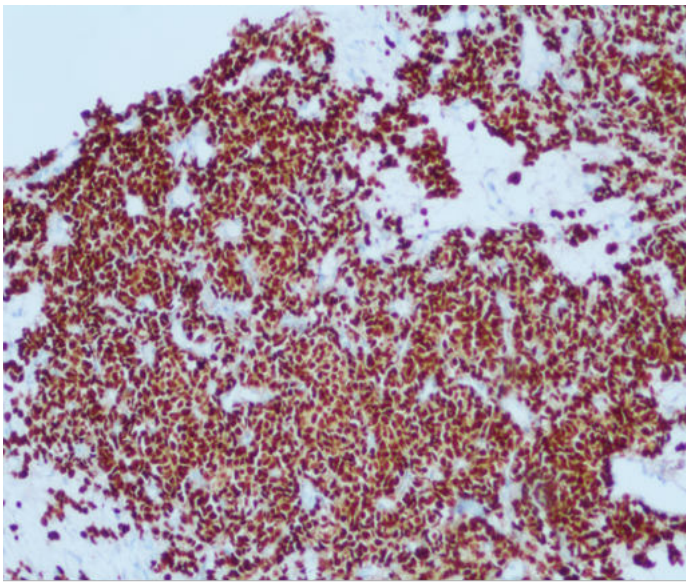

Fig. 4. Immunohistochemical positivitiy in the tumour cells, Estrogen receptor (ER) – Immunohistochemical staining X 100

CONCLUSION

In conclusion, the neuroendocrine tumor of the breast is a diagnosis of exclusion. A biopsy followed by appropriate immunohistochemical staining could help for diagnosis. Primary or metastasis distinction is compulsory for the planning of appropriate treatment. There is still a debate on how neuroendocrine differentiation affects the clinical outcome.

Authors' Contribution

Study Conception: KG; Study Design: KG; Supervision: KG; Funding: KG; Materials: KG; Data Collection and/or Processing: KG; Statistical Analysis and/or Data Interpretation: KG; Literature Review: KG; Manuscript Preparation: KG and Critical Review: KG.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Financing

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Informed Consent

Written informed consent was obtained from the patient for publication of this case and any accompanying images or data.

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