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REVIEW

Revisiting anatomical structures of the superior orbital fissure using with interactive 3D-PDF model

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ABSTRACT

The superior orbital fissure is an important cleft that connects the orbit with the middle cranial fossa. The upper border of this fissure is formed by the lesser wing of the sphenoid bone, anterior clinoid process, and optic strut. The lower border is formed by the greater wing of the sphenoid bone. The oculomotor, trochlear, ophthalmic, abducens nerves and orbital veins pass through this small slit. The aim of this study was to review anatomical structures of the superior orbital fissure, through a 3D-PDF model that simplifies the understanding of complex anatomy of this region. According to the literature, any major artery does not pass through it, but it is closely related to the internal carotid artery. There are numerous intracranial-extracranial anastomoses around it. While extracranial branches originate from the maxillary artery, intracranial branches arise from the inferolateral trunk or the ophthalmic artery. Nerves and vascular structures related with this fissure can be damaged due to post-traumatic sphenoid fractures, infectious diseases, aneurysms, carotid-cavernous fistulas, and neoplasms. Surgeries involving the superior orbital fissure are quite complex as there are many important anatomical structures in this region. The radiological anatomy of this fissure in normal and pathological conditions is still an under-studied subject in the literature. There is a need for more detailed studies related to the superior orbital fissure enriching with anatomic models and including pathological conditions. The 3D-PDF model of the superior orbital fissure is an innovative tool to enhance the knowledge of the anatomical structures related with this region. Better understanding of this critical region is necessary to perform safe and successful surgical procedures.

Keywords: Anatomic models, cranial nerves, orbit, superior orbital fissure, 3D-PDF model.

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INTRODUCTION

The superior orbital fissure (SOF) is a small but functionally important area that gives passage the oculomotor, trochlear, ophthalmic, abducens nerves and orbital veins. Nerves and vascular structures in this fissure can be damaged due to post-traumatic sphenoid fractures, infectious diseases, orbital pseudotumor, Tolosa-Hunt syndrome, aneurysms, carotid-cavernous fistulas, cavernous sinus thrombosis, pituitary adenoma and neoplastic lesions such as meningioma and craniopharyngioma [1,2]. Knowing the detailed anatomy of this region through an interactive 3D-PDF model is crucial for the diagnosis and treatment of pathologies involving orbit and sellar region.

The aim of this study was to review anatomical structures of the SOF, through a 3D-PDF model that simplifies the understanding of complex anatomy of this region.

Image processing and 3D-PDF development

The anonymised images of cranial computed tomography (CT) and magnetic resonance imaging (MRI) of patients were used. Informed consent was obtained from the individual participant included in this study. The study complied with the Declaration of Helsinki principles. Mimics Innovation Suite 24.0 software programme (Materialise, Leuven, Belgium) was used for 3D planning and modelling processes. Dicom format of cranial CT and MRI data taken from the different sequences were added to Mimics software as a study file. Areas were determined by masking process which was undertaken using Hounsfield Unit (HU) values on cranial CT scan and Grey Value (GV) values on MRI images. By using the segment module of Mimics software, the relevant structures were segmented by following the anatomical border relationship. Separately segmented models were superimposed using the Align Global Registration module in Mimics software, and the overlapping process was performed by ensuring the full harmony of the anatomical boundaries. 3D surface-rendered models of different anatomical structures were created in Mimics software. These 3D models were transferred to the design module 3-matic 16.0 (Materialise, Leuven, Belgium) in Mimics for the detailed modeling phase. We reconstructed anatomical structures such as optic nerve, optic chiasm, oculomotor nerve, trochlear nerve, branches of the ophthalmic nerve, abducens nerve, cavernous sinus, internal carotid artery, extraocular muscles, and ophthalmic veins. Digital data in 3-matic module were exported in 3D-PDF format (Online resource). This model allows for zoom, rotation and selective visualization of the structures.

Bony Frame of the Superior Orbital Fissure

The SOF is an important cleft that connects the orbit with the middle cranial fossa. Behind the SOF is the cavernous sinus, and in front of it is the apex of the orbit. The SOF is a triangle wider on the medial, and narrower on the lateral. It extends downward from lateral to medial. The upper edge of the SOF is formed by the lower surface of the lesser wing, the anterior clinoid process, and the optic strut. The anterior clinoid process starts from the medial of the lesser wing and extends posteriorly, and is located at the junction of the medial and lateral parts of the SOF. The optic strut forms the upper medial wall of the fissure and separates the SOF from the optic canal. The upper part of the medial edge of the SOF is formed by the lateral edge of the optic strut, and the lower part by the body of the sphenoid. The anterior part of the carotid groove is located behind the medial edge of the SOF. The lower border of the SOF is formed by the greater wing of the sphenoid bone, and is located at the base of the middle cranial fossa. Its lower edge is separated from the foramen rotundum by a small piece of bone, which is called the maxillary strut [3-6].

Divisions of the Superior Orbital Fissure

Common tendinous ring (annulus of Zinn-CTR) is a ring that encloses the optic canal and the middle part of the SOF. Rectus muscles start from the margins of the CTR and extends to the anterior part of the orbit, attaching to the eyeball. The SOF is divided into 3 parts through the CTR: From its upper part; lacrimal, frontal, trochlear nerves and superior ophthalmic vein pass. Lacrimal nerve is located in the most lateral part of the upper part of the fissure, while frontal nerve is located more medial to the upper part. Trochlear nerve passes through the superomedial edge of the frontal nerve. Superior ophthalmic vein passes through the lower part of the lacrimal and frontal nerves and reaches the cavernous sinus. From the middle section; superior and inferior branches of the oculomotor nerve, nasociliary nerve, abducens nerve and sensory and sympathetic nerve fibers coming to the ciliary ganglion pass. From the lower boundary of middle section; inferior rectus muscle begins. The lower part of the SOF is located below the CTR and through it inferior ophthalmic vein passes. Orbital smooth muscles are found in the lower border of the lower part [3-6].

Cranial nerves passing through the Superior Orbital Fissure

Oculomotor nerve; carries somatomotor and parasympathetic fibers. Somatomotor fibers innervate the extraocular muscles except for the lateral rectus and superior oblique muscles. The parasympathetic fibers innervate the ciliary and sphincter pupillae muscles. It leaves the brainstem through the interpeduncular fossa and pierces the dura mater and enters the cavernous sinus. It runs superiorly on the lateral wall of the cavernous sinus. The oculomotor nerve receives sensory branches

from the ophthalmic nerve and postganglionic sympathetic fibers from the internal carotid plexus, when it is inside the cavernous sinus. As soon as it exits the cavernous sinus, it divides into two branches, superior and inferior. These two branches pass through the middle part of the SOF and enter the orbital cavity.

Trochlear nerve; is a somatomotor nerve that innervates only the superior oblique muscle. After leaving the brainstem posteriorly, it moves forward and penetrates the dura mater and enters the cavernous sinus. On the lateral wall of the cavernous sinus, it runs under the oculomotor nerve. The trochlear nerve receives sensory branches from the ophthalmic nerve and postganglionic sympathetic fibers from the internal carotid plexus, when it is inside the cavernous sinus. After exiting the cavernous sinus, it crosses the oculomotor nerve, passes the upper part of the SOF, and enters the orbital cavity. After entering the orbit, it extends medially and innervates the superior oblique muscle.

Ophthalmic nerve; is a branch of the trigeminal nerve and contains only sensory fibers. This nerve receives general sensation from the eyeball, conjunctiva, lacrimal gland, paranasal sinuses, nasal mucosa, upper eyelids, forehead and anterior part of the scalp. It leaves from the upper-inner part of the trigeminal ganglion and pierces the dura mater and enters the cavernous sinus. It runs on the lateral wall of the cavernous sinus, below the trochlear and oculomotor nerves. Ophthalmic nerve leaves the cavernous sinus and gives off the recurrent meningeal branch at the level of the SOF and then divides into lacrimal, frontal and nasociliary branches. Lacrimal and frontal nerves pass through the upper part of the SOF and the nasociliary nerve passes through the middle part of it and all three branches enter the orbit.

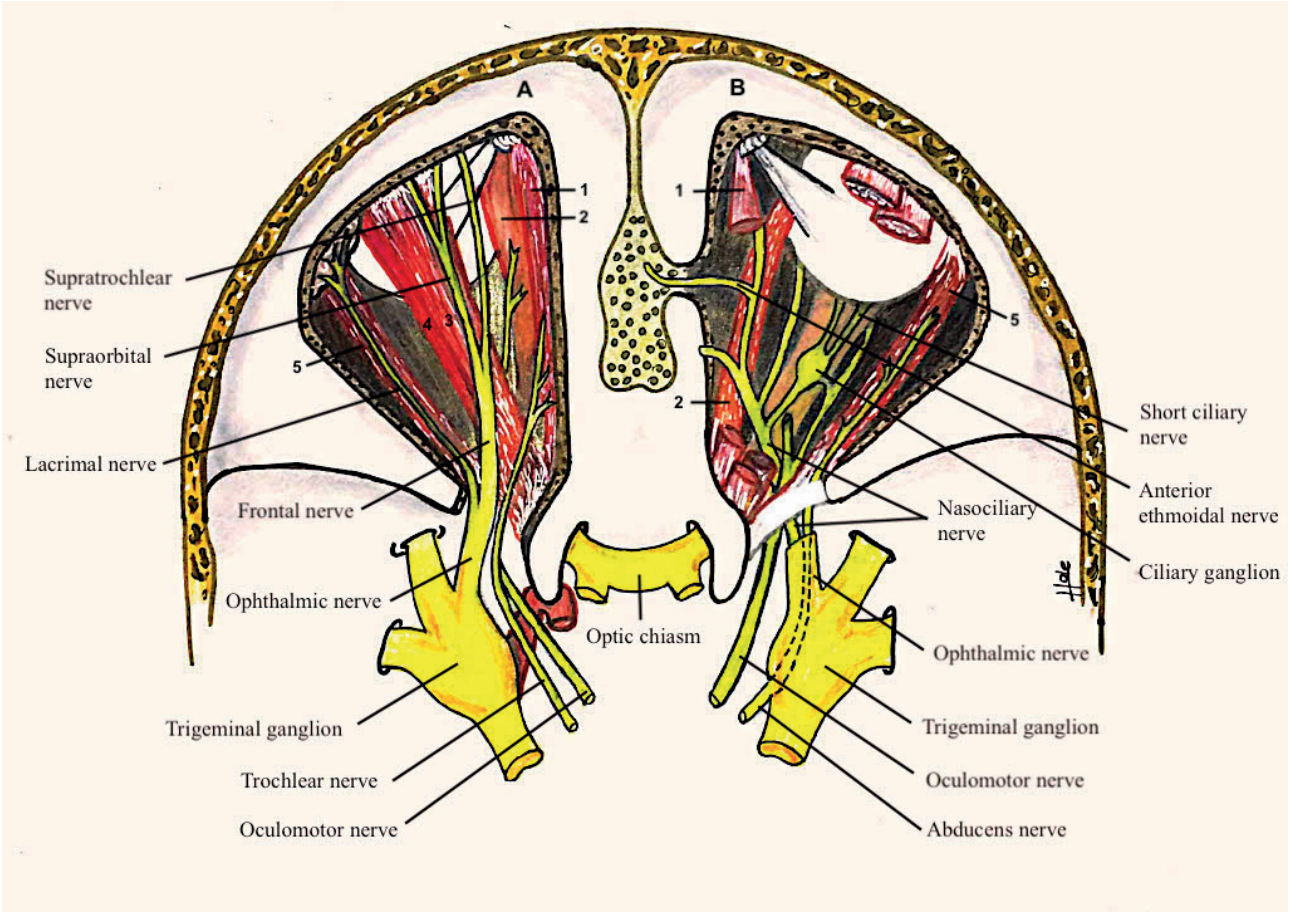

Figure 1. The illustration demonstrates the structures passing through the upper part of the superior orbital fissure (**a**). The illustration demonstrates the structures passing through the middle part of the superior orbital fissure (**b**). (**1:** Superior oblique muscle. **2:** Medial rectus muscle. **3:** Levator palpebrae superioris muscle. **4:** Superior rectus muscle. **5:** Lateral rectus muscle)

Abducens nerve; is a somatomotor nerve that innervates only the lateral rectus muscle. After leaving the brainstem from the bulbopontine groove, it moves forward and penetrates the cavernous sinus by piercing the dura mater. When inside the cavernous sinus, it runs medial to the ophthalmic nerve and lateral to the internal carotid artery. The abducens nerve receives sensory branches from the ophthalmic nerve and postganglionic sympathetic fibers from the internal carotid plexus, when it is inside the cavernous sinus. After exiting the cavernous sinus, it passes through the middle part of the SOF and enters the orbit and innervates the lateral rectus muscle. When passing through the SOF, it courses below the nasociliary nerve and extends laterally (Figure 1) [3-8].

One of the studies evaluating the neural contents of SOF was conducted by Natori and Rhoton [7] in 1995. In this study, 30 SOF dissections were performed on 15 cadavers and the relationships between the nerves and venous structures in the SOF were described in detail. They also measured the distances of these structures to the upper and medial edge of the SOF. As a result of the measurement; the distances to the upper edge and medial edge of the SOF are 1.4 and 3.2 mm for the superior branch of the oculomotor nerve, 3.5 and 3.2 mm for the inferior branch, 2.8 and 4.4 mm for the nasociliary nerve, 4.8 and 5.8 mm for the abducens nerve, 0.6 and 10.9 mm for the superior ophthalmic vein, respectively. The distance of the frontal nerve to the medial edge of the SOF is 6.3 mm, of the trochlear nerve was found to be 4.8 mm. Another study was performed by Shi et al. [8] in 2007. In this study, 36 SOF dissections were performed with the fronto-orbital craniotomy approach and the diameters of the cranial nerves in the fissure and their distances to the fissure margins were measured. As a result of the measurements made; diameter of the superior branch of the oculomotor nerve 1.16 ± 0.21 mm, diameter of inferior branch 1.74 ± 0.26 mm, trochlear nerve diameter 0.85 ± 0.19 mm, lacrimal nerve diameter 0.71 ± 0.26 mm, frontal nerve diameter 1.65 ± 0.43 mm, nasociliary nerve diameter 0.79 ± 0.16 mm and the diameter of abducens nerve was found to be 1.08 ± 0.17 mm. Gövsa et al. [2] examined 57 dry sphenoid bones, 102 skull bases and 58 formalin-fixed cadavers in 1999 to evaluate the SOF anatomy. They examined the shape of the SOF and measured the edge lengths of the fissure. The length of the upper edge of the SOF is 17.3 mm on the right, 16.9 mm on the left. They measured the length of the lower border of the SOF 20.8 mm on the right and 20.1 mm on the left, and the length of the medial edge of the SOF was found 9.5 mm on the right and 9.0 mm on the left.

Arterial anatomy in and around the superior orbital fissure

Any major artery does not pass through the SOF, but it is closely related to the internal carotid artery as shown in the 3D-PDF model (Online resource). The anterior curve of the cavernous segment of the internal carotid artery lies behind the medial edge of the SOF. The internal carotid artery projects along the posterior margin of the optic strut. It then turns upward along the medial edge of the anterior clinoid process and enters the subarachnoid space.

Arterial blood supply to the margins of the SOF is via small branches of many arteries. These arteries are; anterior branch of the middle meningeal, recurrent meningeal branch of the ophthalmic, meningeal branches of the internal carotid, tentorial branch of the meningohypophyseal trunk, anterior branch of the inferolateral trunk and the terminal branches of the maxillary artery [7]. The recurrent meningeal branch, which passes lateral side of the upper part of the SOF, is a small branch and often arises from the lacrimal artery. After this artery passes the SOF, it anastomoses with the orbital branches of the middle meningeal artery in the middle cranial fossa [5,9,10]. The inferolateral trunk is one of the important branches of the cavernous segment of the internal carotid artery. It provides blood supply to the oculomotor, trochlear, trigeminal and abducens nerves during their course in the SOF and cavernous sinus. While it is difficult to see angiographically in healthy individuals, it becomes more visible in pathologies such as vascular malformations or tumors. Three branches are defined as anterior, superior, and posterior. Special attention should be given to the inferolateral trunk in skull base surgeries and endovascular interventional treatments, as it provides blood supply to the cranial nerves [11,12].

In 2015, a separate artery passing through the SOF was defined by Kiyosue et al. [13] and this artery was named the "Artery of the SOF". It arises from the maxillary artery either singly or from a common trunk with the artery of the foramen rotundum.

It rises upward towards the apex of the orbit and turns posteriorly to enter the cavernous sinus. Within the cavernous sinus, it anastomoses with the anteromedial branch of the inferolateral trunk. It is found more prominent in internal carotid artery stenoses/occlusions and parasellar hypervascular lesions [13].

In addition to these small arteries passing through the SOF, there are numerous intracranial-extracranial anastomoses around it. While extracranial branches originate from the maxillary artery, intracranial branches arise from the inferolateral trunk or the ophthalmic artery. Widespread anastomoses were found in this region between the middle meningeal branch of the maxillary artery and the ophthalmic artery, between the middle meningeal and the cavernous branches of the inferolateral trunk, between the accessory meningeal and the artery of the foramen ovale, between the vidian artery and the petrous internal carotid artery and between the artery of the foramen rotundum and the inferolateral trunk [14]. Surgical and radiological identification of the anastomoses in this region and the evaluating of the arteries passing through the SOF are important to minimize the complications that may occur.

Venous structures passing through the superior orbital fissure

The superior and inferior ophthalmic veins leave the orbit through the SOF to drain into the cavernous sinus. The anatomy of the superior and inferior ophthalmic veins is highly variable and differs from person to person. Therefore, there is a controversial on their number, pattern, and nomenclature in the literature [15]. The facial and intracranial veins connect with each other through the superior and inferior ophthalmic veins. **Superior ophthalmic vein;** has a similar course to the ophthalmic artery. It lies between the optic nerve and superior rectus muscle. It extends posteriorly from the superolateral edge of the extraocular muscle cone and passes through the upper portion of the SOF. The medial palpebral, superior vortex, anterior ethmoidal, lacrimal, central retinal, muscular, and the inferior ophthalmic veins drain into this vein. The central retinal vein sometimes drain directly into the cavernous sinus. The superior ophthalmic vein drains into the cavernous sinus approximately 2.8 mm above the inferior margin of the SOF. **Inferior ophthalmic vein;** drains the inferomedial side of the orbit and extends posteriorly within the extraocular muscle cone. It leaves the extraocular muscle cone by passing between the lateral and inferior rectus muscles. It communicates with the pterygoid venous plexus through a branch that passes through the inferior orbital fissure. It courses below the CTR and leaves the orbit by passing through the lower part of the SOF. It drains into the antero-inferior portion of the cavernous sinus. It often joins with the superior ophthalmic vein before draining into the cavernous sinus.

The sylvian veins drain into the cavernous sinus after coursing along the intracranial portion of the lateral border of the SOF. In cases where the SOF is surgically reached, these sylvian veins should also be considered [5,7].

The relationship between the SOF and dura mater

The dura mater surrounding the middle cranial fossa and cavernous sinus passes through the SOF and mixes with the orbital periosteum and CTR in the orbit [7]. Fukuda et al. [16] mentioned the importance of a dura mater that extends from the frontotemporal basal dura to the orbital periosteum and called "**meningo-orbital band**". It is located on the lateral edge of the upper part of the SOF and can be seen during the pterional craniotomy. This band prevents surgical access to deep structures during the pterional craniotomy. Fukuda et al. [16] advised cutting this band in patients planned for extradural anterior clinoidectomy. They performed the detachment of the meningo-orbital band in 4 stages: 1. Partial removal of the lateral wall of the SOF, 2. Incising the lateral periosteal dura of the SOF, 3. Detachment of the meningeal dura of the temporal lobe from the inner cavernous membrane, 4. Removal of the meningo-orbital band from the orbital periosteum. Testing the safety of meningo-orbital band detachment steps in future studies will be an important contribution to the surgical practice.

Radiological Anatomy of the Superior Orbital Fissure

The studies related with the SOF were done mostly on cadavers. Radiological studies examined SOF have often been performed on computed tomography (CT) images. La Marra et al. [17] examined the CT images of 84 patients aged 25-90 years in their

study. They measured the area of the SOF and the distance of the SOF from the substantia nigra. They found the SOF area 69.2 ± 15.8 mm2 in men and 56.8 ± 11.9 mm2 in women. They measured the distance of SOF from the substantia nigra as 38.4 ± 7.6 mm in men and 36.5 ± 6.1 mm in women. Park et al. [18] also analyzed CT images of 142 patients and measured the width of the SOF. They found the width of the SOF 3.79 ± 0.93 mm in men and 3.65 ± 1.26 mm in women. The radiological anatomy of SOF in normal and pathological conditions is still an under-studied subject in the literature. There is a need for more detailed studies related to SOF enriching with anatomic models and including pathological conditions.

CONCLUSION

The SOF is a complex cleft that gives passage the oculomotor, trochlear, ophthalmic, abducens nerves and orbital veins. The radiological anatomy of the SOF in normal and pathological conditions is still an under-studied subject in the literature. There is a need for more detailed studies related to SOF enriching with anatomic models and including pathological conditions. The 3D-PDF model of the SOF is an innovative tool to enhance the knowledge of the anatomical structures related with this region. Better understanding of this critical region is necessary to perform safe and successful surgical procedures.

Online Resource

The 3D-PDF model demonstrates the neurovascular contents passing through the superior orbital fissure and structures locating closely to the fissure. The 3D-PDF model allows for zoom, rotation, and selective visualization of the structures.

Available at: https://actamedica.org/index.php/actamedica/article/view/907/651

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Author contribution

Study conception and design: HAA, ŞH and İT; data collection: HAA, OT and İT; analysis and interpretation of results: HAA, ŞH and İT; draft manuscript preparation: HAA and İT. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

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ORIGINAL ARTICLE

Affective neuroscience personality differences between medical school students and engineering school students

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ABSTRACT

Objective: Medical and engineering faculty students both choose their majors from the field of science. But the educational process differs between the two majors. In this study we aimed to investigate the personality traits that might affect this preference. Affective Neuroscience Personality Scales (ANPS) could be particularly useful in studying the traits linked to the affective formation of the individual.

Materials and Methods: We prepared an online survey form collecting the sociodemographic and clinical data and the ANPS. We investigated the relationship between affective personality traits determined by the ANPS and the selection of the major. Also, we examined the affective personality traits that may influence the development of psychiatric illness in our sample.

Results: 219 medical students and 222 engineering students participated the study. Participants' ages ranged between 18 and 33 (Median=21; IQR=3). Among participants 60,5% were female, 34,7% has a psychiatric illness, 11,3 % had a chronic illness, and 16,8% has a family history of psychiatric illness. ANPS total and subscale scores weren't different between the groups. The SADNESS subscale scores were associated with the occurrence of the psychiatric illness.

Conclusion: The lack of difference between the two groups may indicate that affective personality profile is not a decisive factor in this choice. Our limitations are the small sample size, the lack of representation of our sample and the scarcity of data about other factors that might affect this preference. SADNESS was associated with psychiatric disorders in both groups.

Keywords: medical school, engineering, choice of major, personality.

INTRODUCTION

Choosing a major for university is a critical choice that will affect the whole life. Students may choose a university for many different reasons but being successful and happy in the department they have chosen is not only due to cognitive skills but also personality traits [1]. It has been documented that there are consistent personality differences between groups of students enrolled in different majors [1-10]. Most of the studies utilized the Big -Five inventory that is designed to measure the big five personality traits like extraversion, agreeableness, conscientiousness, neuroticism, and openness.

Being a medical student is a long and difficult process. A consistent finding revealed that 28% of doctors report clinically significant levels of stress [11]. Performance and patient care have been shown to be affected by high levels of stress [12]. The personality trait of a medical student

is an important predictor of long-term success and well-being [1,13]. It also has long-standing implications for postgraduate clinical performance [14]. In a longitudinal study comparing medical school students with other academic majors, medical school students were found to have the highest scores on extraversion and agreeableness [1]. Conscientiousness has emerged as the most prominent personality trait in medical school students that have been associated with academic success [1,14,15].

It has been reported that engineering students, similar to medical students, experience stress under heavy course load. Students feel academic pressure [16]. Engineering programs have high attrition rates. Conscientiousness was reported as a significant predictor of retention [17]. In a study with the big five scales, there was a relationship between academic performance and the personality traits of extraversion, openness, and conscientiousness. Also, the authors claimed that these results led to the characterization of students based on their personality traits and provided elements that may enhance the development of an effective personality that allows the students to successfully face their environment, playing an important role in the educational process [18].

The affective neuroscience theory developed by Jaak Panksepp is one of the most important theories in explaining the neurological substrates of basic affects [19-21]. In order to elaborate on the individual differences in personality in line with the affective neuroscience findings, the Affective Neuroscience Personality Scale (APNS) has been developed [22]. The ANPS assesses the subcortical basic affects; SEEKING, PLAY, CARE as the positive subscales and ANGER, SADNESS, FEAR as the negative subscales. The relationship of the ANPS and the Big Five Scales [23], also showed that ANPS is a valid tool [22,24]. It has been reported that high SEEKING correlates to Openness to Experience, high PLAY to Extraversion, low ANGER and high CARE to Agreeableness, and high FEAR, SADNESS, and ANGER to low Emotional Stability (high Neuroticism). Between subcortical affective systems measured by the ANPS and the cortical cognitive systems measured by the Big Five, support the suggestion that the basic subcortical affective systems need the cortical regions in their regulation [25].

In Turkey, both medical and engineering faculties enroll students via the same nationwide examination through ranking the science field score which derives from the same questions [26]. But the educational process differs between the two majors. In this study, we aimed to investigate the affective personality traits that might influence the choice between the medical school and engineering. We hypothesized that the ANPS, which is assumed to indicate the regulation of cortical structures through subcortical systems, could be particularly useful. We also aimed to investigate whether any personality trait creates resilience against psychiatric illness. We investigated the relationship between personality traits determined by the ANPS and the department selection of the students. In addition, we examined the personality traits that may influence the development of psychiatric illness.

MATERIALS AND METHODS

Study Design and Participants

An online survey comprising a sociodemographic form and the Affective Neuroscience Personality Scales (ANPS) was created via Google forms and shared through the email system of the XXX university, Ankara. We were able to reach out to a total of 1197 medical faculty students and 1718 engineering students (computer engineering, biomedical engineering, electrical and electronics engineering). 441 students completed the surveys. The survey link was shared between April 2021 and October 2021.

The ANPS assesses six basic affects (PLAY, SEEK, CARE, FEAR, ANGER, SADNESS) and "Spirituality" (Davis et al. 2003). The total questionnaire includes 110 items. Each subscale features 14 questions; 7 positively and 7 negatively formulated, whereas

only the Spirituality subscale comprises 12 questions; 6 positively and 6 negatively formulated. The scale had 14 filler items, some of which sought to evaluate deception (e.g., "I always tell the truth."). All the questions are designed to be answered on a four-point Likert scale. The Turkish validity and reliability of the scale were performed by Özkarar-Gradwohl et al. in 2014. The validity and reliability of the scale was previously carried out in university students aged between 18-25 (M=21.66 SD= 1.60). Cronbach's Alphas are .56 for SEEK, .72 for CARE, .70 for PLAY, .70 for FEAR, .73 for ANGER, .55 for SADNESS and .78 for Spirituality. Correlation analyses with the big five scales also showed structural validity [27]. Since the population of our study consisted of students, the same validity and reliability scores were accepted.

Statistical analyses

The data were analyzed using SPSS Statistics 24 (IBM, USA). The normality of data was evaluated by Kolmogorov-Smirnov (K-S) and Shapiro-Wilk tests. The student T-test was used for groups where continuous variables were normally distributed, and the Mann-Whitney U test was used for non-normally distributed groups. A Chi-square test was carried out to assess the differences between categorical variables. Correlation analyses were performed with Pearson or Spearman tests according to the data distribution. Logistic regression analysis was applied for the variables that were related. P values under 0.05 were accepted as statistically significant.

Ethical Approval

Informed consent was obtained from all participants electronically. Ethics committee approval was obtained from the Research Ethics Committee of Baskent University (Protocol No:KA 22/319 date: 05.07.2022).

RESULTS

Descriptive Features

A total of 441 participants completed the survey. 219 were medical school students. Participants' ages ranged between 18 and 33 (Median=21; IQR=3). Females' age (n=267) range between 18-32 (Median=21, IQR =3) and males' age (n=174) range 18-33 (Median=21, IQR=3). Among participants most of them (60,5%) were female, 34,7% has a psychiatric illness, 11,3 % had a chronic illness, and 16,8% has a family history of psychiatric illness.

The age distribution was similar between the groups (p=0,225). Females were significantly more frequent in medical students (p<0,001). While there was no significant difference between the two groups of students in terms of the frequency of chronic medical disease and a history of psychiatric disease, the frequency of psychiatric disease in the family was significantly higher in medical school students (p=0.58, p=0315, p=0.001, respectively). Demographic characteristics for each group are given in Table 1.

Table 1. Demographic Characteristics and ANPS scores of participants in each major

		Medical School Students	Engineering School Students		
		Median (IQR)/ N (%)		X^2/Z	P value
Age		21 (3)	21 (3)	-1,212	0,225
Gender (N(%))	Female	168 (76,7)	99 (44,6)	47,60	<0,001**
	Male	51 (23,3)	123 (55,4)		
Chronic illness (N(%))	Yes	23 (10,5)	27 (12,2)	0,3	0,58
	No	196 (89,5)	195 (87,8)		
Psychiatric illness (N(%))	Yes	81 (37)	72 (32,4)	1,009	0,315
	No	138 (63)	150 (67,6)		
Psychiatric illness in family (N(%))	Yes	50 (22,8)	24 (10,8)	11,40	0.001*
	No	169 (72,2)	198 (89,2)		

Note: Abbreviations: IQR: interquartile range, N: number , X^2: Chi square test, Z: Mann Whitney U test, *p<0,05,**P<0,001

Table 2. The ANPS subscales in medicine and engineering students

	Medical School Students	Engineering School Students		
	Median (IQR)		Z	P value
ANGER (Median(IQR))	25 (7)	25 (9)	-0,648	0,517
FEAR (Median(IQR))	26 (9)	24 (8,25)	-2,027	0,043
SEEK (Median(IQR))	26 (6)	25 (6)	-1,542	0,123
CARE (Median(IQR))	29 (7)	28 (8)	-2,283	0,017
PLAY (Median(IQR))	25 (6)	25 (7)	-0,963	0,336
SADNESS (Median(IQR))	22 (8)	21 (6)	-1,775	0,076
SPIRITUALITY (Median(IQR))	20 (7,25)	19 (8)	-1,842	0,065

Note: Abbreviations: IQR: interquartile range, Z: Mann Whitney U test, Bonferroni corrected p<0.0071

Table 3. Comparison of participants with and without psychiatric disorders in terms of ANPS subscales

	Psychiatric illness			
	Yes	No		
	Median (IQR)		Z	P value
ANGER	26 (9)	24 (7)	-2,544	0,011
FEAR	28 (7)	24 (8)	-6,143	<0.001**
SEEK	25 (6)	25 (6)	-0,838	0,402
CARE	28 (7)	28 (7)	-1,746	0,081
PLAY	24 (7,5)	25 (6)	-2,040	0,041
SADNESS	24 (7)	20 (6)	-6,741	<0.001**
SPIRITUALITY	19 (8,5)	20 (7)	-0,714	0,475

Note: Abbreviations: IQR: interquartile range, Z: Mann Whitney U, *Bonferroni corrected p<0.0071

Medicine and engineering students were compared for ANPS subscale scores. There remained no difference between the groups in ANPS subscales scores after Bonferroni correction (Table 2).

Factors associated with psychiatric disease in the students

We then wanted to investigate the factors associated with psychiatric disease in our sample. The frequency of psychiatric disease was not different between the student groups (Table 1), therefore we proceeded the analysis with the whole group. First, the participants were divided into two as those with and without psychiatric illness, and these two groups were compared in terms of ANPS subscales. FEAR, and SADNESS subscale scores were significantly higher in patients with psychiatric illness after the Bonferroni correction (Table 3).

Then we built up a logistic regression model of factors associated with psychiatric illness using age, gender; FEAR and SADNESS subscales of the ANPS; and psychiatric illness in family as the independent variables. SADNESS and having a psychiatric illness in the family were significantly associated with the occurrence of a psychiatric disease (p<0.05; p<0.05) (Table 4).

Table 4. Logistic regression analysis for factors associated with psychiatric illness

Variable	95%CI	OR	P value
Age	0,833 to 1,002	0,912	0,056
Gender	0,542 to 1,324	0,847	0,467
FEAR	0,99 to 1,004	0,955	0,07
SADNESS	0,867 to 0,965	0,915	0,001*
Psychiatric illness in family	0,255 to 0,743	0.435	0,002*

Note: Dependent variable: psychiatric illness.

Abbreviations: CI: confidence interval, OR: odds ratio-adjusted, *p<0,05,**P<0,001

DISCUSSION

Affective personality traits were examined between medical and engineering students. According to the results of our study, the affective personality profiles did not differ between the students of these two majors.

In the Big-Five approach, compared with the other majors, medical students have the highest scores on extraversion and agreeableness [1]. CARE was found to be associated with "agreeableness" in studies comparing ANPS with the big five [19] For this reason, We hypothesized that CARE scores could be higher in our medical student sample, but the results were not compatible with this. This process may be due to the fact that the choice of profession in Turkey differs from those abroad. Planning new studies which consider cultural differences in the choice of profession may be valuable.

FEAR enables us to cope with sudden dangers by triggering the freeze or flight response by being affected by the defensive distance between the prey and the predator. Its main purpose is to protect us from danger [32,33]. Literature revealed that the medical education itself and the patients they encounter during their internship may have traumatizing stress effects on students [34-36]. However, in our study, there was no difference between engineering faculty and medical faculty in terms of FEAR. There may be different variables that the two departments feel threatened, or the resilience of medical faculty students in Turkey may be higher than in other countries. There is a need for a multicultural analysis of stress factors between departments.

FEAR, and SADNESS were different in participants with and without psychiatric illness. SADNESS was found to have a significant effect in logistic regression. Emotional stability or neuroticism in Big Five Model correspond to ANGER, FEAR, and SADNESS in ANPS. It is also well-known that neuroticism is a risk factor for psychiatric diseases, especially depression [19,37]. Montag (2017) reported that depressed patients exhibit higher scores on SADNESS [38]. In a following study, Fuchshuber investigated primary emotions predicting psychopathology and observed that SADNESS is related to substance abuse, depression, anxiety, and somatization. He also identified SADNESS as the major ANPS predictor of depression [39]. In our study, SADNESS also showed the strongest relationship with a psychological illness. Those with SADNESS personality trait may be considered as more prone to psychiatric disorders and may be prioritised for psychological support.

Although this is the first study that compares medical school students with engineering students in terms of ANPS, we had major limitations. First, there were limitations about our sample. Our sample was collected from one university and might not be generalizable even for Turkey. Also, the lack of differences in ANPS scores might be due to the limited sample size. We were only able to reach out to less than 20% of our target sample which left us with a significant within group heterogeneity. For example, the engineering group was composed of students participating from different engineering departments. Also even though we proposed that the entrance exam scores are similar, due to the heterogeneity of the group there might be significant differences which also may affect the variables investigated in this study. The gender distribution between the two groups is not equal, which affects the results in a study measuring personality traits. Second, factors associated with psychiatric diseases could have been detailed. Third, whether the students' personality traits are shaped in the beginning or through such education should also be investigated. Finally, profession-related variables such as financial expectations from the profession, professional prestige, job security, and opportunities abroad are also effective factors in career choice [40]. Unfortunately, we were not able to collect any data on these variables. In future studies, the effect of these factors on career choice together with personality traits should be examined.

CONCLUSION

In this study on the personality differences of students in the faculty of medicine and engineering, medical school students showed a similar APNS profile to engineering students. SADNESS was associated with psychiatric disorders in our sample.

Author contribution

Study conception and design: YHA, JH, SC; analysis and interpretation of results: SC,YHA, JH; draft manuscript preparation: YHA, SC. All authors reviewed the results and approved the final version of the manuscipt.

Ethical approval

The study was approved by the Clinical Research Ethics Committee of Baskent University (Protocol no. KA22/319).

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Conflict of interest

The authors declare that there is no conflict of interest.

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acta medica

ORIGINAL ARTICLE

Gartland Type III Supracondylar humerus fractures in children: Impact of fracture level on outcomes

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ABSTRACT

Objective: Functional limitation or radiological failure after the treatment may rarely be seen after the surgical treatment of Gartland type 3 supracondylar humerus fractures (SCHF). The present study aims to investigate whether the level of fracture relative to the isthmus of the humerus affects the outcomes.

Materials and Methods: Children who underwent closed reduction and percutaneous pinning (CRPP) due to Gartland typle III SCHFs between 2010 and 2017 were investigated. There were 108 elbows treated with a mean age of 6.1 years (range, 1.4 to 11.2 yrs.). The radiological (Carrying Angle, Baumann Angle, Humerocapitellar Angle), clinical (Flynn grade with elbow range of motion) and complications were used to evaluate outcomes including fracture level. A reference line connecting medial epicondyle, olecranon fossa and lateral epicondyle was drawn on Anteroposterior (AP) and lateral x-rays. The level of the fracture line was decided based on the reference line. Low fractures included the fractures below or involving the reference line, whereas high fractures included those above the reference line.

Results: There were 80 High and 28 Low fractures according to A reference line connecting medial epicondyle, olecranon fossa and lateral epicondyle and passing through the isthmus. Fractures below the humeral isthmus had significantly low Flynn grade (p:0.049) at the latest follow-up of 2.1 years (range, 1 to 5.1 yrs.). There was no statistically significant difference regarding postoperative sixth week Baumann`s angle, carrying angle and humerocapitallar angle between low and high fracture groups.

Conclusions: The present study demonstrates the importance of fracture analysis. Surgeons may consider more stable pin configuration in the low type fractures and future research should aim to analyze the SCHF in terms of fracture morphology.

Keywords: Supracondylar Humerus Fracture, Fracture Morphology, Pediatric Fracture.

INTRODUCTION

Supracondylar humerus fractures (SCHF) in pediatric population are injuries commonly encountered in orthopedic surgery. SCHF accounts for 16% of all pediatric fractures and 60% of all pediatric elbow fractures (1). The injury occurs most commonly in children between 5 and 7 years of age on the non-dominant side as a result of a fall into outstretched hand with the elbow fully extended, causing an extension-type supracondylar fracture (2, 3). Despite the high frequency of SCHF in children, there are no consensus guidelines today. The choice of treatment modality and fixation, patient positioning, timing of surgery, hardware removal, postoperative immobilization, clinical and radiographic follow-up and the need for postoperative physical therapy (PT) are often left to the individual surgeon (4, 5). The treatment of SCHFs can be challenging even for the experienced surgeon, and the complication rate for this type of injury is not negligible (6).

SCHFs are classified by Gartland`s classification system based on the intact periosteum and direction of the displaced distal fragment. Most of the Gartland type III fractures are treated surgically with closed reduction and percutaneous fixation (CRPP) and has been shown to improve outcomes (7). Many studies report satisfactory clinical outcomes after SCHF in children (7, 8). Although elbow stiffness is less common in pediatric population, some surgically treated patients, gain elbow range of motion (ROM) slowly or even with a deficit which might be concerning for the parents and the surgeon (9, 10). Some studies reported that age of the patient and the severity of the fracture have prognostic value in predicting the final ROM of the elbow (10, 11). Vascular and neurologic status of the extremity also plays an important role in surgical decision making. Fracture characteristics like medial column disruption and sagittal orientation was shown to influence outcomes (12). Thus, a more detailed subclassification system is needed to study the prognostic indicators of clinical outcomes (12, 13).

The importance of understanding the fracture level lies in its potential implications on the biomechanical stability of the fixation. Different fracture levels in the coronal plane could lead to varying degrees of displacement and instability, which may significantly influence the overall clinical outcomes in patients with SCHF.

The present study aims to determine whether level of the fracture line in coronal plane affects functional and radiological outcomes following surgical treatment of Gartland-type III SCHF

MATERIALS AND METHOD

After obtaining the institutional review board's approval (GO 23/44), a retrospective review of the medical records of patients who underwent surgical treatment between the years of 2010 and 2017 for extension type III SCHF using the Gartland classification was performed. Patients with Gartland type I or II SCHF, T-condylar fractures, patients who had less than twelve months follow-up, fractures involving both high and low area or who underwent open reduction were excluded. A total of 108 patients included to the study.

All fractures were stabilized with k-wires following closed reduction. two divergent k-wires were placed laterally and a third k-wire was placed medially depending on the intraoperative stability assessment. The wires were cut, bent and remained over the skin. The elbow joint was immobilized in a long arm splint in neutral position. Patients were routinely monitored and radiographs were obtained postoperatively at 1st, 2nd, 4th, 6th, 8th, 12th weeks than annually. The K-wires were removed when the callus appeared or fracture line blurred usually around third or fourth weeks in outpatient setting. Appropriate fracture healing was determined by the presence of visible fracture callus adjacent to the cortices on both frontal and lateral views. After wire removal no patients received routine physical therapy. However, patients were encouraged active and passive movement of the elbow and strenuous activities were restricted for and additional month

A reference line connecting medial epicondyle, olecranon fossa and lateral epicondyle was drawn on Anteroposterior (AP) and lateral x-rays (Figure 1). The level of the fracture line was decided based on the reference line. Low fractures included the fractures below or involving the reference line, whereas high fractures included those above the

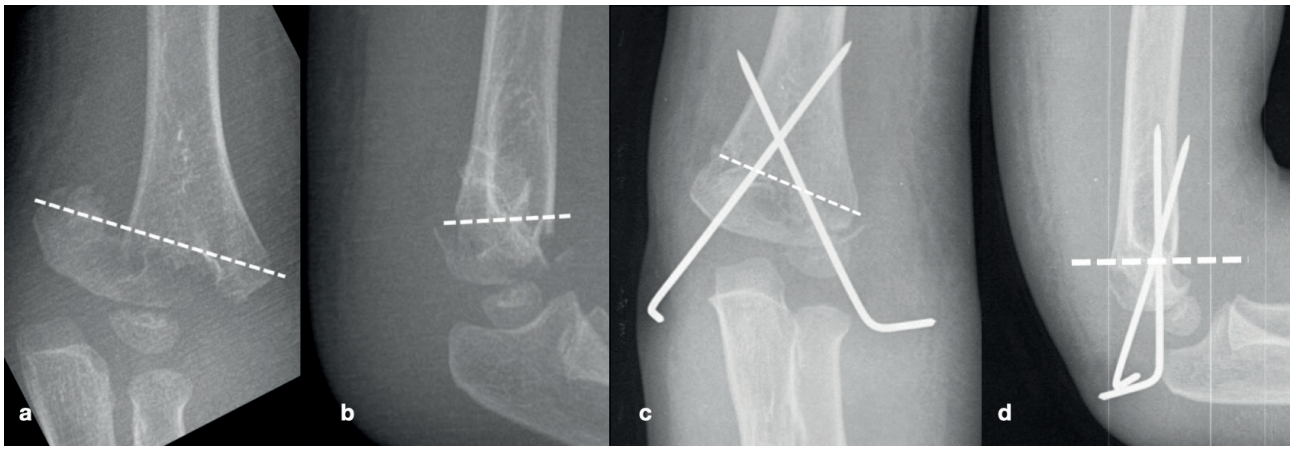

Figure 1. a) Anteroposterior (AP) and b) lateral elbow radiographs demonstrating 3 years old girl with low fracture. c) AP and d) lateral radiograph after K wire fixation with 1 medial 1 lateral pin construct.

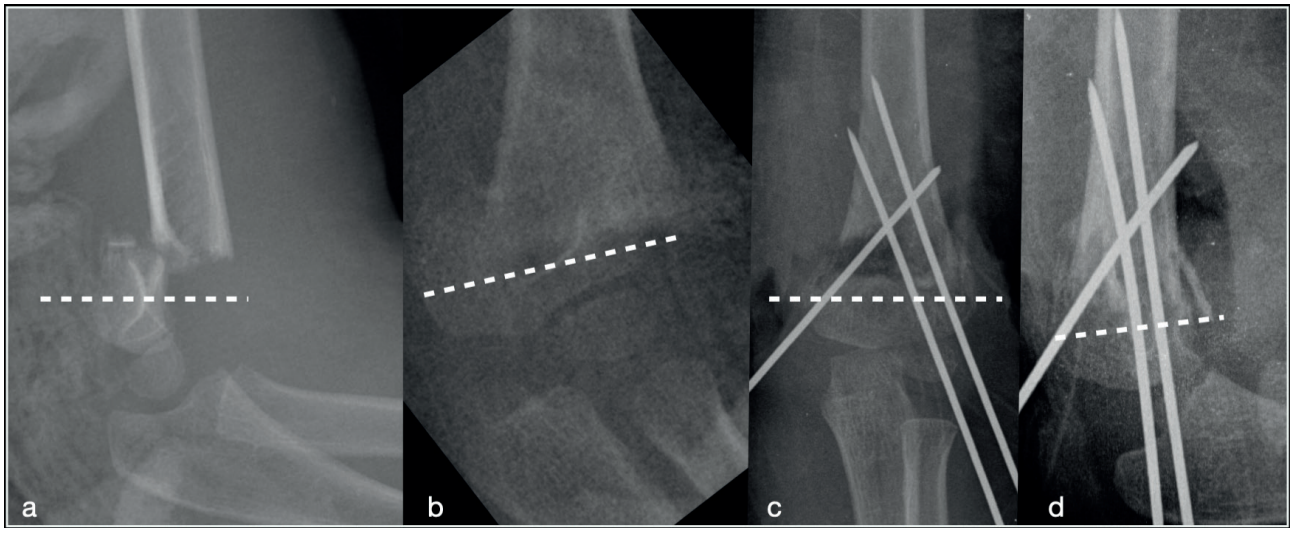

Figure 2. a) Anteroposterior (AP) and b) lateral elbow radiographs demonstrating 5 years old boy with high fracture. c) AP and d) lateral radiograph after K wire fixation.

reference line (Figure 2). Assessments were made on both pre- and intra-operative radiographs to avoid fracture imposition by experienced orthopedic surgeon (S.K).

Age at surgery, gender, level of fracture, pin removal day, loss of reduction and postoperative complications were recorded. The Baumann`s angle, carrying angle and humerocapitellar angle were also measured at the sixth post-operative week (14). Clinical outcomes were recorded based on the modified Flynn`s grading at the latest follow-up (15). Elbows were classified according to Flynn's grades, considering the worst cosmetic/functional outcome (fair or poor) and the best cosmetic/functional outcome (excellent or good)." (Table 1). Postoperative progress notes were evaluated to assess neurovascular status or presence of compartment syndrome.

Table 1. Flynn's criteria

	Functional (Loss of movement (°)	Cosmetic (Loss of carrying angle (°)
Outcomes Satisfactory		
Excellent	0 to 5	0 to 5
Good	6 to 10	6 to 10
Unsatisfactory		
Fair	11 to 15	11 to 15
Poor	>15	>15

The data obtained in the research were analyzed using the SPSS (Statistical Package for Social Sciences) for Windows 22.0 program. Number, percentage, mean and standard deviation were used as descriptive statistical methods in the evaluation of the data. Differences between the ratios of categorical variables in independent

groups were analyzed with Chi-square and Fisher's exact tests. The t-test was used to compare quantitative continuous data between two independent groups. Dependent groups t-test was used to compare within-group measurements.

RESULTS

There were 28 low and 80 high fractures in the cohort. There were 55 males and 53 girls with a mean age of 6.12 (range, 1.4 to 11.2 yrs.). The mean follow-up duration was 2.1 years (range, 1 to 5.1 yrs.). The demographics of the groups were demonstrated in table 2. Eight patients had preoperative nerve palsy (5 radial, 3 Anterior interosseous nerve). There were only 5 complications (%4.62); 3 patients with superficial infection at the pin site, one case with loss of reduction and one case with postoperative anterior interosseous nerve palsy. The patient with loss of reduction had a low type fracture and underwent revision surgery after the first visit (7th days). All the infection with pin site resolved a week after pin removal and anterior interosseous nerve palsy resolved by the twelve post-operative weeks.

In our cohort, Flynn's criteria were used to evaluate both cosmetic and functional results. After 2.1 years of follow-up, 73 (%67.6) of the patients had excellent and 26 (%24.1) patients had good results. 9 patients (%8,3) had unsatisfactory (poor/fair) results due to limited range of motion of the elbow joint. None of the patients had cubitus varus or valgus deformity. There was a significant difference according to Flynn's criteria (satisfactory and unsatisfactory elbows) between low and high fracture groups (p: 0.049). Seven peripheral nerve injury (%) (5 radial, 3 Anterior interosseous) which were observed in the first admission preoperatively resolved spontaneously after an average of 14 weeks (range, 7 to 24 weeks). There was no statistically significant difference regarding postoperative sixth week Baumann`s angle, carrying angle and humerocapitallar angle between low and high fracture groups (Table 3).

DISCUSSION

Most of the patients with type III SCHF treated with closed reduction and percutaneous pinning shows good to excellent outcome. However, there is still poor outcome in selected patients (8, 16). There are many doubts about the Gartland classification predicting the optimal fracture configuration and the clinical outcomes. (17, 18). Therefore, many studies were performed to reveal new classification systems or anatomical analyzes of SCHF. Previously Bahk et al. evaluated 203 children with SCHF and mentioned that the anatomical properties of the fracture may play an effective role in surgical decision making. They stated that more oblique fractures in both coronal and sagittal plane are more prone to comminution, rotational malunion and additional injuries. In our cohort there were no significant difference in terms of complications between low and high fractures. However, future studies with more detailed anatomical

Table 2. Demographics of the patients

	Low Fractures	High Fractures	P value
Number of Patients	28	80	p=0,068
Age			
<5 years	10	26	p=0,464
≥5 years	18	54	
Gender			
Male	16	39	p=0,293
Female	12	41	
Side			
Right	14	27	p=0,098
Left	14	53	
Preoperative Nerve Palsy			
Radial	1	4	p=0,547
Medial	2	1	
Ulnar	0	0	

Table 3. Outcomes and complications

	Low Fractures	High Fractures	Total	p value
Postoperative (4th week)				
Carrying Angle (°)	10.4 (range, 4-19)	10.4 (range, 4-19)		
Baumann Angle (°)	71 (range, 58-79)	71 (range, 58-79)		p=0,692
Humerocapitellar Angle (°)	38 (range, 12-63)	38 (range, 12-63)		
Flynn's Grade				
Satisfactory	76 (%95)	76 (%95)		**p=0,049**
Unsatisfactory	4 (%5)	4 (%5)		
Flynn's Grade				
Excellent (%)	56 (%70)	56 (%70)	73 (%67,6)	
Good (%)	20 (%25)	20 (%25)	26 (%24,1)	p=0,189
Fair (%)	3 (%3,8)	3 (%3,8)	6 (%5,6)	
Poor (%)	1 (%1,2)	1 (%1,2)	3 (%2,8)	
Complications				
Nerve palsy	1	1	1	
Compartment Syndrome	0	0	0	p=0,481
Loss of reduction	2	2	4	
Infection	1	1	3	

subclassification should be conducted to reveal the effect of the fracture biomechanics (17)

In our study, radiological measurement was calculated at the sixth post-operative week to evaluate the quality of the surgical reduction and the Flynn`s grade was obtained at the latest follow-up routine visits. There was a significant difference in favor of high fractures compared to the low fractures between Flynn grades in the short-term follow-up. The most likely explanation is the reduction of the small distal fragment in the low fractures increase instability which makes anatomical reduction more challenging. Moreover, the small distal fragment might be thought to increase the risk of instability and cause loss of reduction. We believe that; presence of a small distal fragment also contributes to the fixation's dynamic instability, posing a higher risk of reduction loss specifically within the low fracture type group. However, we had only one loss of reduction in our cohort but, slight rotational deformity especially in older children may affect the outcomes. Thus, more stable fixation methods may be considered in high or low fracture subtypes to improve outcomes. Additionally, low fractures can be considered as intracapsular fractures and more prone to cause joint stiffness since the surrounding soft tissues are prone to be injured (19). Yet, still the remodeling capacity of the growing child causes mostly final good to excellent outcomes in both low and high SCHF after a year. Previously Kang et al. studied 230 children with Gartland type III supracondylar humeral fracture and reported that low fracture types were significantly seen in children above ten years old. They stated that the increase in the low fracture frequency with age may be related to the ossification stage or higher energy injuries (18). In our study, relationship between high or low fracture type and age during the fracture was also investigated but no significant difference was seen according to the age cut off 5 years.

There are some limitations of the present study; First, it is a retrospective cohort study. Second, the surgeries were performed by different surgeons. Thus, a couple pinning techniques were utilized during surgical fixation. However, in our study all fractures stability were confirmed under fluoroscopy

In conclusion, subclassification of the SCHF according to the anatomical properties of the fracture may be beneficial for the preoperative planning and identifying the patients and parents excepted outcomes. Moreover, surgeons may be aware of the difficulty in low fractures and may want to struct a more stable pin configuration. However, long term prognosis of low type SCHF is comparable with the high type fractures. Future studies on biomechanics of the SCHF subclassification should be verified.

Author contribution

All authors contributed to the study conception and design. Surgical treatment of the patients was performed by SK, SB and CA. Data collection and analysis were performed by UK, AE, SB, and MP. The first draft of the manuscript was written by SB, MP and UK; and MT, CA and SK participated in the reviewing and editing of the manuscript before submission.

Ethical approval

Ethical approval for this study was obtained from the Hacettepe University Faculty of Medicine local ethics committee (GO 23/44, 24.01.2023).

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Conflict of interest

The authors declare that there is no conflict of interest.

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acta medica

ORIGINAL ARTICLE

Evaluating the modified NUTRIC score as a prognostic tool in the intensive care unit for COVID-19 patients

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ABSTRACT

Objective: The modified NUTRIC Score (mNUTRIC) score is a screening test designed for evaluating patients in intensive care units. In this study, our aim is to assess the ability of this test to predict mortality, length of hospital stay, and the need for mechanical ventilation in COVID-19 patients in the intensive care units.

Materials and Methods: In our retrospective study, we evaluated 67 patients admitted to our COVID-19 intensive care unit between October and November 2020. We analyzed their entry scores and conducted general follow-up assessments.

Results: In our study, we found that mortality assessment revealed a significant association between older age ($p<0.001$), the need for mechanical ventilation ($p=0.001$), and the presence of dysphagia ($p<0.001$) in patients who did not survive.

Statistically significant findings indicate that patients classified as having high mNUTRIC scores had higher rates of 28-day mortality, the need for mechanical ventilation, and the presence of dysphagia compared to those classified as having low nutritional scores. When patients with neurodegenerative diseases were evaluated as a separate group, no significant association was found between high nutritional scores and mortality, the need for mechanical ventilation, or length of hospital stay.

Conclusion: The evaluation of nutritional risk in patients being monitored in intensive care is an important step in patient management. The modified NUTRIC score is a preferable assessment test due to its ease of use.

Keywords: COVID-19, mNUTRIC Score, Critically ill, Intensive care, malnutrition, neurodegenerative diseases.

INTRODUCTION

The COVID-19 pandemic has had a significant impact on healthcare systems worldwide, particularly in the management of critically ill patients. In severe cases, COVID-19 can lead to acute respiratory distress syndrome (ARDS) and multiorgan dysfunction, necessitating intensive care unit (ICU) admission. Understanding the characteristics and clinical course of COVID-19 patients in the ICU is crucial for optimizing their care and improving outcomes [1, 2].

The Nutrition Risk in the Critically Ill (NUTRIC) score was developed to identify patients who are at higher nutritional risk and are likely to benefit from early and aggressive nutritional interventions. It incorporates several parameters that are associated with nutritional status and illness severity. The components of the NUTRIC score include age, severity of illness (as measured by the Acute Physiology and Chronic Health Evaluation II score (APACHE II), Sequential Organ Failure Assessment

Table 1. Evaluation of the modified NUTRIC score

Components	Scoring system			
	0	1	2	3
Age (years)	<50	50–75	≥75	
APACHE II *	<15	15–20	20–28	≥28
SOFA **	6	6–10	≥10	
Number of comorbidities	0–1	≥2		
Length of stay in hospital before admit-tance to ICU ***	<1 day	≥1 day		

Low mNUTRIC score 0-4 points, high mNUTRIC score 5-9 points.

* Acute Physiology and Chronic Health Evaluation II; ** Sequential Organ Function Assessment; *** Intensive Care Unit.

(SOFA), the presence of comorbidities, days of mechanical ventilation, and the presence of sepsis. Each parameter is assigned a specific score, and the sum of these scores determines the NUTRIC score for an individual patient. Higher NUTRIC scores indicate a greater risk of malnutrition and poorer clinical outcomes [3]. The modified nutric score is the IL-6 value subtracted from its original form. It was validated by Rahman et al. since IL-6 measurement is not possible in every intensive care unit and is an expensive examination, the modified NUTRIC score has been developed. According to this scoring system, 0-4 is defined as a low score and 5-9 as a high score [4] (Table 1).

The COVID-19 pandemic has posed significant challenges for healthcare systems worldwide, particularly in intensive care units (ICU) where critically ill patients require comprehensive care. Identifying prognostic tools that can aid in assessing disease severity and predicting outcomes is crucial for optimizing patient management. This article aims to explore the potential utility of the mNUTRIC score in the ICU setting specifically for COVID-19 patients.

MATERIALS AND METHODS

In our study, patients hospitalized in our covid intensive care unit during October and November 2020 were evaluated with their intensive care entry APACHE II, GCS, SOFA scores and general follow-up retrospectively. Approvel for this retrospective study granted by Ankara City Hospital, No. 1 Clinical Research Ethics Committee Presidency E. board-E1-21-1573 03/03/2021. Patients who died within 24 hours after ICU admission and who had negative PCR tests were excluded. A total of 67 patients were evaluated. All patients' PCR tests were positive, and 53 patients (79.1%) had covid pneumonia. Fifteen patients had neurodegenerative neurological diseases (%22.7), 10 patients had dementia and 5 patients had Parkinson's disease. Patients' age, gender, comorbid diseases, laboratory values, APACHE II, GCS, SOFA scores within the first 24 hours of admittance to ICU were obtained from hospital records.

Statistics

All statistical analyzes were performed using The Statistical Package for the Social Sciences (SPSS) 21.0 for Windows (SPSS, Inc.; Chicago, USA). Descriptive values are stated as number (n) and percentage (%) for categorical values, mean (standard deviation,SD) for numeric values if they are normally distributed, and median (interquartile range,IQR or minimum-maximum) if not normally distributed. Pearson chi-square and Fisher tests were used to comparing categorical variables. Whether the continuous variables fit the normal distribution was evaluated with Kolmogorov-Smirnov and Shapiro-Wilk tests. Parametric tests for numerical variables with a normal distribution (paired sample t-test and t-test in independent groups), and for numerical variables that do not fit the normal distribution, comparisons were made using Mann-Whitney U test. The relationship between the variables was evaluated with Spearman and Pearson correlation tests. The statistical significance level was accepted as $p<0.05$ in all comparisons.

RESULTS

A total of 67 critically ill COVID-19 patients were included. The mean age of the patients was 71.7 (standard deviation, SD=10.74). Out of the total 67 patients involved in the study, 31 individuals

(46.3%) were female, while the remaining 36 (53.7%) were male. Other systemic disease was present in 83.6% (n=56) of the patient. The most common comorbid diseases are hypertension 50.7% (n=34), diabetes mellitus (DM) 41.8% (n=28) and neurodegenerative diseases 22.8% (n=15). Among the patients with neurodegenerative disease, 10 were diagnosed with intermediate-stage Alzheimer's disease, and 5 were diagnosed with intermediate-stage Parkinson's disease. The median value of the length of stay in the intensive care unit is 11 days (IQR= 5-21), and 58.2% (n=39) of the patients were connected to mechanical ventilator (MV).

During the assessment of 28- day mortality, it was observed that out of 67 patients, 41 (61.2%) were exitus. A comparison of the patients revealed significant findings related to mortality. It was noted that patients with exitus were older (p<0.001), required mechanical ventilation (p=0.001), and had dysphagia (p<0.001). Moreover, patients with exitus displayed elevated levels of various laboratory parameters, including white blood cell count (p=0.034), C-reactive protein (p=0.001), procalcitonin (p=0.001), interleukin-6 (p=0.001), blood urea nitrogen (p=0.021), and creatinine (p=0.022). Conversely, levels of hemoglobin (p=0.010), platelets (p=0.005), total

Table 2. Mortality Variables

Patient variables	Survival	Non survival	P value
Age*	65.8 (13.3)	75.2 (8.6)	**<0.001**
Sex			
Female	12 (46.2)	19 (46.3)	0.99
Male	14 (53.8)	22 (53.7)	
Pneumonia			
Yes	22 (85.6)	31 (75.6)	0.38
None	4 (15.4)	10 (24.4)	
Dysphagia			
Yes	11 (42.3)	36 (91.2)	**<0.001**
None	15 (57.7)	5 (8.8	
Comorbid Diseases			
Yes	22 (84.6)	34 (82.9)	0.86
None	4 (15.4)	7 (17.1)	
Mechanical Ventilator			
Yes	8 (30.8)	31 (75.6)	**0.001**
None	18 (69.2)	10 (24.4)	
Hemoglobin *	11.9 (2.7)	10.4 (2.1)	**0.010**
Hematocrit *	37.4 (7.8)	33.9 (6.5)	0.058
MCV*	90.2 (8.2)	92.5 (7.3)	0.32
White blood cell**	9.3 (7.9-14.8)	13.7 (9.6-15.5)	**0.034**
Lymphocyte **	0.8 (0.6-1.3)	0.6 (0.4-1.2)	0.16
Platelet count**	245.500 (199.750-340.500)	172.000 (116.500-262.500)	**0.005**
CRP**	0.029 (0.01-0.07)	0.08 (0.035-0.17)	**0.001**
Procalcitonin **	0.15 (0.05-0.42)	0.9 (0.12-3.4)	**0.001**
IL- 6**	17.9 (7.3-39.8)	57.4 (22.4-204.8)	**0.001**
Ferritin**	434 (151.8-962)	841 (346.5-1355)	0.089
Total protein*	53.5 (8.6)	47.8 (7.2)	**0.006**
Albumine*	29.8 (6.9)	25.7 (5.8)	**0.018**
BUN**	57.5 (31.8-103.8)	94 (60-140)	**0.021**
Creatinine**	0.80 (0.58-0.99)	1.25 (0.7-2.1)	**0.022**
Length of stay**	10 (4.8-20)	11 (5.5-22.5)	0.50

* MEAN (standard deviation); ** MEDIAN (IQR).

protein (p=0.019), and albumin (p=0.018) were found to be low (Table 2). The median APACHE II score of patients with exitus was 15 (interquartile range [IQR] 11-23), the median SOFA score was 6 (IQR 4-9.25), and the median GCS score was 15 (IQR 10.75-15) (Table 3).

A total of 67 patients were included in the study. Out of these patients, 62.7% (n=42) had low mNUTRIC scores, ranging from 0 to 4, while 37.3% (n=25) had high mNUTRIC scores, ranging from 5 to 9. The median mNUTRIC score was 4 (IQR: 3-6, min-max: 1-9). The mean age of patients with high mNUTRIC scores was 77.7 years and those with low scores were 68.1. Advanced age was statistically significant in terms of the mNUTRIC score (p<0.001). The median mNUTRIC score was calculated as 6 (IQR=3-7) in patients with dysphagia, and the median mNUTRIC score was 3 (IQR=2-4) in patients without dysphagia. The mNUTRIC score was significantly higher in patients with dysphagia (p<0.001). Median mNUTRIC score was calculated as 6 (IQR=3-7) in patients with MV, and median mNUTRIC score was calculated as 3 (IQR=2-4) in patients without MV. The mNUTRIC score was significantly higher in patients with MV (p<0.001). Patients evaluated in terms of 28-day mortality, mortality was observed in 50% of patients with a low mNUTRIC score (0-4), while mortality was observed in 80% of patients with a high mNUTRIC score (5-9). Mortality was significantly higher in patients with a high mNUTRIC score (p=0.015). When laboratory results were evaluated, a significant correlation was found between low hemoglobin (p =0.001), hematocrit (p=0.003), white blood cell count (p=0.014) and high nutric score. In addition, a significant correlation was found between high blood urine nitrogen (p<0.001), creatinine (p= 0.004), procalcitonin (p= 0.002) and IL-6 levels (p=0.008) and high mNUTRIC score. Total protein (p= 0.006) and albumin levels (p= 0.003) were found to be significantly lower in patients with high nutric scores (Table 4).

DISCUSSION

The assessment of nutritional status is becoming increasingly crucial for monitoring patients in the intensive care unit and predicting the progression of their disease. The most recent guideline published by the European Society for Clinical Nutrition and Metabolism (ESPEN) thoroughly examined and emphasized the evaluation of diverse assessment tools employed to assess the malnutrition status of patients [5]. Notably, the guideline highlighted the absence of a universally recognized gold standard in this regard. Furthermore, the guidelines provided by the American Society for Parenteral and Enteral Nutrition (ASPEN) and the Society for Critical Care Medicine (SCCM) emphasized the significance of utilizing specific nutritional screening tools, namely the Nutrition Risk Screening 2002 (NRS2002) and NUTRIC scores, for critically ill patients [6, 7]. Although assessments such as the malnutrition universal screening tool (MUST) and NRS2002 play a crucial role in evaluating nutritional status, their practical application is limited due to the absence of comprehensive nutritional history prior to admission to the intensive care unit and the challenges associated with monitoring weight and measuring muscle volume in these patients [8]. In light of these limitations, the mNUTRIC risk assessment tool emerges as a valuable alternative due to its user-friendly nature and ease of implementation.

According to Rahman et al. patients with a mNUTRIC score of 5 or higher were defined as high scores. Studies have shown that patients with high scores in intensive care follow-up have a worse clinical course and need more effective nutrition regulation [4].

Our study included 67 critically ill patients diagnosed with COVID-19. Among them, 62.7% (n=42) had low nutric scores ranging from 0 to 4, while 37.3% (n=25) exhibited high nutric scores ranging from 5 to 9. Notably, patients with higher Nutric scores were found to be older, had dysphagia, and had a higher likelihood of requiring mechanical ventilation. Furthermore, these patients had a significantly higher mortality rate compared to those with lower nutric scores.

The investigation conducted by Li et al. supported our findings, revealing a significant increase in the mortality rate among COVID-19 patients with high mNUTRIC scores (p<0.001) [9]. Similarly, the study conducted by Zhang et al. demonstrated a strong statistical correlation between a high mNUTRIC score, advanced age, and mortality [10]. Additionally, the research conducted by Osuna Padilla et al., which involved 112 COVID-19 patients requiring mechanical ventilators, showed a significant increase in the mortality rate (p=0.03)

Table 3. APACHE II, SOFA, and GCS Scores And Mortality Rates

Score	Survivals (n=26)	Non-survivals (n=41)	P value
APACHE II score, median (IQR) *	11.5 (8.5-15.8)	15 (11-23)	0.032
SOFA score, median (IQR) **	2 (2-6)	6 (4-10)	<0.001
GCS score, median (IQR) ***	15 (14.8-15)	15 (11-15)	0.093

IQR: interquartile range.

* Acute Physiology and Chronic Health Evaluation II; ** Sequential Organ Function Assessment; *** Glasgow Coma Scale.

Table 4. General Characteristics Of Patients With Low And High mNUTRIC Scores

Patient variables	Low mNUTRIC Score (0-4)	High mNUTRIC Score (5-9)	P value
Age*	68.1 (10.3)	77.7 (8.7)	<0.001
Sex			
Female	19 (45.2)	12 (48)	0.83
Male	23 (54.8)	13 (52)	
Neurological Disease			
Yes	10 (24.4)	5 (20)	0.68
None	31 (75.6)	20 (80)	
Comorbid Diseases			
Yes	32 (76.2)	24 (96)	0.034
None	10 (23.8)	1 (4)	
Dysphagia			
Yes	23 (54.8)	24 (96)	<0.001
None	19 (45.2)	1 (4)	
Mechanical Ventilator			
Yes	18 (42.9)	21 (84)	0.001
None	24 (57.1)	4 (16)	
Nutrition			
Oral	25 (59.5)	3 (12)	<0.001
NG	17 (40.5)	21 (84)	
Hemoglobin *	11.8 (2.5)	9.7 (1.8)	0.001
Hematocrit *	37.3 (7.2)	31.7 (5.7)	0.003
White Blood Cell**	10.3 (8.2-14.3)	14.1 (9.4-18.9)	0.014
Lymphocyte **	0.7 (0.4-1.1)	1.1 (0.4-1.5)	0.23
Platelet count **	242.500 (161.000-340.000)	162.000 (114.500-218.000)	0.001
CRP**	0.04 (0.02-0.11)	0.08 (0.03-0.16)	0.14
Procalcitonin **	0.15 (0.07-0.65)	1.3 (0.25-2.34)	0.002
IL-6**	22.4 (8.6-67.3)	67.2 (23-278)	0.008
Total protein*	52.4 (8.2)	46.2 (6.8)	0.006
Albumine*	29 (6)	24.4 (6.4)	0.003
BUN**	64 (35.7-94.3)	124 (65-195)	<0.001
Creatinine **	0.8 (0.6-1.3)	1.4 (0.8-2.7)	0.004
Length of stay**	11.5 (5-21)	9 (4-29)	0.77
28- day mortality			
Ex	21(50)	20 (80)	0.015
None	21(50)	5 (20)	

* MEAN (standard deviation); ** MEDIAN (IQR).

[11]. These collective findings underline the crucial role of the mNUTRIC score as a reliable prognostic indicator for critically ill COVID-19 patients [12, 13].

In our study, when examining the correlation between the requirement for mechanical ventilation and a high mNUTRIC score, it was observed that patients with elevated scores had a greater need for mechanical ventilation. This observation may be attributed to the fact that 79% of the patients included in our study were diagnosed with COVID-19 pneumonia, which potentially necessitated an increased reliance on mechanical ventilators (p=0.001). Furthermore, Özbilgin et al. conducted a study that also highlighted the association between the incidence of pneumonia and a high mNUTRIC score [14].

The incidence of neurological disorders appears to be on the rise in individuals affected by COVID-19 infection. Consequently, the neurological assessment holds significant importance in the monitoring of patients in COVID-19 intensive care settings [15, 16]. In our study, a total of 15 patients (22.8%; n=15) presented with neurodegenerative diseases. Among these patients, 10 were diagnosed with intermediate-stage Alzheimer's disease, while 5 were diagnosed with intermediate-stage Parkinson's disease. Given the heightened risk of nutritional deficiencies in patients with a history of neurodegenerative disorders, we employed the mNUTRIC score to assess these individuals. However, we did not observe a significant association between a high mNUTRIC score and 28-day mortality, hospital length of stay, or the need for mechanical ventilation in this particular patient subgroup (Table 5). Notably, a literature review highlighted a correlation between a high nutric score and 28-day mortality in the neurology intensive care unit [10]. However, limited literature exists on the application of the nutric score in the context of neurodegenerative diseases. Therefore, we propose that prospective studies be conducted to provide further insights into this area of research.

When comparing the findings from the study by Kucuk et al. and our own study, both studies demonstrated significant associations between various laboratory markers and high mNUTRIC scores in critically ill patients. The consistent findings of elevated inflammatory markers (such as IL-6 and procalcitonin) and impaired nutritional markers (such as albumin) in patients with high mNUTRIC scores across different studies highlight the importance of these biomarkers in assessing the nutritional status and disease severity of critically ill patients. These findings provide valuable insights into the potential use of these markers in risk stratification and clinical management in the context of critical care [17].

In our study, when evaluating the length of stay, no statistically significant correlation was found between high mNUTRIC scores. In the literature, studies conducted in non-COVID intensive care units have demonstrated a positive linear relationship between high mNUTRIC scores and length of stay, whereas in COVID intensive care units, it has been observed to be inversely proportional [18]. This suggests that higher mNUTRIC scores may be associated with shorter lengths of stay. This may be due to the high mortality rate of infections due to COVID-19. These contrasting findings emphasize the importance of further research to understand the factors influencing the length of stay in COVID-19 patients [17, 19, 20].

Our study's primary limitation is the small sample size, potentially impacting the generalizability of our findings. Nonetheless, the dedicated follow-up by a specialized team during the challenging pandemic period strengthens our research. Another constraint is the absence of alternative nutritional assessment tests. Our study significantly

Table 5. Evaluation of patients with neurodegenerative diseases

Patient	Low mNUTRIC (0-4)	High mNUTRIC (5-9)	p value
Lenght of stay, median (IQR)	20.5 (8.8-30.5)	14 (6.5-23)	0.36
Mechanical Ventilator, n(%)			
Yes	3 (30)	3 (60)	0.33
None	7 (70)	2 (40)	
Mortality, n (%)			
Survival	6 (60)	1 (20)	0.28
Ex	4 (40)	4 (80)	

contributes to the literature by demonstrating the efficacy of the mNUTRIC score and guiding future evaluations with larger patient cohorts. However, the limited sample size may compromise statistical power and general applicability, while reliance on a fixed team introduces potential bias. To enhance validity, future research should include larger samples and a broader range of nutritional assessment tools.

CONCLUSION

The mNUTRIC score serves as a valuable assessment tool in predicting 28-day mortality and the need for mechanical ventilation in critically ill patients, particularly when anthropometric measurements are not feasible. Consequently, conducting studies with larger patient cohorts would be more suitable for evaluating neurodegenerative diseases. This approach can help overcome limitations associated with smaller sample sizes and enhance the generalizability and reliability of findings. However, it is important to acknowledge potential biases that may arise from variations in patient characteristics and treatment protocols across different study settings. Future research should aim to address these limitations and provide more robust evidence on the utility of the mNUTRIC score in neurodegenerative disease evaluation.

Author contribution

Study conception and design: GTG and HB; data collection: GTG and NKŞ; analysis and interpretation of results: GTG and YH; draft manuscript preparation: GTG, NKŞ, LY and HB. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Ankara City Hospital, Clinical Research Ethics Committee No. 1 (Protocol no. E1-21-1573).

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Conflict of interest

The authors declare that there is no conflict of interest.

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acta medica

ORIGINAL ARTICLE

Transarterial embolization for delayed bleeding after percutaneous nephrolithotomy

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ABSTRACT

Objectives: The study aimed to evaluate the effectiveness and reliability of transarterial embolization (TAE) in managing delayed bleeding after percutaneous nephrolithotomy (PNL).

Materials and Methods: Patients presenting to our hospital's emergency department with hematuria following PNL and treated with TAE were included in the retrospective analysis. Demographic, clinical, and radiological data were collected. Technical and clinical success rates of TAE were calculated. The impact of the embolization procedure on kidney function was determined using angiographic images, and pre- and post-procedure serum creatinine levels.

Results: A total of 13 patients included in the study presented with intermittent visible hematuria. The average interval between hematuria onset and PNL was 11.92±7.27 days. No hemodynamic instability was observed in any patient. CT angiography identified vascular pathology in 11 patients (84.6%), who subsequently underwent renal angiography for TAE without conservative treatment. Pseudoaneurysms were found in 7 patients (63.6%), and both pseudoaneurysms and arteriovenous fistulae in 4 patients (36.4%). Technical success was achieved in all embolization procedures. Hematuria resolved in all patients during follow up with a clinical success rate of 100%. Renal parenchymal loss after embolization was <%10 in 8 patients (72.7%), %11-24 in 2 patients (18.2%), and %25-50 in 1 patient (7.7%). There was no significant difference in serum creatinine levels before (mean 1.09±0.53 mg/dl) and after (mean 1.06±0.71 mg/dl) TAE (p=0.5). No major procedure related complications were observed.

Conclusions: TAE is an effective and safe method for the treatment of delayed bleeding following PNL. CT angiography facilitates diagnosis and treatment planning for patients with hematuria after discharge. Early TAE for patients with identified vascular pathology can increase technical and clinical success rates.

Keywords: Percutaneous nephrolithotomy, delayed bleeding, hematuria, transarterial embolization, superselective embolization.

INTRODUCTION

Percutaneous nephrolithotomy (PNL) is an effective and safe method that has replaced open surgical techniques, especially in the treatment of large kidney stones. PNL is considered the standard treatment for the management of staghorn/large kidney stones, upper pole stones resistant to other treatments, difficult-to-reach lower pole stones, cystine stones, and stones in kidneys with abnormal anatomy [1]. Although PNL has improved significantly over the years, serious complications such as bleeding can still occur [2]. While a certain amount of bleeding related to manipulations within the pelvicalyceal system is usually self-limiting, major bleeding requiring transfusion after PNL has been reported with an incidence ranging from 2% to 23% [3]. Bleeding can occur in the early postoperative period or as "delayed bleeding" days or weeks later. The most common presentation is the onset of active, macroscopic, and intermittent delayed hematuria after discharge, leading to emergency department visits [3]. Pseudoaneurysms (PAs) are the most common cause of delayed bleeding, followed by arteriovenous fistulas (AVFs) and mixed lesions. Pseudoaneurysms are most commonly observed in interlobar and arcuate arteries, followed by posterior segmental arteries [4, 5].

The treatment approach for delayed bleeding after PNL varies depending on the patient's clinical condition. Initially, conservative treatments such as hydration, hemostatic medications, and blood transfusion are used. Angiographic embolization is reserved for patients with ongoing bleeding despite conservative treatment or those who are hemodynamically unstable [6]. Transarterial embolization (TAE) has been shown to be effective and safe in the management of renal bleedings [7]. Technological advancements in interventional radiology have allowed for superselective arterial embolization (SAE), which preserves most of the renal parenchyma by using smaller microcatheters and embolic agents.

There are no definitive guidelines regarding the duration of conservative treatment and the timing of angiography. Transarterial embolization (TAE) is typically indicated in patients with ongoing bleeding, a drop in hemoglobin level >3 g/dL, and hemodynamic instability [6]. However, in the current practice, patients presenting with delayed bleeding most commonly seek emergency department care, and routine computed tomography (CT) scans are performed, which can demonstrate the presence of active bleeding, PA, or AVF. The primary aim of this study is to evaluate the effectiveness of same-day SAE in treating patients with delayed bleeding after PNL and to assess the reliability of renal function in these patients.

MATERIALS AND METHODS

After approval from our Institutional Ethics Committee (2020/20-81), the study was conducted retrospectively. The study included adult patients (>18 years) who presented to our hospital's emergency department between December 2014 and December 2020 with complaints of hematuria following PNL and were subsequently treated with transcatheter arterial embolization (TAE). Patients with other etiologies of renal bleeding (renal biopsy, trauma, partial nephrectomy etc.) were excluded from the study. Patient characteristics were obtained from the hospital's electronic medical records. Demographic data, known systemic diseases, anticoagulant/antiplatelet medication use, duration between PNL and symptom onset, as well as pre- and post-procedure creatinine values were analyzed. Pre-procedural CT images and angiographic images related to the TAE procedure were evaluated using the hospital's Picture Archiving and Communication System (PACS). Types of kidney injuries related to PNL (side, presence of PA, AVF, active bleeding), number of renal arteries, localization of bleeding, number and level of injured renal artery branches, were evaluated separately using both CT scans and angiographic images and correlated with each other. However, the final decision was based on angiographic images. Additionally, the type of embolic agent used, number and level of embolized branches, and the percentage of renal parenchymal loss after TAE were evaluated based on angiographic images.

Transarterial Embolization

All procedures were performed by experienced interventional radiologists in our hospital's

interventional radiology unit, after obtaining informed consent from the patients. After ensuring standard sterile conditions, access was obtained through the right or left common femoral artery using an 18 G needle under ultrasound guidance, followed by placement of a 4F short vascular sheath (Terumo, Tokyo, Japan). Subsequently, selective access was achieved with a 4F diagnostic catheter (Cobra, Sim1, Shepherd) based on the exit angle of the renal artery of the affected kidney, and selective renal arteriography images were obtained. Following the identification of the vascular injury (contrast extravasation/ active bleeding, presence of PA or AVF), microcatheters (2.0-2.4F) were advanced coaxially to the most distal accessible segment. Detachable coils (Concerto coil, Medtronic, USA) were used for embolization based on the diameter of the responsible vessel. Post-embolization, a control renal arteriography was performed to confirm complete occlusion of the target vessel and absence of any other pathology, and the extent of renal parenchymal loss was evaluated. Hemostasis at the access site was achieved by manual compression, and patients were closely monitored with vital signs in strict bed rest. Following the procedure, patients were discharged based on daily monitoring of hemoglobin levels, presence of hematuria, as well as serum creatinine values.

Definitions and Data Analysis

Technical success was defined as the complete occlusion of the vascular lesion (active bleeding/ PA/AVF) on post embolization angiography. Clinical success was defined as resolution of hematuria, normalization of clinical and laboratory values, and no occurrence of new bleeding requiring repeat TAE or surgical intervention within 4 weeks. Complications were graded according to the classification system by the Society of Interventional Radiology based on clinical outcomes [8]. Major complications included post-procedural death, permanent damage/disability requiring increased level of care, displacement of embolization coils causing hospitalization or prolonging the hospital stay, renal function loss, renal artery dissection, and other events. All other complications were considered minor.

The percentage of renal parenchymal loss after embolization was evaluated based on angiographic images, comparing the maximum extent of parenchymal staining before (pre-TAE) and after (post-TAE) embolization. The maximum length of post-TAE parenchymal defect was divided by the maximum length of pre-TAE parenchymal staining and multiplied by 100. Patients were classified into three groups based on the percentage of renal parenchymal loss: <%10, %11-24, and %25-50. Additionally, the impact of SAE on renal function was assessed by comparing the serum creatinine values at the time of admission and post-procedure.

RESULTS

Patients

A total of 13 patients (9 males, 4 females) with a mean age of 44.08±20.18 were included in the study (Table 1). All patients presented to the emergency department with hematuria complaints following delayed bleeding after discharge from PNL. Only 4 patients underwent PNL at our institution, while the rest were performed at external centers. The mean serum creatinine level at the time of admission was 1.09±0.53 mg/dl. The time interval between the onset of hematuria and PNL was determined to be a mean of 11.92±7.27 days (ranging from 3 to 30 days). None of the patients showed hemodynamic instability. Among the obtained CT scans, the affected side of the kidney was determined to be the right in 9 patients (69.2%) and the left in 4 patients (30.8%). Among them, lesion localization was observed in the middle and lower poles in 3 patients (23.1%) and 10 patients (76.9%), respectively. In two patients, typical pseudoaneurysm or arteriovenous fistula was not observed on CT scans, but on venous phase images there were focal areas of contrast suspicious of leakage into the collecting system.

Angiography and Embolization

A total of 13 patients underwent renal angiography. Among the study population, vascular pathology was detected in 11 (84.6%) patients during angiography. Active contrast extravasation was observed in only one patient. The most common angiographic findings were pseudoaneurysm (PA) in 7 (63.6%) patients and both PA and arteriovenous fistula (AVF) in 4 (36.4%) patients. The type and localization of angiographically detected vascular pathologies were correlated with the patients' CT images. Two patients with significant hematoma in

Table 1. Demographic and clinical characteristics of patients

Gender n (%)	
Female	4 (30.8%)
Male	9 (69.2%)
Age	
Mean± SD	44.08±20.18
Range	16-83
Hypertension	
Yes	4 (30.8%)
No	9 (69.2%)
Diabetes	
Yes	2 (15.4%)
No	11 (84.6%)
Anti-coagulation therapy	
Yes	2 (15.4%)
No	11 (84.6%)
Side	
Right	9 (69.2%)
Left	4 (30.8%)
Presence of staghorn stone	
Yes	7 (53.8%)
No	6 (46.2%)
Lesion localization	
Middle pole	3 (23.1%)
Lower pole	10 (76.9%)
Clinical Characteristics	
Hematuria	13 (100%)
Hypovolemic shock	0 (0%)
Interval between onset and PNL (days)	
Mean ± SD	11.92±7.27
Range	3-30

the collecting system, despite the absence of typical vascular lesions (contrast extravasation/PA/AVF) on CT imaging, did not show any focal bleeding on angiography. All patients with identified vascular pathology were treated with selective arterial embolization. All bleeding foci originated from renal arteries. Detachable coils were used as embolic agents in all patients.

Technical success rate was 100% as complete occlusion of the target vessel was achieved in all 11 patients who underwent embolization. In all patients, the presenting complaint of hematuria resolved, and clinical and laboratory values returned to normal, eliminating the need for repeat SAE or surgical intervention, resulting in a clinical success rate of 100%. In the two patients without detectable vascular foci on angiography no embolization was performed and conservative treatment led to resolution of symptoms.

Renal Function and Complications

The rates of renal parenchymal loss on post-embolization control angiography images were observed as follows: <%10 in 8 (72.7%) patients, %11-24 in 2 (18.2%) patients, and %25-50 in 1 (7.7%) patient. The mean serum creatinine levels after SAE were 1.06±0.71 mg/dl. The decrease between these values was calculated as 0.03±0.27, and no statistically significant difference was found (p=0.50). No major complications were observed in any of the patients after the procedure. Minor complications associated with post-embolization syndrome, such as fever or flank pain, were not observed in any of the patients.

DISCUSSION

The efficacy and safety of SAE in the management of severe and persistent post-PNL bleeding has been demonstrated in several studies [9]. The literature reports technical and clinical success rates ranging from 87% to 100% and 57% to 100%, respectively, and our study's 100% technical and clinical success rates fall within these defined ranges [10-12].

Delayed post-PCNL bleeding is relatively rare and is typically defined as bleeding occurring more than 24 hours after the procedure, with varying degrees of severity [6]. The most common presentation is intermittent gross hematuria. In our study population, the mean time from PNL to presentation was 11 days, and all patients presented to the emergency department with intermittent gross hematuria. According to some studies, most cases of post-PNL bleeding in stable patients can be managed conservatively, while 4-5% may require embolization. Transarterial embolization (TAE) is typically indicated in cases of persistent bleeding, hemoglobin drop >3 g/dL, and hemodynamically unstable patients [6]. However, these indications are independent of the vascular lesions detectable by CT angiography and are based on clinical criteria. Delayed, sudden, intermittent hematuria is characteristic of PAs and AVFs. The sensitivity of CT angiography in detecting these lesions ranges from 86% to 100% [12-13].

For patients suspected of renal bleeding, the required CT protocol is defined as non-contrast, arterial phase, and venous phase, known as triphasic CT angiography (CTA). Non-contrast images can differentiate high-attenuation structures, such as hematomas or residual stones, and residual contrast material from previously administered contrast material. Arterial originated bleedings are visualized as focal areas of high-density (>90 HU) attenuation in arterial phase images, while in the venous phase, these areas increase in both size and attenuation. Pseudoaneurysms on the other hand, remain the same size in the venous phase but show decreased attenuation. Arteriovenous fistulas are visualized as early contrast material filling into the renal vein in arterial phase images [14]. Additionally, CT images provide additional advantages such as providing information about the entry tract of the PNL procedures, identifying the patient's renal artery anatomy, and determining the level of vascular injury (segmental artery, interlobar artery, arcuate artery, etc.). These factors can be advantageous for the operator performing TAE during the procedure [15]. In our study, 69% of the patients (9/13) underwent PNL procedures at external centers, and therefore, detailed information about their surgical procedures was lacking. However, in all patients, the PNL tract was visualized using CT, indicating the entry point in the kidney. Furthermore, there was a 100% correlation between CTA and angiography in determining the type and localization of vascular lesions in our study population. The specificity of CTA has been reported as 83-100% in the literature, which is consistent with our findings [16,17]. The findings obtained from cross-sectional imaging guide the interventional operator, reducing procedure time, the amount of contrast material used during the procedure, and allowing the selection of embolization agents based on the identified lesion [15].

In our study, TAE was performed in 11 patients based on the presence of lesions identified on CT angiography, while in 2 patients, typical lesions were not detected on CT. However, CT revealed the presence of hematomas in the collecting system and suspicious focal areas of attenuation increase within the collecting system in delayed-phase images in these patients. However, renal angiography did not reveal any vascular pathology such as active bleeding, PA, or AVF in these patients. Previous studies have shown that conventional angiography can demonstrate the presence of lesions even in cases where negative findings are observed on cross-sectional imaging, and angiography is still considered the gold standard method [12]. Therefore, although our study showed a correlation between the negative predictive value of CT and angiography, the number of patients in the study is not sufficient to support this finding. In their study, Yang et al. stated that the presence of hydronephrosis and hematomas in the collecting system increases intrarenal pressure, leading to reduced contrast perfusion. They further explained that in their own study, when no findings were detected on CT in patients with negative findings, the presence of lesions on angiography could be attributed to the injection of contrast into intraarterial segmental branches, which can demonstrate pathology independent of intrarenal pressure [17].

In our study group, the clinical success rate was 100%, and none of the patients required a second TAE session or surgical exploration. However, the literature reports cases of clinical failure after the first TAE, and several factors have been identified as risk factors, including multiple PNL access points, the use of large tracts during PNL, multiple bleeding foci, and the use of gelatin sponge as an embolization agent [2,18]. None of the patients in our study had multiple foci. For patients with multiple arterial foci, the main reason for failure is the inability to visualize the lesions angiographically due to arterial vasospasm caused by bleeding [19]. In our study, all patients were hemodynamically stable and underwent TAE directly when the lesion was detected on cross-sectional imaging, which contributed to their appropriate management. Furthermore, gelatin sponge was not used as an embolization agent in any of the patients in our study [19]. Patients with negative angiographic findings also had venous-originated bleeding and self-limited conditions managed conservatively.

Some studies in the literature argue that renal angiography should be the first diagnostic procedure in the presence of delayed bleeding. These studies suggest that in the majority of delayed bleeding cases, traumatic vascular injuries such as pseudoaneurysms and AVFs are the underlying cause. Performing early TAE without compromising the patient's hemodynamics has been shown to reduce hospital stay and the need

for blood transfusion [3]. Additionally, these studies recommend direct TAE instead of performing contrast-enhanced cross-sectional imaging in cases of massive bleeding and renal dysfunction, as it allows both diagnosis and treatment [12]. The main reason for cross-sectional imaging being performed in our study was the fact that most patients had undergone PNL at external centers. Furthermore, in our study, no renal function impairment was observed after CT angiography and subsequent TAE. The preservation of renal function after TAE for renal bleeding has been demonstrated in our study and other studies in the literature [9, 10, 20, 21].

Renal artery dissection and coil migration, which are complications associated with renal embolization, were not observed in our study group. Post-embolization syndrome was also not observed, which can be attributed to the fact that 90.2% of our patients (10/11) had a renal parenchymal loss of less than 25%.

Our study is subject to several limitations that should be acknowledged. Firstly, its retrospective nature introduces inherent biases and limits the ability to establish causality. Secondly, the relatively small sample size might restrict the generalizability of our findings. Furthermore, the acute nature of the clinical presentation poses challenges in conducting a prospective randomized study, as immediate intervention is often necessary. It is also important to note that our assessment of renal function relied solely on creatinine levels, without incorporating more comprehensive methods such as nuclear imaging, which could provide a more accurate evaluation of renal compensatory function. These limitations should be taken into consideration when interpreting the results of our study.

In conclusion, TAE is an effective and safe method for the treatment of delayed hemorrhage following PNL. Particularly in patients presenting to the emergency department with intermittent macroscopic hematuria in the late post-PNL period, CT angiography provides valuable information for both the diagnosis of vascular lesions and treatment planning. Prompt TAE in patients with identified lesions on cross-sectional imaging improves technical and clinical success rates.

Author contribution

Study conception and design: FGE, FÇ, AG, and BP; data collection: FÇ and FGE; analysis and interpretation of results: FGE, FÇ, AG and BP; draft manuscript preparation: FGE, FÇ and BP. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by Institutional Ethics Committee of Hacettepe University (Protocol no. GO 2020/20-81).

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Conflict of interest

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ORIGINAL ARTICLE

An effective technique in nerve defect repair: Analysis of sliding epineural tube graft technique and comparison with autologous nerve graft and turn-over epineural tube graft techniques

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ABSTRACT

Objective: Autologous nerve graft (ANG) is the standard of care in the reconstruction of nerve gaps. However, scarification of a donor nerve, donor-site complications (wound complications, sensory dysfunction, neuroma, etc.) and unpredictable results lead surgeons to search for alternative techniques. Epineural tube graft (ETG) is a good option in the repair of nerve gaps. At this point, the present study aims to analyze the utility of the sliding epineural tube graft (SETG)technique in the reconstruction of nerve gaps.

Materials and Methods: Thirty Wistar albino rats were divided into five groups according to the repair technique of a 7 mm nerve defect created on the right sciatic nerve. In Group 1 the defect was left unrepaired as a negative control group. The defect was repaired with ANG in Group 2, with turn-over ETG (TETG) in Group 3, with one-directional SETG (O-SETG) in Group 4 and with bi-directional SETG (B-SETG) in Group 5. On the 12th week of the experiment, electrophysiologic, gross macroscopic and microscopic evaluation of muscle function and microscopic assessments of muscle and nerve samples were performed. The left limb and proximal nerve segment of the defect area were used as the control side.

Results: Electrophysiologic, macroscopic (wet muscle weight) and microscopic (axonal count, muscle fiber thickness was superior in the ANG group compared with TETG and SETG techniques. B-SETG showed poor results in all of the aforementioned findings. TETG and O-SETG techniques showed similar neuromuscular functions.

Conclusion: Although the ANG technique has some disadvantages depending on the sacrification of a donor nerve and donor side, it has significantly superior reconstructive outcomes compared to ETG techniques. However, since the ETG techniques provide acceptable results, they should be in surgeons' treatment repertoire because of the unique features of the microsurgical intervention.

Keywords: Nerve injury, nerve graft, epineural graft.

INTRODUCTION

Peripheral nerve injuries (PNIs) are commonly associated with traumas with a general incidence of 1% to 3.3% [1-3]. PNIs are frequently seen in the upper extremity with a rate of up to 77%, which causes significant workforce loss [1, 4, 5]. Besides, PNIs are most commonly seen in financially and socially productive ages, between 16 to 35 years [2, 5, 6]. Morbidities due to injury or surgery may affect patients' quality of life and lead this individual clinical situation to a national healthcare problem, not only because of patients' loss of workforce but also high costs of treatment and rehabilitation expenses. Previous studies have reported that PNIs significantly prolong the duration of hospitalization. These aspects of PNIs make these clinical cases and the reconstruction of PNIs considerable.

Although different techniques have been reported in the literature, autologous nerve graft (ANG) is considered the standard of care in PNIs that are not eligible for primary repair [1, 7]. Neurotrophic factors within the nerve graft provide the appropriate microenvironment for axonal regeneration [8, 9]. This is compatible with the concept of "reconstruction of tissue with a similar tissue" in plastic surgery practice. However, because of donor-side morbidity (sensory and wound healing complications, scar, neuroma) and sacrifice of another nerve, previous studies analyzed other types of autologous or synthetic conduits. However, a practical, inexpensive, and minimally morbid surgical technique that provides ideal nerve regeneration and functional recovery has not been widely used in clinical practice yet [1]. On the other hand, some experimental studies have reported remarkable results of epineural sheath grafts and tubes [9-13]. The epineural sheath was used in sleeve or tube formation in some of these studies. Tube formation (epineural tube graft – ETN) was obtained by the pull-out technique [9], turn-over technique [10, 11], or vertical suturing technique [14]. Similar to ANG, the neural origin of ETN can provide superior success of axonal regeneration by secretin neurotrophic agents [8, 9]. This aspect of epineural graft has been confirmed by reported studies in the literature, which reported comparable functional and microscopic results with the ANG technique [10-12, 14, 15]. However, many limitations of the ETG technique in the repair of nerve gaps exist. Firstly, in some studies, ETG was obtained by pulling out the fascicules from a nerve graft [9, 16]. Although the aim of this technique is to demonstrate the effectiveness of ETG on nerve regeneration, the harvesting method of the ETG is not applicable in clinical practice. In the second technique, after harvesting the epineural graft, the tube formation is achieved by longitudinal suturation of the graft [14]. This incision line may cause a significant foreign body reaction, fibrosis and scar block which may prevent the axonal regeneration through the tube [9]. The third technique to obtain ETG is the turn-over technique [10, 11]. In the turn-over ETG (TETG) technique, the outer surface of epineurium becomes the inner surface of ETG. Hypothetically, this may cause fibrosis due to the irregular outer surface of the epineurium. Moreover, in ETG, because of the limited length of ETG, prominent nerve gaps can not be reconstructed with this technique. Eventually, although significant advantages of the ETG technique in the repair of nerve gaps, these prominent limitations prevent its use in clinical cases.

Another technique for harvesting and obtaining ETG is the sliding technique. Instead of turning inside out, the turn-over technique, after circumferential incision of epineurium on the proximal or distal nerve segment, an ETG can be harvested by sliding it into the nerve gap (Figure 1). This technique may prevent the aforementioned limitations. To our knowledge, there is no study analyzing the effect and results of the sliding ETG (SETG) technique in the English literature. Besides, by using the combination of sliding technique from distal and proximal nerve segments, hypothetically, ETG can be used to reconstruct larger nerve gaps. At this point, the aim of the present study is to demonstrate the harvesting of ETG by sliding technique and to analyze its effectiveness on nerve regeneration compared with ANG and previously described TETG techniques. Furthermore, to repair larger gaps, the utility of SETG from both distal and proximal nerve segments will be analyzed.

MATERIALS AND METHODS

After approval of the institutional ethics committee, 30 Wistar albino rats were divided into five groups

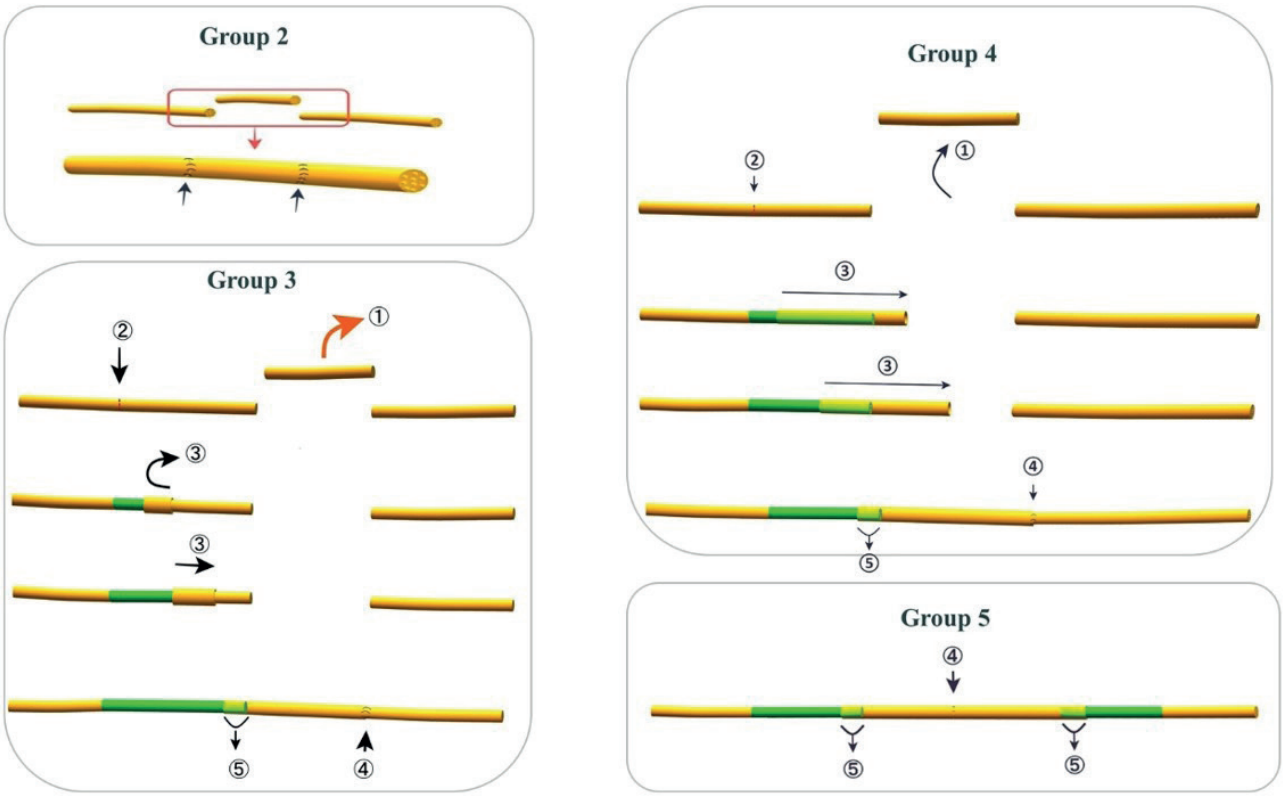

Figure 1. Schematic illustration of surgical technique of the groups. **1**: Excision of 7 mm nerve segment to create nerve defect, **2**: Circumferancial epineural incision, **3**: Harvesting the epineural tube graft by turn over technique (Group 3) and by sliding technique in Groups 4 and 5, **4**: Coaptation of ETG to contralateral nerve stump in Group 3 and 4, suturing two ETGs at the middle of the defect in Group 5, **5**: Preserved nerve segments covering with epineural sheath on distal and proximal nerve stumps to prevent the sheath from avulsion.

according to the repair technique. Group 1 was the negative control group without repair of nerve defect, Group 2 was the control group that defects repaired with ANG, Group 3 was the TETG group, Group 4 was the one-directional SETG (O-SETG) group in which ETG was harvested from the proximal nerve segment. Group 5 was bi-directional SETG (B-SETG) group in which ETG was harvested from the proximal and distal nerve segments. On the postoperative 12th week, after electrophysiological evaluation, wet gastrocnemius muscle weight (WGMW) and microscopic nerve and muscle examinations were performed.

Dissection Technique

In all groups, the right side of the subjects was used as the experimental side and the left side was used as the control side for muscle examination. For nerve samples, proximal nerve segments were used as the control side.

In the prone position, an oblique skin incision was made over the gluteal muscles. Muscle fibers were horizontally dissected with a blunt fashion and the sciatic nerve was exposed from the sciatic notch to the trifurcation point. A 7 mm nerve defect was created on the main trunk of the sciatic nerve, proximal to the branching point [10, 17]. In the B-SETG group, the defect was localized in the middle of the distance between the sciatic notch and trifurcation point, to ensure enough nerve length for proximal and distal sliding epineural tube graft. In other groups, localization of nerve defect was distal 7 mm segment of the main sciatic nerve trunk proximal to the trifurcation point, to ensure enough nerve length for proximal sliding and turn-over ETG.

In Group I, after the excision of the 7 mm nerve segment, the defect was left unrepaired and the wound was closed in layers. In Group 2 (ANG group), the nerve defect was repaired with resected ANG, which was 180 degrees turned (Figures 1 and 2a). In Group 3, the nerve defect was repaired with proximal-based TETG as reported in the literature (Figure 1 and Figure 2b,c and d) [10]. In Group 4 (O-SETG group), a circumferential epineural incision was made on the proximal nerve segment, immediately distal to the sciatic notch (Figure 1

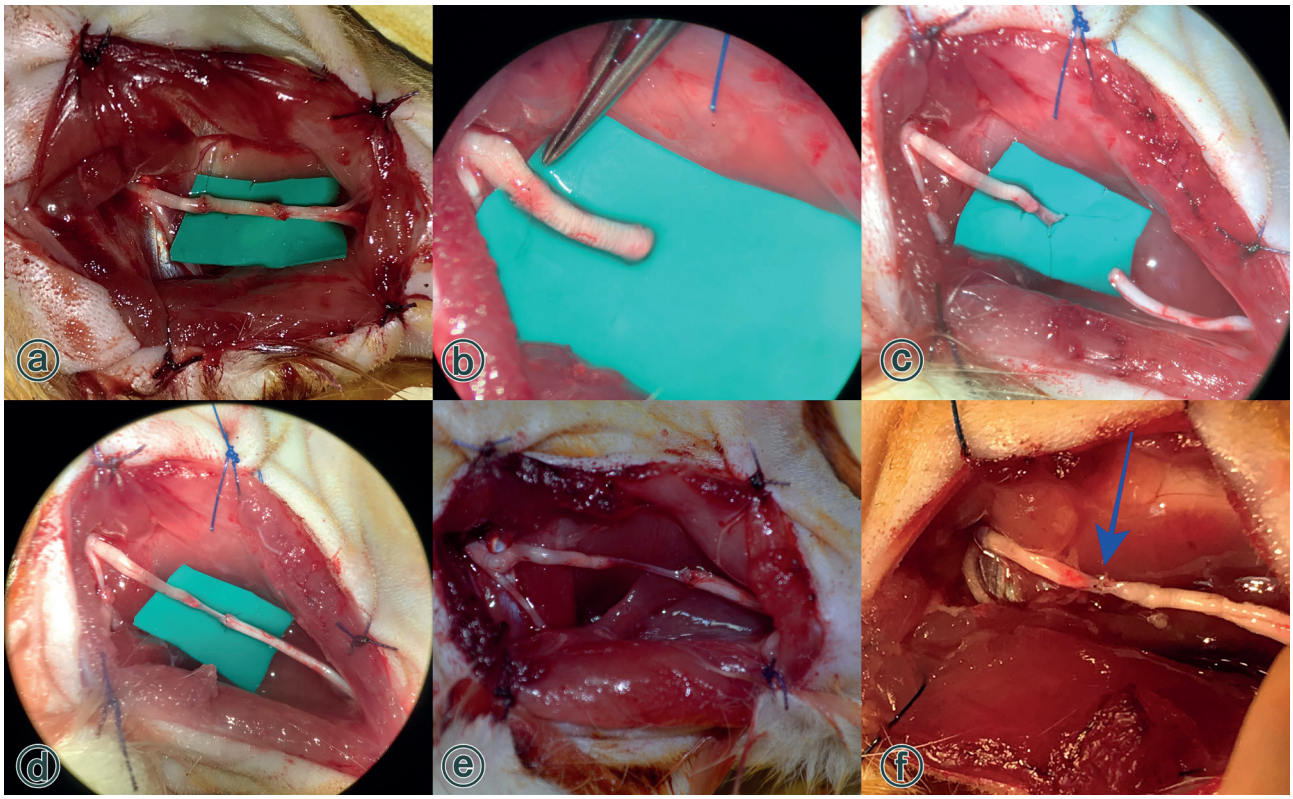

Figure 2. Views of the surgical technique of the groups. **a**: Repaired nerve defect with ANG (Group 2), **b**: Circumferential epineural incision pointed with a forceps. Note the fascicular bulging proximal to the epineural incision, **c**: Harvested ETG from the proximal nerve segment. Although it was harvested from a longer nerve segment, because of contraction ETG looks shorter. To prevent the graft from collapsing and facilitate the coaptation, two traction sutures are placed on the graft, **d**: Reconstruction of nerve defect with TETG (Group 3), **e**: Reconstruction with O-SETG, **f**: Reconstruction with B-SETG.

arrow-2, Figure 2b). Later, the epineural sheath was slid by pulling the distal end of the epineurium distally with two microforceps. A three mm length epineurium was left intact over the proximal nerve stump to prevent ETG from being avulsed from the proximal nerve segment (Figure 1 arrow-5). The distal free end of ETG was sutured to the distal nerve stump with three sutures of 120-degree intervals (Figure 2e). In Group 5 (B-SETG), the same surgical technique as Group 4 was applied. Differently, the nerve gap was placed in the middle of the sciatic notch and trifurcation point to leave sufficient nerve length for harvesting two ETGs from proximal and distal nerve segments. Circumferential epineural incisions were made immediately distal to the sciatic notch on the proximal nerve segment and immediately proximal to the trifurcation point on the distal nerve segment. After sliding the epineurium bi-directionally, obtained two ETGs were sutured each other at the middle of the nerve gap, with three sutures at 120 degrees intervals (Figure 1 and Figure 2f). A three mm epineural sheath was left over the proximal and distal nerve stumps for the stability of the tube graft and to prevent scar formation at the coaptation point (Figure 1 arrow-5, Figure 2-f blue arrow).

Electrophysiological Assessment

The degree of nerve regeneration and muscle function were evaluated with Electromyogram (EMG) objectively, using the Nihon-Kohden Neuropack M1 device (Tokyo, Japan) under general anesthesia 12 weeks after the nerve repair. Data including compound muscle action potential amplitude (CMAP) and distal latency were recorded [18].

The device's stimulation rate was 1 Hz, sampling time was 100 msec, and filter settings were 5kHz for high-cut and 10 kHz for low-cut. Room temperature was 25 degrees and extremity temperatures measured with a needle thermometer were between 34 to 36 degrees.

After hair removal, a bipolar stimulator needle electrode was placed on the left sciatic nerve, 10 mm proximal to the coaptation point, with the

anode tip distally. The monopolar recording needle electrode was placed as the anode electrode was in the middle of the gastrocnemius muscle and the cathode electrode was on its tendon. The ground electrode was placed on the back of the subject. The degree of stimulation was progressively increased till the supramaximal response was taken from the sciatic nerve

Gross Muscle Evaluation

After electrophysiological evaluation, the subjects were sacrificed with high-dose thiopental sodium. In the prone position, after taking visual records of a comparative view of the left and right sides, the skin overlying the gluteal region and distal back was removed for a clear macroscopic comparative view of the muscles (Figure 3). Gastrocnemius muscle was detached from its origin and insertion both from the experimental and control limbs. Wet muscle weight (WMW) was measured with the Sartorius CP225D model analytical scale (Göttingen, Germany) with an accuracy of 10^{-5} g.

Microscopic Evaluation

Two mm cross-sections were obtained from the gastrocnemius muscle belly of experimental and control limbs. Samples were stained with methylene blue and quantitative analyses were performed with a light microscope (Nikon Corporation, Tokyo, Japan) under x100 magnification (Figure 4-c) using semi-automated software (Digimizer 5.4.4, MedCalc Software Ltd., Belgium).

For the nerve samples, 5 mm nerve cross-sections were performed proximal to the proximal nerve stump and distal to the distal nerve stump. After keeping the specimens in 2.5% glutaraldehyde for

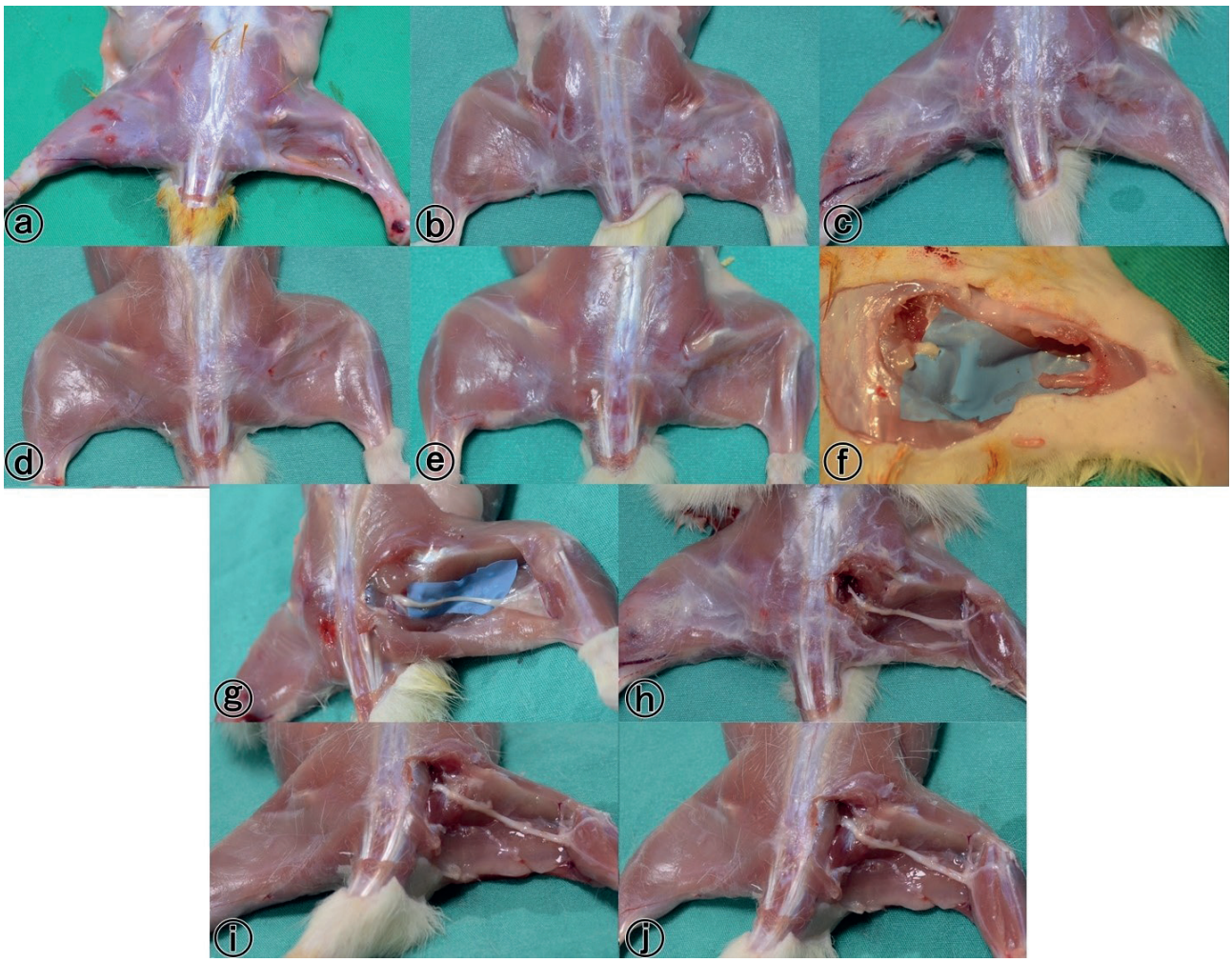

Figure 3. Comparative view of muscle atrophy of experimental (right limb) and control limbs (left) and macroscopic view of nerve regeneration. Severe muscle atrophy is seen in Group 1 (**a**) and prominent atrophy is notable in Group 5 (**e**). Acceptable muscle mass is seen in Groups 3 (**c**) and 4 (**d**). Better muscle mass is seen in Group 2 (**b**). Nerve regeneration is not seen in Group 1(**f**). In other groups, macroscopic continuity of the nerve is observed. g: Group 2, **h**: Group 3, **i**: Group 4, **j**: Group 5.

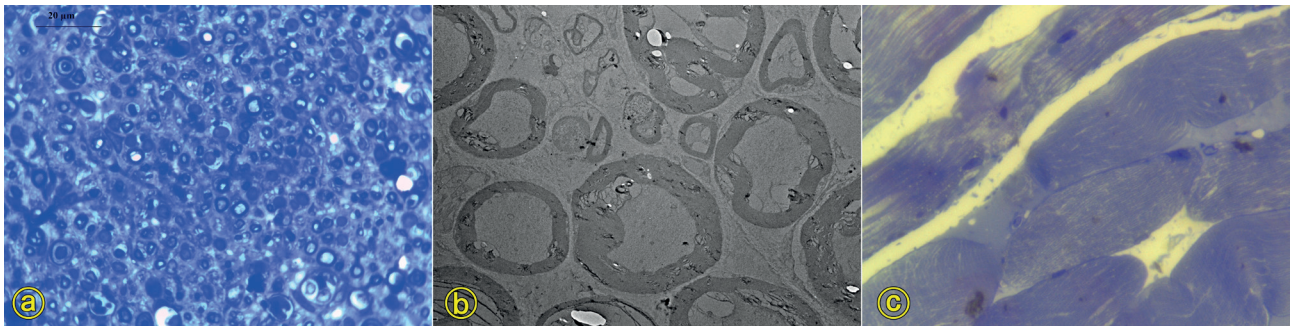

Figure 4. Microscopic view of the nerve and muscle samples. **a**: Light microscopic nerve samples under x100 magnification which were used to count the axons (stained with methylene blue), **b**: Transmission electron microscopic view of the nerve samples under x5000 magnification that shows the ultrastructural architecture (stained with uranyl acetate and lead citrate). Myelin sheath thickness, axonal diameter and surface were measured with these sections, **c**: Light microscopic view of the muscle samples under x100 magnification (stained with methylene blue).

24 hours for primary fixation, they were washed with Sorenson's phosphate buffer solution (pH: 7.4) and post-fixed in 1% osmium tetroxide for two hours. The samples were rewashed with the same phosphate buffer solution and dehydrated with increasing alcohol concentrations. Later, tissue samples were washed with propylene oxide and embedded in the mold containing epoxy resin. Embedded specimens were sliced with LKB-Nova ultra-microtome (LKB-Produkter AB, Bromma, Sweden) to obtain two µm thickness sections. These sections were stained with methylene blue for light microscopic (Nikon Corporation, Tokyo, Japan) examination (Figure 4-a) [19-21]. Myelinated axons were counted under x100 magnification with the same semi-automated software [21].

Ultra-thin sections (60 nm) were obtained using the same microtome for electron microscopic examination. After staining these sections with uranyl acetate and lead citrate [19], the ultrastructural examination of the nerve specimens (myelin sheath thickness, the diameter and surface area of the myelinated axons) was performed using an electron microscope (Jeol JEM 1200 EX, Tokyo, Japan) under 5000x magnification (Figure 4-b). The axonal diameter was calculated by taking the average of the long and short axes, which were perpendicularly crossing each other at the center of the sectional nerve area [21]. Myelin sheath thickness was calculated by taking the average thickness of the sheath at its thickest and thinnest points [20, 21].

Statistical Analysis

Statistical analysis was performed using the Statistical Package for Social Sciences for Windows SPSS 23.0 (IBM Corporation, Armonk, New York, United States). The normal distribution of quantitative data was assessed by the Shapiro-Wilk test. The homogeneity of variances was analyzed with Levene's test. The Kruskal-Wallis test was used the analyze quantitative data between the groups. For post hoc pairwise comparison, the Mann-Whitney U test with Bonferroni correction was used. Descriptive statistics of quantitative variables were presented as "mean ± standard deviation" in the text and tables. The variables were examined at a 95% confidence level, and p values <0.05 were considered statistically significant.

RESULTS

Electrophysiological Findings

Electrophysiological measurements showed similar distal latency and CMAP between the control limbs of the subjects (Table 1). On the other hand, in the experimental limbs, the lowest distal latency measured in Group 2 was 2.08 ms and the highest value in Group 5 with 4.33 ms following Group 1. There was a statistically significant difference in the distal latency of experiment sites (p=0.023). The post hoc pairwise comparison revealed that the difference between Group 1 and other groups except for Group 5, and the difference between Group 2 and Group 5 (p=0.022) and Group 3 and Group 5 (p=0.008) was statistically significant. The mean CMAP of experimental limbs was statistically similar in all groups.

In the comparison of the experimental limbs with the control limbs within each group, the distal latency of the experimental sides was significantly

Table 1. Macroscopic, microscopic and electrophysiologic data of the muscle samples

		Group 1	Group 2	Group 3	Group 4	Group 5	P Value
Muscle Fiber Thickness (µm)	Experimental Limb	20.65±6.84	63.04±1.94	61.62±4.65	61.08±4.3	55.22±6.2	0.001
	Control Limb	64.74±8.81	64.48±3.80	63.58±4.45	63.20±3.58	63.65±5.45	0.779
Wet muscle weight (g)	Experimental Limb	0.87±0.21	3.26±0.45	3.56±0.12	3.42±0.36	1.06±0.64	<0.001
	Control Limb	4.58±0.44	4.18±0.41	4.04±0.60	4.82±0.32	4.66±0.44	0.642
Distal Latency (ms)	Experimental Limb	5.36±0.18	2.08±0.13	2.77±0.01	2.64±0.35	4.33±0.37	0.023
	Control Limb	1.76±0.71	1.73±0.62	1,63±0.78	1,15±0.30	1,76±0.54	0.064
Compound Muscle Action Potential	Experiment Site	6.92±4.64	17.58±7.26	4,06±23.98	21,24±14.27	26,58±17.11	0.965
	Control Site	19.34±5.67	17.36±4.77	11,96±6.95	12,27±4.08	31,61±20.42	0.748

higher compared with their control limbs in all groups (Table 2). However, CMAP was statistically similar in all groups except for Group 1 comparing the experimental and control limbs (Table 2).

Results of Macroscopic Muscle Evaluation

The intergroup comparison of WMW of control limbs showed a statistically similar distribution of gastrocnemius muscle weight (Table 1). However, in the experimental limbs, the weight difference between the groups was statistically significant ($p<0.001$). In the post hoc pairwise comparison, WMW was statistically significantly lower in Group 1 and Group 5 compared with the other groups. The WMW was statistically similar in Group 1 and Group 5 ($p=0.378$). Besides, the difference of WMW in Groups 2,3 and 4 was statistically similar.

In the comparison of the experimental limbs with the control limbs within each group, the level of muscle atrophy was statistically significant in all groups except for Group 2 (Table 2). In group 2, the difference in WMW between experimental and control limbs was statistically similar ($p=0.064$).

Microscopic Data of the Samples

The mean axonal counts of proximal nerve segments were statistically similar in all groups. However, in the distal nerve segments, the difference in mean axonal counts was statistically significant between the groups ($p=0.013$). Post hoc pairwise comparison of the groups revealed a statistically significant difference between Group 2 and Group 4 ($p=0.045$), Group 2 and gr Group 5 ($p=0.008$) and Group 4 and 5 (p=045). The difference between Groups 3 and 4 ($p=0.810$) and Groups 3 and 5 ($p=0.128$) was not statistically significant. In Group 1, the axon number of distal nerve segments were could not counted due to prominent degeneration of the axons. Ultrastructural architecture (axon surface area, myelin sheath thickness and axon diameter) of the nerve samples was similar in all groups for distal and proximal nerve segments (Tables 2 and 3). In the comparison of the proximal and distal nerve segments within each group, the decrease in axon count was statistically significant in Groups 3,4 and 5 (Table 2). In Group 2, proximal and distal nerve segments' axonal count was statistically similar ($p=0.093$).

Table 2. P values of Comparison of control and experimental sides within each group

	Group 1	Group 2	Group 3	Group 4	Group 5
Axon Count	None	0.963	<0.001	<0.001	<0.001
Axon Surface Area	None	0.330	0.147	0.981	0.879
Myelin Thickness	None	0.976	0.744	0.956	0.333
Axon Diameter	None	0.467	0.408	0.793	0.627
Muscle Fiber Thickness	<0.001	0.071	<0.001	<0.001	<0.001
Wet Muscle Weight	<0.001	0.064	<0.001	<0.001	<0.001
Distal Latency	0.011	0.034	0.080	0.013	0.018
CMAP	0.031	0.925	0.356	0.149	0.632

Note. For muscle specimens, the control side was the left limb. For nerve samples, the control side was the proximal nerve segment.

The mean muscle fiber thickness of control limbs was statistically similar between the groups (Table 1). However, in the experimental limbs, the difference between the groups was statistically significant (p=0.001). The pairwise comparison revealed that muscle fiber thickness was statistically similar between Groups 2,3 and 4. However, the mean fiber thickness of Group 1 was statistically significantly lower than the other groups. Furthermore, the mean fiber thickness in Group 5 was significantly lower than Group 2 (p=0.013). This measurement was similar between Group 5 with Groups 3 and 4.

In the comparison of the experimental limbs with the control limbs within each group, mean muscle fiber thickness decreased in experimental limbs compared with their control limbs except for Group 2, similar to WMW (Table 2). Muscle fiber thickness of experimental limbs and control limbs was statistically similar in Group 2 (p=0.071).

DISCUSSION

Despite advances in microsurgical techniques, the reconstruction of nerve defects is still a challenging field in plastic surgery practice. While the gold standard treatment technique is ANG in the literature, morbidities associated with the sacrification of the donor nerve and extra surgical field-associated complications are the main challenges of this reconstruction [1, 7]. Although continuing research is to overcome these pitfalls, a practical and applicable technique has not been accepted and routinely used in clinical practice yet [1].

PNI is commonly associated with traumas and its incidence is up to 3.33% [1-3]. The rate of graft needed nerve reconstruction is 5.7% of reported PNIs [6]. Considering both the high incidence of nerve damage and its individual, medical and social consequences, the importance of treatment and follow-up protocols becomes evident. When considered on an individual basis, it can range from tolerable hypoesthesia to severe motor and sensory losses that can interfere with the patient's daily activities. In the literature, it has been documented that injuries involving PNI are associated with longer durations of hospitalization, treatment, rehabilitation, and greater psychosocial impacts compared to traumas without nerve damage [3]. In addition, considering the high treatment costs, repeated hospital admissions, and loss of workforce due to long rehabilitation periods, the social and national effects of nerve injuries are striking. Moreover, PNIs are frequently seen in young or middle-aged individuals who have a workforce and economic contributions to society [2, 3]. In a study reported by Noble et al., the mean age of nerve damage was 34.6 years, and 59% of them were seen in individuals between the ages of 18 to 35 years [2]. Similarly, McAllister et al. have reported that 57.1% of nerve injuries occur in individuals aged 16 to 35 years. [6] These remarkable data reveal the potential social repercussions of an individual medical problem. In addition, these injuries, which are in productive age, cause loss of function and workforce throughout the life of patients, significantly reducing their quality of life [1].

The ideal treatment method for nerve damage is early, tension-free, end-to-end primary repair, if possible. [6, 10] However, for the nerve gaps not eligible for primary repair, currently, the ANG technique is the standard of care in the literature [1, 7, 22, 23]. The main advantage of this technique is the repair of the nerve defect with a similar tissue that provides the appropriate microenvironment that activates axonal regeneration with neurotrophic factors and mediator cells [24]. However, this technique has some disadvantages such as the sacrification of a donor nerve and associated anesthesia/hypoesthesia, neuroma, additional surgical area, wound complications (scar, infection, hematoma, dehiscence, etc.), long operation time and two coaptation points on the nerve repair line that may negatively affect the axonal regeneration because of foreign body reaction, fibrosis and scar block [1, 12, 25, 26]. Furthermore, repair with the nerve graft technique is challenging and has unpredictable results [22]. Although various studies reported remarkable outcomes in repairing the nerve gap with different types of conduits (autologous grafts, allografts, synthetic grafts, etc.), they have many limitations that prevent their use in clinical practice. For instance, some of the disadvantages of autologous grafts (vein, muscle, tendon, etc.) are that they are not neural origin and they have suboptimal results in nerve defects longer than 3 cm [10, 27]. In some publications, synthetic conduits were proposed to avoid donor-side morbidity and nerve sacrification [28, 29]. Although the focus point is very important in minimally invasive surgical notions, high costs and challenges in producing custom-made

conduits make this technique unpractical [10, 30]. Furthermore, similar to vein grafts, long gaps of more than 3 cm are another limitation of this technique [29].

Although promising outcomes of ETG, the literature has many limitations in the ETG technique that prevent its use in clinical practice. First of all, ETG was harvested with an inapplicable technique, pulling the nerve fascicules from the ANG to obtain ETG [9]. Secondly, for obtaining the tube formation, suturing the epineural graft longitudinally is significantly prone to foreign body reaction, scar formation and fibrosis, which reduce axonal regeneration [14, 26, 31]. Besides, ETG was inserted into nerve defects with two coaptation points in the previous studies [9, 14]. On the other hand, TETG is a practical reconstruction option compared to the aforementioned two ETG harvesting techniques [10, 11]. However, in this technique, harvesting the ETG is challenging and requires advanced microsurgical capability. On the other hand, no study was found in which nerve defect reconstruction was performed using the ETG by sliding technique from the nerve proximal or/and distal segments. The sliding technique is more practical and easier to apply compared with the TETG technique. Besides, in the SETG technique, there is only one coaptation point similar to the TETG technique, which is an advantage compared to the ANG technique which has two coaptation points. Furthermore, the inner surface of SETG is smoother than TETG which may hypothetically facilitate axonal regeneration. Considering the promising advantages of the SETG technique, the current study presents remarkable data on ETG techniques. In the present study, the methodology of harvesting the SETG technique is determined, which is practical to apply and it was used to reconstruct a nerve gap, which is not reported in the literature yet. Moreover, the B-SETG technique was performed to reconstruct the larger defects and the SETG technique was compared with TETG and ANG techniques, which are not analyzed in the literature as well.

On the other hand, many studies reporting the results of the ETG technique in the literature analyzed the nerve and muscle function subjectively using the walking track test [10, 11]. This test is prone to subjectivity and may be affected by many conditions depending on the subjects and environmental factors. On the other hand, EMG is an objective and effective technique to assess neuromuscular functions which provides numeric and precise data [18, 32, 33]. This objectivity lets researchers compare data between studies, series, and centers [32, 33]. In the present study, the assessment of neuromuscular functions was performed with EMG to obtain objective results.

For optimal functional results, the ideal nerve conduit should provide anatomical integrity of the nerve, induce minimal inflammation, stimulate axonal regeneration, cause minimal morbidity and have low costs [12]. The epineural sheath is a good candidate that has these advantages. Besides, it is a neural tissue that activates Schwann cell functions and induces axonal regeneration by secreting the laminin, similar to ANG [8, 9]. Therefore, using an epineural sheath has been applied in some studies in the literature, with ETG, sleeve and strip epineural grafts [9-13, 15]. In these studies, ETG techniques have reported similar outcomes with ANG. In a study reported by Ayhan et al., nerve defect repair was performed experimentally by obtaining ETG with the turn-over (TETG) technique [10]. Similar results were observed between ETG and ANG in the analysis of variables such as muscle function, muscle mass and macroscopic structure, diameters of muscle fibers and microanatomical structure of axons. In a study, Luokkala et al. harvested TETG from the distal nerve segment instead of the proximal nerve segment [11]. In addition, Karacaoğlu et al. reported superior results in the ETG technique in their study, in which they examined the results of ETG and vein graft in nerve defect repair and attributed this to the neurotrophic factors provided by the epineural sheath [14]. These studies revealed that the nerve regeneration of the ETG technique is similar to the ANG technique. According to these studies, the main advantage of the ETG technique was emphasized not to need for the sacrification of donor nerve and the absence of donor-side complications (hypoesthesia, hematoma, infection, neuroma, etc.) compared to ANG. In the literature, it has been reported that in cases where the epineural sheath is used as a donor, an epineurium-like layer forms in the donor area on the nerve [10]. In this case, enlargement of the existing nerve defect or morbidity in the nerve donor area is not expected in the SETG or TETG techniques. In addition, since the graft donor is the proximal and/or distal segment of the damaged nerve, a diameter mismatch is not expected. On the other hand, beyond the possible donor-side complications, microscopic

and objective electrophysiological findings of the current study revealed superior outcomes and data of the ANG technique compared with ETG techniques.

In the present study, the electrophysiological finding suggests similar muscle functions between ANG, TETG and O-SETG techniques. However, the functional outcomes of the B-SETG technique were suboptimal compared with other techniques. This is attributed to the prominent collapse of the ETG caused by the coaptation point that is at the middle of the graft (Figure 2-f, blue arrow). Hypothetically, the collapse caused scar formation and eventually blocked the axonal regeneration through the tube. Similarly, findings of muscular atrophy (WMW and fiber thickness) were well tolerated in the ANG technique. However, in ETG techniques, muscle atrophy was prominent compared to their control limbs. In particular, this was significant in the B-SETG technique (Figure 3).

Similar to muscle functions in experimental limbs, the nerve degeneration was well tolerated in the ANG technique, which suggests lower distal latency and better CMAP measurements in EMG compared with control limbs. Due to better axonal regeneration in the ANG technique, the axon count of the distal nerve segment was similar to the proximal (control) nerve segment. In ETG techniques, although different axonal regeneration levels were observed, the decrease in axon counts in distal nerve segments was prominent, which interprets suboptimal axonal regeneration. Although the functional and microscopic findings of TETG and O-SETG techniques were similar, in the B-SETG technique axonal regeneration was prominently impaired compared with other techniques.

The main limiting factor for ETGs is the localization of the injury. In the injury zone, the presence of nerve branching in the epineural sheath donor area will make it difficult to obtain a sufficient length of the epineural graft. This limitation may be overcome by selecting the better donor side, proximal, or distal nerve segment. Another disadvantage of the technique is the necessity of dissection of the nerve to obtain the appropriate epineural sheath length. As this situation could lead to the nerve being skeletonized from the surrounding tissues, it may result in compromised blood circulation [10]. However, considering the presence of the longitudinal internal vascular network in the peripheral nerves, no circulation problem is expected for the donor nerve segment [34, 35].

CONCLUSION

The findings of the present study confirm that the ANG technique is a more effective treatment option compared to ETG techniques. In particular, the use of SETG from both sides of nerve segments (B-SETG) causes poor results. On the other hand, O-SETG and TETG techniques revealed acceptable results. Therefore, ETG techniques (TETG or O-SETG) should be in surgeons' treatment repertoire to overcome possible challenges during the management of reconstruction. On the other hand, the present study determined a practical and applicable ETG harvesting technique, the sliding method.

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Author contribution

Study conception and design: MK, KG, and UK; data collection: MK, SV, AF and RA; analysis and interpretation of results: MK and UK; draft manuscript preparation: MK. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Clinical Research Ethics Committee of Ankara Training and Research Hospital (Protocol no:632).

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Conflict of interest

The authors declare that there is no conflict of interest.

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acta medica

ORIGINAL ARTICLE

Feasibility of microsurgery in rural area as part of compulsory health service in Turkey: Replantation, free conventional, perforator, thin, and super thin flaps

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ABSTRACT

Objective: Region six in Turkey, an underdeveloped area with limited doctors, lacks experienced healthcare professionals, teamwork, assistants, and instruments, which limits the performance of complex procedures. It is generally discouraged to attempt complex microsurgery in these regions. This study aims to demonstrate the feasibility of microsurgery and provide guidance for ambitious young plastic reconstructive surgeons performing microsurgery in underdeveloped areas as part of a compulsory service program.

Material and Methods: A retrospective analysis was conducted on patients who underwent free flaps, replantation, and revascularization surgeries performed by the author, the sole plastic surgeon in the rural area, between August 2018 and August 2020. The analysis included operation notes, outpatient clinic notes, as well as pre-operative and post-operative pictures.

Results: A total of thirty-six microsurgical operations were performed on thirty-two patients. Two out of nineteen (10.5%) replantation attempts and one out of seventeen (5.8%) free flaps experienced failure. Among the flaps harvested, four were thin and four were super-thin. Furthermore, three out of five (60%) pediatric flaps encountered serious non-surgical complications, while most systemic complications were infection-related. All complications were effectively managed without the need for dispatch.

Conclusion: Microsurgery can be safely performed during the compulsory work period in the region six. Tips such as open-loop anastomoses, staff training, and easy means of flap monitoring can facilitate microsurgery. However, it may be prudent to consider avoiding such procedures in pediatric patients due to potential non-surgical complications and challenges with the dispatch system.

Keywords: Compulsory service, obligatory service, mandatory service, microsurgery, free flap, rural area, replantation, feasibility of microsurgery.

INTRODUCTION

Compulsory service programs have been implemented in seventy countries since the early twentieth century [1]. These programs have been given various names, including 'obligatory', 'mandatory', and 'requisite' programs. In Turkey, a compulsory health service program for doctors was reintroduced under Law No. 5371 in 2005, after its previous implementation from 1981 to 2003, owing to a shortage of doctors [2, 3]. The duration of this compulsory recruitment ranges from 300 to 600 days, depending on the region [2]. The program operates through a draw system where participating doctors are required to indicate their preferences for available positions, and a computerized random selection process is used to assign doctors to each position. The regions are numbered 1 to 6 for the development of cities and A to D for the availability of doctors. 6-D is the least developed and has the least number of doctors in Turkey [4]. The region 6 is generally described where complex procedures are not performed, due to a lack of the following: experienced doctors, available team work, medical assistants, instruments. Additionally, doctors may be hesitant to operate in this region due to potential complications and related malpractice lawsuits. The congestion and lack of experienced consultants in nearby tertiary level hospitals can result in the inefficient dispatch process, leading to patient frustrations caused by long waiting times and suboptimal treatments.

Replantation and free flap surgeries, which require microsurgery in the field of plastic and reconstructive surgery, pose considerable challenges. These procedures demand extensive experience, specific training, and a dedicated team for long and complex postoperative monitoring and rehabilitation. It is generally agreed upon that these types of operations should not be attempted in region 5 or 6.

The author, who received extensive microsurgery training during residency and subsequently completed a two-year microsurgery fellowship, was assigned as the sole plastic and reconstructive surgeon in a rural area classified as region 6-C for plastic and reconstructive surgery [4]. Despite the challenges posed by a scarcity of microsurgical materials and trained medical assistants, the author successfully performed numerous traumatic hand surgeries and complex microsurgical procedures. The objective of this study is to highlight the feasibility of such operations and pave the way for aspiring plastic reconstructive surgeons to perform microsurgery in underdeveloped areas within compulsory service programs. By sharing experiences, the study aims to address challenges related to the lack of materials, trained medical assistants and staff, as well as issues with flap and limb monitoring, and complication management.

MATERIAL AND METHOD

A retrospective analysis was conducted on patients who underwent free flaps, replantation, and revascularization surgeries between August 2018 and August 2020. The analysis involved reviewing operation notes, outpatient clinic records, as well as pre-operative and post-operative photographs. The author, who was the sole plastic surgeon in the rural area during that period, performed all surgeries. The study documented patient demographics, the reasons for surgery, surgical details, complications, and the survival of flaps and replanted body parts. Ethical approval was obtained from the relevant provincial ethics committee (approval no: 2020/1). All study subjects were informed and a written consent was obtained. Although the author performed a significant number of other complex procedures, such as tendon reconstructions, nerve repairs, brachial plexus explorations and repairs, ulnar and radial artery repairs, spaghetti hand injuries, and local perforator island flaps during the compulsory service, these cases were not included in the study to maintain focus on free flaps and replantation cases and avoid data heterogeneity.

RESULTS

During the two-year period, the author performed a total of thirty-six featured microsurgical procedures on thirty-two patients (three female, twenty-nine male). The mean age was thirty years old ranging from four to sixty-nine. It is important to note that other microsurgical repairs, such as nerve repairs and single bundle repairs, were excluded from this analysis. No legal disputes arose from patients

who underwent microsurgery, and the majority of complications observed were infection-related. All complications were successfully managed without requiring patient transfers. Details regarding the complications in pediatric cases are listed in Table 1.

Free Flaps

Fifteen patients underwent a total of seventeen free flap surgeries. Two patients received two free flaps each; one due to a large defect and another due to free flap failure. Of the patients, three were female and twelve were male, with a mean age of twenty-six years (ranging from four to forty-seven). Five patients were pediatric, with an average age of eleven years (ranging from four to seventeen). The mean follow-up period was six months (ranging from one month to three years). Except for one patient with a congenital mass, the etiology of the defects in all patients was trauma. Of the sixteen trauma cases, thirteen were acute (including five gunshot wounds, two mine injuries, a traffic accident, a fall from height, rubble injuries, and others), while three patients presented with chronic sequelae of trauma, including one burn contracture, one scaphoid non-union, and one Volkmann's ischemic contracture.

The distribution of free flaps performed by the author is as follows: six superficial circumflex iliac artery perforator (SCIP) flaps, five anterolateral thigh (ALT) flaps (including one thin flap, one two-island flap, and one chimeric flap), one functional gracilis flap, one osteocutaneous fibula flap, one peroneal artery perforator flap, one deep circumflex artery perforator (DCIA) flap, one iliac bone flap, and one femoral condyle chimeric flap. Among these flaps, eight were harvested as thin flaps (including one ALT flap, six SCIP flaps, and one DCIA flap), and four of them were harvested as super-thin flaps (including three SCIP flaps and one DCIA flap) [5]. End-to-end anastomoses were performed in eleven cases, while end-to-side anastomoses were performed in five cases. One anastomosis was performed in a 'T' type to restore distal circulation. Sixteen flaps (94.1%) had successful outcomes, with only one SCIP flap failing despite a revision attempt. Two flaps (11.7%) that survived required take-back surgeries. Among the pediatric flaps, three out of five (60%) developed severe non-surgical complications, as outlined in Table 1. Detailed information about the complications in the free flaps can be found in Table 2.

Table 1. Pediatric free flaps with high non-surgical complications

Pediatric Free Flaps	Age	Sex	Defect Location	Flap Size	Etiology	Flap Type	Recipient Artery	Flap Survival	Follow-Up	Functional Outcome	Complications
1	17	M	Right heel	16x8 cm	Landmine	Chimeric ALT*	Posterior tibial, EtE**	Success	6 months	Limited ambulation	Neutropenic Fever
2	7	F	Left dorsal foot	10x5 cm	Burn Contracture	Super-thin DCIA† perforator	Dorsalis pedis, EtS††	Success	1 month	Full ambulation	Acute HAV infection with intensive care monitorization
3	10	M	Left lateral elbow and arm	20x10 cm	Traffic Accident	Super-thin SCIP‡	Posterior circumflex radial artery, PtP¶	Success	6 months	Full ambulation	-
4	17	M	Right medial leg	22x8 cm	Gunshot Wound	ALT	Posterior tibial, EtS††	Success	6 months	Full ambulation	Neutropenic Fever
5	4	F	Left medial foot	10x4 cm	Run over by a car	Super-thin SCIP	Dorsalis pedis, EtE**	Success	18 months	Full ambulation	Mild Contracture treated with Z plasty

ALT*: Anterolateral thigh flap; SCIP‡: Superficial circumflex iliac artery perforator flap; DCIA †: Deep circumflex iliac artery perforator flap; EtE **: End to end anastomosis; EtS ††: End to Side anastomosis; PtP ¶: Perforator to perforator anastomosis

Table 2. Complications after free flap surgeries

	Complication	Possible cause	Management
Local complications *(n=5)*	Take-back	Hematoma due to vein kink.	No re-anastomosis performed
	Take-back	Kink over end-to-side anastomosis	Switched to end-to-end anastomosis
	Failure	No obvious reason	Another flap was performed
	Finger contracture	Inadequate physiotherapy	Z-plasty
	Mild lymphedema	Large lower extremity defect over saphenous vein and lymphatics	Physiotherapy
Systemic complication *(n=4)*	Neutropenic fever	Infection or drug related	Consulted to pediatrics with broad-spectrum antibiotics
	Neutropenic fever	Infection or drug related	Consulted to pediatrics with broad-spectrum antibiotics
	Acute Hepatitis A	Orofaceal	Intensive care monitorization
			No available center could be found for dispatch.
			Spontaneous recover
	Bacterial pneumonia	Long operation	Antibiotic treatment was started
(n=9/17)			

Replantation

The replantation cases exclusively involved male patients, with a mean age of thirty-two years (ranging from four to sixty-nine, mean thirty-five). Nineteen replantation procedures were performed on seventeen patients, including the replantation of three fingers in one patient. Out of the total replantations, four cases involved pediatric patients, with an average age of ten years (ranging from four to seventeen). The mean follow-up period was four months (ranging from one month to three years). In addition to finger amputations, attempts were made to replant one ear, one alar rim, and one toe. One patient had five finger amputations, of which four were attempted to be replanted. Two out of the nineteen replantation attempts failed, resulting in a survival rate of seventeen replants (89.4%). The unsuccessful replanted body parts were amputated either during or after surgery following revision attempts. Trauma was the sole cause of amputation in all replantation cases. Four cases presented with clean cut injuries (knife and bread slicer), while fifteen amputations (78.9%) were a result of crush or avulsed injuries, including incidents involving saws, dog bites, motorcycle chains, and agricultural machinery accidents. Among the replants, arterial repairs were performed in ten cases, both arterial and vein repairs were carried out in seven cases, arteriovenous anastomoses were performed in three cases, and two-artery repairs were performed in nine cases. Vein grafts were used in a total of five instances, with two utilized for vein defects and three for artery defects. Details regarding complications observed in the replantation cases are listed in Table 3.

DISCUSSION

The author achieved a success rate of 16 out of 17 (94.1%) for free flaps and 16 out of 18 (88.8%) for replantation or revascularization cases. This demonstrates that performing microsurgery as the sole plastic surgeon in an underdeveloped

Table 3. Complications after replantation

	Complication	Possible cause	Management
Local complications *(n=4)*	Osteomyelitis	Dirty wound	Half of replant was debrided
	Sudeck's atrophy	Trauma in an old patient	Physiotherapy
	Take-back	Skin compression	
	Failure	A-V shunt, very small piece and small vessels, avulsion by dog bite, lack of 11/0	Reconstructed with local flaps
Systemic complication *(n=1)*	CMV hepatitis	Incidental	Spontaneous recovery
(n=5/19)			

area is feasible, despite the lack of instruments and trained staff, with certain acceptable complications. However, the high rate of non-surgical complications in pediatric cases is concerning, despite the limited number of cases. The author aims to discuss indications, complications management, lack of instruments, patient care, and patient monitoring in detail to provide insight into the challenges and potential solutions in this specialized area.

Indications

As expected, the majority of cases were emergent cases, primarily involving extremity flap reconstructions. It should be noted that head and neck reconstruction or breast reconstruction surgeries could not be performed due to the absence of an oncology team for tumor resections and the lack of suitable intensive care facilities. Plastic and reconstructive surgeons working in region 5 or 6 should be well-versed in extremity and trauma reconstruction.

Management of Non-Surgical Complications

Three pediatric cases undergoing free flap surgeries experienced serious postoperative non-surgical complications. Two cases exhibited neutropenic fever, a pediatric emergency often caused by infection [6], which required the administration of broad-spectrum antibiotics and close monitoring for sepsis. Both cases were discharged after their neutrophil levels recovered. The third pediatric case developed acute Hepatitis A and required close monitoring in the pediatric intensive care unit for one week to monitor for potential fulminant progression. Attempts were made to transfer the patient to a tertiary level pediatric gastroenterology department, but no available spot or suitable center was found. The patient recovered spontaneously and was discharged safely. One adult replantation case was diagnosed with acute CMV hepatitis postoperatively, which was only a mild form, and the patient recovered spontaneously. Infectious disease-related complications in children, such as neutropenic fever and hepatitis, are not uncommon and may require management at a tertiary level. Although microsurgical reconstruction in pediatric cases, including complex super-thin flaps, was feasible for the author, it is suggested to avoid pediatric microsurgical reconstruction in region 6 due to delays and issues in the dispatch system.

Management of Microsurgical Complications

Microsurgery operations and emergency take-backs can be physically demanding and may impact routine elective outpatient clinic work. This can potentially lead to official complaints and a reduction in performance-based salary. The author proposes educating the staff on each case and scheduling elective flap surgeries on Thursdays or Fridays, considering the possibility of take-backs over the weekend. This recommendation is based on research by Wei et al. [7], which indicates that 95% of vascular problems occur within the first three days and that they are mostly salvageable (85%) during this time frame.

Management of Lack of Material and Instruments

To perform microsurgery, surgical sets, an operation microscope, and microsurgical sutures are necessary. Among these, the operation microscope holds the utmost importance, as it may be more challenging to find or replace compared to other equipment. Currently, most rural hospitals near the border have at least one operation microscope available for neurosurgeons, particularly in cases of cranial trauma or war surgery. The author had to utilize the only available microscope shared with neurosurgeons in the hospital for microsurgery procedures. However, the hospital did not possess suitable microsurgery instrument sets. Thus, the author resorted to using his personal microsurgical instrument set. To obtain conventional jeweler's forceps at a more affordable price, the author purchased them from a jewelry store. While it is possible to procure specific instruments and materials through a direct purchase system as outlined in Article 22 of Law No. 4734 [8], permission for such purchases lies in the hands of the administration and finance department. Microsurgical sutures, on the other hand, are more readily available and cost-effective. However, it's important to note that the micro sutures used by ophthalmologists, which have spatula tips, are not designed for use in vessels and nerves. For hand and flap surgeries, sutures with round tips and smaller-sized needles (preferably less than 5mm for 9/0) are preferred. The author successfully convinced the hospital administration to procure microsurgical sutures when supplies ran out, leading to the resumption of emergency

hand surgeries. Additionally, the author personally purchased some sutures for emergency purposes. It is noteworthy that all perforator flaps were raised using a free-style technique, as the only available Doppler device in the hospital was out of order. The osteocutaneous flaps were performed using a gigli saw or osteotome as an electrical saw was not available.

Assistance During Surgery

The presence of skilled assistance during surgery is another crucial factor in microsurgical procedures. While it is commonly believed that an experienced resident or nurse should assist the surgeon during microsurgery, the author's clinical fellowship experience involved raising flaps and performing anastomoses without any assistance, except for bone flaps that may require a large retractor. Although it may initially seem challenging, the use of automatic retractors, fish hooks, and open-loop anastomosis techniques [9] can facilitate these surgeries with minimal assistance. In fact, it is often preferable for the surgeon to have less help from the assistant, unless the assistant possesses extensive experience in microsurgery. This is because an inexperienced assistant may unintentionally move unnecessarily or use sharp retractors, potentially causing distractions or even injuring important perforators. For these reasons, the author suggests that the assistant scrub nurse adopt a passive approach and wait for clear directions instead of being overly active throughout the procedure.

Flap and Replant Monitoring

The need for flap and replant monitoring is another concern that may discourage microsurgeons from performing these operations in underdeveloped regions. In such areas, a shortage of experienced nurses and residents can result in the surgeon bearing the responsibility of monitoring flaps and replants alone. To address this issue, the author provided a ten-minute training talk to clinic nurses on flap and replant monitoring. This training focused on simple signs and terms that could be easily understood, such as oozing, hematoma, assessment of flap temperature, and color. The use of an infrared thermometer was found to be helpful and easy for the nurses to utilize [10]. In replantation cases, a saturation probe was also employed for improved monitoring [11]. These monitoring techniques are straightforward to use and alleviate the burden on the surgeon. However, it is important to note that these techniques can sometimes be misleading, and infrared thermometers may detect flap coldness too late, especially when extremity flaps are covered with a blanket. Consequently, physical examination remains the gold standard for most microsurgeons [12]. The author implemented a routine of monitoring the flaps immediately after surgery in the recovery room, as well as during the patient's transfer to the clinic room. This routine facilitated the salvage of one flap in the case of arterial thrombosis. After the immediate postoperative monitoring, clinical nurses monitored the flaps on an hourly basis. Whenever there was doubt, photographs and videos were shared with the author through WhatsApp. If there were suspicions regarding flap circulation, a nurse would initiate dermal bleeding by making a small cut with a blade. The author would then conduct further monitoring the following morning. Weekdays involved monitoring the flaps three times a day, while on weekends, they were monitored twice a day by the author and on an hourly basis by nurses for the first forty-eight hours. After forty-eight hours post-surgery, the frequency of monitoring was reduced to every three hours to alleviate the burden on the nurses.

Patient Care

Patient care in the context of microsurgery requires advanced experience, which is often lacking among nurses and other healthcare workers in underdeveloped areas. Therefore, it is crucial for the reconstructive surgeon to train healthcare workers in patient care, monitoring, and follow-up. This training should encompass basic principles specific to microsurgery patients, including maintaining a warm environment and a warm patient, elevating the extremity, avoiding any compression around the flap or replant, monitoring the patient's position, the importance of pain management to prevent vasospasm, and performing flap monitoring as discussed in a previous section. In the author's experience, training is made easier by the fact that staff in smaller and underdeveloped centers tend to be few in number, yet eager to learn new approaches.

Dispatch System

Due to a lack of instruments or experience, cases requiring microsurgery are often dispatched to larger centers. However, with a limited number of academic staff in plastic surgery at peripheral tertiary centers, many reconstructive surgery centers have been suspended, making it challenging to find a tertiary center that can admit patients needing microsurgery. The author avoided dispatching any patients requiring microsurgery, except on two occasions for short periods. In one instance, this was due to a shortage of micro sutures, and in the other, it was due to ongoing renovations in the operating rooms. Fortunately, despite the long waiting periods, the author was able to successfully dispatch the patients in these two cases through effective communication and negotiation. Given the high systemic complication rate in pediatric patients in this study, dispatching should be prioritized in pediatric patients requiring microsurgery, not because of possible complications but because of the problematic dispatching system if a systemic complication occurs in an underdeveloped area.

Handling Supermicrosurgery and Free Thin-Flaps

Handling supermicrosurgery, which involves dealing with vessels less than 0.8mm in diameter, presents significant challenges. It not only requires technical expertise but also necessitates specialized instruments with fine tips and extremely fine sutures, such as 11/0 with smaller needles (preferably less than 4mm). Supermicrosurgery is commonly employed in pediatric replantation, tip replantation, and thin free flaps. While the author successfully performed supermicrosurgery for these indications during his compulsory service, the lack of available 11/0 sutures, which were not accessible at the nearest tertiary level at the time, may have contributed to one of the failures. Although thin flap dissections and anastomosis of smaller vessels to larger vessels in an end-to-side manner can be accomplished with larger sutures, performing replantation on extremely small pieces becomes nearly impossible with them. Consequently, the author recommends refraining from supermicrosurgery unless suitable instruments and sutures are readily available.

Strengths and Limitations

This study boasts several strengths. Firstly, patients with different indications were operated on by the same surgeon, illustrating the feasibility of a wide range of microsurgery procedures. Secondly, there is a scarcity of studies addressing microsurgery in rural areas, making this study a valuable source of firsthand insight. The primary limitation of this study lies in the assumption based on the experience and motivation of a single surgeon, which can influence the feasibility and results. Furthermore, the mean follow-up time was relatively short. The rural setting, where doctors often resign after two years upon fulfilling their compulsory work, as well as the presence of refugees who may need to be deported or illegally escape to another country, pose challenges to maintaining long-term follow-up.

CONCLUSION

Performing microsurgery, including replantation and free flap surgeries, is deemed safe within the context of compulsory work in region 6, even with just one microsurgeon present at the center. Implementing technical tips such as open-loop anastomosis, along with staff training and the use of easy means for flap monitoring, contribute to the successful execution of microsurgery procedures. However, the author advises caution when considering microsurgery in pediatric patients within the region 6 compulsory work period due to potential non-surgical complications and challenges associated with the dispatch system. Additionally, it is recommended to delay supermicrosurgery, if elective, until suitable fine sutures are available.

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I acknowledge that the manuscript has been read and approved by all the authors, that the requirements for authorship as stated earlier in this document have been met, and that each author believes that the manuscript represents honest work. This work has not been presented in a congress or symposium before.

Author contribution

Study conception and design: AHS; data collection: AHS; analysis and interpretation of results: AHS; draft manuscript preparation: AHS. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Clinical Research Ethics Committee of XXX (Protocol no. XXX).

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Conflict of interest

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ORIGINAL ARTICLE

Evaluation of small airway dysfunction in patients with pneumoconiosis, a cross-sectional study

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ABSTRACT

Objective: Pneumoconiosis is an irreversible, progressive parenchymal lung disease caused by inhalation of mineral dust. Inhaled particles in the working environment can cause inflammation and fibrosis in the lung, affecting all respiratory tracts, including the large and small airways. Our study aimed to evaluate the frequency and risk factors of small airway dysfunction (SAD) in patients diagnosed with pneumoconiosis.

Methods: The study population consisted of 331 patients diagnosed with pneumoconiosis between 01/01/2018 and 31/05/2023. Pneumoconiosis was diagnosed with a history of occupational inorganic dust exposure, radiologic findings compatible with pneumoconiosis, and exclusion of other diagnoses. Two readers evaluated the chest radiographs of the patients according to the International Classification of Pneumoconiosis Radiographs of the International Labor Organization. SAD was defined as at least two FEF50, FEF75, and FEF25-75 measurements below 65% of their predicted values.

Results: SAD was found in 47.7% of the patients. There was a statistically significant difference between age and the prevalence of SAD, but there was no statistically significant difference between smoking status and the prevalence of SAD. It was observed that 41.9% of the patients with pneumoconiosis who had never smoked had SAD. As the cigarette pack-years increased, the incidence of SAD increased. SAD was presented 38.7% in Stage 1, 50.7% in Stage 2, and 57.6% in Stage 3 pneumoconiosis cases. SAD was seen in 35.1% of pneumoconiosis cases without PMF. In pneumoconiosis patients with PMF, the frequency of SAD increased with increasing opacity size.

Conclusion: It was found that the frequency of SAD increased as the stage of pneumoconiosis increased. In patients with pneumoconiosis, SAD was observed in both smokers and never smokers, independent of large airway obstruction. Therefore, early small airway dysfunction should be considered when monitoring the health of patients with pneumoconiosis.

Keywords: Pneumoconiosis, small airway dysfunction, progressive massive fibrosis.

INTRODUCTION

Pneumoconiosis is an irreversible lung disease caused by prolonged inhalation of inorganic dust and fibers. Since these inhalants are usually encountered in the workplace, they are known as occupational diseases. Inhalation-induced lung diseases are among the most important occupational diseases. The most common occupational mineral dust are silica, asbestos fibers, coal dust, and silicate dust. The development of the disease depends on the susceptibility of the lungs,

the size, density, solubility, fibrogenic properties, and duration of exposure of the inhaled particles. These particles can cause inflammation and fibrosis in the lung, affecting all airways, including the large and small airways [1-4].

Inhalation of dust, gases, and vapors at work remains prevalent worldwide and significantly contributes to the burden of occupational respiratory disease [5]. Between 1990 and 2017, pneumoconioses increased by 66% worldwide [6]. The prevalence of pneumoconiosis is approximately 527,500 cases, with more than 60,000 new cases reported worldwide in 2017 [7]. According to 2019 data, it remains a significant public health problem, with 200,000 new cases and 920,000 disability-adjusted life years (DALYs) worldwide [8]. In our country, the true extent of the problem is not fully known, but it is commonly observed that pneumoconiosis constitutes most cases diagnosed with occupational diseases. In this respect, pneumoconiosis is an important public health problem in our country as in the world.

Small airways are less than 2 mm in diameter between the 8th and 23rd bronchial branches. They act as a bridge between the central airways and the gas-exchanging lung compartment and are recognized as the main site of airflow limitation in obstructive lung disease [9,10]. According to recent studies, small airway dysfunction (SAD) is defined as at least two of maximum mid-expiratory flow (MEF), forced expiratory flow 50 (FEF 50%), and forced expiratory flow 75 (FEF 75%) being less than 65% of the expected normal value [11]. SAD is a common but poorly understood respiratory problem. To date, there have been many epidemiologic studies on the contribution of workplace exposure to chronic airflow limitation. Most studies have focused on occupational asthma and occupational chronic obstructive pulmonary disease (COPD) caused by workplace exposure [12]. However, small airway evaluations have not been performed sufficiently. However, a recent study in China evaluated SAD risk factors in pneumoconiosis and emphasized their importance in the follow-up of patients with pneumoconiosis [13]. In our country, there are no studies assessing the development of SAD in patients diagnosed with pneumoconiosis, and it was thought that the evaluation of small airway parameters in the follow-up of patients with pneumoconiosis would contribute to determining the severity of the disease. Therefore, we aimed to evaluate the frequency and risk factors of SAD in patients with pneumoconiosis.

METHODS

Study design

This retrospective study was conducted in the Occupational Diseases Training Clinic of Ankara Atatürk Sanatorium Training and Research Hospital, an important reference center for pneumoconiosis in Turkey. The study was initiated after obtaining the approval of the ethics committee (2012-KAEK-15/2750). Patients over the age of 18 who were diagnosed with pneumoconiosis and had a medical examination report issued between 01/01/2018 and 31/05/2023 were included in the study. Pneumoconiosis was diagnosed with a history of occupational inorganic dust exposure, radiologic findings compatible with pneumoconiosis, and exclusion of other diagnoses. Demographic characteristics, pneumoconiosis stages, detailed occupational history, smoking history, exposure history, pulmonary function tests (PFTs), and radiologic images of the patients at the time of diagnosis were obtained from the hospital information management system and patient files. Patients' current and past employment patterns were recorded in the detailed occupational history, and the types of dust to which they were exposed at their workplace were described. Recorded smoking history was calculated as tobacco pack years by multiplying the average number of cigarettes smoked per day by the total number of years of smoking.

Patients whose spirometry data could not be accessed from their files and the system and whose spirometry results were incompatible were not included in the study. Of the 400 patients diagnosed with pneumoconiosis, 69 patients were excluded because their PFTs were incompatible or could not be accessed, and a total of 331 patients were included in the study (Figure 1). Spirometry was performed using a Zan 100 flow-sensitive spirometry device (ZAN MessgerateGmbH,

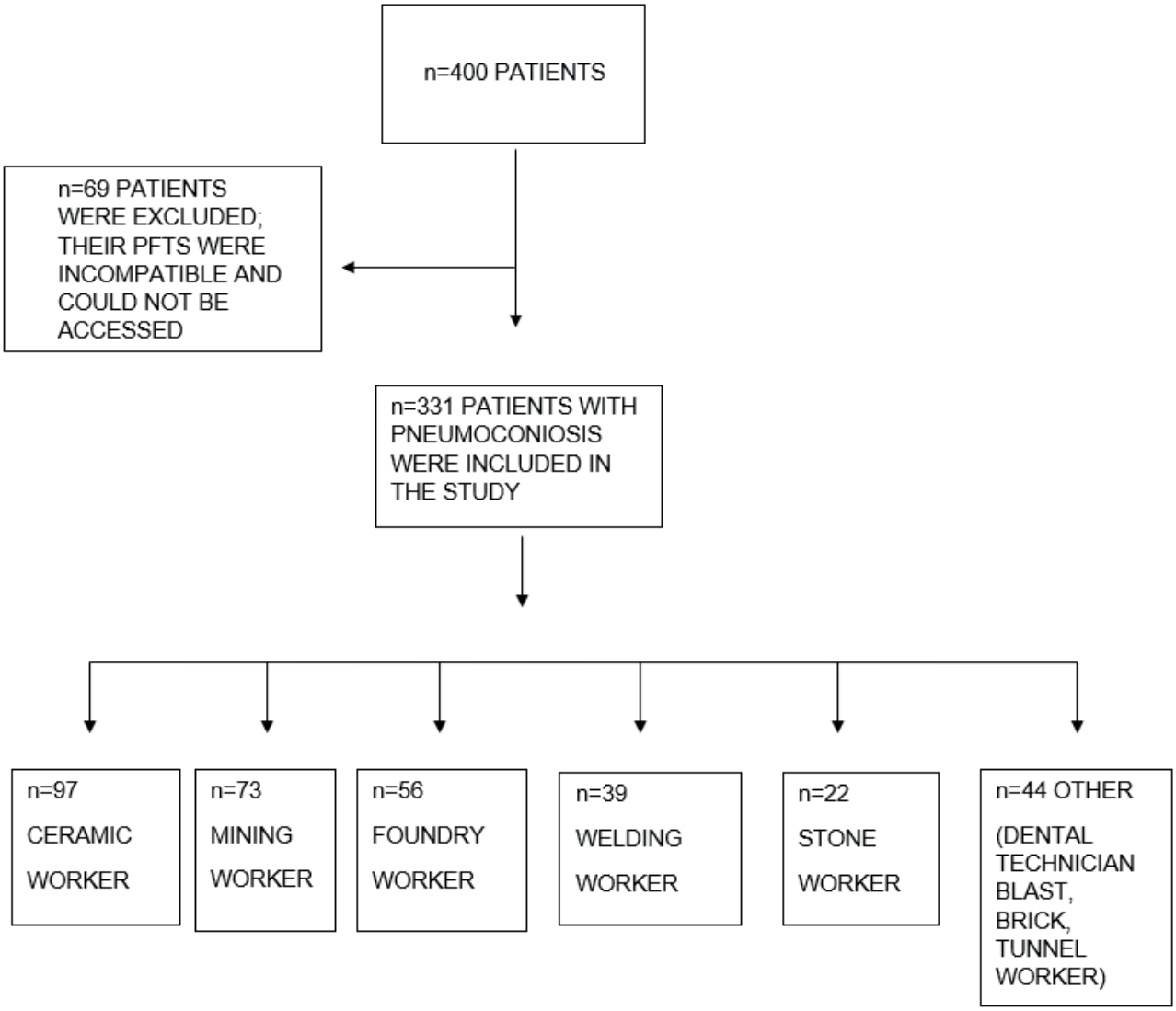

Figure 1. Study group

Oberthulba, Germany). Spirometry was calibrated daily, and temperature and humidity measurements were used for calibration. Spirometry results were analyzed according to the acceptability and reproducibility criteria presented in the ATS/European Respiratory Society statement updating the standardization of spirometry [14]. Spirometry measurements of the patients were evaluated according to the percentage of reference values.

Chest X-rays were taken with a digital X-ray system. Two readers evaluated chest radiographs according to the International Classification of Pneumoconiosis Radiographs of the International Labor Organization (ILO). Small opacities were defined by profusion, shape (round or irregular), and size. Small opacity profusion was divided into four stages (0, 1, 2, 3), each with three subcategories (0/- to 3/+).

In this study, three expiratory volume parameters, including FEV1, FVC, and FEV1/FVC, and the forced expiratory flow parameter at the 25th, 50th, and 75th percentile of FVC were recorded (FEF50, FEF75, and FEF25-75). In this study, SAD was defined as at least two of maximum mid-expiratory flow (MEF), forced expiratory flow 50 (FEF50 %), and forced expiratory flow 75 (FEF75 %) being less than 65% of the expected normal value.

Statistical analyses

The data of this study were evaluated using the IBM SPSS Statistics 22.0 statistical package program.

Categorical data were presented as number (n) and percentage (%), and numerical data were presented as mean and standard deviation. Data were tested for normality using the Kolmogorov-Smirnov test. In independent groups, t-test was utilized to compare continuous variables between the two groups. The chi-square test was used to compare categorical data. P-value < 0.05 was considered statistically significant.

RESULTS

Demographic Characteristics

The mean age of 331 patients included in the study was 51±11 (30-92), all patients were male, and 269 (81.3%) were smokers. Ninety-seven patients were ceramic workers, 73 were mine workers, 56 were foundry workers, 39 were welding workers, 22 were stone workers, and 44 were working in other occupational groups (dental technician, sandblaster, brick, and tunnel worker). The characteristics of patients with pneumoconiosis are presented in Table 1.

Table 1. Characteristics of the pneumoconiosis patients

		n (%)
Age	51±11 (30-92)	331(100)
Age Group	30-39	38 (%11.5)
	40-49	120 (%36.5)
	50-59	99 (%29.9)
	60-69	45 (%13.6)
	70+	29 (%8.8)
Smoking Status	Smoker	269 (81.3)
	Non-smoker	62 (18.7)
Cigarette (Package/Year)	0-19	187 (%56.5)
	≥20	144 (%43.5)
Occupation	Mine worker	73 (%22.1)
	Foundry worker	56 (%16.9)
	Welding worker	39 (%11.8)
	Stone worker	22 (%6.6)
	Ceramic worker	97 (%29.3)
	Other	44 (%13.3)
Exposure Duration (Year)	0-10	51 (%15.4)
	11-20	164 (49.5)
	21-30	96 (%29)
	≥31	20 (%6.04)
ILO Stage	Stage 1	119 (%36)
	Stage 2	146 (%44.1)
	Stage 3	66 (%19.9)
Large Opacity (PMF)	None	228 (%68.9)
	A	45 (%13.6)
	B	32 (%9.7)
	C	26 (%7.9)
Small Airway Dysfunction	Yes	158 (%47.7)
	None	173 (%52.3)
FVC ≥%80, FEV1/FVC≥%70	Yes	183 (%55.3)
	None	148 (%44.7)

Prevalence of SAD in pneumoconiosis patients

SAD was present in 158 (47.7%) of the patients. A statistically significant difference was found between age distribution and SAD frequency (p<0.001). SAD was found in 41.9% of never smokers with pneumoconiosis. There was no statistically significant difference between smoking status and the incidence of SAD (p=0.327). However, the incidence of SAD increased with increasing cigarette pack years (p=0.002).

SAD pneumoconiosis patients were 38.7% in Stage 1, 50.7% in Stage 2, and 57.6% in Stage 3 (p=0.030). SAD was seen in 35.1% of pneumoconiosis without progressive massive fibrosis (PMF). Pneumoconiosis patients with PMF increased the frequency of SAD with the opacity size (p<0.001).

Of the 331 pneumoconiosis patients, 163 had FEV1<80%, and 77.9% had SAD. In 168 patients, FEV1 was ≥80%, and 18.5% had SAD (p<0.001). One hundred sixteen pneumoconiosis patients had FVC <80% and 71.3% had SAD. 31.3% of those with FVC ≥80% had SAD (p<0.001).

In addition, SAD was found in 26.8% of pneumoconioses with FVC ≥80% and FEV1/FVC≥70%, while SAD was found in 73.6% of those with FVC <80% and FEV1/FVC <70% (p<0.001). SAD was seen in 41.8% of patients with pneumoconiosis with FEV1 ≥80%, FEV1/FVC≥70% (p<0.001). SAD was observed in all 34 patients with pneumoconiosis with FEV1 <80% and FEV1/FVC <70% (Table 2).

Table 2. Association between characteristics of patients with pneumoconiosis and SAD

	Small Airway Dysfunction		p
	NONE	YES	
Age Group			
30-39	21 (%55.3)	17 (%44.7)	
40-49	82 (%68.3)	38 (%31.7)	**<0.001**
50-59	54 (%54.5)	45(%45.5)	
60-69	13 (%28.9)	32 (%71.1)	
70+	3 (%10.3)	26 (%89.7)	
Smoking Status			
Non-smoker	36 (%58.1)	26 (%41.9)	0.327
Smoker	137 (%50.9)	132 (%49.1)	
Package/Year			
0-19	111(%59.4)	76 (%40.6)	**0.002**
≥20	62 (%43.1)	82 (%56.9)	
Occupation			
Mine worker	18 (%24.7)	55 (%75.3)	
Foundry worker	39 (%69.6)	17 (%30.4)	
Welding worker	23 (%59)	16 (%41)	**<0.001**
Stone worker	13 (%59.1)	9 (%40.9)	
Ceramic worker	66 (%68)	31 (%32)	
Other	14 (%31.8)	30 (%68.2)	
ILO Stage			
Stage 1	73 (%61.3)	46 (%38.7)	**0.030**
Stage 2	72 (%49.3)	74 (%50.7)	
Stage 3	28 (42.4)	38 (%57.6)	
Large Opacity (PMF)			
None	148 (%64.9)	80 (%35.1)	
A	13 (%28.9)	32 (%71.1)	**<0.001**
B	8 (25)	24 (%75)	
C	4 (%15.4)	22 (%84.6)	
FVC ≥%80, FEV1/FVC≥%70			
None	39 (%26.4)	109 (%73.6)	**<0.001**
Yes	134 (%73.2)	49 (%26.8)	
FEV1≥%80, FEV1/FVC≥%70			
None	0	34 (%100)	**<0.001**
Yes	173 (%58.2)	124 (%41.8)	
FEV1			
<%80	36 (%22.1)	127 (%77.9)	**<0.001**
≥%80	137 (%81.5)	31 (%18.5)	
FVC			
<%80	39 (%28.7)	97 (%71.3)	**<0.001**
≥%80	134 (%6.7)	61 (%31.3)	
FEV1/FVC <%70			
None	173(%58.6)	122 (%41.4)	**<0.001**
Yes	0	36(%100)	

DISCUSSION

This retrospective cross-sectional study evaluated the association between pneumoconiosis and small airway dysfunction. In our study, age, heavy smoking, pneumoconiosis stage, occupational group, duration of exposure, and presence of PMF were independent risk factors for developing SAD in patients with pneumoconiosis. In the study, SAD was mostly seen in mine workers, which may be related to more intense dust exposure of mine workers underground.

Until now, few studies have demonstrated the development of SAD in patients with pneumoconiosis. In the early 1970s, Seaton et al. evaluated dynamic compliance in 25 miners with evidence of pneumoconiosis and normal spirometry and found that dynamic compliance was decreased in 15 of them. Small airways were pointed out as the site of abnormality in this decrease in dynamic compliance [15]. In a study designed in California, autopsies of 112 agricultural workers showed wall thickening, remodeling, and inflammation associated with carbonaceous and mineral dust accumulation in small airways, with little or no accumulation in large airways [12].

In a study by Churg et al., mineral dust-related small airway pathology was found in lung tissue from 174 patients who underwent lung resection for lung carcinoma. It was reported that 53 of these patients were exposed to mineral dust, and 13 of these 53 patients had mineral dust-related airway disease pathology in the respiratory bronchioles. When patients with small airway disease associated with mineral dust in histopathology were compared with the control group, FEV1, FVC, and FEF 25-75 values were found to be significantly decreased [16].

In recent studies showing the development of SAD in patients with pneumoconiosis, the prevalence of SAD was reported as 43.5% and 66.3% [11]. In our study, in which we used the same diagnostic criteria for SAD, the prevalence was 47.7%. In addition, studies have emphasized that SAD may be one of the early functional abnormalities of lung damage developing in pneumoconiosis, and it has been reported that the prevalence of SAD increases as the stage of pneumoconiosis increases [13]. Our study found that the frequency of SAD increased significantly with increasing disease stages in patients with pneumoconiosis. In addition, for the first time in our research, it was found that the incidence of SAD increased as the size of the large opacity increased in patients with PMF.

The results of studies evaluating the effect of smoking on airway pathologies associated with occupational exposure are conflicting. One study reported that smoking did not affect small airway function in occupationally induced airway pathologies and was consistent with a previous study investigating biological dust. In another study, respiratory symptoms were more frequent in smokers, but smoking did not change the relationship between occupation and pulmonary function [17]. In our study, no relationship was found between smoking status and SAD due to different occupational exposure, in line with the literature data. Still, the relationship between the development of SAD in smokers who smoked 20 pack-years or more was statistically significant.

Jong et al. investigated the association of occupational exposure to vapors, gases, dust, and smoke with small airway obstruction. They showed that the effects of occupational exposure in the small airways were a primary response in those with normal FEV1/FVC and normal estimated FEV1 values. They emphasized that this was independent of the effects on the large airways. It has also been shown that smoking does not affect small airway function in those whose small airways are affected by occupational exposure [18]. In our study, consistent with this study, SAD was observed independently of large airways in 26.8% of pneumoconiosis patients with normal FVC, FEV1/FVC, and 41.8% of pneumoconiosis patients with normal FEV1, FEV1/FVC.

Although our study evaluated SAD development and risk factors in a large series of pneumoconiosis cases, it has some limitations. The limitations include the small number of patients, heterogeneous occupational groups, and retrospective study; therefore, the relationship between the symptoms and SAD could not be evaluated.

CONCLUSION

In our study, a significant correlation was found between the stage of pneumoconiosis and SAD. In post-occupational pneumoconiosis, SAD

was observed independently of large airway obstruction in both smokers and never smokers. Therefore, early small airway obstruction should be considered when monitoring the health of patients with pneumoconiosis.

Author contribution

Study conception and design: AAK, AK, GS, and CŞ; data collection: AAK, AK, and GS; analysis and interpretation of results: AAK and AK; draft manuscript preparation: AAK, AK, and GS. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Ankara Atatürk Sanatorium Education and Research Hospital Ethics Committee (Protocol no: 2012-KAEK-15/2750).

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Conflict of interest

The authors declare that there is no conflict of interest.

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ORIGINAL ARTICLE

Prognostic importance of systemic immune inflammation index in chronic obstructive pulmonary disease

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ABSTRACT

Objective: Chronic obstructive pulmonary disease (COPD) is associated with various immunopathophysiological pathways. Therefore, several inflammatory, hematological and immunological biomarkers are essential for diagnosis, prognosis, and survival of COPD. Among these inflammatory markers, such as C-reactive protein (CRP), neutrophil, lymphocyte and platelet counts were shown to have strong correlations with prognosis, survival and mortality. Recently, a novel inflammatory marker stated as systemic immune-inflammation index (SII) were presented as the most accurate in predicting inflammatory status and prognosis in various clinical settings. We aimed to investigate whether SII can be a useful tool for predicting prognosis and survival in COPD patients.

Material and Methods: We aimed to evaluate retrospectively the effect of SII (the ratio of platelet and lymphocyte multiplication to neutrophil count) on the course of the COPD in 270 patients. The effect of hemogram values, spirometric measurements, such as FEV1, and CRP on the number of attacks in COPD patients seen in the outpatient clinic and the effect of SII on clinical or intensive care hospitalization in COPD patients were evaluated. Whether the SII correlates with symptoms and one-month survival in COPD patients were evaluated. FEV1 and CRP values, duration of hospitalization, smoking and modified Medical Research Council (mMRC) scales were correlated among each other.

Results: mMRC was significantly correlated with FEV1(%) and FEV1(lt) levels, and CRP. The effects of mMRC, FEV1/FVC and smoking on survival in COPD patients were also significantly shown. CRP values were significantly correlated with WBC, neutrophil and lymphocyte counts, and SII values. Unfortunately, SII values were non-significantly correlated with FEV1 values, duration of hospitalization, smoking and mMRC, due to earlier stage and small number of cases.

Conclusion: We investigated the clinical significance of SII on prognosis of COPD patients. SII might assist the identification of high-risk patients with low FEV1 and high CRP values. This study sheds light on future research on SII as a prognostic marker.

Keywords: Systemic immune inflammation index, COPD, prognosis.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death in the world, with a prevalence of 5-20% in the world, with a prevalence of 19.2% in Turkey [1]. COPD patients constitute the majority of applications to the pulmonary outpatient clinic [2]. COPD is a disease with chronic inflammation in the airways and has a high mortality and morbidity rate [3].

COPD is a common, preventable and treatable condition that has a complex pathophysiology and an even more complex immunopathological process [4]. In this process, there are both immune and non-immune inflammatory changes with oxidative stress imbalance and alterations in the protease/anti-protease ratio caused by genetic, epigenetic and environmental defects. COPD produces irreversible tissue damage and chronic inflammation with tissue repair alteration, which induces chronic obstruction of the airway, bronchitis and systemic damage [5, 6].

Most common resulting comorbidities include cardiovascular disease, metabolic syndrome, osteoporosis, depression, musculoskeletal dysfunction, increased biological age, lung cancer and other types of malignancies [7]. In the conception of COPD, recognizing that it is a non-transmittable and preventable disease is indispensable.

The systemic immune-inflammation index (SII), is calculated by multiplying neutrophil and platelet counts and then dividing the result by the lymphocyte count, is a recently introduced inflammation parameter and a prognostic indicator of adverse outcomes and survival in various cancer types. The clinicopathological features and follow-up data were evaluated to compare SII with other systemic inflammation-based prognostic indices such as neutrophil-to-lymphocyte ratio (NLR) and platelet-to lymphocyte ratio (PLR) in patients with colorectal cancer [8]. Higher SII levels was associated with poor prognosis in cervical cancer patients [9], bladder cancer patients [10], hepatocellular carcinoma patients [11], endometrial cancer patients [12], breast [13] and NSCLC [14] patients. The SII was an independent predictor of survival in multivariate analysis. Moreover, recent studies have demonstrated that the SII can also be used as a prognostic indicator in different cardiovascular diseases (CVD) [15]. Individuals with higher SII had an increased risk of CVD and SII at the onset of CVD was significantly higher than that in the general population [15].

In addition, SII is a predictor of Contrast-Induced Nephropathy in patients with ST-segment elevation Myocardial Infarction [16]. Last, but not the least, NLR, PLR, and SII values of the COPD patients with pulmonary hypertension were significantly higher in the group of COPD patients with the acute exacerbation, so NLR, PLR, and SII values could be early indicators of pulmonary hypertension in patients with acute exacerbation of COPD [17]. Higher SII levels were associated with worse clinical outcome in pneumonia [18]. The hemogram indexes PLR, SII, and SIRI (monocyte × neutrophil/lymphocyte ratio; systemic inflammation response index) were associated with COPD exacerbation in 275 stable COPD patients [18]. SII and NLR is a potential new diagnosed biomarker in severe-patients with COVID-19 pneumonia [19]. Sarcopenia and a higher SII levels are significantly linked with morbidity and mortality in patients with COPD [20].

Finally, a recent study on 16,636 COPD patients showed a significant positive correlation among SII and different age groups, gender, Body Mass Index, smoking status, and those with a history of hypertension [21]. Higher SII levels are significantly linked to higher prevalence of COPD. COPD patients with a higher SII levels have a higher risk of all-cause mortality [21]. Additional long-term studies in different stages of COPD with different comorbidities and treatments are necessary to confirm these results.

Therefore, we aimed to investigate the clinical significance of SII on prognosis of patients with COPD. We correlated SII levels with one-month survival in 270 COPD patients in order to understand whether SII can be a useful tool for predicting prognosis and survival in patients with COPD, among other inflammatory markers.

MATERIAL AND METHODS

This study is a retrospective study. Patients over the age of 18 who applied to Lokman Hekim Chest Diseases outpatient clinic between January 2018

and May 2023 and followed up with the diagnosis of chronic obstructive pulmonary disease (COPD) were included in the study with an ethical approval of Lokman Hekim University Ethical Committee Approval No: 2023120. Patients under the age of 18 and pregnant, who have a history of malignancy, active systemic disease, collagen tissue disease, interstitial lung disease and those who use drugs that could affect the hemogram level were excluded from the study.

Patients over 18 years old and retrospective analysis of the files of patients admitted to the outpatient clinic with the diagnosis of COPD. The files of these patients were examined. Pulmonary function tests were recorded from their files for COPD disease. Platelet, lymphocyte and neutrophil count rates were examined from the patients' admission hemogram results.

We evaluated retrospectively the effect of SII (the ratio of platelet and lymphocyte multiplication to neutrophil count) on the course of the disease in 270 COPD patients.

The effect of hemogram values, spirometric measurements, such as FEV1, and CRP on the number of attacks in COPD patients seen in the outpatient clinic and the effect of SII on clinical or intensive care hospitalization in COPD patients were evaluated. Whether the SII correlates with symptoms and one-month survival in COPD patients were evaluated. All parameters were correlated among each other, by using correlation analysis.

The one-month survival of the patients from the day of admission to the hospital were recorded. The patients were divided into two groups, according to their survival or death status.

FEV1 (lt), FVC (lt) and FEV1/FVC levels were measured by spirometry.

The mMRC scale is a self-rating tool to measure the degree of disability that breathlessness poses on day-to-day activities on a scale from 0 to 4: 0, no breathlessness except on strenuous exercise; 1, shortness of breath when hurrying on the level or walking up a slight hill; 2, walks slower than people of same age on the level because of breathlessness or has to stop to catch breath when walking at their own pace on the level; 3, stops for breath after walking ~100 m or after few minutes on the level; and 4, too breathless to leave the house, or breathless when dressing or undressing [22].

In their initial blood tests which were obtained at admission, following parameters were studied: White Blood Cells (WBC) numeric value (normal range 4.6-10.2 $x10^3$/μL), neutrophil numeric value (normal range 1800-7700/μL), lymphocyte numeric value (normal range 1500-4000/μL), platelet numeric value (normal range 142-450x10 3/μL), CRP value (normal range 0-0.5 mg/dL) and creatinine value (normal range 0.5-1.2 mg/dL).

WBC, neutrophil and lymphocyte counts were measured by fluorescent flow scatter. Platelet counts were measured by electric impedance.

Serum CRP levels were measured by nephelometric/turbidometric method (Beckman). Serum creatinine levels were measured by alkaline picrate based assay (Beckman).

In order to determine the number of samples, a power analysis (α =0.05, β =0.80) was performed by taking a study with similar methodology and a sample size of n=275 was obtained [18], but because of their missing data, the number of people were excluded from the analysis, and a total sample of 270 people was obtained.

Analysis was performed with the SPSS v.25 software. Significance was set at $p < 0.05$ for all comparisons/analyses. Continuous data were summarized with mean ± standard deviation values, categorical data were summarized with frequency (n) and relative frequency (%). Univariate comparisons for continuous data were performed with the Mann-Whitney U test due to the fact that parametric assumptions were not met for any of the comparisons or variable sets. Categorical data distributions were compared with the Pearson Chi-square or the Fisher's exact test depending on assumptions. The binary logistic regression model to identify factors that were independently associated with mortality (odds ratio (OR) for one-month survival) was created by including all variables that demonstrated significant differences in univariate analysis. The model included age, hypertension, diabetes mellitus, smoking package-years, FEV1 (lt), FVC (lt), FEV1/FVC levels, and mMRC scales. The forward conditional parameter selection method was used.

RESULTS

41 female and 229 male COPD patients were included in our study. Median age were 65 years old. We found older age, comorbities such as hypertension and diabetes mellitus; smoking, lower FEV1(%), FEV1(lt), FVC(%), FVC(lt), FEV1/FVC levels and mMRC scales were significantly associated with one-month survival by univariate analysis in these 270 COPD patients (Table 1).

Low mMRC scales and low FEV1(%) and FEV1(lt) levels were significantly correlated (Table 2). Additionally, low mMRC scales and high CRP levels were significantly correlated (Table 2). SII values were non-significantly correlated with FEV1, duration of hospitalization, smoking and mMRC scales (Table 2). CRP values were significantly correlated with WBC, neutrophil and lymphocyte counts, and SII values (Table 2b).

By regression analysis of these COPD patients, mortality risk increases 1.043 fold, if smoking package/year increases one level (OR=1.043) (Table 3). If FEV1/FVC level increases one level, mortality risk increases 0.945 fold (OR=0.945) (Table 3). If mMRC scale increases one level, mortality risk increases 4.138 fold (OR=4.138) (Table 3).

Table 1. Comparison of patients based on one-month survival by using univariate analysis of possible risk factors in 270 COPD patients

		Survivors	Deceased	p
Gender	female	34 (15%)	7 (16.3%)	0.827
	male	193 (85%)	36 (83.7%)	
Age (years)		62.6 ± 8.2	67.3 ± 9	**0.001**
Rheumatologic diseases	-	227 (100%)	43 (100%)	N/A
	+	0 (0%)	0 (0%)	
Coronary artery diseases	-	206 (90.7%)	37 (86%)	0.403
	+	21 (9.3%)	6 (14%)	
Hypertension	-	168 (74%)	25 (58.1%)	**0.035**
	+	59 (26%)	18 (41.9%)	
Diabetes Mellitus	-	199 (87.7%)	32 (74.4%)	**0.023**
	+	28 (12.3%)	11 (25.6%)	
Smoking (package/year)		28.6 ± 14.2	44.7 ± 22.6	**<0.001**
Smoking habit	none	0 (0%)	0 (0%)	0.868
	Still smoking	182 (80.2%)	34 (79.1%)	
	Quitted	45 (19.8%)	9 (20.9%)	
BMI	30 and less	118 (52%)	24 (55.8%)	0.645
	30 and more	109 (48%)	19 (44.2%)	
FEV1(%)		51.1 ± 12.4	43.9 ± 15.7	**0.002**
FEV1(lt)		1.3 ± 0.5	1.1 ± 0.5	**0.001**
FVC		66.1 ± 13.5	60.2 ± 19.2	**0.045**
FVC(lt)		2.3 ± 0.7	2 ± 0.7	**0.028**
FEV1/FVC		59 ± 8.4	53.3 ± 11.5	**0.003**
mMRC scales		2 ± 0.5	2.7 ± 0.8	**<0.001**
WBC (mm^3)		12.9 ± 4.9	12.5 ± 5.9	0.642
Platelet count (mm^3)		235.6 ± 83.1	227.9 ± 135	0.616
Neutrophil count (mm^3)		10.5 ± 4.8	10.1 ± 5.4	0.667
Lymphocyte count (mm^3)		1.6 ± 1.3	1.46 ± 1.3	0.602
CRP (mg/L)		38 ± 72.1	40.2 ± 70.8	0.853
Creatinine (mg/dL)		1.1 ± 0.6	1.1 ± 0.8	0.552
SII		2462 ± 2778	2449 ± 2163	0.978

DISCUSSION

COPD is a major cause of death and morbidity worldwide. The pathogenesis of disease is briefly characterized by irreversible expiratory airflow limitation, uncontrolled chronic inflammation with acute exacerbations, and emphysematous pulmonary damage. Even though this disease is an increasing unmet global healthcare problem; unfortunately, the conventional therapies are still symptomatic, and regenerative therapies are undergoing clinical trials [5, 6]. Sub-optimal COPD patient phenotyping, an incomplete understanding of COPD pathogenesis and a shortage of sensitive tools, such as effective diagnostic, prognostic and predictive biomarkers, that provide patient-relevant intermediate endpoints likely all result in the lack of novel and effective COPD interventions [23]. Therefore, COPD patients are still diagnosed based on the presence of persistent airflow limitation, which is measured by spirometry. These measurements reflect the global sum of all the different possible COPD pathologies, so we cannot differentiate different effects of airway and parenchymal defects on the disease pathogenesis. Imaging techniques are helpful to diagnose pulmonary structural and functional pathologies, but COPD pathogenesis covering deregulated inflammation, proteolysis/anti-proteolysis imbalance, and destroyed repair mechanisms, dysbiosis, smoking-related damage,

Table 2a. Correlations among continuous variables (Smoking, FEV1(%), FEV1(lt), FVC, FVC (lt) FEV1/FVC and mMRC scales) , CRP and creatinine examined by using correlation analysis in 270 COPD patients

		Smoking Package/year	FEV1(%)	FEV1(lt)	FVC	FVC(lt)	FEV1/FVC	mMRC scales	crp	Creatinine
Smoking Package/year	r	1								
	p									
FEV1(%)	r	-0.035	1							
	p	0.570								
FEV1(lt)	r	-0.032	**0.694**	1						
	p	0.600	**<0.001**							
FVC	r	-0.123	**0.722**	**0.597**	1					
	p	0.045	**<0.001**	**<0.001**						
FVC(lt)	r	-0.038	**0.506**	**0.843**	**0.644**	1				
	p	0.540	**<0.001**	**<0.001**	**<0.001**					
FEV1/FVC	r	-0.053	**0.715**	**0.412**	**0.310**	**0.073**	1			
	p	0.388	**<0.001**	**<0.001**	**<0.001**	**0.235**				
mMRC scales	r	**0.242**	**-0.232**	**-0.298**	**-0.246**	**-0.211**	**-0.221**	1		
	p	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**<0.001**			
WBC	r	-0.019	0.103	0.028	0.048	-0.021	0.111	0.038		
	p	0.762	0.092	0.644	0.440	0.730	0.070	0.538		
Platelet count	r	-0.004	-0.008	-0.009	-0.022	-0.009	0.032	0.010		
	p	0.949	0.900	0.883	0.723	0.881	0.607	0.875		
Neutrophil count	r	-0.010	0.068	0.004	0.034	-0.032	0.080	0.039		
	p	0.868	0.268	0.953	0.581	0.598	0.193	0.528		
Lymphocyte count	r	-0.014	0.026	-0.026	0.006	-0.045	0.021	0.062		
	p	0.818	0.678	0.676	0.926	0.463	0.732	0.310		
CRP	r	-0.063	-0.082	-0.082	-0.054	-0.048	-0.051	-0.046	1	
	p	0.306	0.178	0.182	0.380	0.432	0.404	0.451		
Creatinine	r	0.017	0.043	0.007	-0.010	-0.001	-0.001	-0.041	-0.006	1
	p	0.786	0.484	0.907	0.876	0.984	0.991	0.507	0.918	
SII	r	-0.009	0.025	0.001	0.016	0.002	0.032	0.016	**0.134**	0.034
	p	0.882	0.680	0.981	0.790	0.976	0.609	0.794	**0.029**	0.575

Table 2b. Correlations among continuous variables (WBC, platelet, neutrophil and lymphocyte count, CRP and Creatinine) examined by using correlation analysis in 270 COPD patients

		WBC	Platelet count	Neutrophil count	Lymphocyte count	CRP	Creatinine
Smoking Package/year	r						
	p						
FEV1(%)	r						
	p						
FEV1(lt)	r						
	p						
FVC	r						
	p						
FVC(lt)	r						
	p						
FEV1/FVC	r						
	p						
mMRC scales	r						
	p						
WBC	r	1					
	p						
Platelet count	r	**0.151**	1				
	p	**0.014**					
Neutrophil count	r	**0.965**	**0.126**	1			
	p	**<0.001**	**0.040**				
Lymphocyte count	r	0.101	0.064	-0.092	1		
	p	0.100	0.294	0.134			
CRP	r	**0.165**	-0.068	**0.187**	**-0.122**	1	
	p	**0.007**	0.266	**0.002**	**0.045**		
Creatinine	r	0.033	0.172	0.017	0.015	-0.006	1
	p	0.587	**0.005**	0.788	0.802	0.918	
SII	r	**0.510**	**0.257**	**0.618**	**-0.386**	**0.134**	0.034
	p	**<0.001**	**<0.001**	**<0.001**	**<0.001**	**0.029**	0.575

Table 2c. Summary table of significant correlations among FEV1(%), FEV1(lt), Smoking (package/year), CRP and mMRC scales

		FEV1(%)	FEV1(lt)	Smoking Package/year	CRP
FEV1(%)	r	1.000			
	p	-			
FEV1(lt)	r	0.687	1.000		
	p	**<0.001**	-		
Smoking Package/year	r	-0.043	-0.041	1.000	
	p	0.483	0.508	-	
CRP	r	-0.010	-0.071	-0.033	1.000
	p	0.868	0.249	0.592	-
mMRC scales	r	-0.275	-0.330	0.224	-0.053
	p	**<0.001**	**<0.001**	**<0.001**	0.386

Table 3. Forward-conditional logistic regression model, final step (Step 3)

	Beta Coefficient	Std. Error	Wald	Df	**P value**	**Exp. Beta (OR)**	95% CI for OR	
							Lower	Upper
Smoking package/year	0.043	0.011	15.913	1	**<0.001**	**1.043**	1.022	1.065
FEV1/FVC	-0.057	0.020	7.797	1	**0.005**	**0.945**	0.908	0.983
mMRC scales	1.420	0.302	22.060	1	**<0.001**	**4.138**	2.288	7.484
Constant	-3.318	1.339	6.142	1	**0.013**	0.036		

OR: odds ratio.

CI: confidence interval

Nagelkerke R2: 0.367

and autoimmune pulmonary defects have to be evaluated, regarding the complex pathologic process of the disease [24]. Therefore, several inflammatory, hematological and immunological biomarkers are essential for diagnosis, prognosis, and survival of COPD. These can be useful for better phenotyping of these patients, in addition to the support of imaging. Among these inflammatory markers, such as CRP, CRP-to albumin ratio, fibrinogen-to-albumin ratio, neutrophil, lymphocyte, platelet counts, NLR and PLR have been shown to have strong correlations with prognosis, clinical outcomes and survival/mortality. Recently, a novel inflammatory marker SII were suggested to be more powerful than either NLR or PLR alone in predicting inflammatory process and prognosis in various clinical settings, such as cancer, cardiovascular diseases, nephropathy, pneumonia and COPD. Inflammatory markers will be helpful in order to reveal COPD phenotypes and what COPD really 'looks' like, beyond spirometric and imaging measurements [24].

Similar to the findings in the recent literature [17-20], we found older age, COPD comorbities such as hypertension and diabetes mellitus; smoking, lower FEV1 (%), FEV1(lt), FVC(%), FVC(lt), FEV1/FVC levels and mMRC scales were significantly associated with one-month survival in 270 COPD patients. Additionally, low FEV1(%) and FEV1(lt) and high CRP levels were significantly correlated with low mMRC scales. By regression analysis of these COPD patients, mortality risks increase 1.043, 0.945 and 4.138 fold, respectively: if smoking package/year, FEV1/FVC levels and mMRC scales increase one level.

We investigated the clinical significance of SII on prognosis of COPD patients. SII has a potential to be a beneficial tool for predicting prognosis and survival outcome in patients with COPD in several studies in the literature. It might assist COPD patient phenotyping and importantly, the identification of high-risk patients with low FEV1 and high CRP values.

Recently, Ye et al. showed that higher SII levels are significantly linked to higher prevalence of COPD and their patients with a higher SII levels have a higher risk of all-cause mortality [21]. In this study, logistic regression analysis was performed to assess the correlation between COPD, lung function, chronic respiratory symptoms and SII. They used Cox proportional hazards model to analyze the relationship between SII and mortality in COPD patients and healthy individuals. They used propensity score matching method to match the COPD population with similar baseline levels with the normal population for further analyzing the correlation between SII and COPD [21] .

SII values were non-significantly correlated with FEV1 values, duration of hospitalization, smoking and mMRC. CRP values were correlated with WBC, neutrophil and lymphocyte counts, and SII values. Therefore, further comprehensive studies in larger groups are necessary to assess whether SII is a powerful tool to predict prognosis and survival in COPD patients. In addition, considering the various stages, different pathogenesis, and overall complex process of the COPD disease, patients were in earlier stages of COPD in our study, so this may affect the non-significant SII differences among our patients, since SII is an inflammatory marker. Designing a study with additional advanced stage patients in larger groups will overcome this significancy problem. In addition, even though we chose patients in the earlier stage to be consistent, choosing patients in various stages, especially acute exacerbations, of COPD, categorizing according to

their various treatments and co-morbidities, and comparing every group of COPD patients with healthy controls will be more powerful to evaluate SII as a prognostic marker. Last, but not the least Cox proportional hazards analysis will be helpful in order to analyze the correlation between SII and mortality in COPD patients and healthy controls, and propensity score matching analysis will be useful to match the COPD population with similar baseline levels with the normal population.

Author contribution

Study conception and design: ESG and BC; data collection: ESG and BC; analysis and interpretation of results: ESG and BC; draft manuscript preparation: BC. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Lokman Hekim University Ethical Committee (Approval No: 2023120/17.07.2023).

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Conflict of interest

The authors declare that there is no conflict of interest.

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ORIGINAL ARTICLE

Comparison of the effects of intravenous analgesic agents used in the intraoperative period on pentraxin-3 levels in patients undergoing on-pump coronary artery bypass surgery

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ABSTRACT

Objective: The aim of this study was to compare the effects of fentanyl, dexmedetomidine, and remifentanil on serum pentraxin 3 levels in patients undergoing on-pump coronary artery bypass surgery.

Materials and Methods: In this retrospectively designed study, 36 patients who underwent elective on-pump coronary artery bypass surgery for coronary artery disease in the Cardiovascular Surgery Clinic of our hospital between 01.01.2020 and 31.12.2021 and whose serum pentraxin 3 levels were studied in the pre-operative and post-operative period were included. Patients were divided into 3 groups as fentanyl (Group F), dexmedetomidine (Group D), and remifentanil (Group R) based on the analgesic agent used during the intraoperative period. The data of the patients were obtained by scanning their files and information in the hospital automation system.

Results: Demographic characteristics, duration of anesthesia, cardiopulmonary bypass duration, and aortic cross-clamp duration were similar. When serum pentraxin 3 levels were evaluated within groups, the difference between pre-operative and post-operative results was significant. In the intergroup evaluation, only the results obtained from Group F in the pre-operative period were significant compared to the other groups, but there was no significant difference between the results obtained in the post-operative period.

Conclusion: When the data of this study were evaluated, it was determined that the analgesic agent used in the intraoperative period of on-pump coronary artery bypass surgery did not significantly affect post-operative serum pentraxin 3 levels.

Keywords: Coronary artery bypass surgery, dexmedetomidine, fentanyl, pentraxin 3, remifentanil.

INTRODUCTION

Pentraxin-3 (PTX 3), a current acute phase reactant, was first discovered in the early 1990s, and the human PTX 3 gene is located on chromosome 3q25 [1]. It has been reported to be predominantly present in macrophages, neutrophils, dendritic cells, smooth muscle cells, atherosclerotic lesions, and inflammatory endothelial cells [2,3]. It plays a role in vascular inflammation and endothelial dysfunction through various mechanisms. It is a good indicator of mortality and a useful marker for monitoring treatment success. Studies have confirmed a significant connection between PTX 3 and endothelial dysfunction [4].

The most effective treatment method for atherosclerosis and related coronary artery disease (CAD) is coronary artery bypass graft (CABG) surgery. When performed with the cardiopulmonary bypass

(CPB) pump, it can lead to a systemic inflammatory response that can cause major organ dysfunction [5], adversely affect post-operative outcomes, and even result in systemic inflammatory response syndrome, which can lead to mortality, and an increase in serum PTX 3 levels in the early post-operative period [6].

In addition to the anesthetic agent used, fentanyl, dexmedetomidine or remifentanil are routinely used by intravenous (IV) infusion for analgesic activity during anesthesia maintenance. These agents can exhibit antioxidant and cytoprotective effects to varying degrees in addition to their analgesic activity [7]. It has been shown that the preferred anesthesia management during surgery can be effective on serum PTX 3 levels [8].

In this retrospective study, we aimed to compare the effects of the IV analgesic agents fentanyl, dexmedetomidine, and remifentanil, which were used for anesthesia maintenance in patients undergoing elective on-pump CABG surgery, on post-operative PTX 3 levels. We conducted our study with the hypothesis that dexmedetomidine would have a greater cytoprotective effect.

MATERIALS AND METHODS

This study protocol was approved by the Hacettepe University Non-Interventional Clinical Studies Ethics Committee on May 31, 2022, with decision number GO 22/525.

This retrospective case-control study, which we designed after obtaining ethical approval, was conducted at Hacettepe University Adult Hospital between June 1, 2022, and September 1, 2022. It was planned to include patients who underwent elective on-pump CABG surgery at the Department of Cardiovascular Surgery of Hacettepe University School of Medicine due to CAD between January 1, 2020, and December 31, 2021, and whose serum PTX 3 levels were obtained in the pre-operative and post-operative period. The files of a total of 38 patients were reviewed, and 36 patients with complete data were included in the study. The patients included in the study were divided into three groups: the fentanyl group (Group F), the dexmedetomidine group (Group D), and the remifentanil group (Group R), based on the analgesic agent used during anesthesia maintenance. Blood samples were obtained and evaluated for PTX 3 levels at three different times: pre-operative period (T1), 7th hour post-operatively (T2), and 24th hour post-operatively (T3). Patient data such as age, weight, height, gender, anesthesia management, surgical duration, anesthesia duration, aortic cross-clamp duration, and the agent used for anesthesia maintenance were obtained through scanning the patients files, while laboratory data, including PTX 3 level, were obtained from the database of the hospital.

In addition to the standard ASA monitoring applied to the patients taken to the operating room for surgery, invasive arterial blood pressure, central venous pressure, urinary catheter, body temperature, and near-infrared spectroscopy (NIRS) monitoring, which are routine in our clinic, were also applied. For all patients included in the study, induction and subsequent endotracheal intubation were performed using our clinic's standard anesthesia protocol with midazolam 0.01-0.1 mg/kg, propofol 1-2.5 mg/kg, fentanyl 1-2 mcg/kg, and rocuronium 0.6-1 mg/kg. Fentanyl at a dose of 2 mcg/kg/hour, dexmedetomidine at a dose of 0.4 mcg/kg/hour, or remifentanil at a dose of 0.05 mcg/kg/minute was used intravenously throughout the maintenance period, with one of these agents being started with induction. All patients received 16 mg of IV dexamethasone. Anesthesia was maintained using 2% sevoflurane, 50% O_2/air mixture, and IV fentanyl, dexmedetomidine, or remifentanil. In all cases of CABG surgery, performed on-pump technique, and during the CPB period, anesthesia maintenance was provided through 2% sevoflurane administered via the CPB pump and fentanyl, dexmedetomidine, or remifentanil administered intravenously. After the administration of all anesthetic agents used after surgery was stopped, all patients were transferred to the cardiac surgery intensive care unit while still intubated.

Statistics

Descriptive statistics were used for patient demographic information, anesthesia duration, cardiopulmonary bypass duration, and aortic cross-clamp duration. Continuous variables were presented as means and standard deviations or

medians and interquartile ranges depending on the distribution. Categorical variables were presented as frequencies and percentages. Statistical significance was determined using the chi-square or Fisher's exact test for categorical variables and the Kruskal-Wallis or Friedman test for continuous variables ($p < 0.05$). The Statistical Package for the Social Sciences (SPSS) software package (Version 27.0, IBM, New York, USA) was used for all analyses. Sample size calculation, primary and secondary endpoints, and record details were not applicable to this retrospective study.

RESULTS

A total of 36 participants (30 males, 6 females) were included in this study, and these participants were divided into three groups: the fentanyl group consisted of 13 participants (13 males, 0 females), the dexmedetomidine group consisted of 13 participants (9 males, 4 females), and the remifentanil group consisted of 10 participants (8 males, 2 females). The average age of the participants was calculated as 57.92 (±9.97).

Demographic and Clinical Characteristics

The basic demographic and clinical characteristics of the study participants were carefully evaluated (Table 1). The average ages of the participants did not show a significant difference between the fentanyl group (mean age 54.00 ± 8.84 years), the dexmedetomidine group (mean age 58.85 ± 6.79 years), and the remifentanil group (mean age 61.80 ± 13.44 years) ($p = 0.164$). Similarly, there was no significant difference in gender distribution among the three groups ($p = 0.103$).

When anesthesia duration, cardiopulmonary bypass duration, and aortic cross-clamp duration were examined in detail, the average anesthesia duration was 329.23 ± 64.48 minutes, the average cardiopulmonary bypass duration was 114.00 ± 40.44 minutes, and the average aortic cross-clamp duration was 67.54 ± 24.64 minutes for the fentanyl group. For the dexmedetomidine group, the average anesthesia duration was 352.31 ± 73.75 minutes, the average cardiopulmonary bypass duration was 116.00 ± 47.00 minutes, and the average aortic cross-clamp duration was 68.31 ± 31.69 minutes. In the remifentanil group, the average anesthesia duration was 318.00 ± 69.21 minutes, the average cardiopulmonary bypass duration was 105.50 ± 26.74 minutes, and the average aortic cross-clamp duration was 64.20 ± 17.32 minutes. These analysis results indicate that the baseline characteristics of the participants in each group were statistically similar ($p = 0.480$; $p = 0.809$; $p = 0.925$).

Table 1. Demographic characteristics of participants, anesthesia duration, cardiopulmonary bypass duration, aortic cross-clamp duration, and pentraxin 3 levels

	Fentanyl Group (n=13)	Deksmedetomidin Group (n=13)	Remifentanil Group (n=10)	Total (n=36)	p
Age	54.00(±8.84)	58.85 (±6.79)	61.80(±13.44)	57.92(±9.97)	0.164
Sex	F=0 (0%) M=13(100%)	F=4 (30.0%) M=9 (69.2%)	F=2 (20%) M=8 (80%)	F=6 (16.7%) M=30 (83.3%)	0.103
Anesthesia duration	329.23 (±64.48)	352.31 (±73.75)	318.00 (±69.21)	334.44 (±68.76)	0.480
Cardiopulmonary bypass duration	114.00 (±40.44)	116.00 (±47.00)	105.50 (±26.74)	112.36 (±39.00)	0.809
Aortic cross-clamp duration	67.54 (±24.64)	68.31 (±31.69)	64.20 (±17.32)	66.89 (±25.15)	0.925
Pentraxin 3 levels					
T1	1.79 (0.66-2.55)	0.77 (0.10-1.48)	1.06 (0.22-4.77)	1.16 (0.10-4.47)	**<0.001**
T2	46.27 (25.86-183.13)	60.81 (34.03-141.87)	52.16 (21.98-197.49)	54.25 (21.98-197.49)	0.615
T3	19.95 (5.49-179.18)	18.38 (10.31-57.53)	25.79 (6.13-68.31)	20.80 (5.49-179.18)	0.604

Age information is given in years, anesthesia, cardiopulmonary bypass , and aortic cross-clamp durations are expressed in minutes. Pentraxin 3 levels are recorded as ng/ml. When indicating gender, "F" represents female, and "M" represents male. T1 represents the pre-operative period; T2 represents the post-operative 7th hour; T3 represents the post-operative 24th hour. Age, anesthesia duration, cardiopulmonary bypass duration, and aortic cross-clamp duration were analyzed using the ANOVA method. The gender variable was evaluated using the Chi-square test. The values were provided as mean (± SD), median (min–max).

Table 2. Comparison of pentraxin 3 levels within groups

Group		n	x^2	df	p
Fentanil	Difference 2-1	13	21.385	2	0.000
	Difference 3-2				
	Difference 3-1				
Deksmedetomidin	Difference 2-1	13	26.000	2	<0.001
	Difference 3-2				
	Difference 3-1				
Remifentanil	Difference 2-1	10	15.800	2	0.000
	Difference 3-2				
	Difference 3-1				

The Friedman test was used for analysis. Difference 2-1 represents the difference in pentraxin 3 levels between pre-operative and post-operative 7th hour, Difference 3-1 represents the difference in pentraxin 3 levels between pre-operative and post-operative 24th hour, and Difference 3-2 represents the difference in pentraxin 3 levels between post-operative 7th hour and post-operative 24th hour.

Table 3. Comparison of pentraxin 3 levels between groups

	Group	n	Mean	df	x^2	p
Difference 2-1	Fentanil	13	18.08	2	1.060	.588
	Dexmedetomidin	13	20.69			
	Remifentanil	10	16.20			
Difference 3-2	Fentanil	13	18.08	2	3.365	.186
	Dexmedetomidin	13	20.69			
	Remifentanil	10	16.20			
Difference 3-1	Fentanil	13	18.08	2	0.660	.719
	Dexmedetomidin	13	20.69			
	Remifentanil	10	16.20			

The Kruskal-Wallis test was applied in the analysis. Difference 2-1 represents the difference in pentraxin 3 levels between pre-operative and post-operative 7th hour, Difference 3-1 represents the difference in pentraxin 3 levels between pre-operative and post-operative 24th hour, and Difference 3-2 represents the difference in pentraxin 3 levels between post-operative 7th hour and post-operative 24th hour.

Pentraxin 3 Levels

Pre-operative PTX 3 levels showed a significant difference between the groups (Table 1) ($p < 0.001$). In the pre-operative period, the PTX 3 level of the fentanyl group was 1.79 ng/ml (95% CI: 0.66 – 2.55), the PTX 3 level of the dexmedetomidine group was 0.77 ng/ml (95% CI: 0.10 – 1.48), and the PTX 3 level of the remifentanil group was 1.06 ng/ml (95% CI: 0.22 – 4.77).

Comparison of Pentraxin 3 Levels Within Groups

In the fentanyl group, a significant differentiation in PTX 3 levels over time was observed (χ^2 (df = 2, n = 13) = 21.385, $p < 0.001$). Similarly, a significant change was observed in the dexmedetomidine group (χ^2 (df = 2, n = 13) = 26.000, $p < 0.001$). In the remifentanil group, a similar significant change was also observed (χ^2 (df = 2, n = 13) = 15.800, $p < 0.001$). These analysis results are shown in Table 2.

Comparison of Pentraxin 3 Levels Between Groups

Differences in PTX 3 levels obtained within three different time periods did not show a significant variation between the groups (Table 3). The difference between the post-operative 7th hour and the pre-operative period did not show a significant difference between the groups (χ^2 (df = 2, n = 36) = 1.060, $p > 0.05$). Similarly, the difference between the post-operative 24th hour and 7th hour did not show a significant difference between the groups (χ^2 (df = 2, n = 36) = 3.365, $p > 0.05$). Finally, the difference between the post-operative 24th hour and the pre-operative period did not create a significant difference between the groups (χ^2 (df = 3, n = 36) = 0.660, $p > 0.05$). These findings indicate that changes in PTX 3 levels during the specified time periods did not show a significant difference between the groups. Figure 1 shows the PTX 3 levels measured at three different time periods on the graph.

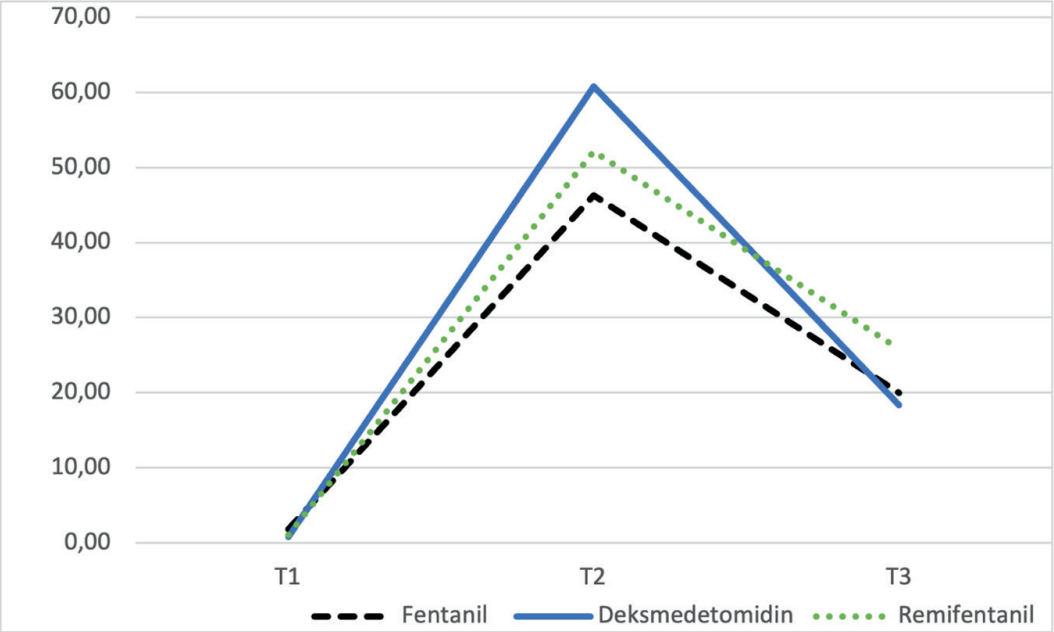

Figure 1. Changes in pentraxin 3 levels over time among groups
T1: Pre-operative, T2: Post-operative 7th hour, T3: Post-operative 24th hour.

DISCUSSION

In this study, we investigated the effects of the IV analgesic agents fentanyl, dexmedetomidine, and remifentanil, used for anesthesia maintenance during surgery, on post-operative PTX 3 levels in patients undergoing on-pump CABG surgery. As far as we know, this study is the first clinical study to investigate the effects of fentanyl, dexmedetomidine, and remifentanil on serum PTX 3 levels in patients undergoing on-pump CABG surgery. In the intra-group evaluations, it was found that the differences in PTX 3 levels measured at different time points were significant in all three groups. In the inter-group comparisons, significant differences were observed among the results obtained at the T1 time point (Table 1), while when evaluating the differences between time points, no significant differences were found among the results (Table 2).

In a study conducted by Jaworski et al. [9], which evaluated post-operative PTX 3 kinetics in children undergoing on-pump cardiac surgery due to congenital heart diseases, it was observed that PTX 3 levels peaked on the first post-operative day and then decreased to baseline values in the following days. Similarly, in a study by Hamada et al. [5], investigating the effect of dexmedetomidine on PTX 3 in patients undergoing on-pump cardiac surgery, it was observed that both the control and study groups reached their highest serum PTX 3 levels on the first post-operative day. Wang et al. [10], as a result of a study focusing on children with congenital heart diseases undergoing on-pump cardiac surgery, suggested that CPB could lead to an increase in serum PTX 3 levels. Consistent with the literature, our study also showed that serum PTX 3 levels reached their highest point at the 7th hour post-operatively and decreased to lower levels by the 24th hour post-operatively.

Altınışık et al. [8] compared general anesthesia and spinal anesthesia methods in their study evaluating the effects of anesthesia methods applied for cesarean section surgery on PTX 3. They found that serum PTX 3 levels increased significantly over time in the group receiving general anesthesia, while the difference in serum PTX 3 levels between time points was not significant in the spinal anesthesia group. Another study focused on the effect of dexmedetomidine on PTX 3 in patients undergoing on-pump cardiac surgery, suggesting that dexmedetomidine infusion could decrease PTX 3 levels after cardiac surgery with CPB [5]. In our study, while intra-group evaluations showed significant changes in PTX 3 levels over time, inter-group comparisons revealed no significant differences in PTX 3 levels between the T2 and T3 time points. Therefore, our results indicate that there were no superior effects of the administered agents on PTX 3 levels during the intraoperative period.

As a limitation of our study, it could be considered that blood samples were taken only twice in the post-operative period, and the last sample was taken 24th hour post-operatively. It would have been possible to evaluate how the results changed in the long term by evaluating them in a longer period and with more samples in the post-operative period. In addition, standardization could have been better achieved by homogenizing the groups with respect to comorbidities.

CONCLUSION

In conclusion, considering the data obtained from this study, it was observed that the IV analgesic agents fentanyl, dexmedetomidine, or remifentanil used for anesthesia maintenance during surgery did not have a significant effect on post-operative PTX 3 levels, and it was concluded that there was no superiority among them. We believe that randomized controlled prospective studies with larger group sizes are needed to confirm our observations.

Author contribution

Study conception and design: Mİ and BÇ; data collection: Mİ and MT; analysis and interpretation of results: Mİ, MT and BÇ; draft manuscript preparation: Mİ and MT. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Hacettepe University Non-Interventional Clinical Studies Ethics Committee (Protocol no. GO 22/525).

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Conflict of interest

The authors declare that there is no conflict of interest.

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acta medica

ORIGINAL ARTICLE

Knowledge of isolation precautions among the healthcare workers in the emergency department of a university hospital

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ABSTRACT

Objectives: Prevention and control of healthcare-associated infections are important for patients and personal safety and for fighting against antimicrobial resistance. In order to achieve the goal of zero infection, it is necessary to know and apply standard and transmission-based precautions. The aim of this study was to evaluate the knowledge of healthcare professionals working in the Adult Emergency Department of university hospital about isolation precautions.

Methods: A cross-sectional study was conducted in the Emergency Department of Hacettepe University Hospital between May 16, 2023 to June 23, 2023. Data were collected electronically with a standardized data collection form specially prepared for this study to examine the knowledge about isolation precautions. Each correct answer was calculated as one point. Participants could receive a score between a minimum of 0 and a maximum of 20.

Results: The 90 healthcare workers who agreed to participate in the study had a median age of 24 years and 40% were male. The median knowledge score was 13 (IQR = 4). The knowledge score of two pregnant healthcare workers was significantly higher than non-pregnant ones (p=0.04). 93.3% of the participants stated that they received education for isolation precautions. There was no significant difference in knowledge scores between those who received education and those who did not (p=0.02). Knowledge of isolation precautions to be followed in clinical scenarios (1.1% - 54.4%) and personal protective equipment to be used correctly (3.3% - 21.1%) was low.

Conclusion: The knowledge of healthcare professionals working in the Adult Emergency Department of university hospital about isolation precautions is at a moderate level. Periodical education programs on clinical scenarios is important regarding raising awareness.

Keywords: Healthcare provider, knowledge, emergency room, patient isolation, infection prevention precautions.

INTRODUCTION

The development of concepts such as employee safety, patient safety, pandemics, and antimicrobial resistance interest in the prevention and control of infectious diseases in hospitals is of great interest [1, 2]. "Zero" is targeted in hospital infections [3]. Infection prevention and control are important in all units of hospitals. However, emergency departments are different because they are units where new patient applications are high, a significant number of patients are transferred to the inpatient wards and intensive care units of the hospital, fast turnover of patients and healthcare workers, and provide uninterrupted healthcare services [4]. From the first moment the patients enter the emergency room triage is performed, healthcare professionals should quickly review the risks regarding infection transmission, and take isolation precautions for transmission-based infections when necessary, especially standard precautions [5].

Exploring knowledge of healthcare professionals on isolation precautions would provide robust data to guide in-job trainings (as needed), besides boosting their awareness on importance of this topic. This study aimed to determine the knowledge of the employees working in Adult Emergency Department of Hacettepe University Hospital about isolation precautions and the factors associated with their knowledge.

METHODS

This cross-sectional study was conducted in Adult Emergency Department of Hacettepe University Hospital between May 16, 2023 to June 23, 2023. Hacettepe University Hospital is an institution that serves many patients from Türkiye and abroad. The emergency room has a critical care area that can serve 17 patients at the intensive care level, an emergency care area (yellow area) with nine monitored follow-ups, one Chemical Biological Radiological Nuclear Threats (CBRN) room, one seclusion room, one psychiatric interview and follow-up room, three interventional procedure rooms where surgical interventions can be performed, three resuscitation rooms where all kinds of resuscitative procedures can be performed and six examination rooms where rapid care patients are evaluated. The number of patients applied daily is around 200-250.

During data collection, it was aimed to reach all employees working in the adult emergency room (physicians, nurses, paramedics, emergency medical technicians, secretaries, cleaning, and auxiliary services, etc.). No sample was selected. A standardized data collection form consisting of 33 questions specially designed for this study was used for data collection. Participants' age, gender, time in the profession and working time in emergency room, school of graduation, occupation, having children, pregnancy, having care patients in their homes, having chronic diseases and immunosuppressive diseases, having a member of the infection control team in the family were reviewed. They were asked about their status of education on isolation precautions, if they received education which course they received, when they received the last course, whether they found their knowledge on isolation precautions sufficient, their compliance with isolation precautions, the reasons for non-compliance, contracting an infection for which isolation precautions should be taken, warning someone else for not complying with isolation precautions, and whether the warned person considered the warning.

The frequency of access to personal protective equipment and tools available at the bedside for hand hygiene practice was obtained using a five-point Likert scale (always, frequently, occasionally, rarely, never). They were asked how many patients they had been involved in the care process in the last week for whom contact, droplet and, airborne precautions were applied.

Five multiple-choice (two out of five, three out of three), two premise, and eight two-choice (true-false) questions were asked Supplementary Table 1 and 2. There were five scenarios (patient colonized with carbapenem-resistant Enterobacterales discharged 24 hours ago, patient with disseminated zona zoster, patient with hepatitis B, patient with hemorrhagic fever, patient with influenza) in which the isolation precaution(s) to be taken and personal protective equipment(s) to be used were selected Supplementary Table 3. The US Centers for Disease

Prevention and Control (CDC)[6], the Turkish Ministry of Health's "Crimean-Congo Hemorrhagic Fever (CCHF) 2020"[7] and the "Hacettepe Hospitals Standard Precautions and Isolation Instructions" were taken as a reference when deciding on the accuracy of the answers. Answers were considered correct if all required options were selected and those not required were not selected. Each question was evaluated as one point and the lowest score was "0" and the highest score was "20".

Data were collected through an electronic form. The link address was shared in the instant messaging groups of the employees in the emergency room. No identifying information was collected.

Since the number of participants per group was small, the school of graduation was combined into three groups high school, associate degree/ bachelor's degree, medical school/master's degree - medical specialty/doctorate. The duty in the emergency service was handled in 5 groups: resident, intern doctor, nurse-paramedic-emergency medical technician, patient caregivers-service assistant personnel.

Statistical Analysis

All continuous variables were non-normally distributed and analyzed using the Mann Whitney U or Kruskal-Wallis test and expressed as median (interquartile range = IQR). Categorical variables were presented as percentages (%). No data imputation was performed. Statistical significance was accepted for $p<0.05$ (two-sided). The statistical analysis was performed with Statistical Package for the Social Sciences (IBM SPSS, Armonk, New York, USA) version 23.

Ethical Considerations

This study was ethically approved by the Hacettepe University Non-Interventional Clinical Research Ethics Committee (Approval date: April 18, 2023, register number: 2023/07-42). There was written information at the beginning of the electronic data collection form. Participants were able to continue if they gave their consent to participate in the research. They could stop answering when they wanted. In accordance with ethical responsibility, the results of the study were shared with the Hospital Infection Control Committee and the Department of Emergency Medicine.

RESULTS

The Department of Emergency Medicine informed that approximately 190 people worked in Adult Emergency Department between June and July 2023. There were 90 (approximately 47.4%) healthcare professionals who accessed and responded to the data collection form electronically. The median age of the participants was 24 years (IQR = 4.25) and 40% were male. Among the participants, 38.9% were intern doctors, 31.1% were residents, 25.6% were nurses, paramedics, and emergency medical technicians, and 4.4% were auxiliary workers (Table 1).

It was observed that gender, occupation, graduated school, having a child, having chronic or immunosuppressive disease, and having a member of the infection control team in the family were not statistically significantly different on the knowledge scores of the participants. However, the median knowledge score of two pregnant participants was 16, while the median knowledge score of 52 non-pregnant participants was 14 (IQR=2.8). The difference in scores between the two groups was statistically significant (p=0.04). The median knowledge score of two participants who cared for patient at home was 9, and the median knowledge score of the other 88 participants was 13.5 (IQR = 4), and there was a significant difference (p=0.02) (Table 2).

There was no correlation between the knowledge level score of the healthcare workers who participated in the study regarding receiving education on isolation precautions and the source from which they received the course. Of the 76 healthcare workers who had received education on isolation precautions, 75 of them reported that a median of 6 (IQR= 8) months had elapsed since the last course they received. There was no statistically significant correlation between the knowledge score and the time elapsed (p=0.013, p=0.92). No statistically significant correlation was found between the knowledge score and self-sufficient in isolation knowledge, complying with isolation precautions, warning another one for not complying with isolation precautions, having an infection because of not complying with isolation precautions, and considering isolation precautions necessary for the prevention and control of infectious

Table 1. Demographic characteristics of participants

	Mean ± SD	Median (IQR)
Age (years) (n=90)	24.6 ± 4.0	24.0 (4.25)
Time in the profession (years) (n=90)	3.4 ± 4.2	2.0 (3.0)
Time in the emergency room (years) (n= 90)	2.3 ± 2.9	1.4 (2.8)
	n	%
Gender		
Female	54	60.0
Graduated school		
High school	21	23.3
Associate degree	5	5.6
Bachelor's degree	28	31.1
Master's degree / Medical School	35	38.9
Doctorate / Specialist in medicine	1	1.1
Occupation		
Intern doctor	35	38.9
Emergency medicine resident	28	31.1
Nurse	16	17.8
Paramedic	6	6.7
Patient caregiver	3	3.3
Emergency medicine technician	1	1.1
Service assistant personnel	1	1.1

SD: standard deviation, IQR: interquartile range

diseases. Fifty-five (61.1%) participants reported that they warned a co-worker for not following isolation precautions. Of the 55 participants who stated that they warned, 47 (85.5%) were intern doctors, 31 (56.4%) were auxiliary staff, 28 (50.9%) were cleaning staff and residents, 26 (47.3%) were paramedics and intern doctors, 22 (40. 0%) were trainee nurses, 14 (25.5%) were emergency medical technicians, 11 (20.0%) were general practitioners, six (10.9%) were lecturers and four (7.3%) were faculty members. Of the participants who warned a co-worker for not following isolation precautions, 23 (41.8%) were stated that the warned people complied with warning, 29 (52.7%) were sometimes complied, and three (5.5%) could not remember. Due to non-compliance with isolation precautions, 18 participants reported getting Coronavirus 2019 Disease (COVID-19), four reported influenza, and one each tuberculosis and diphtheria. Two of these participants contracted both COVID-19 and influenza. Healthcare workers who reported

Table 2. The distribution of knowledge scores of the participants by demographic characteristics and their occupations

	n	Knowledge score	
		Median (IQR)	*p*
Gender			0.11
Female	54	14.0 (3.0)	
Male	36	12.0 (4.8)	
Graduated school			0.21
High school	21	14.0 (3.0)	
Associate / Bachelor's degree	33	14.0 (4.0)	
Medical school / Specialist in medicine / Postgraduate	36	13.0 (4.0)	
Occupation			0.41
Intern Doctor	35	13.0 (4.0)	
Emergency medicine resident	28	13.0 (4.8)	
Nurse/paramedic/emergency medicine technician	23	14.0 (3.0)	
Patient caregiver / assistant service personnel	4	12.5 (2.5)	
With children	12	14.0 (2.8)	0.21
Without children	78	13.0 (4.0)	
Pregnant	2	16.0 (-)	**0.04**
Not pregnant	52	14.0 (2.8)	
Caregiving at home	2	9.0 (-)	**0.02**
No caregiving at home	88	13.5 (4.0)	
With chronic disease	16	14.0 (3.3)	0.16
Without chronic disease	74	13.0 (4.0)	
With immunosuppressive disease	2	11.0 (-)	0.41
Without immunosuppressive disease	88	13.0 (4.0)	
Family member of the infection control team	8	13.0 (5.8)	0.91
No family member of the infection control team	82	13.5 (4.0)	

IQR: Interquartile range

knowing the location of all personal protective equipment had a significantly higher knowledge score than those who did not (p=0.02) (Table 3).

Regarding the witnessing transmission-based precaution taken in the emergency room in the last week, 69 of the participants made a statement for contact, 68 for droplet, and 70 for airborne precaution. Participants reported that a median of 3 (IQR = 4) contact, 2 (IQR = 3) droplet, and 1 (IQR = 2) airborne precautions were applied to patients during the week.

Table 3. Distribution of knowledge scores of the participants by training, complying with isolation precautions, and warning the non-compliant employees

	n	Knowledge score	
		Median (IQR)	*p*
Educated	76	14.0 (3.8)	0.18
Non-educated	6	11.5 (4.5)	
Source of education			
Theoretical education in the pre-graduate period	72	14.0 (4.0)	0.60
No theoretical education in the pre-graduate period	4	13.5 (2.5)	
Practical education in the pre-graduate period	58	13.5 (4.0)	0.51
No practical education in the pre-graduate period	18	14.0 (2.5)	
Education given by Infection Control Team	59	13.0 (4.0)	0.18
No education given by Infection Control Team	17	14.0 (3.5)	
Education in courses, meetings, symposiums, and congresses	20	13.0 (3.8)	0.088
No education in courses, meetings, symposiums, and congresses	56	14.0 (3.0)	
Self-sufficient in isolation precaution knowledge	33	13.0 (4.0)	0.54
Self-partially sufficient in isolation precaution knowledge	49	13.0 (3.0)	
Self-insufficient in isolation precaution knowledge	8	12.0 (5.5)	
Always comply with isolation precautions	36	14.0 (3.5)	0.47
Often comply with isolation precautions	51	13.0 (4.0)	
Never comply with isolation precautions	3	11.0 (-)	
Infection due to non-compliance with isolation precautions	22	13.0 (3.0)	0.29
No infection due to non-compliance with isolation precautions	61	14.0 (3.5)	
Warn another person for non-compliance with isolation precautions	55	13.0 (3.0)	0.67
Do not warn another person due to non-compliance with isolation precautions	24	13.5 (4.0)	
Believing that isolation precautions are partially or completely unnecessary for the prevention of infectious diseases	8	13.0 (4.8)	0.47
Believing that isolation precautions are completely necessary for the prevention of infectious diseases	72	13.5 (4.0)	
Knowing the location of all personal protective equipment	75	14.0 (3.0)	0.02
Not knowing the location of all personal protective equipment	15	11.0 (4.0)	

IQR: Interquartile range

Among the 54 (60%) participating healthcare workers who did not always comply with isolation measures, the most frequently reported reasons for non-compliance were workload (96.3%), inappropriate physical conditions such as room and bed (63.0%), and lack of personal protective equipment (48.3%) (Table 4).

Regarding always having access to personal protective equipment, it was revealed that the participants had access to gloves, medical masks, gowns, respirators, caps, and eye protection, respectively. There were 20 (22.2%) participants who could access all personal protective equipment at any time. At the bedside of the patients who were in isolation, having access to the necessary tools for

Table 4. Distribution of reasons for non-compliance with isolation precautions by participants

	n	%*
Workload	52	96.3
Inappropriate physical conditions such as room-bed	34	63.0
Lack of personal protective equipment	26	48.1
Lack of knowledge	22	40.7
Inadequate conditions for hand hygiene	11	20.4
Other†	1	1.9

* It was calculated on 54 participants who reported that they did not comply with the isolation precautions. More than one answer was given.

† One person stated that there were cases where he did not comply with the isolation measures due to emergencies.

Table 5. Distribution of the frequency of access to personal protective equipment and tools required for hand hygiene by participants

Access to Personal Protective Equipment	Always n (%)	Usually n (%)	Often n (%)	Rarely n (%)	Never n (%)
Gloves	71 (78.9)	19 (21.1)	-	-	-
Medical mask	68 (75.6)	22 (24.4)	-	-	-
Respiratory mask	49 (54.4)	190 (21.1)	16 (17.8)	6 (6.7)	-
Apron	49 (54.4)	27 (30.0)	9 (10.0)	4 (4.4)	1 (1.1)
Eye protection/goggles	23 (23.6)	14 (15.6)	19 (21.1)	26 (28.9)	8 (8.9)
Head	27 (30.0)	19 (21.1)	18 (20.0)	18 (20.0)	8 (8.9)
Hand hygiene tools	Always n (%)	Usually n (%)	Often n (%)	Rarely n (%)	Never n (%)
Sink	79 (87.8)	10 (11.1)	1 (1.1)	-	-
Soap	71 (78.9)	13 (14.4)	6 (6.7)	-	-
Disposable towel	45 (50.0)	19 (21.1)	16 (17.8)	5 (5.6)	5 (5.6)
Hand sanitizer (antiseptics)	62 (68.9)	20 (22.2)	7 (7.8)	1 (1.1)	-

hand hygiene at all times was listed as sink, soap, hand antiseptic, and disposable towel, respectively. Forty-four (48.9%) of the participants stated that they always had access to all necessary tools for hand hygiene (Table 5).

Participants received a median score of 13 (IQR = 4) (minimum 8 - maximum 19) from the questions asked to examine the knowledge of participating healthcare workers about isolation precautions. Fewer than 50% of the participants knew that the statements " The patient with the airborne precautions should wear a vented-respirators during transfer. " and "Respirators should be worn in case of droplet precaution." were incorrect (Supplementary Table 2). For the isolation precautions to be taken and personal protective equipment to be used for five clinical scenarios, the best-known clinical scenario was the patient with hepatitis B infection, while less than 10% of the participants correctly answered the isolation precautions to be applied for the patient with disseminated zona zoster, the patient with hemorrhagic fever, and the patient with influenza (Supplementary Table 3).

DISCUSSION

Infection prevention and control practices in emergency rooms constitute an important step in achieving the "zero" target in nosocomial infections and protecting the health of healthcare workers [3, 5]. The first step to be taken on the way to the right practice is to have true knowledge. Within the scope of this study, the knowledge of healthcare professionals working in the Adult Emergency Department of university hospital on isolation precautions, which is a part of infection prevention and control practices, was examined. The median score of the healthcare workers on the standard knowledge questions prepared for this study was 13 out of 20, in other words, 65 points out of 100, and there is a need for improvement.

In a systematic review of 30 articles conducted between 2006 and 2021, in which the level of infection prevention and control knowledge and factors affecting compliance in healthcare workers were examined, it was reported that risk perception was associated with compliance [8]. Based on this information, the association between the knowledge score and risk perception was analyzed. Two healthcare workers stated that they were pregnant, and their knowledge scores were significantly higher. There was no statistically significant difference in the knowledge score of workers whose immune system was suppressed due to diseases or treatments, and individuals with chronic diseases. Children and home care patients are more vulnerable to the negative outcomes of infectious diseases [9]. Participants with children and home care patients are expected to have higher risk perceptions. Although there was no statistically significant difference between the participants who had children and those who did not, the knowledge score of the two healthcare professionals (intern doctors) who reported that they had home care patients was lower than the others. However, it is not known whether they

provide direct care to home care patients. In addition, their risk perception may differ from those who work long-term because they work temporarily in the emergency room. All situations in which risk perception is expected to be high are found in a small group among the participants. Considering the risk of infection and work tempo in the emergency room, workers who have a low risk of adverse outcomes of infection may have been assigned and it is called "the healthy worker effect".

In a systematic review, experience, having received education for infection control and, graduating with a bachelor's degree or higher were reported to be associated with increased knowledge [10]. In this study, no significant difference was found in graduation level. Of the participants who reported having received course for isolation precautions, 80% reported having received education after graduation. Almost all of the participants received education by the hospital infection control team. It was thought that this may be the reason why there was no association between graduation school and knowledge level. Although there was no statistical significance, it was found that personnel working in auxiliary services had a lower level of knowledge than physicians and nurses/emergency medical technicians/paramedics. In a systematic review, it was emphasized that physicians and nurses have higher responsibilities due to their better knowledge [8]. The World Health Organization declares that one of the core components of infection prevention and control is continuity of education [8]. In addition to the regular education, it is clear that the course be given by the clinic supervisors at the bedside will make a significant contribution in this context.

There were six participants (6.7%) who reported that they had not received education on isolation precautions. In the emergency rooms of two hospitals in Erzurum, it was reported that more than three-quarters of t he staff received education on isolation precautions [11]. In a study conducted with 800 healthcare workers in a region affected by infections such as Lassa and Ebola in Nigeria, it was reported that half of the participants received course on infection prevention and control [12]. Due to the small number of the group that did not receive education, no association was found between receiving education and knowledge score. Similarly, in a study conducted in Jordan to determine the knowledge score about isolation precautions among nurses, no association was found between education and knowledge score [13]. Aloush et al. [13] concluded in their study that the low nurse-patient ratio affected nurses' compliance with infection control measures and education would not increase compliance unless the workload decreased. In support of this interpretation, more than 90% of the healthcare workers participating in this study reported that workload was a barrier to compliance with isolation precautions and the knowledge score was not found to be related to compliance with precautions.

Forty percent of the participating healthcare workers reported that they complied with isolation precautions. An objective and external audit may lead to lower compliance. In a study involving 400 nurses from eight centers in Jordan, 47.3% of nurses reported that they always complied with infection control measures, similar to the participating healthcare workers in this study [13]. It was reported that the most common barriers to compliance were workload, lack of appropriate conditions for physical and hand hygiene, problems in accessing personal protective equipment, and lack of information. In a study conducted in Türkiye, it was reported that workload and lack of personal protective equipment were the most important barriers to compliance [14]. However, in a teaching hospital in Geneva, lack of knowledge and forgetting were reported to be as important barriers as workload [15]. If the centers increase their workforce and solve the time problem, it may be possible for lack of knowledge and forgetting to become the dominant problems.

In a study involving 41 centers in Türkiye, accessibility to the necessary tools for hand hygiene was examined on a weekday and a weekend day in summer and autumn, and it was found that 3-11% soap, 10-18% paper towels, and 1-4.7% hand antiseptic were not available [16]. Similarly, in the emergency room where this study was conducted, it was reported that the most common difficulty was to always have access to paper towels.

Healthcare workers are expected to warn each other for not complying with isolation precautions. However, it is observed that there is a hierarchical ranking regarding the frequency of warnings by the participants. Of course, the number of faculty members and staff is low compared to other

personnel and that they may be meticulous about isolation precautions may cause the frequency of warnings to be low, but hesitation was also considered to be effective.

One of the ultimate goal of isolation measures is to protect the health of healthcare workers [2]. More than a quarter of the participants reported getting an infection due to non-compliance with isolation precautions. Most of these people stated that they had COVID-19 and influenza with the effect of awareness. It is thought to be underreported.

It is determined that the questions answered with the lowest accuracy are the selection of isolation precautions and personal protective equipment by the clinical scenarios given. Although it is not possible to make a one-to-one comparison because the knowledge questions are not the same, in a study conducted in Nigeria, it was reported that two-thirds of healthcare workers had good isolation knowledge about standard precautions, and less than one-tenth had good knowledge about transmission-based precautions [12]. A study conducted on nurses in Jordan found better compliance with standard precautions, but less compliance with transmission-based precautions [13]. Considering the education they received before graduation, it is more difficult for people working in auxiliary and cleaning services to have a high knowledge score. However, it is thought that their knowledge score is low because physicians and nurses assign this task to the infection control team.

This study is one of the few studies addressing the level of knowledge and problems in practice for isolation precautions in the emergency room, which is one of the riskiest units for the spread of infection. On the other hand, the participation rate was below 50% and it was a single-center study reduces the external validity of the findings. The small number of participants and the lack of participation from faculty and staff members due to concerns about their identities may have caused bias. It is considered that the small number of participants may cause type 2 errors and failure to show the existing association. Since it is not a standardized scale with validity and reliability, it is not possible to compare the findings one-to-one. The data were not collected face-to-face to avoid giving "desired answers". However, collecting the data electronically may have decreased participation and may have caused the participants not to feedback about questions which they did not understand about the questions.

In conclusion, the knowledge of healthcare workers about isolation precautions in Adult Emergency Department, one of the most critical units for infection control, is at a moderate level. If educational programs provided, it will be important for effective infection control to include measures to prevent infection transmission through clinical scenarios that are likely to be encountered in emergency department conditions in the education program and to ensure the continuity of the personal protective equipment.

Author contribution

Study conception and design: AS, BÇ, GM; data collection: VA; analysis and interpretation of results: AS, VA, EK, HU, BÇ, GM; draft manuscript preparation: AS, VA, EK, HU. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Hacettepe University Non-Interventional Clinical Research Ethics Committee (Approval date: April 18, 2023, register number: 2023/07-42).

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Conflict of interest

The authors declare that there is no conflict of interest.

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Supplementary Table 1. Distribution of answers to multiple choice knowledge questions of the participants

	n	%
In which situation is it most appropriate to apply standard measures as a minimum?		
All patients (T)	69	76.7
Patients with an infection (F)	-	-
Patients with the infection suspicion (F)	16	17.8
Patients with the contagious infection (F)	5	5.6
Patients with the contagious infection suspicion (F)	-	-
Which of them are included in "the five moments for hand hygiene" according to the World Health Organization?		
Before and after touching a patient (T)	89	98.9
After using the toilet (F)	72	80.0
Before eating (F)	72	80.0
After touching a patient's surroundings (T)	90	100.0
Before and after a procedure (T)	90	100.0
Which personal protective equipment is required when approaching a patient with contact isolation?		
Apron and gloves (T)	74	82.2
Medical mask (F)	10	11.1
Respirators (F)	5	5.6
Eye protection (F)	1	1.1
Cap (F)	-	-
Which personal protective equipment is required during procedures where blood or bloody bodily fluids may splash?		
Eye protection (T)	88	97.8
Apron (T)	86	95.6
Gloves (T)	90	100.0
Respirators (F)	31	34.4
Choose the correct one for the isolation precaution with the sign.		
Contact precaution	87	96.7
Droplet precaution	78	86.7
Airborne precaution	76	84.4

Supplementary Table 2. Distribution of knowing the propositions as true or false by the participants

True propositions	**n**	**%**
Gloves should be disposable for each interventional procedure.	87	96.7
Gloves should be used for single use only when contacting mucous membranes, non-intact skin, and sterile areas.	87	96.7
The door of the patient's room should be kept closed in case of droplet precautions.	83	92.2
In the case of contact precautions, the patient's thermometer and sphygmomanometer should only be used on the patient.	84	93.3
Patients with transmission-based precautions should be placed in single-patient rooms, if available, otherwise, patients should be cohorted with the same infection.	69	76.7
False propositions		
Respirators should be worn in case of droplet precaution.	30	33.3
For each infection requiring isolation precaution, it is sufficient to take only one transmission-based precaution.	82	91.1
After applying hand hygiene, it is sufficient to wear gloves on top of each other and to remove the top glove while passing from patient to patient and use hand sanitizer.	73	81.1
The patient with the airborne precautions should wear vented-respirators during transfer.	25	27.8

Supplementary Table 3. Distribution of answers to knowledge questions for the determination of isolation precautions and personal protective equipment appropriate for the clinical scenarios

	Patient colonized with CRE bacteria was discharged the day before, n (%)	Patient with a disseminated zona zoster, n (%)	Patient with hepatitis B, n (%)	Patient with hemorrhagic fever, n (%)	Patient with influenza, n (%)
Standard precautions	41 (45.6)	34 (37.8)	63 (70.0)	48 (53.3)	32 (35.6)
Contact precautions	71 (78.9)	62 (68.9)	39 (43.3)	50 (55.6)	9 (10.0)
Droplet precautions	4 (4.4)	25 (27.8)	4 (4.4)	25 (27.8)	61 (67.8)
Airborne precautions	2 (2.2)	22 (24.4)	1 (1.1)	13 (14.4)	26 (28.9)
Total accuracy	**21 (23.3)**	**5 (5.6)**	**49 (54.4)**	**5 (5.6)**	**1 (1.1)**
Apron	68 (75.6)	56 (62.2)	29 (32.2)	58 (64.4)	23 (25.6)
Gloves	76 (84.4)	82 (91.1)	76 (84.4)	76 (84.4)	55 (61.1)
Medical mask	48 (53.3)	45 (45.0)	35 (38.9)	48 (53.3)	54 (60.0)
Respirators	12 (13.3)	25 (27.8)	1 (1.1)	31 (34.4)	33 (36.7)
Eye protection	13 (14.4)	13 (14.4)	11 (12.2)	38 (42.2)	15 (16.7)
Total accuracy	**11 (12.2)**	**3 (3.3)**	**19 (21.1)**	**9 (10.0)**	**12 (13.3)**

CRE: Carbapenem-resistant *Enterobacterales*

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ORIGINAL ARTICLE

Use of molnupiravir in patients who developed SARS-CoV2-Infection during hospitalization

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ABSTRACT

Background: Molnupiravir is an oral anti-viral that inhibits SARS-CoV-2 replication and reduces viral load. We aimed to investigate mortality rates and the factors affecting mortality in patients receiving molnupiravir who were hospitalized for reasons other than COVID-19 in a tertiary care university hospital.

Methods: Patients who received molnupiravir for COVID-19 according to Turkish Ministry of Health guidelines and were hospitalized for reasons other than COVID-19 were included in the study. Demographic and clinical characteristics of patients were compared according to survival status defined as 30-day mortality.

Results: The mortality rate of 101 patients with Covid-19 was found to be 6.93 %. The rates of corticosteroid use, oxygen support, and mechanical ventilation requirement were significantly higher in patients who died within 15 days of the PCR positivity. Although not statistically significant, the ratio of concomitant bacterial pneumonia was higher in patients who did not survive. Also, the mortality rate was lower in patients who were vaccinated three doses or more without statistical significance.

Conclusion: In patients who were hospitalized for other reasons and received molnupiravir treatment with a diagnosis of COVID-19, the development of respiratory failure was the only demographic factor that was statistically different in terms of mortality.

Keywords: Molnupiravir, COVID-19, SARS-CoV-2.

INTRODUCTION

Early treatment with anti-virals is crucial for preventing severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) associated hospitalization and mortality [1]. Molnupiravir is an oral pro-drug of the ribonucleoside analogue N-hydroxycytidine (NHC). NHC spreads into cells, where it is metabolized to its triphosphate form, and inhibits SARS-CoV-2 replication and reduces viral load [2].

The effectivity of molnupiravir against SARS-CoV-2 was shown in preclinical trials. It was also evaluated in phase-1, 2, and 3 trials, and was reported as safe and well tolerated at a dose of 800 mg twice daily [3-8]. Placebo-controlled, industry-funded phase-3 trial (MOVe-OUT) was conducted in unvaccinated, non-hospitalized patients with at least one risk factor for severe Coronavirus disease 2019 (COVID-19). Treatment was initiated within the first five days of the symptoms and resulted with a 31% reduction in risk of hospitalization and death compared to placebo [8]. In another recent retrospective cohort study from Hong Kong involving 33,217 outpatients and 21,138 inpatients, 16.1% and 3.8% received molnupiravir, respectively. Molnupiravir treatment was found to be associated with reduced all-cause mortality and cost savings [9]. However, there was no reduction in the frequency of COVID-19-associated hospitalization or death for high-risk vaccinated adults in the largest randomized trial that compared molnupiravir plus usual care with usual care alone [1].

Molnupiravir started to be used in Turkey according to the COVID-19 treatment guideline of the Ministry of Health published on February 12th, 2022. Treatment was given to adult patients with mild to moderate COVID-19 at increased risk of adverse outcomes regardless of vaccination status [10].

In this study, we aimed to investigate mortality rates and the factors affecting mortality in patients receiving molnupiravir who were hospitalized for reasons other than COVID-19 and diagnosed with COVID-19 during their hospitalization in a tertiary care university hospital.

MATERIAL AND METHODS

Setting

This retrospective observational study was conducted in Hacettepe University Adult and Oncology Hospitals in Ankara, the capital city of Turkey. These tertiary care hospitals include 1040 and 119 beds, respectively.

Study Population

Patients who received molnupiravir for COVID-19 according to Turkish Ministry of Health guidelines and were hospitalized for reasons other than COVID-19 between 01.08.2022 and 01.12.2022 were extracted from the hospital pharmacy records. All patients were diagnosed with a positive SARS-CoV-2 reverse-transcriptase–polymerase-chain-reaction (RT-PCR) test from a nasopharyngeal sample. Adult patients (>18 years) with mild to moderate disease with at least one risk factor for severe COVID-19, regardless of vaccination status included in the study. Molnupiravir was initiated as soon as possible but not later than five days after the onset of signs or symptoms.

Advanced age, primary immunodeficiency, solid tumor or hematological malignancy (patients who have received chemotherapy in the last year and radiotherapy in the previous six months), solid organ or hematopoietic stem cell transplantations, Acquired Immune Deficiency Syndrome (AIDS), Down syndrome, liver cirrhosis, chronic renal failure with dialysis, sickle cell anemia, diabetes mellitus with end-organ damage, myocardial infarction, stroke, multiple sclerosis, motor neuron diseases, myasthenia gravis, Huntington's disease, Alzheimer, morbid obesity (Body mass index, (BMI) >40), stage 3 and stage 4 chronic obstructive pulmonary disease, emphysema and immunosuppressive therapies were defined as risk factors for severe COVID-19 according to the Turkish Ministry of Health Guideline. Molnupiravir, with a dose of 800 mg twice daily for five days, was provided by the Turkish Ministry of Health for these patients [10].

Study Outcome

Demographic and clinical data such as; age, gender, PCR status, symptom day at onset of the therapy, comorbidities, Charlson Comorbidity Index (CCI), and vaccination status (vaccine types, date of last vaccine administration) were recorded.

Corticosteroid use, requirement of oxygen and mechanical ventilation support, and presence of concomitant bacterial pneumonia were also noted. Bacterial pneumonia was defined according to Centers for Disease Control and Prevention (CDC) definitions by evaluating clinical, radiological, microbiological features and laboratory results together. Follow-up SARS-CoV-2 PCR test after initial positive PCR was recorded for at least 28 days or until death, which came first.

Statistical analysis

Demographic and clinical characteristics of patients were compared according to survival status defined as 30-day mortality. Categorical variables were presented as numbers and percentages. Means and standard deviations were calculated for continuous variables. Categorical variables were compared using the Pearson chi-square test/Fisher's exact test. Continuous variables were compared using the Student's t-test or Mann–Whitney U test according to the distribution of variables. For all statistical analyses, Statistical Packages for the Social Sciences (v17.0 SPSS 24 Inc. Chicago, IL) software was used.

The study was approved by the Institutional Non-Interventional Clinical Research Ethics Committee, Ankara, Turkey (2022/14-21).

RESULTS

A total of 101 patients with COVID-19 were included in the study. All patients completed the 5-day treatment course. Discontinuation due to side effects was not observed. The mean age of the patients was 66 years (±17.46), and 59 (58.4 %) patients were female. Mortality rate was 6.93 % (Table 1). COVID-19 was diagnosed in mean 7.08 (±14.8) days of hospitalization. The most common reasons for hospitalization were malignancies and neurological disorders. The mean duration between symptom onset and molnupiravir treatment was 2.08 days (±1.026). All patients had a comorbid disease, and the most common comorbidities were malignancies and hypertension. Mean CCI was higher in patients who did not survive (6,71±1.11 vs 5,25±2.23), but this difference was not statistically significant (p=0.096).

Nineteen of the patients were unvaccinated, and no difference was detected in mortality rates between vaccinated patients and unvaccinated patients or those who were vaccinated at least one dose. The mortality rate was lower in patients who were vaccinated with three doses or more without statistical significance.

The rates of corticosteroid use, oxygen support, and mechanical ventilation requirement were found to be significantly higher in patients who died within 15 days of the PCR positivity.

Persistence SARS-CoV-2 PCR positivity one week after the first positive PCR test and positivity ten days after the first negativity were not different according to mortality status.

Secondary bacterial pneumonia was detected in 29 (29%) of all patients. Although not statistically significant presence of concomitant bacterial pneumonia ratio was higher in patients who did not survive (three of seven patients, 42.9 % vs. 26 of 93 patients, 28 %).

DISCUSSION

Seven of the 101 patients at high risk for severe COVID-19 died (6.93%) who received molnupiravir regardless of the vaccine status in our study. The mortality rate was reported as 2.6% in a prospective observational multicenter study involving 856 patients who received a third dose of COVID-19 vaccination and were treated with molnupiravir [11]. In another retrospective cohort trial, molnupiravir was found associated lower risk of death, like nirmatrelvir-ritonavir, or sotrovimab, compared with no anti-viral treatment in high-risk patients [12]. Although there are many studies among outpatient or inpatient COVID-19 patients receiving molnupiravir, studies did not focus on patients with mild to moderate symptoms of COVID-19 who were hospitalized for other reasons. In a brief report including 44 hospitalized patients admitted for other diseases than COVID-19,

Table 1. Distribution of demographic and clinical characteristics between dead and survived patients

Characteristic		Survived N:94	Dead N:7	All Cases N: 101	p
Gender n (%)					0.131
	Female	53(52.5)	6 (5.9)	59 (58.4)	
	Male	41(40.6)	1 (1)	42 (41.6)	
Age (Mean±SD) Year		65,71±17.46	60,14±16.09	65,32 ±17.46	0,418
Age Intervals n (%)					,214
The interval between symptom onset and initiation of molnupiravir (mean±SD)		2,06 ± 1.02	2,28±0.75	2,08 ±1.026	0,584
CCI* (mean±SD)		5,25±2.23	6,71±1.11	5,35 ± 2.23	0,096
Vaccination status					,179
(Mean±SD)		2,68 ±1.56	1,85± 1.46	2,62±1.561	
n (%)	0	17(16.8)	2(2)	19(18.8)	
	1	2(2)	0(0)	2(2)	
	2	15(14.9)	3(3)	18(17.8)	
	3	30(29.7)	1(1)	31(30.7)	
	4	20(19.8)	1(1)	21(20.8)	
	5	10(9.9)	0(0)	10(9.9)	
	4	8(7.9)	0(0)	8(7.9)	
	5	2(2)	0(0)	2(2)	
Corticosteroid use** n (%)					<0.001
	No	76(75.2)	1(1)	77(76.2)	
	Yes	18(17.8)	6(5.9)	24(23.8)	
Oxygen Support*** n (%)					,006
	No	76(76)	2(2)	78(78)	
	Yes	18(18)	4(4)	22(22)	
Mechanical ventilation support *** n (%)					<0.001
	No	91(90.1)	2(2)	93(92.1)	
	Yes	3(3)	5(5)	8(7.9)	
PCR status one week after positivity n (%)					,247
	Negative	61(60.4)	3(3)	64(63.4)	
	Positive	33(32.7)	4(4)	37(36.6)	
PCR positivity ten days after first negativity n (%)					,849
	Negative	82(82)	6(6)	88(88)	
	Positive	11(11)	1(1)	12(12)	
Presence of Concomitant Bacterial Pneumonia n (%)					,407
	No	67(67)	4(4)	71(71)	
	Yes	26(26)	3(3)	29(29)	

*Charlson comorbidity index

**Fifteen days within PCR positivity

molnupiravir was found safe and well tolerated. The mortality rate was reported as 11.4 %, and no patients' characteristics were found significantly associated with hospital mortality [13].

Advanced age and comorbidities were shown to be the most important risk factors for COVID-19 mortality [14]. In our study, the mean age of the patients who received molnupiravir was found to be similar between survivors and non-survivors. We investigated the impact of comorbidities with CCI. CCI is an easy-to-perform method that was also used for COVID-19 to estimate the risk of death related to comorbid diseases. A higher CCI score was reported as an independent risk factor for mortality in COVID-19 patients in two retrospective

studies from other centers in Turkiye [15, 16]. We also found a higher mean CCI score among non-survivors, which was not statistically significant. However, no mortality was detected in patients with a CCI score lower than six.

Early administration of anti-viral treatments was reported to be associated with lower hospitalization and mortality rates in several studies [8, 17, 18]. Most of these studies compared patients who were treated within 5–7 days of symptom onset with those treated in later periods. However, in a recent retrospective observational study that included 206 patients who received anti-viral agents, the interval between diagnosis and treatment as two days was found to be a significant independent predictor of moderate disease (OR = 2.27, 95% CI = 1.58–3.24, p <0.0001) [19]. We initiated anti-viral therapy within five days after symptom onset to all patients, with a mean of two days.

Early treatment with molnupiravir was found to be associated with a 30% reduced risk of hospitalization and mortality among high-risk unvaccinated adults with COVID-19 in an industry-conducted phase 3 trial [8]. However, in a recent pooled analysis of nine RCTs, any benefit of molnupiravir was not shown in hospitalized patients due to COVID-19 [20]. Our study included a different group of patients in whom hospitalization was not due to COVID-19. However, they had similar risk factors for developing severe COVID-19 like the patients in the community. The relatively low mortality rate in this study might encourage the use of molnupiravir in these patients despite the remaining controversy in the absence of a control group. In a study that analyzed 45 patients who were hospitalized for other reasons and used molnupiravir for COVID-19 that developed in the hospital, the use of molnupiravir was found to be safe[13], but further studies are required to understand the role of molnupiravir in this setting regarding respiratory insufficiency and mortality.

Our study has several limitations. First, it is a retrospective single-center trial, and the number of patients was limited because of the nature of the study. Second, there was no control group to compare patients who received molnupiravir or not due to ethical issues. Since all of the patients received molnupiravir, it was not possible to discuss the effects of treatment on mortality. Additionally, due to the low number of patients, factors influencing mortality could not be evaluated through multivariate analyses. Lastly, only pneumonia was recorded as a secondary bacterial infection that can affect mortality rates.

CONCLUSION

In patients who were hospitalized for other reasons and received molnupiravir treatment with a diagnosis of COVID-19, the development of respiratory failure was the only demographic factor that was statistically different in terms of mortality. Multicenter case-control studies might be useful to understand the efficacy of molnupiravir in this setting.

Competing interests

Gökhan Metan has received honoraria for speaking at symposia and lectures organized by Gilead; Merck, Sharp, and Dohme (MSD), and Pfizer. He received consultation fee from United Nations Turkiye Office. He has also received travel grants from MSD, Pfizer, and Gilead to participate in conferences. All other authors declare that they have no competing interests.

Author contribution

Study conception and design: GTD, YÇ, GK, GM and SÜ; data collection: GTD, YÇ, and GK; analysis and interpretation of results: GTD ,YÇ, GM and SÜ; draft manuscript preparation: GTD, YÇ and GM. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

The study was approved by the Institutional Non-Interventional Clinical Research Ethics Committee (Protocol no. 2022/14-21).

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Conflict of interest

The authors declare that there is no conflict of interest.

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CASE REPORT

Ambulatory management of a patient with bartter syndrome under general anesthesia

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ABSTRACT

A rare inherited renal tubulopathy, Bartter Syndrome is characterized by salt-wasting in the kidneys, resulting in the effects resembling those of loop diuretics: hypokalemia, hypochloremia, metabolic alkalosis, and volume contraction leading to low to normal blood pressure. The marked electrolyte and hemodynamic instability that is often seen in these patients can sometimes result in catastrophic consequences. Because of the relative rarity of this condition, there are only sparse reports on anesthetic management that typically involve preoperative testing carried out prior to the day of surgery. We herein describe a case of a 54-year-old patient with Bartter Syndrome who presented to the hospital for an outpatient dental surgery under general anesthesia. Preoperative consultation with a nephrologist helped to establish our strategy in maintaining the patient's electrolyte balance. Point-of-care blood gas monitoring was carried out at regular intervals and guided the perioperative potassium supplementation. Patient remained stable for the entire course of the surgery and was discharged home the same day after one hour in the recovery unit.

Keywords: Anesthesia, point-of-care systems, Bartter Syndrome, ambulatory surgery, electrolyte management.

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INTRODUCTION

Bartter Syndrome is a rare inherited renal tubulopathy characterized by salt-wasting in the loop of Henle. It thus mimics the effects of loop diuretics resulting in hypokalemia, hypochloremia, metabolic alkalosis, and volume contraction effecting low to normal blood pressure [1]. Unsurprisingly, patients who carry this diagnosis often encounter marked electrolyte and hemodynamic instability, sometimes resulting in catastrophic consequences. Because of the relative rarity of this condition, there is not a wealth of literature on anesthetic management, and patients who require surgical procedures may encounter providers who are not familiar with the implications of their diagnosis. The few case reports discussing anesthetic management of these patients typically describe the need for preoperative labwork and evaluation followed by significant intraoperative testing and monitoring [2-4]. Herein we describe an ambulatory management of an adult patient with Bartter Syndrome under general anesthesia. We report how we approached testing, consultation, and monitoring for this same-day case.

The syndrome was first described in 1962 by Frederic Bartter as a constellation of hypokalemic alkalosis, hyperaldosteronism, and hyperplasia of the juxtaglomerular complex [5]. The term is now used to cover a set of genetically heterogeneous diseases that show significant clinical variability, making overarching characterization and guidelines complex [1]. Five different forms have been identified based on molecular genetics, though these forms have much phenotypic overlap. Often, the condition is diagnosed in childhood, presenting with polyuria and failure

to thrive, though others are not detected until adulthood. It is estimated that current prevalence [6] is approximately 1 in 1,000,000.

The genetic mutations in the Bartter Syndrome primarily lead to impaired sodium reabsorption in the thick ascending limb of the loop of Henle, leading to its increased resorption in the distal convoluted tubule and concomitant increase of potassium loss. Activation of the renin-angiotensin-aldosterone (RAA) system along with inappropriate prostaglandin synthesis creates a feedback loop that exacerbates the abnormalities. Hypomagnesemia and hypocalcemia may also occur. Patients with the hypercalciuria/hypocalcemia phenotype may present with frequent nephrolithiasis, as well as bone resorption from the jaw and dental mobility and dislocation [7].

Treatment includes lifelong supplementation of deficient electrolytes, chiefly potassium, but magnesium and calcium may also be required. Potassium-sparing diuretics such as spironolactone, as well as non-steroidal anti-inflammatory drugs (NSAIDs) have been employed as therapy [8].

Patients with Bartter Syndrome may require surgery and/or anesthetic care at some point in their lives. The complexity of preoperative workup and perioperative management may depend on the duration and level of invasiveness of the procedure, and whether general anesthesia is called for. Attention should still be paid to correcting any gross electrolyte abnormalities to ensure safe conduct of anesthesia.

CASE PRESENTATION

A 54 year-old woman presented to the county hospital for extraction of two decayed and necrotic teeth, a pneumatised sinus requiring sinus lift with bone grafting along with platelet rich plasma placement, and an osseointegrated implant placement. Due to her severe anxiety, she could not tolerate the surgery in an office setting and was scheduled for general anesthesia. She presented without preoperative workup, but proved to have keen insight into her condition. During the pre-anesthetic assessment, she reported that she had been diagnosed with Bartter Syndrome at the age of 37 after suffering from a cardiac arrest triggered by hypokalemia. She had since undergone pacemaker/ICD placement and has had no further cardiac or hemodynamic abnormalities. Her medications included potassium chloride 160 mg daily and spironolactone. She did not require magnesium or calcium supplementation and did not take NSAIDs on a regular basis.

After discussion with the surgical team, the case was briefly delayed to obtain a consult from the in-hospital nephrology service. The nephrologist recommended to check a preoperative potassium and supplement intravenously to maintain near her baseline. Since serial intraoperative potassium checks were anticipated, an iStat point of care testing (POCT) device was used, utilizing the Chem8+ cartridge, thereby facilitating timely assays in the operating room. Her initial potassium was 2.5 mEq/L. The patient stated she felt she was "low," describing mild fatigue. Administration of 20 mEq KCl was achieved through a peripheral IV over two hours. When rechecked, the patient's potassium had surprisingly risen to 3.5 mEq/L, though this was likely elevated from hemolysis, as the pCO_2 and bicarbonate were elevated and pH was lower (Table 1). The patient stated she felt better, and a repeat sample was deferred until the start of the case.

Preoperative vital signs were: blood pressure 106/84 mmHg, heart rate 97 bpm, SpO_2 100% on room air, respiratory rate 16 breaths/min, temperature 36.7°C. Patient stated that the above blood pressure was normal. To account for fasting, 700 mL of lactated Ringer's solution were administered in the preoperative area with little change of her vital signs.

The patient experienced a stable operative course. She was premedicated with intravenous midazolam 2 mg and fentanyl 100 µg. Induction consisted of lidocaine 100 mg, propofol 200 mg, and rocuronium 50 mg, with no hypotension noted. Succinylcholine was specifically avoided to decrease the risk of sudden potassium shifts.

Intraoperatively, repeat potassium was drawn after induction and was found again to be 2.5 mEq/L. An additional 10 mEq was infused over the next hour. A second 10 mEq bag of KCl was started, however a repeat check revealed a potassium of 3.0 mEq/L and this was stopped, as overcorrection is as dangerous as undercorrection in patients with chronic severe hypokalemia.

Table 1. Values of Successive iStat Chem8+ Blood Tests

Tests	Times Samples Resulted			
	09:47	11:34	14:35	15:27
Sodium (mEq/L)	133	136	136	133
Potassium (mEq/L)	2.5	3.5	2.5	3.0
Glucose (mg/dL)	113	103	97	124
Hgb (g/dL)	15.6	13.6	12.2	12.6
Hct (%)	46	40	36	37
pH	7.42	7.33	7.41	7.47
pCO_2 (mmHg)	41	60	39	34
pO_2 (mmHg)	30	18	81	64
HCO_{3-} (mEq/L)	27	32	25	25
Total CO_2 (mmHg)	28	34	26	26
O_2 Saturation (%)	58	24	96	95

Symbols: mEq/L – milliequivalents/liter; mg/dL – milligrams/deciliter; g/dL – grams/deciliter; mmHg – millimeters mercury.

The patient remained hemodynamically stable throughout the case, with blood pressures at or higher than her baseline. She did exhibit occasional premature atrial contractions (PAC's) on telemetry, and occasionally her pacemaker initiated some beats when her heart rate fell below 70 bpm. We elected not to place a magnet on the pacemaker as she was not pacer-dependent, and we wished to keep the ICD function intact in case of life-threatening arrhythmias. In addition, the patient return electrode pad was placed on the right thigh with the surgery taking place on the right maxilla, decreasing the possibility of an electrical arc passing through the pacemaker's left chest location.

Emergence was uneventful, and the patient recovered in the post-anesthesia care unit for approximately 1 hour prior to discharge home. She gave her consent to report this case. In a follow-up phone call the next day the patient reported faring well apart from some soreness at the surgical site.

DISCUSSION

We present this case to establish the feasibility of management of a patient with Bartter Syndrome in an ambulatory setting while managing the type of evaluation, workup, and monitoring such environments afford. While some patients undergoing more extensive procedures would benefit from more robust preoperative preparation, there are many others like our patient who present for relatively brief and minimally invasive procedures for which anesthesia is required. Anesthesia providers faced with these patients must decide their level of comfort with the degree of testing and monitoring available to them.

Our patient's anxiety and duration of the procedure dictated the choice of general anesthesia. While monitored anesthesia care (MAC) was also an option, we elected to have a controlled airway that general anesthesia afforded. We were fortunate in our patient's knowledge of her disease (she reported her phenotype does not suffer from hypocalcemia and hypomagnesemia so as to require regular supplementation), the timely response of our in-hospital nephrologist, and a facility that could accommodate a several hour delay in the case. While we did encounter some inconsistency in our iStat POCT monitoring (a likely hemolyzed sample in preop and a more robust than expected response to 10 mEq KCl intraoperatively), our discussion with the nephrologist reassured us that a gentle replacement was a safer course than attempting to achieve exact blood levels of potassium. The patient was also able to give us feedback when she was awake, stating that the preoperative replacement was helpful symptomatically. We erred on the side of cautious replacement rather than disrupting the delicate electrolyte balance of chronic hypokalemia to which her body had become accustomed.

We discussed with the surgeons whether to admit the patient to observation postoperatively. Some providers may have chosen this option out of an abundance of caution. However, given that the

patient required minimal potassium correction, was hemodynamically stable throughout the perioperative period, and had a remotely-monitored pacemaker/ICD, we felt comfortable releasing her home. We did advise her to contact her primary care physician, be particularly vigilant to any new symptoms, and gave her strict return precautions. On her follow-up phone call, the patient reported a high level of satisfaction with her experience.

Author contribution

Study conception and design: EK; data collection: EK; analysis and interpretation of results: EK and RK; draft manuscript preparation EK and RK. All authors reviewed the results and approved the final version of the manuscript.

Ethical approval

Ethical Approval is not required for this article. Patient provided us with a written consent to submit her case for publication.

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Conflict of interest

The authors declare that there is no conflict of interest.

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CASE REPORT

Meningococcal septicemia in a young immunocompetent girl

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ABSTRACT

Meningococcal septicemia is a bloodstream infection caused by Neisseria meningitis. Clinical manifestations vary, from mild disease to severe meningococcaemia which may present first with high fever, severe myalgia, headache, skin and mucosal petechiae and can progress rapidly to septic shock with multi-organ dysfunction syndrome (MODS).

Case presentation: A 17-year-old immunocompetent girl was admitted to the Infectious Disease ward, Mother Theresa University Hospital with a 3-4-days history of headache, vomiting, diarrhea, fever, cough, arthralgia. She had hypotension, tachypnea, tachycardia, pharyngeal erythema and generalized ecchymotic spots. She was transferred immediately to the Intensive Care Unit. Laboratory findings showed decrease of hemoglobin, platelet count, albumin; increase of AST, ALT, LDH, CPK. Neisseria meningitidis was cultured from cerebrospinal fluid. Latex agglutination test resulted positive for N. meningitidis Gr B. She was immediately treated with Ceftriaxone, hydrocortisone, i.v. fluids, albumin, dopamine/dobutamine, fresh frozen plasma, platelet mass, bicarbonate, cryoprecipitate. The meningococcal rash began to spread rapidly taking on the appearance of ecchymotic lesions. Her clinical condition worsened rapidly and was placed under mechanical ventilation and died within 31 hours of admission to the hospital as a result of septic shock.

Conclusions: Young patients presenting with fever, severe myalgia, headache, skin and mucosal petechiae must be tested for Neisseria meningitis. This infection is a medical emergency that requires rapid diagnosis, immediate antimicrobial therapy and intensive care support as it may be deadly in a matter of hours. People including health workers who have been in prolonged and close contact with the patient should receive antibiotic prophylaxis.

Keywords: Neisseria meningitidis, meningococcal disease, multi-organ failure, septic shock, young adults.

INTRODUCTION

Meningococcalsepticemiaisabloodstreaminfection caused by Neisseria meningitis a gram-negative, aerobic diplococcic bacterium. N. meningitidis infection was first reported by Vieusseux in 1805 and was first isolated approximately 80 years later, in 1887 [1]. Six serogroups are responsible for most meningococcal disease worldwide, namely serogroups, A, B, C, W-135, X, and Y; the epidemiology of disease caused by each serogroup is unique [2]. Serogroups A, B, and C account for most cases of meningococcal disease throughout the world. The two most common types are meningococcal meningitis and meningococcal septicemia. About one in 10 people have Neisseria meningitis bacteria in the back of their nose and throat without being sick [3]. Currently, the annual reported incidence rates of meningococcal disease fluctuate from less than 1 case per 100,000 to greater than 500 cases per 100,000, changing with time and geographic location [4]. People spread bacteria to others by sharing respiratory and throat secretions, saliva or spit. It appears mainly in children or young people. The bacteria enter the bloodstream and multiply, causing damage to the blood vessels walls causing skin and internal organs bleeding. Symptoms of disease include: fever, chills, fatigue, vomiting, cold hands and feet, severe aches or pain in the muscles or joints, rapid breathing, diarrhea and in later stages, a dark purple rash. The manifestations include pharyngitis, fever, renal failure, disseminated intravascular coagulation, meningococcemia with or without meningitis. This disease may progress to purpura fulminans, hypotension, acute adrenal hemorrhage, severe septic shock and multi-organ failure [4]. All these make this disease with high mortality and morbidity. Until the 90s, the antibiotic of choice was penicillin. This treatment was subsequently replaced by a third-generation cephalosporin. Subjects who had a close contact with infected patients, should initiate antibiotics prophylaxis to prevent meningococcal disease development.

CASE PRESENTATION

A 17-year-old immunocompetent girl was hospitalized at the Infectious Disease ward, Mother Theresa University Hospital, Tirana Albania in August. The patient had a 3-4-days history of headache, vomiting, diarrhea, fatigue, fever 39°C, cough, arthralgia. Physical findings included pharyngeal erythema, tachycardia (117/min), tachypnea (22/min), hypotension (95/60 mmHg) and generalized ecchymotic spots over her trunk and extremities (Figure 1).

She was not taking any medication. She did not recall any contact with affected subjects. She was transferred immediately to the Intensive Care Unit. Chest radiography showed: bilateral bronchopneumonia. Laboratory findings showed decrease of hemoglobin, platelet count, albumin, platelet count; increase of aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, creatinine phosphokinase (Table 1). Coagulation test showed APTT 26.7 s (NR, 10.1-15), INR 2.34 (NR, 0.7-1.2), PTHS 28.2 % (NR, 70-120). Arterial blood gas analysis showed: pH 7.17 (NR, 7.35-7.45); pO_2 70.6 mmHg (NR, 80-100), pCO_2 47.2 mmHg (NR, 35-45); BE -11.2 mmol/L (NR, 2-3) and SpO_2 91.4% (NR, 95-99%), Na 145.4 mmol/l (NR, 135-148), K 3.2 (NR, 3.5-4.5mmol/l).

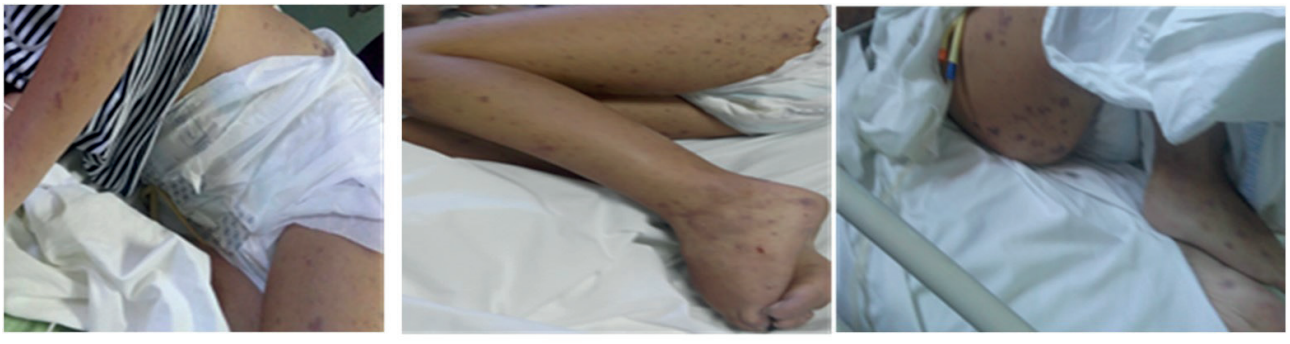

Figure 1. Widespread purpuric and ecchymotic rash

Table 1. Hematochemical parameters

Parameter	Day 0	Day 1	Reference range
White blood cells	3900	21500	4000-10000 cells/μL
Neutrophils	80.02	84.9	43-76%
Lymphocytes	16.8	12.9	17-48%
Monocytes	3	2.2	4-10%
Red blood cells	4370000	3560000	4.2-6.1x10^6 cells/μL
Hemoglobin	11.2	8.4	11-16.5 g/dl
Hematocrit	37.2	27.4	35-50%
Platelets	120000	72000	150-390x10^3 cells/μL
Creatinine	2.4	4.4	0.6-1.4 mg/dl
Urea	37	75	10-43 mg/dl
Bilirubin	1.3	2.4	0.3-1.2 mg/dl
International Normalized Ratio	1.45	2.34	0.7-1.2
Aspartate aminotransferase	26	187	0-35 U/L
Alanine aminotransferase	10	128	0-45 U/L
Alkaline phosphatase	155	65	30-120 U/L
Creatine phosphokinase	184	644	0-171 U/L
Lactate dehydrogenase	292	1254	125-250 U/L
Total proteins	6	4.9	6.2-8.3 g/dl
Albumin	3.1	2.7	3.5-5.2 gr/dl

A lumbar puncture resulted with 6 white blood cells in the cerebrospinal fluid examination and Neisseria meningitidis was cultured from cerebrospinal fluid. Latex agglutination test resulted positive for N. meningitidis Gr B. Microscopy resulted in abundant diplococcus Gram negative. Serological tests for hepatitis C, B, HIV and CMV were negative. She was immediately treated with intravenous Ceftriaxone, symptomatic adjuvant medication as well: hydrocortisone, i.v. fluids, albumin solution, dopamine/ dobutamine, omeprazole solution, vitamin therapy, fresh frozen plasma, platelet mass, bicarbonate, cryoprecipitate. The meningococcal rash began to spread rapidly taking on the appearance of ecchymotic lesions. Her clinical condition worsened rapidly with persisted hypotension, tachycardia, tachypnea, metabolic acidosis and oliguria. She was placed under mechanical ventilation. Our patient died within 31 hours of admission to the hospital as a result of septic shock.

DISCUSSION

Human carriers are only natural reservoir of this microorganism. The disease can occur as sporadic cases, outbreaks, or as large epidemics. We presented a sporadic case with this pathology. Our patient was immunocompetent, although patients with compromised immunity (HIV positive, alcoholics, asplenia state) are more vulnerable to fulminant meningococcus disease. Our patient was 17-year-old. There are numerous known risk factors for meningococcal disease; incidence is strongly influenced by age, with infants having the highest risk [5]. Meningococcal disease occurs year-round, but the majority of cases occur during the winter and early spring, although our patient hospitalized in August. Physical findings of our patient included purpuric rash over her trunk and extremities. The purpuric ecchymotic rash is a characteristic of the disease, first maculopapular and then petechial. The size of the skin lesions can be used, to a certain extent, to predict the clinical severity and the ongoing coagulopathy [6]. Coagulation tests of our case showed APTT 26.7 s (NR, 10.1-15), INR 2.34 (NR, 0.7-1.2), PTHS 28.2 % (NR, 70-120). On the other hand, laboratory findings showed decrease of hemoglobin, platelet count, albumin, increase of aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, creatinine phosphokinase, creatinine, urea, bilirubin. During the 30 hours of survival in the intensive care unit, our patient's rash progressed extremely quickly to ecchymotic lesions. Her clinical

condition rapidly deteriorated with persistent hypotension, tachycardia, tachypnea, metabolic acidosis, and oliguria, and she was recently placed on mechanical ventilation. The severity of manifestations of meningococcal infection ranges from bloodstream infection, associated with mild non-specific symptoms to fulminant sepsis with multi-organ failure and death in approximately 10-15% of cases [7]. Meningococcal disease can be difficult to diagnose because the signs and symptoms are often similar to those of other diseases. Meningococcus can be detected by gram stain of a skin biopsy specimen, blood culture or cerebrospinal fluid culture. Meanwhile, we performed prophylaxis, both to close family contacts and to the medical personnel who assisted our patient all the time.

CONCLUSION

Young patients presenting with symptoms such as with fever, chills, severe myalgia, headache, skin and mucosal petechiae must be tested for bacteria Neisseria meningitis. This infection is a medical emergency that requires rapid diagnosis, immediate specific antimicrobial therapy, intensive care support as it may be deadly in a matter of hours. People including health workers who have been in prolonged and close contact with the patient should be treated with antibiotic prophylaxis.

Author contribution

Study conception and design: EM. Revision of the manuscript: AK, DK. All authors approved the final version of the manuscript.

Ethical approval

Not applicable.

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Conflict of interest

The authors declare that there is no conflict of interest.

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