YU ISSN 0042-8450

ВОЈНОСАНИТЕТСКИ ПРЕГЛЕД

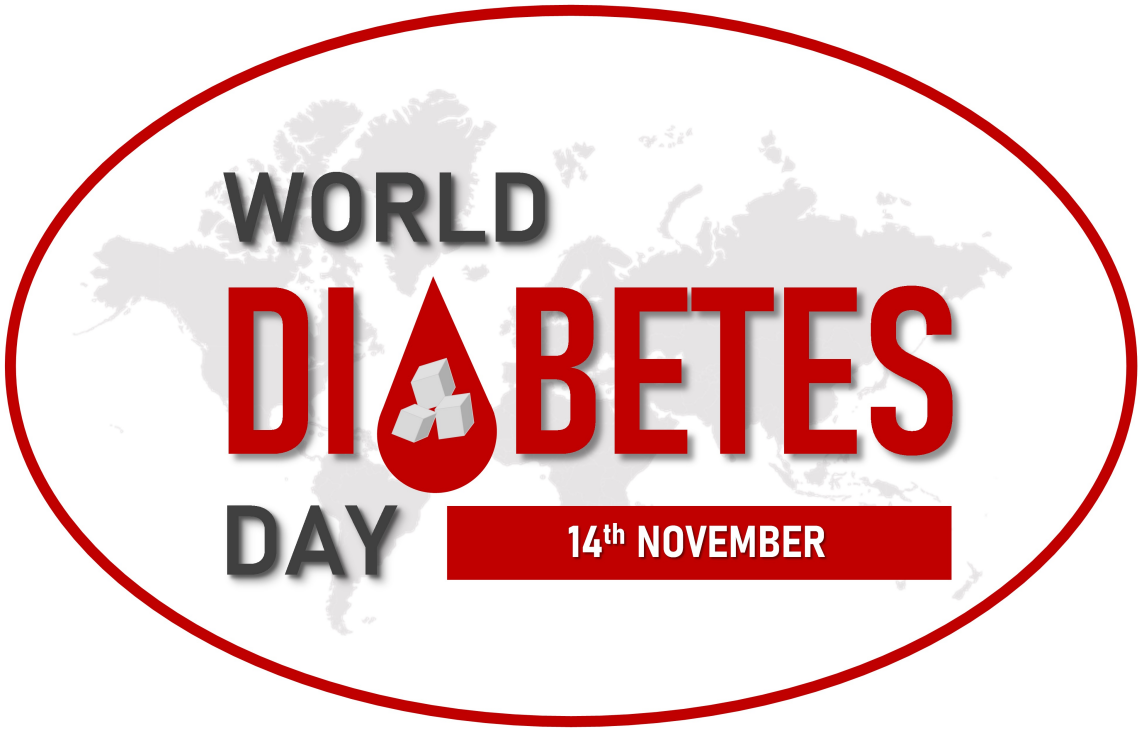
Часопис лекара и фармацеута Војске Србије

Military Medical and Pharmaceutical Journal of Serbia

Vojnosanitetski pregled

Vojnosanit Pregl 2024; November Vol. 81 (No. 11): pp. 659–718.

Vojnosanitetski Pregled 2024 November Vol. 81 (No. 11): pp. 659–718.



Vol. 81, No. 11, 2024

VOJNOSANITETSKI PREGLED

The first issue of *Vojnosanitetski pregled* was published in September 1944
The Journal continues the tradition of Vojno-sanitetski glasnik which was published between 1930 and 1941

PUBLISHER
Ministry of Defence of the Republic of Serbia, University of Defence, Belgrade, Serbia

ISSN 0042-8450
eISSN 2406-0720
Open Access
(CC BY-SA)

Editorial Office: University of Defence, Faculty of Medicine of the Military Medical Academy, Center for Medical Scientific Information, Crnotravska 17, 11 040 Belgrade, Serbia. E-mail: **vsp@vma.mod.gov.rs**

Papers published in the Vojnosanitetski pregled are indexed in: Science Citation Index Expanded (SCIE), Journal Citation Reports/Science Edition, SCOPUS, Excerpta Medica (EMBASE), Google Scholar, EBSCO, Biomedicina Serbica, Serbian Citation Index (SCIndex), DOAJ. Contents are published in Giornale di Medicine Militare and Revista de Medicina Militara. Reviews of original papers and abstracts of contents are published in International Review of the Armed Forces Medical Services.

The Journal is published monthly. Subscription: Giro Account No. 840-19540845-28, refer to number 122742313338117. To subscribe from abroad phone to +381 11 3608 997. Subscription prices per year: individuals 5,000.00 RSD, institutions 10,000.00 RSD, and foreign subscribers 150 €.

Printed by: Vojna štamparija, Beograd, Resavska 40b

Vol. 81, br. 11, 2024

VOJNOSANITETSKI PREGLED

Prvi broj *Vojnosanitetskog pregleda* izašao je septembra meseca 1944. godine
Časopis nastavlja tradiciju *Vojno-sanitetskog glasnika*, koji je izlazio od 1930. do 1941. godine

IZDAVAČ
Ministarstvo odbrane Republike Srbije, Univerzitet odbrane, Beograd, Srbija

ISSN 0042-8450
eISSN 2406-0720

Adresa redakcije: Univerzitet odbrane, Medicinski fakultet Vojnomedicinske akademije, Centar za medicinske naučne informacije, Crnotravska 17, 11 040 Beograd, Srbija. Informacije o pretplati (tel.): +381 11 3608 997. E-mail (redakcija): **vsp@vma.mod.gov.rs**

Radove objavljene u „Vojnosanitetskom pregledu" indeksiraju: Science Citation Index Expanded (SCIE), Journal Citation Reports/Science Edition, SCOPUS, Excerpta Medica (EMBASE), Google Scholar, EBSCO, Biomedicina Serbica, Srpski citatni indeks (SCIndeks), DOAJ. Sadržaje objavljuju Giornale di Medicine Militare i Revista de Medicina Militara. Prikaze originalnih radova i izvoda iz sadržaja objavljuje International Review of the Armed Forces Medical Services.

Časopis izlazi dvanaest puta godišnje. Pretplate: Žiro račun br. 840-19540845-28, poziv na broj 122742313338117. Za pretplatu iz inostranstva obratiti se službi pretplate na tel. +381 11 3608 997. Godišnja pretplata: 5 000 dinara za građane Srbije, 10 000 dinara za ustanove iz Srbije i 150 € za pretplatnike iz inostranstva. Kopiju uplatnice dostaviti na gornju adresu.

Štampa: Vojna štamparija, Beograd, Resavska 40b

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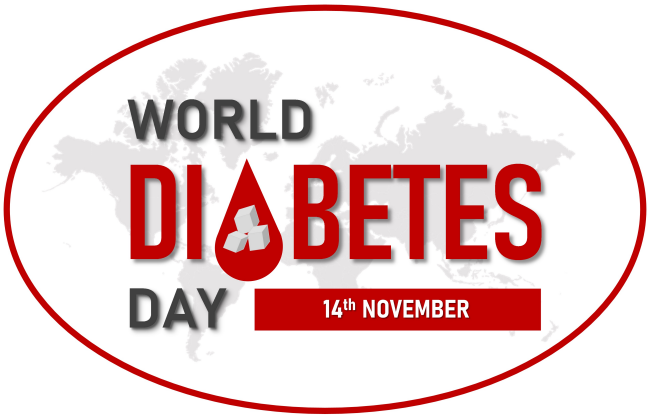

World Diabetes Day, November 14, was established in 1991 on the initiative of the International Diabetes Federation and the World Health Organization. Diabetes is a major public health problem globally. More than 530 million adults live with diabetes, and it is predicted that the number of people affected will increase to over 640 million by 2030. The theme of this year's World Diabetes Day, "Breaking Barriers, Bridging Gaps," should encourage us to help ensure that all people with diabetes have the opportunity to receive comprehensive and high-quality treatment.

Svetski dan borbe protiv dijabetesa, 14. novembar, ustanovljen je 1991. godine na inicijativu Međunarodne federacija za dijabetes i Svetske zdravstvene organizacije. Dijabetes je veliki problem javnog zdravlja na globalnom nivou. Više od 530 miliona odraslih živi sa dijabetesom, a predviđanje je da će broj obolelih porasti na preko 640 miliona do 2030. godine. Tema ovogodišnjeg Svetskog dana dijabetesa „Rušenje barijera, premošćenje praznina" bi trebalo da nas podstakne da pomognemo da svi ljudi koji su oboleli od dijabetesa imaju mogućnost da budu sveobuhvatno i kvalitetno lečeni.

C U R R E N T T O P I C

UDC: 616.24-005-08
DOI: https://doi.org/10.2298/VSP240320072O

Challenges and considerations in the management of acute pulmonary embolism: a critical analysis of European Society of Cardiology guidelines

Izazovi i razmatranja u lečenju akutne plućne embolije: kritička analiza smernica Evropskog društva kardiologa

Slobodan Obradović*†, Boris Džudović†‡, Tamara Simpson§

Military Medical Academy, *Clinic of Cardiology, ‡Clinic of Emergency Internal Medicine, Belgrade, Serbia; †University of Defence, Faculty of Medicine of the Military Medical Academy, Belgrade, Serbia; §Jacobi/North Central Bronx Hospital, New York, New York, USA

Key words:
heart arrest; practice guidelines as topic; pulmonary embolism; therapeutics; thrombolytic therapy.

Ključne reči:
srce, zastoj; lekarska praksa, oblici, vodiči; pluća, embolija; lečenje, fibrinolitici.

Introduction

In 2019, the European Society of Cardiology (ESC) published guidelines for the management of acute pulmonary embolism (PE), with no revisions planned until 2026 [1]. This absence of updates is primarily due to the lack of significant randomized trials influencing current clinical practices. Nevertheless, this raises concerns, as the 2019 ESC PE guideline leaves substantial gaps in addressing critical clinical scenarios. This article aims to evaluate these unaddressed issues, focusing on the challenges faced in the everyday management of patients with acute PE.

Patients with pulmonary embolism in resuscitation

The mortality rate among patients experiencing acute PE and requiring resuscitation is inadequately addressed in current guidelines. Three possible scenarios necessitate consideration. First, in cases where it is unknown whether a patient admitted in a state of reanimation has acute PE, physicians must swiftly estimate the probability that cardiac arrest (CA) is due to this condition. Crucial information, such as recent surgery, trauma, immobilization, malignant disease, and previous venous thromboembolism (VTE), is imperative. A swollen leg may serve as a potential clue. Information from bystanders is also significant, and if acute dyspnea or severe cyanosis precedes unconsciousness, the likelihood of acute PE increases. The second scenario involves a patient known to have acute PE whose condition suddenly deteriorates. In such cases, it is highly likely that acute PE is the cause of CA. The third scenario presents an acute PE patient in CA with an absolute contraindication for thrombolysis.

In each instance, prompt resuscitation measures are warranted, utilizing urgent transthoracic echocardiography (TTE). TTE is critical for the differential diagnosis of CA of unknown cause. The most common causes that should be rapidly differentiated by TTE include cardiac tamponade, dilated cardiomyopathy, or myocardial infarction. In cases where acute PE causes CA, an enlarged and dysfunctional right ventricle is expected to be the dominant finding on TTE [2].

If acute PE is suspected, a bolus of unfractionated heparin, usually 5,000 units, must be administered immediately. If a strong suspicion exists that acute PE is the cause of CA, and there are no obvious absolute contraindications for thrombolytic therapy, a 50 mg tissue plasminogen activator i.v. bolus should be administered [3–7].

If clear contraindications for thrombolysis are present, the only treatment option is catheter-directed therapy (CDT), involving aspiration with or without thrombus fragmentation, or surgical embolectomy [8–10]. However, these options are rarely available.

Correspondence to: Boris Džudović, Military Medical Academy, Clinic for Emergency Internal Medicine, Crnotravska 17, 11 000 Belgrade, Serbia. E-mail: dzuda1977@gmail.com

Patients with high-risk pulmonary embolism and significant contraindications for thrombolysis

Absolute contraindications for thrombolysis become relative in the presence of life-threatening high-risk PE, given that the mortality rate among high-risk PE patients exceeds 50%. However, certain contraindications pose a substantial hazard for classic systemic thrombolytic therapy. Recent major surgery, intracranial hemorrhage, aortic dissection, or major trauma present almost insurmountable challenges for systemic thrombolysis. Recent years have seen the development of new and highly efficient catheters for thrombus aspiration and fragmentation, such as the FlowTriever® and "Penumbra" systems®, which have undergone relatively large cohort studies demonstrating good efficacy and safety results [8–12]. Despite this, these systems have not been tested according to ESC guidelines recommendations in high-risk PE patients with contraindications for systemic thrombolysis, failed thrombolysis, or in intermediate-high-risk PE patients who deteriorate. Additionally, no randomized trials compare systemic thrombolysis or anticoagulant therapy with these CDTs. The suitability of low-dose catheter-directed thrombolysis in patients at very high risk for bleeding on systemic thrombolytic therapy remains unknown. Local thrombolysis may have an advantage over mechanical devices for lysing distal thrombi and those unreachable with large aspiration catheters. However, local thrombolysis is likely slower in achieving the reperfusion of occluded arteries than mechanical devices. The probable significant obstacle for CDT is the need for relatively large randomized studies to achieve the necessary hard endpoint, which is all-cause mortality for each catheter system in use. Probably more than 500 patients for the experimental and control groups are needed for intermediate-high-risk PE, or at least 100 *per* group for high-risk PE patients.

When to use reperfusion therapy in patients with intermediate-high risk pulmonary embolism

Approximately 10–15% of patients initially presenting with intermediate-high-risk PE experience deterioration in the next few days, evolving into features indicative of high-risk PE. Physicians handling acute PE often choose not to wait for clinical improvement after sole anticoagulation therapy due to concerns about hemodynamic collapse. Many experts advocate for the early initiation of reperfusion therapy to forestall hemodynamic deterioration. Recognizing this critical juncture involves considering small and simple factors, including an increase in heart rate, a decrease in oxygen saturation, an elevation in breathing rate, a slight decrease in arterial blood pressure, or specific laboratory markers (elevated troponin, leukocytosis, increased lactate in arterial blood samples) [13–16]. All these factors carry significance in intermediate-high-risk PE with substantial right ventricle dysfunction (tricuspid annular plane systolic excursion – TAPSE, less than 1.5 cm) and significantly elevated B-type natriuretic peptide – BNP or cardiac troponin blood levels. Should any of these parameters worsen during the initial hours of the treatment, the decision for reperfusion should be promptly made. The assessment of bleeding risk, such as using the Pulmonary Embolism Bleeding Score Index – PEBSI, could aid in determining the appropriate reperfusion therapy [17].

The organization of pulmonary embolism management

In the last decade, the role of Pulmonary Embolism Response Teams – PERT has gained recognition for treating complex patients with acute PE, necessitating a multidisciplinary approach [18]. However, the organization of a PE network is equally essential, as not all hospitals possess the facilities to manage all types of complex PE cases. Some hospitals may emerge as leaders in this field by mastering catheter-guided therapy and surgical thrombectomy as the exclusive options for treating certain PE patients. To achieve this, a robust local infrastructure comprising specialized centers strategically located in specific geographic areas must be operational around the clock. Ensuring effective communication between local health centers, ambulances, and specialized hospitals is pivotal for determining the optimal treatment approach for patients grappling with the intricacies of acute PE.

The timing and choice of anticoagulant therapy

For high-risk PE patients, accurate estimation of renal function is crucial, with unfractionated heparin emerging as the safest therapy from that perspective. If rapid improvement is evident, low-molecular-weight heparins could also serve as the initial choice. In cases of "unclear" patients, considering risk estimation or other diagnostic challenges, low-molecular-weight heparins are recommended if renal clearance exceeds 30 mL/min. Hemodynamically stabilized patients can promptly receive direct oral anticoagulants. Among them, rivaroxaban, with the highest loading dose, may be most suitable for younger patients with a low bleeding risk, while apixaban could present an advantage for older patients and those with higher bleeding risk. Edoxaban has demonstrated favorable outcomes in intermediate-high-risk patients, and the lower dose is permitted and tested in acute VTE based on renal clearance. Dabigatran stands as a viable option when short-term anticoagulation is necessary, such as after major surgery or trauma, given that the lower dose of this drug is not validated for prolonged anticoagulation [19–24]. Following thrombolysis, a delay of at least 1–2 days is advisable before introducing direct oral anticoagulants to ensure patient stabilization. In contemporary practice, the trend is towards shorter hospitalization durations for the treatment of acute PE, even in severe cases, emphasizing the early use of direct oral anticoagulants.

How to manage long-term anticoagulant therapy in patients who had acute pulmonary embolism

The risk of recurrent PE generally diminishes over time for the majority of patients, with two notable exceptions being active-progressive malignant disease and triple-positive anti-phospholipid syndrome. After major surgery or trauma,

the recurrence rate is low in VTE. However, in all other cases, an increased risk of recurrent thromboembolic events exists, presenting similarly to the initial occurrence. Consequently, the majority of patients typically require long-term anticoagulation therapy following the first PE. If the therapy is discontinued 3–6 months after the index event, the recurrent risk is approximately 5–7% *per* year and up to 10% in the first year [25, 26]. Notably, patients with severe PE face a higher risk of mortality with recurrent events, prompting a more liberal approach to the decision for prolonged anticoagulation. This includes patients with some degree of present bleeding risk. Conversely, patients with low-risk PE may not necessitate long-term anticoagulation if they have a high bleeding risk. The authors' stance in this article is that younger patients lacking thrombotic risk factors (such as severe obesity or chronic disease) after a minor transient or persistent risk factor for PE (like minor surgery or trauma, pregnancy, postpartum, long journeys, the use of prothrombotic drugs, or the presence of mild thrombophilia) may not require anticoagulant therapy after 12 months of treatment. However, spontaneous PE and PE related to chronic diseases likely warrant long-term anticoagulation, extending for years. In each case, patients with a higher bleeding risk (where the VTE-BLEED score may assist in risk estimation) should receive a lower dose of direct oral anticoagulants after 3–6 months from the index event or even consider discontinuation of therapy in specific cases [27].

Conclusion

In conclusion, this critical analysis reveals the existing challenges and unaddressed issues in the European Society of Cardiology guidelines for acute pulmonary embolism. Swift evaluation, differentiation through urgent transthoracic echocardiography, and careful consideration of treatment options are pivotal. The need for ongoing research, comprehensive testing of emerging therapies, and a multidisciplinary approach is underscored to enhance acute pulmonary embolism management. This evolving landscape urges clinicians to integrate emerging evidence with established guidelines for optimal patient outcomes.

Funding

The study did not receive any external funding.

Conflict of interest

The authors declare no conflict of interest or disclosures related to this manuscript.

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Received on March 20, 2024
Accepted on August 13, 2024
Online First September 2024

ORIGINAL ARTICLES

UDC: 616-006.81-033.2
DOI: https://doi.org/10.2298/VSP240528073P

Analysis of the vascular patterns of 52 amelanotic cutaneous melanoma metastases: a prospective descriptive study

Analiza vaskularnih obrazaca 52 amelanotične kutane metastaze melanoma: prospektivno deskripitvna studija

Danijela Popović*, Željko Mijušković†‡, Andrija Jović*, Sladjana Cekić*, Nataša Vidović§, Danica Tiodorović*‖

University Clinical Center Niš, *Clinic for Dermatovenereology, §Center for Pathology and Pathological Anatomy, Niš, Serbia; †Military Medical Academy, Department for Dermatology and Venereology, Belgrade, Serbia; ‡University of Defence, Faculty of Medicine of the Military Medical Academy, Belgrade, Serbia; ‖University of Niš, Faculty of Medicine, Niš, Serbia

Abstract

Background/Aim. Early diagnosis of amelanotic cutaneous melanoma metastases (ACMM) represents a great challenge and is essential for determining the stage, treatment, and prognosis of the disease. The aim of the study was to evaluate the vascular structures and their arrangement and frequency in ACMM. **Methods.** The study was conducted as a prospective, descriptive, multicenter study of pathohistologically confirmed ACMM. **Results.** The study included a total of 52 ACMM from 17 patients (8 men and 9 women, with an age range of 32–91 years, median 63.12 years) with a previous history of primary melanoma. The most prevalent were elevated ACMM – 39 (75.0%) lesions, while 13 (25.0%) ACMM were flat. Linear irregular blood vessels were statistically significantly more often associated with elevated ACMM, compared to flat ACMM (92.3% vs. 50.0%, $p < 0.001$). Dotted blood vessels were statistically significantly more frequent in flat ACMM, compared to elevated ACMM (76.9% vs. 28.2%, $p = 0.003$). Diffuse distribution of blood vessels was the most prevalent, with 92.3% of flat ACMM and 76.9% of elevated ACMM ($p = 0.416$). Peripheral arrangement of blood vessels was detected in 15.4% of elevated ACMM and 7.7% of flat ACMM ($p = 0.815$). The central arrangement of blood vessels was seen in 2.6%, while the cluster (segmental) schedule was present in 5.1% of elevated ACMM. The monomorphic vascular pattern was the predominant pattern in 84.6% of flat ACMM and 61.5% of elevated ACMM ($p = 0.232$). **Conclusion.** Our study supports the finding that linear irregular blood vessels are more commonly associated with elevated ACMM, while the dotted ones are dominant in flat ACMM.

Key words:
blood vessels; dermoscopy; diagnosis; melanoma, amelanotic; neoplasm metastasis; skin.

Apstrakt

Uvod/Cilj. Rana dijagnoza amelanotičnih kutanih metastaza melanoma (AKMM) predstavlja veliki izazov i od izuzetnog je značaja za određivanje stadijuma, lečenje i prognozu bolesti. Cilj rada bio je da se procene vaskularne strukture i njihov raspored i učestalost u AKMM. **Metode.** Studija je sprovedena kao prospektivna, deskriptivna, multicentrična studija patohistološki potvrđenih AKMM. **Rezultati.** Istraživanje je uključilo ukupno 52 AKMM kod 17 bolesnika (8 muškaraca i 9 žena, starosti 32–91 godina, prosečno 63,12 godina) sa prethodnom istorijom primarnog melanoma. Najzastupljenije su bile uzdignute AKMM – 39 (75,0%) lezija, dok je 13 (25,0%) AKMM bilo u nivou kože, ravnih. Linearni iregularni krvni sudovi bili su statistički značajno češće povezani sa uzdignutim AKMM u odnosu na ravne AKMM (92,3% vs. 50,0%, $p < 0,001$). Tačkasti krvni sudovi bili su statistički značajno češći kod ravnih AKMM u odnosu na uzdignute AKMM (76,9% vs. 28,2%, $p = 0,003$). Difuzna distribucija krvnih sudova bila je najzastupljenija, u 92,3% ravnih AKMM i 76,9% uzdignutih AKMM ($p = 0,416$). Periferni raspored krvnih sudova utvrđen je u 15,4% uzdignutih AKMM i u 7,7% ravnih AKMM ($p = 0,815$). Centralni raspored krvnih sudova uočen je u 2,6%, a klaster (segmentni) raspored u 5,1% uzdignutih AKMM. Monomorfni vaskularni obrazac bio je prisutan kod 84,6% ravnih AKMM i 61,5% uzdignutih AKMM ($p = 0,232$). **Zaključak.** Naša studija podržava nalaz da

Correspondence to: Danijela Popović, University Clinical Center Niš, Clinic for Dermatovenereology, Bulevar Dr. Zorana Djindjica, 48, 18 000 Niš, Serbia. E-mail: danijelapopovicnis@gmail.com

su linearni iregularni krvni sudovi češće povezani sa uzdignutim AKMM, dok su tačkasti krvni sudovi dominantni kod AKMM u nivou kože.

Ključne reči:
krvni sudovi; dermoskopija; dijagnoza; melanom, amelanotičan; neoplazme, metastaze; koža.

Introduction

Dermatoscopic evaluation of amelanotic or hypomelanotic melanomas (AHM) and amelanotic cutaneous melanoma metastases (CMM) – ACMM is still challenging. Prompt diagnosis of such lesions is crucial due to the potential implications for prognosis and management. As ACMM has no specific dermatoscopic features, diagnosis is still based on evaluating vascular structures [1].

The clinical appearance of ACMM varies widely and may mimic other benign and malignant tumors, including hemangiomas, intradermal nevi, sebaceous hyperplasia, basal cell carcinoma, Bowen's disease, and primary amelanotic melanomas [2–6]. Both AHM and ACMM have a poor prognosis, most probably due to a delay in diagnosis and subsequent treatment [7].

The aim of the study was to analyze vascular morphology and distribution patterns in ACMM.

Methods

Our research was a prospective, descriptive, multi-center study of pathohistologically confirmed ACMM carried out in two centers: the Clinic for Dermatovenerology of the University Clinical Center Niš, Serbia, and the Clinic for Dermatovenerology of the Military Medical Academy in Belgrade, Serbia, from July 2019 to July 2023. The Medical Ethics Committees of the University Clinical Center Niš (No. 16297/6, from May 2019) and the Faculty of Medicine, University of Niš (No. 12-74-76-2/4, from July 2019) approved the study design. Informed consent was previously obtained from all study participants.

The study recorded general data such as gender, age, Breslow index of primary melanoma, the interval time to metastasis (defined as the time in months between the diagnosis of the primary melanoma and the appearance of the first cutaneous metastasis), and anatomical location of primary melanoma and ACMM (head, arms, legs, trunk).

ACMM were divided into flat (macules) and elevated (papules/nodules) and categorized into regional (satellites or in-transit metastases) or distant skin metastases.

Clinical and contact polarized dermatoscopic photographs were taken for each lesion using a Nikon Coolpix 4300® camera attached to a DermLite Foto II Pro®. High-resolution dermatoscopic images of ACMM were evaluated independently by three dermatologists with more than ten years of experience in the field of dermatoscopy. Dermatoscopic images with insufficient resolution or image quality, including cases without histopathological confirmation of ACMM, were excluded from the study.

Dermatoscopic evaluation of ACMM included vascular pattern assessment and arrangement, predominant morphological pattern (monomorphic or polymorphic), and evaluation of additional dermatoscopic features.

The following vascular structures were evaluated: linear irregular, dotted, glomerular, arborizing, and hairpin-like vessels. Predominant morphologic patterns included a monomorphic pattern (one morphological type of vessel within the lesion) and a polymorphic one (two or more morphological types of vessels).

Statistical analysis

Continuous variables are reported as mean ± standard deviation (SD). Further, *t*-tests or Mann-Whitney *U* tests were used to compare continuous variables, and Chi-square tests or the Fisher exact test were used for proportions. A value of $p < 0.05$ was considered statistically significant. All statistical analyses were performed using the R software, Version 3.0 [8].

Results

General data

The study included data on 52 ACMM from 17 patients, including 8 (47.1%) men and 9 (52.9%) women. Demographic and clinical characteristics of patients with ACMM are shown in Table 1.

The mean age of patients was 63.12 years (SD: 17.01 years). The mean time to ACMM onset after primary melanoma surgery was 22.59 months (SD: 12.64 months). Clinical evaluation revealed 11 (64.7%) patients with elevated ACMM, flat ACMM in 4 (23.5%), and there were 2 (11.8%) patients with both types of lesions. Location-wise, the lower extremities were the most frequently affected (64.7%), followed by the trunk (17.6%), head (11.8%), and arms (5.9%). As for the number of ACMM, most patients (82.4%) had less than 10 lesions, 11.8% had 11 to 50 lesions, and 5.9% had more than 50 ACMM.

Dermatoscopic findings

We analyzed 52 ACMM in 17 patients with a previous history of primary melanoma. All 52 (100.0%) ACMM showed the presence of vascular structures.

Generally speaking, as far as the vascular patterns observed in ACMM are concerned, the results (Table 2) indicate that the linear irregular vessels are the most common (78.8%), while dotted vessels account for 40.4% of all cases. Moreover, the diffuse distribution pattern is the most prevalent (80.8%). The research also revealed that the

Table 1

Demographic and clinical features of patients with amelanotic cutaneous melanoma metastases (ACMM) (n = 17)

Parameter	Values
Gender	
male	8 (47.1)
female	9 (52.9)
Age, years	63.12 ± 17.01 (32–91)
Tumor thickness according to Breslow	4.70 ± 3.42 (0.75–12.00)
Time to ACMM onset after surgical excision of primary melanoma	22.59 ± 12.64 (12–48)
Morphological type of cutaneous metastases	
flat lesions (macules)	4 (23.5)
elevated lesions (papules, nodules)	11 (64.7)
flat and elevated lesions	2 (11.8)
Localization	
head	2 (11.8)
trunk	3 (17.6)
arms	1 (5.9)
legs	11 (64.7)

All values are given as mean ± standard deviation (minimum-maximum) or numbers (percentages).

Table 2

Dermatoscopic characteristics of the vascular pattern in amelanotic cutaneous melanoma metastases (ACMM) (n = 52)

Parameters	Values
Vessels	
dotted	21 (40.4)
glomerular	4 (7.7)
linear irregular	41 (78.8)
arborizing	1 (1.9)
hairpin-like	7 (13.5)
Distribution pattern	
diffuse	42 (80.8)
peripheral	7 (13.5)
central	1 (1.9)
cluster	2 (3.8)
Morphologic pattern	
monomorphic	35 (67.3)
polymorphic	17 (32.7)
Additional features	
ulceration	11 (21.1)
white lines	16 (30.8)

All values are given as numbers (percentages).

dominant morphologic pattern is the monomorphic one (67.3%). Regarding the additional features of the ACMM, it was noticed that 21.1% developed ulceration, whereas white lines were found in 30.8% of the analyzed cases.

Clinical and dermatoscopical presentations of ACMM are shown in Figure 1.

Linear irregular vessels were statistically more associated with elevated ACMM compared to flat lesions (92.3% vs. 50.0%, $p < 0.001$), while dotted blood vessels were more associated with flat ACMM (76.9% vs. 28.2%, $p = 0.003$). Glomerular vessels were detected in 10.3% of ACMM ($p = 0.563$). Arborizing and hairpin-like vessels were equally detected in ACMM ($p = 1.000$ and $p = 0.171$, respectively) (Table 3).

Diffuse vessel distribution was the most prevalent, with 92.3% in flat ACMM and 76.9% in elevated ACMM ($p = 0.416$). Peripheral distribution was found in 15.4% of elevated and 7.7% of flat ACMM ($p = 0.815$). The central and cluster distributions were seen in 2.6% and 5.1% of elevated ACMM, respectively (Table 3).

Regarding patterns, a monomorphic pattern was present in 84.6% of flat ACMM and in 61.5% of the elevated ones ($p = 0.232$) (Table 3) (Figure 1D).

Concerning additional dermatoscopic features, white lines were statistically more often present in patients with elevated ACMM (38.5% vs. 7.7%, $p = 0.044$) (Figure 1F). Additionally, ulcerations and erosions were found in 25.6% of elevated ACMM and 7.7% of the flat ones (Table 3).

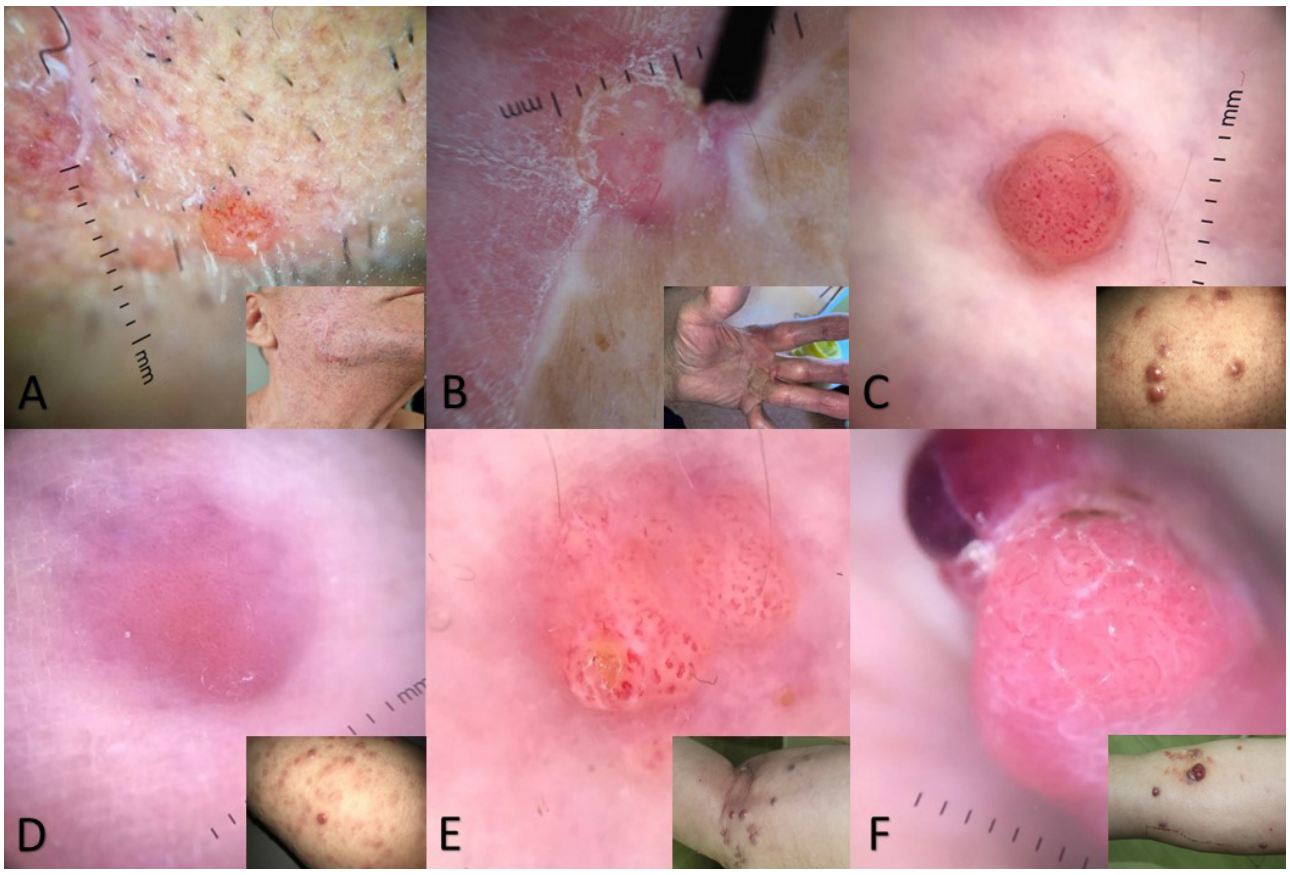

Fig. 1 – Clinical and dermatoscopical presentations of amelanotic cutaneous melanoma metastases (ACMM): pinkish papule 3 mm in diameter, located 5 mm from the surgical scar showing linear irregular vessels (A); pinkish papule 5 mm in diameter on the scar showing arborizing vessels (B); numerous flat and elevated in-transit ACMM on the leg, dermatoscopy revealed dotted, glomerular, and linear irregular vessels (C); monomorphic pattern of dotted vessels in a flat lesion (D); vascular pattern with linear irregular and corkscrew-like vessels (E); elevated ACMM with linear irregular vessels and white lines (F).

Table 3

Dermatoscopic characteristics of vascular pattern according to the morphologic type of 52 amelanotic cutaneous melanoma metastases (ACMM)

Parameter	Lesions		*p*-values[1]
	flat (n = 13)	elevated (n = 39)	
Vessels			
dotted	10 (76.9)	11 (28.2)	0.003
glomerular	0 (0.0)	4 (10.3)	0.563
linear irregular	5 (38.5)	36 (92.6)	0.001
arborizing	0 (0.0)	1 (2.6)	1.000[2]
hairpin-like	0 (0.0)	7 (17.9)	0.171[1]
Distribution pattern			
diffuse	12 (92.3)	30 (76.9)	0.416
peripheral	1 (7.7)	6 (15.4)	0.815
central	0 (0.0)	1 (2.6)	1.000[2]
cluster	0 (0.0)	2 (5.1)	1.000[2]
Morphologic pattern			
monomorphic	11(84.6)	24 (61.5)	
polymorphic	2 (15.4)	15 (38.5)	0.232
Additional features			
ulceration	1 (7.7)	10 (25.6)	0.252[2]
white lines	1 (7.7)	15 (38.5)	0.044[2]

[1] Chi-square test; [2] Fisher test.

All values are given as numbers (percentages).

Discussion

Early diagnosis of ACMM is essential for determining the stage, treatment, and prognosis of the disease. Unfortunately, ACMM are still challenging due to their ambiguous clinical and dermatoscopic appearance. Misdiagnosing due to a number of benign and malignant lesions resembling ACMM is a common occurrence [1–6]. So far, a rare small series of ACMM and individual cases have been described in the literature [9–12].

The most common anatomical localization of CMM in the study of Plaza et al. [2] were the lower extremities and the scalp, followed by the upper extremities, face, and feet. Kostaki et al. [13] reported that 45.24% of CMM cases were located on the lower limbs, with the trunk being the second most common site at 23.08%, followed by the head (21.43%) and upper limbs (4.76%). Our findings are consistent with those of Kostaki et al. [13], showing the lower extremities as the most common site of ACMM (64.7%), followed by the trunk (17.6%), head (11.8%), and upper extremities (5.9%). A recent study by Tiodorovic et al. [14] also reported the lower extremities as the most common localization at 28.1%, followed by the trunk (19.3%), head and neck (17.5%), and upper extremities (12.3%). The notable differences in ACMM localization observed in our study could be attributed to the primary melanoma site and the locoregional distribution of ACMM.

From the clinical perspective, the most common clinical manifestations of CMM are erythematous papules with a linear arrangement [10]. In our study, papular appearances were also the dominant clinical finding (64.7%) (Figure 1A, B).

In a study by Savoia et al. [15], the average time from the diagnosis of primary melanoma to the appearance of locoregional metastases is 1.3 years, while for distant metastases on the skin was 2.9 years. In Bono et al. [5], the average time of occurrence of CMM was 1.7 years after the diagnosis of primary melanoma. In the study by Reed et al. [16], the average time of occurrence of locoregional CMM was 15.6 months. In a series of 47 ACMM in 18 patients, Jaimes et al. [10] found that the average onset time of CMM was 17 months from the diagnosis of primary melanoma. In our study, the average time from diagnosis of primary melanoma to onset of CMM was 22.59 months.

All (100%) ACMM in our study were locoregional (satellites and in transit). In the study by Jaimes et al. [10], 89.0% of ACMM were regional.

Zalaudek et al. [17] emphasized the importance of dermatoscopic observation of vascular structures in their series of seven AHM in six patients, indicating that atypical blood vessels with a central pink or white veil represent dermatoscopic hallmarks of AHM. Due to neoangiogenesis, vascular structures are more common in CMM than in primary cutaneous melanomas [6, 18, 19]. Rubegni et al. [19] point out that punctate blood vessels predominate in thin lesions, while corkscrew-like vessels are the most common in the thick ones [20]. Mendes et al. [11] also highlight the finding of punctate blood vessels in thin melanomas, while in melanomas with a Breslow index greater than 1 mm, the vascular structure is a mixture of irregular linear, hairpin-like, corkscrew-like, and punctate blood vessels. Melanoma metastases follow this pattern of appearance with a high prevalence of irregular linear blood vessels to thicker lesions. Our results were in line with this finding, indicating that dotted vessels are statistically more associated with flat ACMM (76.9%), while linear irregular vessels were statistically more associated with elevated ones (92.3%).

In a 2012 study by Jaimes et al. [10], the predominant dermatoscopic finding in patients with ACMM was a vascular pattern with serpentine, glomerular, hairpin-like, and corkscrew-like blood vessels. Our study also revealed linear irregular blood vessels were the most prevalent (92.3% of elevated and 50.0% of flat lesions), then come the dotted blood vessels (76.9% of flat and 28.8% of elevated lesions), hairpin-like vessels (17.9% of elevated lesions), glomerular (10.3% of elevated lesions), and finally, arborizing vessels (2.6% of elevated lesions) (Figure 1B, C).

The arrangement of vascular structures can be a valid diagnostic indicator and contribute to the possible differentiation of metastatic from primary melanoma. While vascular structures in CMM are closer to the edge of the tumor (peripheral arrangement), they are centrally located in primary tumors [9, 19, 21]. In our study, diffuse distribution of vascular structures was dominant (80.8%), while peripheral distribution was found in 13.5%.

Our results regarding an additional dermatoscopy feature – ulcerations, are in line with the literature [9, 10, 22], appearing in 25.6% of elevated lesions and 7.7% of the flat ones.

Like the prognosis of patients with AHM, the prognosis of patients with ACMM is worse than that of those with pigmented lesions, probably due to delayed treatment [7]. Even though early detection of CMM does not necessarily mean longer survival, some studies show that it does result in a better survival rate of patients compared to those where CMM were detected at a late stage [14, 23–25].

Limitations of the study

Although this study is limited by a low number of patients, it emphasizes the importance of dermatoscopic recognition of vascular structures and patterns for a more accurate diagnosis of ACMM. However, further research is needed on a larger number of patients to achieve a more precise identification of vascular findings.

Conclusion

When using dermatoscopy to assess amelanotic lesions, examining the blood vessel patterns is crucial. Recognizing and observing specific vascular patterns is important to diagnose ACMM early. The absence of pigment in ACMM makes detecting the vessels within the lesion easier. Our study supports the finding that linear irregular blood vessels are more commonly associated with elevated ACMM, while the dotted ones are dominant in flat ACMM. However, while specific vascular patterns strongly indicate a malignant condition, in the case of an apigmentic single lesion, no differentiation can be made between primary amelanotic melanoma or ACMM.

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Received on May 28, 2024
Revised on July 31, 2024
Accepted on August 13, 2024
Online First October 2024

ORIGINAL ARTICLE

UDC: 618.19:616.428-006.03/.04-079.4
DOI: https://doi.org/10.2298/VSP230130077Z

Value of real-time tissue elastography diffusion quantitative analysis combined with tumor markers for differential diagnosis of benign and malignant breast nodules

Vrednost elastografije mekih tkiva u realnom vremenu sa kvantitativnom analizom u kombinaciji sa tumorskim markerima za diferencijalnu dijagnozu benignih i malignih nodusa dojke

[1]Ling Zhu*, [1]Lina Mei†, Xuekui Pan*

Huzhou Maternal and Child Health Hospital, *Department of Ultrasound, †Department of Internal Medicine, Huzhou, Zhejiang Province, China

[1]The two authors contributed equally to this study.

Abstract

Background/Aim. Serum tumor markers (TMs) are commonly combined with imaging examinations to differentiate benign and malignant breast nodules (BNs), but there are still limitations. The aim of the study was to determine the value of real-time tissue elastography (RTE) diffusion quantitative analysis combined with serum TMs for the differential diagnosis of benign and malignant BNs. **Methods.** A total of 149 patients with BNs were included in this study. They were assigned to the benign BN group (n = 87) and malignant BN group (n = 62). All patients were examined using RTE diffusion quantitative analysis. Venous blood was collected to detect the levels of TMs carcinoembryonic antigen-CAE, cancer antigen (CA) 153, and CA 199. The value of RTE diffusion quantitative analysis parameters, TMs, and their combination for the differentiation of benign and malignant BNs was analyzed using the receiver operating characteristic-ROC curve. **Results.** Among all the above indicators, the area ratio of the blue region (AREA%) had the highest differential value, with an area under the curve (AUC) of 0.916 [95% confidence interval (CI): 0.812–0.967], while sensitivity and specificity were 88.90% and 86.79%, respectively ($p < 0.05$). Compared to RTE diffusion quantitative analysis parameters or TMs alone, the combination of the two showed the highest value for the differentiation of benign and malignant BNs, with an AUC of 0.957 (95% CI: 0.834–0.982), while sensitivity and specificity were 95.50% and 94.33%, respectively ($p < 0.05$). **Conclusion.** RTE diffusion quantitative analysis combined with TMs has a high value for the differentiation of benign and malignant BNs.

Key words:
breast, neoplasms; biomarkers, tumor; diagnosis, differential; elasticity imagine techniques; sensitivity and specificity.

Apstrakt

Uvod/Cilj. Za razlikovanje benignih i malignih nodusa (čvorića) dojke (ND) često se kombinuju serumski tumorski markeri (TM) i analize snimaka nodusnih promena, mada ograničenja još uvek postoje. Cilj rada bio je da se utvrdi korisnost elastografije mekih tkiva u realnom vremenu (EMTRV) sa kvantitativnom analizom u kombinaciji sa serumskim TM za diferencijalnu dijagnozu benignih i malignih ND. **Metode**. Ukupno 149 žena sa ND bilo je uključeno u ovu studiju. Bolesnice su podeljene na grupu sa benignim ND (n = 87) i grupu sa malignim ND (n = 62). Sve bolesnice su bile ispitane primenom EMTRV sa kvantitativnom analizom. Iz venske krvi, određivani su nivoi TM: karcinoembrionskog antigena-CAE, karcinomskog antigena (*cancer* antigen – CA) 153 i CA 199. Za diferencijalnu dijagnozu benignih i malignih ND, analizirane su vrednosti parametara EMTRV sa kvantitativnom analizom, TM i njihove kombinacije, korišćenjem *receiver operating characteristic*-ROC krive. **Rezultati**. Među navedenim pokazateljima, najveću diferencijalnu vrednost imala je *area ratio of the blue region* (AREA%) sa površinom ispod krive (*area under the curve* – AUC) od 0,916 [95% *confidence interval* (CI): 0,812–0,967], dok su senzitivnost i specifičnost iznosile 88,90% i 86,79%, redom ($p < 0,05$). U poređenju sa

Correspondence to: Ling Zhu, Huzhou Maternal and Child Health Hospital, Department of Ultrasound, Huzhou 313 000, Zhejiang Province, China. Email: zhulinghmchh@csc-edu.cn

EMTRV sa kvantitativnom analizom ili samo sa TM, njihova kombinacija je pokazala najvišu vrednost za razlikovanje benignih i malignih ND, sa AUC 0,957 (95% CI: 0,834–0,982), dok su senzitivnost i specifičnost iznosile 95,50% i 94,33%, redom. **Zaključak**. EMTRV sa kvantitativnom analizom u kombinaciji sa TM ima veliku vrednost za razlikovanje benignih i malignih ND.

Ključne reči:
dojka, neoplazme; tumorski markeri; dijagnoza, diferencijalna; elasticitet, tehnike snimanja; osetljivost i specifičnost.

Introduction

Breast cancer (BC) is a common disease that affected about 2.26 million people in 2020 worldwide, which accounted for 11.7% of all malignancies [1]. The global 5-year survival rate is 82% [2] and the global mortality rate is 17.7 *per* 100,000 people [1]. Although the incidence rate of BC in China is lower than the global value [3], it is increasing annually and poses serious threats to women's lives and health. Breast nodules (BNs) are the common manifestations of benign and malignant breast lesions, and the treatment and prognosis of the two types of BNs vary considerably [4]. Therefore, the early identification of benign/malignant breast lesions is of great significance for timely treatment, contributing to an obvious reduction in the mortality rate and improvement of women's quality of life [5].

Presently, many methods are used to differentiate benign and malignant BNs, mainly including imaging and serum tumor markers (TMs), the latter of which refer to special substances that cause some functional abnormalities and, thus, change in the presence of malignant lesions [6, 7]. TMs play vital roles in the screening, adjuvant diagnosis, treatment, and prognosis of BC [8]. However, the detection of serum TMs is prone to influences by external factors during tests [9].

Real-time tissue elastography (RTE), as a novel ultrasound diagnostic technique, can closely monitor tissue elasticity using diffusion quantitative analysis [10, 11]. It has been used in the differential diagnosis of various benign and malignant diseases, which contributes to evaluating the nature of lesions [12–14]. Xu et al. [15] reported that RTE had a high diagnostic rate for BC with axillary lymph node metastasis. In addition to a diagnostic tool for BC, Fang and Yang [16] also proved the predictive role of RTE in the effect of neoadjuvant chemotherapy on patients with BC. Nevertheless, there are few studies regarding the differentiation of benign and malignant BNs using RTE.

Therefore, the aim of this study was to determine the value of RTE diffusion quantitative analysis used to analyze the tissue parameters of lesions in patients with benign and malignant BNs, combine their results with TMs to accurately differentiate benign and malignant BNs, and improve the treatment and prognosis.

Methods

Subjects

A total of 149 patients with BNs, who were admitted to our hospital from April 2020 to April 2021, were included in this study. The patients were all females, aged 25–70 years (mean 47.89 ± 5.63 years). RTE diffusion quantitative analysis was performed and serum TMs were measured before pathological examination; then, the ultrasound-guided needle biopsy was performed. The subjects were then assigned to the benign and malignant BN groups using pathological examination results as the gold standard. Informed consent was obtained from all patients and this study was reviewed and approved by the Ethics Committee of the Huzhou Maternal and Child Health Hospital, China (from April 4, 2020).

Inclusion and exclusion criteria

Inclusion criteria were as follows: 1) patients with a single BN; 2) no contraindications to imaging examination; 3) no previous treatment of breast lesions; 4) normal expressive and cognitive abilities of the patients allowing a normal description of symptoms and cooperation with examinations; 5) complete clinical records.

Exclusion criteria involved the following: 1) patients with a previous history of malignancy; 2) breast implants; 3) history of resection of the breast mass; 4) pregnancy or lactation to avoid the influence of hormone changes; 5) calcified lesions in the breast; 6) cardiovascular or cerebrovascular diseases to avoid the occurrence of sudden cardiac or cerebral adverse events; 7) poor compliance and patients unable to cooperate to affect examinations.

Real-time tissue elastography diffusion quantitative analysis

All patients were examined by the HI VISION Ascendus ultrasound platform using an L-52 linear array probe (Hitachi Aloka Medical, Ltd., Japan) with a frequency of 6–13 MHz. The size and location of BNs were observed following the routine ultrasound examination. Then, the instrument was switched to an elastography mode to observe the gray-scale echogram and elastogram using the dual-view display function, and the position of the probe was adjusted to ensure that the BN was in the center of the screen. During the examination, the pressure was manually applied. After a slight jitter, the stable and repeatable dynamic elastogram was displayed and obtained when the pressure value was within the range of 3–4. Images were analyzed using Strain Histogram Measurement software along with the platform. With the largest rectangular area not exceeding the extent of the lesion as the sampling location, 11 RTE parameters, including mean strain (MEAN), standard deviation (SD),

area ratio of the blue region (AREA%), complexity (COMP), kurtosis (KURT), skewness (SKEW), contrast (CONT), entropy (ENT), inverse difference moment (IDM), angular second moment (ASM), and correlation (CORR), were acquired. The examination was repeated three times to take the corresponding mean value.

Tumor marker tests

Fasting venous blood was drawn from each subject in the early morning. The serum was then separated, followed by the detection of the levels of TMs carcinoembryonic antigen (CEA), cancer antigen (CA) 153, and CA199 using the E411 electrochemiluminescence analyzer (Roche, Switzerland).

Observation of indicators

Firstly, the patients were assigned to the benign BN group (n = 87) and malignant BN group (n = 62) with pathological examination results as the gold standard, and the RTE diffusion quantitative parameters and TM levels were compared between the two groups. Secondly, the differences in RTE diffusion quantitative parameters and TM levels were compared among patients with different degrees of differentiation (poor, moderate, and good) and different stages (I, II, III, and IV) of malignant BNs. Thirdly, the value of RTE diffusion quantitative analysis and TMs in differentiating benign and malignant BNs was analyzed using pathological examination results as the gold standard.

Statistical analysis

The SPSS software version 22.0 was used for statistical analysis. The Kolmogorov-Smirnov test was applied to determine whether the data conformed to normal distribution. Normally distributed measurement data were expressed as mean ± SD and analyzed by the independent samples *t*-test for comparison between groups. If the data did not conform to normal distribution, they were expressed as a median and interquartile range [M (Q1, Q3)] and analyzed by the Wilcoxon test to compare between groups. Count data were expressed as numbers (percentages) and analyzed using the Chi-square (χ^2). The value of RTE diffusion quantitative parameters, TMs, and the combination of the two in the differentiation of benign and malignant BNs was analyzed by plotting receiver operating characteristic (ROC) curves. With the area under the curve (AUC) > 0.7 representing the differential value, a larger AUC corresponded to a higher differential diagnosis value. The value of $p < 0.05$ was considered statistically significant.

Results

Among 149 pathology-proven BNs, there were 87 benign lesions and 62 malignant lesions (Table 1).

Considering the 11 obtained RTE diffusion quantitative parameters, all of them had statistically significant differences between benign and malignant BN groups, except for COMP and CORR. Specifically, the MEAN, SD, CONT, and ENT were lower and the AREA%, KURT, SKEW, IDM, and ASM were higher in the malignant nodule group than those in the benign BN group ($p < 0.05$). Compared with those in the benign BN group, the levels of TMs CEA, CA153, and CA199 were higher in the malignant BN group ($p < 0.05$) (Table 2).

The nine RTE diffusion quantitative parameters with statistically significant differences between benign and malignant BNs were further analyzed. It was found that patients with poor differentiation of malignant BNs showed lower MEAN, SD, CONT, and ENT and higher AREA%, KURT, SKEW, IDM, and ASM than those with moderate/good differentiation of malignant BNs ($p < 0.05$). The levels of TMs CEA, CA153, and CA199 were also compared among patients with different degrees of differentiation of malignant BNs, and it was seen that patients with poor differentiation had higher CEA, CA153, and CA199 levels than those with moderate/good differentiation ($p < 0.05$) (Table 3).

With the increasing stage of malignant BNs, the MEAN, SD, CONT, and ENT declined gradually and the AREA%, KURT, SKEW, IDM, and ASM rose gradually

Table 1

Pathological examination results

Pathological finding	n (%) of nodules
Benign breast nodules (n = 87)	
mammary inflammatory granuloma	19 (21.84)
intraductal papilloma	17 (19.54)
fibroadenoma	24 (27.59)
breast adenopathy	21 (24.14)
usual-type ductal epithelial hyperplasia	6 (9.68)
Malignant breast nodules (n = 62)	
invasive ductal carcinoma	18 (29.03)
invasive lobular carcinoma	20 (32.26)
ductal carcinoma in situ	14 (22.58)
medullary carcinoma	10 (16.13)

n – number.

Table 2

Real-time tissue elastography (RTE) diffusion quantitative parameters and tumor marker levels of patients with benign and malignant breast nodules (BNs)

Parameter	BNs group		*t*	*p*-value
	benign (n = 87)	malignant (n = 62)		
RTE diffusion quantitative parameters				
MEAN	84.53 ± 10.19	24.53 ± 2.13	45.620	0.001
SD	39.18 ± 3.20	28.29 ± 2.19	23.190	0.001
AREA%	42.32 ± 2.89	84.43 ± 1.09	109.200	0.001
COMP	24.31 ± 1.89	24.35 ± 1.20	0.147	0.883
KURT	3.12 ± 0.67	5.64 ± 1.12	17.130	0.001
SKEW	0.68 ± 0.12	1.42 ± 0.28	22.000	0.001
CONT	28.97 ± 3.42	17.78 ± 1.10	24.840	0.001
ENT	3.12 ± 0.29	2.25 ± 0.21	20.150	0.001
IDM	0.31 ± 0.07	0.58 ± 0.12	17.280	0.001
ASM	0.03 ± 0.01	0.09 ± 0.03	17.370	0.001
CORR	5.62 ± 0.89	5.69 ± 0.72	0.511	0.610
Tumor marker levels				
CEA (ng/mL)	5.32 ± 1.09	11.23 ± 2.54	19.360	0.001
CA153 (U/mL)	23.41 ± 2.39	42.31 ± 5.62	28.040	0.001
CA199 (U/mL)	20.19 ± 2.32	37.64 ± 3.12	39.160	0.001

MEAN – mean strain; SD – standard deviation; AREA% – area ratio of the blue region; COMP – complexity; KURT – kurtosis; SKEW – skewness; CONT – contrast; ENT – entropy; IDM – inverse difference moment; ASM – angular second moment; CORR – correlation; CEA – carcinoembryonic antigen; CA – cancer antigen. All values are given as mean ± SD.

Table 3

Real-time tissue elastography (RTE) diffusion quantitative parameters and tumor marker levels of patients with different degrees of differentiation of malignant breast nodules

Parameter	Degree of differentiation			*F*	*p*
	good (n = 20)	moderate (n = 24)	poor (n = 18)		
RTE diffusion quantitative parameters					
MEAN	37.75 ± 2.31	26.31 ± 3.89[a]	18.97 ± 1.65[ab]	42.810	0.001
SD	32.42 ± 4.52	28.78 ± 2.11[a]	25.63 ± 2.10[ab]	8.741	0.001
AREA%	79.98 ± 6.12	86.75 ± 7.85[a]	92.31 ± 9.06[ab]	7.442	0.001
KURT	4.10 ± 0.42	5.90 ± 0.78[a]	7.89 ± 1.13[ab]	20.971	0.001
SKEW	1.18 ± 0.21	1.50 ± 0.12[a]	1.87 ± 0.14[ab]	17.670	0.001
CONT	20.19 ± 2.23	17.85 ± 1.96[a]	14.53 ± 1.20[ab]	14.375	0.001
ENT	2.89 ± 0.28	2.10 ± 0.23[a]	1.67 ± 0.15[ab]	24.705	0.001
IDM	0.40 ± 0.03	0.59 ± 0.10[a]	0.70 ± 0.15[ab]	13.146	0.001
ASM	0.06 ± 0.02	0.08 ± 0.03[a]	0.11 ± 0.03[ab]	9.153	0.001
Tumor marker levels					
CEA (ng/mL)	8.77 ± 1.09	11.32 ± 2.31	15.63 ± 2.45	17.025	0.001
CA153 (U/mL)	32.42 ± 2.31	40.51 ± 3.42[a]	45.64 ± 3.41[ab]	21.180	0.001
CA199 (U/mL)	30.92 ± 2.39	36.73 ± 2.19[a]	42.31 ± 4.78[ab]	14.154	0.001

[a] $p < 0.05$ vs. good differentiation; [b] $p < 0.05$ vs. moderate differentiation.
For abbreviations, see Table 2.
All values are given as mean ± SD.

($p < 0.05$), while the levels of tumor markers CEA, CA153, and CA199 were elevated gradually ($p < 0.05$) (Table 4).

Using pathological examination results as the gold standard, it was revealed that the sensitivity, specificity, and accuracy of RTE diffusion quantitative analysis in differentiating benign and malignant BNs were 88.71% (55/62), 88.51% (77/87), and 88.59% (132/149), respectively (Table 5). The sensitivity, specificity, and accuracy of TMs in differentiating benign and malignant BNs were 79.03% (49/62), 78.16% (68/87), and 78.52% (117/149), respectively (Table 6). Besides, the sensitivity, specificity, and accuracy of RTE diffusion quantitative analysis combined with TMs

Table 4

Real-time tissue elastography (RTE) diffusion quantitative parameters and tumor marker levels of patients with different stages of malignant breast nodules

Parameter	Stage I (n = 15)	Stage II (n = 20)	Stage III (n = 17)	Stage IV (n = 10)	*F*	*p*
RTE diffusion quantitative parameters						
MEAN	30.97 ± 4.55	27.53 ± 3.16[a]	22.94 ± 2.25[ab]	17.63 ± 1.12[abc]	13.547	0.001
SD	34.24 ± 3.15	30.12 ± 2.89[a]	27.89 ± 2.11[ab]	22.31 ± 2.07[abc]	15.780	0.001
AREA%	71.42 ± 4.51	80.32 ± 5.63[a]	88.06 ± 8.94[ab]	97.68 ± 9.12[abc]	14.396	0.001
KURT	3.99 ± 0.78	5.13 ± 0.43[a]	6.98 ± 1.24[ab]	8.12 ± 1.69[abc]	12.440	0.001
SKEW	1.03 ± 0.12	1.56 ± 0.13[a]	1.93 ± 0.16[ab]	2.35 ± 0.21[abc]	30.060	0.001
CONT	24.53 ± 2.18	20.31 ± 2.23[a]	17.85 ± 2.18[ab]	15.63 ± 1.12[abc]	17.775	0.001
ENT	2.78 ± 0.32	2.34 ± 0.15[a]	2.00 ± 0.19[ab]	1.78 ± 0.13[abc]	13.994	0.001
IDM	0.42 ± 0.03	0.54 ± 0.04[a]	0.65 ± 0.04[ab]	0.79 ± 0.05[abc]	34.800	0.001
ASM	0.05 ± 0.02	0.07 ± 0.02[a]	0.10 ± 0.03[ab]	0.13 ± 0.04[abc]	9.968	0.001
Tumor marker levels						
CEA (ng/mL)	7.85 ± 0.97	13.42 ± 1.10[a]	16.98 ± 2.31[ab]	19.74 ± 2.41[abc]	25.905	0.001
CA153 (U/mL)	30.21 ± 2.19	39.09 ± 3.42[a]	46.64 ± 4.51[ab]	50.98 ± 6.12[abc]	18.210	0.001
CA199 (U/mL)	28.38 ± 2.11	36.64 ± 4.51[a]	38.97 ± 2.19[ab]	45.53 ± 6.76[abc]	13.887	0.001

[a] $p < 0.05$ vs. stage I; [b] $p < 0.05$ vs. stage II; [c] $p < 0.05$ vs. stage III.
For abbreviations, see Table 2.
All values are given as mean ± SD.

Table 5

Value of real-time tissue elastography diffusion quantitative analysis for differentiating benign and malignant breast nodules (BNs)

BNs	Gold standard		Total
	malignant BNs	benign BNs	
Malignant	55	10	65
Benign	7	77	84
Total	62	87	149

Note: Gold standard means pathohistological finding.

Table 6

Value of tumor markers for differentiating benign and malignant breast nodules (BNs)

BNs	Gold standard		Total
	malignant BNs	benign BNs	
Malignant	49	19	68
Benign	13	68	81
Total	62	87	149

Note: Gold standard means pathohistological finding.

Table 7

Value of real-time tissue elastography (RTE) diffusion quantitative analysis combined with tumor markers for differentiating benign and malignant breast nodules (BNs)

BNs	Gold standard		Total
	malignant BNs	benign BNs	
Malignant	60	6	66
Benign	2	81	83
Total	60	6	66

Note: Gold standard means pathohistological finding.

in differentiating benign and malignant BNs were 96.77% (60/62), 93.10% (81/87), and 94.63% (141/149), respectively (Table 7). Overall, the value of RTE diffusion quantitative analysis combined with TMs was optimal in differentiating benign and malignant BNs.

According to the ROC curve analysis, among all the RTE diffusion quantitative parameters and TMs, AREA% had the highest differential value, with an AUC of 0.916 [95% confidence interval (CI): 0.812–0.967], while sensitivity and specificity were 88.90% and 86.79%,

respectively ($p < 0.05$). In contrast to RTE diffusion quantitative parameters or TMs alone, the combination of the two showed the highest value in the differentiation of benign and malignant BNs, with an AUC of 0.957 (95% CI: 0.834–0.982), while sensitivity and specificity were 95.50% and 94.33%, respectively ($p < 0.05$) (Figure 1).

The typical RTE diffusion quantitative analysis images are exhibited in Figures 2 and 3.

Discussion

Many TMs are currently available in differentiating benign and malignant BNs, among which CEA, CA153, and CA199 are most commonly used [17]. The combination of CA153 and CA199 has the highest value in diagnosing BC and identifying benign and malignant BNs. Additionally, Can et al. [18] reported that CEA positivity was related to the

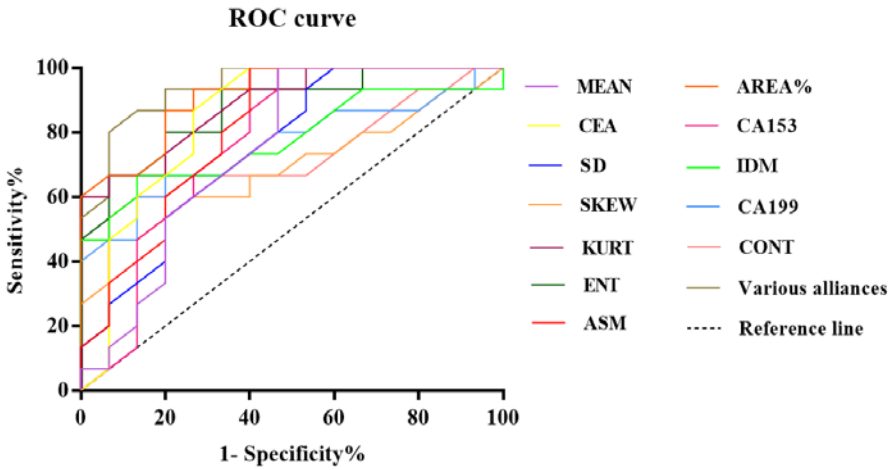

Fig. 1 – Receiver operating characteristic (ROC) curve analysis of real-time tissue elastography diffusion quantitative parameters and tumor markers in differentiating benign and malignant breast nodules. For abbreviations, see Table 2.

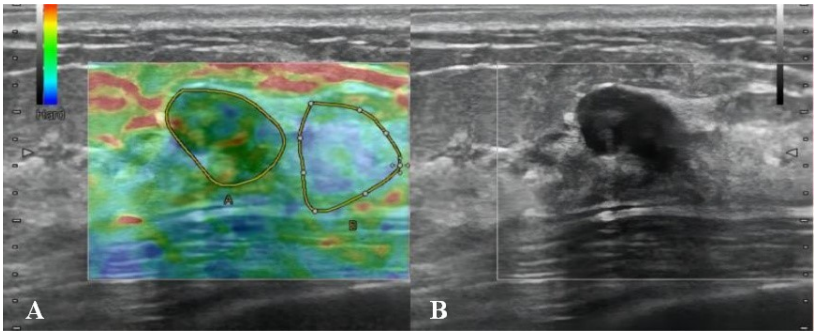

Fig. 2 – A 30-year-old female presented with a right breast nodule. Real-time tissue elastography diffusion quantitative analysis showed an area ratio of the blue region (AREA%) of 21.89 and soft tissues, suggesting it was a benign breast nodule (A and B).

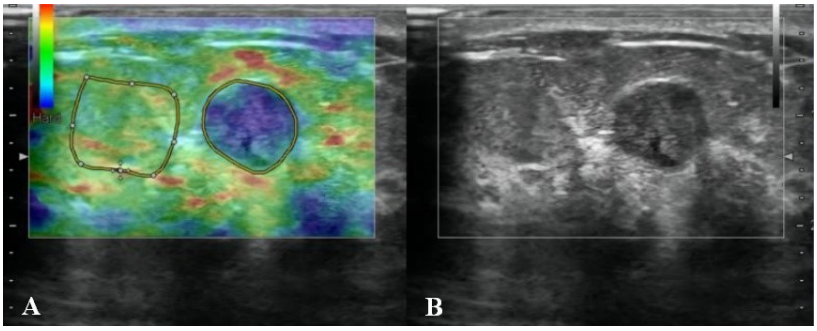

Fig. 3 – A 28-year-old female with a right breast nodule identified by physical examination. Real-time tissue elastography diffusion quantitative analysis revealed an area ratio of the blue region (AREA%) of 89.72 and hard tissues, suggesting it was a malignant breast nodule (A and B).

increased preoperative tumor burden of malignant BNs, which was beneficial to the diagnosis. In this study, the differences in the levels of these serum TMs between patients with benign and malignant BNs were analyzed using pathological examination results as the gold standard, and the results showed that CEA, CA153, and CA199 levels in malignant BNs were higher than in benign BNs, being consistent with the literature mentioned above. Moreover, we found that CEA, CA153, and CA199 levels were significantly higher in poorly differentiated and stage IV patients than in patients with moderate to good differentiation and stages I to III. Hence, CEA, CA153, and CA199 may be involved in the progression of malignant BNs.

Ultrasound and color Doppler ultrasound are usually employed to diagnose benign and malignant BNs. However, they are unsuitable for BC with no or small masses, because no image is obtained or the image is obscure [19]. Thus, RTE diffusion quantitative analysis was used to differentiate benign and malignant BNs in this study to improve the accuracy of evaluating differentiation. The results exhibited that, except for COMP and CORR, all the diffusion quantitative parameters obtained by RTE diffusion quantitative analysis had statistically significant differences in differential diagnosis of benign and malignant BNs. Specifically, lower MEAN, SD, CONT, and ENT indicated higher tissue stiffness, while higher AREA%, KURT, SKEW, ENT, IDM, and ASM represented higher tissue stiffness. Besides, in comparison with benign BNs, MEAN, SD, CONT, and ENT were lower and AREA%, KURT, SKEW, ENT, IDM, and ASM were higher in malignant BNs, which were associated with the degree of differentiation and stage of patients with malignant BNs. Similarly, Guo et al. [20] conducted an RTE diffusion quantitative analysis and found that except for COMP and CORR, the other nine characteristic parameters showed statistically significant differences in the differentiation of benign and malignant prostate nodules. Theoretically, it may be explained by the tissue stiffness of malignant breast lesions higher than that of benign lesions, and such tissue stiffness gradually increases as the disease progresses.

With pathological findings as the gold standard, the value of RTE diffusion quantitative analysis in differentiating benign and malignant breast lesions was analyzed. The results indicated that 55 out of the 62 malignant nodules were identified by RTE diffusion quantitative analysis. The remaining seven cases of medullary carcinoma were misdiagnosed as fibroadenoma and usual-type ductal epithelial hyperplasia, probably because medullary carcinoma has less collagen content, small amounts of fibrous tissues, and abundant cancer cells, making the texture relatively soft [21]. Besides, 77 out of the 87 benign nodules were identified by RTE diffusion quantitative analysis, and the remaining ten were misdiagnosed as fibroadenoma, possibly because fibroadenoma principally presents as mesenchymal hyperplasia, and the complex mesenchymal hyperplasia may increase the stiffness of tissues [22].

In this study, ROC curves were plotted to analyze the values of RTE diffusion quantitative analysis and TMs for the differentiation of benign and malignant BNs. AREA% had the highest differential value, probably because it reflects the area of the blue region, of which the proportion has a positive relationship with the tissue stiffness [23]. However, RTE diffusion quantitative analysis still needs to be combined with other methods to reduce the misdiagnosis rate in the clinical differentiation of benign and malignant BNs [24]. We found that the value of RTE diffusion quantitative parameters combined with TMs was markedly higher than that of RTE diffusion quantitative parameters or TMs alone, suggesting that the combination may improve the detection accuracy and prognosis.

Conclusion

In conclusion, real-time tissue elastography diffusion quantitative analysis combined with tumor markers is effective in differentiating benign and malignant breast nodules and has a highly differential diagnosis. Nonetheless, this study is limited because this study was, first of all, a single-center study with a small sample size. Second, we did not consider other histopathological parameters such as tumor type, size, and dissemination. Therefore, additional multicenter studies with large sample sizes are still needed for further validation.

Acknowledgment

This study was financially supported by Project No. 2022KY1226.

Conflict of interest

The authors declare no conflict of interest concerning authorship and/or publication of this article.

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Received on January 30, 2023
Revised on February 25, 2024
Revised on June 26, 2024
Accepted on July 30, 2024
Online First October 2024

ORIGINAL ARTICLE

UDC: 616.831-005.1-08
DOI: https://doi.org/10.2298/VSP240305063M

Clinical outcome in patients monitored by the NIHSS after mechanical thrombectomy in relation to time and cerebrovascular risk factors

Klinički ishod praćen primenom skale NIHSS kod bolesnika posle mehaničke trombektomije u odnosu na vreme i cerebrovaskularne faktore rizika

Valentina Mileusnić*, Irena Grkić†, Aleksandra Zečević†

***University Hospital Medical Center Bežanijska Kosa, Belgrade, Serbia; †Special Hospital for Cerebrovascular Diseases "Sveti Sava", Belgrade, Serbia**

Abstract

Background/Aim. Mechanical thrombectomy (MT) is an endovascular treatment that involves the extraction of thrombotic masses in the first hours of acute ischemic stroke (AIS) from the large blood vessels of the head and/or neck. The aim of the study was to determine the role of predictors (time and vascular risk factors) of the clinical outcome of patients with AIS monitored by the National Institute of Health Stroke Scale (NIHSS). **Methods.** The study included 134 patients diagnosed with occlusion of a blood vessel of the head and/or neck with a clinical picture of AIS who met the criteria for MT and in whom, upon admission to the hospital, existing vascular risk factors were observed. In relation to the time parameter from the onset of the clinical picture of AIS to the start of MT, the patients were divided into two groups. The first, the examined group, consisted of 85 (63.4%) patients in whom recanalization was initiated within the first four hours from the onset of symptoms, and the second, the control group, consisted of 49 (36.6%) patients in whom recanalization was initiated after the fourth hour. The results were monitored by the change of the NIHSS score at the time of discharge of the patient, on the 30th and 90th day, in relation to the NIHSS score on admission. **Results.** There was no statistically significant difference between the groups except for the variables endovascular treatment (EVT) and previous vascular event [cardiovascular disease (CVD)] ($p < 0.05$). A statistically significant correlation was found between improvement and the time when EVT was performed in relation to the onset of complaints ($\chi^2(1) = 4.756$; $p < 0.05$). A statistically significant correlation was also found between improvement and CVD ($\chi^2(1) = 4.756$; $p < 0.05$). **Conclusion.** The results of our study support MT as a promising stand-alone therapy for AIS. Clinical outcome monitored by the NIHSS after MT in relation to time and cerebrovascular risk factors shows that patients in whom EVT was performed in the first four hours have an improvement more often than patients in whom EVT was performed four hrs after the onset of symptoms. Likewise, patients without CVD were more likely to show improvement than patients with CVD.

Key words:
endovascular procedures; ischemic stroke; risk factors; time-to-treatment; treatment outcome.

Apstrakt

Uvod/Cilj. Mehanička trombektomija (MT) je endovaskularno lečenje koje uključuje uklanjanje trombotičnih masa iz velikih krvnih sudova glave i/ili vrata u prvim satima akutnog ishemijskog moždanog udara (AIMU). Cilj rada bio je da se utvrdi uloga prediktora (vreme i vaskularni faktori rizika) kliničkog ishoda obolelih od AIMU praćenih primenom skale *National Institute of Health Stroke Scale* (NIHSS). **Metode.** Ispitivanjem su obuhvaćena 134 bolesnika sa dijagnozom okluzije krvnog suda glave i/ili vrata sa kliničkom slikom AIMU, koji su zadovoljavali kriterijume za MT, a kod kojih su pri prijemu u bolnicu postojali faktori rizika od vaskularnih bolesti. U odnosu na period od nastanka kliničke slike AIMU do vremena početka MT, bolesnici su bili podeljeni u dve grupe. Prvu, ispitivanu grupu, činilo je 85 (63,4%) bolesnika kojima je rekanalizacija započeta u prva četiri sata od pojave simptoma, a drugu, kontrolnu grupu, 49 (36,6%) bolesnika kojima je rekanalizacija započeta posle četvrtog sata. Rezultati su praćeni na osnovu skora primenom skale NIHSS prilikom otpusta bolesnika, 30-og i 90-og dana, u odnosu na NIHSS rezultat pri prijemu bolesnika. **Rezultati.** Nije bilo statistički značajne razlike između grupa, osim za varijable endovaskularni tretman (EVT) i raniji vaskularni događaj [kardiovaskularna bolest (KVB)] ($p < 0,05$). Utvrđena je statistički značajna povezanost između poboljšanja i vremena kada je EVT

Correspondence to: Valentina Mileusnić, University Hospital Medical Center Bežanijska Kosa, Bolnica Bežanijska kosa bb, 11 000 Belgrade, Serbia. E-mail: mileusnicvalentina@yahoo.com

urađen u odnosu na pojavu tegoba ($\chi^2(1) = 4,756$; $p < 0,05$). Nađena je statistički značajna povezanost i između poboljšanja i prisutva KVB ($\chi^2(1) = 4,756$; $p < 0,05$). **Zaključak.** Rezultati naše studije ukazuju na MT kao obećavajuću samostalnu terapijsku proceduru u lečenju AIMU. Klinički ishod posle MT praćen NIHSS skalom, u odnosu na vreme i cerebrovaskularne faktore rizika, pokazuje da bolesnici kod kojih je EVT urađen u prva četiri sata češće imaju poboljšanje od bolesnika kod kojih je EVT urađen posle četiri sata od pojave tegoba. Takođe, bolesnici bez KVB češće imaju poboljšanje od bolesnika sa KVB.

Ključne reči:
endovaskularne procedure; moždani udar, ishemijski; faktori rizika; vreme do početka lečenja; lečenje, ishod.

Introduction

Acute stroke is defined as a focal or global disorder of brain function that occurs suddenly and is the consequence of a disorder of cerebral circulation or a condition in which the blood flow is not sufficient to meet the metabolic needs of neurons for oxygen and glucose [1]. Stroke is the second leading cause of death and the third leading cause of disability in the world [2, 3].

Modern acute treatment, secondary prevention measures, and prognosis largely depend on the pathophysiological mechanisms of acute ischemic stroke (AIS) formation. More than one-third of ischemic strokes are caused by embolization.

Mechanical thrombectomy (MT) is an endovascular treatment (EVT) that involves the extraction of thrombotic masses in the first hours of AIS from the large blood vessels of the head and/or neck. In 2015, five randomized controlled trials [4–8] reported the superiority of MT compared to medical therapy in stroke patients due to large vessel occlusion, leading to its adoption as the standard of care for this subset of patients. The time frame for MT application has become increasingly variable. Recently, the DAWN trial demonstrated that the period for MT can be extended up to 24 hrs in selected cases of large vessel occlusion [9, 10].

Previous studies suggest that the benefit was the greatest with the time from the onset of symptoms to arterial puncture for thrombectomy under 2 hrs and became insignificant after 7.3 hrs [11].

The aim of this study was to determine the degree of efficiency, outcome, and adverse events of MT administration in patients with a clinical picture of AIS and existing vascular risk factors, in whom MT was initiated in the shortest possible period of time.

Methods

The research was conducted as an observational, clinical, nested cohort, single-center, case-control study.

Selection of patients

Patient data was obtained retrospectively from medical records in concordance with the Helsinki Declaration and with the approval of the local Ethics Committee (No. 3/3116, from June 30, 2021). The patients who were included in the study were treated at the Special Hospital for Cerebrovascular Diseases “Sveti Sava” in Belgrade, Serbia, from March 1, 2014, until December 31, 2020; they were diagnosed with blood vessel occlusion of the head and/or neck and had a clinical picture of AIS. The patients also had to meet the criteria for MT.

The sample in this research comprised 134 patients, male and female aged 18 and above, who met the aforementioned inclusion and MT criteria; existing vascular risk factors were observed upon admission to the hospital.

Since the time from the onset of symptoms to EVT was defined as the main variable of the study, we divided the patients into two groups. The first group consisted of 85 (63.4%) patients in whom EVT started within the first four hrs from the onset of the first symptoms of the clinical picture of AIS, and the second, i.e., the control group, consisted of 49 (36.6%) patients in whom EVT was started after the fourth hour from the onset of symptoms.

Treatment of patients

Anamnesis and/or heteroanamnesis were taken; a neurological examination and scoring with the National Institute of Health Stroke Scale (NIHSS) and a somatic examination were performed for all patients with a clinical picture of AIS. The following data was taken from the patients: sex, age, smoking history, presence of associated diseases defined as vascular risk factors [previous cerebrovascular disease (CVD), hypertension arterialis (HTA), atrial fibrillation (AF), diabetes mellitus (DM), hyperlipoproteinemia (HLP)].

All of the selected patients underwent computerized tomography (CT) of the endocranium without contrast and CT angiography of the blood vessels of the neck and head, standard laboratory analyses, and X-ray of the lungs [12–14].

The decision on the intervention was made in consultation between the neurologist, neuroradiologist, and interventional neuroradiologist. Digital subtraction angiography and MT [15] were performed after the decision. The results were monitored by the change in NIHSS score at the time of discharge of the patients, on the 30th and 90th day after EVT, in relation to the NIHSS score on admission of the patients [16].

The NIHSS for neurological deficits in stroke was used. The scale assesses 11 parameters: state of consciousness, bulbar movements, visual field width, facial motor skills, hand motor skills, leg motor skills, limb ataxia, sensibility, speech, dysarthria, and the phenomenon of neglect. The scores in the NIHSS range from 0 to 42 points [17].

An increase in the score indicates an increase in neurological deficit (0–4 mild, 5–15 moderate, 16–20 moderately severe, > 20 severe neurological deficit) [18–20].

The transition of the patient's score from greater to lesser stroke severity on the scale at the time of discharge and/or on the 30th and 90th day after EVT was defined as an improvement in the patient's neurological status.

Statistical analysis

We used descriptive statistical parameters in the statistical data processing (frequencies, percentages, mean value, median, standard deviation, and range). The normal Q-Q plot and histogram graphs, as well as the Kolmogorov-Smirnov test, were used to test the match of sample distributions of numerical data with the normal distribution. Statistical significance was determined by Student's *t*-test and ANOVA for samples with normal distribution and by Mann-Whitney and Kruskal-Wallis tests for samples without normal distribution. Other statistical tests (e.g., correlation) were used according to the results of the basic exploratory analysis. The independent influence of the examined independent and confounding variables on quality of life outcomes was examined using univariable linear and logistic regression. The simultaneous influence of the selected significant variables was examined using a multivariable linear and logistic regression model. The statistical significance of the probabilities of the investigated differences in the values of the variables between the study groups was assumed to be $p < 0.05$. All statistical analyses were performed using the standard program package SPSS v20.0.

Results

Table 1 shows the demographic and stroke risk factors of the patients who participated in this study.

The division of patients into NIHSS groups on different time points and according to stroke severity are presented in Table 2.

A fatal outcome occurred in 29 (21.6%) of the total number of 134 patients who underwent EVT. More precisely, a fatal outcome occurred in 12 patients in whom EVT was initiated within the first 4 hrs from the onset of the first complaint and in 17 patients in whom EVT was initiated 4 hrs after the onset of the first complaint. These patients were not statistically monitored in this study.

After statistical processing of demographic data, vascular risk factors, and time, and in relation to the change of the NIHSS score, improvement was observed in 80 patients (Table 3).

There was no statistically significant difference between the groups, except for the EVT and CVD variables ($p < 0.05$), based on the results of the Chi-square test of independence and the *t*-test for independent samples.

Based on the results of the Chi-square test of independence, it can be concluded that there was a statistically significant relationship between improvement and the time when EVT was performed in relation to the onset of complaints ($\chi^2_{(1)} = 4.756$; $p < 0.05$).

In the group of 25 patients who showed no improvement, EVT was performed in 13 patients within the first four hrs from the onset of symptoms. On the other hand, in the group of 80 patients who showed improvement, EVT was performed in 60 patients within the first four hrs from symptom occurrence.

Table 1

Demographic data of the 134 examined patients with acute ischemic stroke

Parameter	Values
Gender	
female	63 (47.0)
male	71 (53.0)
Age, years	65.87 ± 12.752
Smoker	
yes	26 (19.4)
no	101 (75.4)
former	7 (5.2)
Hyperlipoproteinemia	
yes	41 (30.6)
no	93 (69.4)
Hypertension arterialis	
yes	107 (79.9)
no	16 (11.9)
de novo	11 (8.2)
Diabetes mellitus	
yes	24 (17.9)
de novo	6 (4.5)
no	104 (77.6)
Atrial fibrillation	
yes	29 (21.6)
no	79 (59.0)
de novo	26 (19.4)

All values are expressed as numbers (percentages) except for age which is shown as mean ± standard deviation.

Additionally, based on the results of the Chi-square test of independence, it can be concluded that there was a statistically significant relationship between improvement and CVD ($\chi^2(_1) = 4.756$; $p < 0.05$).

In the group of 25 patients who did not show improvement, CVD was present in 12 (48%) patients, whereas in the group of 80 patients whose condition improved, CVD was present in 20 (25%) patients.

In addition to the above, logistic regression was performed to evaluate the influence of these two factors (CVD and EVT) on the probability that a patient undergoing MT would show an improvement. The model is statistically significant ($\chi^2(_2) = 8.740$; $p < 0.05$), which means that the model differentiates well between patients whose health condition improved and those whose health condition did not improve. The model explains 12% of the variance in patient classification and correctly classifies 77.1% of cases.

Based on the results presented in Table 4 it can be concluded that both variables (EVT and CVD) made a unique statistically significant contribution to the model.

The odds ratio (OR) for CVD was 2.735, indicating that subjects without CVD were 2.735 times more likely to show improvement than patients with CVD (Figure 1).

The OR for EVT was 0.366, which showed that people who underwent EVT within the first four hrs were 2.735 times more likely to have an improvement than those who underwent EVT four hrs after the onset of symptoms (Figure 2).

Table 2

Stroke severity classification of patients according to the National Institute of Health Stroke Scale (NIHSS)

NIHSS on different time points	Patients, n	Median	IQR
On admission (n = 134)			
mild deficit	5	4	3–4
moderate deficit	63	13	9–14
moderately severe deficit	52	19	17–20
severe deficit	14	23	21–23
On discharge (n = 108)			
mild deficit	41	2	1–3
moderate deficit	59	9	6–13
moderately severe deficit	8	17	17–19
After 30 days (n = 105)			
mild deficit	55	0	0–2
moderate deficit	42	10	7–13
moderately severe deficit	8	17	17–19
After 90 days (n = 105)			
mild deficit	57	0	0–2
moderate deficit	40	10	7–14
moderately severe deficit	8	17	17–19

n – number of patients; IQR – interquartile range.

Table 3

Risk factors associated with improvement following endovascular treatment

Parameter	Improvement		*p*-values
	no (n = 25)	yes (n = 80)	
Gender, female	12 (48)	35 (44)	0.709
Age, years	68.56	64.43	0.162
Smoker, yes/no/former	2 (8)/22 (88)/1 (4)	17 (21)/58 (73)/5 (6)	0.270
Hyperlipoproteinemia	10 (40)	20 (25)	0.147
Hypertension arterialis, yes/no/*de novo*	20 (80)/4 (16)/1 (4)	63 (79)/10 (13)/7 (9)	0.690
Diabetes mellitus, yes/no/*de novo*	6 (24)/17 (68)/2 (8)	13 (16)/64 (80)/3 (4)	0.425
Atrial fibrillation, yes/no/*de novo*	7 (28)/17 (68)/1 (4)	18 (23)/48 (60)/14 (18)	0.238
Endovascular treatment [#]	13 (52)	60 (75)	**0.029**
Cardiovascular diseases	12 (48)	20 (25)	**0.029**

[#] – the first 4 hrs from the onset of symptoms.

All values are given as numbers (percentages) except for age for which the unit is average number.

Table 4

Odds ratio for EVT and CVD

Parameter	B	S.E.	Wald	df	Sig.	Exp(B)	95% CI for Exp(B)
EVT	1.006	0.488	4.245	1	0.039	2.735	1.050–7.123
CVD	-1.006	0.488	4.245	1	0.039	0.366	0.140–0.952
Constant	0.880	0.420	4.388	1	0.036	2.412	

EVT – endovascular treatment; CVD – cardiovascular diseases; CI – confidence interval.

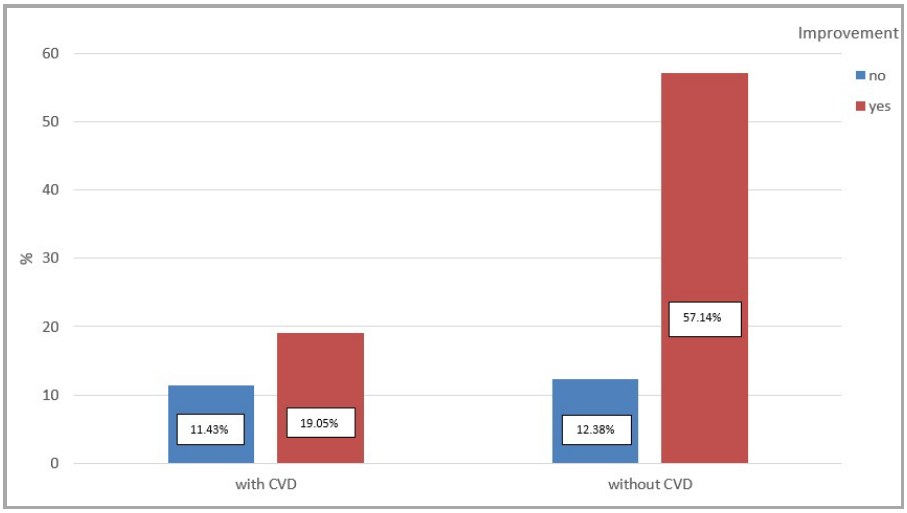

Fig. 1 – Improvement in patients with and without cardiovascular diseases (CVD).

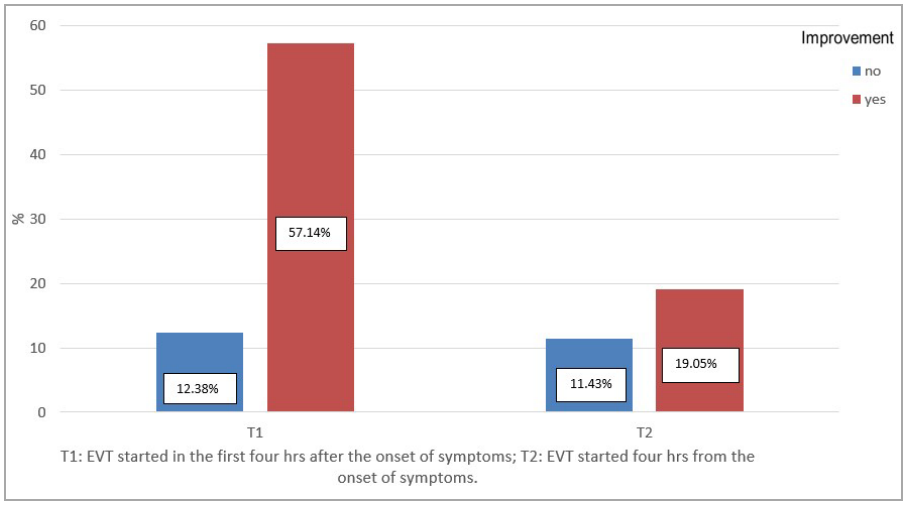

Fig. 2 – Patient improvement over time after endovascular treatment (EVT).

Discussion

The aim of this study was to determine whether the time of onset of MT and the absence of cerebrovascular risk factors are predictors of better clinical outcomes.

Of the 134 patients included in the study, 29 (21.6%) ended fatally, namely, 12 patients in whom EVT was initiated within the first 4 hrs from the onset of the first complaints and 17 patients in whom EVT was initiated 4 hrs after the onset of the first complaints. A high percentage of fatal outcomes was recorded in the group of patients who underwent an endovascular procedure 4 hrs after the onset of symptoms [1, 21].

Previous studies have shown that among patients with AIS treated with MT, those with DM showed worse outcomes than those without DM [22].

One study confirmed that HTA is associated with a poor outcome three months after MT in patients with AIS. However, the causal relationship between HTA and poor outcomes remains undetermined, and further research is needed to determine whether AIS patients undergoing MT benefit from intensive blood pressure control [23].

Another study showed that patients with AF responded significantly better to EVT than those without AF. Intracranial atherosclerotic diseases in patients without AF that were particularly refractory to EVT may contribute to the difference in functional outcomes between the two groups [24].

Based on statistical analysis, this study found that factors such as sex, age, smoking, HTA, HLP, AF, and DM were not statistically significant.

Only the time of MT onset and the existence of an earlier cerebrovascular event in the patient were shown to be statistically significant variables. In earlier studies, time was also shown to be a significant independent variable [25–28]. Some data show that the outcome of MT is better if MT is performed at night, as stated in the given study, because AIS at that time occurred in slightly younger patients [29].

Eighty patients experienced significant improvement of the clinical picture after their stroke severity score lowered on the NIHSS. In 60 (75%) patients, EVT was performed in the first 4 hrs after the onset of symptoms

In the group of 25 patients in whom there was no improvement, EVT was performed in 13 (52%) patients.

Furthermore, in the group of patients with significant improvement, a previous cerebrovascular event was present in only 20 (25%) subjects.

In the group of 25 patients with no improvement, an earlier cerebrovascular event was recorded in 12 (48%) patients.

Although other factors such as HLP, HTA, DM, and AF were monitored under the assumption that they would prove statistically significant, almost no group difference was observed in patients with and without improvement.

This showed that the time of onset of MT and earlier cerebrovascular traumas greatly influence the outcome of recovery and the clinical picture of patients. It was observed that patients in whom EVT was performed in the first 4 hrs from the onset of symptoms have 2.735 more frequent improvement compared to patients in whom EVT was performed in later hours. Furthermore, patients who did not have previous cerebrovascular traumas had 2.735 times more frequent improvement than those who did.

Conclusion

Application of MT in patients with initially lower NIHSS score gives a better outcome of the clinical picture in terms of neurological findings and reperfusion. Clinical outcome monitored by the NIHSS after MT in relation to time and cerebrovascular risk factors shows that people in whom EVT was performed in the first four hrs had an improvement of 2.735 times more often than patients in whom EVT was performed four hrs after the onset of symptoms. Patients without CVD were 2.735 times more likely to improve than patients with CVD.

Considering the results of our study, we believe that CVD and EVT affect the clinical outcome of patients after MT. A small number of patients were included in this study, so we cannot say with certainty that other risk factors known for the occurrence of AIS do not affect the clinical outcome of patients after MT.

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Received on March 5, 2024
Revised on May 14, 2024
Revised on June 28, 2024
Accepted on July 9, 2024
Online First August 2024

ORIGINAL ARTICLE

UDC: 613.98:616-053.9
DOI: https://doi.org/10.2298/VSP240315070S

Chronic diseases and self-assessment of health as predictors of unmet health needs of the elderly population in the Republic of Serbia: national health survey

Hronične bolesti i samoprocena zdravlja kao pokazatelji neostvarenih zdravstvenih potreba populacije starijih ljudi u Republici Srbiji: nacionalno istraživanje zdravlja

Nikola Savić*, Saša Sovilj†, Gordana Grbić‡, Aleksandra Arnaut*, Verica Jovanović§, Sanja Kocić*‖

***University of Kragujevac, Faculty of Medical Sciences, Kragujevac, Serbia; †Military Medical Academy, Belgrade, Serbia; ‡Academy of Vocational Studies Belgrade, Department of High School of Health, Belgrade, Serbia; §Institute for Public Health of Serbia "Dr. Milan Jovanović Batut", Belgrade, Serbia; ‖Institute of Public Health Kragujevac, Kragujevac, Serbia**

Abstract

Introduction/Aim. Unmet health needs are the difference between the health services considered necessary to solve a particular health problem and the health services that were actually received. Unmet health needs in the elderly population with chronic diseases can lead to deterioration of the health condition and complications. The aim of the study was to analyze the connection between the presence of chronic diseases and self-assessment of health with the unmet health needs of the elderly population. **Methods.** The study was part of the latest National Population Health Survey of the Republic of Serbia, conducted as a cross-sectional study on a representative stratified two-stage sample. Data from 3,450 respondents aged 65 and above were used for the purposes of the research. The research was conducted according to the European population health research methodology. Univariate and multivariate logistic regression were used to assess predictors of unmet health needs. **Results.** Every third respondent with a chronic disease did not receive the necessary form of health care (36.3%). Dominant predictors of unmet health needs were self-assessment of health [odds ratio (OR) = 0.63; 95% confidence interval (CI) = 0.58–0.68] along with chronic diseases (OR = 2.29; 95% CI = 1.87–2.81) and depression (OR = 2.12; 95% CI = 1.71–2.64). Respondents with a chronic health disorder were 2.2 times more likely to fail in the realization of the necessary health service compared to respondents who did not have long-term illnesses. Respondents who assess their own health as poor/very poor report unfulfilled health needs two times more often than respondents in good health. **Conclusion.** Unmet health needs in the elderly population are associated with self-reported health and the presence of chronic diseases. The results of such research can be the basis for a better organization of health care and the creation of health policies in order to improve the health of this population group.

Key words:
aged; chronic disease; health inequities; health status; self-assessment; surveys and questionnaires.

Apstrakt

Uvod/Cilj. Pod neostvarenim zdravstvenim potrebama podrazumeva se razlika između zdravstvenih usluga koje se smatraju potrebnim za rešavanje određenog zdravstvenog problema i realno ostvarenih zdravstvenih usluga. Neostvarene zdravstvene potrebe u populaciji starijih ljudi sa hroničnim bolestima mogu dovesti do pogoršanja zdravstvenog stanja i komplikacija. Cilj rada bio je da se analizira veza između prisustva hroničnih bolesti i samoprocene zdravlja i neostvarenih zdravstvenih potreba populacije starih ljudi. **Metode.** Studija je bila deo najnovijeg Nacionalnog istraživanja zdravlja stanovništva Republike Srbije, sprovedenog kao studija preseka na reprezentativnom stratifikovanom dvoetapnom uzorku. Za potrebe rada korišćeni su podaci 3 450 ispitanika starosti 65 i više godina. Istraživanje je sprovedeno prema Evropskoj metodologiji istraživanja zdravlja stanovništva. Za procenu pokazatelja neostvarenih zdravstvenih potreba korišćene su univarijantna i multivarijantna logistička

Correspondence to: Nikola Savić, University of Kragujevac, Faculty of Medical Sciences, Svetozara Markovića 69, 34 000 Kragujevac, Serbia. E-mail: nikolasavicvzs@gmail.com

regresija. **Rezultati.** Svaki treći ispitanik koji je imao hroničnu bolest nije ostvario neophodan oblik zdravstvene zaštite (36,3%). Dominantni pokazatelji neostvarenih zdravstvenih potreba bili su samoprocena zdravlja [*odds ratio* (OR) = 0,63; 95% *confidence interval* (CI) = 0,58–0,68] uz hronične bolesti (OR = 2,29; 95% CI = 1,87–2,81) i depresiju (OR = 2,12; 95% CI = 1,71–2,64). Ispitanici sa hroničnim poremećajem zdravlja su 2,2 puta češće bili neuspešni u realizaciji potrebne zdravstvene usluge u poređenju sa ispitanicima koji nisu imali dugotrajne bolesti. Ispitanici koji su sopstveno zdravlje procenili kao loše/vrlo loše, dva puta češće su prijavljivali neostvarene zdravstvene potrebe u poređenju sa ispitanicima dobrog zdravlja. **Zaključak.** Neostvarene zdravstvene potrebe starijih ljudi povezane su sa samoprocenom zdravlja i prisustvom hroničnih bolesti. Rezultati istraživanja mogu biti osnova za bolju organizaciju zdravstvene zaštite i za kreiranje zdravstvene politike čiji cilj će biti unapređenje zdravlja ove populacione grupe.

Ključne reči:
stare osobe; hronična bolest; zdravstvena zaštita, nejednakost; zdravstveno stanje; samoprocena; ankete i upitnici.

Introduction

The unmet health needs of the elderly are a major public health problem. This problem indicates systematic deficiencies in the provision of health care for this population. Unmet health needs can lead to a decline in health potential and the development of various diseases [1]. It is also important to understand the social aspects of this problem. The unmet health needs of older people can cause feelings of isolation and loneliness, which can have a negative impact on mental health. This can lead to depression, anxiety, and other mental problems, which further complicate the general condition of the person and require additional support and interventions [2, 3]. Addressing the unmet health needs of older adults includes improving access to health care, educating and empowering older adults, and promoting social support networks. This is critical to ensure that seniors receive the timely and adequate health care they need [4]. Chronic diseases in the elderly have a significant impact on unfulfilled health needs because they often require regular medical treatment, therapies, and controls. Lack of access to appropriate health care can result in a lack of adequate management of these conditions, leading to worsening health conditions and an increased frequency of complications. The presence of chronic diseases and personal perception of health have a great influence on the emergence of unfulfilled health needs of the elderly population [5]. Unfavorable social and financial conditions can result in older people giving up the necessary treatment or therapy, which further worsens their health condition and increases the risk of complications of existing chronic diseases. It is very important to ensure affordable and timely health care for elderly people with chronic diseases in order to reduce unmet health needs and improve quality of life [6]. Chronic diseases can lead to a decrease in mobility and independence, which makes it difficult for older people to access healthcare facilities or independently perform daily activities related to their health, which is in direct correlation with unmet health needs. Unfulfilled health needs in the old population with chronic diseases can affect the emergence of serious complications that can end in death. It is important to understand the complexity of interactions between chronic diseases and unmet health needs in the elderly in order to develop targeted interventions and health policies that will improve their health potential and quality of life [7, 8]. Self-assessment of the health of elderly residents significantly affects their quality of life and healthcare needs. The self-assessment of health is influenced by numerous factors, including the present symptoms of the disease, but also the general satisfaction with life. Economic independence and the availability of health care have a positive effect on the personal perception of health [9].

The aim of the study was to indicate the influence of chronic diseases and self-reported health status as predictors of unmet health needs of the elderly population.

Methods

Type of study

The survey is part of the fourth National health survey of the population of the Republic of Serbia (RS) from 2019. The research was conducted in the form of a cross-sectional population study on a representative sample of residents of the RS. The national population health survey was conducted by the Republic Institute of Statistics, the Institute for Public Health of Serbia "Dr. Milan Jovanović Batut", and the Ministry of Health of the RS.

The target population involved in the research

This research study analyzed the population of the elderly population of the RS, who were 65 years old or above. The sample consisted of a total of 3,540 respondents. It is important to emphasize that this study did not include persons living in the territory of Kosovo and Metohija, persons who were placed in collective households and specialized institutions, including persons serving prison sentences, penal institutions, psychiatric institutions, institutions for care and accommodation of the elderly, as well as monasteries.

Characteristics of the observed sample of respondents and data collection

The sample of residents of the RS was a stratified two-stage sample, and it was chosen to adequately reflect the health characteristics of the population at the level of four geographic regions: Belgrade, Vojvodina, Šumadija, and West, South, and East Serbia. These regions represent the

main strata in the sample. The sample was divided according to the respondent's place of residence and further divided into rural and urban areas, in order to show the different characteristics and needs of the elderly population throughout the RS. This approach makes it possible to obtain representative data that can be useful for understanding the health needs of the elderly population. The sample size was calculated according to the requirements and in accordance with the recommendations of the statistical office of the European Union (Eurostat) for the implementation of the National Population Survey of Serbia. The framework for the selection of the sample was based on the official Census of the RS from 2011. The interviewers were given adequate training during which they received detailed instructions for their work. There were 70 teams in total, with each team covering a corresponding field. Each team consisted of two members – one health worker and one interviewer with experience in conducting surveys. Sixteen field supervisors were responsible for the supervision and control of fieldwork. On average, each supervisor was hired to supervise the work of four teams. The Republic Institute of Statistics carried out the survey implementation control by direct contact with households by phone, while 10% were contacted through field control by visiting households. The methodology of the National Population Health Survey was fully respected. The population health survey was conducted over a period of three months in 2019. Data collection was carried out in October, November, and December according to the methodology and recommendations of the European Population Health Survey. In the course of data collection, the rules of scientific research work and ethical codes were respected, with respect for data privacy.

Research instrument

According to the guidelines for the implementation of the National Population Health Survey, the standardized instrument of the European Health Interview Survey (EHIS) was used. The instrument provides numerous data on the health characteristics of the population. Our focus was on unmet health needs and related predictors, such as chronic diseases.

Ethical and legal aspects

The ethical and legal aspects of the research were carefully managed to ensure compliance with legal and ethical norms. In the National Health Research, the International Declaration of Helsinki was respected as a standard of ethical principles without deviating from the principles of scientific research work. Each research participant was informed about the purpose of the study and the scope of their legal rights. All participants were informed through a written document. The respondents voluntarily agreed to participate in the research. This was documented by signing the informed consent. The anonymity of the participants during the research was ensured by not using data that could identify the individual in accordance with the law. This approach guarantees compliance with ethical standards and rules, thus ensuring the impossibility of data misuse. The research results were published in aggregate form, which fully guarantees the confidentiality of individual data. The authors of this study were given consent to use data for scientific purposes and publication of data in scientific journals by the Ethics Committee of the Institute for Public Health of Serbia "Dr. Milan Jovanović Batut" (Resolution number: 5179/1) [10, 11].

Statistical methods

The statistical software package SPSS 23.0 (Statistical Package for Social Sciences) on the Windows platform was used for data processing. Descriptive and inferential statistical methods were used in data analysis. Given that the data were of a categorical type, structural indicators expressed in percentages were used to describe the data. Applications of the inferential statistics method included the Chi-square (χ^2) test and logistic regression. In the analysis of the distribution of one characteristic, the χ^2 test in the form of the agreement test was used. Testing the difference in the distribution of two or more observational characteristics was performed with the χ^2 test. The relationship between the dependent variable and a series of independent variables was tested by bivariate and multivariate logistic regression. First, all variables were tested in the univariate model, and afterward, only statistically significant variables ($p \leq 0.05$) in the univariate regression were included in the multivariate model. The risk was estimated using the size of the odds ratio (OR) with a confidence interval (CI) of 95%.

Results

A total of 3,540 respondents participated in the research: 1,528 (43.2%) men and 2,012 (56.8%) women (χ^2 = 66.17, df = 1, $r < 0.01$). All respondents belong to the elderly population group, aged 65 and above. The average age of the subjects was 73.9 ± 6.3 years. The largest number (29.9%) of respondents were 65–69 years old, and the smallest (19.5%) were 80 years old and above. Slightly more than half of the respondents lived in a marital union. Respondents lived more often in urban areas (53.8%) (χ^2 = 19.99, df = 1, $r < 0.01$), most often in the region of Šumadija and Western Serbia (28.6%), and the least (20.4%) in Belgrade (χ^2 = 49.19, df = 3, $r < 0.01$). Among respondents with a long-term illness, one-third (36.3%) did not receive the necessary form of health care in the previous year, while among the healthy ones (without a long-term illness), 16.5% did not receive the necessary health care (χ^2 = 355.53, df = 2, $r < 0.01$). Among the hypertensive respondents, 34.9% lacked the required form of health care, and among the normotensive ones, 24.9% did not get adequate health care (χ^2 = 203.41, df = 2, $r < 0.01$). Patients suffering from coronary disease did not receive the expected health services in 39.5% of cases, compared to 28.1% of respondents who did not suffer from coronary disease (χ^2 = 99.03, df = 2, $r < 0.01$). Among respondents with diabetes mellitus, 36.3% reported the absence of necessary health services, and among subjects who did not

have diabetes mellitus, 30.5% had the same issue ($\chi^2 = 49.57$, df = 2, $r < 0.01$) (Table 1).

Respondents rate their satisfaction with their own state of health differently ($\chi^2 = 1455.78$, df = 4, $r < 0.01$). The largest number of respondents (37.7%) consider their health average. Every third respondent rates their health as poor, and every tenth as very poor. At the same time, 19.4% of respondents consider their health good or very good (2.9%). A clear difference can be observed in the respondent's self-assessment of the state of health in relation to the presence of chronic health disorders ($\chi^2 = 730.89$, df = 4, $r < 0.01$). Among respondents who rate their health as very good, three-fourths do not have any chronic disease. Respondents who rate their health condition as bad have a chronic disease in 94.8% of cases. The self-assessment of health as poor was associated with an increase in lack of a necessary form of health care ($\chi^2 = 394.9$, df = 8, $r < 0.01$). The percentage of respondents who rated their health as very good and who did not receive the necessary form of health care was 7.8%, while 17.8% of respondents who considered their health as good did not get adequate health care (Figure 1).

The necessary form of health care was not provided to 46.1% of respondents with urinary incontinence and 29.4% without this health problem ($\chi^2 = 56.95$, df = 2, $r < 0.01$). Similarly, 42.9% of respondents with a kidney problem and 30% without this problem did not receive the necessary health care ($\chi^2 = 39.89$, df = 2, $r < 0.01$). Half of the subjects with depression (49.1%) and 29.4% without it did not receive the necessary health care in the previous year ($\chi^2 = 77.63$, df = 2, $r < 0.01$). The stated ratio is very similar in patients with and without chronic bronchitis ($\chi^2 = 29.57$, df = 2, $r < 0.01$), myocardial infarction ($\chi^2 = 32.69$, df = 2, $r < 0.01$), asthma ($\chi^2 = 16.3$, df = 2, $r < 0.01$), stroke ($\chi^2 = 21.82$, df = 2, $r < 0.01$), and malignant disease ($\chi^2 = 12, 58$, df = 2, $r < 0.05$) (Table 2).

Univariate regression analysis identified self-assessment of health as a predictor of the impact on unmet health needs as well as the presence of a chronic disease. Important predictors of unmet health needs are almost all chronic health disorders, such as hypertension (OR = 1.37; 95% CI = 1.17–1.61), coronary disease (OR = 1.49; 95% CI = 1.28–1.74), hyperlipidemia (OR = 1.53; 95% CI = 1.29–1.81), arthrosis (OR = 1.79; 95% CI = 1.53–2.11), and other observed chronic health disorders. Statistically significant predictors were identified by multivariate regression analysis: self-assessment of health, existence of a long-term illness, elevated blood fat (cholesterol), osteoarthritis, chronic back problems, urinary incontinence, and presence of depression. Respondents who rate their health as poor/very poor report unmet health needs 50% more often compared to respondents who are in good/very good health. Respondents who have a chronic health disorder are 1.5 times more likely not to receive the necessary health services compared to respondents who do not have long-term illnesses (Table 3).

Table 1

Unmet health needs in relation to the presence of the most common chronic health disorders in the previous 12 months

Chronic health disorders	Unmet health needs		No health care required	*p*-value
	yes	no		
Long-term illness				
yes	972 (36.3)	1,513 (56.5)	194 (7.2)	< 0.01
no	140 (16.5)	449 (52.9)	260 (30.6)	
Hypertension				
yes	804 (34.9)	1,337 (58.0)	163 (7.1)	< 0.01
no	298 (24.9)	616 (51.4)	285 (23.8)	
Coronary heart disease or angina pectoris				
yes	400 (39.5)	561 (55.4)	51 (5.0)	< 0.01
no	701 (28.1)	1,392 (55.7)	404 (16.2)	
Diabetes mellitus				
yes	232 (36.3)	378 (59.2)	29 (4.5)	< 0.01
no	877 (30.5)	1,580 (54.8)	424 (14.7)	
Hyperlipidemia				
yes	408 (54.3)	300 (39.9)	43 (5.7)	< 0.01
no	1,504 (56.4)	765 (28.7)	400 (14.9)	
Arthrosis, excluding arthritis				
yes	362 (42.9)	423 (50.1)	59 (7.0)	< 0.01
no	747 (27.9)	1,536 (57.3)	397 (14.8)	
Neck deformity/chronic cervical spine problem				
yes	323 (41.4)	407 (52.1)	51 (6.5)	< 0.01
no	787 (28.7)	1,551 (56.6)	404 (14.7)	
Lower spine deformity/chronic back problem				
yes	502 (40.5)	643 (51.9)	95 (7.7)	< 0.01
no	610 (26.7)	1,314 (57.5)	360 (15.8)	

Results are shown as numbers (percentages). Chi-square test.

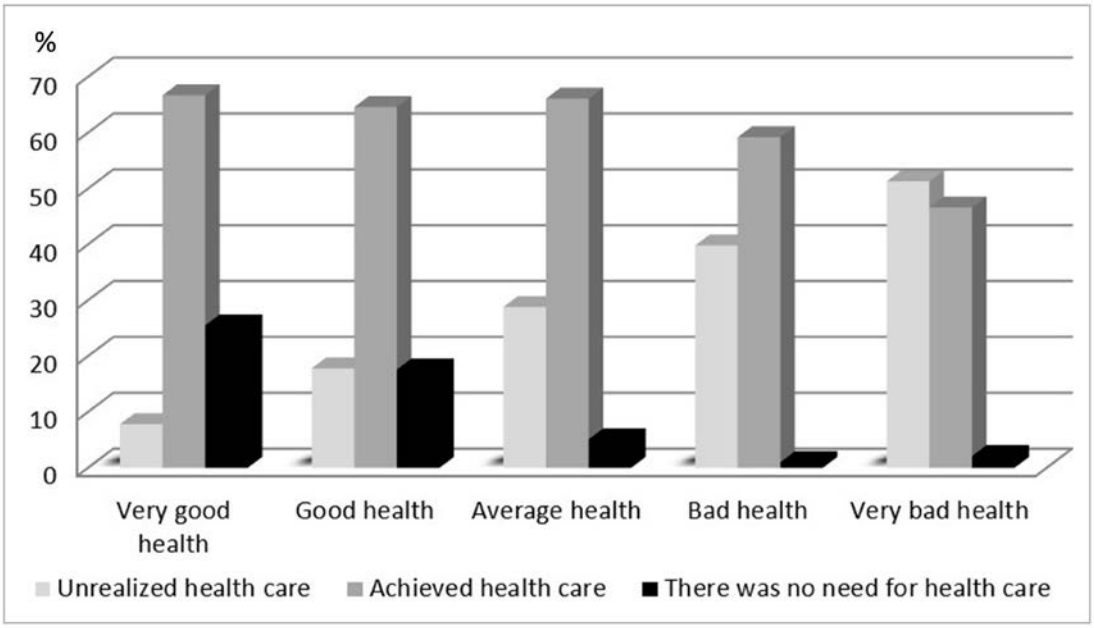

Fig. 1 – Unrealized health care and self-assessment of health in the elderly population.

Table 2

Unmet health needs in relation to the presence of chronic health disorder in the previous 12 months

Chronic health disorder	Unmet health needs		No health care was required	*p*-value
	yes	no		
Urinary incontinence				
yes	206 (46.1)	212 (47.4)	29 (6.5)	< 0.01
no	906 (29.4)	1,748 (56.7)	427 (13.9)	
Kidney problems				
yes	173 (42.9)	208 (51.6)	22 (5.5)	< 0.01
no	935 (30.0)	1,749 (56.1)	433 (13.9)	
Depression				
yes	186 (49.1)	181 (47.8)	12 (3.2)	< 0.01
no	923 (29.4)	1,776 (56.5)	443 (14.1)	
Allergy, excluding allergic asthma				
yes	137 (41.6)	166 (50.5)	26 (7.9)	< 0.01
no	973 (30.5)	1,791 (56.1)	429 (13.4)	
Chronic bronchitis, chronic obstructive pulmonary disease, pulmonary emphysema				
yes	124 (41.9)	159 (53.7)	13 (4.4)	< 0.01
no	986 (30.5)	1,802 (55.8)	443 (13.7)	
Myocardial infarction and chronic consequences of infarction				
yes	108 (42.5)	139 (54.7)	7 (2.8)	< 0.01
no	1,002 (30.6)	1,826 (55.7)	450 (13.7)	
Asthma (including allergic asthma)				
yes	102 (42.3)	120 (49.8)	19 (7.9)	< 0.01
no	1,008 (30.7)	1,839 (56.0)	437 (13.3)	
Stroke				
yes	87 (45.1)	95 (49.2)	11 (5.7)	< 0.01
no	1,024 (30.7)	1,869 (56.0)	446 (13.4)	
Malignant disease				
yes	44 (45.4)	49 (50.5)	4 (4.1)	< 0.05
no	1,066 (31.1)	1,914 (55.8)	452 (13.2)	
Liver cirrhosis				
yes	3 (21.4)	11 (78.6)	/	> 0.05
no	1,107 (31.5)	1,952 (55.6)	454 (12.9)	

Results are shown as numbers (percentages). Chi-square test.

Table 3

Chronic health disorders and self-assessment of health in the previous 12 months as predictors of unmet health needs

Parameters	Univariate model		Multivariate model	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Self-assessment of health	good/very good (referential)			
	0.63 (0.58–0.68)			
bad/very bad	1.74 (1.48–2.04)	< 0.01	2.00 (1.54–2.59)	< 0.01
average	2.99 (2.40–3.72)		1.53 (1.20–1.96)	< 0.05
Chronic disease	2.29 (1.87–2.81)	< 0.01	1.47 (1.16–1.86)	< 0.05
hypertension	1.37 (1.17–1.61)	< 0.01	> 0.05	
coronary heart disease	1.49 (1.28–1.74)	< 0.01	> 0.05	
diabetes mellitus	1.19 (0.99–1.42)	> 0.05	> 0.05	
hyperlipidemia	1.53 (1.29–1.81)	< 0.01	1.22 (1.01–1.47)	< 0.05
arthrosis	1.79 (1.53–2.11)	< 0.01	1.24 (1.03–1.50)	< 0.05
spinal problems	1.64 (1.39–1.93)	< 0.01	> 0.05	
back problem	1.77 (1.52–2.05)	< 0.01	1.30 (1.07–1.58)	< 0.05
urinary incontinence	1.86 (1.52–2.27)	< 0.01	1.31 (1.05–1.65)	< 0.05
kidney problems	1.62 (1.31–2.01)	< 0.01	> 0.05	
depression	2.12 (1.70–2.64)	< 0.01	1.46 (1.14 –1.86)	< 0.05
allergy	1.55 (1.23–1.97)	< 0.01	> 0.05	
chronic bronchitis	1.52 (1.19–1.94)	< 0.05	> 0.05	
myocardial infarction	1.52 (1.17–1.97)	< 0.05	> 0.05	
asthma	1.57 (1.20–2.06)	< 0.05	> 0.05	
stroke	1.70 (1.27–2.28)	< 0.01	> 0.05	
malignant disease	1.66 (1.11–2.49)	< 0.05	> 0.05	
liver cirrhosis	0.54 (0.15–1.92)	> 0.05	> 0.05	

OR – odds ratio; CI – confidence interval.

Discussion

Elderly people often suffer from chronic diseases. This population often has one or more associated chronic diseases that affect overall health potential and quality of life. Chronic diseases can lead to numerous complications in the elderly, which can affect health care needs [12]. The unmet health needs of the elderly population increase the risk of complications of chronic health disorders and mortality [13]. Research on unmet needs for health care is limited, and it is very important to analyze how chronic diseases affect as a predictor of their occurrence [14]. In our research, 39.5% of patients suffering from coronary disease did not realize all their needs for health care. This data agrees with the research of other authors. Inequalities in health care are a significant problem for these patients [15]. Lack of implementation of necessary health care is also an important predictor in other chronically ill elderly patients. Patients with diabetes mellitus, arthrosis, and spine problems are also at risk for complications due to inadequate health care and untimely medical treatment. This problem has been identified by other researchers, which is very important for the improvement of the health and social system [16, 17]. A large number of elderly patients with urinary incontinence and kidney problems have not received the necessary health care. This can have a very negative effect on the control of these chronic health disorders. Older chronic patients with these problems require continuous medical controls and affordable health care in order to preserve and improve their level of health potential [18]. Half of the respondents in our study who suffer from depression did not receive all the necessary health care in the previous year. This is very serious information that shows the availability of health care for people with mental illnesses. This data matches the results obtained in Belgium, where it is also stated that various factors have influenced the emergence of unmet health needs in people with mental problems [19]. Unmet health needs are very common in other chronic patients as well, for instance, in people who suffer from allergies, chronic bronchitis, consequences of myocardial infarction or stroke [20, 21]. Unmet health needs are an important predictor that affects patients with malignant diseases. Elderly people with malignant diseases require intensive medical treatment and health care. The lack of adequate health care in these chronic patients can irreversibly impair health and lead to complications [22]. The unmet health needs of the elderly population are often related to the self-assessment of health as bad. Our study concluded that self-reported health status is an important predictor that correlates with the unmet health needs of chronically ill patients. Numerous studies also confirm that people who rate their health as bad or very bad have a higher percentage of unfulfilled health needs. Elderly people often have numerous health problems that affect their health, independence, and quality of life. Self-reported health is an important predictor that must not be neglected in the assessment of population health [23–25].

Limitations

Our study is based on data from the National Health Survey from 2019, and this method of data analysis has its limitations. Since the study is cross-sectional, it can identify associations between the presence of chronic diseases and self-reported health with aspects of unmet health needs of the elderly population but cannot track variables over a longer period of time. Data based on self-assessment of one's own health

leaves the possibility for a subjective view of health. Although this research study is based on a national survey, certain population groups or those who are institutionalized, staying in institutions for the care of the elderly, were not represented in the observed sample. Since the data was collected in 2019, certain aspects observed in the survey may have changed, especially given the impact of the COVID-19 pandemic on the health of the elderly population. Understanding the presented limitations is very important for the analysis of future population health research, as well as the planning of future scientific studies, which could lead to a better understanding of the unmet health needs of the elderly population in our country.

Conclusion

Unmet health needs are associated with the presence of chronic diseases in the elderly population. Our data can help in the organization of the health system and the creation of new health policies. The most dominant predictors are the presence of a chronic disease and self-assessment of health. In addition, one of the prominent predictors is the presence of depression. Unmet health needs of the elderly population with chronic diseases should be considered in the course of healthcare planning and the organization of health systems. A poor level of health potential in the self-assessment of the health of the elderly population is associated with the presence of chronic diseases and unmet needs for health care. It is necessary to overcome barriers and health inequalities in the availability of health care in this population group.

Conflict of interest

The authors declare no conflict of interest.

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Received on March 15, 2024
Revised on July 15, 2024
Accepted on July 30, 2024
Online First September 2024

ORIGINAL ARTICLE

UDC: 159.9:615.15
DOI: https://doi.org/10.2298/VSP240304074J

Strengthening psychological resilience: the effectiveness of autogenic training of community pharmacists

Jačanje psihološke otpornosti: efikasnost autogenog treninga farmaceuta zaposlenih u javnim apotekama

Dragana Jocić

PHOENIX Group Serbia, BENU Pharmacy, Belgrade, Serbia; University Business Academy – Faculty of Pharmacy, Novi Sad, Serbia

Abstract

Background/Aim. Psychological resilience is essential for healthcare professionals like community pharmacists. It enables them to navigate daily challenges effectively. Autogenic training (AT) has emerged as a promising psychological technique for enhancing resilience and reducing stress in this population. The aim of this study was to investigate the impact of AT on resilience among community pharmacists. **Methods.** The study recruited licensed pharmacists from community pharmacies. Participants received information about the aims and procedures of the research. Resilience was assessed using a scale that measured five domains: Confidence, Agility, Coping with Stress, Interpersonal Relationships, and Developmental Thinking. Using a controlled trial design, participants were randomly divided into two experimental groups, which underwent AT, and a control group, which did not undergo AT. Statistical analyses, including the Kruskal-Wallis and Wilcoxon rank-sum tests, were conducted to analyze the data. **Results.** Participants who underwent AT showed statistically significant improvements in resilience compared to the control group, particularly in the domains of Confidence, Coping with Stress, and Interpersonal Relationships. Furthermore, a notable shift towards higher resilience categories was observed in the experimental groups after the intervention. **Conclusion.** AT appears promising as an intervention to enhance resilience and reduce stress among community pharmacists. Integrating AT into pharmacist education and practice guidelines could significantly affect pharmacist welfare and patient care outcomes.

Key words:
autogenic training; community pharmacy service; pharmacists; resilience, psychological; stress psychological.

Apstrakt

Uvod/Cilj. Psihološka otpornost (PO) je od suštinskog značaja za zdravstvene radnike poput farmaceuta zaposlenih u javnim apotekama. Ona im omogućava da efikasno prevazilaze svakodnevne izazove. Autogeni trening (AT) se pojavio kao obećavajuća psihološka tehnika za unapređenje PO i smanjenje stresa u ovoj populaciji. Cilj rada bio je da se ispita uticaj AT na PO farmaceuta zaposlenih u javnim apotekama. **Metode.** U istraživanje su bili uključeni licencirani farmaceuti zaposleni u javnim apotekama. Učesnici su dobili informacije o ciljevima i postupcima istraživanja. PO je procenjivana korišćenjem skale koja je merila pet domena: Samopouzdanje, Agilnost, Savladavanje stresa, Međuljudske odnose i Razvojno mišljenje. Koristeći dizajn kontrolisanog ispitivanja, učesnici su nasumično podeljeni na dve eksperimentalne grupe, koje su bile podvrgnute AT, i na kontrolnu grupu, koja nije bila podvrgnuta AT. Statističke analize, uključujući Kruskal-Volisov test i Vilkoksonov test ranga, korišćene su za analizu podataka. **Rezultati.** Učesnici koji su prošli kroz AT pokazali su statistički značajno poboljšanje PO u poređenju sa kontrolnom grupom, posebno u domenima Samopouzdanje, Savladavanja stresa i Međuljudski odnosi. Takođe, primećen je značajan pomak ka višim PO kategorijama u eksperimentalnim grupama nakon intervencije. **Zaključak.** AT, kao intervencija za unapređenje PO i smanjenje stresa među farmaceutima zaposlenim u javnim apotekama, se čini obećavajućom. Uključivanje AT u smernice za praksu i obrazovanje farmaceuta može značajno uticati na dobrobit farmaceuta i ishode lečenja bolesnika.

Ključne reči:
autogeni trening; farmaceutske službe, komunalne; farmaceuti; rezilijentnost, psihološka; stres, psihički.

Correspondence to: Dragana Jocić, PHOENIX Pharma d.o.o., BENU Pharmacy, Bore Stankovića 2, 11 030 Belgrade, Serbia.
E-mail: jocicdragana@yahoo.com

Introduction

Resilience in psychology refers to the ability of an individual to confront life challenges, stressors, or adverse conditions and emerge with positive adaptation and preserved mental well-being [1]. It involves adapting, recovering, or maintaining well-being despite facing challenges or adverse circumstances. This entails withstanding emotional or mental difficulties and confronting adversities with a positive perspective, thereby preserving mental health. Active coping, adaptation, and development of internal resources are crucial components in overcoming difficulties [2]. Resilience, combined with low levels of stress, predicts overall well-being, countering the negative impacts of stress on psychological health. Despite its crucial role, resilience remains insufficiently explored, particularly in relation to stress and psychological well-being [3]. While individual analyses on resilience, psychological well-being, and stress exist, a comprehensive study elucidating the intricate interplay among these concepts is notably absent. The intriguing nexus between stress, resilience, and psychological well-being warrants further inquiry [3]. Challenging life circumstances often present obstacles to maintaining psychological well-being, but responses to these adversities vary considerably. Some individuals navigate them with relative ease or even experience personal growth, exhibiting psychological resilience. Understanding the mechanisms of resilience is crucial both theoretically and practically. However, psychology's understanding of resilience remains incomplete, primarily due to a lack of precise conceptualization and limited integration between dominant approaches to resilience – managing stress and coping and regulating emotions [4]. In healthcare, efforts have been made to educate professionals about resilience, yet a clear understanding of responses to resilience and stress is still lacking [5]. Various methods such as autogenic training (AT), biofeedback, and occupational therapy are employed to manage stress effectively [6]. Developed by the renowned German psychiatrist Schultz, AT comprises six fundamental components aimed at inducing a state of deep relaxation and self-regulation. It involves focusing on sensations such as warmth and heaviness in different parts of the body, along with deep breathing and visualization techniques, to reduce stress and anxiety [7–9]. Interest in alternative health approaches is growing, with AT emerging as a promising method for community pharmacists, who are pivotal in holistic health care. AT, a self-guided relaxation method, enhances resilience [6]. Resilience, linked to stress reduction [10], requires further study, particularly regarding relaxation techniques. Understanding how AT and similar methods enhance resilience is vital for mental health promotion [11]. Exploring these avenues can bridge gaps in the literature and provide insights for comprehensive stress management. Nonetheless, given the acknowledged link between resilience and reduced stress levels, AT holds the potential to bolster resilience [6]. This study explores the impact of AT on resilience, stress reduction, and overall well-being, aiming to provide insights pertinent to community pharmacists' practice in promoting comprehensive health and wellness. It examines AT effects and implications for community pharmacy practice.

The aim of this study was to investigate the impact of AT on enhancing resilience among pharmacists employed in community pharmacies. It pursued to deepen the understanding of how relaxation techniques like AT contribute to psychological resilience, emphasizing the interconnectedness between these phenomena.

Methods

The study was approved by the Ethics Committee of the Pharmaceutical Chamber of Serbia (No. 316/2-6, from March 8, 2022). Prior to participation, all pharmacists received detailed explanations about the study procedures, assurances of anonymity, and comprehensive information. Furthermore, all participants were provided with detailed information and explanations about the study procedures. No rewards or financial incentives were offered to any participant.

Study design

The target population for this research comprised licensed pharmacists employed in community pharmacies who were invited to participate in the education and application of AT aimed at enhancing resilience. The invitation to participate was extended to all registered pharmacists in the Pharmaceutical Chamber's database, providing every licensed pharmacist with an equal opportunity to respond. Eligible participants were required to be licensed pharmacists employed in community pharmacies who voluntarily agreed to take part in the research and provided informed consent. Exclusion criteria included pharmacists on medical leave, interns, and those who declined voluntary participation. This recruitment strategy facilitated the engagement of pharmacists from diverse demographic backgrounds. Pharmacists who expressed interest in participating in the study were contacted by phone to receive an explanation about the study's purpose and the entire procedure. The participants who confirmed their participation were given a week to sign an informed consent form.

The sample size was determined utilizing a suitable statistical method, specifically computed through the G-power program, version 3.1. The calculation was grounded on a significance level (α) set at 0.05 and an effect size of 0.5. Determining the sample size involved several steps. Initially, the minimum clinically important difference for the primary outcome was identified based on previous research, clinical expertise, or consensus among experts. This difference represents the smallest change in the outcome measure deemed clinically significant. Subsequently, specific statistical parameters such as effect size, α, and power were specified. The effect size indicates the magnitude of the difference between groups, while the α signifies the likelihood of making a Type I error (false positive). Lastly, the desired power level represents the

likelihood of detecting a true effect if present, with a commonly accepted value of 0.8 indicating a high probability of detecting meaningful effects.

In the study, power analysis was conducted as part of the data processing methods to calculate test power when applicable. This was crucial to ascertain the minimum sample size required to detect statistically significant effects, ensuring robust outcomes with the desired power level set at 80%. An effect size of 0.80 was utilized, indicating a substantial impact of the variable or intervention on the outcomes, thereby bolstering confidence in the significance and practical relevance of the results. Furthermore, *post hoc* analyses on existing samples confirmed the consistency and reproducibility of the findings across different subgroups and conditions, thus further validating the study's conclusions.

Resilience Scale

This study utilized a meticulously developed Resilience Scale (RS) to assess participants' resilience levels (RLs). Prior to administering the scale, its validity and internal consistency (IC) were evaluated. Expert panelists, selected based on their qualifications and expertise in resilience-related fields, including two psychologists, three pharmacy experts, and a scale development specialist, were recruited to assess item relevance and clarity. These experts evaluated the scale items using predefined rating scales and provided written feedback where necessary. Following this assessment by the expert panel, the scale underwent content and face validation processes. In addition, a group of test respondents recruited through targeted sampling methods, assessed the clarity and comprehensibility of the scale items. The resulting indices, including the Content Validity Index (CVI) and Face Validity Index (FVI), were calculated to ensure the robustness and clarity of the scale. Items not meeting the predefined thresholds were either revised or removed to enhance the scale's quality and clarity. Finally, the validated scale was distributed to a larger sample of respondents for further review and feedback. Moreover, factor analysis confirmed the proposed five-factor structure of the scale, validating the significance of each component. These components, including Confidence, Agility, Coping with Stress, Interpersonal Relationships, and Developmental Thinking, were integral to the assessment.

Through this meticulous development process, the reliability and validity of the scale in evaluating resilience across multiple dimensions were ensured. Comprising 30 items, the scale utilized a 5-point Likert scale ranging from "Never" to "Always". The total score range of the scale used in the study spans from 30 to 150. Aggregating scores across all items allowed for the categorization of individuals into specific RLs: low resilience (scores ranging from 30 to 90), moderate resilience (scores ranging from 91 to 120), and high resilience (scores ranging from 121 to 150).

Procedure

An open controlled trial was conducted. The study was conducted from November 2022 to April 2023, with the AT itself being implemented from February 1 until the end of March. There were 60 participants in total divided into two experimental groups [experimental group 1 (E1) and experimental group 2 (E2)] and one control group (C), each consisting of 20 participants. The participants were randomly assigned to either the control or the experimental groups. From a pool of 60 participants, every third individual was selected for the control group, resulting in a cohort of 20 participants. The remaining 40 participants were further divided into two subgroups within the experimental group: every odd-numbered participant was allocated to E1, while every even-numbered participant was assigned to E2. This random allocation method was implemented to minimize potential biases and ensure a balanced representation of participants across groups, thus enhancing the reliability of the study's outcomes.

Participants in the experimental groups underwent AT sessions, whereas those in the control group did not engage in AT. Due to group dynamics and recommended session sizes, participants were divided into two experimental groups. This division aimed to accommodate the maximum number of participants *per* group, facilitating the successful adoption of AT techniques. Participants were guided through AT sessions by a certified professional with expertise in this area. The professional leading the sessions, a psychologist by primary education, had 13 years of experience delivering individual and group AT practices. Their extensive background included specialized education and training in autogenic therapy, ensuring they were well-qualified to deliver the sessions safely and effectively. Participants in the experimental groups underwent AT, totaling eight sessions with a professional, each lasting 60 minutes. To mitigate attrition and ensure the participation of individuals from various regions across the country, a segment of the skill acquisition was conducted online *via* the Teams platform. Over the 8-week training period, the participants practiced AT three times a day individually and maintained personal daily logs to record their experiences with AT. Additionally, their AT-licensed professional was consistently available for consultations throughout the training period. Resilience was assessed using RS before the commencement of AT and again after eight weeks of AT implementation. The control group did not receive AT. However, resilience was also assessed in control group participants at the beginning and after eight weeks.

AT consists of six main exercises, each focusing on inducing relaxation and promoting self-awareness. These exercises are the following: heaviness – participants focus on a specific body part and imagine it becoming heavy, sinking into a state of deep relaxation; warmth – participants concentrate on a particular body area, visualizing warmth spreading throughout, promoting relaxation and comfort; heartbeat – by directing attention inward, individuals focus on their heartbeat, fostering a sense of calmness and tranquility; breathing – this exercise involves deep and rhythmic breathing, promoting relaxation and reducing tension; abdominal warmth – participants visualize warmth spreading in the abdominal area, promoting relaxation and soothing any tension; coolness

– participants imagine a cool sensation, promoting relaxation and reducing any remaining stress or tension. These exercises are practiced sequentially, allowing participants to progressively deepen their state of relaxation and enhance their overall well-being [6, 7].

The study aimed to investigate whether participants' RS scores changed between Time 1 (baseline) and Time 2 (after eight weeks of AT), as well as to identify any differences among participants in the control group (who did not undergo AT) and the two experimental groups (who underwent AT).

Statistical analysis

Prior to conducting statistical analyses, the normality of the distribution was checked, revealing a statistically significant deviation from normality (Kolmogorov-Smirnov test, $p < 0.001$). Consequently, non-parametric techniques were employed, namely the Kruskal-Wallis and the Wilcoxon rank-sum tests. These tests were employed to assess inter-group differences and mitigate potential confounding variables when fundamental statistical assumptions were unmet. Both the Kruskal-Wallis and Wilcoxon tests were used to examine differences between the experimental groups overall and the control group (Kruskal-Wallis), as well as between all pairs of groups (two experimental individually and one control) using the Wilcoxon test, thus eliminating any potential biases in the conclusions.

Statistical analyses were performed utilizing the SPSS software package, with a specific focus on version 29.0.1.

Results

Of all the respondents invited, 95 participants expressed their willingness to participate, with 89 participants confirming their participation after receiving detailed information and providing informed consent. Five participants did not return the signed informed consent, resulting in 84 participants initially being assessed using RS. Prior to the commencement of the education, 24 participants withdrew, leaving a total of 60 participants who were randomly assigned to two experimental groups, both of which completed the resilience test after three months, and one control group that did not undergo AT but also completed the resilience test three months later. The flowchart illustrating the sample formation procedure is presented in Figure 1.

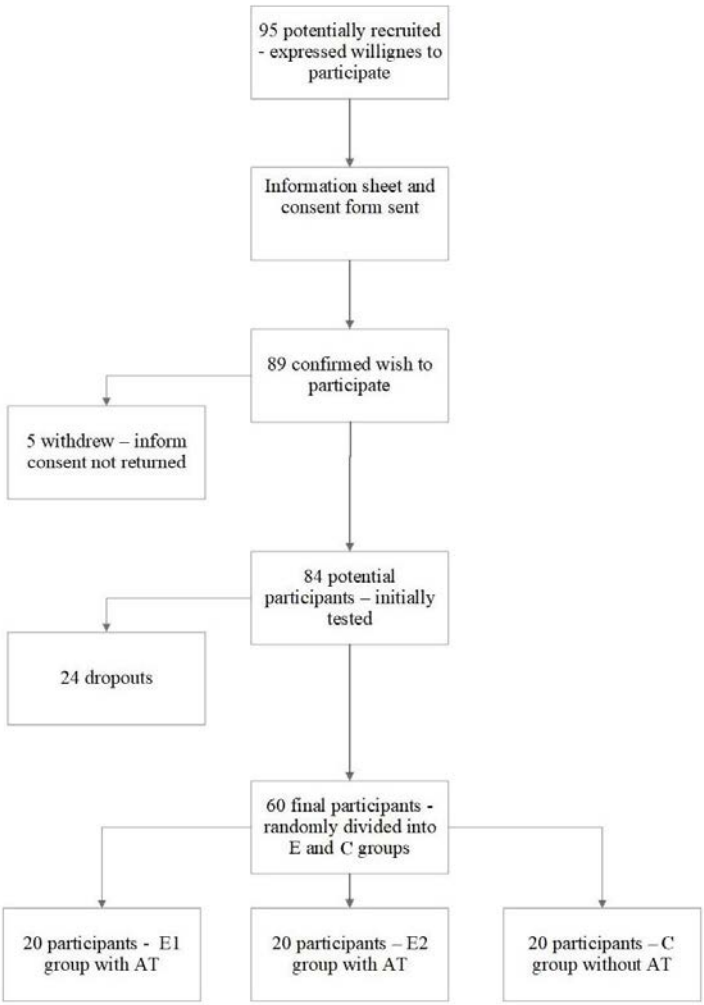

Fig. 1 – Flowchart of sample formation procedure (values represent the number of participants). E – experimental group; C – control group; AT – autogenic training. Description of the groups is given in the paragraph Methods.

Descriptive statistics outline key characteristics in both control and experimental groups. In the control group (n = 20), the mean age was 37.30 years [standard deviation (SD) = 7.58], average years of service were 11.50 years (SD = 7.18), and study duration was 5.48 years (SD = 0.55). In the experimental groups (n = 40), the mean age was 42.47 years (SD = 12.35), average years of service were 16.69 years (SD = 12.53), and study duration was 5.83 years (SD = 1.66). Further details are available in Table 1.

The process of checking the validity and IC of the scale for assessing resilience showed that the scale that was used demonstrated strong validity, with both the CVI and FVI exceeding 0.80. Additionally, the scale exhibited robust IC, as indicated by a Cronbach's alpha coefficient of over 0.9.

Table 2 provides a comparison of mean scores for RS and its respective subscales between the control group and experimental groups at two key time points: at baseline and after eight weeks of AT.

At baseline, the mean resilience score for the control group was 117.05, while for the experimental groups, it was slightly lower, 106.08. However, after eight weeks of AT, there is a noticeable increase in the mean resilience score for the experimental groups, rising to 118.05, whereas the mean resilience score of the control group remains relatively stable. This pattern was consistent across all subscales, where the control group generally had higher mean scores than the experimental groups at the start of the study. However, after eight weeks, there was a trend of improvement in mean scores for the experimental groups across most subscales, with some reaching or approaching the mean scores of the control group. For instance, in the Confidence subscale, the mean score for the experimental groups increased from 20.7 to 23.45, approaching the control group's mean score of 22.95. Notably, there were consistent improvements in mean scores for the experimental groups in the Coping with Stress and Interpersonal Relationships subscales after eight weeks, indicating the potential benefits of the intervention in these areas.

Table 1

Demographic characteristics of study participants

Characteristics	Control group	Experimental groups
Gender		
female	19 (95)	37 (92.5)
male	1 (5)	3 (7.5)
Marital status		
single	5 (25)	11 (27.5)
married	15 (75)	26 (65)
divorced	0 (0)	3 (7.5)
Shift work distribution		
alone in shift	5 (25)	9 (22.5)
with a pharmacist	4 (20)	2 (5)
with a pharmacy technician	3 (15)	20 (50)
with more colleagues in a shift	8 (40)	9 (22.5)
Postgraduate education category		
master	2 (10)	2 (5)
specialization	5 (25)	5 (12.5)
doctoral degree	1 (5)	1 (2.5)
no postgraduate education	12 (60)	32 (80)
Branch of the Pharmaceutical Chamber of Serbia		
Belgrade	6 (30)	16 (40)
Kragujevac	5 (25)	9 (22.5)
Niš with Kosovo and Metohija	3 (15)	5 (12.5)
Vojvodina	6 (30)	10 (25)
Type of pharmacy		
independent pharmacy (1 pharmacy)	1 (5)	5 (12.5)
small chain (2–100 pharmacies)	12 (60)	15 (37.5)
medium chain (100–200 pharmacies)	3 (15)	10 (25)
large chain (more than 200 pharmacies)	4 (20)	10 (25)
Managerial position		
yes	13 (65)	24 (60)
no	7 (35)	16 (40)
Job satisfaction		
yes	12 (60)	20 (50)
no	8 (40)	20 (50)

All results are given as numbers (percentages) of participants.

Table 2

Comparison of mean scores of the Resilience Scale and subscales between the control and experimental groups of participants at baseline and eight weeks after autogenic training

Scale and subscales	Control group (n = 20)	Experimental groups (n = 40)
Resilience Scale		
baseline	117.050 ± 17.470	106.080 ± 28.764
eight weeks	116.350 ± 20.638	118.050 ± 24.225
Confidence subscale		
baseline	22.950 ± 4.559	20.700 ± 6.297
eight weeks	22.350 ± 4.626	23.450 ± 4.851
Agility subscale		
baseline	24.950 ± 3.913	21.875 ± 6.907
eight weeks	24.150 ± 4.660	23.275 ± 5.344
Coping with Stress subscale		
baseline	28.650 ± 6.089	26.725 ± 8.277
eight weeks	29.700 ± 6.174	30.300 ± 7.484
Interpersonal Relationships subscale		
baseline	12.300 ± 1.593	11.300 ± 2.972
eight weeks	12.050 ± 2.585	12.300 ± 2.312
Developmental Thinking subscale		
baseline	28.200 ± 3.488	25.475 ± 6.733
eight weeks	24.400 ± 3.844	24.900 ± 4.618

All values are given as mean ± standard deviation.

Table 3 illustrates the RS according to three categories observed in both the control and experimental groups at two key time points: at baseline and after eight weeks.

Initially, at baseline, the control group exhibited resilience distributions similar to those of the experimental groups. However, after the eight-week AT period, notable differences emerged. While the control group's RLs remained relatively stable, the experimental groups displayed distinct changes. Notably, the experimental groups showed a reduction in the number of individuals classified in the Low resilience category after eight weeks, indicating potential positive effects of the intervention on enhancing resilience. Conversely, there was a noticeable increase in individuals categorized under Moderate and High RLs within the experimental groups post-intervention, suggesting potential improvements in resilience over the eight weeks compared to the control group.

The Kruskal-Wallis test revealed a statistically significant difference in RLs among three distinct groups [experimental groups (E1 and E2), and control group (C)], χ^2 (2, n = 60) = 5.7–18.3, $p < 0.05$. These differences were shown on the scale as a total Resilience Score, and on all subscales at the beginning (baseline) and after eight weeks of AT (Table 4).

A difference in the levels of resilience was observed on the Scales and subscales measured at baseline and after eight weeks of AT. This difference was statistically significant in the experimental groups (Asymp. Sig. < 0.05), except on the Developmental Thinking subscale, and not statistically significant in the control group (Asymp. Sig. > 0.05) (Table 5).

At baseline, the control and the experimental groups displayed similar median resilience scores, with experimental groups showing a slightly higher 75th percentile score. After eight weeks of AT, the experimental groups exhibited noticeable improvements in resilience, as evidenced by higher median and 75th percentile scores compared to their scores at baseline and from the control group. Across all subscales, the experimental groups generally showed higher median scores than the control group at baseline and after eight weeks of AT. After eight weeks of AT, the experimental groups demonstrated consistent improvements in most subscales, indicated by higher median and 75th percentile scores compared to their scores at baseline and from the control group. There was a statistically significant difference between the Resilience Score after eight weeks of AT compared to baseline within the experimental groups (Z = -5.136, $p < 0.001$). In contrast, there was no statistically significant

Table 3

Comparison of Resilience Scale scores between the control and experimental groups at baseline and eight weeks after autogenic training

Parameters	Control group		Experimental groups	
	baseline	eight weeks	baseline	eight weeks
Resilience (score)				
Low (30–90)	2 (10)	2 (10)	17 (42.5)	4 (10)
Moderate (91–120)	9 (45)	9 (45)	8 (20)	16 (40)
High (121–150)	9 (45)	9 (45)	15 (37.5)	20 (50)
Total	20 (100)	20 (100)	40 (100)	40 (100)

All results are given as numbers (percentages) of participants.

Table 4

The Kruskal-Wallis test: difference in resilience levels between the control and experimental groups

Scale and subscales	H	df	Asymp. Sig.
Resilience Scale			
baseline	8.065	2	0.018
eight weeks	8.740	2	0.013
Confidence subscale			
baseline	8.101	2	0.017
eight weeks	5.697	2	0.058
Agility subscale			
baseline	7.288	2	0.026
eight weeks	8.002	2	0.018
Coping with Stress subscale			
baseline	6.869	2	0.032
eight weeks	9.450	2	0.009
Interpersonal Relationships subscale			
baseline	18.304	2	< 0.001
eight weeks	9.831	2	0.007
Developmental Thinking subscale			
baseline	7.148	2	0.028
eight weeks	7.706	2	0.021

H – difference between group ranks; df – degree of freedom; Asymp. Sig. – asymptotic significance.

Table 5

Statistical significance of differences in Wilcoxon signed-rank test scores for Resilience Scale and related subscales between the control and experimental groups

Scale and subscales	Experimental groups		Control group	
	Z	Asymp. Sig. (2-tailed)	Z	Asymp. Sig. (2-tailed)
Resilience Scale eight weeks baseline	-5.136[a]	< 0.001	-0.168[a]	0.866
Confidence subscale eight weeks baseline	-4.467[a]	< 0.001	-1.624[a]	0.104
Agility subscale eight weeks baseline	-2.967[a]	0.003	-1.853[a]	0.064
Coping with Stress subscale eight weeks baseline	-4.765[a]	< 0.001	-1.427[b]	0.153
Interpersonal Relationships subscale eight weeks baseline	-3.272[a]	0.001	-0.207[a]	0.836
Developmental Thinking subscale eight weeks baseline	-0.994[b]	0.320	-3.775[a]	< 0.001

[a] – based on positive ranks; [b] – based on negative ranks; Asymp. Sig. – asymptotic significance.

difference in the Resilience Score between eight weeks of AT and baseline within the control group (Z = -0.168, $p = 0.866$). Similar patterns are observed across all subscales, where there were statistically significant differences between eight weeks of AT and baseline within the experimental groups, indicating improvements in these aspects of resilience ($p < 0.001$ for Confidence, Coping with Stress, Interpersonal Relationships, $p = 0.003$ for Agility). Conversely, within the control group, there were no statistically significant differences in most subscales between eight weeks of AT and baseline, except for Developmental Thinking ($p < 0.001$). When comparing each experimental group individually to the control, the participant distribution is equal (20 : 20), while the collective comparison reveals a disparity between the control and the experimental groups (20 : 40). Yet, statistical analyses confirm comparable efficacy of AT in enhancing resilience across all experimental groups compared to the control.

For the Wilcoxon signed-rank test, a priori power analysis was performed based on predefined parameters, including an effect size of 0.80, a power of 0.80, and an alpha error probability of 0.05. The results indicated that a

minimum of 12 participants *per* group was needed to power the study adequately given these parameters. With 20 participants *per* group included, the sample size exceeded the required minimum. Furthermore, a *post hoc* analysis of the same group of 20 participants *per* group revealed an effective test power of 0.96, surpassing the initially targeted 0.80. This heightened power level enhances the reliability of the study's results, emphasizing its capability to detect true effect sizes with high confidence, and at the same time confirms that the sample size not only met but also exceeded the requirements for achieving statistically significant and reliable results, thereby ensuring the robustness of the study's conclusions.

Discussion

The results of the present study are consistent with previous research on AT as a method for stress reduction and anxiety management. Ernst and Kanji [12] conducted a systematic review of controlled AT trials and found that most trials reported positive effects of AT in reducing stress. However, they noted methodological flaws in many studies, highlighting the need for further well-designed controlled trials. Stetter and Kupper [13] conducted a meta-analysis of clinical outcome studies of AT and found medium-to-large effect sizes for pre-post comparisons of disease-specific AT effects. They concluded that AT is effective for various conditions, including tension headaches, essential hypertension, anxiety disorders, depression, and functional sleep disorders. A systematic review and meta-analysis evaluating the effectiveness of AT on stress responses was conducted and found that AT decreased anxiety and depression and increased heart rate variability, suggesting its effectiveness in stress management [14]. Kohler et al. [15] conducted a systematic review and meta-analysis focusing on AT for chronic pain. They found a significantly positive, moderate effect of AT on pain reduction compared to passive control groups. However, they noted the need for high-quality randomized controlled trials to strengthen the evidence for AT in individuals with chronic pain. Breznoscakova et al. [16] reviewed studies examining the effects of AT on mental disorders and found consistent efficacy of AT in reducing anxiety and medium-range positive effects for mild-to-moderate depression. They concluded that AT represents a promising adjunctive intervention in the prevention and clinical management of mental disorders.

Overall, the findings from these studies support the effectiveness of AT in reducing stress, anxiety, and pain, as well as improving psychological well-being. However, further research, particularly high-quality randomized controlled trials, is needed to confirm and expand upon these findings.

Several studies have demonstrated the potential benefits of AT in various populations and contexts. Litwic-Kaminska et al. [17] conducted a pilot study to evaluate the effectiveness of AT in improving sleep quality and reducing physiological stress reactions among university athletes. The study found that AT, delivered in an audio recording form, significantly increased subjective sleep quality in the experimental groups compared to the control group. Dobos et al. [18] investigated the effects of AT on migraine frequency and brain activation patterns in response to fearful visual stimuli. The study found that regular practice of AT led to a reduction in migraine attacks and induced changes in brain activation patterns, suggesting a potential mechanism through which AT exerts its effects. Ramirez Garcia et al. [19] conducted a mixed-method randomized controlled trial to assess the effects of AT on quality of life and symptoms in people living with human immunodeficiency virus (HIV). The study found significant improvements in social and mental dimensions of quality of life and sleep quality among participants in the AT group compared to the control group. These findings collectively suggest that AT may effectively improve sleep quality, reduce migraine frequency, and enhance the quality of life in various populations. However, further research is needed to confirm and expand upon these results, as well as explore the underlying mechanisms of action of AT. Additionally, research has shown that AT can have a positive impact on sleep quality and the reduction of stress symptoms in various populations, including student athletes and people living with HIV [18, 20]. Furthermore, a study conducted by Atkins and Hayes [21] on adolescents in school settings demonstrated that structured AT significantly reduced anxiety levels. Similarly, a pilot study involving people living with HIV and experiencing symptoms of depression found that AT and progressive muscle relaxation were feasible and potential therapeutic options for reducing depressive symptoms [22]. Regarding methodology, the study by Hoge et al. [23] highlighted that mindfulness-based stress management was equally effective as escitalopram, the standard treatment, for treating anxiety disorders. This supports the inclusion of alternative therapeutic approaches such as AT in the treatment of anxiety disorders. Furthermore, a systematic review on the effectiveness of interventions to improve resilience among healthcare workers emphasizes the importance of developing resilience-building programs, which could contribute to reducing stress and improving the well-being of healthcare workers [24]. The study by Kemper and Khirallah [25] indicates the acute benefits of online mind-body skills training in improving stress, mindfulness, empathy, and resilience among healthcare professionals. This suggests that such intervention programs should be further researched and implemented. Moreover, a review by Yumkhaibam et al. [26] encompassing 162 research papers underscores that AT can effectively reduce symptoms of anxiety disorders in various populations, highlighting its positive role in improving overall well-being.

Taking all of this into consideration, AT appears to be a promising relaxation technique that can have a significant positive impact on reducing anxiety, improving sleep quality, and overall well-being in various populations [27].

Based on the comprehensive body of research discussed, it can be concluded that AT holds promise in addressing a wide range of symptoms and phenomena. With its demonstrated effectiveness in reducing anxiety,

improving sleep quality, and enhancing overall well-being across diverse populations, AT emerges as a multifaceted technique with far-reaching benefits [6, 8, 9]. Given the intricate nature of resilience, the findings suggest that AT plays a pivotal role in bolstering resilience by targeting key factors such as anxiety and stress reduction. By mitigating these significant stressors, AT contributes to the enhancement of resilience, which is crucial for effectively coping with adversity and maintaining psychological well-being. In essence, AT serves as a foundational practice that fosters resilience by addressing core elements of mental health and adaptive functioning. Its ability to alleviate anxiety, improve sleep, and mitigate stress underscores its potential as a holistic approach to promoting overall resilience and well-being.

However, some research on healthcare workers facing high-stress levels suggests that simply enhancing resilience may not necessarily decrease anxiety and stress. Instead, interventions targeting coping skills have demonstrated effectiveness in bolstering resilience. Implementing capacity-building initiatives like resilience training can yield significant benefits for both healthcare staff and patients. Poor well-being among healthcare professionals has been associated with reduced clinical care capacity and increased vulnerability to mental illness. Therefore, investing in interventions that enhance resilience can positively impact both staff performance and patient outcomes [28].

The research underscores the pivotal role of resilience in mitigating the detrimental impact of burnout on the subjective well-being of healthcare workers. This highlights the significance of introducing resilience training programs to combat burnout and protect the mental well-being of healthcare professionals during demanding periods [29].

The results of this study suggested that the experimental groups showed improvements over time, particularly after eight weeks of intervention. These findings imply that the intervention effectively enhanced various dimensions of resilience among participants, highlighting its potential value in promoting psychological well-being and adaptive functioning. The results indicate that the intervention implemented with the experimental groups has contributed to significant improvements in overall RLs, as well as in various aspects contributing to resilience, compared to the control group over the eight weeks. Overall, these results underscore the effectiveness of the intervention in enhancing resilience-related factors among participants in the experimental groups, while no significant changes are observed in the control group. This suggests that the intervention has been successful in producing positive outcomes and highlights the importance of the intervention in promoting resilience.

While this study offers valuable insights into the potential benefits of AT on resilience and well-being, there are opportunities for further refinement and expansion in future research endeavors. Firstly, expanding the sample size and diversifying participant demographics could enhance the robustness and generalizability of the findings. It is crucial to emphasize that, although the sample size in the study was relatively small, power analysis concluded that the sample was sufficiently large to achieve adequate statistical power for detecting the effects of interest. However, it is important to note that increasing the number of participants could further enhance the generalizability and robustness of the findings. Therefore, while the current sample was deemed adequate for achieving the research objectives, further expansion of the sample could strengthen the conclusions and their applicability to a broader population. Employing a more comprehensive data collection approach, perhaps incorporating objective measures alongside self-reported data, could provide a more nuanced understanding of the effects of AT. Additionally, implementing a control group receiving an alternative intervention or usual care would strengthen the ability to draw causal inferences about the efficacy of AT. Longitudinal studies tracking participants over an extended period could illuminate the sustainability of AT effects on resilience and well-being, particularly by allowing for the assessment of whether any observed changes persist beyond the intervention period while maintaining a relatively consistent number of participants throughout the study duration. This extended follow-up would provide valuable insights into the long-term impact of AT and its potential benefits for resilience and overall well-being.

Given the type of sampling, there was awareness of potential confounders, including factors such as years of experience, gender, age, workload, and previous health conditions. To control the influence of these confounders, a power analysis was utilized for the statistical methods employed, taking into account the sample size. Future research should thoroughly investigate the potential impact of confounding variables, such as varying job positions, levels of responsibility among pharmacists and pharmaceutical technicians, events outside of work, and personal life stressors or changes, as these variables may influence participants' resilience and study outcomes. Additionally, participants' experience with AT or other relaxation techniques, along with their individual characteristics, could also impact study results independently of the intervention. Integrating qualitative assessments to capture participants' experiences, perceptions, attitudes, and beliefs in greater depth would enrich our understanding of the subjective effects of AT. Furthermore, considering potential moderating or mediating factors, such as concurrent therapies, could shed light on the factors influencing the effectiveness of AT interventions. Collaborating with diverse stakeholders, including healthcare providers and policymakers, could facilitate the integration of AT into existing healthcare models and enhance its accessibility. Finally, conducting cost-effectiveness analyses would provide valuable insights into the economic implications of implementing AT interventions in various healthcare settings. By addressing these suggestions, future research endeavors can further advance our knowledge of AT and its potential to promote resilience and well-being.

While the benefits of AT for stress reduction are well-documented, further research is needed to comprehensively

understand its potential role in enhancing resilience – the ability to bounce back from adversity and maintain psychological well-being amidst challenging circumstances. Examining how relaxation techniques, including AT, may bolster resilience could provide valuable insights into holistic approaches to mental health promotion and stress management. Thus, future research endeavors should aim to address this gap in the literature to fully grasp the therapeutic potential of relaxation practices in fostering resilience and mitigating the detrimental effects of stress [11].

Conclusion

Autogenic training has proven effective in strengthening resilience among community pharmacists, contributing to various aspects such as Confidence, Agility, Coping with Stress, Interpersonal Relationships, and Developmental Thinking. Integrating autogenic training techniques into practice can aid in stress management, enhance resilience, and improve the overall well-being of professionals and patients. Emphasizing autogenic training as a complementary approach to conventional healthcare practices, especially in pharmacy and public health, is crucial.

Acknowledgement

Sincere appreciation is extended to all study participants for their invaluable contributions, which have greatly enriched the research endeavor.

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Received on March 4, 2024
Revised on April 8, 2024
Revised on August 6, 2024
Accepted on August 13, 2024
Online First October 2024

CASE REPORT

UDC: 617.547
DOI: https://doi.org/10.2298/VSP240513067J

Operative treatment of calcified thoracic disc herniation: a case report on natural fusion method following spinal canal decompression

Operativno lečenje kalcifikovane torakalne diskus hernije: prikaz slučaja lečenog metodom prirodne fuzije nakon dekompresije kičmenog kanala

Bojan Jelača*†, Nebojša Lasica*†, Jagoš Golubović*†, Filip Pajičić*†, Milorad Bijelović†‡, Djula Djilvesi*†

***University Clinical Center of Vojvodina, Clinic of Neurosurgery, Novi Sad, Serbia; †University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia; ‡Institute for Pulmonary Diseases of Vojvodina, Clinic for Thoracic Surgery, Novi Sad, Serbia**

Abstract

Introduction. The literature describes several ways to approach the thoracic spinal segment, but there are still many dilemmas regarding what is best to do after a complete discectomy, regardless of the surgical approach chosen. The incidence of postoperative kyphosis is higher if a posterior surgical approach to the spine is performed, and there are no clearly defined indications for the application of intervertebral fusion (IF) after an anterior approach. The aim of the paper was to highlight the low morbidity of the transthoracic multidisciplinary approach, as well as a potential solution for a good, natural IF of the adjacent vertebrae without expanding and prolonging the duration of the surgical procedure itself. **Case report.** A 44-year-old woman presented with severe anterior compressive myelopathy caused by a calcified thoracic disc herniation in the space between the T10-11 vertebrae. A minimally invasive, open, transthoracic approach was performed with decompression of the spinal canal at the specified level and IF was achieved with an autologous rib graft during the same procedure. A control examination of the thoracolumbar segment using the magnetic resonance imaging showed that there is no more compression of the spinal cord and also showed a good IF without an increase in the level of kyphosis. **Conclusion.** Significant thoracic disc herniation is a rare and challenging surgical lesion. The anterior mini-open transthoracic approach provides good exposure to the relevant structures and is considered minimally invasive. The benefits of subsequent IF after the transthoracic surgical approach should always be taken into account for each individual patient, thus minimalizing the postoperative morbidity.

Key words:
intervertebral disc displacement; spinal cord compression; spinal fusion; neurosurgical procedures; thorax.

Apstrakt

Uvod. U literaturi je opisano nekoliko načina pristupa torakalnom segmentu kičmenog stuba, ali postoji još uvek mnogo dilema u vezi sa tim šta je najbolje učiniti nakon završene diskektomije, bez obzira na izabrani hirurški pristup. Incidencija postoperativne kifoze je viša ako se izvodi posteriorni hirurški pristup kičmenom stubu, a ne postoje jasno definisane indikacije za primenu intervertebralne fuzije (IF) nakon anteriornog pristupa. Cilj rada bio je da se istakne nizak morbiditet transtorakalnog multidisciplinarnog pristupa, kao i potencijalno rešenje za dobru, prirodnu IF susednih pršljenova bez proširivanja i produženog trajanja same hirurške procedure. **Prikaz bolesnika.** Kod bolesnice stare 44 godina nađena je izražena prednja kompresivna mijelopatija izazvana kalcifikovanom torakalnom diskus hernijom u prostoru između pršljena T10-11. Izveden je minimalno invazivni, otvoreni, transtorakalni pristup sa dekompresijom kičmenog kanala na navedenom nivou i u istom aktu je postignuta IF autolognim graftom rebra. Kontrolni pregled torakolumbalnog segmenta magnetnom rezonancom pokazao je da više nije bilo kompresije kičmene moždine a takođe je pokazao i dobru IF bez povećanja kifoze. **Zaključak.** Velika hernijacija torakalnog diskusa je retka i hirurški veoma zahtevna lezija. Prednji transtorakalni pristup omogućava jasnu ekspozicju relevantnih struktura i smatra se minimalno invazivnim. Prednosti naknadne IF nakon transtorakalnog hirurškog pristupa uvek treba uzeti u obzir za svakog bolesnika ponaosob, čime se postoperativni morbiditet svodi na minimum.

Ključne reči:
hernija diskusa; kičmena moždina, kompresija; kičma, fuzija pršljenova; neuhirurške procedure; toraks.

Correspondence to: Bojan Jelača, University Clinical Center of Vojvodina, Clinic of Neurosurgery, Hajduk Veljkova 1, 21 137 Novi Sad, Serbia. E-mail: bojan.jelaca@mf.uns.ac.rs

Introduction

Thoracic disc herniation (TDH) is rare compared to cervical and lumbar segment degenerative conditions [1]. TDH is mainly treated conservatively. However, if indicated, there is a broad spectrum of described surgical techniques in the literature [2]. Calcified discs are typically observed on computerized tomography (CT) or CT-myelography as substantial bony masses extending into the spinal canal from the posterior aspect of the neighboring thoracic vertebra. Preoperative magnetic resonance imaging (MRI) does not consistently reveal calcification in the lesion [3]. The preferred surgical approach should provide complete access to the TDH, enable good visibility of the spinal cord, and cause minimal morbidity to the patient. Surgical approaches are summarized in the following three groups: posterior approach, lateral extra-cavitary approach, and anterior transthoracic approach. The major factors that determine the surgical approach include the neurological status of the patient, disc size, location, degree of calcification, and amount of spinal cord compression [4]. The anterior transthoracic approach offers the benefit of accessing the herniated disc in front of the compressed spinal cord, thereby avoiding direct manipulation of the cord [5]. There is reasonable doubt that the anterior transthoracic approach can, in some cases, lead to postoperative axial spine pain, progressive kyphotic deformity, and even neurological deterioration. Therefore, some authors recommend additional intervertebral fusion [5–8].

The wide range of the above-mentioned and available techniques indicate that a single method may not be suitable for every patient, and surgeons should consider different factors when choosing the appropriate approach. The anterior approach (mini-thoracotomy or thoracoscopic approach), as mentioned, lowers the likelihood of spinal cord injury, though the risk of lung, pleura, and major vessel damage remains [6]. Destabilization of spinal alignment happens more often with posterior approaches, and there is an apparent need for subsequent fusion [9]. Based on several studies, partial resection of the rib head and postero-lateral part of the vertebral body during the anterior transthoracic approaches does not cause any significant instability [5–7]. On the contrary, the transition between the thoracic and lumbar region is more susceptible to postoperative kyphosis and can lead to significant axial pain [10, 11]. The objective of this paper was to describe the surgical technique and outcome of microsurgical removal of TDH *via* the transthoracic approach and subsequent fusion with autogenous rib graft without the use of artificial materials. We would like to emphasize the low morbidity of the transthoracic multidisciplinary approach, as well as optional natural fusion without the need for expansion and prolongation of the surgical procedure.

Case report

A 44-year-old female presented with a six-month history of progressive paresis of the lower extremities, back pain, and numbness along the pelvis and legs. Physical examination revealed a moderate to severe lower spastic paraparesis. The patient could not ambulate independently, and there was decreased sensation below the T11 vertebral distribution with a positive Babinski sign. CT and MRI demonstrated a calcified disc herniation at the T10-11 intervertebral level located centrally with spinal cord compression (Figure 1). The calcified herniated disc occupied a significant volume of the central spinal canal. The mini-open transthoracic approach was performed with decompression of the spinal canal and a fusion with an autogenous rib bone graft. Postoperatively,

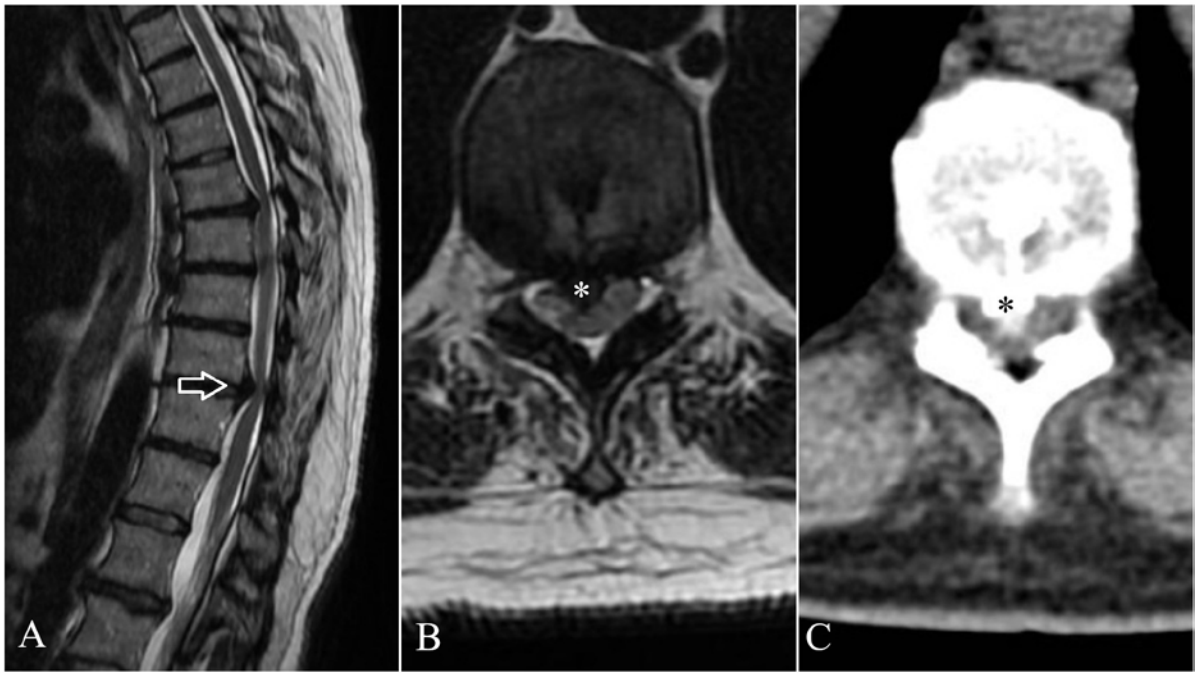

Fig. 1 – (A) Sagittal T2 weighted magnetic resonance imaging (MRI) image of the thoracic segment reveals T10-11 intervertebral disc herniation with myelopathic signal (arrow); (B) axial T2 MRI and (C) computed tomography images show centrally displaced and calcified intervertebral disc with compression on the medulla (asterisk).

the patient had relief from her symptoms and was fully ambulatory on the ninth postoperative day. The patient returned to work six months after her operation, reporting complete recovery with no axial back pain. The control CT and MRI showed no spinal cord compression and good fusion without an increase in kyphosis (Figure 2).

Surgical technique

The patient was placed in the lateral–decubitus position, with the rib cage as the highest point in the center. The thoracic surgeon performed the mini-open thoracotomy and exposure. With the aid of topographic and anatomical orientation, fluoroscopy was used to determine the T10-11 intervertebral level. The rib head related to the T10-11 intervertebral space and vertebral bodies was resected and preserved. The T11 ipsilateral part of the vertebral body near the pedicle was partially resected using a high-speed drill, and the posterolateral portions of the vertebral bodies above and below the disc space were drilled to expose the spinal canal and disc herniation. Using a neurosurgical microscope, dissector, and rongeurs, the calcified disc was resected and pushed into previously created space without the manipulation of the *dura mater*. Sufficient decompression was achieved, and *dura mater* was observed completely free. Some adhesions to the *dura mater* were noted and dissected, and local haemostatic material was placed over. In the end, the autogenous rib graft was tailored and placed into the drilled cavity, thus achieving good vertebral interbody fusion (Figure 3). During closure, the thoracic drain was placed, and when the pleural effusion decreased to less than 100 mL *per* day, it was removed, and the patient was mobilized out of the bed.

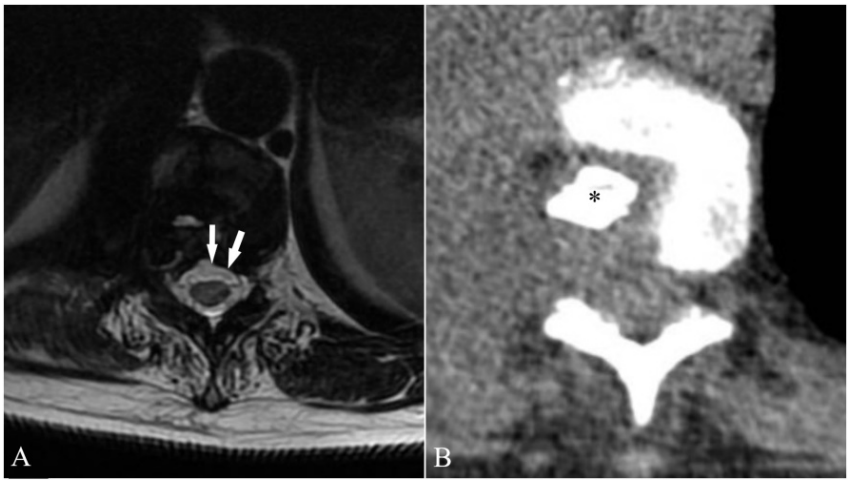

Fig. 2 – (A) Postoperative axial T2 weighted magnetic resonance imaging demonstrates complete decompression of the medulla (arrows) at the T10-11 intervertebral level; (B) correct placement of the autogenous rib graft (asterisk) was confirmed on computerized tomography axial image at the same intervertebral level.

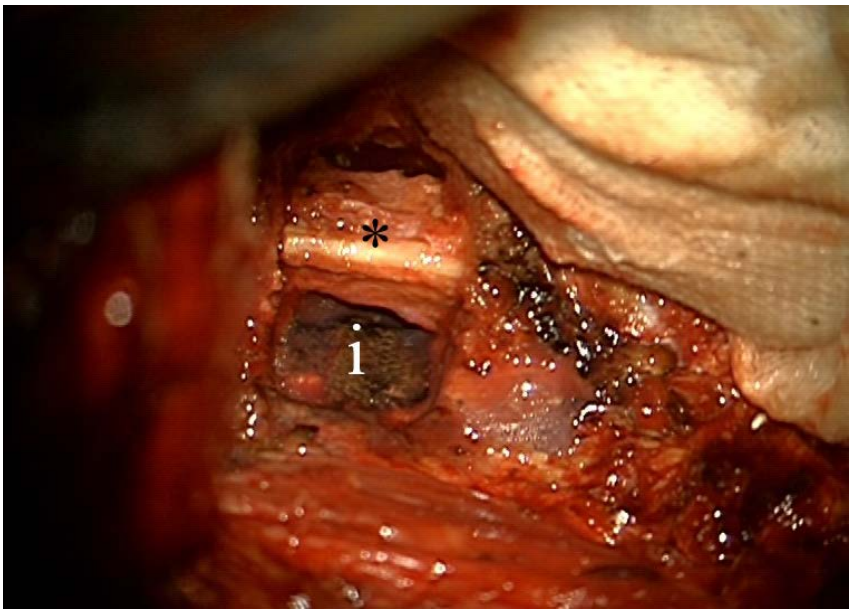

Fig. 3 – Intraoperative image after removal of intervertebral disc showing tailored autogenous rib graft (asterisk) placed into the T10-11 intervertebral space (i).

Discussion

Understanding the symptoms relies on the specific anatomical features of the thoracic spine and the thoracic segment of the cord and its associated vasculature. The kyphosis of the spine brings the cord nearer to the posterior aspect of the vertebral body, restricting its mobility [10]. The normal intervertebral height, sagittal alignment, and general vertebral stability are maintained by columns described by Denis [11].

A recent study comparing 63 patients, who received anterior decompression, to 123 patients, who underwent posterior circumspinal decompression and spinal fusion for calcified thoracic discs, revealed significantly shorter operation duration, reduced intraoperative blood loss, shorter hospital stays, and lower rates of perioperative and surgery-associated complications in the posterior approach group [12]. Operative management of large calcified discs situated medially is best accomplished *via* an anterolateral approach, while a posterior approach may be employed for soft or lateral herniations [13]. Posterior approaches to the thoracic spine involve much bone removal and, therefore, almost always require instrumented fusion [14]. Pseudoarthrosis or kyphotic deformity may occur in anterior transthoracic approaches, but these complications are not so frequent because the rib cage provides good support. Furthermore, that can depend on surgical technique and amount of bone drilling, so many authors advise interbody fusion [6, 7]. Complications observed with this approach included dural tears and cerebrospinal fluid leaks, as well as approach-related issues like pneumothorax, effusion, rib fractures, intercostal neuralgia, and atelectasis [15]. These issues can be managed successfully, especially with a multidisciplinary team. Augmented reality has also been documented for enhancing the safety and precision of spine surgery, and it helps with this kind of complex surgical approach [16].

TDH in the region of the thoracolumbar junction, as in our case, is more susceptible to instability, but there are no well-defined indications for interbody fusion or guidelines on how to achieve it in the best possible way. Additional rib resection for fusion should be avoided, but as a part of the approach, the bone graft can be safely harvested and subsequently used for fusion [8]. Placement of thoracic transvertebral pedicle screws requires additional resources and time [14, 17]. Fusion using only bone grafts is delayed compared to instrumentation techniques. The middle thoracic segment of the spine has a very limited range of motion, and we think that the rib cage provides the necessary stability for fusion to occur. While the endoscope can function as a minimally invasive technique and save time, its drawbacks may include compromised visualization, inadequate decompression, and challenges during graft placement [18, 19]. Some authors have recently described a direct transdural posterior approach, noting that careful manipulation of the spinal cord can be used to access the ventral part of the spinal canal [20]. However, potential drawbacks compared to the anterior approach include excessive manipulation of the cord, which can lead to severe neurological deficits and the challenging repair of the ventral dura within the spinal canal. In such cases, intraoperative neurosurgical monitoring should be mandatory.

The absolute indications for intervertebral fusion still need to be precisely defined through more adequately designed studies. The aim of this paper was to present the relatively straightforward approach and follow-up on the patient who underwent the transthoracic calcified disc resection and good natural fusion. Interbody fusion after the transthoracic approach should always be considered a part of the technique because it significantly reduces axial pain and prevents postoperative deformity [12, 21, 22].

Conclusion

Thoracic disc herniation is a rare and challenging surgical lesion. The anterior mini-open transthoracic approach provides good exposure and is considered minimally invasive. As a part of the procedure itself, rib bone grafting in patients undergoing thoracic discectomy should be considered safe. The benefits of subsequent fusion should always be taken into account and individualized.

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Received on May 13, 2024
Revised on June 25, 2024
Revised on July 14, 2024
Accepted on July 30, 2024
Online First September 2024

HISTORY OF MEDICINE

UDC: 617.7(091)
DOI: https://doi.org/10.2298/VSP240521059N

Bicentennial of keratoplasty: thus spoke the pioneers

Dvestota godišnjica keratoplastike: tako su govorili začetnici

Ljubiša B. Nikolić

LaserFocus Center for Eye Microsurgery, Belgrade, Serbia

Key words:
corneal transplantation; history of medicine; history, 19th century; history, 20th century; ophthalmologic surgical procedures.

Ključne reči:
rožnjača, transplantacija; istorija medicine; istorija, XIX vek; istorija, XX vek; hirurgija, oftalmološka, procedure.

Introduction

Two hundred years ago, Franz Reisinger [1], a German professor of surgery, obstetrics, and ophthalmology, coined the term "keratoplasty" for a new corneal procedure promoted by his experiments on a rabbit eye six years earlier. The bicentennial of the appearance of this term used in his paper, as well as of a novel, revolutionary surgical attempt at curing blindness, is the opportunity to shed light on Reisinger's landmark achievement.

Yet another jubilee celebrated in 2024 is the 190th anniversary of the introduction of "corneal transplantation" (CT) as a new term that was to become a widely used synonym for "keratoplasty." Therefore, the current year is the right time to revisit the site of its origin – Wilhelm Thomé's [2] inaugural dissertation, using a recent translation.

These first attempts at corneal grafting have often been used as an introduction to many texts on transplantation in ophthalmology. With a few remarkable exceptions, the tendency of using secondary sources has led to a multiplication of inaccurate presentations of Reisinger's [1] experiment, such as stating that he had sutured a graft from one animal to the other, using hundreds of rabbits and chickens, all without success. On the other hand, Thomé's [2] significant work has been reduced to a mere date when the term CT appeared in literature and was overshadowed by more attractive experiments performed by his follower Samuel Bigger [3]. The best way to rectify this injustice is to consult primary sources and let these pioneers of keratoplasty speak for themselves.

Reisinger's ipsilateral autokeratoplasty

In a paper published in 1824 under the title "Keratoplasty, a search for the broadening of ophthalmology", Reisinger [1] wrote: "In February 1818, I separated the cornea of a young rabbit close to the sclera, up to the line (2.18 mm, author's remark), using a cataract knife and a pair of scissors subsequently. Now, this almost totally excised cornea was spread over the iris again, and the lids were closed with an appropriate bandage, which was taken off by the animal two and a half days later; the cornea was almost white and opaque, but more than its half became clear after it had reunited. The second operation was done on the same eye of this rabbit on June 6, 1818. I performed a complete corneal separation, but not quite close to the sclera, which was left with a narrow remnant of the cornea. This completely separated cornea was put back in its place, and the lids were closed with an appropriate bandage.". Forty days later, gross edema had been resolved, revealing the attached cornea with only a small, convex, and opaque dot at its mid-periphery [1].

Reisinger's [1] idea was to check if a completely excised corneal button would create an "organic connection" with the remaining cornea and retain its transparency after having been put back into its place. The result can be described in modern terms as an ipsilateral autokeratoplasty, a neat experiment devoid of rough sutures and foreign tissue – no more, no less.

The promise of "a special treatise on this matter, to my best knowledge unmentioned before, with a presentation of my investigation and proposals, is soon to be published" [1] seems not to have been fulfilled. The burden of being an editor of Bavarian Annals, the journal in which his paper was

Correspondence to: Ljubiša Nikolić, LaserFocus Center for Eye Microsurgery, Cara Nikolaja 25, 11 000 Belgrade, Serbia.
E-mail: lj.b.nikolic@gmail.com

published, as well as a professor of surgery, ophthalmology, and obstetrics, might be an adequate explanation for the lack of time.

In the words of a contemporary, it was inevitable that Reisinger's [1] essay would cause a general commotion and various controversies.

Thome's allografts and the use of direct suturing

The answer to some of these controversies was offered by Wilhelm Thomé [2] in his inaugural dissertation *"De Corneae Transplantatione"*, published in 1834. He performed six experiments in which he sutured cornea from one rabbit to the other; in one of these, the recipient cornea was made opaque with the use of sulfuric acid. The additional two experiments included corneal grafting between a rabbit and a dog.

His first task was to construct a cage for holding unanesthetized animals during surgery. After having excised the donor cornea with a cataract knife and a pair of scissors, he fixed it with a suture: "For that purpose, a manufacturer of surgical instruments supplied me with the adequate needles, unknown to the medical theory, very fine, 2/3 circle curved, made from English steel, with a red wax coated thread intended to be recognizable within the pus. The edge of the corneal button was stabbed with one needle and pulled out until the middle of the thread reached the canal, while the opposite edge was stabbed with the other needle. Next, these sutures were pulled through the recipient cornea in the horizontal diameter, and the knots were tied." [2]. The follow-up was eight weeks, except for two rabbits with a fatal outcome after one and three weeks, respectively. The results were only partially successful, as shown in beautiful lithographs: five transplants coalesced with the recipient's corneoscleral rim, of which two were completely transparent, while three were semitransparent and vascularized. There were two cases of lens expulsion and one complete failure with a retracted opaque graft. Even so, we believe that Thomé [2] was the first to introduce direct corneal sutures and to show that allografts and xenografts of the cornea were possible, even in a traumatized recipient tissue.

His work immediately gave a strong impetus to further experiments with keratoplasty. Sadly, it was consigned to oblivion in decades to come due to Thomé's [2] untimely death. Furthermore, the use of Latin has limited the interest in his dissertation to collectors and dealers of antique books. A recent German translation of this text may help Thomé in retrieving his place in the history of keratoplasty [2].

Bigger's optic keratoplasty and veterinary ocular surgery

One of those who "tried to faithfully follow the plan laid out by Thomé" [2] was Dr. Samuel Bigger [3]. His lecture on keratoplasty was published in 1837, "with the permission of the author, from the notes taken by Mr. Swift". This article stood out in that issue of the Dublin Journal of Medical Science as the only one written in the third person. It enabled the author to get "the highest credit on the ingenuity, patience, and manual dexterity" in his own paper. Although his experiments on rabbits are not substantially different from those performed by Thomé [2], this master of presentation fires the imagination of a reader with his sight-saving act of the corneal allotransplantation in which a mortally wounded gazelle was the donor and a pet gazelle the recipient; this scene took place in 1835, during the surgeon's captivity in the Egyptian desert, at the moment of an outbreak of plague in a country shaken by a rebellion. Back in Dublin, the good doctor repeated the procedure on a dog with a corneal scar, with a dead wolf as the donor. The dog ran away to a forest two days after surgery, only to return with the excellent function of the operated eye.

Our opinion is that these two transplantations might be considered the first optic keratoplasties and unique attempts at sight-saving surgical procedures in animals. As an author who published in English, the lingua franca of the future, Bigger [3] was able to convey the ideas and surgical techniques of his two predecessors to the New World and later communicate them globally.

Immediately, these ideas influenced Richard Kissam [4], a surgeon from New York who used a piglet as a donor and performed the first human xenograft in 1838. This premature attempt ended with a complete graft melting, as Kissam [4] seemingly failed to follow Bigger's [3] advice and "give this matter his attentive consideration."

Lamellar versus penetrating keratoplasty

Although the technique introduced by Reisinger [1] and developed by Thomé [2] and Bigger [3] was occasionally used almost unchanged even a century later [5, 6], and throughout the whole twentieth century as a modified procedure called penetrating keratoplasty, the history of CT took a sharp turn in 1840, when Franz Mühlbauer [7] published his inaugural dissertation with a lithograph which illustrated his triangular lamellar corneal grafts fixed to the recipient rabbit eyes with one or two direct sutures. From that moment to the present day, the approach to CT has been oscillating from lamellar to penetrating keratoplasty and back.

Almost half a century had passed until Arthur von Hippel [8] invented a motor-driven trephine and performed the first successful CT in a patient by placing a small-diameter, full-thickness rabbit corneal button into a young woman's lamellar bed.

His technique was immediately accepted except for the use of the lamellar xenograft. On the contrary, it was penetrating keratoplasty using a human donor that made a comeback after the publication of Eduard Zirm's [9] famous case in 1905. As both von Hippel's [8] and Zirm's [9] patients had similar postoperative visual acuity, the result of the competition between the two methods was still a draw. It was Anton Elschnig's [10] twenty years long work and his epochal series of 174 patients with a 22 percent overall success and about three-quarters of clear grafts in the eyes with interstitial keratitis that confirmed the leading role of penetrating keratoplasty.

A giant step further was made when Vladimir Petrovich Filatov [11, 12] presented his success with a modified André Magitot's procedure [13] for storage and transplantation of cadaver donor corneas on a large scale. Closely followed by Zdravko Nižetić [14, 15], Filatov [12] was instrumental in paving the way for the establishment of the first eye bank. Established in 1944 as a result of a combined effort invested by Townley Paton [16], John MacLean, and Aida de Acosta Brackinridge, this institution was soon joined by a web of similar ones and enabled piling of still larger series of keratoplasties mounting to several thousand cases in the hands of masters like Ramon Castroviejo [17].

A short and promising revival of lamellar keratoplasty in 1948, created by Paufique et al. [18], was overcome by a tide of visually more successful penetrating keratoplasties enabled by the introduction of corticosteroids and microsurgery. From the sixties to the end of the twentieth century, penetrating keratoplasty ruled the scene, and a few generations of corneal surgeons kept this "gold standard" serenely. Yet, there were those like José Barraquer [19] in the fifties and Gerrit Melles [20] in the nineties who could not comply with the drawbacks of this standard, mainly the unpredictable high and often irregular astigmatism, as well as its open sky technique. These surgeons invented some new approaches. José Barraquer [19] came up with refractive corneal surgery, while Gerrit Melles [20] invented selective lamellar transplantation, crowned with Descemet stripping endothelial keratoplasty (DSEK) and Descemet membrane endothelial keratoplasty (DMEK). Refractive corneal surgery can correct most of the refractive errors, while DSEK and DMEK do not create significant errors at all, thanks to a small limbal opening for the transplantation of endothelium on a thin carrier and its sutureless fixation with air.

Future trends in corneal transplantation

History of science teaches us that the seeds of breakthroughs in physics, chemistry, and biology, unknown to us at present, become future game changers in medicine. The history of keratoplasty reveals that such seeds grow silently even, or shall we say, especially during the stagnant periods of a particular surgical discipline. It was Pasteur's [21] proof of germ theory of diseases, Lister's [22] introduction of antiseptic methods in surgery, Morton's application of general anesthesia [23], and Koller's [24] announcement of local anesthesia that happened during those forty years between Mühlbauer's [7] and von Hippel's [8] achievements, a period of a stand-still in CT. These discoveries saved more eyes and lives and helped both patients and surgeons more than any innovation in the technique of keratoplasty.

Likewise, the greatest discoveries of the twentieth century, quantum mechanics [25] and the structure of deoxyribonucleic acid [26] led to quantum electronics, the invention of lasers, and genetic engineering, respectively. First of these changed the approach to surgery and imaging procedures, while the ability to change genes could eliminate some indications for transplantation. Further, the discovery of immunity [27] has brought corticosteroids to the scene, lowered graft rejection, and saved more transplants than any microsurgical device, while the knowledge of the role of corneal endothelium enabled DSEK and DMEK.

Finally, polymer chemistry [28] and tissue culture [29] led to the development of tissue engineering, helped the construction of a more tolerable keratoprosthesis, and offered hope for the creation of either an artificial cornea or a method of replacing a part of the cornea with cultured cells arranged on a polymer scaffold.

Conclusion

The moral of these stories from the two previous centuries can be summarized in the following way: there are more things happening in the basic sciences of the twenty-first century than are dreamt of in our clinically oriented minds; therefore, it will be prudent to restrain from any prediction of their influence on corneal transplantation in the future.

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Received on May 21, 2024
Accepted on June 25, 2024
Online First August 2024

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Rukopis se piše sa proredom 1,5 sa levom marginom od **4 cm**. Koristiti font veličine 12, a načelno izbegavati upotrebu **bold** i *italic* slova, koja su rezervisana za podnaslove. Originalni članci, opšti pregledi i metaanalize i članci iz istorije medicine ne smeju prelaziti 16 stranica (bez priloga); aktuelne teme – deset, seminar praktičnog lekara – osam, kazuistika – šest, prethodna saopštenja – pet, a komentari i pisma uredniku – tri, izveštaji sa skupova i prikazi knjiga – dve stranice.

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a) Poželjno je da naslov bude kratak, jasan i informativan i da odgovara sadržaju, podnaslove izbegavati.

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Na drugoj stranici nalazi se strukturisani apstrakt (250-300 reči za originalne članke i meta-analize) sa naslovom rada. Kratkim rečenicama na srpskom i engleskom jeziku iznosi se **Uvod/Cilj** rada, osnovne procedure **– Metode** (izbor ispitanika ili laboratorijskih životinja; metode posmatranja i analize), glavni nalazi **– Rezultati** (konkretni podaci i njihova statistička značajnost) i glavni **Zaključak**. Naglasiti nove i značajne aspekte studije ili zapažanja. Strukturisani apstrakt za kazuistiku (do 250 reči), sadrži podnaslove **Uvod, Prikaz bolesnika** i **Zaključak**). Ispod apstrakta, „Ključne reči“ sadrže 3–10 ključnih reči ili kratkih izraza koje ukazuju na sadržinu članka.

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Tekst sadrži sledeća poglavlja: **uvod**, **metode**, **rezultate** i **diskusiju**. **Uvod.** Posle uvodnih napomena, navesti cilj rada. Ukratko izneti razloge za studiju ili posmatranje. Navesti samo važne podatke iz literature a ne opširna razmatranja o predmetu rada, kao ni podatke ili zaključke iz rada o kome se izveštava.

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Rezultate prikazati logičkim redosledom u tekstu, tabelama i ilustracijama. U tekstu naglasiti ili sumirati samo značajna zapažanja.

U **diskusiji** naglasiti nove i značajne aspekte studije i izvedene zaključke. Posmatranja dovesti u vezu sa drugim relevantnim studijama, u načelu iz poslednje tri godine, a samo izuzetno i starijim. Povezati zaključke sa ciljevima rada, ali izbegavati nesumnjive tvrdnje i one zaključke koje podaci iz rada ne podržavaju u potpunosti.

Literatura

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Primeri referenci:

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Balint B. From the haemotherapy to the haemomodulation. Beograd: Zavod za udžbenike i nastavna sredstva; 2001. (Serbian)

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Tabele

Sve tabele pripremaju se sa proredom 1,5 na posebnom listu. Obeležavaju se arapskim brojevima, redosledom pojavljivanja, u levom uglu (**Tabela 1**), a svakoj se daje kratak naslov. Objašnjenja se daju u fus-noti, ne u zaglavlju. Svaka tabela mora da se pomene u tekstu. Ako se koriste tuđi podaci, obavezno ih navesti kao i svaki drugi podatak iz literature.

Ilustracije

Slikama se zovu svi oblici grafičkih priloga i predaju se kao dopunske datoteke u sistemu **aseestant**. Slova, brojevi i simboli treba da su jasni i ujednačeni, a dovoljne veličine da prilikom umanjivanja budu čitljivi. Slike treba da budu jasne i obeležene brojevima, onim redom kojim se navode u tekstu (**Sl. 1; Sl. 2** itd.). Ukoliko je slika već negde objavljena, obavezno citirati izvor.

Legende za ilustracije pisati na posebnom listu, koristeći arapske brojeve. Ukoliko se koriste simboli, strelice, brojevi ili slova za objašnjavanje pojedinog dela ilustracije, svaki pojedinačno treba objasniti u legendi. Za fotomikrografije navesti metod bojenja i podatak o uvećanju.

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Skraćenice i akronimi u rukopisu treba da budu korišćeni na sledeći način: definisati skraćenice i akronime pri njihovom prvom pojavljivanju u tekstu i koristiti ih konzistentno kroz čitav tekst, tabele i slike; koristiti ih samo za termine koji se pominju više od tri puta u tekstu; da bi se olakšalo čitaocu, skraćenice i aktinome treba štedljivo koristiti.

Abecedni popis svih skraćenica i akronima sa objašnjenjima treba dostaviti pri predaji rukopisa.

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