YU ISSN 0042-8450

ВОЈНОСАНИТЕТСКИ ПРЕГЛЕД

Часопис лекара и фармацеута Војске Србије

Military Medical and Pharmaceutical Journal of Serbia

Vojnosanitetski pregled

Vojnosanit Pregl 2025; February Vol. 82 (No. 2): pp. 69–128.

Vojnosanitetski Pregled 2025 February Vol. 82 (No. 2): pp. 69–128.

Vol. 82, No. 2, 2025

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. 82, br. 2, 2025

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
Open Access
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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

CONTENTS / SADRŽAJ

International Epilepsy Day (IED) is celebrated in February every year since 2015. The goal of establishing the MDE is to raise awareness and level of understanding of the challenges faced by people with epilepsy in order to provide them with the best possible care and support that will improve their quality of life. The theme of this year's IED is "My Epilepsy Journey".

Međunarodni dan epilepsije (MDE) obeležava se u februaru svake godine, od 2015. godine. Cilj uspostavljanja MDE je podizanje svesti i nivoa razumevanja izazova sa kojima se suočavaju oboleli od epilepsije kako bi im se obezbedila najbolja moguća nega i podrška koja će im poboljšati kvalitet života. Tema ovogodišnjeg MDE je „Moje putovanje sa epilepsijom".

ORIGINAL ARTICLES

UDC: 616.24-07
DOI: https://doi.org/10.2298/VSP240607008Y

Quantitative study of lung structure in COPD patients based on low-dose Karl iterative reconstruction

Kvantitativna studija strukture pluća kod obolelih od HOBP na osnovu niskodozne Karlove iterativne rekonstrukcije

[1]Yizhai Ye*, [1]Juehui Li[†], Weigen Wang*, Jianhua He*, Qi Yang[‡]

***Ninghai First Hospital, Department of Radiology, Ningbo, Zhejiang Province, China; [†]Baoan District Hospital of Traditional Chinese Medicine, Department of Pulmonary Diseases/Respiratory and Critical Care Medicine, Shenzhen, China; [‡]The First Hospital of Jiaxing (Affiliated Hospital of Jiaxing University), Department of Respiratory, Jiaxing, Zhejiang Province, China**

[1]The two authors contributed equally to this study

Abstract

Background/Aim. Low-dose Karl iterative reconstruction (KIR) is a commonly used technique in medical imaging. An iterative algorithm reduces the dose of X-ray radiation while ensuring image quality, making it a safer and more convenient imaging method. The aim of the study was to analyze the assessment value of low-dose KIR for the lung structure of patients with chronic obstructive pulmonary disease (COPD). **Methods.** The study included a total of 135 COPD patients undergoing bronchoscopic biopsy from August 2022 to July 2023. Low-dose KIR was conducted. Two groups were formed according to the lung structure examined by bronchoscopic biopsy: an airway remodeling group and a non-airway remodeling group. The examination indicators of low-dose KIR were compared. Receiver operating characteristic curves were plotted to analyze the clinical value of low-dose KIR for assessing the lung structure. **Results.** According to the examination results of chest X-ray, airway remodeling was done in 85 out of 135 (62.96%) COPD patients. The sensitivities, specificities, and areas under the curves of computed tomography value, noise value, signal-to-noise ratio, and contrast-to-noise ratio were 0.976 vs. 0.965 vs. 0.953 vs. 0.980, 0.960 vs. 0.940 vs. 0.927 vs. 0.753, and 0.623 vs. 0.643 vs. 0.670 vs. 0.640, respectively. **Conclusion.** Low-dose KIR proved to be a very accurate and fast method for the quantitative study of lung structure in COPD patients.

Key words:
airway remodeling; algorithms; tomography, x-ray computed; diagnostic techniques and procedures; pulmonary disease, chronic obstructive.

Apstrakt

Uvod/Cilj. Karlova iterativna rekonstrukcija (KIR) niskom dozom je tehnika koja se često koristi u medicinskom snimanju. Iterativni algoritam smanjuje dozu rendgenskog zračenja istovremeno osiguravajući kvalitet slike, što ga čini sigurnijom i pogodnijom metodom snimanja. Cilj rada bio je da se analizira vrednost procene niskodozne KIR za strukturu pluća obolelih od hronične opstruktivne bolesti pluća (HOBP). **Metode.** Studijom je obuhvaćeno ukupno 135 obolelih od HOBP podvrgnutih bronhoskopskoj biopsiji od avgusta 2022. do jula 2023. godine. Sprovedena je niskodozna KIR. Formirane su dve grupe prema strukturi pluća ispitanih bronhoskopskom biopsijom: grupa za remodelovanje disajnih puteva i grupa bez remodelovanja disajnih puteva. Upoređeni su indikatori ispitivanja KIR niskim dozama. Za analizu kliničkog značaja niskodozne KIR u proceni strukture pluća korišćene su *receiver operating characteristic* krive. **Rezultati.** Prema rezultatima ispitivanja rendgenskog snimka grudnog koša, remodeliranje disajnih puteva urađeno je kod 85 od 135 (62,96%) obolelih od HOBP. Senzitivnost, specifičnost i površina ispod krive vrednosti kompjuterizovane tomografije, vrednosti šuma, odnosa signal-šum i odnosa kontrast-šum iznosile su 0,976 vs. 0,965 vs. 0,953 vs. 0,980, 0,960 vs. 0,940 vs. 0,927 vs. 0,753, i 0,623 vs. 0,643 vs. 0,670 vs. 0,640, redom. **Zaključak.** Niskodozna KIR se pokazala kao veoma precizna i brza metoda za kvantitativno proučavanje strukture pluća kod obolelih od HOBP.

Ključne reči:
disajni putevi, remodeliranje; algoritmi; tomografija, kompjuterizovana, rendgenska; dijagnostičke tehnike i procedure; pluća, opstruktivna bolest, hronična.

Correspondence to: Qi Yang, Department of Respiratory, The First Hospital of Jiaxing (Affiliated Hospital of Jiaxing University), Jiaxing 314 000, Zhejiang Province, China. E-mail: yangqifhj@elnu-edu.cn

Introduction

Chronic obstructive pulmonary disease (COPD) is a common and devastating lung condition characterized by incomplete reversible airflow limitation [1, 2]. The morbidity rate of COPD is very high globally [3]. The risk factors for COPD include smoking, air pollution, occupational exposure, etc. Structural changes in the lungs are an important part of the pathophysiological process of COPD [4], including airway wall inflammation and mucus hypersecretion, airway remodeling (AR)-induced airway structural changes, and pulmonary emphysema-induced alveolar destruction.

AR in COPD patients is associated with disease severity [5], which has a complex mechanism and causes great harm. Therefore, it is important to assess whether AR occurs in COPD patients in order to improve their quality of life and prognosis. In routine clinical practice, AR in COPD patients is assessed by lung function tests, high-resolution computed tomography (CT), bronchoscopy, and histopathological examination. Both early diagnosis and standardized treatment are essential for ameliorating the prognosis of COPD patients.

Low-dose Karl iterative reconstruction (KIR) is a commonly used technique in medical imaging. An iterative algorithm reduces the dose of X-ray radiation while ensuring image quality, making it a safer and more convenient imaging method.

The aim of this study was to assess the effect of low-dose KIR on the lung structure of COPD patients in order to explore its diagnostic value for structural changes.

Methods

A total of 135 COPD patients undergoing bronchoscopic biopsy from August 2022 to July 2023 were recruited. Low-dose KIR was performed for all patients. There were 89 male and 46 female patients aged 56–84 years, with a mean age of 70.39 ± 13.82 years. Among them, 63 patients had a smoking history, 55 had occupational exposure (harmful gases or dust in the work environment), and 39 had a family history (similar diseases in the family). Meanwhile, 62 cases were complicated with cardiovascular diseases, 71 had diabetes mellitus, and 59 had a history of cardiovascular disease. This study was approved by the local Ethics Committee, the First Hospital of Jiaxing, Jiaxing, Zhejiang Province, China (from August 6, 2022).

Inclusion and exclusion criteria

Inclusion criteria were as follows: patients who met the diagnostic criteria for COPD in the Global Initiative for Chronic Obstructive Lung Disease Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease 2018 [6], i.e., without any other diseases that may cause lung volume changes, such as chest deformity; those with forced expiratory volume in 1 second (FEV1)/forced vital capacity (FVC) – FEV1/FVC < 0.70 after inhalation of bronchodilators; those with very clear and complete dual-gas phase CT images of the chest and very clear images of the lung tissue; those who signed the informed consent form.

Exclusion criteria were as follows: patients with poor cooperation or blurred images; those with conditions that may affect the lung volume, including a history of lung surgery (such as lobectomy or segmentectomy) or morphological abnormalities of the chest; those with tumors or tumor-like lesions in the lungs; those with diseases that may affect CT scan results, such as infections in most of the lungs, severe atelectasis, or lung consolidation; those with more severe health problems, such as heart-, liver-, or kidney-related diseases.

Low-dose Karl iterative reconstruction

The examination method and purpose were explained to the patients in detail before they signed the informed consent form. Prior to the examination, the patients were guided to receive breathing training until meeting the requirements in the scan, and they were instructed to hold their breath by command at the end of deep inspiration and deep expiration. CT scanner uCT-760 128-slice spiral (Shanghai United Imaging Healthcare Co., Ltd., China) was used.

The scanning conditions and parameters were as follows: for the routine dose – tube voltage of 120 kV, tube current of 150 mA, 40 mm collimation, pitch of 1.0875, 0.5 s/r, 5 mm slice thickness, 1-mm thin-slice reconstruction on inspiratory and expiratory phase images, field of view of 35 mm, and 1024 × 1024 matrix; under a low dose – tube voltage of 120 kV, tube current of 80 mA, 40 mm collimation, pitch of 1.0875, 0.5 s/r, 5 mm slice thickness, 1-mm thin-slice reconstruction on inspiratory and expiratory phase images, field of view of 35 mm, and 1024 × 1024 matrix.

The patient held the head with both hands facing forward in a supine position, and the whole lung was scanned after breath-holding at the end of deep inspiration and deep expiration. The scanning range was consistent.

Examination parameters of low-dose Karl iterative reconstruction

All images were imported into the “digital lung” test platform for lobe segmentation and bronchus quantification. Lobe segmentation procedures are described in the text that follows. The whole lung tissue was extracted using the adaptive border marching method. Interlobular fissures were detected and segmented by computational geometry, and the implicit function method was used for segmenting a few interlobular fissures. Bronchus quantitative analysis software had been verified, automatically extracting the bronchial skeleton and measuring quantitative indicators required by the skeleton extraction algorithm when used for bronchus segmentation. To be specif-

ic, following lobe segmentation, the quantitative data, including the whole lung volume, volumes less than -910 Hounsfield units (HU) and -950 HU in both lungs, percentage of total lung area occupied by low attenuation area – LAA (LAA-950%, LAA-910%), emphysema index, and mean lung density, were measured. The quantitative indicators, including the number, length, and volume of bronchi, were obtained using the bronchus quantitative analysis software.

Evaluation of airway remodeling in COPD patients undergoing bronchoscopic biopsy

The airway wall thickness was measured to assess whether it was beyond the normal range. The morphology and arrangement of epithelial cells, as well as stromal changes, were observed. The collagen content and distribution were detected. The number and distribution of smooth muscle cells were observed. The type and number of inflammatory cells were assessed.

Statistical analysis

SPSS 26.0 software was used for statistical analysis. All measurement data were analyzed using the Shapiro-Wilk normality test. The normally distributed measurement data were described by mean ± standard deviation and compared by the independent-samples *t*-test between the two groups. Count data were described by percentages and analyzed using the Chi-square test. Receiver operating characteristic (ROC) curves were plotted to detect the clinical value of low-dose KIR for assessing the lung structure by the area under the curve (AUC): AUC ≤ 0.50 – no assessment value; 0.50 < AUC ≤ 0.70 – low assessment value; 0.70 < AUC ≤ 0.90 – medium assessment value; AUC > 0.90 – high assessment value. The value of $p < 0.05$ was considered statistically significant.

Results

Bronchoscopic biopsy showed that AR occurred in 85 out of 135 (62.96%) COPD patients.

There was no significant difference in the general data between the two groups ($p > 0.05$) (Table 1).

The AR group had significantly higher CT value, noise value, and signal-to-noise ratio, and a lower contrast-to-noise ratio than those of the non-AR group ($p < 0.05$) (Table 2).

The ROC curves were plotted with the results of bronchoscopic biopsy as a state variable (presence of airway remodeling = 1, absence of airway remodeling = 0) and the criteria for objective evaluation of low-dose KIR image quality as a test variable (Figures 1 and 2). The results revealed that low-dose KIR had a high value for assessing lung structure in COPD patients (Table 3).

Table 1

General data of patients with chronic obstructive pulmonary disease

Variable	Pathological results by bronchoscopic biopsy		t/χ^2	p
	AR Group (n = 85)	non-AR Group (n = 50)		
Age, years	71.32 ± 14.56	69.29 ± 9.89	0.874	0.384
Gender				
male	63	26	1.639	0.201
female	22	24		
Smoking history				
yes	41	22	0.052	0.821
no	44	28		
Occupational exposure				
yes	32	23	0.209	0.648
no	53	27		
Family history				
yes	15	24	3.559	0.059
no	70	26		
Complications with cardiovascular disease				
yes	35	27	0.477	0.490
no	50	23		
Complications with diabetes mellitus				
yes	46	25	0.049	0.825
no	39	25		
History of cardiovascular diseases				
yes	36	23	0.039	0.844
no	49	27		

Values are given as mean ± standard deviation or numbers.
AR – airway remodeling.

Table 2

Objective evaluation results of low-dose Karl iterative reconstruction image quality

Lung structural changes in COPD	CT value (HU)	Noise	Signal-to-noise ratio	Contrast-to-noise ratio
Group				
AR (n = 85)	63.40 ± 9.36	37.61 ± 7.41	2.25 ± 0.80	0.32 ± 0.29
non-AR (n = 50)	59.46 ± 7.53	34.04 ± 6.60	1.82 ± 0.43	0.44 ± 0.30
t	2.532	2.812	3.510	2.292
p	0.013	0.006	0.001	0.024

COPD – chronic obstructive pulmonary disease; CT – computed tomography; AR – airway remodeling; HU – Hounsfield unit. Values are given as mean ± standard deviation.

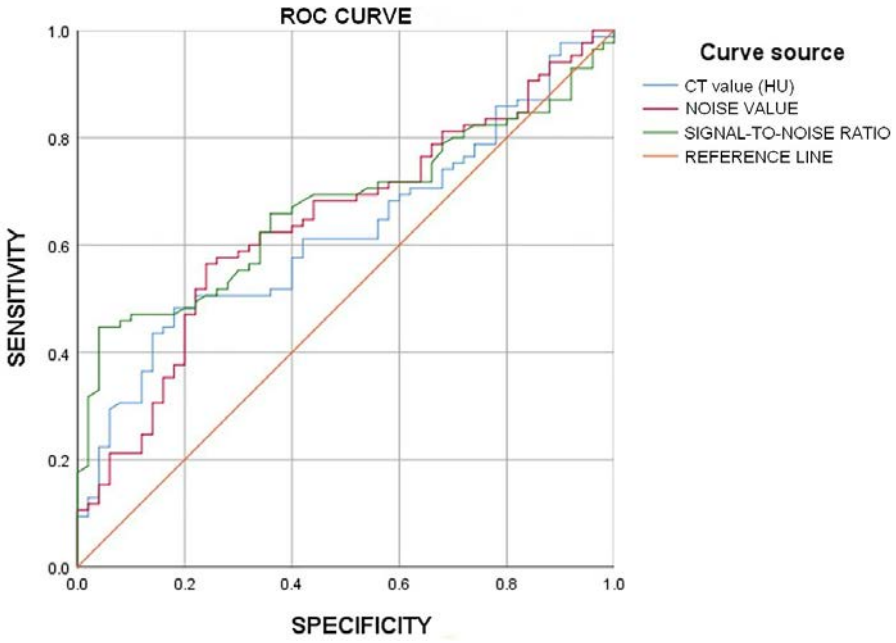

Fig. 1 – ROC curve analysis of low-dose Karl iterative reconstruction for assessing lung structural changes in COPD patients [CT value (HU), noise value, and signal-to-noise ratio].
ROC – receiver operating characteristics. For other abbreviations, see Table 2.

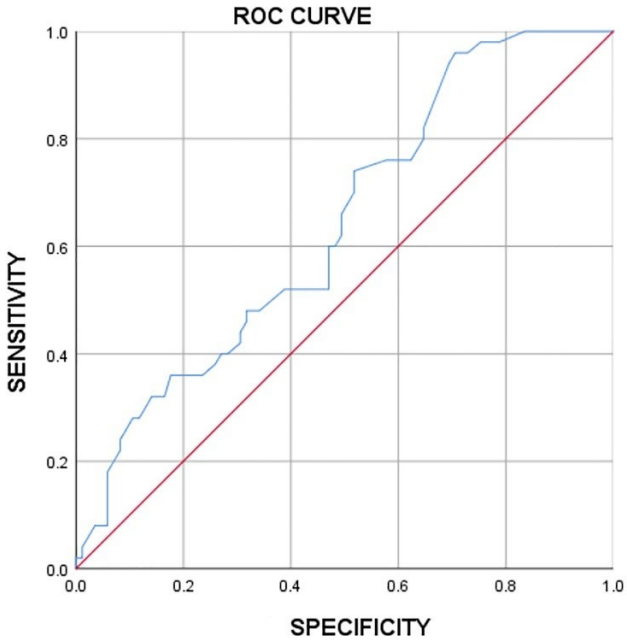

Fig. 2 – ROC curve analysis of low-dose Karl iterative reconstruction for assessing lung structural changes in COPD patients (contrast-to-noise ratio).
ROC – receiver operating characteristics; COPD – chronic obstructive pulmonary disease.

Table 3

Clinical value of low-dose Karl iterative reconstruction for assessing the lung structure in COPD patients

Variable	Area under the curve	95% CI	*p*	Sensitivity	Specificity	Youden index
CT value (HU)	0.623	0.530–0.717	0.017	0.976	0.960	0.016
Noise value	0.643	0.548–0.737	0.006	0.965	0.940	0.025
Signal-to-noise ratio	0.670	0.581–0.760	0.001	0.953	0.927	0.026
Contrast-to-noise ratio	0.640	0.547–0.734	0.007	0.980	0.753	0.227

CI – confidence interval.

For other abbreviations, see Table 2.

Discussion

With the aggravation of population aging, the morbidity rate of COPD has also been gradually increasing [7]. As the CT technique develops continuously, people have also had an increasing demand for routine CT examinations or diagnosis and determination of the severity of disease [8]. However, the damage of high radiation doses in CT to mental and physical health is inevitable. To address these problems, low-dose CT scans have been proposed to reduce the radiation dose [9]. Nevertheless, the image resolution declines and the image noise increases due to dose reduction, affecting the evaluation of the severity of disease and decision-making on the correct treatment. Iterative reconstruction has also been widely used, gradually becoming a new research hotspot. It is important to reduce the dose without compromising the image quality [10].

Low-dose KIR is an image reconstruction algorithm with specific functions. Generally, it is applied in the quantitative study of the lung structure in COPD patients. It has been verified that the KIR algorithm can be used as a substitute for routine doses for diagnosing COPD, achieving similar diagnostic efficacy to the routine dose [11].

In this study, the AR group had a higher CT value, noise value, and signal-to-noise ratio, and lower contrast-to-noise ratio than the non-AR group. Thus, low-dose KIR had a high value for assessing the lung structure in COPD patients. Moreover, the AUCs of CT value, noise value, signal-to-noise ratio, and contrast-to-noise ratio were 0.623, 0.643, 0.670, and 0.640, respectively, suggesting high diagnostic values for airway remodeling.

Low-dose KIR has many advantages in assessing the lung structure in COPD patients. For instance, compared with traditional CT, the radiation dose significantly declines, weakening the risks and potential hazards to the health of patients, especially those who need frequent CT examinations [12, 13]. The technique is also cost-effective, with shorter scanning time and fewer consumables due to decreased radiation dose [14]. In addition, surgeons and radiologists involved are safe against radiation exposure [15]. The low-dose KIR with a strong ability of lung structure detection in COPD patients can detect AR better by optimizing the image quality and reconstruction algorithm, thereby helping doctors assess the lung structure more accurately. Moreover, this technique also allows accurate quantitative analysis, which can provide more accurate parameters of lung structure to help assess disease progression and monitor the condition changes in COPD [16, 17]. Meanwhile, this technique can reduce image noise through the iterative reconstruction algorithm, and clear images can still be acquired at low doses, which is conducive to discovering subtle structural changes and displaying lung microstructure and lesion characteristics. Through regular examinations, doctors can also understand the changes in disease conditions to provide a basis for individualized treatment [18].

The low-dose KIR is of great clinical significance for assessing the lung structure in COPD patients due to the following advantages [19]. Firstly, it can provide more detailed and accurate information about the lung structure, assist in early identification and diagnosis of COPD, provide a basis for individualized treatment by tracking disease progression and monitoring condition changes, guide treatment decision-making, determine the outcomes of therapeutic regimen, and help predict the prognosis. Secondly, it causes less radiation damage in order to reduce potential risks and improve safety. Thirdly, clearer images can be acquired with optimized image quality to facilitate diagnosis, provide a more reliable basis for doctors, and enhance diagnostic confidence. Finally, it can provide data support for related research, improve patient experience, and enhance medical quality [20].

Conclusion

Low-dose Karl iterative reconstruction has high value for assessing lung structure in COPD patients. This method not only quantitatively studies the lung structure in COPD patients but also determines the health of lung structure in COPD patients more comprehensively in combination with the actual condition of lung structure. Hence, more targeted treatment plans can be developed, the progression of disease predicted, and individualized suggestions for prevention and healthcare can be given to patients.

Conflict of interest

The authors declare no conflict of interest.

Funding

This study was financially supported by the Key Construction Disciplines of Provincial and Municipal Construction of Zhejiang Province (No. 2023-SSGJ-002).

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Received on June 7, 2024
Revised on November 20, 2024
Accepted on November 27, 2024
Online First February, 2025

ORIGINAL ARTICLE

UDC: 616-053.9:[616.712-001-036:616.26
DOI: https://doi.org/10.2298/VSP240626006T

Diaphragm thickness is associated with overall survival in elderly thoracic trauma patients

Debljina dijafragme je povezana sa preživljavanjem kod starijih pacijenata sa povredom grudnog koša

Zeynep Nilufer Tekin*, Zeynep Bilgi†

Istanbul Medeniyet University, *Goztepe Prof. Dr. Suleyman Yalcin City Hospital, Department of Radiology, †Faculty of Medicine, Department of Thoracic Surgery, Istanbul, Turkey

Abstract

Background/Aim. Diaphragm thickness (DT) has been associated with advanced age and adverse outcomes, especially in severe conditions such as prolonged intubation. The aim of this study was to assess the prognosis of elderly patients with thoracic trauma (TT) and to investigate DT and psoas muscle thickness as potential prognostic indicators. **Methods.** A retrospective study included TT related consultations, taken from hospital records, performed between November 2015 and January 2021. Demographic data, injury characteristics, trauma mechanisms, overall survival, etc., were documented. Radiological imaging was re-evaluated to measure DT and psoas muscle thickness. **Results.** Among 394 patients, 129 were classified as elderly (> 65 years old). The most common mechanism of trauma was falls (n = 71), followed by pedestrian traffic accidents (n = 16). The overall survival of all patients was 43.9 ± 3.6 months, with an 82% two-year survival rate for elderly patients. DT was significantly higher in elderly survivors compared to deceased patients (4.0 ± 1.19 mm vs. 3.57 ± 1.0 mm; $p = 0.015$). **Conclusion.** Decreased DT is associated with an increased mortality risk in the elderly population. Elderly patients with TT and reduced DT may benefit from screening programs for early intervention targeting potential contributing factors such as frailty, trauma recidivism, and missed cancer screening. Furthermore, DT may serve as a potential indicator within a scoring system for risk assessment.

Key words:
aged; biomarkers; diaphragm; frailty; injuries; thorax; tomography, x-ray computed.

Apstrakt

Uvod/Cilj. Debljina dijafragme (DD) povezana je sa starijim životnim dobom i neželjenim ishodima, posebno u teškim stanjima kao što je prolongirana intubacija. Cilj rada bio je da se proceni prognoza kod starijih pacijenata sa povredom grudnog koša (PGK) i da se ispitaju DD i debljina mišića psoasa kao potencijalni prognostički pokazatelji. **Metode.** Retrospektivna studija je uključivala konsultacije u vezi sa PGK, preuzete iz bolničkih kartona, obavljene između novembra 2015. i januara 2021. godine. Dokumentovani su demografski podaci, karakteristike povreda, mehanizmi povreda, ukupno preživljavanje, itd. Radiološki snimci su ponovo procenjivani u cilju merenja DD i debljine mišića psoasa. **Rezultati.** Od ukupno 394 pacijenata, 129 je svrstano u populaciju starijih osoba (> 65 godina). Najčešći mehanizam povrede bili su padovi (n = 71), a sledili su ih saobraćajne nesreće pešaka (n = 16). Ukupno preživljavanje svih pacijenata iznosilo je 43,9 ± 3,6 meseci, sa stopom dvogodišnjeg preživljavanja od 82% za starije pacijente. DD je bila značajno veća kod starijih preživelih nego kod preminulih pacijenata (4,0 ± 1,19 mm vs. 3,57 ± 1,0 mm; $p = 0,015$). **Zaključak.** Smanjena DD povezana je sa povišenim rizikom od mortaliteta u populaciji starijih osoba. Starije osobe sa PKG i smanjenom DD mogu imati koristi od programa skrininga ranih intervencija usmerenih prema potencijalno doprinosećim faktorima kao što su slabost, recidivi povreda i propušteni skrining na karcinome. Osim toga, DD može služiti kao potencijalni pokazatelj u sklopu sistema bodovanja u proceni rizika.

Ključne reči:
stare osobe; biomarkeri; dijafragma; krhkost; povrede; toraks; tomografija, kompjuterizovana, rendgenska.

Correspondence to: Zeynep Nilüfer Tekin, Istanbul Medeniyet University Goztepe Prof. Dr. Suleyman Yalcin City Hospital, Department of Radiology, Dr. Erkin Street, 34 722 Istanbul, Turkey. E-mail: drnilufer@gmail.com

Introduction

The elderly population is rapidly growing in many parts of the world, including developing nations. Correspondingly, their representation in various medical conditions is also on the rise [1]. In cases of trauma, elderly patients (EPs) are overrepresented, and these numbers are expected to rise further. This highlights the need for updates in guidelines to ensure effective triage and specialized care [2].

Age is recognized as a crucial prognostic factor in trauma patients, along with trauma severity and comorbidities; however, age dichotomies have been found to be unreliable at times. This indicates the need for additional, easily obtainable markers to facilitate a more comprehensive assessment of impaired physiological reserve or frailty [1, 2].

Frailty has emerged as a more comprehensive assessment of functional reserves than age stratification alone. Notably, up to one-third of adults over 85 years old were found to be non-frail despite their advanced age. On the other hand, increased frailty is consistently associated with adverse outcomes following various stressor events such as cancer diagnosis, surgery, infection, and trauma [1]. However, the measurement of frailty is a relatively complex process involving the use of several scoring modalities and specialized equipment for assessments such as grip strength [3].

Sarcopenia, characterized by the progressive loss of skeletal muscle mass, strength, and power, is a key component of frailty [1, 3]. It overlaps with frailty scores and clinical outcomes. Various methods can be used to assess sarcopenia, but currently, there is no consensus on a gold standard method. Proposed methods include measuring psoas muscle (PM) thickness – PMT, PM index, and skeletal muscle mass at different thoracic and lumbar vertebral levels, all showing strong correlations with different outcomes [4–6]. Additionally, diaphragm thickness (DT) has been associated with advanced age and adverse outcomes, such as prolonged intubation, both clinically and in experimental settings [7]. While some sarcopenia measurements require specialized software, the measurement of DT *via* computerized tomography (CT) scans has been shown to be reproducible and clinically relevant [8].

Thoracic trauma (TT) in the elderly is expected to become a significant public health burden, both as isolated cases and as part of multi-trauma situations. TT places additional stress on the physiologic reserve of patients due to impaired respiratory dynamics, clearance of secretions, pain, and restricted mobility. Therefore, EPs with TT may represent a particularly vulnerable population for worse outcomes.

The aim of this study was to assess DT and PMT and evaluate their association with clinical outcomes and overall mortality in patients presenting to the emergency room (ER) with TT.

Methods

All thoracic surgery consultations from the ER between November 2015 and January 2021 were collected from hospital electronic medical records (EMR). Trauma-related consultations were identified using both the contents of consultation requests and the International Classification of Diseases (ICD) coding information. Cases were confirmed through clinical and radiological data from the EMR before inclusion. Patients under active cancer treatment and those with injuries directly affecting the measurement area (e.g., retroperitoneal hematoma) were excluded. Mortality data were obtained from the central health ministry death registry, which is also integrated into the hospital EMR. EPs were defined as those aged > 65 years.

The study design is non-interventional and, it was conducted with the approval of the Ethics Committee of the Istanbul Medeniyet University Goztepe Education and Research Hospital (No. 2021/0051, from January 27, 2021). All patients consented to using their anonymized data for scientific purposes.

Demographic information, disposition type (admission, admitting department, discharge from the ER), length of hospital stay, type of thoracic injury, surgical procedures, overall mortality, and survival after the ER presentation were recorded.

All multi-slice thoracic and abdominal CT examinations were conducted using a 64-detector CT scanner (GE Optima CT660 GE Healthcare, Milwaukee, WI) with or without intravenous contrast medium, employing a trauma protocol. The CT image data were collected using a GE system equipped with a 512 × 512 matrix detector.

Helical scanning was performed in the supine position without gantry angulation, covering the region from the lung apices to the symphysis. Images were acquired with a 24 × 1.2 mm acquisition, slice collimation of 1.2 mm, slice width of 2.5 mm, pitch of 0.98, 120 kV, and 75 mAs. Axial imaging data were post-processed using a GE workstation (GE Healthcare, Milwaukee, Wisconsin, USA), and 1.25 mm coronal and sagittal reconstructions were generated. Chest and abdominal CT scans were retrospectively re-evaluated, and measurement data were obtained by a radiologist (board-certified with 15 years of experience) who was blinded to the clinical data.

PMT was defined as the largest transverse diameter of PM perpendicular to the longest diameter (anterior-posterior oblique) of PM at the level of the transverse process of the third lumbar vertebra. Maximum DT at the level of the origin of the celiac artery, identified as the most reliable single measurement point on axial CT images, was performed (Figure 1). PMT and DT were measured bilaterally using the Radx PACS system (Simplex Radx 3D).

The data were analyzed using SPSS 23.0 software. Mean, standard deviation, and median values were calculated as appropriate. The distribution of variables was assessed using the Shapiro-Wilk test. The Mann-Whitney *U* test was employed for non-parametric testing. The Chi-Square test was utilized for quantitative assessment when conditions were met; otherwise, Fisher's exact test was performed. A p-value < 0.05 was considered statistically significant. Cox regression analysis was conducted to ascertain the relationship between different variables and survival.

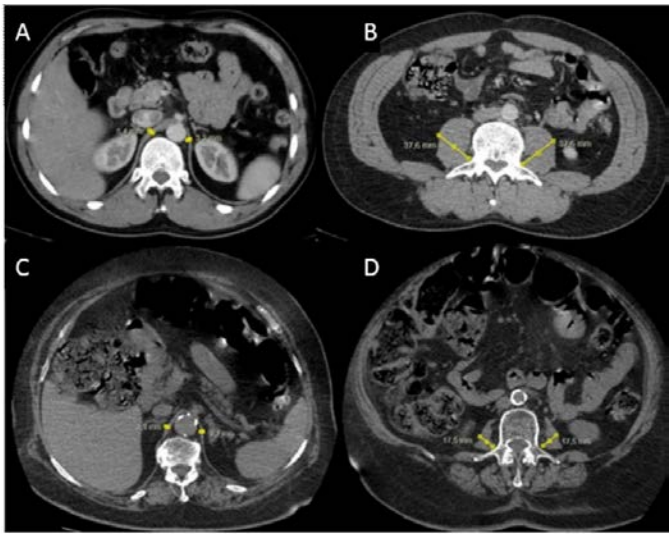


Fig. 1 – Axial contrast-enhanced computed tomography images of 34-year-old male (A, B) and 74-year-old female (C, D) patients showing measurements of maximum diaphragm thickness (A, C) at the celiac artery origin level and psoas muscle diameter (B, D) at the level of L3 vertebra (marked by yellow arrows).

Results

A total of 394 thoracic surgery consultations were identified in the ER due to trauma between November 2015 and January 2021. Of these cases, 129 involved EPs aged 65 years or older. Patient characteristics are shown in Table 1. There was a statistically significant difference between the appearance of pneumothorax and pulmonary contusion. However, the distribution of hemothorax, sternal fracture, and overall multi-trauma rates were comparable between EPs and non-EPs. EPs were less likely to be admitted to in-patient wards, but the need for intensive care was similar. The distribution of types of in-patient wards and length of hospital stay in case of admission are summarized in Table 1.

Table 1

Characteristics of patients with thoracic trauma

Characteristic	Patients			*p*-value
	total (n=394)	elderly (n=129)	non-elderly (n=265)	
Age (years)	51.6 ± 21.8	77.6 ± 8.1	38.9 ± 13.7	n/a
Gender (m/f)	280/114	67/62	213/52	0.000
Multitrauma (y/n)	107/287	29/100	78/187	0.14
Inpatient admission (y/n)	228/165	53/75	175/90	< 0.001
Intensive care unit stay (y/n)	45/349	14/115	31/234	0.80
Length of hospital stay (days)	7.7 ± 7.9	6.9 ± 5.7	7.9 ± 8.5	0.69
Admission				
orthopedics (y/n)	35/359	7/122	28/237	0.09
neurosurgery (y/n)	27/369	9/120	18/247	0.94
general surgery (y/n)	22/372	0/129	22/246	0.001
Pneumothorax (y/n)	97/297	15/114	82/183	0.001
Hemothorax (y/n)	87/307	27/102	60/205	0.70
Sternum facture (y/n)	16/378	6/123	10/255	0.67
Pulmonary contusion (y/n)	59/335	8/121	51/214	0.001
Thoracic procedure (y/n)	64/330	9/120	55/210	0.001
Non-thoracic procedure (y/n)	18/376	5/124	13/252	0.64
Overall mortality (y/n)	76/318	57/72	19/246	< 0.001
Overall survival (estimate, month)	61.1 ± 1.3	43.9 ± 2.84	69.0 ± 1.1	< 0.001
Diaphragm thickness (mm)	4.3 ± 1.3	3.8 ± 1.14	4.5 ± 1.3	< 0.001
Psoas muscle thickness* (mm)	28.4 ± 7.7	21.9 ± 6.6	30.6 ± 6.7	< 0.001

n/a – not applicable; n – number; m/f – male/female; y/n – yes/no.
Values are given as numbers or mean ± standard deviation.
***59 elderly and 59 non-elderly patients did not have psoas muscle thickness data as they did not undergo an abdominal computed tomography scan during the emergency room care.**

EPs were less likely to undergo a thoracic procedure (such as tube thoracostomy or rib fixation) compared to their non-elderly counterparts. However, the rate of non-thoracic procedures (such as orthopedic or general surgery) was comparable between the two groups. While DT was comparable between EPs with and without thoracic procedures, PMT was significantly lower in those who underwent thoracic procedures (3.7 ± 0.9 mm vs. 3.8 ± 1.1 mm, $p = 0.82$ for DT; 4.2 ± 8.3 mm vs. 12.4 ± 12.0 mm, $p = 0.048$ for PMT).

For EPs, both DT and PMT were higher in those who had undergone non-thoracic operations compared to those who had not (5.3 ± 0.81 mm vs. 3.7 ± 1.11 mm, $p = 0.003$ for DT; 25.5 ± 11.2 mm vs. 11.3 ± 11.7 mm, $p = 0.026$ for PMT).

Overall survival was significantly worse in the EP population compared to non-EPs (43.9 vs. 69.0 months, $p = 0.00$) (Figure 2). Further analysis revealed that ICU admission, orthopedic admission, rib fractures, hemothorax, and gender were related to overall survival among the entire study population (log-rank test). However, after age stratification, none of these factors were found to be significantly associated with survival in the EP group (Table 2).

The mean PMT and DT were found to be lower in EPs than in non-EPs (3.8 ± 1.14 mm vs. 4.5 ± 1.3 mm, $p < 0.001$ for PMT; 21.9 ± 6.6 mm vs. 30.6 ± 6.7 mm, $p < 0.001$ for DT). Both PMT and DT were found to be related to overall survival among the whole study population and the elderly age group. However, the same relationship was not observed for the younger cohort (Table 3). DT and PMT according to subgroups (survival in relation to age) are shown in Table 4. Within EPs, the average PMT had moderate sensitivity and specificity for predicting death compared to the average DT (area under the curve – AUC = 0.603, $p = 0.045$ for PMT vs. AUC = 0.455, $p = 0.379$ for DT) (Figure 3).

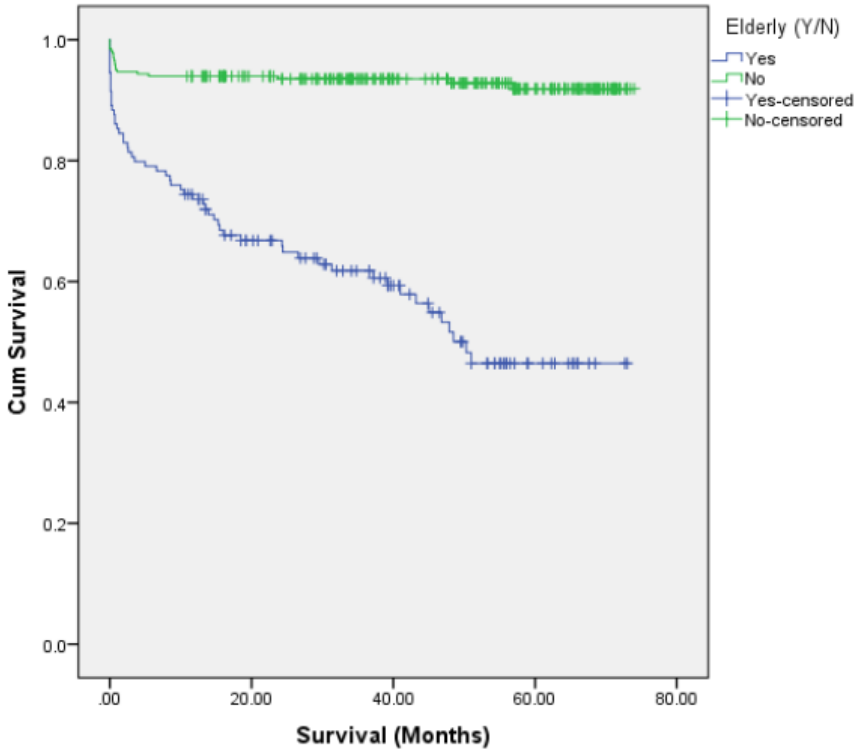


Fig. 2. – Kaplan-Meier plots for overall survival in patient population according to age group. y/n – yes/no.

Table 2

Kaplan-Meier survival analysis for elderly patients

Parameter	Survival estimate error	95% CI	*p*-value
Gender (m/f)	42.8 ± 3.6/43.7 ± 4.1	35.0–49.1/35.6–51.9	0.98
Multitrauma (y/n)	39.3 ± 5.8/44.6 ± 3.1	27.9–50.7/38.3–50.8	0.67
Intensive care unit stay (y/n)	28.8 ± 7.8/45.7 ± 2.9	13.4–44.1/39.8–51.5	0.059
Inpatient admission (y/n)	41.9 ± 4.5/45.8 ± 3.6	33.0–50.8/38.7–52.9	0.53
Neurosurgery admission (y/n)	44.9 ± 9.0/43.9 ± 2.9	27.2–62.7/38.1–49.7	0.93
Pneumothorax (y/n)	37.4 ± 8.9/44.6 ± 2.9	19.9–55.0/38.8–50.5	0.42
Hemothorax (y/n)	38.0 ± 4.8/44.1 ± 3.2	28.4–47.6/37.8–50.4	0.86
Rib fracture (y/n)	45.5 ± 3.0/30.8 ± 7.0	39.6–51.4/17.1–44.6	0.15
Pulmonary contusion (y/n)	25.4 ± 8.5/44.8 ± 2.9	8.7–42.1/39.1–50.5	0.19
Thoracic procedure (y/n)	33.4 ± 9.8/44.4 ± 2.9	14.0–52.8/33.6–50.1	0.58

CI – confidence interval. Values are given as mean ± standard deviation.

Table 3

Kaplan-Meier survival analysis for non-elderly patients

Parameter	Survival estimate error	95% CI	*p*-value
Gender (m/f)	68.4 ± 1.3/69.5 ± 1.7	65.8–70.9/66.1–72.9	0.29
Multitrauma (y/n)	61.1 ± 2.6/70.7 ± 1.0	58.9–69.2/68.6–72.8	0.019
Inpatient admission (y/n)	62.7 ± 1.4/70.7 ± 1.5	64.4–70.0/67.6–73	0.22
Intensive care unit stay (y/n)	61.4 ± 4.9/70.0 ± 1.0	52.7–70.2/67.9–72.1	0.006
Neurosurgery admission (y/n)	69.4 ± 1.4/68.8 ± 1.1	66.5–72.3/66.5–71.1	0.75
Pneumothorax (y/n)	68.0 ± 1.9/69.0 ± 1.3	64.1–71.8/66.4–71.6	0.91
Hemothorax (y/n)	61.4 ± 3.4/70.7 ± 0.9	54.6–68.2/68.9–72.6	< 0.001
Rib fracture (y/n)	67.3 ± 1.5/70.8 ± 1.2	64.1–70.4/68.3–73.2	0.038
Pulmonary contusion (y/n)	67.3 ± 2.7/69.1 ± 1.2	61.9–72.6/66.8–71.5	0.86
Thoracic procedure (y/n)	62.8 ± 2.7/69.6 ± 1.1	57.5–68.1/67.3–71.9	0.20

CI – confidence interval. Values are given as mean ± standard deviation.

Table 4

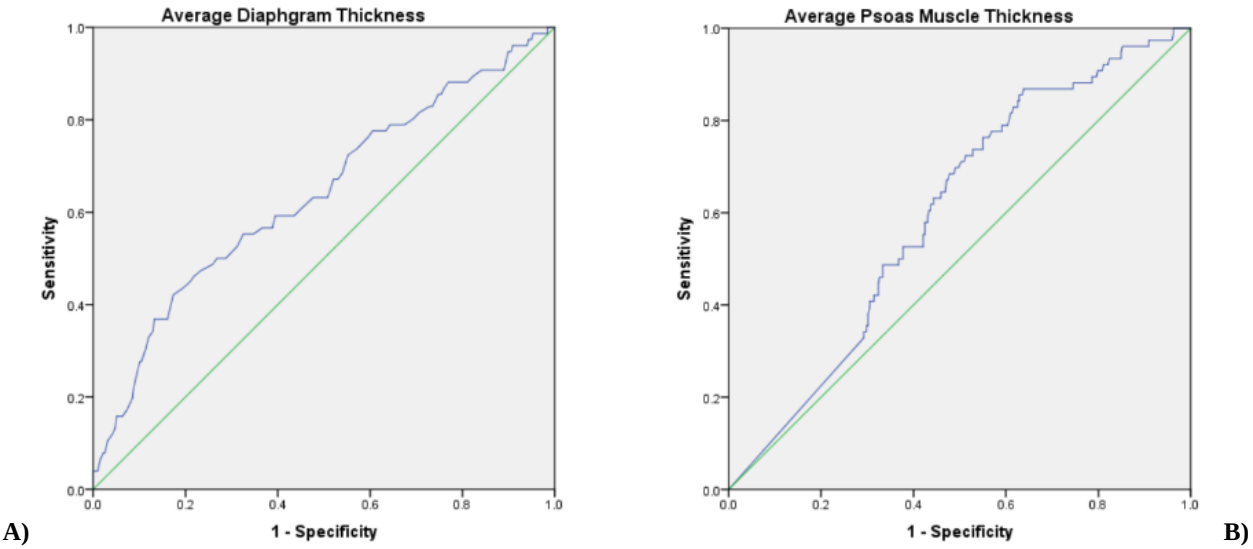
Diaphragm and psoas muscle thickness according to subgroups

Parameter	Alive	Exitus
Diaphragm thickness (mm)		
elderly	4.0 ± 1.19**	3.57 ± 1.0**
non-elderly	4.5 ± 1.3***	4.6 ± 1.4***
Psoas muscle thickness* (mm)		
elderly	10.9 ± 11.9	13.1 ± 12.1
non-elderly	23.6 ± 14.3	26.7 ± 10.7

Values are given as mean ± standard deviation.

***59 elderly and 59 non-elderly patients did not have psoas muscle thickness data as they did not undergo an abdominal computed tomography scan during the emergency room care; ** Cox regression analysis *p*-value was 0.015 (Exp(B) = 0.72, 95% CI = 0.56–0.93); *** Cox regression analysis *p*-value was 0.07 (Exp(B) = 1.04, 95% CI = 0.76–1.43).**

Exp(B) – odds ratio.



A) **B)**

Fig. 3 – Receiver operating characteristic curves for average diaphragm thickness (A) and psoas muscle thickness (B) in relation to overall mortality.

Discussion

TT poses a significant public health challenge, especially in the elderly population. As life expectancy and the proportion of elderly individuals steadily increase, the incidence of trauma among the elderly is expected to rise accordingly. This trend is not exclusive to trauma cases; the unique needs of EPs have been acknowledged across various medical specialties and interventions. Discussions on this topic emphasize that while age is an important

factor, it must be evaluated within the broader context of general frailty [1].

Frailty itself can be challenging for universal screening especially in non-acute outpatient settings [9]. Parameters like grip strength require specialized equipment, while others, like the assessment of walking speed, may be difficult to accommodate in the ER or inpatient settings [10]. On the other hand, sarcopenia has been found to correlate with the presence and severity of frailty and has been discussed as a negative prognostic risk factor in various contexts [4, 11–13]. For instance, sarcopenia, as measured by the lumbar (L)3-total psoas area (TPA)/vertebral body area (VBA) – L3-TPA/VBA technique on CT, was found to be a worse prognostic indicator for spinal surgery performed for metastatic lesions, whereas frailty assessment failed to predict adverse outcomes in this patient population [4]. Additionally, sarcopenia defined using PM area as a surrogate marker was a stronger predictive factor for suboptimal outcomes after spinal metastasis surgery compared to other well-known scoring systems such as the Karnofsky score [5].

Age bias in patient selection for surgery has been a topic of discussion, particularly in oncologic cases. EPs undergoing lung resection often face higher mortality and morbidity rates and lower survival benefits [14]. However, this issue could potentially be addressed by establishing high-volume centers equipped with multidisciplinary care and offering minimally invasive surgical techniques [15, 16]. In both oncologic and non-oncologic contexts, EPs have been observed to receive less aggressive treatment, such as forgoing surgery for neoplastic and non-neoplastic indications or adjuvant chemotherapy, leading to suboptimal outcomes. Despite evidence suggesting that factors beyond age alone influence these outcomes, there is still a tendency towards age-based classification rather than a more holistic approach [17–21]. In our study, we found that EPs undergoing non-thoracic post-traumatic operations tended to have preserved muscle mass, possibly indicating a surgical selection bias favoring less frail patients, which could lead to better short-term outcomes. However, this pattern was not observed for thoracic procedures, which mainly included tube thoracostomy and video-assisted thoracic surgery for hemostasis and lung expansion. These procedures are often more time-sensitive than the non-thoracic operations captured in our database, such as long bone fixation or vertebral instrumentation.

Life expectancy steadily increased in both developed and developing countries. For instance, the average life expectancy for individuals above 65 years is currently estimated to be 20–30 years longer in the United Kingdom [20]. However, our observations in this article indicate that EPs with TT continue to face an increased risk of mortality compared to the crude death rate for their demographic group [21–23]. This increased risk persists even though these patients were initially well enough to be discharged from the ER after observation or an inpatient stay. The overall two-year survival rate for EPs was 82%, despite our study excluding patients receiving treatment for malignancy.

Decreased DT has been identified as a useful marker for predicting difficulty in weaning from invasive mechanical ventilation [24, 25]. It has also been weakly associated with peripheral muscle wasting in the acute term [24]. In chronic diseases such as autoimmune conditions [26], chronic renal failure [27], muscular degeneration [28], and chronic obstructive pulmonary disease - COPD [29], changes in DT and morphology have been documented and linked to functional impairment, mortality, and morbidity. Similar relationships have been observed for PM measurements. Therefore, in this study, we focused on DT and PMT measured during post-trauma diagnostic work-up CT scans of these patients to gather additional information.

CT evaluation of these parameters has been shown to be reliable and reproducible in the literature [30, 31], requiring no additional resources beyond those already needed for the standard of care. Our findings suggest that although EPs, on average, have thinner diaphragms, subgroup analysis within the elderly population still revealed significant associations with mortality risk. Thus, DT can serve as a useful surrogate marker for frailty/sarcopenia. Further studies on larger populations are warranted to assess its full prognostic potential, as this measurement is straightforward to obtain and requires minimal additional effort, resources, or testing beyond the current clinical work-up protocols.

The limitations of this study include a relatively small number of cases and the fact that it was conducted at a single center. Although mortality data is automated and updated in real-time across the universal single-payer social security system, accurate determination of mortality cause was challenging in a retrospective setting. Additionally, PMT was not evaluated in all patients since there was no intervention beyond the standard of care assessment.

Conclusion

Elderly patients presenting to the emergency room with thoracic trauma face a higher risk of adverse long-term prognosis compared to the average population. This subgroup may benefit from screening for probable causes of mortality. Defining this subgroup could be enhanced by incorporating surrogate sarcopenia markers, such as diaphragm thickness or psoas muscle thickness, which can be easily obtained without additional testing beyond standard care in a trauma setting. Further studies with larger case numbers are needed to determine optimal cutoff points or develop scoring systems to identify vulnerable patients for referral to rehabilitation, social services for mobility issues, medical optimization, or cancer screening.

Conflict of interest

The authors declare no conflict of interest.

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Received on May 26, 2024
Revised on October 8, 2024
Revised on November 18, 2024
Accepted on November 27, 2024
Online First January 2025

ORIGINAL ARTICLE

UDC: 618.19-006-07
DOI: https://doi.org/10.2298/VSP240606005N

Contrast-enhanced mammography in breast cancer screening: our experiences

Kontrastna mamografija u skriningu karcinoma dojke: naša iskustva

Dijana Nićiforović*†, Marijana Basta Nikolić*†, Zorka Drvendžija†, Olivera Nikolić*†, Aleksandra Mijatović*, Sonja Lukač*, Sanja Stojanović*†

***University Clinical Center of Vojvodina, Center for Radiology, Novi Sad, Serbia;**
†University of Novi Sad, Faculty of Medicine, Novi Sad, Serbia

Abstract

Background/Aim. Breast cancer is a leading global health concern. Contrast-enhanced mammography (CEM) presents a promising advancement in early breast cancer detection, excelling in sensitivity, specificity, and cost-effectiveness. The aim of the study was to assess the overall diagnostic efficacy of CEM in breast cancer screening, particularly in distinguishing benign from malignant lesions in dense breasts. **Methods.** A two-year retrospective study was conducted at the Center for Radiology, including a total of 279 women undergoing CEM following standard mammography. **Results.** CEM demonstrated high sensitivity (92.4%), specificity (75.1%), and a noteworthy negative predictive value of 97.0%, significantly reducing unnecessary biopsies. **Conclusion.** CEM is a valuable screening tool, offering enhanced diagnostic capabilities and the potential to reduce the number of unnecessary biopsies. It is particularly beneficial for patients with dense breasts or inconclusive traditional mammography results.

Key words:
breast cancer; diagnosis; differential diagnosis; mammography; mass screening; sensitivity and specificity; ultrasonography, mammary.

Apstrakt

Uvod/Cilj. Karcinom dojke je vodeći globalni zdravstveni problem. Kontrastna mamografija (KM) koju odlikuje osetljivost, specifičnost i ekonomičnost predstavlja obećavajući napredak u ranom otkrivanju karcinoma dojke. Cilj rada bio je da se utvrdi ukupna dijagnostička efikasnost KM u skriningu karcinoma dojke, posebno u razlikovanju benignih od malignih lezija dojki čije tkivo je „gusto". **Metode.** Retrospektivnom studijom, sprovedenom tokom dve godine u Centru za radiologiju, obuhvaćeno je 279 žena, kojima je posle standardne mamografije urađena KM. **Rezultati.** Primenom KM utvrđeni su visoka osetljivost (92,4%), specifičnost (75,1%) i značajna negativna prediktivna vrednost od 97,0%, što je značajno smanjilo broj nepotrebnih biopsija. **Zaključak.** KM je dragocena alatka za skrining, koja omogućava poboljšane dijagnostičke mogućnosti i potencijal da se smanji broj nepotrebnih biopsija. Posebno je korisna za bolesnice čije dojke imaju „gusto" tkivo ili kod neuverljivih rezultata tradicionalne mamografije.

Ključne reči:
dojka, neoplazme; dijagnoza; dijagnoza, diferencijalna; skrining; senzitivnost i specifičnost; ultrasonografija, dojka.

Introduction

Breast cancer (BC) is a leading cause of cancer-related death among women globally. It presents a significant challenge in early detection and treatment and remains one of the most prevalent cancers worldwide, significantly affecting women's health across all demographics. According to the World Health Organization (WHO), BC accounts for approximately 12% of all new annual cancer cases globally [1]. The American Cancer Society reports that in the United States alone, an estimated 287,850 new cases of invasive BC were expected to be diagnosed in women in 2021, alongside 51,400 new cases of non-invasive (*in situ*) BC [2]. These statistics highlight the widespread nature of this disease and the critical importance of early detection and effective treatment strategies. The five-year relative survival rate for localized BC is 99%. However, this rate drops to 86% for regional spread (to nearby structures or lymph nodes) and plummets to 28% for distant spread (metastasized cancer) [3]. These figures underscore the urgent need for access to early treatment and advancements in diagnostic technologies, such as contrast-enhanced mammography (CEM), to improve early detection rates, particularly in

Correspondence to: Dijana Nićiforović, University of Novi Sad, Faculty of Medicine, Hajduk Veljkova 3, 21 000 Novi Sad, Serbia.
E-mail: dijana.niciforovic@mf.uns.ac.rs

populations at higher risk, including those women with dense breast (DB) tissue.

Traditional mammography has been the cornerstone of BC screening for decades, significantly contributing to reduced mortality rates through early detection. However, its sensitivity is compromised in women with DB tissue, where the fibroglandular tissue can obscure cancerous lesions, leading to a higher rate of missed diagnoses [4]. Despite its widespread use, the limitations of mammography highlight the need for complementary or alternative imaging techniques to enhance detection rates, especially in this subgroup of patients. While breast ultrasound (US) is frequently used as an adjunct to mammography, increasing the detection rate of BCs, particularly in DBs, it also has a higher false-positive rate, leading to more frequent and often unnecessary biopsies [5].

Breast magnetic resonance imaging (MRI) offers high sensitivity and is particularly useful for screening high-risk populations and assessing the extent of disease in known cancer cases. Its ability to provide detailed images without ionizing radiation is a significant advantage. However, the high cost, limited availability, and contraindications for some patients (e.g., those with certain implants or claustrophobia) restrict its routine use in the general population [6].

CEM represents a significant advancement in breast imaging technology, offering enhanced diagnostic capabilities, particularly in DB tissue [7]. CEM utilizes a dual-energy imaging technique performed after the intravenous administration of an iodinated contrast agent [8]. The process involves acquiring low- and high-energy images in rapid succession: the low-energy images are comparable to standard mammography, while the high-energy images are more sensitive to the contrast agent [9]. This dual-energy approach allows radiologists to isolate and highlight areas with increased contrast uptake, typically indicative of malignant tissue due to higher blood supply [10].

CEM has demonstrated its utility in detecting cancers not visible on standard mammograms, distinguishing benign from malignant lesions, and ultimately reducing unnecessary biopsies [11]. Besides detecting cancers in DBs and high-risk patients, another important indication for CEM is its use in the preoperative assessment of known BC to determine accurately the extent of disease. CEM has proven effective in identifying multifocal, multicentric, and contralateral diseases, which are critical factors in treatment planning [12]. Additionally, CEM is useful in monitoring responses to neoadjuvant chemotherapy, allowing clinicians to assess tumor response and residual disease, influencing surgical decisions and further treatment planning [11].

Compared to traditional digital mammography (DM), CEM offers superior sensitivity and specificity, especially in DB tissue. This is crucial for early BC detection, leading to potentially better treatment outcomes [13]. It also aids in differentiating benign from malignant lesions, which can reduce unnecessary procedures and patient anxiety [14]. Compared to breast MRI, CEM is more cost-effective, widely accessible, and less time-consuming, making it an attractive alternative in many healthcare settings [12]. Both CEM and breast MRI play vital roles in BC imaging. MRI remains the gold standard for screening high-risk populations and evaluating DB tissue, offering unparalleled sensitivity for detecting small lesions, especially in women with DBs. However, MRI can be more expensive and less widely available than CEM and requires more time and specialized equipment.

While it involves radiation exposure, CEM is faster, more cost-effective, and widely available. It has been shown to have higher specificity than breast MRI, reducing the likelihood of false positives and unnecessary biopsies [15]. Moreover, CEM can be more comfortable for patients since it does not require the prolonged prone positioning and confinement associated with MRI. In patients who cannot undergo MRI due to contraindications, such as claustrophobia, the presence of certain implants, or limited availability, CEM can serve as a valuable alternative [16].

Despite its many advantages, CEM does come with limitations. While it involves additional radiation exposure compared to standard mammography, the risk is generally considered low, though it remains a factor for patients requiring frequent imaging [8]. Using iodinated contrast agents can cause allergic reactions in some individuals, though severe reactions are rare [17]. Furthermore, CEM requires specialized equipment and trained personnel, and its accessibility can be limited in certain regions due to the costs involved [18]. Patients with impaired renal function are at higher risk for nephropathy, given the use of iodinated contrast agents [19].

The aim of the study was to assess the capability of CEM in decreasing the frequency of biopsies following screening recalls and to evaluate the overall diagnostic value of CEM in BC screening.

Methods

This retrospective study was conducted at the Center for Radiology, University Clinical Center of Vojvodina, Serbia, between December 2021 and December 2023. The study included 279 women who underwent CEM following standard 2D mammography. The study was approved by the Ethics Committee of the University Clinical Center of Vojvodina (No. 00–43, February 9, 2024). Participants were selected based on their recall from the initial national and opportune screening mammography, indicating the need for further evaluation. All CEM procedures were performed using the Hologic Selenia® Dimensions® 3D machine. Standard protocol in image acquisition was followed: after a standard 2D mammography in mediolateral oblique and craniocaudal projections of both breasts, which urged further workup, CEM was performed in all patients, with intravenous application of a low-osmolarity iodine-based contrast material (Omnipaque™) in the total volume of 1.5 mL/kg of body weight (not more than 150 mL) with the use of an injector, with an injection rate of 2–3 mL/sec, followed by a saline flush. Image acquisition began about 2–2.5 min after contrast material injection, in standard craniocaudal and mediolateral views, first of the symptomatic breast, followed by the presumably healthy breast. Both low- and high-energy images were obtained in quick succession while the breast remained compressed. The whole image acquisition process lasted for approximately 6 to 7 min in total. The images were described using Breast Imaging Reporting & Data System (BI-RADS)

classification, with results BI-RADS ≥ 3 considered positive and BI-RADS < 3 negative. Participants initially underwent standard 2D mammography. Based on these results, CEM was performed for further assessment. In cases where CEM indicated potential malignancies, patients were referred for biopsy. Core biopsy was the method of choice whenever we visualized the lesion. If that was not the case, the patient was transferred to vacuum-assisted biopsy. Eventually, all the patients were graded based on BI-RADS. The primary outcomes set for the study were the detection rate of BC using CEM and the reduction in biopsy rates post-CEM.

Statistical analysis

Statistical analyses were performed to compare the diagnostic efficacy of CEM against traditional methods and to evaluate the impact of CEM on the decision-making process regarding biopsies. From statistical analyses, we utilized cross-tabulation, binary logistic regression, and receiver operating characteristic (ROC) analysis, and determined sensitivity, specificity, and negative predictive value.

Results

A total of 279 women who underwent CEM, standard mammography, and US were analyzed. The average age of all participants was 59 years, with the oldest one being 81 years old and the youngest 40 years old.

The mammography findings were pathological (BI-RADS ≥ 3) in 249 women. A BI-RADS score of 2 was found in 30 women, but due to having DBs, they were referred to additional breast US. US findings were pathological (BI-RADS ≥ 3) in 150 women, while the remaining 129 women had normal results (Figure 1).

Due to insufficient agreement between mammographic and US findings and the need to determine whether biopsies were truly necessary for changes characterized by BI-RADS ≥ 4, CEM was performed in all 279 patients. Among them, 114 exhibited changes in CEM that raised suspicion of malignant alterations, while 165 women had normal CEM findings (negative CEM, BI-RADS < 3). Employing CEM in these patients prevented unnecessary biopsies that would otherwise be indicated by mammography or US (Figure 1). Out of the 114 patients with positive CEM findings, biopsies were conducted for 107 patients. For seven patients with BI-RADS 3 lesions, radiologists opted for monitoring and follow-up after three months. Core biopsy was performed in 86 women and vacuum-assisted biopsy in 23, with both biopsies conducted for two patients.

All patients with negative CEM were followed up on six-month intervals and showed stability of findings. Histopathological findings revealed that 66 women had malignant changes, while 41 biopsied patients had benign changes. This determined that out of a total of 279 women, 66 had BC, and 213 had benign findings on the breasts (Table 1).

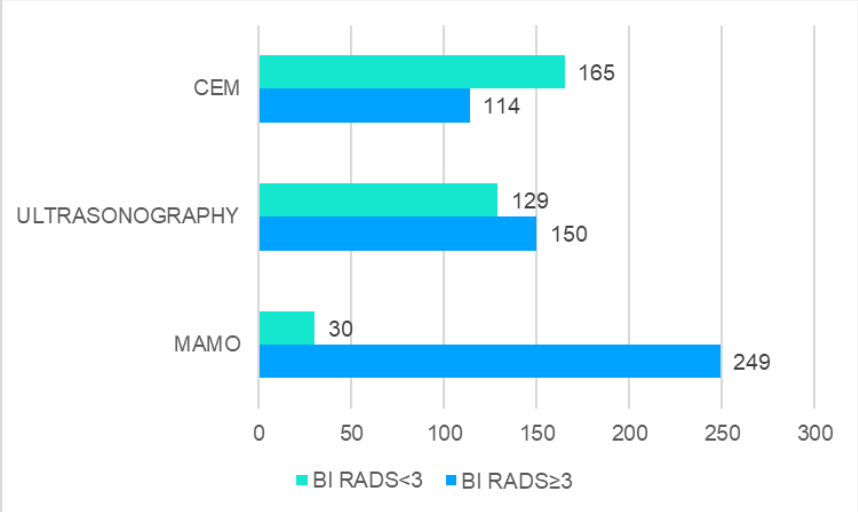

Fig. 1 – Structure of the examined group based on radiological imaging results. MAMO – mammography; CEM – contrast-enhanced mammography; BI-RADS – Brest Imaging Reporting Data System ≥ 3 considered positive; BI-RADS < 3 considered negative. All values are given as numbers.

Table 1

Correlation between breast findings (based on pathohistological and radiological imaging) and CEM findings

Parameter	BC	BBF	Total
CEM positive	61	53	114
CEM negative	5	160	165
Total	66	213	279

CEM – contrast-enhanced mammography; BC – breast cancer; BBF – breast benign finding.
All values are given as numbers.

Out of the 114 women with positive CEM results, 61 were confirmed to have cancer (Table 1). However, 5 patients with cancer had normal CEM findings because they had ductal carcinoma *in situ*, presented as microcalcifications, with no enhancement on CEM or subtle enhancement that was misinterpreted as BC.

The sensitivity of CEM was 92.42%, specificity was 75.11%, positive predictive value (PPV) was 53.51%, and negative predictive value (NPV) was 96.97% (Table 2).

According to binary logistic regression results, significant predictors for the presence of BC were CEM, US, and age, with CEM being the strongest predictor. Conventional mammography findings were not statistically significant (Table 3). Persons with a positive CEM result were 60 times more likely to have BC than those with a negative CEM result (Exp(B) = 60.07). Through ROC analysis, we determined that, in terms of age, the cut-off value for the occurrence of BC was 55.50 years (Table 4, Figure 2).

Table 2

Diagnostic performance of CEM in detecting breast cancer

Measure	Value (%)
Sensitivity	92.42
Specificity	75.11
PPV	53.51
NPV	96.97

CEM – contrast-enhanced mammography; PPV – positive predictive value; NPV – negative predictive value.

Table 3

Prediction of the probability that a patient has breast cancer

Parameter	B	S.E.	Wald	*df*	Sig.	Exp(B)	95% CI for Exp(B)	
							lower	upper
Age	0.09	0.03	12.40	1	0.00	1.09	1.04	1.14
MAMO	1.23	0.84	2.15	1	0.14	3.43	0.66	17.86
US	1.77	0.48	13.60	1	0.00	5.87	2.29	15.03
CEM	4.09	0.65	39.29	1	0.00	60.07	16.69	216.16

MAMO – mammography; US – ultrasound; CEM – contrast-enhanced mammography; CI – confidence interval; Exp(B) – odds ratio.

Table 4

Cut-off value of age for the presence of breast cancer

Parameter	AUC	*p*	Cut-off	Sensitivity	Specificity
Age	0.59	0.03	55.50 years	82.80 %	63.00 %

AUC – area under the curve.

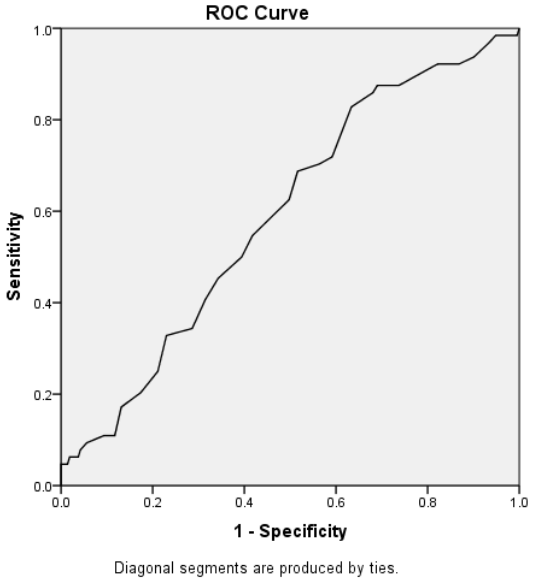

Fig. 2 – Receiver operating characteristic (ROC) curve analysis of age for the presence of breast cancer.

Discussion

The results of our study on the diagnostic performance of CEM in BC screening provide significant insights, particularly when compared to traditional mammography methods. Our findings indicate a high sensitivity (92.42%) and a reasonable specificity (75.11%) for CEM, alongside a PPV of 53.51% and an NPV of 96.97%. It is similar to the recent study showing a 95.4% sensitivity in cancer detection using CEM [20]. Additionally, the authors of the mentioned article also highlight the positive correlation between the intensity of the *post*-contrast enhancement of the suspicious lesion and the aggressiveness of the malignant process, which our study did not include but is a very interesting perspective worth further investigation.

Some authors state that CEM adoption is simple, especially for radiologists experienced in DM and MRI [12, 21]. The study published by Cheung et al. [13] states that an average of 75 CEM readings is sufficient for reaching a 90% probability of correct prediction.

This increased sensitivity is crucial in the context of BC screening, as it implies a greater likelihood of detecting cancer, especially in its early stages (Figures 3 and 4). The increased specificity of CEM also makes it a valuable tool in screening, particularly for DB tissues where mammography often falls short, mainly because of its ability to provide additional vascular imaging [22]. In a study involving 89 women with DBs and 100 lesions, CEM, in addition to mammography, showed improved sensitivity from 71.5% to 92.7%, along with specificity from 51.8% to 67.9% [13]. Another study reported that out of 14 cancers, CEM detected 13 (93%) cancers that were not seen at full-field DM in women with DBs [11]. Our study comprised only inconclusive mammographies that required additional work, and, therefore, we did not calculate the diagnostic performance of DM alone, as we assumed that these data would show unrealistic and incorrectly low sensitivity and specificity of DM alone. In this scenario in our study, DM findings were not statistically significant predictors for BC. The role of US in BC detection, especially in DBs, has been well documented [23]. Meta-analysis of 526 studies by Sood et al. [24] showed that US had

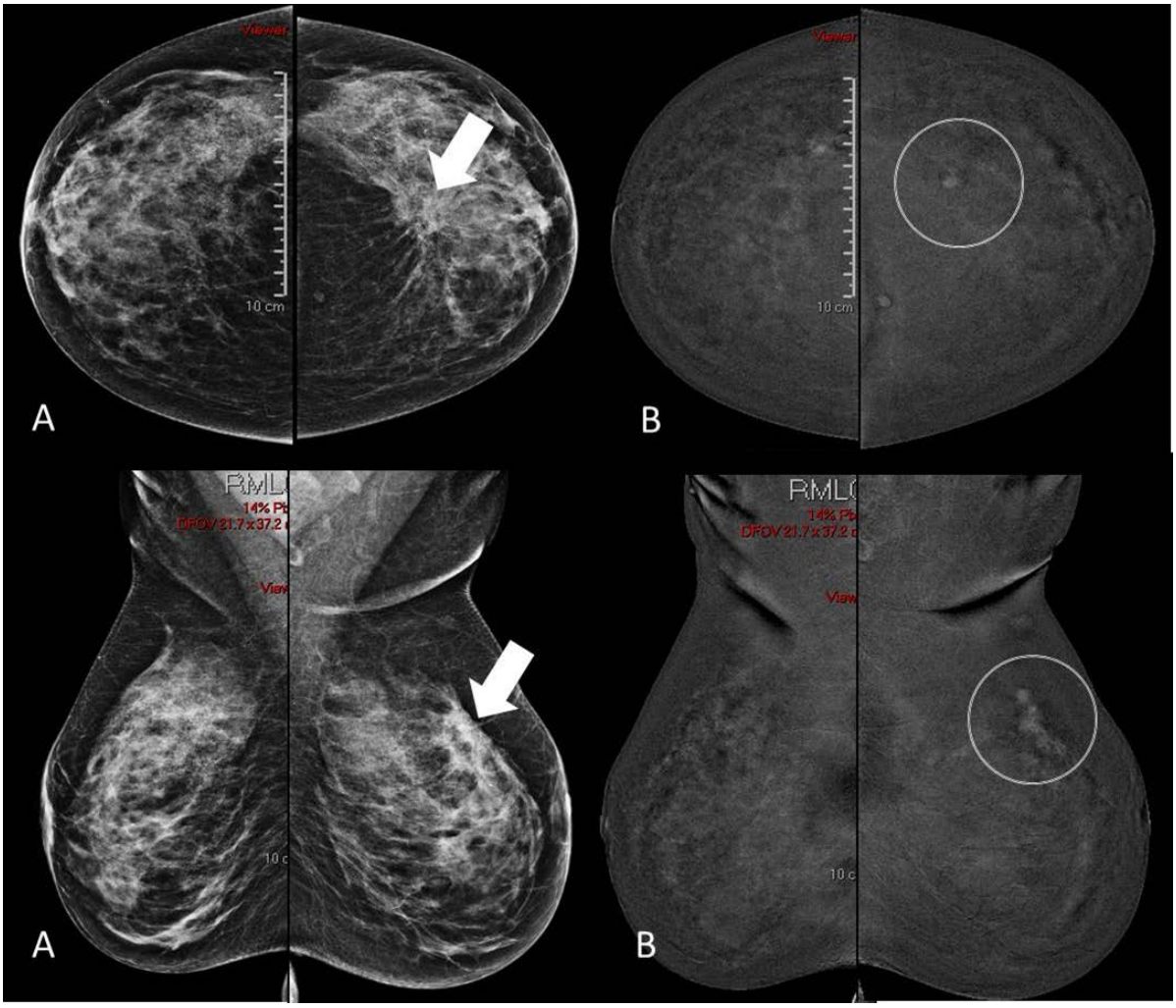

Fig. 3 – Digital mammography demonstrates architectural distortion at the junction of the upper quadrants of the left breast (white arrow) (A), which shows intense post-contrast enhancement on contrast-enhanced mammographic images (marked by white circle) (B). Histopathology following biopsy confirmed invasive lobular cancer grade 2.

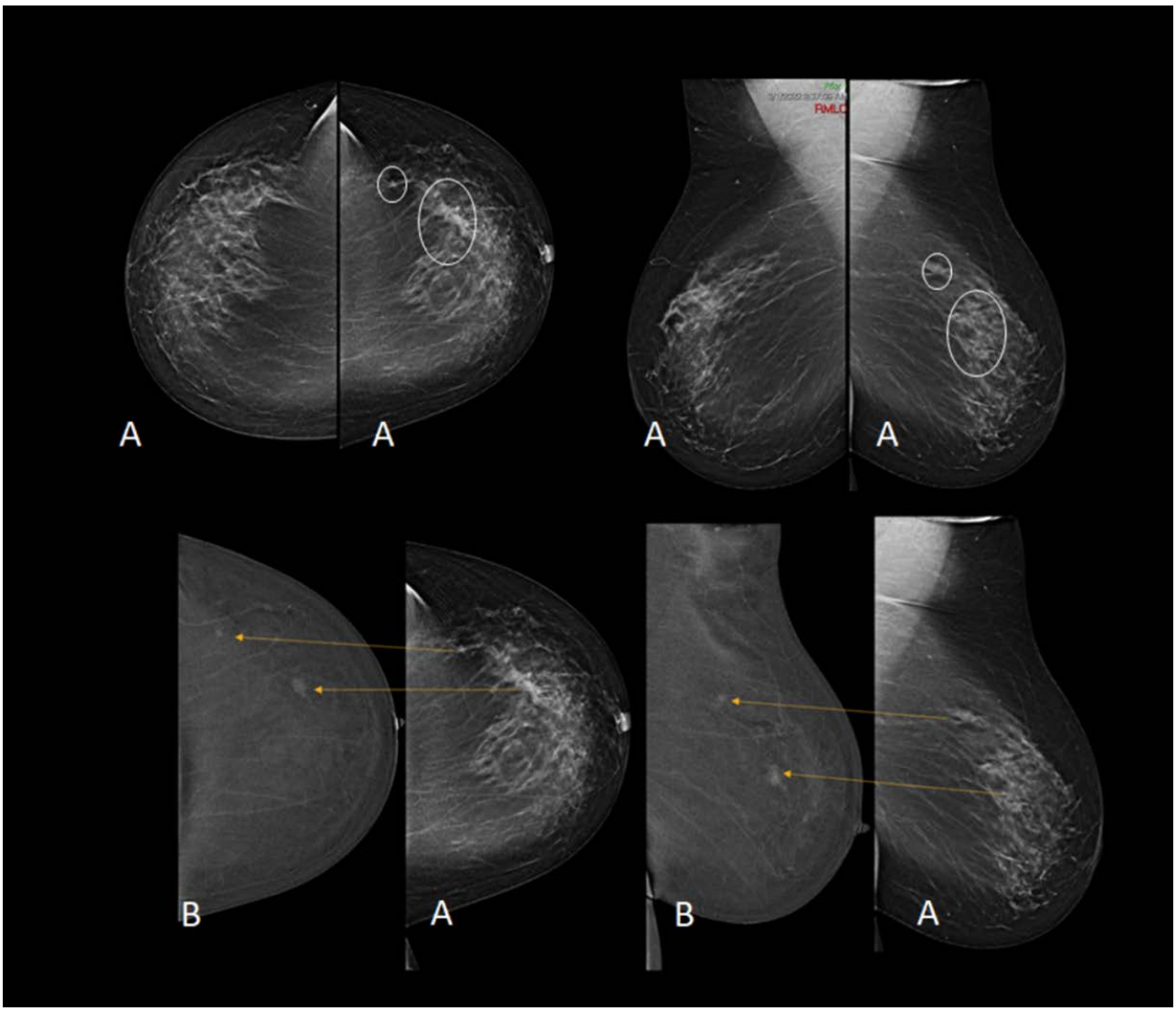

Fig. 4 – A) Digital mammography with tomosynthesis demonstrates architectural distortion in the upper lateral quadrant of the left breast, not depictable by ultrasound. A zone of focal asymmetry is also present in the axillary tail of the same breast (marked by a circle). B) Contrast-enhanced mammography demonstrates contract enhancement of both mammographically detected lesions (yellow arrows). Since the lesions were not visualized by ultrasound, a vacuum-assisted biopsy was performed confirming invasive ductal breast cancer no special type grade 2.

an overall pooled sensitivity, specificity, diagnostic odds ratio, PPV, and NPV (95% confidence interval – CI) of 80.1%, 88.4%, 30.7, 0.86, and 0.80, respectively, for the detection of BC. It is particularly beneficial as an adjunct to mammography for evaluating palpable abnormalities and clarifying indeterminate mammographic findings. US excels in differentiating solid from cystic masses and has proven effective in further investigating areas of concern detected on mammograms [25].

However, US also presents challenges, notably its operator-dependent nature, which can lead to variability in diagnostic performance. Its higher false-positive rate can lead to additional follow-up tests and biopsies, which may not be necessary with more definitive imaging techniques like CEM [26]. Our study showed increased sensitivity of CEM compared to US (92.42%), somewhat lower specificity of 75.11%, and PPV of 53.51%. The most significant advantage of CEM compared to US is the high NPV of 96.97%, which grants high confidence that no cancer is present when CEM is negative, thus allowing a significant decrease in follow-up and biopsy rates.

A study conducted in Korea highlighted that approximately 90% of cancers were detected using CEM, which was just marginally lower than MRI. Furthermore, the visibility of the tumor was superior using CEM compared with full-field DM or digital tomosynthesis for US-detected BCs [27].

Several studies have demonstrated a similar diagnostic performance of CEM to breast MRI along with other advantages, such as lower costs, the possibility of upgrading existing DM units, broader availability, and fewer contraindications [28]. In addition, a shorter learning curve, higher specificity, and NPV compared to breast MRI make CEM a solution tool for inconclusive findings on screening mammography limited by glandular density [29].

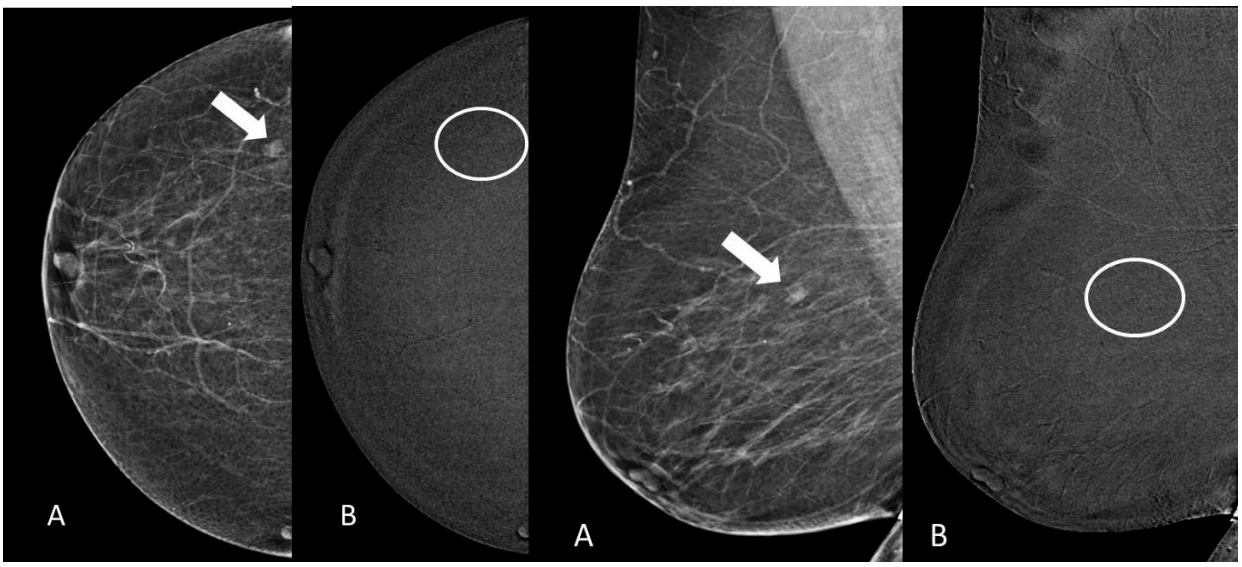

Fig. 5 – Digital mammography with tomosynthesis demonstrates a small lesion, with lobulated, somewhat indistinct margins in the upper lateral quadrant of the right breast (white arrow) (A). The lesion shows no enhancement on contrast-enhanced mammography (depicted by a white circle) (B), thus follow-up was recommended instead of the biopsy. The lesion remained stable on a 6-month follow-up examination.

In institutions like ours, lacking dedicated MRI-guided biopsy tools, CEM emerges as a valuable alternative that showcases superiority over traditional MRI for biopsy procedures. This inherent adaptability positions CEM as an efficient and pragmatic choice for biopsy procedures in settings without MRI-guided biopsy capabilities, providing a reliable and accessible solution for targeted tissue sampling in breast diagnostics [29].

This high NPV of 96.97% suggests that patients can be reassured with a high degree of confidence when CEM indicates no cancer. This aspect of CEM can be a significant advantage in clinical practice, reducing patient anxiety and the need for unnecessary biopsies [30, 31]. However, in our study, five patients with later proven cancer had negative CEM. In all five cases, histopathology confirmed pure ductal carcinoma *in situ*, which, according to the known data [32, 33], usually shows non-mass contrast enhancement but, in certain cases, may show no enhancement at all.

Our study highlighted the potential of CEM to reduce unnecessary biopsies. With 62.5% of women avoiding biopsies based on CEM findings (in 23 of them vacuum-assisted biopsy was performed), there is a clear indication that CEM can effectively discriminate between benign and malignant lesions (Figure 5). This reduction in biopsy rates is not only beneficial in terms of patient comfort and reducing healthcare costs but also in minimizing the risk of complications associated with invasive procedures. A recent prospective study observed a potential 16.4% net reduction of the biopsy rate that could be obtained using CEM [31].

Although the average age of all participants in our study was 59 years, based on the ROC curve analysis results, we observed that the cut-off value for the presence of BC was 55.5 years. This indicates a need for caution with women of this age group in our population and may facilitate easier decision-making regarding CEM, provided clear indications exist.

Conclusion

Our study supports the growing body of evidence that contrast-enhanced mammography is a valuable tool in breast cancer screening, offering high sensitivity and the potential to reduce unnecessary biopsies, together with significant performance simplicity and patient acceptance. As breast cancer screening continues to evolve, contrast-enhanced mammography stands out as a promising technology, particularly for patients with dense breast tissue or inconclusive traditional mammography results.

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Received on June 6, 2024
Revised on October 23, 2024
Revised on November 29, 2024
Accepted on December 11, 2024
Online First January 2025

ORIGINAL ARTICLE

UDC: 613.955/.96:616.89-008.441.3]:001.891
DOI: https://doi.org/10.2298/VSP240826003C

Validation and adaptation of the Serbian adaptation of the Marijuana Effect Expectancies Questionnaire among adolescents

Validacija i adaptacija srpske verzije upitnika *Marijuana Effect Expectancies Questionnaire* među adolescentima

Dušan Čanković*†, Bojana Dinić‡, Dalibor Bokan§, Snežana Ukropina†, Sonja Čanković*†

University of Novi Sad, *Faculty of Medicine, ‡Faculty of Philosophy, Department of Psychology, Novi Sad, Serbia; †Institute of Public Health of Vojvodina, Novi Sad, Serbia; §Secondary Medical School "April 7th", Novi Sad, Serbia

Abstract

Background/Aim. Expectancies about the effects of cannabis have been related to the onset and frequency of its consumption. One of the most used instruments to measure cannabis effect expectancies is the Marijuana Effect Expectancy Questionnaire (MEEQ). The aim of this study was to determine the psychometric properties of the Serbian adaptation of the MEEQ among secondary school pupils. **Methods.** The retrospective study included 1,642 secondary school pupils (52.3% female) from the South Bačka District, Vojvodina, Serbia. In addition to the MEEQ, the Cannabis Use Intention Questionnaire (CUIQ) was also used, as well as a self-report measure of cannabis use. **Results.** The original six-factor MEEQ model showed the best fit indices with the following factors: Cognitive and Behavioral Impairment, Relaxation and Tension Reduction, Social and Sexual Facilitation, Perceptual and Cognitive Enhancement, Global Negative Effects, and Craving and Physical Effects. All MEEQ scales showed positive and expected correlations with the CUIQ scales, among which the highest correlation was with the Attitudes toward Consumption scale. Correlations with self-report cannabis use were significant for all MEEQ scales, except for Cognitive and Behavioral Impairment. **Conclusion.** The results suggested good psychometric properties of the Serbian adaptation of the MEEQ. The results also confirmed the originally proposed factor structure, good reliabilities of the scales' scores based on internal consistency, as well as convergent and criterion validity.

Key words:
adolescent; serbia; substance-related disorders; surveys and questionnaires; validation study.

Apstrakt

Uvod/Cilj. Očekivanja o dejstvu kanabisa povezana su sa početkom i učestalošću njegovog korišćenja. Jedan od najčešće korišćenih instrumenata za merenje očekivanog dejstva kanabisa je Upitnik očekivanih efekata upotrebe marihuane (*Marijuana Effect Expectancy Questionnaire – MEEQ*). Cilj rada bio je da se utvrde psihometrijska svojstva srpske adaptacije MEEQ za primenu kod učenika srednjih škola. **Metode.** U retrospektivnu studiju uključeno je 1 642 učenika srednjih škola (52,3% ženskog pola) iz Južnobačkog okruga, Vojvodina, Srbija. Uz MEEQ, korišćen je i Upitnik o nameri upotrebe kanabisa (*Cannabis Use Intention Questionnaire* – CUIQ), kao i mera samoprocene upotrebe kanabisa. **Rezultati.** Originalni šestofaktorski model MEEQ pokazao je najbolje fit indekse sa sledećim faktorima: Kognitivno oštećenje i poremećaj ponašanja, Relaksacija i smanjenje napetosti, Socijalna i seksualna facilitacija, Perceptualno i kognitivno poboljšanje, Globalni negativni efekti i Žudnja i fizički efekti. Sve MEEQ skale pokazale su pozitivne i očekivane korelacije sa CUIQ skalama, među kojima je najviša korelacija bila sa skalom Pozitivni stavovi prema konzumaciji. Korelacije sa samoprocenom upotrebe kanabisa bile su značajne za sve MEEQ skale, osim za Kognitivno oštećenje i poremećaj ponašanja. **Zaključak.** Rezultati su ukazali na dobre psihometrijske karakteristike srpske adaptacije MEEQ. Rezultati su takođe potvrdili i originalno predloženu faktorsku strukturu, dobru pouzdanost skorova na skalama zasnovanu na internoj konzistenciji, kao i konvergentnu i kriterijumsku validnost.

Ključne reči:
adolescenti; srbija; poremećaji izazvani supstancama; ankete i upitnici; istraživanje, validaciono.

Correspondence to: Sonja Čanković, University of Novi Sad, Faculty of Medicine, Hajduk Veljkova 3, 21000 Novi Sad, Serbia; Institute of Public Health of Vojvodina, Futoška 121, 21000 Novi Sad, Serbia. E-mail: sonja.cankovic@mf.uns.ac.rs

Introduction

Adolescence is a period of changes not only in hormones and the body but also in social roles in peer and other interpersonal relationships, which coincides with an increase in mental health problems [1, 2]. In this vulnerable period of life, there is an increase in risk-taking behaviors, including substance misuse [3, 4]. These behaviors are often established during youth, extend into adulthood, increase the risk of adult harm, and are interrelated [5, 6]. Recent literature indicates small negative associations between cognitive functioning and cannabis use [7]. In addition, cannabis use during adolescence, especially heavy use and earlier age at onset of cannabis use, is associated with poorer educational outcomes and mood disorders, particularly depressive symptoms, and should be considered when assessing suicide risk [8–11].

According to the World Health Organization (WHO), cannabis is the most commonly used illicit drug globally [12]. Within the WHO European Region, an estimated 9 million people aged 15–24 years (19.1% of this age group) used cannabis in 2020 [13]. European School Survey Project on Alcohol and Other Drugs (ESPAD) data also reveals that, on average, 16% of students reported having used cannabis at least once in their lifetime, and in Serbia, the reported number was 2.9–7.3% [14]. Moreover, the data from the latest Serbian National Health Survey show that cannabis was used by 1.2% of the population in the previous 12 months, significantly more common in the 18 to 34 age group (2.4%), among men (1.6%), urban residents (1.5%), residents of higher education (1.8%), and those belonging to the wealthiest households (2.1%) [15].

There are various reasons and expectations for cannabis use, and according to extended expectancy theory [16], drug effect expectancies are shown to be related to the actual use of drugs [17]. Individuals learn, through observation and experimentation, and get beliefs, both positive and negative, about how a drug will affect them. One of the most frequently used questionnaires created to assess cannabis effect expectancies is the Marijuana Effect Expectancies Questionnaire (MEEQ). It was based on expectancy theory, extended to drug use, and it was designed to allow completion by both cannabis users and adolescents who have never used cannabis [17]. The MEEQ assesses six domains of marijuana effect expectancies, which could be divided into positive expectations [Relaxation and Tension Reduction (RTR), Social and Sexual Facilitation (SSF), and Perceptual and Cognitive Enhancement (PCE)], negative expectations [Cognitive and Behavioral Impairment (CBI) and Global Negative Effects (GNE)], and neutral expectations [Craving and Physical Effects (CPE)]. For instance, one will use it to feel relaxed and reduce stress, which is an important motivator to initiate and maintain drug use. However, others will expect adverse effects, such as impaired cognition, which can inhibit the initiation and continuation of drug use behaviors. Therefore, adolescents use illicit drugs when they hold strong positive and weak negative expectancies for these behaviors [18]. Moreover, non-users endorsed more GNE than infrequent and frequent users [19].

Among six MEEQ scales, non-users scored lower on RTR and CPE, while they showed higher scores on GNE compared to past- and present-users among United States male inpatients [20]. In the study of Hayaki et al. [21] on adult women who use marijuana, the main positive predictor of frequency and severity of marijuana use was RTR. At the same time, CBI was a negative predictor of the frequency of marijuana use, and GNE was a predictor of the severity of marijuana use. Furthermore, non-users of marijuana had significantly higher expectations for GNE from marijuana and lower expectations for CPE than quitters, infrequent users, and frequent users. On the other hand, frequent marijuana users reported significantly lower expectations for CBI from marijuana than quitters and non-users [22].

However, there are inconsistent results regarding the factor structure of the MEEQ. Aarons et al. [22] offered composite scores of negative and positive effects, indicating the hierarchical structure of the MEEQ. GNE composite captures CBI and GNE scales, while the rest of the scales formed Global Positive Effects (GPE). The hierarchical model proposed by Hayaki et al. [23] was used. They suggested that the higher-order negative expectancy factor should include CBI, CPE, and GNE, while the remaining three scales should constitute a positive expectancy factor. However, these composites are not formed by empirical evidence. Some research on French-speaking adolescents suggested a four-factor structure based on exploratory factor analysis [24]. Although in the Confirmatory Factor Analysis (CFA) study [25], the four-factor solution had a better model fit compared to the six-factor solution, both model fits are below the recommended cut-off criteria for fit indices, indicating poor model fit for both solutions. Thus, we could conclude that the four-factor structure is not the common use of the MEEQ.

To the best of our knowledge, there is no validated Serbian adaptation of the MEEQ. Therefore, the aim of this study was to examine the psychometric properties of the Serbian adaptation of the MEEQ among secondary school pupils. More precisely, factor structure was tested *via* CFA, and the internal reliability was tested *via* alpha and omega coefficients. In addition, convergent validity was tested *via* average variance extraction and correlation with the Cannabis Use Intention (CUI) Questionnaire (CUIQ) scales, which measure similar constructs. Furthermore, criterion validity was tested through correlations with self-report cannabis use. We expect to confirm the originally proposed factor structure, as well as convergent and criterion validity.

Methods

Participants and procedure

The sample consisted of 1,642 secondary school children (52.3% female) from the territory of the South Bačka District, Vojvodina, Serbia, aged 15–19 years [mean value (M) = 16.40, standard deviation (SD) = 1.02], of which 59.8% attended a four-year vocational school, 23.8% gymnasium, and 16.4% a three-year vocational school. Google Form was used to administer instruments from September 15 to December 15, 2021. Class teachers shared the link with their students *via* the Google Classroom platform. Secondary school

children who did not want to complete the online questionnaire did not participate in this research.

Instruments

The MEEQ is the 48-item measure of six expectancy domains on the following subscales: CBI, RTR, SSF, PCE, GNE, and CPE. Each item is scored on a 5-point Likert scale (from 1 = 'strongly disagree' to 5 = 'strongly agree'), with scales containing 6–10 items.

The Serbian adaptation of the MEEQ was made in line with the report of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force for Translation and Cultural Adaptation [26]. This procedure included several steps: 1) preparation – consent to use the MEEQ and translate it into Serbian was obtained from the copyright holder, Prof. Dr. Sandra Brown; 2) forward translation – the translation process, after preparation, included forward translations from English to Serbian by two health professionals who were native speakers of Serbian and fluent in the English language; 3) reconciliation – a comparison and merging of forward translation versions into a single translation was made at a consensus meeting; 4) back translation – a professional translator translated the Serbian language back to the original English language; 5) harmonization – the forward translations were similar to and consistent with the original version; 6) cognitive debriefing – the Serbian version was then piloted on a group of 40 participants, pupils of Secondary Medical School "April 7th", Novi Sad, Serbia, who filled in the questionnaire, to check the comprehensibility of the items. All items were clear, and only minor linguistic modifications were made; 7) proofreading – a final review of the translation to correct grammatical, printing, or other errors was done by the research team members; 8) final report – at the end of the process, all steps were documented as a part of the doctoral thesis of one of the team members.

CUIQ [27, 28] operationalized four scales: Attitudes toward consumption (ATC), measured with two sets of four items that assess expected outcomes of cannabis consumption as well as the desirability of these outcomes (α = 0.93); Subjective norms, measured with two sets of three items that assess how significant others would view the consumption of marijuana as well as their motivation to comply with them (α = 0.70); Self-efficacy to abstinence, a five-item scale which assesses beliefs about the extent to which the person feels capable of not using cannabis in different circumstances (α = 0.95); CUI, a three-item scale which assesses the perceived likelihood to consume marijuana (α = 0.95). Each item is scored on a 5-point Likert scale (from 1 = 'not at all' to 5 = 'very much').

ESPAD [14] measures the cannabis lifetime use, cannabis use in the last year, and cannabis use in the last month (0; 1–2 times; 3–5 times; 6–9 times; 10–19 times; 20–39; 40 or more).

Data analysis

First, CFA was used in R package "lavaan" [29] in order to test several proposed models of the MEEQ. Due to multivariable normality violation, a diagonally weighted least squares (DWLS) estimator was used. Model fit was evaluated using several fit indices: the Chi-square test, comparative fit index (CFI), Tucker-Lewis index (TLI), root mean square error of approximation (RMSEA), and standardized root mean square residual (SRMR). Although there are no absolute standards, the determination of model fit requires consideration of a range of fit indices that may evidence a good fit (e.g., RMSEA and SRMR < 0.06, TLI and CFI > 0.95) or an acceptable fit (e.g., RMSEA < 0.08, TLI and CFI > 0.90) [30]. Second, descriptive statistics and reliability were calculated in R package 'psych' [31]. Reliability was calculated as Cronbach's α and Guttman split-half coefficients (with values $\geq$ 0.70 indicating satisfactory reliability) and as McDonald's ω (with values $\geq$ 0.41 indicating satisfactory, $\geq$ 0.61 moderate, and $\geq$ 0.81 high reliability) [32]. Additionally, the average variance extracted (AVE) [33] was calculated as a measure of convergent validity, with values higher than 0.50 indicating good convergent validity. Third, convergent validity was estimated *via* Pearson's correlations with CUIQ scales, and criterion validity was assessed *via* correlations with cannabis use.

Ethical aspects

The research was approved by the Ethics Committee of the Institute of Public Health of Vojvodina, Serbia (No. 01-1184/2, issued on July 22, 2021). School principals who agreed to participate in the study informed the Parent Councils. According to the Patient Rights Law of the Republic of Serbia, public health research involving a child who has reached the age of 15 and is capable of reasoning and which does not produce direct benefit or risk to the child may be approved if the research aims to contribute to a better understanding of the state of health of this population, with the written consent of the child or his/her legal representative [34]. In line with that, participants were fully informed about the objectives and methods of the study orally by the teachers who shared the link with them at the very beginning of the online questionnaire. They had a right to make an independent decision as to whether or not they wanted to participate in a study dealing with issues that were relevant to them. The respondents expressed their consent by answering the first mandatory question on whether they agreed to participate, and those who marked 'yes' were considered to participate in the study. They could withdraw at any time before submitting the online form.

Results

Results of CFA showed that the originally proposed six-factor model had good fit indices (Table 1). However, item 26, which belongs to two factors, had remarkably low loading on the second factor (-0.39) and loading over 1 on the fourth factor (1.13); hence, it was omitted from the second factor. Similarly, item 33 had remarkably low loading on the first factor (0.31) compared to loading on the sixth factor (0.53); hence, it was omitted from the first factor. Omitting those two items from factors where loadings were lower and keeping them only on factors where their loadings were high resulted again in good model fit indices. Loading was in a range from 0.41 to 0.87 (Figure 1). Correlations between factors were high, which

Table 1

Model fit indices of proposed MEEQ models

Models	DWLS $\chi^2(df)$	CFI	TLI	RMSEA (90% CI)	SRMR
Original six-factor model	7,049.66 (1,063)	0.987	0.986	0.059 (0.058–0.060)	0.062
Original six-factor model without double items	7,145.35 (1,065)	0.987	0.986	0.059 (0.058–0.061)	0.062
Hierarchical model	8,465.81 (1,073)	0.984	0.983	0.065 (0.064–0.067)	0.068
Two-factor model	9,938.21 (1,079)	0.981	0.980	0.071 (0.070–0.072)	0.073

MEEQ – Marijuana Effect Expectancy Questionnaire; DWLS – diagonally weighted least squares; CFI – Comparative fit index; TLI – Tucker-Lewis Index; RMSEA – root mean square error of approximation; CI – confidence interval; SRMR – standardized root mean square residual.

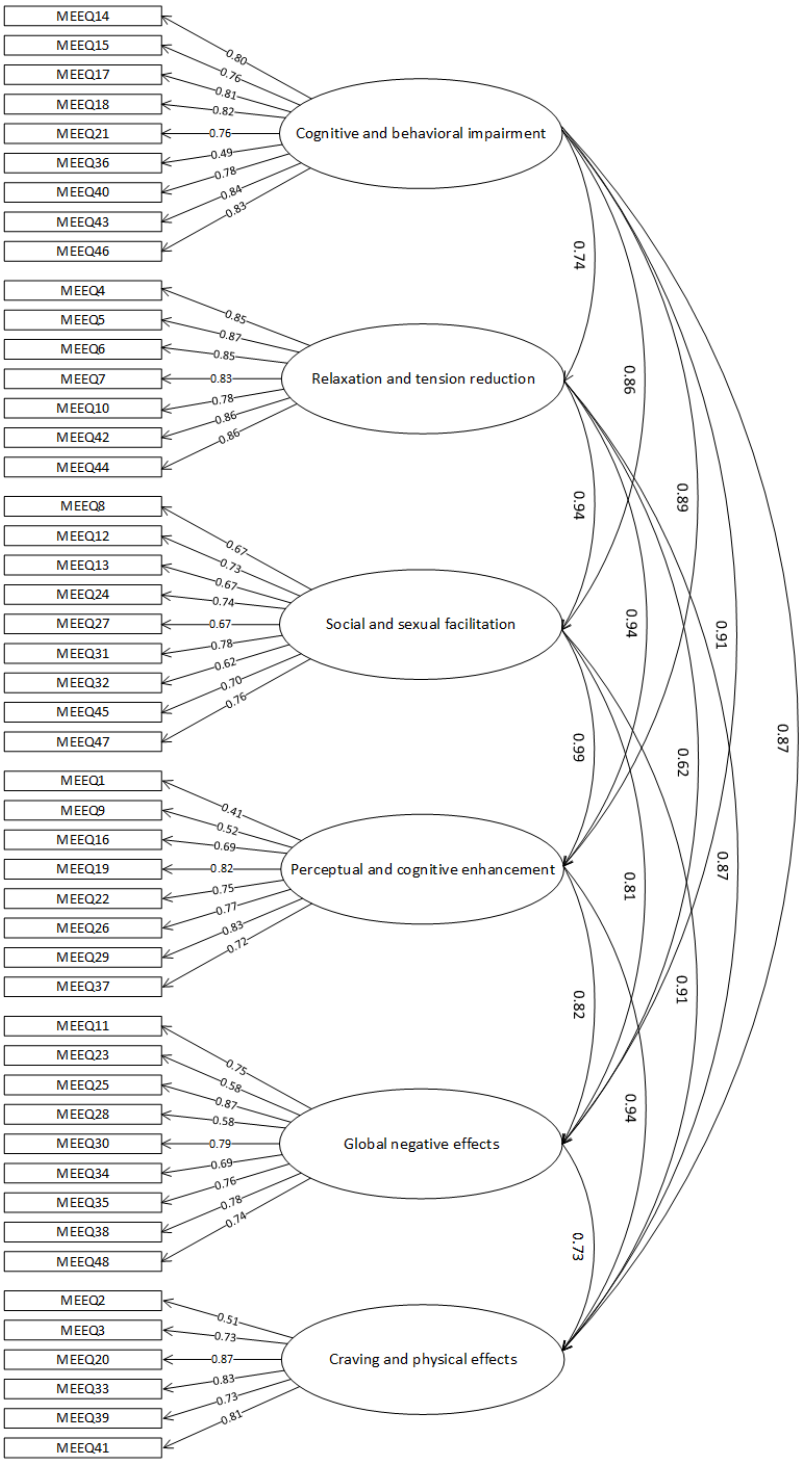

Fig. 1 – Parameters of the six-factor model of the MEEQ.
MEEQ – Marijuana Effect Expectancy Questionnaire.

could indicate that the hierarchical factor structure was more suitable. Although the hierarchical model proposed by Hayaki et al. [23] with two higher-order factors showed good model fit, it was significantly worse than the proposed six-factor model ($\Delta\chi^2(8) = 1{,}320.5$; $p < 0.001$) and more importantly, loadings of the third and the fourth factors on a higher-order factor of positive expectancy were over 1. Finally, a two-factor model was tested, with positive and negative expectancy factors, but it showed a worse model fit compared to the proposed six-factor model ($\Delta\chi^2(14) = 2{,}792.9$; $p < 0.001$). Thus, the six-factor model with items 26 and 33 only loaded on one factor showed the best model fit indices (Table 1) and parameters (Figure 1).

Alpha, split-half, and omega reliabilities for each scale indicated good reliability, and AVE indicated good convergent validity of the scale scores (Table 2).

Convergent and criterion validity correlations

All MEEQ scales correlated substantially with ATC from the CUIQ, with the highest correlation between RTR and ATC (Table 3). Furthermore, all MEEQ scales showed higher correlations with the Subjective norms and Self-efficacy to abstinence scales from the CUIQ. The correlations between the MEEQ and CUI scales from CUIQ were lower, and the only nonsignificant correlation was between GNE and CUI. Among all MEEQ scales, GNE showed the lowest correlations with CUIQ scales. Correlations with cannabis use were significant for all MEEQ scales, except for CBI. The CPE scale had the highest correlations with cannabis use, while the GNE scale showed only negative correlations.

Discussion

This research aims to explore the psychometric properties of the Serbian adaptation of the MEEQ among secondary school pupils. Among all tested models, results supported the original six-factor structure [17]. More importantly, a six-factor solution showed better model fit compared to the hierarchical solution often used in research. It should also be noted that although negative and positive expectancy factors were used in previous research [23], no study has yet tested the hierarchical factor structure. Thus, we raised concerns about the interpretation of the higher-order factor of the MEEQ. In addition, results showed that items 26 and 33 should be loaded only on one factor because this solution provided no overestimated loadings.

All six MEEQ scales demonstrated good Cronbach's α coefficient, ranging from 0.88 (PCE scale) to 0.94 (RTR scale). Internal reliability was generally good and similar to previous studies [21, 24]. McDonald's ω coefficient, considered a more sensible index of internal consistency and with less risk of overestimation or underestimation of reliability [35], has shown high values for MEEQ scales, between 0.88 and 0.95.

Convergent validity was tested through correlation with CUIQ, with the highest correlation between RTR (MEEQ) and ATC (CUIQ). Adolescents with greater positive expectancies of RTR were more likely to report a positive attitude toward substance use. On the other hand, GNE (MEEQ) showed the lowest correlations with CUIQ scales.

Criterion validity was evaluated through correlations with self-reported cannabis use. The correlations were

Table 2

Descriptive statistics and reliabilities for MEEQ scales

Scale	M	SD	α	Split-half	McDonald's ω	AVE
Cognitive and behavioral impairment	2.86	1.20	0.92	0.87	0.95	0.60
Relaxation and tension reduction	3.09	1.34	0.94	0.88	0.95	0.71
Social and sexual facilitation	2.69	1.07	0.90	0.89	0.91	0.50
Perceptual and cognitive enhancement	2.81	1.07	0.88	0.86	0.89	0.51
Global negative effects	2.65	1.09	0.91	0.90	0.90	0.54
Craving and physical effects	2.97	1.18	0.89	0.87	0.88	0.57

MEEQ – Marijuana Effect Expectancy Questionnaire; M – mean; SD – standard deviation; AVE – average variance extracted.

Table 3

Correlations between MEEQ and CUIQ scales and cannabis use

MEEQ	CUIQ				ESPAD – cannabis use		
	Attitudes toward consumption	Subjective norms	Self-efficacy to abstinence	Cannabis use intention	Lifetime	In the past 12 months	In the last 30 days
Cognitive and behavioral impairment	0.48	0.36	0.45	0.15	0.03	0.05	0.04
Relaxation and tension reduction	0.74	0.41	0.43	0.35	0.25	0.24	0.21
Social and sexual facilitation	0.69	0.44	0.40	0.33	0.15	0.16	0.17
Perceptual and cognitive enhancement	0.67	0.42	0.42	0.31	0.13	0.14	0.13
Global negative effects	0.31	0.29	0.38	0.01	-0.17	-0.16	-0.11
Craving and physical effects	0.65	0.42	0.46	0.36	0.35	0.35	0.27

MEEQ – Marijuana Effect Expectancy Questionnaire; CUIQ – Cannabis Use Intention Questionnaire; ESPAD – European School Survey Project on Alcohol and Other Drugs.
Note: All correlations ≥ 0.13 are significant at $p < 0.001$.

significant for all MEEQ scales except for the CBI scale. This is not in line with previous studies [22, 21] in which the CBI scale was negatively associated with the frequency of marijuana use. One explanation is that the participants in our study were younger than participants in the previous studies because the period of cannabis use in our sample was shorter.

Furthermore, the highest and most positive correlation was found between cannabis use and the CPE scale, followed by the RTR, which is in line with previous studies [20–22]. It should be noted that some authors suggested the CPE scale as a part of the negative expectancy factor [23]. However, the CPE scale showed a positive correlation with marijuana use. The results are more in line with the decision by Aarons et al. [22] that this scale should not be a part of the higher-order GNE dimension but of the GPE dimension. However, as we already stated, hierarchical structure is questionable. According to the findings of Buckner and Schmidt [19], the users who especially value marijuana's physical and craving effects characteristics (hunger, craving for things and snacks, laughter, dry mouth) are likely to become more frequent users. These results showed that, at least in community youth, the frequency of marijuana use is more associated with positive expectancies compared to negative ones. Regarding the RTR scale, other research pointed out that it predicted not only frequency but also severity of marijuana use, and this scale emerged as a robust belief in adults 18–24 years old [21].

The only negative correlation was found between marijuana use and the GNE scale, indicating that maybe only this scale contains clearly negative expectations and effects of marijuana use, compared to others that are also considered indicators of negative consequences of marijuana use. Therefore, the GNE scale assesses expectations that may include clinical severity indicators that only appear in more serious cases [21].

There are several limitations of this study. First, the study includes a convenient sample comprised solely of secondary school pupils from mostly urban areas of Serbia. Thus, the generalization of the results is limited to adolescents but not to the general population of Serbia. Second, self-report data on marijuana use among adolescents could be biased or under social desirability response despite the anonymity. Third, all measures were self-reported, which can influence the correlations among them, i.e., correlations can be higher than expected because of the same method used (self-report). We tested common method variance *via* Harman's single factor method [36], and results of joint principal component analysis on all included items in the study showed that the first component included 32.51% of shared variance. Since this is smaller than the recommended cut-off of 50% of shared variance, we can conclude that common method variance did not affect the results. However, in line with good practices, we recommend using a multitrait-multimethod design to validate further the MEEQ. Fourth, only reliability based on internal consistency was tested as well as congruent and criterion validity. Future studies should include testing of test-retest reliability as well as discriminant validity. Fifth, given that participants completed questionnaires online, a person's motivation to answer carefully may be decreased.

Conclusion

Despite the limitations of this study, the presented results provide important information regarding the psychometric properties of the Serbian adaptation of the Marijuana Effect Expectancy Questionnaire and confirm the originally proposed factor structure and convergent validity as well as good internal reliability. The relations with the criterion variable were rather small, but results indicated that the Global Negative Effects scale may be a protective factor in the initiation of marijuana use during adolescence. To sum up, the results of this study add further to the cross-cultural validity and use of the Marijuana Effect Expectancy Questionnaire.

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Received on August 26, 2024
Revised on October 22, 2024
Accepted on October 29, 2024
Online First January 2025

ORIGINAL ARTICLE

UDC: 614.253.5:374.713.98
DOI: https://doi.org/10.2298/VSP240902009Z

Study on the application effect of CDIO-based training mode in ECMO training for ICU nurses

Studija o efektu primene režima obuke zasnovanog na CDIO u ECMO obuci medicinskih sestara na odeljenju intenzivne nege

[1]Rui Zhu, [1]Yufang Geng, Jingjing Li, Min Shao

Anhui Medical University, First Affiliated Hospital, Hefei, Anhui, China

[1]These authors contributed equally to this study

Abstract

Background/Aim. Nurses in the intensive care unit (ICU) must have strong professional skills due to excessive workloads, high nursing risk events, and frequent nurse-patient disagreements. The aim of the study was to examine the use of Conceive, Design, Implement, and Operate (CDIO)-based teaching modalities in ICU nurses' extracorporeal membrane oxygenation (ECMO) training and find ways to increase training quality and professional capabilities. **Methods.** This study included 60 nurses and 100 ICU patients, selected from January 2020 to December 2021. They were split into an observation group (OG) and a control group (CG) (30 nurses and 50 patients each) based on ECMO nurse training methods. OG used CDIO-based training, whereas CG used ordinary training. Nurses' theoretical knowledge, fundamental nursing skills, professional nursing skills, Competency Inventory for Registered Nurses (CIRN) score, Critical Thinking Disposition Inventory-Chinese Version (CTDI-CV) score, and self-efficacy (General Self-Efficacy Scale – GSES) score were assessed. **Results.** Nurses' theoretical knowledge, basic skills, and professional skills were significantly greater ($p < 0.05$) in OG (95.34 ± 1.97, 56.84 ± 1.97, 36.19 ± 2.04) than in CG (87.11 ± 2.82, 51.17 ± 2.42, 31.52 ± 2.38). After training, nurses in OG had higher combined scores in CIRN, CTDI-CV, and GSES (75.84 ± 9.59) compared to CG (67.35 ± 8.43, $p < 0.05$). **Conclusion**. ICU nurses' ECMO training benefits from CDIO-based modalities. It may considerably increase nurses' evaluation outcomes, core competency, critical thinking, self-efficacy, and self-learning. Training quality is far greater than traditional training, making it worthy of promotion and utilization.

Key words:
extracorporeal membrane oxygenation; intensive care units; education; nurse clinicians; professional competence.

Apstrakt

Uvod/Cilj. Medicinske sestre na odeljenju intenzivne nege (*intensive care unit* – ICU) moraju imati napredne profesionalne veštine zbog prevelikog opterećenja, događaja visokog rizika kojima su izložene i čestih neslaganja između sestara i bolesnika. Cilj rada bio je da se ispita upotreba nastavnih modaliteta zasnovanih na konceptu, dizajnu, primeni i rukovanju (*Conceive, Design, Implement, and Operate* – CDIO) u obuci medicinskih sestara za ekstrakorporalnu membransku oksigenaciju (*extracorporeal membrane oxygenation* – ECMO) na ICU i da se nađe način za povećanje kvaliteta obuke i profesionalnih sposobnosti. **Metode.** Studijom je obuhvaćeno 60 medicinskih sestara i 100 bolesnika na ICU, izabranih u periodu od januara 2020. do decembra 2021. godine. Bili su podeljeni na posmatranu grupu (PG) i kontrolnu grupu (KG) (u svakoj po 30 sestara i 50 bolesnika) na osnovu metoda obuke medicinskih sestara za ECMO. Grupa PG je koristila obuku zasnovanu na CDIO, dok je KG koristila uobičajenu obuku. Procenjivani su teorijsko znanje medicinskih sestara, osnovne veštine, zahtevnije veštine, skor *Competency Inventory for Registered Nurses* (CIRN), skor *Critical Thinking Disposition Inventory-Chinese Version* (CTDI-CV) i skor *General Self-Efficacy Scale* (GSES). **Rezultati.** Teorijsko znanje, osnovne veštine i profesionalne veštine medicinskih sestara bile su značajno veće ($p < 0,05$) u PG (95,34 ± 1,97, 56,84 ± 1,97, 36,19 ± 2,04) nego u KG (87,11 ± 2,82, 51,17 ± 2,42, 31,52 ± 2,38). Posle obuke, medicinske sestre u grupi PG imale su više rezultate kombinacije skorova CIRN, CTDI-CV i GSES (75,84 ± 9,59) u poređenju sa KG (67,35 ± 8,43, $p < 0,05$). **Zaključak.** Primena modaliteta zasnovanih na CDIO je korisna za obuku medicinskih sestara na ICU za ECMO. To može značajno povećati ishod procene, osnovnu

Correspondence to: Min Shao, Anhui Medical University, First Affiliated Hospital of Hefei, Anhui, China, 230 001.
E-mail: minshao130@gmail.com, shaomin@ahmu.edu.cn

kompetenciju, kritičko razmišljanje, samoefikasnost i samoučenje medicinskih sestara. Kvalitet obuke je daleko veći od tradicionalne obuke, što je čini vrednom promocije i primene.

Ključne reči:
oksigenacija, ekstrakorporalna, membranska; intenzivna nega, odeljenja; obrazovanje; medicinski tehničari; kompetencija, profesionalna.

Introduction

The intensive care unit (ICU) has the characteristics of heavy workloads, a high incidence of nursing risk events, and easy-to-cause nurse-patient disputes, so it requires very high professional skills from nurses [1]. However, due to the influence of educational level, training, and other factors, ICU nurses' professional skills are uneven, and some ICU nurses' clinical thinking ability is not high, resulting in their poor emergency response ability, low work efficiency, and frequent nursing errors [2]. For that reason, it is necessary to train ICU nurses systematically in order to improve their professional skills. Extracorporeal membrane oxygenation (ECMO) is a new technology for rescuing the lives of critically ill patients [3]. The establishment, maintenance, and removal of the tubing need to be completed by skilled nurses. Therefore, it is necessary to enhance ECMO training for ICU nurses. Conceive, Design, Implement, and Operate (CDIO) is a new training mode. This training mode attaches importance to "learning and doing", requiring students to practice constantly by learning and mastering skills in practice in order to cultivate their comprehensive ability [4].

With the progress of science and technology, innovation has been raised to the height of national strategy in countries all over the world [5]. Nursing is the key force in medical development, but its professional and academic level lags behind clinical medical treatment. The fundamental reason is the lack of nursing innovation [6]. Some studies have shown that the innovative behavior of clinical frontline nursing staff is at a medium level [7]. Therefore, it is necessary to take the initiative to adjust the talent training mode to meet the demand for innovative nursing talents for the current development of health care [8]. Curriculum education is the core of innovation education. However, the development of the nursing innovation curriculum in China is still in its nascent stage. Hence, the most important task is to develop nursing education to create an innovative nursing curriculum and to seek a reasonable teaching design [9]. CDIO is a classic mode of engineering education at Massachusetts Institute of Technology that emphasizes that engineering education should focus on practice and place the education process in the specific context of the product or system life cycle. It is also an educational mode based on cultivating students' abilities with the aim of cultivating innovative talents. The CDIO concept has been widely applied in the field of applied talent cultivation because of its obvious effect on improving teaching quality and promoting talent cultivation [10].

Applying CDIO to ECMO training for ICU nurses can improve their training effect and professional skills to a certain extent [11]. The aim of the study was to analyze the application effect of CDIO-based training mode in ICU nurses' ECMO training regarding their assessment results, core competence, critical thinking ability, self-efficacy, and self-learning ability.

Methods

The study included a total of 60 nurses and 100 patients who were chosen as the subjects from the ICU of the First Affiliated Hospital of Anhui Medical University, China between January 2020 and December 2021. The participants were categorized into a control group (CG) and an observation group (OG), with 30 nurses and 50 patients each. The division was based on the various types of ECMO training for nurses.

The nurses in CG were all female, aged 20 to 42 years, with an average age of 28.87 ± 3.36 years. The length of service was 1–8 years, with a mean length of 4.43 ± 1.60 years. Among the professional titles were 2 head nurses, 5 staff nurses, and 23 junior nurses. Among them, there were 12 junior college students, 8 undergraduate students, and the other 10 nurses. The patient sample size consisted of 28 males and 22 females, with a mean age of 35.47 ± 7.25 years.

In OG, all the nurses were female, aged 20 to 43 years, with an average age of 28.91 ± 3.34 years. The length of service was 1–8 years, with a mean length of 4.45 ± 1.58 years. Among the professional titles, there were 2 head nurses, 5 staff nurses, and 23 junior nurses. Among them, there were 13 junior college students, 7 undergraduate students, and the other 10 nurses. There were 50 patients in total, 27 males and 23 females. The median age was 35.50 ± 7.23 years.

This study was approved by the Ethics Committee of the First Affiliated Hospital of Anhui Medical University, China (Reg. No. 45546/CDIO/2020) and was executed according to the ethical standards outlined in the Declaration of Helsinki. Written informed consent was obtained from each participant.

Study requirement criteria

Inclusion criteria for nurses were as follows: ICU nurses who were in service in 2020 and 2021; nurses with certain ICU nursing knowledge and operation skills; those who completed the ECMO training and passed the examination; those who were able to accept a questionnaire survey and understand the purpose of the questionnaire survey; those who know about the research and participate voluntarily. Exclusion criteria were as follows: those who failed to complete the training or pass the assessment; those who were unable to express personal wishes accurately; nurses unwilling to cooperate with the investigation.

Patient inclusion criteria were as follows: those with complete medical records; patients who stayed in the ICU for treatment; those who understood the purpose of the questionnaire and participated voluntarily. Exclusion criteria were the following: mental illness; death due to ineffective treatment; patients unable to express personal wishes accurately; patients unwilling to cooperate with the investigation.

Both groups of nurses completed the training under the guidance of the teachers, and the teachers' qualifications were the same. Prior to the training, the teachers prepare lessons and access relevant materials *via* the Internet to master the relevant knowledge of the training mode.

For the CG routine, ordinary training mode was used. According to the training plan formulated by the department, nurses should be organized to carry out unified training, focusing on theoretical teaching. The teachers use multimedia equipment and courseware to explain relevant knowledge to nurses according to the content of the syllabus. Nurses listen, take notes, and recap on their own after class. At the same time, teaching was conducted in stages according to the different teaching contents. The teacher led the nurses to make ward rounds, asked them questions, and gave explanations according to the characteristics of cases, clinical diagnoses, and treatment problems. During the training, a demonstration of an operation is performed using the traditional method, and then the operation is performed by a nurse.

In contrast, the CDIO-based training mode was applied for the OG routine. The CDIO-based training includes contents described in the following paragraphs.

Conception – used to evaluate nurses before training using the scales of core competence, critical thinking ability, emergency response ability, post-competence, self-efficacy, and self-learning ability. This is done in order to understand their professional level, professional ability, and cognition and formulate training plans according to the requirements of ICU nurses. At the same time, conception summarizes the problems and causes in the ECMO regarding the work of nurses with the ICU patients, including the pre-flushing of the membrane lung and tubing, ECMO puncture and catheterization, membrane lung replacement, etc. It defines the methods and objectives to improve the quality of ECMO care and devises the CDIO-based training framework.

Design – based on evidence-based medicine, consulting relevant data, analyzing and summarizing CDIO training mode and ECMO nursing guidance and literature, combining department nursing requirements, improving the nurse training system, and designing an ICU nurse training scheme based on CDIO training mode.

Implementation – the main contents include pre-training, joint exchange of retraining, and simulation exercise. First, in the pre-training, the following steps are taken: establish a WeChat group, require all nurses to join, and pay attention to group messages. Before each training, the instructor uploads the training-related materials (including graphic materials and videos) to the WeChat group, requiring nurses to download the materials in advance, learn by themselves, mark the contents they do not understand, and consult the materials to supplement and expand the relevant knowledge points. Second, in the joint exchange of retraining, the teacher will systematically explain ECMO knowledge, including indications and contraindications of ECMO, preparations before operation, key points of operation and precautions, treatment, and remedial measures for complications, and provide reference materials and literature. Reserve some time in class, let the nurses exchange and discuss the learned knowledge in the form of group discussion, and guide the teachers to design problems, such as: should ECMO be used for severe hypoxia, how to select an ECMO mode, what are the common complications of ECMO, how to select an ECMO puncture tube, etc. A representative chosen by the group answers the questions. The teacher will supplement and improve the answers and summarize the main knowledge points. Finally, in the simulation exercise, the following should be done: provide training and guidance for nurses on ECMO nursing operation technology; use simulators to conduct on-site simulation exercises; nurses can also play different roles in conducting situational simulation exercises to feel the clinical atmosphere and improve operation technology.

Operation – formulate the evaluation system, systematically evaluate the nurses in the middle of the training, summarize the deficiencies in the training process, and put forward improvement measures to correct and improve after the later training. At the same time, the nursing operation process and specifications were compiled as the assessment standard manual to provide a quantifiable reference for the training effect of nurses.

Observation indicators

Assessment results, core competence, critical thinking ability, emergency response ability, post-competence, self-efficacy, self-learning ability, work efficiency, and patient satisfaction were compared between the two groups.

Assessment results: a unified assessment was conducted after the training, including theoretical knowledge, basic nursing skills, and professional nursing skills. The scores range from 0 to 100, 0 to 60, and 0 to 40, respectively. A higher score indicates superior performance.

Core competence: assessed before and after the training using the Competency Inventory for Registered Nurses (CIRN) scale with five features, a five-level scoring technique (1–5 points), and a total score for each item. The higher the score, the better.

Critical thinking ability: evaluated before and after the training using the Critical Thinking Disposition Inventory–Chinese Version (CTDI-CV) scale, which includes thirst for knowledge, seeking the truth, analytical ability, an open mind, cognitive maturity, and confidence. To compute the average score for each item, the 6-level scoring system is used. The greater the score, the better [12].

Emergency response-ability: the evaluation should be conducted before and after the training, including condition observation, emergency cooperation, and first aid operations.

There are 10 questions in total, and a 6-level scoring method is adopted. The higher the score, the better [13].

Post-competency: evaluated before and after the training, with 8 items including theory, skills, management, and teaching, for an overall score of 100 points. The greater the score, the better [14, 15].

Self-efficacy: assessed before and after the training using the General Self-Efficacy Scale (GSES), which has 10 items and adopts the 4-level scoring method (1–4 points). The overall score ranges from 10 to 40 points. The greater the score, the better [16].

Autonomous Learning Ability: evaluated before and after the training using the autonomous learning ability evaluation scale, which includes self-motivation belief, task analysis, self-monitoring and adjustment, self-evaluation, and the overall score calculation for each item. The higher the score, the better [17].

Work efficiency: includes drug preparation time, instrument and equipment preparation time, venous access opening time, and rescue time.

Patient satisfaction: evaluated after the training, according to the nurses' nursing service to the patients, the patients were guided to fill out the questionnaire. The evaluation contents included service attitude, communication skills, nursing operation, problem-solving, etc., with an overall score of 100 points. According to the scoring results, they were divided into very satisfied (> 90 points), satisfied (70–90 points), and dissatisfied (< 70 points). Patient satisfaction = (very satisfied cases + satisfied cases) / total cases × 100%.

Statistical analysis

SPSS 21.0 software was used to analyze the measurement data presented as mean ± standard deviation, run *t*-tests, analyze count data in percentages, and perform the Chi-square test. The value of $p < 0.05$ was considered statistically significant.

Results

OG and CG were examined for their nurses' theoretical knowledge, fundamental nursing abilities, and professional nursing skills. The basic nursing skills of CG were 51.17 ± 2.42, while those of OG were 56.84 ± 1.97, which also showed significant differences ($p < 0.05$). The professional nursing skills of CG were 31.52 ± 2.38, while those of OG were 36.19 ± 2.04. There is a significant difference ($p < 0.05$) (Table 1).

The CTDI-CV scores of nurses in both groups were comparable before training ($p > 0.05$). However, following the training, the CTDI-CV score of nurses in OG was significantly higher than that of CG ($p < 0.05$) (Table 2). Figure 1 illustrates the projected rate of survival in the external validation group of hospitals, as determined by the CTDI-CV

Table 1

Comparison of nurses' assessment scores (expressed as points)

Group	Theoretical knowledge	Basic nursing skills	Professional nursing skills
CG (n = 30)	87.11 ± 2.82	51.17 ± 2.42	31.52 ± 2.38
OG (n = 30)	95.34 ± 1.97	56.84 ± 1.97	36.19 ± 2.04
p	< 0.05	< 0.05	< 0.05

CG – control group; OG – observation group.
Values are given as mean ± standard deviation.

Table 2

Effect of CDIO-based training on certain work characteristics according to nurse groups

Parameter	Before training*	After training**
CTA		
CG	1.95 ± 0.15	4.93 ±0.90
OG	0.91 ± 0.08	2.68 ± 0.74
NJC		
CG	67.68 ± 5.19	78.07 ± 5.84
OG	67.70 ± 5.15	85.38 ± 6.23
NSE		
CG	23.68 ± 4.69	28.89 ± 5.16
OG	23.70 ± 4.65	34.61 ± 5.01

CDIO – Conceive, Design, Implement, and Operate; CTA – critical thinking ability of nurses (according to Critical Thinking Disposition Inventory–Chinese Version Scale); CG – control group; OG – observation group; NJC – nurse job competencies; NSE – nurse self-efficacy (according to General Self-Efficacy Scale).
Values (in points) are given as mean ± standard deviation.
Both nurses' groups consisted of 30 respondents each.
Note: *–A statistically significant difference was not found between CG and OG groups for CTA, NJC, and NSE ($p = 0.08$, $p = 0.752$, and $p = 0.067$, respectively); **– A statistically significant difference was found between CG and OG groups for all observed parameters ($p < 0.05$).

score. The survival rate was significantly lower in risk classes V and VI (i.e., Respiratory Extracorporeal Membrane Oxygenation Survival Prediction – RESP score < -2) compared to risk classes III, II, and I (i.e., CTDI-CV score ≥ -1) (15.5% vs. 91.5%, respectively). The CTDI-CV score showed outstanding performance in external validation [c = 0.92 (95% confidence interval – CI: 0.89–0.97)], but the Simplified Acute Physiology Score (SAPS) II showed substantially weaker discrimination [c = 0.60 (95% CI: 0.51–0.70)].

The pre-training competence scores of nurses in both groups were statistically equivalent ($p > 0.05$). However, the post-training competency score of nurses in OG was significantly greater than that of CG ($p < 0.05$) (Table 2).

GSES scores of nurses in both groups before training showed no significant difference ($p > 0.05$). However, after the training, the GSES score of nurses in OG surpassed that of CG ($p < 0.05$) (Table 2). Further, the influence of GSES score on patient in-hospital survival was evaluated, which revealed a significant positive connection (Figure 2). GSES

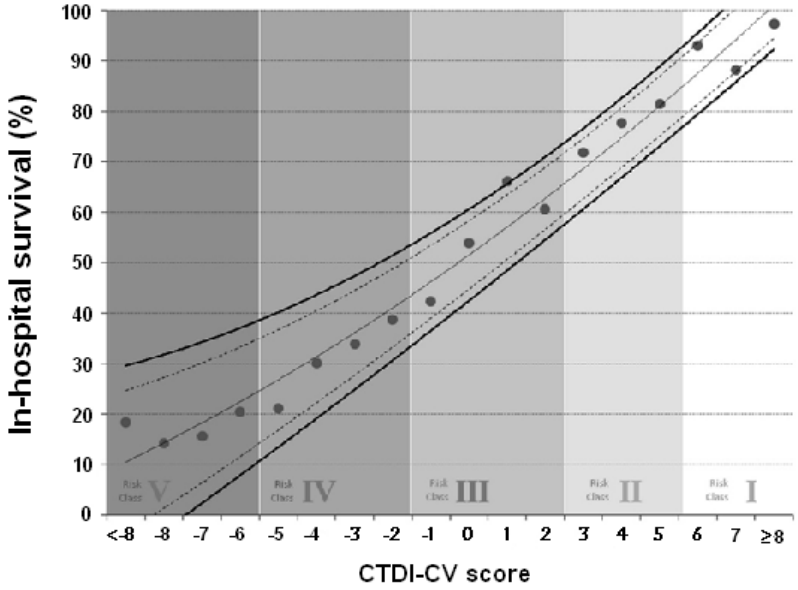

Fig. 1 – Individuals observed survival regarding CTDI-CV score within a 95% confidence interval. Each dot represents the observed survival percentage in the study population. Curved dotted gray lines and curved black lines represent 95 and 99% confidence intervals, respectively, for predicted survival at each score level. CTDI-CV – Critical Thinking Disposition Inventory-Chinese Version.

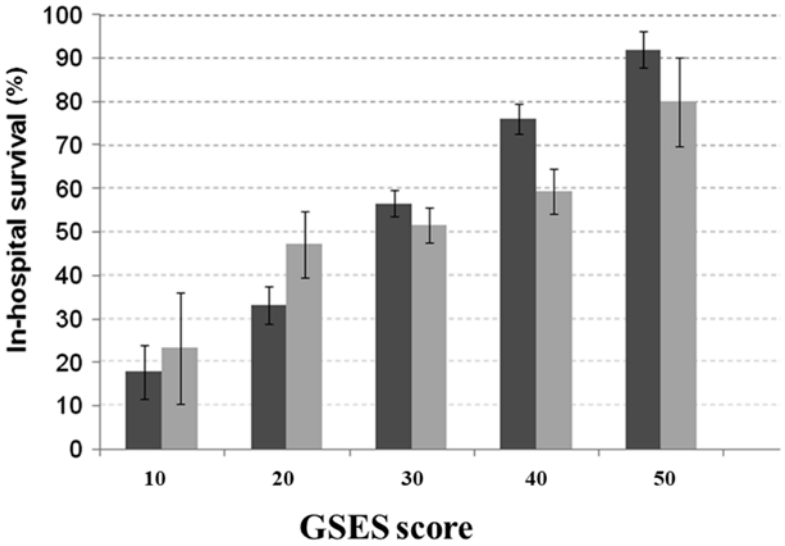

Fig. 2 – Correlation of GSES score and in-hospital survival of patients. Observed survival is expressed as mean ± standard deviation. Missing GSES score variables were allocated a zero score. GSES – General Self-Efficacy Scale. Note: the darker gray columns indicate the observation group and the lighter gray columns indicate the control group.

score was internally validated and showed fair discrimination [c = 0.73 (95% CI: 0.71–0.75)] and satisfactory calibration with a Hosmer-Lemeshow C statistic of 12.81 ($p = 0.12$).

After training, the mean ± standard deviation of the combined scores of CIRN, CTDI-CV, and GSES for nurses in the OG was 75.84 ± 9.59, while for those in the CG, it was 67.35 ± 8.43. The difference was statistically significant ($p < 0.05$).

Discussion

With the advancement of people's living standards, patients' expectations for the quality of nursing care have risen in recent years [18]. Especially for ICU patients, because of the critical condition and high mortality, it is particularly important to do a good job of nursing [19]. ECMO is an important means to rescue critically ill patients. Statistics show that the success rate of this treatment method for critically ill patients can reach 57% [20]. However, ECMO has high technical requirements for operation, and there are great nursing risks in practice. Therefore, standardized training is a top priority [21].

Empirical evidence has shown that implementing scientific and efficient training programs may greatly enhance nurses' expertise and abilities, prevent nursing mistakes, and contribute to the general advancement of the department's diagnostic and treatment capabilities [22]. The conventional training mode is a "cramming and inculcating" training mode, which mainly focuses on teaching, helping, and leading. The teacher is the main body of the training [23]. The nursing students listen and absorb, and the teaching content is mainly theoretical knowledge, lacking training in clinical practice and operation technology, resulting in poor results. In addition, the status of nursing students is weakened under this mode, so their learning enthusiasm is also low, resulting in a poor learning effect [24]. Therefore, it is essential to innovate the ECMO training mode for nurses in the ICU. CDIO training mode has been widely used in many fields. This training mode advocates "doing while learning" and "learning by doing". It not only attaches importance to the accumulation of theoretical knowledge but also to the improvement of practical ability and the cultivation of professional quality. In this mode, the teachers first investigate and understand the current situation of nurses, evaluate their abilities in all aspects, and then conceive and design training programs and objectives, which lay a good foundation for the smooth development of later training. During the training, the nurses should preview and mark the places they do not understand. This will help improve the nurses' initiative in classroom learning and improve their understanding of knowledge and learning effects. Group discussion was conducted before the end of the class to cultivate nurses' team spirit and ability to solve problems independently. In practice teaching, situational teaching has been adopted to improve nurses' sense of clinical experience and clinical thinking, which helps stimulate nurses' analysis ability and emergency response-ability.

The present investigation was conducted to clarify the application advantages of CDIO-based training modes and provide references for the formulation of training programs.

This study has compared the application effects of the conventional training mode and the CDIO-based training mode. The findings indicated that the nurses in OG exhibited superior assessment outcomes. Specifically, their CIRN score, CTDI-CV score, emergency response ability score, post-competency score, GSES score, and self-learning ability score all demonstrated higher values following the training. These results suggest that the patients in OG experienced significant enhancements in their abilities after the training, thereby instilling greater confidence in their post-work performance. In contrast, previous situations and research on nursing innovation education in our country are not objective. As a first-level discipline, the nursing specialty needs to keep up with medical development, carry out innovative education for nurses, and cultivate innovative abilities, the driving force for the development of the discipline. We cannot ignore that nurses are currently limited to the role of doctors' assistants and finish the nursing work passively. They ought to give full play to their subjective initiative, find work-related problems on time, innovate and improve constantly, and apply the results to clinical practice to improve patient service quality and realize self-value. Innovation education is fundamental for enhancing innovation ability, but nursing innovation education and research in China started late. From the perspective of this study, we need to seek to set up a "nursing innovation" course, advocating the combination of professional education and innovation. The study's drawback was attributed to the absence of lucidity in the mechanism. Furthermore, the patient population is not substantial, which necessitates further verification.

Conclusion

In a nutshell, the application of Conceive, Design, Implement, and Operate-based training mode in intensive care unit nurse extracorporeal membrane oxygenation training has a notable effect, which can significantly improve nurses' assessment results, core competence, critical thinking ability, emergency response ability, post competence, self-efficacy, and self-learning ability, and can improve nurses' work efficiency and patient satisfaction. The training quality is significantly higher than that of the conventional training mode, which is worthy of promotion and application.

Conflicts of interest

The authors declare no conflict of interest.

Funding

This paper was funded by the Key Specialty Program of Acute and Critical Care in Anhui Province (236434/2020).

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Received on September 2, 2024
Accepted on November 27, 2024
Online First February 2025

ORIGINAL ARTICLE

UDC: 615.322:615.45
DOI: https://doi.org/10.2298/VSP240415007H

Formulation optimization of the powder for suspension of flixweed seeds (*Descurainia sophia* L.), a Persian medicinal drink

Optimizacija formulacije praha za suspenziju od semena biljke *flixweed* (*Descurainia sophia* L.), persijskog lekovitog napitka

Zahra Hesari*, Heshmatollah Ebrahimi-Najafabadi†, Sanaz Beheshti-Kisomi‡, Maryam Naseri‡, Shirin Parvinroo‡

Guilan University of Medical Sciences, School of Pharmacy, *Department of Pharmaceutics, †Department of Medicinal Chemistry, ‡Department of Pharmacognosy, Rasht, Iran

Abstract

Background/Aim. Flixweed (*Descurainia sophia* L.) beverage has been used in Persian medicine as an effective remedy for constipation. Allyl isothiocyanate (AITC), the main ingredient of flixweed essential oil, has been claimed to regulate gastrointestinal contractility. The aim of the study was to stabilize the flixweed beverage, enhance its flavor, and determine the AITC content in the flixweed seeds (FS). **Methods.** To prepare a stable formulation of flixweed with desirable organoleptic properties, the optimal amount of tragacanth as a stabilizer, stevia as a sweetener, and lime and cinnamon powders as flavoring agents were mixed with flixweed solution. The shelf lives of the suspensions at room temperature (25 ºC) and refrigerator temperature (5 ºC) were evaluated. The viscosity and pH of the suspensions were also investigated. Finally, flixweed essential oil was obtained using the Clevenger apparatus. The amount of AITC in FS essential oil was determined by gas chromatography coupled with mass spectroscopy (GC-MS). **Results.** Based on our findings, two formulas, including FS (5 g), stevia (3 g), cinnamon (300 mg) or lime (400 mg), and 100 mL of water, had the optimum textural and organoleptic properties. Furthermore, adding 0.5% tragacanth gum as a suspending agent was able to stabilize the FS beverage. From 200 g of FS, 0.14 mL of essential oil was extracted, which corresponded to 0.07% (v/w). GC-MS analysis revealed that each 100 g of FS contained 24.85 mg of AITC, equating to 0.025% w/w AITC. **Conclusion.** Due to the presence of AITC in FS and the favorable characteristics of the FS suspension, this formulation, in the form of a sachet, can be suggested as an herbal supplement product for industrial production.

Key words:
beverages; constipation; dietary supplements; herbal medicine; plants, medicinal; plant weeds; seeds; suspensions; tragacanth.

Apstrakt

Uvod/Cilj. Napitak od biljke *flixweed* (*Descurainia sophia* L.), koristi se u persijskoj medicini kao efikasan lek za konstipaciju. Smatra se da alil izotiocijanat (AITC), glavni sastojak eteričnog ulja biljke *flixweed*, reguliše gastrointestinalnu kontraktilnost. Cilj rada bio je da se uradi stabilizacija i poboljša ukus napitka od biljke *flixweed*, kao i da se utvrdi sadržaj AITC u semenkama ove biljke. **Metode**. Da bi se pripremila stabilna formulacija biljke *flixweed* sa poželjnim organoleptičkim svojstvima, optimalna količina tragakanta kao stabilizatora, stevije kao zaslađivača i praha limete i cimeta kao arome, pomešana je sa rastvorom biljke *flixweed*. Procenjivani su rokovi trajanja suspenzija na sobnoj temperature (25 ºC) i temperaturi u frižideru (5 ºC). Takođe su ispitivani i viskozitet i pH suspenzija. Konačno, eterično ulje biljke *flixweed* dobijeno je pomoću aparata Clevenger. Količina AITC u eteričnom ulju semena biljke *flixweed* određena je gasnom hromatografijom u kombinaciji sa masenom spektrometrijom (GH-MS). **Rezultati**. Na osnovu naših nalaza, dve formule, koje su uključivale seme biljke *flixweed* (5 g), steviju (83 g), cimet (300 mg) ili limetu (400 mg) i 100 mL vode, imale su optimalnu teksturu i organoleptička svojstva. Takođe, dodavanje 0,5% tragakant gume kao sredstva za suspendovanje, omogućilo je da se napitak od semena biljke *flixweed* stabilizuje. Iz 200 g semena ove biljke, ekstrahovano je 0,14 mL eteričnog ulja, što je odgovaralo 0,07% (v/w). Analizom pomoću GH-MS otkriveno je da svakih 100 g semena biljke *flixweed* sadrži 24,85 mg AITC, što odgovara 0,025% w/w. **Zaključak**. Zbog prisustva AITC u semenu biljke *flixweed* i povoljnih karakteristika

Correspondence to: Shirin Parvinroo, School of Pharmacy, Guilan University of Medical Sciences Campus, Guilan, Fouman - Saravan Rd, Rasht, Iran. E-mail: shirinparvinroo@yahoo.com

suspenzije semena ove biljke, ta formulacija se u obliku kesice može predložiti kao biljni dodatak za industrijsku proizvodnju.

Ključne reči:
napici; opstipacija; ishrana, dopune; fitomedicina; biljke, lekovite; korovi; seme; suspenzije; tragakant.

Introduction

Descurainia sophia (L.) Webb ex Prantl (DS), with the common name of flixweed, belongs to the Brassicaceae family [1, 2]. In Persian medicine (PM), it is named *khobbah*, *khaksheer*, and *khakshee* [3, 4].

The main ingredients of the fixed oil from the seeds of flixweed are fatty acids, including oleic, erucic, linolenic, linoleic, palmitic, and stearic acid. However, monoterpenes, sesquiterpenes, and their derivatives are the major constituents in aerial parts [5]. In addition, the volatile oils of flixweed seed (FS) contain benzyl, allyl, propenyl isothiocyanate, and allyl disulfide [6].

Allyl isothiocyanate (AITC) or mustard oil is the most prevalent natural thiocyanate. AITC, with the chemical formula $CH_2 = CHCH_2N = C = S$, is a yellowish oily compound insoluble in water with a boiling point of 152 ºC. Various techniques, including spectroscopic, silver nitrate titration, and chromatographic approaches, have been reported for determining AITC [7–9]. However, gas chromatography (GC) is mainly used for measurements of isothiocyanates in samples of plant origin [10–12].

Anticancer [13], antioxidant [14], analgesic, anti-inflammatory [15], gastric antiulcer [16], and chemopreventive properties [17] are the different beneficial effects of AITC, which various studies have illustrated. Capasso et al. [18] investigated the effects of AITC on gastrointestinal motility in mice. Their *in vitro* experiments demonstrated that AITC decreased contractility in the ileum while promoting contractions in isolated colonic smooth muscle. *In vivo*, AITC was found to reduce upper gastrointestinal transit following intraperitoneal injection but enhance motility when administered intragastrically. Their research indicated that AITC could either stimulate or inhibit motility, depending on the specific area of the gut and the method of administration. Interestingly, these effects were shown to be independent of transient receptor potential ankyrin 1 (TRPA1), a receptor known to regulate gastrointestinal contractions. Additionally, Kojima et al. [19] confirmed AITC may be effective on both types of atonic and spastic constipation induced by clonidine and loperamide, respectively.

According to the reports in the manuscripts of PM, flixweed has several therapeutic advantages. The seeds are aphrodisiacs and digestive tonics, possess appetizing properties, and facilitate childbirth. Not only does PM highlight the therapeutic benefits of medicinal plants, but it also investigates their potential side effects. Furthermore, it proposes suitable interventions to alleviate these adverse effects. In the description of flixweed, headache is introduced as a potential side effect, which can be alleviated by applying tragacanth. Additionally, topical dosage forms of flixweed, whether used alone or in combination with other medications, have been employed in the treatment of conditions such as uterine wounds, mastitis, gout, eye ulcers, testicular swelling, and cancer [3, 4]. Dr. Ahmadieh [20], in his book *Raze Darman* (Secret of treatment), has prescribed DS as an effective remedy for the evacuation of black bile (soda) from the body as a main cause of diseases such as palpitation, eczema, low libido in men and women, dyspepsia, varicose veins, hematologic diseases, varicoceles, constipation, and hemorrhoids. Moreover, different pharmacological effects of flixweed have been addressed by several studies, including antiashmatic [21, 22], anti-tussive and expectorant [23], antioxidant [24], antipyretic and analgesic [25], as well as anti-inflammatory properties [23–25]. Furthermore, its role in the treatment of constipation [26–28] and its cardioprotective [29], anthelmintic [30], cytotoxic [31], anti-hyperthyroid [32], and antidiuretic qualities [33], as well as the ability to alleviate thirst, have been stated [34].

Constipation is one of the most common gastrointestinal complaints [35]. Flixweed remedy (made of flixweed, hot water, and sugar) has been introduced in PM as an effective intervention in constipation [20]. Despite health benefits, instability due to the precipitation of FS is one of the most important challenges for the commercial production of beverages as a supplementary remedy for constipation.

Due to the lack of medicinal products from flixweed in the pharmaceutical market, the aim of this study was to design an oral dosage form of flixweed and examine its physicochemical properties. For the determination of AITC in the extracted essential oils of FSs, GC coupled with mass spectrometry – MS (GC-MS) was used.

Methods

FSs, tragacanth and acacia gums, stevia, red sugar, cinnamon (*Cinnamomum verum* J. Presl) bark, lime [*Citrus aurantifolia* (Christm.) Swingle] fruit, and damask rose (*Rosa damascena* Mill.) flower powder were purchased from an herbal medicine shop in Rasht, Iran. The standard form of AITC was purchased from Titrachem Co. All formulations were prepared with deionized water. A voucher specimen of FS (GUMS-D2) was deposited at the Herbarium of the School of Pharmacy, Guilan University of Medical Sciences, Rasht, Iran. This study was approved by the Ethics Committee of Guilan University of Medical Sciences on May 19, 2021 (No. IR.GUMS.REC.1400.068).

Essential oil extraction

Due to the presence of AITC in flixweed, for this study, we used the Clevenger apparatus and water distillation method to extract the essential oil. Flixweed in the

amount of 200 g was powdered and added to a round-bottom flask, and then distilled water was added. The optimum essential oil amount was obtained after 3 hrs.

Gas chromatography – mass spectroscopy analysis

GC-MS analyses were performed using an Agilent gas chromatograph (Agilent Technologies 7890B) equipped with an HP-5MS fused silica column (5% phenyl methyl polysiloxane 30 m × 0.25 mm i.d., film thickness 0.25 μm), interfaced with an Agilent mass selective detector 5977B (Agilent Technologies, USA) operated by Agilent MassHunter data acquisition software. The oven temperature program initiated at 50 ºC rose at 15 ºC/min to 180 ºC. Other operating conditions were as follows: carrier gas, helium (He) (99.999%), with a flow rate of 1 mL/min; injector temperature 200 ºC; split ratio 1 : 20; mass spectra were taken at 70 electronvolts (eV) and solvent delay 1.7 min; the mass range was from 30–200 atomic mass units (AMU).

The extracted essential oil in the amount of 10 μL was mixed with 10 μL of internal standard (anisole) and finally diluted with methanol up to 10 mL. Subsequently, 1 μL of the solution was analyzed by GC-MS. The concentration of AITC in the FSs was assessed using the internal standard calibration curve (300–900 ppm).

Formulation of powder for suspension of flixweed seeds

First, flixweed was formulated as a suspension in order to figure out the appropriate ingredients and their quantities. Then, the optimized ingredients were utilized as a dry homogenous powder dosage form to be packaged as "flixweed powder for suspension".

Selection and optimization of proper suspending agent

Tragacanth and acacia gums were evaluated as the viscosity modifying and suspending agents in order to stabilize the flixweed suspension and elongate the sedimentation rate for at least 24 hrs. Various concentrations of tragacanth and acacia were hydrated and stirred in distilled water overnight to form a homogenous colloidal dispersion (Table 1). To figure out the minimum required concentration of gums for suspending the FSs, 5% w/v flixweed was added to each medium.

Selection and optimization of proper sweetener and flavoring agent

The selected basic formulation containing gum and flixweed was subjected to stevia and red sugar as natural sweeteners, alone and in combination. After optimization of the sweetening agent, cinnamon, lime, and rose flower powder were utilized as natural flavoring agents (Table 1).

Taste and physicochemical evaluation of flavored formulations

Two optimized final formulations were subjected to a taste panel study: O_2 containing 0.3% w/v cinnamon and O_4 containing 0.4% w/v lime (Table 1). The panel consisted of eight healthy, non-smoking volunteers aged 23–67 years,

Table 1

Formulation optimization of flixweed suspension ingredients (%)

BF	Flixweed seed	Tragacanth	Acacia	Stevia	Red sugar	Cinnamon	Lime	Rose	DW
S_1	5	0.1	0	0	0	0	0	0	100
S_2	5	0.5	0	0	0	0	0	0	100
S_3	5	1	0	0	0	0	0	0	100
S_4	5	0	1	0	0	0	0	0	100
S_5	5	0	3	0	0	0	0	0	100
S_6	5	0	4	0	0	0	0	0	100
K_1	5	0.5	0	1	0	0	0	0	100
K_2	5	0.5	0	3	0	0	0	0	100
K_3	5	0.5	0	5	0	0	0	0	100
K_4	5	0.5	0	0	1	0	0	0	100
K_5	5	0.5	0	0	3	0	0	0	100
K_6	5	0.5	0	0	5	0	0	0	100
K_7	5	0.5	0	1.5	2.5	0	0	0	100
K_8	5	0.5	0	2.5	2.5	0	0	0	100
O_1	5	0.5	0	3	0	0.2	0	0	100
O_2	5	0.5	0	3	0	0.3	0	0	100
O_3	5	0.5	0	3	0	0	0.2	0	100
O_4	5	0.5	0	3	0	0	0.4	0	100
O_5	5	0.5	0	3	0	0	0	0.2	100
O_6	5	0.5	0	3	0	0	0	0.3	100

BF – basic formulation; DW – distilled water.

both male and female. Panel members were asked to rate the taste and aftertaste using the following scale: 0 (undesired) to 5 (ideal). All members tasted both formulations with a washing time of 24 hrs.

Suspension viscosity was measured for the finally selected formulation with the 0.5% w/v concentration of tragacanth as the suspending agent 24 hrs after preparation (Brookfield DVI-Prime, USA) at room temperature.

The pH of the final formulation was measured using a pH meter (QIS, Proline B210, Oosterhout, Netherlands) at 25 °C with three replicates.

The stability of organoleptic properties (visual examination, smell, taste) of the formulations was checked at 5 °C and 25 °C at 24 and 48 hrs.

Results

The minimum required concentrations of tragacanth and acacia that stabilized the FSs suspension were 0.5% and 3.5% w/v, respectively. Since a 3.5% acacia solution presented a high viscosity, which is undesirable for a drink, 0.5% tragacanth was considered the optimal suspending agent for this product. Hence, formulation S_2 was selected for sweetener optimization.

Stevia and red sugar produced a desired sweet taste with at least 3% and 5% w/v, respectively. As red sugar was only available in paste form, it could not be used in powder dosage form, therefore, 3% stevia was used as the favorable sweetener (formulation K_2).

Flavoring agents, including cinnamon, lime, and rose flower powder, could successfully create an eligible taste, masking the undesired flavor of flixweed with minimum amounts of 0.3%, 0.4%, and 0.1% w/v, respectively. Despite the desirable flavor of rose flowers, the fine particles disfigured the suspension. Consequently, the two final formulations, O_2 and O_4, were subjected to a taste panel study.

The mean scores for taste and aftertaste of formulation O_2 (cinnamon flavor) were 4 ± 0.961 and 3.5 ± 0.534, and for formulation O_4 (lime flavor), they were 4.5 ± 0.534 and 4 ± 0.462, respectively (Figure 1). However, the difference was not statistically significant. Due to its higher taste score, O_4 was selected as the final formulation for further evaluation.

The viscosity and pH of O_4 as finally selected formulation were reported to be 974 centipoise (cps) and 5.54 ± 0.012 at room temperature.

Formulations were stable at 24 hrs at 5 °C and 25 °C, and no changes in color, smell, or taste were observed. Moreover, the FSs remained suspended. However, after 48 hrs of storage at both temperatures, an unpleasant bitter smell was detected.

Allyl isothiocyanate content of flixweed seeds

A calibration curve was created using four standard solutions with concentrations of 300 ppm, 500 ppm, 750 ppm, and 900 ppm. The analytical response was determined by the peak area ratio of AITC compared to anisole (at 1,000 ppm). The R-squared (R^2) value for the calibration curve (Equation 1) was 0.994.

The equation is: y = 0.0007x–0.1624; R^2 = 0.944 Eq.(1). Figure S1 (in the Supplementary materials) displays the total ion currents (TIC) for the standard solutions, while the calibration curve for AITC is shown in Figure S2. Figure S3 shows the flow of the formulation optimization of powder for suspension of FS.

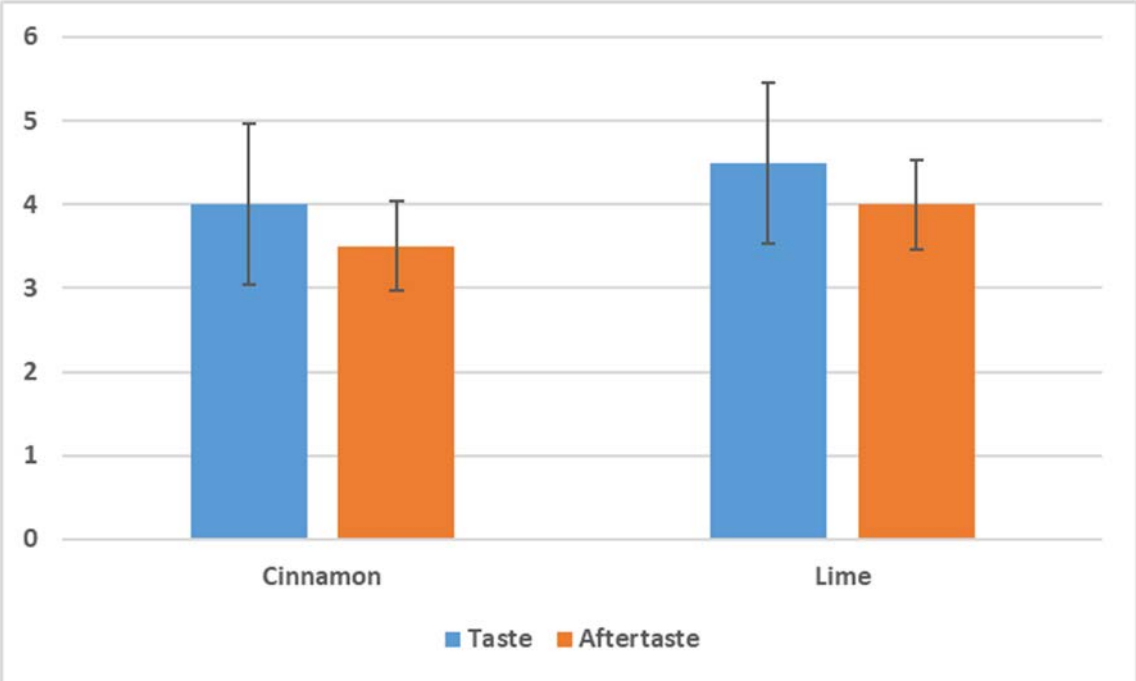

Fig. 1 – Taste panel scores for O_2 (cinnamon) and O_4 (lime) flavors of flixweed seed suspensions.
Note: Scale ranges from 0 (undesirable) to 5 (ideal).

Supplementary materials:

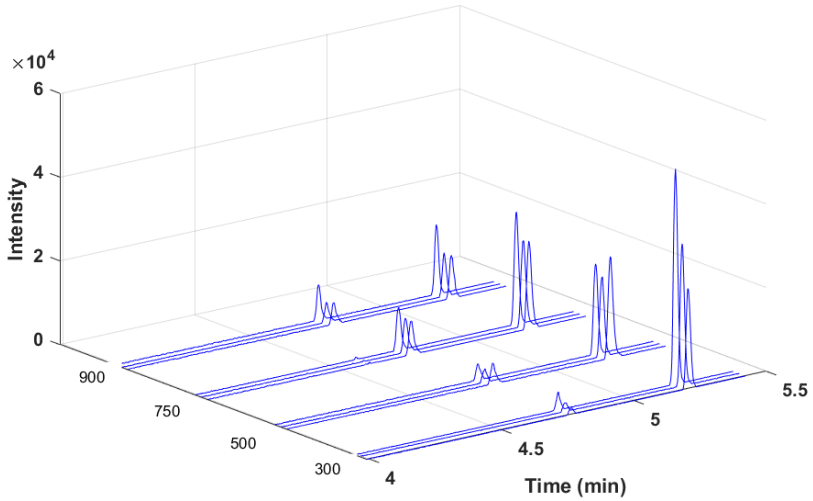

Fig. S1 – Total ion currents of standard AITC solutions at different concentrations (300, 500, 750, and 900 ppm) replicated three times. AITCs came out around 4.76 min while anisole emerged around 5.21 min. AITC – allyl isothiocyanate.

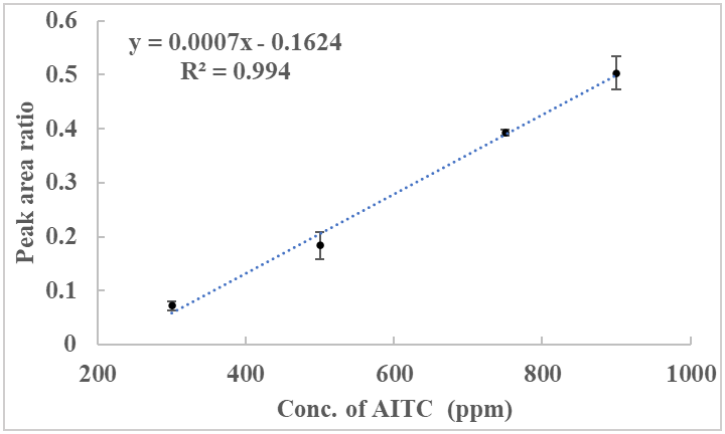

Fig. S2 – Calibration curve of AITC standards. Error bars present standard deviation based on three replicates. Conc. – concentration; AITC – allyl isothiocyanate; ppm – part per million.

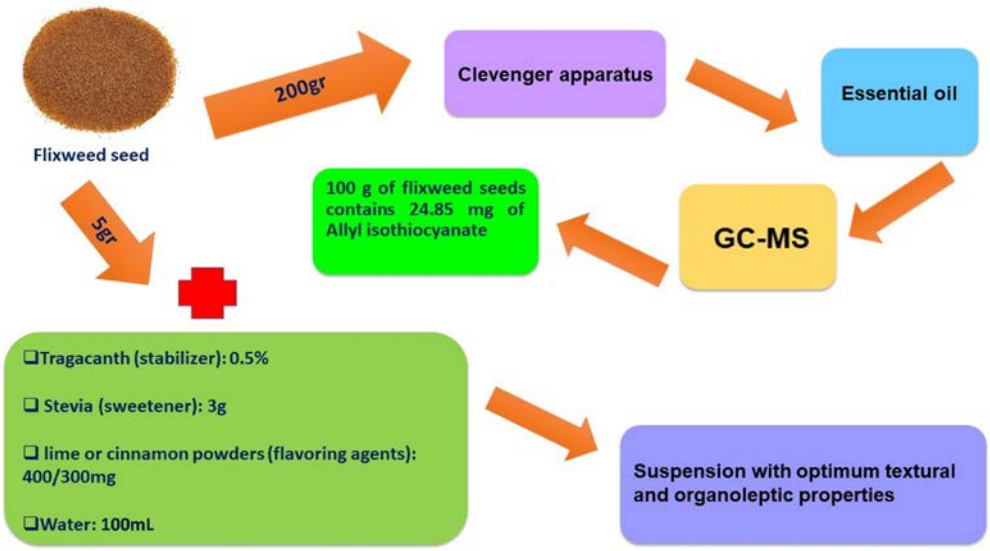

Fig. S3 – The process of formulation optimization of the powder for suspension of flixweed seeds. GC-MS – gas chromatography coupled with mass spectroscopy.

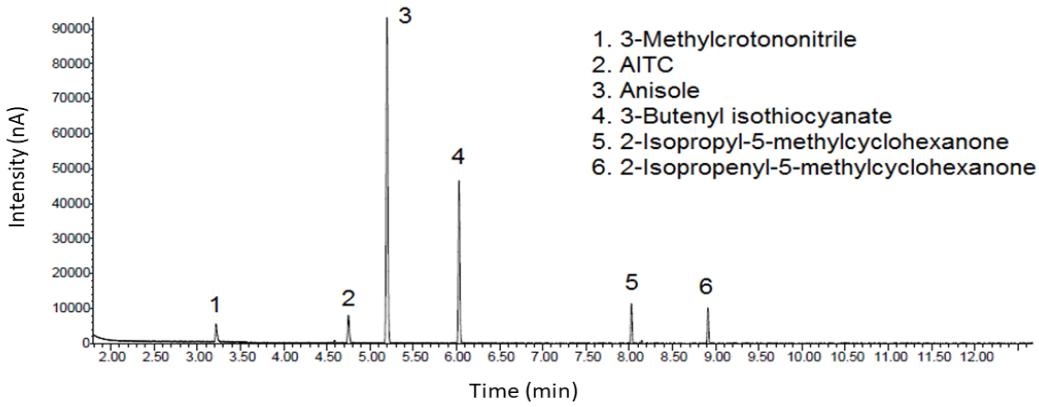

Fig. 2 – Total ion current of flixweed seeds essential oil. The chromatographic peaks represent: 1) 3-methylcrotononitrile; 2) allyl isothiocyanate (AITC); 3) anisole; 4) 3-butenyl isothiocyanate; 5) 2-isopropyl-5-methylcyclohexanone; 6) 2-isopropenyl-5-methylcyclohexanone.

From 200 g of FSs, 0.14 mL of essential oil was extracted, which corresponded to 0.07% v/w. The essential oils of FSs were also analyzed by GC-MS, as shown in Figure 2.

The identity of each peak was assigned using a National Institute of Standards and Technology (NIST) library search. The data revealed that 100 g of FS contained 24.85 mg of AITC, indicating that there was a 0.025% w/w concentration of AITC in the FS.

Discussion

The main objective of this study was to stabilize the flixweed beverage and improve its flavor. Based on our findings, two optimal formulas for the beverage were identified. These formulas included FS (5 g), stevia (3 g), and either cinnamon (300 mg) or lime (400 mg) mixed with 100 mL of water. These formulas exhibited the best textural and organoleptic properties. Additionally, including 0.5% tragacanth gum as a suspending agent stabilized the FS suspension effectively. It has been suggested that tragacanth gum may alleviate the potential side effects associated with FS, as mentioned in the previous studies [3, 4]. However, further research is necessary to provide more evidence for this claim.

Considering the recommended dose of FS in PM texts [3, 4], a 10 g sachet of flixweed (along with the required ingredients) would be a desirable dosage form, leading to increased stability. In PM, the flixweed drink has been traditionally prescribed as a cold or hot syrup, serving as a cooling or laxative agent, respectively [25]. Therefore, the designed sachet can be recommended for dual therapeutic goals in line with these traditional practices.

According to the study conducted by Mohamed and Mahrous [25] in 2009, FS has been determined to be non-toxic up to a dosage of 2,500 mg/kg of body weight. This finding provides valuable information about the safety of FS when used within the recommended dosage range.

In the field of flixweed formula research, numerous studies have been undertaken to investigate the utilization of different ingredients as flavoring agents or stabilizers.

In their study, Hojjati et al. [36] demonstrated that the optimal formulation for a flixweed drink consisted of 5% seed, 6% sugar, and 4% grape syrup. Furthermore, they found that incorporating a concentration of 0.3% xanthan gum effectively prevented the separation of the syrup phase during a thirty-day storage period.

Behbahani and Abbasi [37] investigated the impact of different concentrations of two native gums, Persian gum and gum tragacanth, along with their soluble and insoluble fractions, on the stabilization of a Persian refreshing drink containing flixweed or London rocket seeds (5% wt), basil seeds (0.5% wt), and sucrose (10% wt). Additionally, they examined the effect of ferric chloride ($FeCl_3$) on the rheological and sensory properties of the drink. The results revealed that the insoluble fraction of Persian gum at a concentration of 0.8% wt, the soluble fraction of gum tragacanth at 0.05% wt, and the insoluble fraction of gum tragacanth at 0.14% wt were effective in stabilizing flixweed in the syrup. Additionally, the presence of $FeCl_3$ at a concentration of 0.0025 mol/L induced the formation of a reversible gel when combined with the soluble fraction of gum tragacanth. In terms of sensory characteristics, the drink stabilized with the soluble fraction of gum tragacanth at a concentration of 0.05% wt, demonstrating the highest similarity to the control sample.

In another study, Hassanpour et al. [38] determined that a mixture of xanthan-guar gum and xanthan gum at a concentration of 0.05 g/L had the most favorable effect on stabilizing flixweed particles in a suspension containing 15 g seed, 25 g sugar, and 250 mL of water.

To determine the content of AITC, FS essential oil extraction was done with a yield of 0.07% v/w. In the study by Dekić [39], the percentage of extracted essential oil from fresh plants was 0.022% w/w. In a study conducted by Li et al. [5], the essential oil obtained from the entire aerial parts of the flixweed plant varied from 0.26% to 0.31%. Ara et al. [40] extracted essential oil from FS with a yield of 0.25% v/w. This difference can be related to the difference in the collection place of the plant, the time passed since the collection time, and the extraction method. Li et al. [5] proved in their study

that plant growth in different geographical areas significantly affects the amount and content of essential oil. Different ecological environments, weather conditions, and other biological factors can cause the observed difference.

Our research found that AITC constituted 24.85% w/w of the total essential oil extracted from FSs. In a study by Dekić [39], it was noted that AITC made up 0.3% of the essential oil derived from the underground parts of flixweed. However, there was no specific information regarding the presence or amount of AITC in the aerial parts or seeds of the plant. It is important to note that in Dekic's [39] research, the reported AITC content was based on the peak area of AITC relative to the total peak area of the TIC. On the contrary, we determined the content using a calibration curve, which is a more reliable method. In our study, the peak area percentage of AITC was measured at 3.47%, based on three replicates. One possible reason for the differences in results may stem from the various plant parts used or differences in the geographic locations of the plants studied and extraction methods employed. In addition to AITC, several other compounds were detected in the prepared essential oil, with their peak area percentages relative to the TIC presented in parentheses: 3-methylcrotononitrile (3.05%), 3-butenyl isothiocyanate (18.28%), 2-isopropyl-5-methylcyclohexanone (3.77%), and 2-isopropenyl-5-methylcyclohexanone (3.24%). Among these compounds, 3-butenyl isothiocyanate was found to be the predominant component in the essential oil. This means that it was present in the highest concentration compared to the other detected compounds.

In a study by Breme et al. [41], the essential oil composition of two species, *Brassica cretica* and *Brassica insularis*, from the Brassicaceae family was analyzed using GC-MS. The results revealed that 3-butenyl isothiocyanate was the second dominant compound in the essential oil of both species.

According to Dekić et al. [39], 3-butenyl isothiocyanate was identified in flixweed's underground parts and constituted 27.3% of the total essential oil. However, it was not found in the aerial parts of the plant. This finding suggests that the composition and concentration of compounds can vary between different parts of the flixweed plant.

Conclusion

In the presented study, a flixweed seed suspension with desirable sensory properties and stability was formulated. It was found that a 10 g sachet was a suitable dosage form with stable organoleptic properties. A natural stabilizer was also identified, which could stabilize this supplementary drink and potentially alleviate the adverse effects of flixweed. Additionally, allyl isothiocyanate was quantitatively determined in the formulation. Based on the presence of allyl isothiocyanate in flixweed seeds and the acceptable stability, organoleptic properties, pH, and viscosity of the flixweed seed suspension, it can be suggested that this formulation in the form of a sachet is suitable for industrial production as an herbal supplement product.

Acknowledgement

The authors would like to thank Guilan University of Medical Sciences for supporting this study.

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Received on April 15, 2024
Revised on October 2, 2024
Revised on November 6, 2024
Accepted on November 13, 2024
Online First February, 2025

CASE REPORTS

UDC: 616.61-07:616-006.31
DOI: https://doi.org/10.2298/VSP240630089L

Anastomosing hemangioma of the kidney: a case report

Anastomozirajući hemangiom bubrega

Aleksandar Lazić*, Predrag Marić*, Jelena Tadić†, Božidar Kovačević‡§, Bojana Jovanović‡, Bojana Krća‖, Mirjana Mijušković†§

Military Medical Academy, *Clinic for Urology, †Clinic for Nephrology, ‡Pathology and Forensic Medicine Institute, ‖Institute of Radiology, Belgrade, Serbia; §University of Defence, Faculty of Medicine of the Military Medical Academy, Belgrade, Serbia

Abstract

Introduction. Renal anastomosing hemangioma (AH) is a very rare vascular tumor. This type of tumor is named so because of its unique histological structure, which resembles splenic sinusoidal structures. It may mimic malignant neoplasms, like angiosarcoma, which is why clinical and radiological examinations are insufficient for accurate diagnosis. **Case report.** We present a case of a 39-year-old male admitted to the Clinic for Nephrology at the Military Medical Academy, Belgrade, Serbia, for considering a living-related kidney transplant due to the development of end-stage renal disease (ESRD). His father was identified as the prospective donor. During the patient's pre-transplant evaluation, a suspect tumorous lesion in the left kidney was observed, and multislice computed tomography scanning of the abdomen and small pelvis was performed. This imaging revealed a lobulated soft tissue lesion measuring approximately 25 × 15 mm in the lower pole of the left kidney. Based on this finding, it was decided to proceed with a left nephrectomy to obtain a histopathological assessment of the lesion. The histopathological examination, complemented by immunophenotyping, led to the diagnosis of an AH in the kidney. **Conclusion.** The presented case emphasizes the importance of urgent surgical resection of the tumor mass in order to confirm the diagnosis and avoid any delay in patients scheduled for kidney transplantation.

Key words:
diagnosis, differential; hemangioma; immunohistochemistry; kidney failure, chronic; kidney transplantation; multidetector computed tomography; vascular neoplasms.

Apstrakt

Uvod. Anastomozirajući hemangiom (AH) bubrega je veoma redak vaskularni tumor. Ovaj tip tumora je tako nazvan zbog njegove jedinstvene histološke strukture, koja podseća na sinusoidne strukture slezine. Može ličiti na maligne neoplazme, kao što je angiosarkom, zbog čega kliničko i radiološko ispitivanje nije dovoljno za tačnu dijagnozu. **Prikaz bolesnika.** Prikazujemo 39-godišnjeg muškarca, koji je primljen na Kliniku za nefrologiju Vojnomedicinske akademije u Beogradu, Srbija, radi razmatranja transplantacije bubrega od živog srodnika zbog razvoja terminalne bubrežne bolesti. Kao potencijalni donor bubrega određen je otac bolesnika. Tokom pretransplantacijske procene bolesnika, primećena je sumnjiva tumorska lezija u levom bubregu i urađena je multislajsna kompjuterizovana tomografija trbuha i male karlice. Ovim pregledom je u donjem polu levog bubrega otkrivena lobulirana mekotkivna promena, veličine približno 25 × 15 mm. Zbog navedenog nalaza, odlučeno je da se uradi uklanjanje levog bubrega, radi histopatološke potvrde promene. Patohistološkom analizom, dopunjenom imunofenotipizacijom, dijagnostikovan je AH u bubregu. **Zaključak.** Prikazani slučaj naglašava značaj hitne hirurške resekcije tumorske mase radi potvrde dijagnoze i izbegavanja odlaganja planirane intervencije kod bolesnika kod kojih je planirana transplantacija bubrega.

Ključne reči:
dijagnoza, diferencijalna; hemangiom; imunohistohemija; bubreg, hronična insuficijencija; transplantacija bubrega; tomografija, kompjuterizovana, multidetektorska; krvni sudovi, neoplazme.

Introduction

Primary vascular tumors of the kidney are exceedingly rare, which represents a paradox considering the kidney's robust blood supply, as it is believed to receive nearly one-quarter of the cardiac output. The majority of such cases have been documented as isolated reports in medical literature. Montgomery and Epstein [1] have described a new

Correspondence to: Aleksandar Lazić, Military Medical Academy, Clinic for Urology, Crnotravska 17, 11 000 Belgrade, Serbia. E-mail: medalazic@gmail.com

variant of renal capillary hemangiomas, characterized by distinctive features that combine sinusoidal and hobnail patterns, typical of hemangiomas of the skin and soft tissues. Hemangiomas, more prevalently found in the skin and subcutaneous tissues, are less frequent in visceral locations, with the liver being the most common site [2]. Histologically, hemangiomas are broadly categorized into cavernous and capillary types [3, 4]. A novel variant of renal capillary hemangiomas, characterized by distinct features amalgamating both sinusoidal and hobnail patterns, typically observed in skin and soft tissue hemangiomas, was delineated by Montgomery and Epstein [1] in 2009. This tumor type was designated as "anastomosing hemangioma" (AH) due to its unique histological structure reminiscent of splenic sinusoids. AH was acknowledged in the 2020 World Health Organization classification of soft tissue tumors. Isolated renal AH accounts for 22% of cases and is typically identified as an incidental finding during imaging. The lesion usually presents as solitary, although instances of bilateral and multifocal occurrence have been documented. The radiological characteristics of AH are nonspecific, which complicates the presurgical diagnostic process. Differential diagnoses, which depend on the location of the AH, include, among others, angiosarcoma, clear-cell renal cell carcinoma (RCC), ectopic paraganglioma, and pheochromocytoma [5].

Interestingly, AHs are predominantly observed in patients with end-stage renal disease (ESRD) [6]. Initially believed to be exclusive to the genitourinary system, with a particular affinity for the kidneys [1, 7, 8], AH has since been identified in other parts of the body, including the testes, thighs, the abdominal wall [1], ovaries [7], the adrenal gland [8], the liver, and the gastrointestinal tract [9]. Despite its benign nature, the radiological profiles of AHs closely resemble those of RCCs [1, 10], the most prevalent form of kidney cancer in patients with ESRD [11].

We present a case of AH, definitively diagnosed by histological examination after nephrectomy.

Case report

A 39-year-old male was admitted to the Clinic for Nephrology at the Military Medical Academy, Belgrade, Serbia, for a potential living-related kidney transplantation (KT) from his father as the donor. The patient has been on maintenance hemodialysis since October 2022. Primary kidney disease was focal segmental glomerulosclerosis.

During the pre-transplantation evaluation, a suspicion of a tumorous change in the left kidney led to a multislice computed tomography scan of the abdomen. The scan revealed a lobulated soft tissue change of approximately 25 × 15 mm in the lower pole of the left kidney, which showed a post-contrast peripheral increase in density. Additionally, a similar lesion of about 10 mm was identified in the lower pole of the right kidney, raising the possibility of primary and infiltrative lesions (Figure 1).

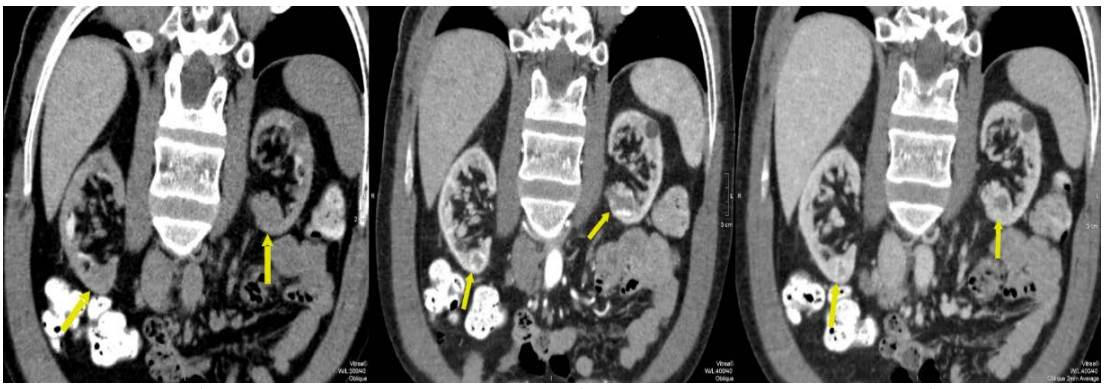
A histopathological examination, complemented by immunophenotyping, was performed.

Macroscopically, the kidney, with a fibrous and fatty capsule and a segment of the ureter measuring 60 mm in length, was observed. On sectioning the renal tissue near one pole, a clearly demarcated, hemorrhagic-looking field measuring 10 × 15 mm was present, processed entirely in molds marked with numbers 3–5.

Microscopically, the renal tissue contained a benign mesenchymal tumor of the hemangioma type, with the largest diameter of up to 15 mm. The tumor was mostly well-demarcated and partly expansively growing with an irregular border towards the surrounding hilus and renal tissue. Histologically, the tumor comprised anastomosing channels of vascular spaces of varying widths with thin walls lined by flat or low cuboidal endothelium. The central zone of the tumor showed sclerosis with foci of hemorrhage and/or hemorrhagic necrosis (Figure 2).

Immunohistochemical analyses yielded diffuse positivity for CD31, CD34, factor VIII, and vimentin in the tumor cells, while reactions for pan-cytokeratin (PanCK), CD10, CK7, α-methylacyl-CoA racemase (AMACR), RCC, and epithelial membrane antigen (EMA) were negative. The proliferative potential of the tumor cells, determined using antibodies for Ki67, was less than 2% (Figure 3).

The histopathologic appearance, along with the immunophenotypic feature of this tumor, indicated a diagnosis of AH of the kidney.



A) **B)** **C)**

Fig. 1 – A) In the lower pole of both kidneys, lobulated soft tissue hypodense lesions are visible, measuring 25 × 15 mm on the left and up to 10 mm on the right. The described changes exhibit pronounced marginal nodular post-contrast enhancement in density during the arterial phase of the examination (B), with slight washout in the venous phase of the examination (C).

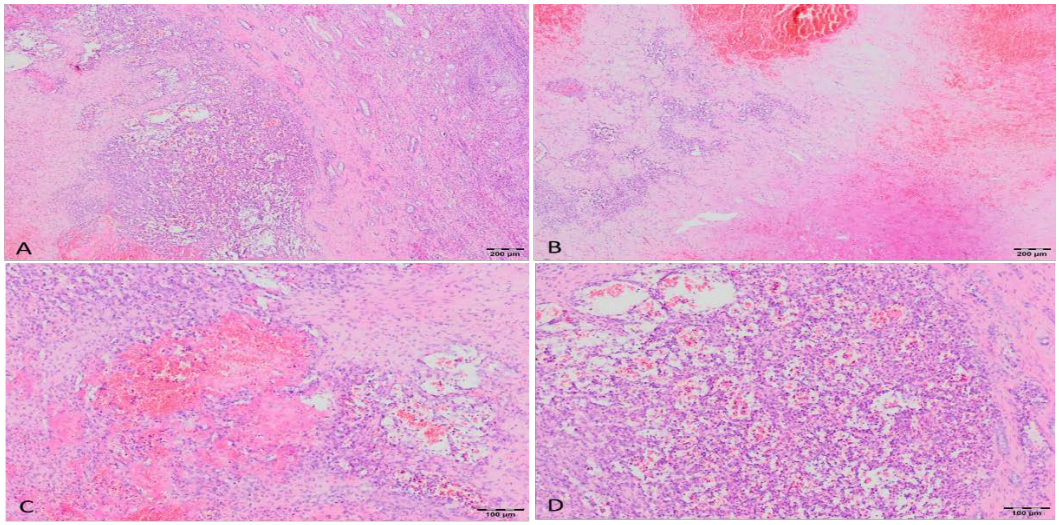


Fig. 2 – A) Expansive growth of anastomosing hemangioma with irregular border to the renal parenchyma [hematoxylin and eosin (HE) staining, ×4]; B) and C) sclerosing zone with foci of hemorrhage (HE staining, ×4 and ×10, respectively); D) focus of prominent thin-walled anastomosing vascular structures, lined by single layer of bland endothelial cells (HE staining, ×10).

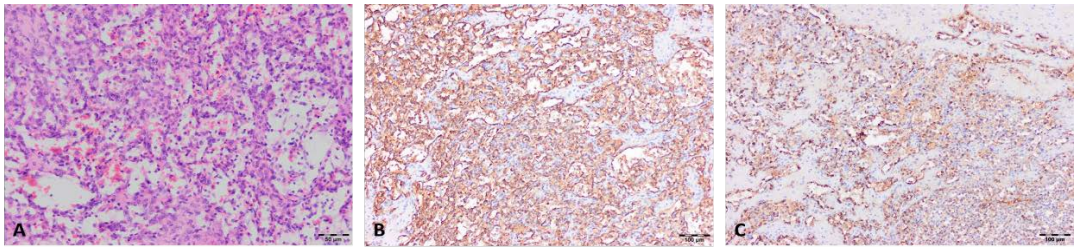


Fig. 3 – A) Higher magnification of prominent thin-walled anastomosing vascular structures, lined by single layer of bland endothelial cells [hematoxylin and eosin (HE) staining, ×20]; B) endothelial cells lining thin-walled anastomosing vascular channels positive to CD34 marker (HE staining, ×10), and C) factor VIII (HE staining, ×10).

Given these findings, due to the differential diagnostic suspicion of RCC and in consultation with a urologist, a decision was made to perform a left nephrectomy for histopathological verification of the change in the lower pole. Given that the patient was already on maintenance hemodialysis and was anuric, there was no need for a spare operation on the left kidney.

The postoperative course was marked by transient fevers, peaking at 38 °C, and the patient was initially treated with third-generation cephalosporins (ceftazidime) and transiently with carbapenems. The blood culture sample showed no increase in bacterial colonies until discharge. The drain from the surgical wound was removed on the second postoperative day, and the wound healed primarily. A secondary anemic syndrome was corrected with the administration of erythropoietin. Four months after the surgical treatment, the patient underwent a successful KT in February 2024.

Discussion

Despite the kidney's good vascularization, primary vascular tumors of the kidney are rare. AHs predominantly affect middle-aged adults, with a mean age of 52.6 years, ranging from 21 to 83 years, and are most commonly observed in individuals in their fifth to sixth decades. Literature indicates a slight male predominance in renal hemangioma cases, with a male-to-female ratio of 1.8 : 1 [12]. The presented case aligns with this demographic, involving a 39-year-old male.

Lesions in this context are typically unilateral, though one bilateral instance has been documented [7]. These tumors can affect both kidneys equally and may involve any renal region. Recent studies have identified activating mutations of *GNA* genes that drive the molecular pathogenesis of AHs [13].

The clinical manifestations of these tumors are nonspecific. While hemangiomas of the bladder have been associated with conditions such as tuberous sclerosis, Klippel-Trenaunay syndrome, and Sturge-Weber syndrome [14], there is no established correlation between AHs of the kidney and any systemic or syndromic conditions [3, 15]. Common clinical presentations include intermittent hematuria, flank pain [1], and lower urinary tract symptoms [4]. However, many lesions are incidentally detected during radiographic investigations for unrelated reasons [7] or due to other diseases at the time of nephrectomy [3, 7]. Nevertheless,

specific features can assist the radiologist in forming a diagnosis. A solid renal mass exhibiting significant T2 hyperintensity, almost resembling a cyst, may serve as an indicator [16]. In the presented case, the patient did not exhibit any symptoms associated with the neoplastic change in the kidney, which can be explained by the fact that the patient was anuric and that the tumor was relatively small in size. Radiological diagnostic procedures prompted suspicion of renal lesions, with nephrectomy leading to a definitive diagnosis. To the best of our knowledge, this is the second case of AH during a medical workup before KT [17].

Approximately 37% of AH cases reported in the literature are associated with ESRD [3, 7, 15]. Büttner et al. [18] found eight hemangiomas, all histologically capillary type with a sinusoidal pattern, indicative of AH in a retrospective examination of 90 nephrectomy specimens from ESRD patients. This, coupled with our case, suggests a propensity for these particular hemangiomas to develop in ESRD. The pathogenesis of ESRD-associated AH remains unclear, but there is a known tendency for kidneys damaged by chronic disease to develop both epithelial renal tumors and benign mesenchymal tumors [18]. It is also important to note that AH can develop in kidneys without chronic disease.

Macroscopically, AHs typically appear well-demarcated yet non-encapsulated with a mahogany brown, spongy consistency, usually situated in the renal hilum [1, 3]. Microscopically, they are well-marginated, often with normal renal tubules entrapped at their periphery [3, 7]. Cytologically, the tumor cells typically lack malignant features, and immunochemically, they consistently express endothelial markers while being negative for other markers, confirming their endothelial origin [1, 4]. These characteristics were also validated in the presented case, with positivity for CD31, CD34, factor VIII, and vimentin in the tumor cells, while reactions for PanCK, CD10, CK7, AMACR, RCC, and EMA were negative.

Differential diagnosis includes malignant vascular tumors such as angiosarcoma and Kaposi sarcoma. Both of these entities, which are infrequent in renal presentations, may exhibit hyaline globules. Specifically, the former often demonstrates an anastomosing vascular pattern and hobnail endothelial cells. This particular histological presentation can lead to diagnostic confusion with AH, particularly when examining needle core biopsy specimens. AH can also be confused with other vascularized renal neoplasms like clear cell RCC [7], hemangioblastoma [19], and glomus tumor [20].

The median size of renal AHs is reported to be 15 mm, with most lesions being smaller than 40 mm [13]. According to this criterion, our case aligns with those previously described in the literature, given that the size of the tumor lesion measured 25 mm in its largest diameter.

Current treatment guidelines for renal hemangioma consider tumor size, location, and patient symptoms [2]. Although AH is benign, surgical intervention is recommended due to its similarities with malignant lesions. In our case, we adhered to these guidelines, opting for left radical nephrectomy. Given the patient's diminished renal function and the need for adequate surgical margins, radical nephrectomy was deemed necessary despite the tumor's small size. It was decided to monitor the lesion in the patient's right kidney, as it shares the same radiological characteristics as the lesion in the operated kidney. We feel disposed to emphasize the importance of conducting regular ultrasound monitoring and, if necessary, computed tomography scanning of the right kidney lesion.

Conclusion

This specific subtype of hemangioma is likely more prevalent than initially perceived and frequently arises in the setting of end-stage renal disease. However, the morphological similarities between anastomosing hemangiomas and renal neoplasms like renal cell carcinomas and angiosarcoma may present a significant challenge. The presented case underlines the importance of prompt surgical resection of suspicious malignant tumor changes in the kidney in order to confirm the diagnosis and avoid any delay in patients scheduled for kidney transplantation. The presented patient underwent a successful kidney transplantation in February 2024, four months after a left-sided nephrectomy.

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Received on June 30, 2024
Revised on August 5, 2024
Revised on November 4, 2024
Accepted on November 13, 2024
Online First December 2024

CASE REPORT

UDC: 616.89-008.441.42:616.24-007.288/.63
DOI: https://doi.org/10.2298/VSP231018001D

Spontaneous air leak syndrome – a very rare pulmonary complication of an eating disorder

Sindrom spontanog curenja vazduha – veoma retka plućna komplikacija poremećaja u ishrani

Marija Djurović*, Nemanja Rančić†‡, Milica Pantić§

***Clinical Hospital Center "Dr. Dragiša Mišović-Dedinje", Clinic for Psychiatry, Department of Adolescent Psychiatry and Psychotherapy, Belgrade, Serbia; †University of Defence, Faculty of Medicine of the Military Medical Academy, Belgrade, Serbia; ‡Military Medical Academy, Center for Clinical Pharmacology, Belgrade, Serbia; §University of Kragujevac, Faculty of Medical Sciences, Kragujevac, Serbia**

Abstract

Introduction. Eating disorders are characterized by persistent body dissatisfaction and unhealthy weight control. Spontaneous air leak syndrome (ALS) is a rare but potentially fatal complication of a perennial eating disorder that can lead to malnutrition with hypoproteinemia. We present a young male suffering from anorexia nervosa who developed a severe form of spontaneous ALS. **Case report.** The 25-year-old male patient was initially treated for problems with an eating disorder of the persistent anorexia nervosa type. He deliberately lost about 40 kg during the previous four years. During hospital treatment, the patient suddenly developed severe pain in the abdomen, for which he was urgently referred to a surgeon. He was admitted to the Intensive Care Unit exhausted and afebrile, with the abdomen below the level of the chest and diffuse painful tenderness, with peristalsis audible and petechiae present on the skin of the back, arms, and thoracic wall. Computed tomography of the thoracoabdominal region was performed, which showed air in the mediastinum, in the spinal canal, around the stomach, in the rectum, and in the small pelvis. After an emergency laparotomy, a drainage of the abdominal cavity and intraoperative esophagogastroduodenoscopy were performed. The patient developed neurological complications postoperatively. After a successful recovery, he was treated psychiatrically on an outpatient basis and monitored for several months. Further similar complaints did not occur. **Conclusion.** Patients with nutritional disorders should be closely monitored because a significant protein deficit with spontaneous ALS can occur. Timely diagnosis and treatment can prevent further somatic deterioration and save the patient's life.

Key words:
anorexia nervosa; diagnosis; emphysema; feeding and eating disorders; laparotomy; surgical procedures, operative; tomography, x-ray computed.

Apstrakt

Uvod. Poremećaje u ishrani odlikuju uporno nezadovoljstvo sopstvenim telom i nezdrava kontrola telesne mase. Sindrom curenja vazduha (SCV) koji se javlja spontano je retka ali potencijalno fatalna komplikacija višegodišnjeg poremećaja u ishrani, koji dovodi do pothranjenosti sa hipoproteinemijom. Prikazujemo mladića lečenog od anoreksije nervoze, kod koga se razvio težak oblik spontanog SCV. **Prikaz bolesnika.** Bolesnik star 25 godina je prvobitno lečen zbog problema sa poremećajem u ishrani po tipu uporne anoreksije nervoze. Namerno je izgubio oko 40 kg tokom prethodne četiri godine. Tokom bolničkog lečenja, bolesnik je iznenada dobio jak bol u trbuhu, zbog čega je hitno upućen hirurgu. Na odeljenje intenzivne nege primljen je iscrpljen, afebrilan, sa trbuhom ispod nivoa grudnog koša, difuzno bolno osetljivim, sa čujnom peristaltikom i petehijama na koži leđa, ruku i zidu grudnog koša. Urađena je kompjuterizovana tomografija torakoabdominalne regije, kojom je viđen vazduh u medijastinumu, u kičmenom kanalu, oko želuca, rektuma i u maloj karlici. Posle hitne laparotomije, urađena mu je drenaža trbušne duplje i intraoperativno ezofagogastroduodenoskopija. Bolesnik je postoperativno imao neurološke komplikacije. Posle uspešnog oporavka, ambulantno je psihijatrijski lečen i praćen tokom više meseci. Nadalje se nisu javljale slične tegobe. **Zaključak.** Bolesnike sa poremećajima u ishrani treba pažljivo pratiti, jer kod njih može doći do značajnog deficita proteina, sa spontanim SCV. Blagovremena dijagnoza i lečenje mogu sprečiti dalje somatsko pogoršanje i spasiti život bolesnika.

Ključne reči:
anoreksija nervoza; dijagnoza; emfizem; ishrana, poremećaji; laparotomija; hirurgija, operativne procedure; tomografija, kompjuterizovana, rendgenska.

Correspondence to: Milica Pantić, University of Kragujevac, Faculty of Medical Sciences, Svetozara Markovića 69, 34 000 Kragujevac, Serbia. E-mail: mpantic2013@gmail.com

Introduction

Eating disorders are characterized by a persistently disturbed eating pattern and perception of body appearance, which results in significant impairment of psychological health and social functioning. A disturbed eating pattern includes skipping meals, restriction of energy intake, or intake of specific macronutrients, with or without vomiting, further complicating the disease's clinical course [1]. Emphysema is a pathological loss of alveolar tissue with increased air space and consequent respiratory function disorder. When it occurs in patients with eating disorders, it presents a serious complication that requires immediate care. In the 1970s, emphysema research was started on animal models of anorexia. The results of initial research indicate that in starved rats, there is a reduction of surfactant with an increase in intraalveolar tension and a tendency towards lung collapse. Surfactant is surface-active fluid/liquid rich in proteins and lipids, and it is produced by alveolar cells to maintain adequate surface tension in the alveoli and the resulting gas exchange at the level of the alveocapillary membrane. Starved rats had reduced protein synthesis and increased proteolysis [2, 3].

Clinical studies have shown that in patients suffering from eating disorders, there is an increase in proteolysis, which, together with previously used lipids, become the material for energy metabolism. Due to the general energy deficit and hypoproteinemia, there is weakness in the respiratory muscles and the functionality of the diaphragm, with systemic oxygen hypoperfusion [4]. Spontaneous air leak syndrome (ALS), characterized by the development of emphysema with pneumothorax, pneumomediastinum, and/or pneumoperitoneum, is a rare but life-threatening complication. It is associated with eating disorders, primarily anorexia nervosa (AN). The syndrome is a consequence of prolonged malnutrition with hypoproteinemia, alveolar damage, and subsequent emphysema leading to additional complications [5]. In this regard, every patient suffering from AN who has respiratory problems or sudden unexplained pain in the abdomen should be taken seriously and examined somatically. Patients who often vomit and who otherwise have a history of frequent respiratory diseases or chronic diseases such as asthma and bronchitis are at particular risk. Pneumomediastinum, subcutaneous emphysema, epidural emphysema, and interstitial emphysema have also been reported in severe AN cases [6, 7].

Although the medical complications of AN are numerous, pulmonary complications are still very rare. Although the exact pathogenetic mechanism has yet to be determined, we can agree that these complications in our patient are secondary and caused primarily by permanent nutritional starvation.

Case report

In our study, we present a 25-year-old male patient, who initially came for an examination in May 2019 due to symptoms of significant body mass loss (he lost 32 kg) in a period of three years (from 2015 to 2018). Due to the need for additional examination, he was admitted to the Department of Adolescent Psychiatry and Psychotherapy at the Clinical Hospital Center "Dr. Dragiša Mišović-Dedinje", Belgrade, Serbia.

The patient is the second of two children from a complete family. The mother's pregnancy and delivery went well, as did the patient's early psychomotor development. He went to school on time and achieved very good and excellent results.

Problems in terms of eating disorders started early in life. During most of his life, the patient was obese, but he had no problems in social relations. After a long, stressful life period, the patient weighed 120 kg in 2015. Then, he started to feel tired in his daily activities, so he decided to lose weight. He started exercising intensively, changed his diet in terms of eating healthy food and regular meals, and reduced his total daily caloric intake. From December 2018 until he reported to the psychiatrist (five months later), he lost 20 kg. In December, while preparing for the last exam, he lost 3–4 kg and regained weight during the New Year holidays. From 2015 to 2018, he lost a total of 32 kg, which, considering his height, was a lot, and at the time of admission, it was life-threatening.

At the time of admission to the Department of Adolescent Psychiatry and Psychotherapy in 2019, he was visibly cachectic, preoccupied with thoughts about food, physical appearance, and his own health. In the first act of treatment, the patient was in the hospital for three days. He left at his own request. The second admission to the Department was realized one month after the previous discharge, in June 2019, after the patient lost another 10 kg (body weight 53 kg, height 187 cm, body mass index 15.156 kg/m^2). On the very day of admission, in order to "prove" that he will start eating adequately and that he does not have to be hospitalized, he ate a large amount of pastries and other high-calorie foods. On the day of admission, in the afternoon, the patient began to complain of severe, diffuse pain in the abdomen that did not stop. Because of the above, a consultation with a surgeon and further somatic treatment was performed.

After a general surgeon examination, the patient was admitted to the Intensive Care Unit. Somatic status showed that the patient was exhausted and afebrile, with the abdomen below the level of the chest and diffuse painful tenderness, peristalsis audible and clear and petechiae present on the skin of the back, arms, and thoracic wall. A computed tomography (CT) scan of the abdomen and pelvis was indicated. The CT scan showed air in the mediastinum and spinal canal. In the arterial phase, there was a filling defect of the *truncus brachiocephalicus*, which could correspond to a thrombus. Pronounced collaterals behind the spinal column were also noted, and air was present around the stomach, rectum, and in the small pelvis (Figures 1–4).

The patient was treated operatively – an exploration of the abdominal cavity with drainage and intraoperative esophagogastroduodenoscopy was performed. Preoperatively,

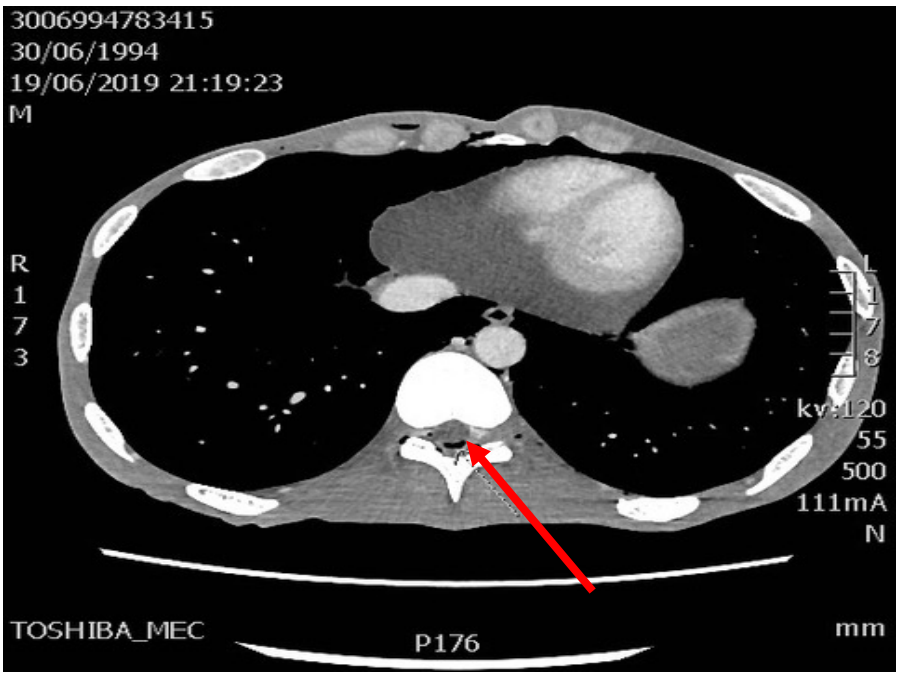

Fig. 1 – Computed tomography scan shows air in the spinal canal (red arrow indicates change).

Fig. 2 – Computed tomography scan shows air retroperitoneally (red arrow indicates change).

minimal duodenal hemorrhage and cardiac insufficiency were noted. Postoperatively, the patient had a prolonged recovery with additional complications. Physical therapy, breathing exercises, and gradual verticalization were prescribed. Due to the catheterization and general poor physical condition, he developed a urinary infection and a bilateral hydrocele. A neurologist was consulted due to a foot drop. On the clinical examination, the following was found: a reduced trophism on the upper extremities, decreased gross motor power, reduced trophism on the lower extremities, no ability to dorsiflex the foot to the left, decreased patellar and Achilles reflexes, no ability to perform Mingazzini's test, Lazarevic's sign positive bilaterally at 110 degrees, left fanned plantar response. Investigation for porphyria was performed but returned negative. Magnetic resonance imaging of the lumbosacral part of the spinal column was performed, and the findings showed the existence of a focal change in the projection of the left transverse process of the second lumbar (L2) spinal vertebral body, which would be a differential diagnosis in favor of a hemangioma. During hospital treatment, laboratory analyses were performed on several occasions, in which elevated parameters of inflammation and hypoproteinemia dominated. After rehabilitation, one month later, the patient was discharged in a better general condition. A selective serotonin reuptake inhibitor (paroxetine) in a dose of 20 mg in the morning and olanzapine were prescribed as psychopharmaceuticals. Follow-up was continued for another year, after which the patient had no new somatic

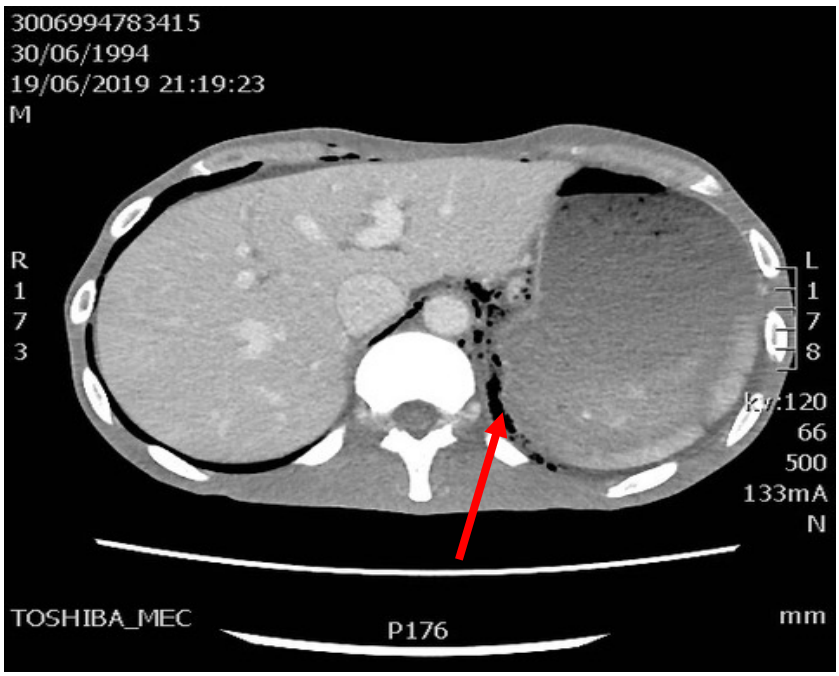

Fig. 3 – Computed tomography scan shows pneumoretroperitoneum (red arrow indicates change).

Fig. 4 – Computed tomography scan shows pneumomediastinum (red arrow indicates change).

complications. Since an adequate nutritional intake was established, there was a restoration of body mass as well as an improvement of psychological functioning. After thi, the patient did not come for follow-up psychiatric examinations.

Discussion

Eating disorders, predominantly AN, carry numerous somatic complications. Although pulmonary complications are rarely described, we believe that in our patient, ALS, with the consequent development of pneumothorax, pneumomediastinum, and pneumoperitoneum, arose as a result of permanent long-term nutritional restriction with a significant protein deficit.

Insufficient protein intake with hypoproteinemia leads the organism to a state of proteolysis. This further leads to the reduction of surfactant, an alveolar fluid that is rich in proteins and lipids and has the function of maintaining adequate surface tension in the alveoli. With the reduction of surfactant, alveolar collapse occurs, which in severe cases further leads to rupture of the alveolar walls with the development of emphysema. This emphysema was named “nutritional emphysema” since the main cause in its genesis is malnutrition [8, 9]. The condition can be complicated further

with the development of pneumothorax and pneumomediastinum. From the mediastinum, air leaks further to the peritoneum *via* the fascial planes of the perivascular space. It is known that the neck and mediastinum communicate with the peritoneum and retroperitoneum through a common visceral space that surrounds the esophagus and trachea and then follows the esophagus through the diaphragmatic opening. There is also an explanation that the presence of a diaphragmatic hernia, combined with anatomical variations where the parietal layer of the peritoneum is missing, leads to the communication of the peritoneum with the mediastinum. These sites of potential communication are called the *foramina* Morgagni, a parasternal defect of the diaphragm, and the *foramina* Bochdalek, a posterolateral defect of the diaphragm [10, 11].

The observed research findings in experimental animal models have been confirmed clinically to some extent. In order to demonstrate the mechanism of elasticity reduction, the content of connective tissue was examined in starved and normally fed rats. In starved animals, a significantly lower amount of connective tissue, hydroxyproline, elastin, and protein was found in the lungs. With the resumption of regular feeding, the hydroxyproline content normalized, but the protein, connective tissue, and elastin content were still at a level lower than normally expected. This showed that, in addition to the reduction of surfactant, changes in the lung tissue can also be explained by the loss of connective tissue [12]. The observed findings in experimental animals have been clinically confirmed to some extent [5].

The risk of developing spontaneous pneumothorax, pneumoperitoneum, and pneumomediastinum is present in all patients with persistent restrictive food intake, especially in patients who vomit due to increased intrathoracic and intraabdominal pressure, which triggers a cascade reaction at the level of previously present alveolar damage [13].

The presented patient had an extremely restrictive caloric intake for a long time. For some time, before being admitted to the hospital, he tried to gain weight by consuming a large amount of caloric food. Because of that, a sudden onset of stomach pain occurred, causing suspicion of somatic complications from the gastroenterological domain. However, after performing imaging diagnostics and obtaining information that the patient has a pneumothorax with pneumoperitoneum and pneumomediastinum, the diagnosis was made in the direction of ALS, a rare but potentially fatal complication in patients who have been exposed to a nutritional deficit for a long time, especially in eating disorders characterized by a long term pattern of starvation and malnutrition.

A phenomenon called the McLean effect has been described in which air trails/leaks after alveolar rupture spread along the bronchovascular bundle back to the mediastinum, leading to pneumomediastinum [13]. Pneumothorax, as a spontaneous secondary phenomenon, has also been reported in avoidant/restrictive food intake disorder - ARFID. This has also been linked to a nutritional deficit, although in this type of eating disorder, body weight may be within the normal range or even excessive. Furthermore, a higher frequency of chronic pulmonary diseases, such as asthma and cystic fibrosis, has been shown in cases of bowel disorders. Namely, these chronic, debilitating diseases were more often associated with inadequate nutrition, lower caloric intake, malnutrition, and, in predisposed cases, with the development of eating disorders [14, 15].

ALS has been described as a complication of numerous internal diseases [bleomycin-induced pneumonia, coronavirus disease 2019 (COVID-19) pneumonia, bronchiolitis obliterans, systemic sepsis, rheumatoid arthritis] and conditions (foreign body in the bronchus, traumatic nasolaryngeal suction), in premature babies with acute respiratory distress syndrome, after transplantation as part of the graft *versus* host disease reaction, and in patients with human immunodeficiency virus [16–20]. However, as a complication of psychiatric disorders, ALS has been described in a very small number of patients with AN. Our case presentation is in positive correlation with the results of other clinical studies stating that vomiting is a rare cause of the development of ALS with consequent pneumothorax. In other research, as well as in our report, it was shown that patients with AN recover more slowly from this complication compared to patients with other diseases with the same complication. Moreover, some papers write about the recurrence potential of ALS in patients with AN due to lung tissue damage, which was not the case in our patient [21, 22].

Conclusion

Eating disorders are among the leading causes of mortality among psychiatric phenomenology. However, the fatal outcome is primarily a consequence of permanent starvation or the act of suicide in these patients. Spontaneous air leakage syndrome, as a potentially fatal complication of permanent malnutrition, should be taken seriously, diagnosed urgently, and promptly treated.

The importance of the presentation of this clinical case is primarily reflected in spreading awareness that eating disorders, although they have a core psychiatric component, are systemic disorders with potentially disabling and fatal complications, which makes them one of the most serious disorders in psychiatry and medicine in general. The importance is also reflected in the fact that such complications are very often not diagnosed in clinical practice because sometimes the symptoms do not have to be dramatic, and the consequences can remain and lead to other somatic problems later in the patient's life. It is always necessary to think about pulmonary complications in any patient suffering from an eating disorder who experiences pain in the region of the neck and chest, difficulty breathing, dysphagia, and abdominal pain. Furthermore, even in cases where the listed symptoms are absent, one should think about this complication of the underlying disease because timely, adequate diagnosis and therapy can prevent further somatic damage and save the patient's life.

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Received on October 18, 2023
Revised on February 23, 2024
Revised on October 28, 2024
Accepted on November 13, 2024
Online First January 2025

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