Publishing Sector of the Society of Physicians of Vojvodina of the Medical Society of Serbia, Novi Sad, Vase Stajica 9
Copublisher: Faculty of Medicine Novi Sad

MEDICAL REVIEW

JOURNAL OF THE SOCIETY OF PHYSICIANS OF VOJVODINA OF THE MEDICAL SOCIETY OF SERBIA
THE FIRST ISSUE WAS PUBLISHED IN 1948

MEDICAL REVIEW is published bimonthly (six issues per year) with a circulation of 1.000 copies. The annual payment fee in 2024, for individuals from the territory of Serbia, is 3,000.00 dinars (the value-added tax included), 5,000.00 dinars for individuals from Serbia who are not members of the Society of Physicians of Vojvodina of the Medical Society of Serbia, 70 Euros for members outside the territory of Serbia, and 9,000.00 dinars (+ VAT) for institutions. The payment account is: 340-1861-70 or 115-13858-06, "Annual membership fee for Medical Review".

The manuscripts are submitted at: aseestant.ceon.rs/index.php/medpreg/. Editorial Office Address: Društvo lekara Vojvodine Srpskog lekarskog društva, 21000 Novi Sad, Vase Stajića 9, Tel. 021/521-096; 063/81 33 875, E-mail: dlvsldnovisad@gmail.com; Website: www.dlv.org.rs

Printed by: "Feljton" Novi Sad

Izdavačka delatnost Društva lekara Vojvodine Srpskog lekarskog društva, Novi Sad, Vase Stajića 9
Suizdavač: Medicinski fakultet Novi Sad

MEDICINSKI PREGLED

ČASOPIS DRUŠTVA LEKARA VOJVODINE SRPSKOG LEKARSKOG DRUŠTVA
***PRVI BROJ JE ŠTAMPAN 1948. GODINE*.**

MEDICINSKI PREGLED izlazi dvomesečno (šest dvobroja godišnje), u tiražu od 1000 primeraka. Pretplata za pojedince sa teritorije Srbije za 2024. godinu iznosi 3.000,00 dinara (sa uračunatim PDV-om), a 5.000,00 dinara za pojedince iz Srbije koji nisu članovi DLV-SLD, 70 eura za članove van Srbije, a za ustanove 9.000,00 dinara (uz dodavanje PDV-a). Uplate se vrše na račun broj 340-1861-70 ili 115-13858-06, s naznakom „Dodatna članarina za Medicinski pregled".

Prijem rukopisa vrši se u elektronskoj formi na stranici: aseestant.ceon.rs/index.php/medpreg/.
Adresa Redakcije: Društvo lekara Vojvodine Srpskog lekarskog društva,
21000 Novi Sad, Vase Stajića 9, Tel. 021/521-096; 063/81 33 875
E-mail: dlvsldnovisad@gmail.com; Web: www.dlv.org.rs

Štamparija: »Feljton« Novi Sad

M E D I C A L R E V I E W
JOURNAL OF THE SOCIETY OF PHYSICIANS OF VOJVODINA OF THE MEDICAL SOCIETY OF SERBIA
Novi Sad Vase Stajića 9 Serbia

Med Pregl 2024; LXXVII (3-4): 75-138 Novi Sad: March-April.

CONTENTS

M E D I C I N S K I P R E G L E D
ČASOPIS DRUŠTVA LEKARA VOJVODINE SRPSKOG LEKARSKOG DRUŠTVA
Novi Sad *Vase Stajića 9* *Srbija*

Med Pregl 2024; LXXVII (3-4): 75-138. Novi Sad: mart-april.

SADRŽAJ

EDITORIAL
UVODNIK

University of Novi Sad, Faculty of Medicine Novi Sad[1]
Clinical Center of Vojvodina, Novi Sad[2]

Uvodnik
Editorial
UDK 616-005.6-092
https://doi.org/10.2298/MPNS2404079V

A NEOTERIC APPROACH TO UNDERSTANDING THROMBOSIS

SAVREMENI PRISTUP RAZUMEVANJU TROMBOZE

Biljana VUČKOVIĆ[1,2]

Summary

Pathophysiology of thrombosis. Thrombosis, a leading cause of morbidity and mortality worldwide, results from an imbalance between procoagulant, anticoagulant, and fibrinolytic factors. Virchow's triad – endothelial injury, stasis of blood flow, and hypercoagulability – has long been the cornerstone for understanding thrombosis. However, evolving knowledge has refined our interpretation of how these factors contribute to venous and arterial thrombosis. **Arterial thrombosis.** Historically, arterial and venous thromboses were viewed as distinct pathophysiological entities. Over the past two decades, research has highlighted the complexity of etiopathogenesis of the thrombotic process, recognizing mutual risk factors offering a more comprehensive understanding the pathophysiological mechanism behind these diseases. **Venous thrombosis.** Recent insights focus on thrombotic potential, defined as an individual's susceptibility to thrombosis resulting from a combination of congenital and acquired risk factors.. It has become clear that the interaction of these factors is not merely additive but synergistic, significantly increasing the risk of thrombosis. The significant social impact of thrombosis underscores the necessity of thoroughly understanding its underlying mechanisms to develop effective preventive and therapeutic strategies.

Key words: Thrombosis; Arteries; Venous Thrombosis; Pathology; Risk Factors

Sažetak

Patofiziologija tromboze. Tromboza predstavlja krajnji produkt disbalansa između prokoagulantnih, antikoagulantnih i fibrinoliznih faktora i jedan od vodećih uzroka morbiditeta i mortaliteta širom sveta. Kamen temeljac razumevanja patofiziološkog mehanizma ove bolesti je koncept Virhovljeve trijade, koji je već vekovima neosporni postulat. Ipak, interpretacija načina na koji individualne komponente ove trijade doprinose pojavi venskih i arterijskih tromboza menja se tokom vremena u skladu sa napretkom saznanja na ovom polju. **Arterijska tromboza.** Arterijska i venska tromboza dugo su smatrane odvojenim patofiziološkim entitetima. Tokom poslednje dve dekade kompleksnost etiopatogeneze tromboze potvrđena je prepoznavanjem zajedničkih faktora rizika koji nude značajno sveobuhvatniji koncept razumevanja patofiziološkog mehanizma odgovornog za pojavu ove bolesti. **Venska tromboza.** Jedna od novina u vezi sa razumevanjem ove teme fokusira se na trombozni potencijal definisan kao individualni „potencijal" pojedinca da doživi trombozu kao rezultat kombinovanja svih urođenih i stečenih faktora rizika za pojavu ove bolesti prisutnih kod ove osobe. Takođe, postalo je očigledno da tokom delovanja različitih etioloških faktora uključenih u patofiziološki mehanizam odgovoran za pojavu tromboze ne dolazi do njihovog jednostavnog sumiranja, nego kombinovanja po tipu multipliciranja uticaja. Veliki negativni socioekonomski uticaj tromboze postavlja imperativ za što bolje razumevanje mehanizma u osnovi nastanka ove bolesti kako bi se postigle što efikasnije preventivne i terapijske strategije.

Ključne reči: tromboza; arterije; venska tromboza; patologija; faktori rizika

ORCID NUMBER
Biljana Vučković 0000-0001-6018-1219

Pathophysiology of thrombosis

Thrombosis is the formation of an obstructive coagulum, resulting from an imbalance among procoagulant, anticoagulant, and fibrinolytic factors. Rudolph Virchow established the foundational concept known as Virchow's triad, which includes changes in the blood vessel wall, blood flow, and blood composition [1]. There three components are integral to the etiopathogenesis of both arterial and venous thrombosis, though the dominance of each component varies, adding complexity to understanding different types of thrombosis.

Historically, arterial and venous thromboses were seen as distinct pathophysiological entities. Arterial thrombosis was thought to result to result

Corresponding Author: Biljana Vučković, Univerzitet u Novom Sadu, Medicinski fakultet, Univerzitetski klinički centar Vojvodine, 21000 Novi Sad, Hajduk Veljkova 1-7, E-mail: biljana.vuckovic@mf.uns.ac.rs

Abbreviations
NO – nitric oxide
FV – factor V

primarily from the changes in the blood vessel wall due to factors like hypertension, hyperlipoproteinemia, smoking, and carbohydrate metabolism disorders, all of which promote endothelial dysfunction. Venous thrombosis, conversely, was attributed to changes in blood flow (venous stasis) and blood composition favoring procoagulant factors. However, recent research over the past two decades has revealed mutual risk factors spanning all three components of Virchow's triad, offering a much more comprehensive understanding of thrombosis [2–4].

Arterial thrombosis

Arterial thrombosis is a leading cause of morbidity and mortality globally, with significant social implications. It causes an acute imbalance between the blood supply and the oxidative demand of organs due to a sudden drop in arterial blood flow, leading to necrosis in the affected organ segment [5].

The primary component of Virchow's triad in arterial thrombosis is damage to the blood vessel wall. This damage is now understood not just as a mechanical defect but as any change in the functionality of the blood vessel wall, particularly endothelial dysfunction, which precedes atherosclerotic plaque formation [6].

Endothelial dysfunction

The endothelium should not be seen merely as a mechanical barrier that separates the blood inside the vascular bed from the subendothelial structures. Healthy endothelium provides a protective, nonthrombogenic surface with vasodilatory and anti-inflammatory characteristics, which is metabolically extremely active tissue maintaining blood homeostasis. Endothelial cells produce antithrombotic molecules (e.g., heparan sulfate, thrombomodulin, prostacyclin, nitric oxide (NO), plasminogen activators) and prothrombotic and antifibrinolytic molecules as needed [7]. Maintaining the balance between these factors is crucial for physiological hemostasis, and a shift towards prothrombotic factors increases the risk of thrombosis. Endothelial cells also modulate smooth muscle cell media through both vasodilators (e.g., NO and prostacyclin) and vasoconstrictors (e.g., endothelin), with a slight physiological predominance of vasodilators. Furthermore, they play a role in immune response modulation during local inflammation, expressing adhesion molecules that bind mononuclear cells and secreting chemokines to recruit leukocytes to the damage site [8]. From the above, it is evident that maintaining hemostatic balance at the endothelial level is highly complex. Subtle disruptions, caused by various etiological factors, are the most common drivers in the pathophysiological mechanism initiating arterial thrombosis.

A wide range of factors can lead to endothelial damage and dysfunction, including mechanical forces and various other etiological factors. Hydrodynamic circumstances play a significant role, as certain arterial regions (such as branching sites) have a greater predisposition for atheroma development. In straight arterial sections, laminar blood flow creates a protective environment by favoring the production of nitric oxide [7], an endogenous vasodilator with anti-inflammatory properties that inhibits platelet aggregation and promotes production of antioxidant enzymes opposing reactive oxygen radicals. These protective functions are compromised at arterial bifurcations, which are predominant sites for atheroma formation. Endothelial dysfunction can also result from chemical irritants, such as smoking, which leads to the production of reactive superoxide anions. These anions interact with intracellular molecules, causing metabolic and synthetic dysfunction in endothelial cells and resulting in local inflammation.

Disruption of endothelial homeostasis due to various factors leads to increased permeability, proinflammatory cytokine release, increased production of surface adhesion molecules, leukocyte recruitment, increased release of vasoactive substances, and loss of antithrombotic characteristics [6]. This endothelial dysfunction is the initial step in atherosclerotic plaque formation, forming the basis for arterial thrombus.

Venous thrombosis

Venous thrombosis, encompassing deep vein thrombosis and pulmonary embolism, has significant population importance [9]. This importance is not just reflected in the incidence rate of 1-3 per 1000 persons per year but also in the high mortality rate of 21% during the first year after the initial episode. Additionally, there is a very high recurrence rate of over 30% in the first ten years and a substantial disability rate due to post-thrombotic syndrome, which affects approximately 20% of venous thrombosis patients [10, 11].

Etiological factors

Understanding the etiopathogenesis of venous thrombosis involved recognizing and comprehending the interplay of various etiological factors [12]. These factors can be congenital or acquired. Key congenital factors include gene mutations like FV Leiden and the prothrombin gene G20210A mutation, and deficiencies in natural coagulation inhibitors such as antithrombin, protein C, and protein S. Important acquired factors include immobilization, surgical procedures, trauma, pregnancy, and antiphospholipid syndrome. Moreover, many factors traditionally associated with arterial thrombosis also increase the risk of venous thrombosis [13–15]. Despite recognizing many etiological factors, it remains unclear why some individuals develop venous thrombosis under certain circumstances while others do not [16].

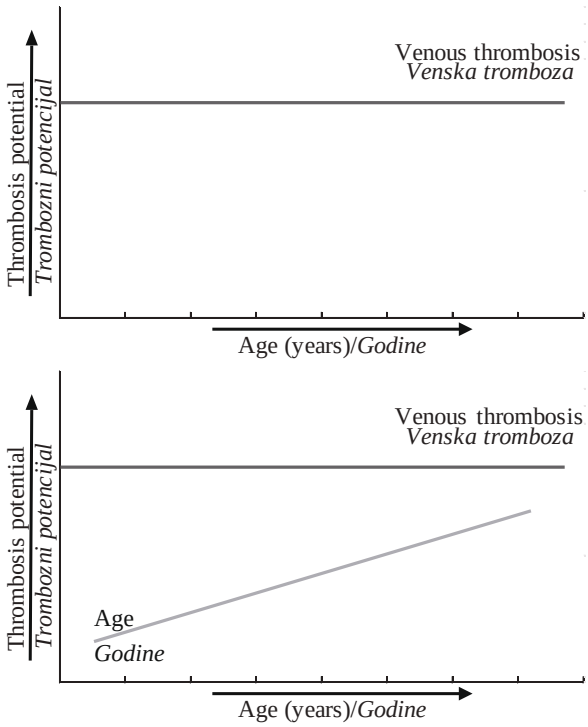


Figure 1. The relationship between thrombotic potential and thrombotic threshold in the light of years as an etiology factor
Slika 1. *Odnos tromboznog potencijala i tromboznog praga u slučaju godina kao etiološkog činioca*

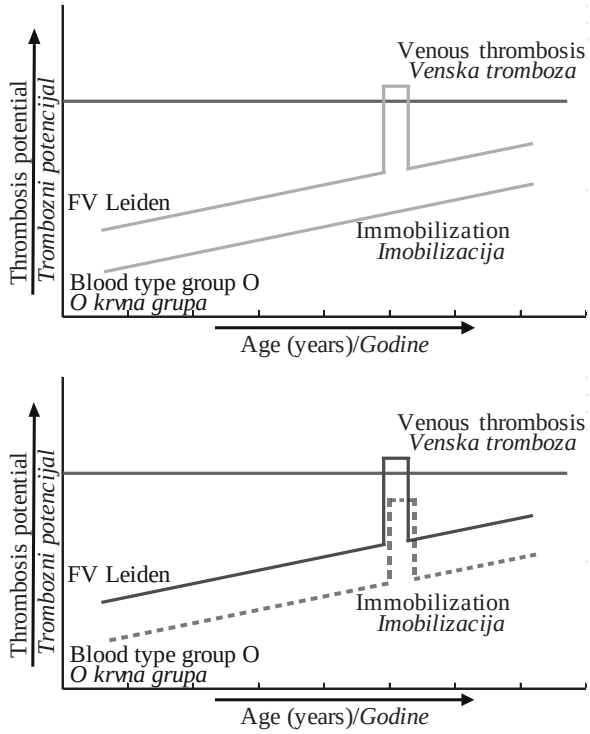


Figure 2. The relationship between thrombotic potential and thrombotic threshold is shown in the case of transient etiological factor action
Slika 2. *Odnos tromboznog potencijala i tromboznog praga u slučaju dejstva tranzitornog etiološkog faktora*

Understanding the impact of etiological factors

The term "thrombotic potential" defines the individual's likelihood of experiencing venous thrombosis, considering all congenital and acquired risk factors. Given the multitude of risk factors, each individual has a unique combination and associated risk [17]. The "thrombotic threshold" is reached when this combination results in a venous thrombosis event. For example, age significantly increases venous thrombosis risk, increasing linearly with aging, implying that everyone would eventually experience venous thrombosis if they lived long enough [18, 19]. The individual's thrombotic potential determines whether the disease occurs within their lifespan. Those with a higher thrombotic potential due to an unfavorable combination of risk factors will experience venous thrombosis sooner than those with a lower thrombotic potential **(Figure 1).**

Transient etiological factors, like immobilization or pregnancy, uniformly increase thrombotic potential across individuals. Whether venous thrombosis occurs in such transient situation depends on the individual's pre-existing thrombotic potential. The thrombotic threshold is reached only in those with a sufficiently high pre-existing thrombotic potential **(Figure 2).**

Understanding how etiological factors combine is crucial. For instance, the heterozygous FV Leiden mutation increases venous thrombosis sevenfold, while oral contraceptive use increases it threefold. If both factors are present simultaneously, the risk increases by over thirty times. This illustrates that the influence of various etiological combines multiplicatively rather than additively [20].

Pathophysiological mechanism

In addition to understanding how etiological factors combine, it is essential to understand how each risk factor contributes to the disease's pathogenesis. Each factor typically increases thrombotic potential in several ways simultaneously. The following examples of various effects of a single etiological factor shed light on this very fact.

Malignancy is a significant etiological factor for venous thrombosis. Mechanisms include a humoral effect, disputing hemostatic homeostasis towards a procoagulant state due to tissue factor production by malignant cells and increased apoptosis leading to microparticle formation. Larger tumors can cause direct venous compression and obstruction. Additionally, immobilization, often associated with malignancy, leads to venous stasis, and chemotherapy further increases thrombotic potential [21].

Pregnancy and the puerperium are significant acquired etiological factors for venous thrombosis. This involves a complex combination of factors from Virchow's triad. Pregnancy increases body weight and the compressive effect of the pregnant uterus on pelvic and lower extremity veins, increasing thrombotic potential. Simultaneously, thrombin

activity stimulation increased as a physiological preparation for bleeding control during labor [22].

These examples highlight the complexity of the pathophysiological mechanism responsible for venous thrombosis and the synergistic combination of synergistic combination of various etiological factors. Considering all the above, it is evident that individual thrombotic potential is the key to understanding this disease.

References

1. Virchow R. Gesammelte Abhandlungen zur Wissenschaftlichen Medizin. Frankfurt: Medinger Sohn & Comp; 1856. p. 219-732.
2. Lippi G, Favaloro EJ. Venous and arterial thromboses: two sides of the same coin? Semin Thromb Hemost. 2018;44(3):239-48.
3. Riva N, Donadini MP, Ageno W. Epidemiology and pathophysiology of venous thromboembolism: similarities with atherothrombosis and the role of inflammation. Thromb Haemost. 2015;113(6):1176-83.
4. Delluc A, Lacut K, Rodger MA. Arterial and venous thrombosis: what's the link? A narrative review. Thromb Res. 2020;191:97-102.
5. Asada Y, Yamashita A, Sato Y, Hatakeyama K. Pathophysiology of atherothrombosis: mechanisms of thrombus formation on disrupted atherosclerotic plaques. Pathol Int. 2020:70(6);309-22.
6. Xu S, Ilyas I, Little PJ, Li H, Kamato D, Zheng X, et al. Endothelial dysfunction in atherosclerotic cardiovascular diseases and beyond. Pharmacol Rev. 2021;73(3):924-67.
7. Cyr AR, Huckaby LV, Shiva SS, Zuckerbraun BS. Nitric oxide and endothelial dysfunction. Crit Care Clin. 2020;36(2):307-21.
8. Laridan E, Martinod K, De Meyer SF. Neutrophil extracellular traps in arterial and venous thrombosis. Semin Thromb Hemost. 2019;45(1):86-93.
9. Wendelboe AM, Raskob GE. Global burden of thrombosis. Circ Res. 2016;118(9):1340-7.
10. Khan F, Tritscheler T, Kahn SR, Rodger MA. Venous thromboembolism. Lancet. 2021;398(10294):64-77.
11. Nicholson M, Chan N, Bhagirath V, Ginsberg J. Prevention of venous thromboembolism in 2020 and beyond. J Clin Med. 2020;9(8):2467.
12. Crous-Bou M, Harrington LB, Kabrhel C. Environmental and genetic risk factors associated with venous thromboembolism. Semin Thromb Hemost. 2016;42(8):808-20.
13. Mackman N. New insights into the mechanisms of venous thrombosis. J Clin Invest. 2012;122(7):2331-6.
14. Poredos P, Jezovnik MK. Endothelial dysfunction and venous thrombosis. Angiology. 2018;69(7):564-7.
15. Henke P. Endothelial cell-mediated venous thrombosis. Blood. 2022;140(13):1459-60.
16. Nikolić D, Basta-Nikolić M, Manojlović V, Milojković J, Batinić N. Cerebral venous sinus thrombosis associated with oligosymptomatic COVID-19 infection – a case report. Med Pregl. 2021;74(9-10):315-9.
17. Pastori D, Cormaci VM, Marucci S, Franchino G, Del Sole F, Capozza A, et al. A comprehensive review of risk factors for venous thromboembolism: from epidemiology to pathophysiology. Int J Mol Sci. 2023;24(4):3169.
18. Wang H, Rosendaal FR, Cushman M, van Hylckama Vlieg A. Procoagulant factor levels and risk of venous thrombosis in the elderly. J Thromb Haemost. 2021;19(1):186-93.
19. Wang Q, Zenaddi R. Oxidative stress and thrombosis during aging: the roles of oxidative stress in RBCs in venous thrombosis. Int J Mol Sci. 2020;21(12):4259.
20. Navarrete S, Solar C, Tapia R, Pereira J, Fuentes E, Palomo I. Pathophysiology of deep vein thrombosis. Clin Exp Med. 2023;23(3):645-54.
21. Hisada Y, Mackman N. Cancer-associated pathways and biomarkers of venous thrombosis. Blood. 2017;130(13):1499-506.
22. Devis P, Knuttinen MG. Deep venous thrombosis in pregnancy: incidence, pathogenesis, and endovascular management. Cardiovasc Diagn Ther. 2017;7(Suppl 3):309-19.

Rad je primljen 9. VII 2024.
Recenziran 9. VII 2024.
Prihvaćen za štampu 9. VII 2024.
BIBLID.0025-8105:(2024):LXXVII:3-4:79-82.

ORIGINAL STUDIES
ORIGINALNI NAUČNI RADOVI

University Clinical Center of Vojvodina, Novi Sad
Clinic of Obstetrics and Gynecology[1]
University of Novi Sad, Faculty of Medicine Novi Sad[2]

Original study
Originalni naučni rad
UDK 618.177-089.888.11:612.63.021]-073
https://doi.org/10.2298/MPNS2404083J

IVF PREGNANCY DATING: COMPARATIVE ANALYSIS OF GESTATIONAL AGE ESTIMATION BASED ON EMBRYO TRANSFER DATE AND ULTRASOUND MEASUREMENTS OF CROWN-RUMP LENGTH

DATIRANJE TRUDNOĆE VANTELESNO REALIZOVANE – UPOREDNA ANALIZA PROCENE GESTACIJSKE STAROSTI NA OSNOVU DATUMA EMBRIOTRANSFERA I ULTRAZVUČNOG MERENJA DUŽINE TEME–TRTICA

Bojana JOVANČEVIĆ[1,2] and Đorđe ILIĆ[1,2]

Summary

Introduction. In in-vitro fertilization pregnancies, the precise date of conception is known. Relying solely on the embryo transfer date for pregnancy dating can lead to inaccuracies and mismanagement in prenatal care. This study aimed to compare gestational age estimated by first-trimester ultrasound measurements with gestational age determined by the known date of embryo transfer. **Material and Methods.** This retrospective study included 30 patients who conceived through in-vitro fertilization. Only patients with singleton pregnancies who underwent first-trimester ultrasound screening by a single sonographer between January 2008 and March 2024 were included. Gestational age was calculated for each patient based on ultrasound measurements of crown-rump length and the date of embryo transfer. **Results.** Gestational age estimated by ultrasound in our study was statistically significantly higher than that determined by the embryo transfer date. The mean difference was 0.9 days (±2.14, 95% confidence interval [0.1, 1.7]) ($p<0.05$), and a median difference was 0.5 days (interquartile range 0-2.75) ($p<0.05$). **Conclusion.** Gestational age estimated by crown-rump length was higher than that calculated by the known date of conception. For pregnancies conceived through in-vitro fertilization, it is advisable to consider both the date of embryo transfer and the gestational age calculated from ultrasound measurements for more accurate pregnancy dating.

Key words: Fertilization in Vitro; Gestational Age; Crown-Rump Length; Ultrasonography; Predictive Value of Tests; Embryo Transfer; Pregnancy Trimester, First

Sažetak

Uvod. U trudnoćama začetim vantelesnom oplodnjom, tačan datum začeća je poznat. Datiranje trudnoća samo na osnovu poznatog datuma embriotransfera potencijalno može dovesti do greške u proceni, te neadekvatnog postupanja u prenatalnom periodu. Naša studija je imala za cilj da uporedi gestacijsku starost procenjenu ultrazvučnim merenjima u prvom trimestru sa onom utvrđenom na osnovu poznatog datuma embriotransfera. **Materijal i metode.** Retrospektivnom studijom obuhvaćeno je 30 pacijentkinja koje su zatrudnele vantelesnom oplodnjom. Uključili smo samo pacijentkinje sa jednoplodnim trudnoćama koje je ultrazvučno pratio isti sonograf u periodu od januara 2008. do marta 2024. Za svaku pacijentkinju, gestacijska starost je izračunata na osnovu ultrazvučnog merenja dužine teme–trtica i datuma embriotransfera. **Rezultati.** Gestacijska starost procenjena ultrazvukom u našoj studiji bila je značajno viša, sa prosečnom razlikom od 0,9 dana (± 2,14, 95% interval poverenja [0,1, 1,7]) ($p < 0,05$) i srednjom razlikom od 0,5 dana (interkvartilni opseg 0–2,75) ($p < 0,05$). **Zaključak.** Gestacijska starost procenjena na osnovu dužine teme-trtica bila je viša u našoj studiji. Pored datiranja trudnoća dobijenih u vantelesnoj oplodnji na osnovu poznatog datuma začeća, bilo bi dobro uzeti u obzir i vrednost dobijenu ultrazvučnim merenjima radi veće preciznosti.

Ključne reči: vantelesna oplodnja; gestacijska starost; dužina teme-trtica; ultrasonografija; prediktivna vrednost testova; embriotransfer; prvi trimestar trudnoće

ORCID NUMBER
Bojana Jovančević 0009-0002-7021-0583
Đorđe Ilić 0000-0001-6448-8795

Introduction

Gestational age (GA) is defined as the time elapsed from the first day of the last menstrual period to the current date. It is a critical parameter used by obstetricians to manage pregnancies and assess fetal growth and development.

Corresponding Author: Bojana Jovančević, Medicinski fakultet Novi Sad, UKCV - Klinika za ginekologiju i akušerstvo, 21000 Novi Sad, Branimira Ćosića 37, bojana.jovancevic@mf.uns.ac.rs

Abbreviations

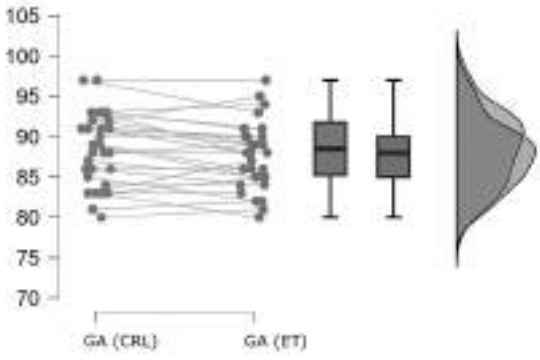
GA – gestational age
IVF – in vitro fertilization
ET – embryo transfer
CRL – crown-rump length
FMF – Fetal Medicine Foundation
IQR – interquartile range
BMI – body mass index

Accurate determination of GA is essential in obstetrics, as errors can impact both maternal and fetal health outcomes. GA is vital for the timing of various prenatal interventions, such as labor induction and corticosteroid therapy administration, and it is crucial in managing pregnancies with small-for-gestation age fetuses [1].

Throughout history, several methods have been employed to estimate GA, ranging from menstrual history-based calculations to advanced ultrasound measurements. Each method has its limitations, and accurate GA estimation remains a challenge for obstetricians worldwide [1].

In the context of in vitro fertilization (IVF), the absence of natural menstrual cycle means that conventional GA estimation methods may not be directly applicable. GA in IVF pregnancies can be determined using various milestones within the IVF procedure [2].

The most common method involves dating the pregnancy from the date of embryo transfer (ET), which is the introduction of the fertilized embryo(s) into the uterine cavity. The date of the oocyte retrieval is considered the date of conception. Depending on the stage of embryo development (cleavage-stage embryo or blastocyst), the ET date serves as the starting point for pregnancy dating in IVF cycles. In frozen IVF cycles, the stage of embryo development at cryopreservation and the dates of embryo thawing and transfer, are considered. GA may also be calculated from the date of embryo biopsy in cases of pre-implantation genetic testing. These methods are generally reliable and widely used [2, 3].



Graph 1. Comparison between gestational age estimated by crown-rump length in the first trimester and by the known date of embryo transfer.

Grafikon 1. *Poređenje gestacijske starosti određene na osnovu dužine teme–trtica i poznatog datuma embriotransfera*

*GA (CRL) – gestational age estimated by crown-rump length/*gestacijska starost određena na osnovu dužine teme-trtica*

*GA (ET) – gestational age estimated by the known date of embryo transfer/*gestacijska starost određena na osnovu poznatog datuma embriotransfera*

However, dating pregnancies solely by the known date of embryo can lead to inaccuracies and mismanagement of prenatal care due to variations in embryo development and implantation timing. Embryos transferred during IVF cycles may develop at different rates compared to those in natural cycles, causing discrepancies between the actual age of the embryo and the calculated GA [4]. Factors such as embryo quality, uterine cavity conditions, and maternal hormonal settings in IVF cycles can further influence embryo development and implantation timing [5, 6].

First-trimester ultrasound dating provides direct visualization of the embryo and allows precise measurement of the gestational sac size and crown-rump length (CRL). This method can minimize the uncertainties associated with embryo transfer dating [7].

The aim of this study was to compare GA estimated by first-trimester ultrasound measurements with GA determined by the known date of ET. The goal is to enhance the understanding of GA determination in IVF pregnancies and support improvements in prenatal care practices.

Material and Methods

This retrospective study was conducted at the Clinic of Gynecology and Obstetrics, University Clinical Center of Vojvodina, covering the period from January 2008 to March 2024. The study received approval from the ethical committee of the University Clinical Center of Vojvodina.

Data including maternal age, weight, height, smoking status, ultrasound findings, date of ultrasound examination, and date and time of embryo transfer were collected anonymously and retrospectively from patients' medical records, eliminating the need for informed consent from the patients.

We enrolled 30 patients who conceived pregnancies through conventional IVF at our department, including both fresh and frozen IVF cycles. Pregnancies achieved by intracytoplasmic sperm injection were excluded. Only singleton pregnancies were considered, and multifetal pregnancies were excluded. Additionally, patients with first-trimester screening results indicating an increased risk for genetic anomalies were excluded, as genetic anomalies can affect fetal growth rates, as observed in fetuses with trisomy 18 and triploidy [8].

All patients underwent first-trimester screening for chromosomal abnormalities in accordance with the Fetal Medicine Foundation (FMF) guidelines [9]. All ultrasound examinations were performed by the single experienced and FMF-certified sonographer.

For each patient, gestational age (GA) was calculated based on ultrasound measurements and the date of embryo transfer.

The crown-rump length (CRL) of each fetus was used as the ultrasound parameter. This measurement was taken using a transabdominal beam, and in some cases, a transvaginal beam when necessary. The fetus was positioned horizontally so that the line from crown to rump is approximately 90° to the ultrasound beam, and assessed in a neutral position without hyperflexion or hyperextension. The image was zoomed to fill most of the screen, and calipers were placed on the endpoints of the crown and rump. GA calculations were based on the highest quality measurement between 45 and 84 mm [9]. The formula developed by Robinson and Fleming was then used to calculate GA from CRL: GA (weeks) = 8.052 × CRL (cm) + 23.73 [10].

GA was calculated for each patient from known conception dates using the following steps: for fresh cycles, the date of oocyte retrieval was set as the date of conception; in frozen-thawed cycles, conception was dated as 4 days prior to cleavage stage embryo transfer or 6 days before blastocyst transfer [11].

The Shapiro-Wilk test was initially conducted to verify the normality of the data distribution. Descriptive statistical methods used included mean ± SD, median, and interquartile range (IQR). Additional descriptive statistics, such as frequencies and percentages, were also employed. Comparisons were made using both the Student's t-test for paired samples and the Wilcoxon signed-rank test. P values less than 0.05 were considered statistically significant. Data was visually represented using tables and graphs. Statistical analysis was conducted using the open-source statistical software JASP (JASP Team, 2024, Version 0.18.3, Amsterdam, Netherlands).

Results

The median age of the women at the beginning of pregnancy was 33.5 years (IQR 31-36). The median height was 168.5 cm, and the median weight was 63.5 kg (IQR 165-172; 59.25-71, respectively). The median BMI was 23.5 (IQR 21.8-24.6). Only two patients (6.67%) had a body mass index (BMI) over 25, while the remaining 28 patients (93.33%) were within the normal weight range.

Three patients (10%) were smokers.

The Shapiro-Wilk test confirmed that the data representing GA estimated by CRL and by the known date of ET followed a normal distribution. Therefore, a paired samples t-test was performed to compare the two methods, which showed statistical significance (t=2.304; p=0.029). A non-parametric Wilcoxon signed-rank test was also indicated statistical significance (t=194; p=0.028).

The mean value of GA estimated by CRL was 88.43 days (±4.48 95% CI [86.76, 90.10]). The mean value of GA estimated by the known date of ET was 87.53 days (±4.15 95% CI [85.98, 89.08]). The median GA values were 88.5 days (IQR 85.25–91.75) and 88 days (IQR 85–90), respectively. GA estimated by ultrasound was higher than GA estimated by the known date of ET, with a mean difference of 0.9 days (±2.14, 95% CI [0.1, 1.7]) ($p<0.001$) and a median difference of 0.5 days [0-2.75] ($p<0.001$). The median GA values were 88.5 days (IQR 85.25–91.75) and 88 days (IQR 85–90), respectively ($p<0.001$). GA estimated by ultrasound was higher than GA estimated by the known date of ET, with a mean difference of 0.9 days (±2.14, 95% CI [0.1, 1.7]) and a median difference of 0.5 days [0-2.75]. In a sample of 30 patients, three (10%) showed a four-day difference in gestational age when assessed by the two methods, and six (20%) showed a three-day difference. **Figure 1** illustrates the comparison between GA estimated by ultrasound measurements in the first trimester and by the known date of ET.

Of all the pregnancies studied, 23 (77%) were obtained through fresh embryo transfer, and the remaining 7 pregnancies (23%) were obtained through frozen embryo transfer.

Discussion

The median age of the women at the beginning of pregnancy was 33.5 years (IQR 31-36), which falls within the typical childbearing age range. The median height of the women in our study was 168.5 cm (IQR 165-172), median weight was 63.5 kg (IQR 59.25-71), and the median BMI was 23.5 (IQR 21.25-24.6). Only two patients were overweight, with a BMI exceeding 25, and there were no obese patients, indicating that our sample generally consisted of women within the healthy weight range according to WHO classifications [12].

In our study sample, only 3 patients (10%) were smokers. Maternal smoking during pregnancy has been shown to impact embryo development early in the first trimester, potentially leading to delayed or altered development [13].

Given the small sample size, we conducted not only a t-test for paired samples but also sensitivity analyses using a non-parametric Wilcoxon signed-rank test to determine if there was a difference between GA calculated by ultrasound and by the known date of ET. Consistent with the findings of the paired samples t-test, the Wilcoxon signed-rank test also showed a statistically significant difference between the two methods of GA estimation. This underscored the robustness of our conclusion regarding the observed difference.

GA estimated by ultrasound in our study was significantly higher, with a mean difference of 0.9 days (±2.14, 95% CI [0.1, 1.7]) and a median difference of 0.5 days (IQR 0-2.75). Our findings were consistent with those of Rapisarda et al. [11], who reported a median difference of 1 day (IQR 0-2), with ultrasound GA being significantly higher than GA calculated by the known date of ET. Bonne et al. showed similar results, with a median difference of 2.3 days (SD 2.36 days), indicating that GA estimated by ultrasound resulted in higher values [14]. Knight et al. noted a mean difference of 3 days (95% CI [2.7, 3.36]), demonstrating that the ultrasound dating method reported higher values [15].

Currently, there is no clear scientific consensus on why ultrasound-estimated GA may be higher, but several hypotheses exist. The selection and culture of embryos in a lab environment may accelerate early embryonic development, leading to greater ultrasound measurement values [16]. Additionally, hormonal treatments used in IVF cycles may influence embryonic growth rates [17]. It has been shown that early implantation of an embryo leads to a larger CRL [18], which may also explain the observed difference, but further research regarding ovulation and implantation timing is needed.

On the other hand, some studies provide evidence suggesting there are no differences in embryonic growth trajectories between naturally conceived and IVF pregnancies [19, 20].

Our findings showed that patients exhibited differences of three days (6 patients, 20%) and even four days (3 patients, 10%) in GA when assessed by two methods used in our study. This variability should not be overlooked, as it is common enough to potentially lead to incorrect decisions in obstetrics. Inaccurate GA can result in either premature or delayed interventions. Precise GA estimation is crucial, particularly when considering assessments for small for gestational age, timing of labor induction, and administration of corticosteroid therapy [1, 21–24]. This is especially important in IVF pregnancies, which are associated with higher risks compared to spontaneously conceived pregnancies [25, 26].

According to ISUOG practice guidelines, CRL measured by ultrasound should be used for GA estimation in all cases except pregnancies conceived by IVF [8]. However, it would be prudent to also consider the date obtained through CRL measurements for additional accuracy.

Conclusion

The gestational age estimated by ultrasound is significantly higher than the gestational age based on the date of embryo transfer.

When dating IVF pregnancies, it would be prudent to consider not only the gestational age based on the date of embryo transfer but also the gestational age obtained through CRL measurements for additional accuracy.

References

1. Committee opinion No 700: methods for estimating the due date. Obstet Gynecol. 2017;129(5):e150-4.

2. Wennerholm UB, Bergh C, Hagberg H, Sultan B, Wennergren M. Gestational age in pregnancies after in vitro fertilization: comparison between ultrasound measurements and actual age. Ultrasound Obstet Gynecol. 1998;12(3):170-4.

3. Alteri A, Cermisoni GC, Pozzoni M, Gaeta G, Cavoretto PI, Viganò P. Obstetric, neonatal, and child health outcomes following embryo biopsy for preimplantation genetic testing. Hum Reprod Update. 2023;29(3):291-306.

4. Lensen S, Lantsberg D, Gardner DK, Sophian AD, Wandafiana N, Kamath MS. The role of timing in frozen embryo transfer. Fertil Steril. 2022;118(5):832-8.

5. Mumusoglu S, Polat M, Ozbek IY, Bozdag G, Papanikolaou EG, Esteves SC, et al. Preparation of the endometrium for frozen embryo transfer: a systematic review. Front Endocrinol (Lausanne). 2021;12:688237.

6. Anagnostopoulou C, Maldonado Rosas I, Singh N, Gugnani N, Chockalingham A, Singh K, et al. Oocyte quality and embryo selection strategies: a review for the embryologists, by the embryologists. Panminerva Med. 2022;64(2):171-84.

7. Salomon LJ, Alfirevic Z, Da Silva Costa F, Deter RL, Figueras F, Ghi T, et al. ISUOG Practice Guidelines: ultrasound assessment of fetal biometry and growth. Ultrasound Obstet Gynecol. 2019;53(6):715-23.

8. Bilardo CM, Chaoui R, Hyett JA, Kagan KO, Karim JN, Papageorghiou AT, et al. ISUOG Practice Guidelines (updated): performance of 11-14-week ultrasound scan. Ultrasound Obstet Gynecol. 2023;61(1):127-43.

9. Victoria H, Kypros N. Sonographic features of chromosomal defects. In: Kypros N, editor. The 11–13+6 weeks scan. London: Fetal Medicine Foundation; 2004. p. 45-58.

10. Loughna P, Chitty L, Evans T, Chudleigh T. Fetal size and dating: charts recommended for clinical obstetric practice. Ultrasound. 2009;17(3):160-6.

11. Rapisarda AMC, Somigliana E, Dallagiovanna C, Reschini M, Pezone MG, Accurti V, et al. Clinical implications of first-trimester ultrasound dating in singleton pregnancies obtained through in vitro fertilization. PLoS One. 2022;17(8):e0272447.

12. Vats H, Saxena R, Sachdeva MP, Walia GK, Gupta V. Impact of maternal pre-pregnancy body mass index on maternal, fetal and neonatal adverse outcomes in the worldwide populations: a systematic review and meta-analysis. Obes Res Clin Pract. 2021;15(6):536-45.

13. Pietersma CS, Mulders AGMGJ, Sabanovic A, Willemsen SP, Jansen MS, Steegers EAP, et al. The impact of maternal smoking on embryonic morphological development: the Rotterdam Periconception Cohort. Hum Reprod. 2022;37(4):696-707.

14. Bonne S, Sauleau E, Sananes N, Akaladios C, Rongières C, Pirrello O. Influence of medically assisted reproduction techniques on crown-rump length and biochemical markers of trisomy 21 in the first trimester of pregnancy. Fertil Steril. 2016;105(2):410-6.

15. Knight B, Brereton A, Powell RJ, Liversedge H. Assessing the accuracy of ultrasound estimation of gestational age during routine antenatal care in in vitro fertilization (IVF) pregnancies. Ultrasound. 2018;26(1):49-53.

16. Sunde A, Brison D, Dumoulin J, Harper J, Lundin K, Magli MC, et al. Time to take human embryo culture seriously. Hum Reprod. 2016;31(10):2174-82.

17. Viganò P, Alteri A, Busnelli A, Vanni VS, Somigliana E. Frozen IVF cycles to circumvent the hormonal storm on endometrium. Trends Endocrinol Metab. 2 020;31(4):296-307.

18. Mahendru AA, Daemen A, Everett TR, Wilkinson IB, McEniery CM, Abdallah Y, et al. Impact of ovulation and implantation timing on first-trimester crown-rump length and gestational age. Ultrasound Obstet Gynecol. 2012;40(6):630-5.

19. Eindhoven SC, van Uitert EM, Laven JS, Willemsen SP, Koning AH, Eilers PH, et al. The influence of IVF/ICSI treatment on human embryonic growth trajectories. Hum Reprod. 2014;29(12):2628-36.

20. Conway DA, Liem J, Patel S, Fan KJ, Williams J 3rd, Pisarska MD. The effect of infertility and assisted reproduction on first-trimester placental and fetal development. Fertil Steril. 2011;95(5):1801-4.

21. Bennett KA, Crane JM, O'shea P, Lacelle J, Hutchens D, Copel JA. First trimester ultrasound screening is effective in reducing postterm labor induction rates: a randomized controlled trial. Am J Obstet Gynecol. 2004;190(4):1077-81.

22. Naidu K, Fredlund KL. Gestational age assessment. In: StatPearls [Internet]. Treasure Island: StatPearls Publishing; 2023. [cited 2024 Jun 1]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK526000/

23. Kaelin Agten A, Xia J, Servante JA, Thornton JG, Jones NW. Routine ultrasound for fetal assessment before 24 weeks' gestation. Cochrane Database Syst Rev. 2021;8(8):CD014698.

24. Whitworth M, Bricker L, Mullan C. Ultrasound for fetal assessment in early pregnancy. Cochrane Database Syst Rev. 2015;2015(7):CD007058.

25. Ochsenkühn R, Strowitzki T, Gurtner M, Strauss A, Schulze A, Hepp H, et al. Pregnancy complications, obstetric risks, and neonatal outcome in singleton and twin pregnancies after GIFT and IVF. Arch Gynecol Obstet. 2003;268(4):256-61.

26. Kopitović V, Milatović S, Pjević AT, Bjelica A, Bujas I, Tabs N. Results and experiences after 1000 IVF cycles at the Clinic for Gynecology and Obstetrics in Novi Sad. Med Pregl. 2011;64(11-12):565-9.

Rad je primljen 28. V 2024.
Recenziran 24. VI 2024.
Prihvaćen za štampu 25. VI 2024.
BIBLID.0025-8105:(2024):LXXVII:1-2:83-87.

University Clinical Center of Vojvodina, Novi Sad, Clinic for Infectious Diseases[1]
University of Novi Sad, Faculty of Medicine Novi Sad
Department for Infectious diseases[2]
Department of Pediatrics[3]
Institute for Child and Youth Health Care of Vojvodina, Novi Sad[4]

Original study
Originalni naučni rad
UDK 616.986.7-07
https://doi.org/10.2298/MPNS2404088D

COMPARISON OF DIFFERENT SCORING SYSTEMS AS PREDICTORS OF THE SEVERITY OF LEPTOSPIROSIS

POREĐENJE RAZLIČITIH SKORING SISTEMA KAO PREDIKTORA TEŽINE KLINIČKE SLIKE OBOLELIH OD LEPTOSPIROZE

Tijana ĐUKIĆ[1], Maria PETE[1,2], Diamela ŽIGIĆ[3,4], Aleksandra BULOVIĆ[1], Danijela PRAŠTALO[1] and Dajana LENDAK[1,2]

Summary

Introduction. Leptospirosis is a zoonotic disease in which 10% of patients develop a severe form that leads to multiorgan dysfunction. Therefore, early identification of high-risk patients is crucial. Existing scoring systems, along with newer ones, can aid in this identification. The study aims to compare the effectiveness of various scoring systems as predictors of severe leptospirosis. **Material and Methods.** This retrospective study included 45 patients, divided into two groups: those with a mild form of the disease and those with a severe form requiring intensive treatment. Demographic, clinical and laboratory parameters were compared between the groups. The scoring systems were evaluated for their effectiveness as predictors of the severity of the clinical presentation. **Results.** Eleven patients (24.4%) developed a severe form of leptospirosis. These patients exhibited significantly higher levels of urea (p=0.001), creatinine (p=0.007), total (p=0.009) and direct bilirubin (p=0.006), and lower levels of hemoglobin (p=0.00) and hematocrit (p=0.00). The Sequential Organ Failure Assessment score emerged as the most statistically significant predictor of severe leptospirosis. **Conclusion.** While The Sequential Organ Failure Assessment score proved to be the best predictor of the severity of the clinical presentation, the QuickLepto score and the scoring system that includes three criteria – hypotension, oliguria and respiratory abnormalities – also have their practical significance. These symptoms are based on clinical criteria that can be assessed upon admission.

Key words: Leptospirosis; Systemic Inflammatory Response Syndrome; Organ Dysfunction Scores; Predictive Value of Tests; Severity of Illness Index; Early Diagnosis

Sažetak

Uvod. Leptospiroza je svetski rasprostranjena zoonoza koja se manifestuje različitom kliničkom slikom. Samo 10% obolelih razvija tešku formu bolesti koja dovodi do multiorganske disfunkcije zbog čega je rana identifikacija visokorizičnih pacijenata veoma važna. U tome nam mogu pomoći već postojeći, ali i noviji skoring sistemi. Stoga je cilj našeg rada bio da uporedimo efikasnost različitih skoring sistema kao prediktore teškog oblika leptospiroze. **Materijal i metode.** Retrospektivna studija je obuhvatila 45 pacijenata koji su podeljeni u dve grupe − na pacijente sa lakšim oblikom bolesti koji nisu zahtevali mere intenzivnog lečenja i na one sa teškim oblikom bolesti koji to jesu zahtevali. Upoređivani su demografski, klinički i laboratorijski parametri između ove dve grupe pacijenata. Međusobno su poređeni skoring sistemi kao prediktori težine kliničke slike obolelih od leptospiroze. **Rezultati.** Jedanaest pacijenata (24,4%) razvilo je težak klinički oblik bolesti. Kod pacijenata koji su razvili težak oblik bolesti značajno su više vrednosti uree (p = 0,001), kreatinina (p = 0,007), ukupnog (p = 0,009) i direktnog bilirubina (p = 0,006), odnosno značajno su niže vrednosti hemoglobina (p = 0,00) i hematokrita (p = 0,00). Kao statistički najznačajniji prediktor težine kliničke slike obolelih od leptospiroze pokazao se *The Sequential Organ Failure Assessment* skor. **Zaključak.** Iako se *The Sequential Organ Failure Assessment* skor pokazao kao najbolji prediktor težine kliničke slike obolelih od leptospiroze, *QuickLepto* skor i skoring sistem koji obuhvata tri kriterijuma – hipotenziju, oliguriju i respiratorne abnormalnosti imaju svoj praktični značaj s obzirom da su bazirani na kliničkim kriterijumima koji se mogu oceniti pri samom prijemu bolesnika na lečenje.

Ključne reči: leptospiroza; sindrom sistemskog inflamatornog odgovora; skorovi disfunkcije organa; prediktivna vrednost testova; indeks težine kliničke slike; rana dijagnoza

ORCID NUMBER
Tijana Đukić - 0009-0005-7252-6241
Danijela Praštalo - 0009-0004-0584-7769
Aleksandra Bulović - 0009-0004-3636-5949
Dajana Lendak - 0000-0003-4323-1776
Maria Pete - 0000-0002-1772-5564
Diamela Žigić - 0009-0009-0817-4834

Introduction

Leptospirosis is a systemic bacterial infection caused by a spirochete belonging to the genus *Leptospira* [1]. Literature indicates that 10% of patients with leptospirosis develop a severe form of the disease, characterized by high leptospiremia, multiorgan dysfunction, and a dramatic increase in mortality, akin to sep-

Corresponding Author: Tijana Đukić, Univerzitetski klinički centar Vojvodine - Klinika za infektivne bolesti, 21000 Novi Sad, Hajduk Veljkova 1-7, E-mail: tijana.cukic22@gmail.com, dajana.lendak@mf.uns.ac.rs

Abbreviations

SIRS – Systemic Inflammatory Response Syndrome
SOFA score – Sequential Organ Failure Assessment score
SPiRO – Systolic blood Pressure, Respiratory auscultation abnormalities, Oliguria

sis [2]. Weil's syndrome is the most severe manifestation, accompanied by jaundice, azotemia, bleeding, anemia and impaired consciousness [3]. Mortality from this disease remains high, often due late diagnosis stemming from an atypical clinical presentation [4]. Early identification of high-risk patients is crucial for timely intervention, which can reduce complications and mortality [5]. Traditional scoring systems for assessing multiorgan dysfunction in sepsis, such as the SIRS criteria (Systemic Inflammatory Response Syndrome criteria) and the SOFA score (Sequential Organ Failure Assessment score), have not proven to be reliable predictors of outcomes in leptospirosis patients [6]. Consequently, researchers have developed new scoring systems such as the QuickLepto score and the SPiRO score (Systolic blood Pressure ≤100 mmHg, Respiratory auscultation abnormalities, Oliguria), to swiftly identify high-risk patients and expedite their referral to intensive care units [7,8]. The study aims to compare the effectiveness of these existing and new scoring systems as predictors of severe leptospirosis.

Material and Methods

This retrospective study included 45 patients diagnosed with leptospirosis and treated at the Clinic for Infectious Diseases of the University Clinical Center of Vojvodina in Novi Sad from January 2008 to August 2017. The study received approval from the Ethics Committee for Clinical Trials on Humans of the Clinical Center of Vojvodina (approval number 00-20/68).

Data were obtained from the patients' medical records, encompassing demographic (gender, age), epidemiological data, and clinical symptoms (myalgia, jaundice, oliguria, gastrointestinal complaints, changes in mental status, cough) observed at the time of admission. Clinical findings included tachycardia, tachypnea, and signs of hemorrhagic syndrome. Furthermore, data on the causative agent were collected.

Laboratory parameters monitored were complete blood count, hemoglobin, hematocrit, C-reactive protein (CRP), fibrinogen, procalcitonin, liver function indicators (alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma–glutamyl transferase (GGT), alkaline phosphatase (ALP), total and direct bilirubin), renal function indicators (urea, creatinine, sodium, potassium and chloride), creatinine phosphokinase (CPK), and prothrombin time (PT) at hospital admission.

The diagnosis of leptospirosis was established on the basis of clinical, laboratory, and epidemiological data and confirmed by serological tests, including microscopic agglutination, ELISA test, and PCR diagnostics.

Patients were divided into two groups: those with a mild form of the disease who did not require intensive treatment and those with a severe clinical form who did. A severe form of the disease was defined as shock requiring vasoactive support, acute renal failure requiring hemodialysis, need for blood product transfusion, acute pulmonary failure requiring mechanical ventilatory support, admission to the intensive care unit, or death [7, 9].

Five scoring systems were used to predict severe leptospirosis: SIRS criteria, SOFA and qSOFA scores, SPiRO score, and QuickLepto score.

The SIRS diagnosis is based on the Centers for Disease Control and Prevention (CDC) criteria: body temperature >38°C or <36°C, heart rate >90 beats/min, respiratory rate >20 respirations/min or PaCO2 <32 mmHg, leukocytes >12,000 cells/mm^3 or <4,000 cells/mm^3 or >10% immature forms of white blood cells [10]. Patients meeting two or more SIRS criteria were defined as having SIRS [11].

The SOFA score assesses the function of six organ systems (PaO_2/FiO_2, platelet count, bilirubin value, hypotension, Glasgow Coma Score, creatinine or diuresis value), with each system scored from 0 (no functional impairment) to 4 (severe functional impairment). Individual scores are summed to obtain a total score ranging from 0 to 24 [12]. The qSOFA score is a simplified version of the SOFA score, using blood pressure (SBP <100 mmHg), respiration rate (RR >22 respirations/min), and mental status (GCS <15) as criteria [13].

The SPiRO score, formulated by Smith and colleagues [7], includes three criteria: oliguria (urine output <500 ml in 24h), abnormal lung auscultation findings, and hypotension (SBP <100 mmHg). Each criterion scores 1 point, with a SPiRO score >1 indicating a severe form of the disease.

Galdino and colleagues [8] developed the QuickLepto score, which uses criteria including age (>40 years), mental status disorder, respiratory problems (cough, abnormal lung auscultation findings, or hemoptysis), mean arterial pressure <80 mmHg, and hematocrit <30%. Each criterion is scored 1 point, except for age, which scores 2 points.

Data processing and statistical analysis were performed using IBM SPSS Statistics version 23.0. The χ^2 test was used to determine the statistical significance of differences between categorical variables. The distribution and variance homogeneity of continuous variables were checked, revealing significant deviations from normal distribution and inhomogeneous variances. Therefore, mean values are presented as median and interquartile range, and the non-parametric Mann-Whitney test was used to compare two groups (mild and severe forms). ROC curves were constructed to assess the predictive significance of each scoring system in predicting severe diseases, and the area under the ROC curve was determined. A p-value <0.05 was considered statistically significant.

Results

During the observed period, 45 cases of leptospirosis were recorded at the University Clinical Center of Vojvodina. The vast majority of patients

Table 1. Age, comorbidities, clinical symptoms and causative agents (serological types of Leptospirosis) in patients with mild and severe forms of the disease
Tabela 1. *Godine života, komorbiditeti, klinički simptomi i uzročnici (seroloski tipovi Leptospiroze) kod bolesnika sa lakšim i težim oblikom bolesti*

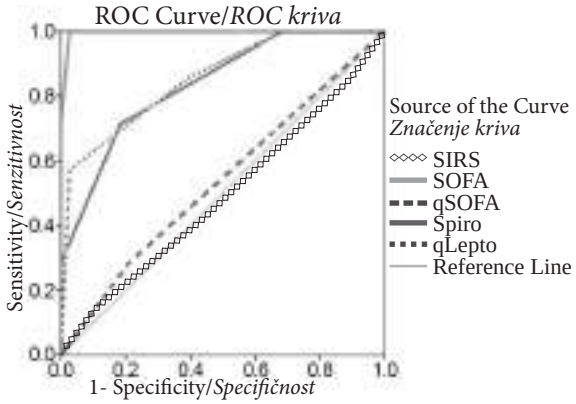
Parameter *Parametar*	Mild form/*Lakši oblik* n=34; n (%)	Severe form/*Teži oblik* n=11; n (%)	p value *p–vrednost*
Age/*Godine života*	49.0 (35.7-61.0)	54.0 (45.0-65.0)	0.285
Diabetes mellitus/*Dijabetes*	4 (57.1%)	3 (42.9%)	0.217
Hypertension/*Hipertenzija*	6 (17.6%)	3 (27.3%)	0.488
Other comorbidities/*Drugi komorbiditeti*	2 (66.7%)	1 (33.3%)	0.711
Hemorrhagic syndrome/*Hemoragijski sindrom*	13 (81.3%)	3 (18.8%)	0.509
Myalgia/*Bolovi u mišićima*	30 (78.9%)	8 (21.1%)	0.217
Jaundice/*Žutica*	20 (71.4%)	8 (28.6%)	0.408
Vomiting/*Povraćanje*	9 (75%)	3 (25%)	0.958
Diarrhea/*Dijareja*	4 (57.1%)	3 (42.9%)	0.217
Stomach pain/*Bol u stomaku*	3 (60%)	2 (40%)	0.391
Oliguria/*Oligurija*	**16 (64,0)**	**9 (36%)**	**0.044**
L. grippotyphosa	7 (100%)	0 (0%)	
L. icterohemorrhagica	3 (75%)	1 (25%)	
L. Bratislava	11 (73.3%)	4 (26.7%)	0.215
L. unspecified	11 (78.6%)	3 (21.4%)	
Other/*Drugi*	2 (40%)	3 (60%)	

Table 2. Presentation of laboratory parameters in patients with severe and mild forms of leptospirosis, and length of hospitalization and days until diagnosis
Tabela 2. *Prikaz laboratorijskih parametara kod pacijenata sa težim i lakšim oblikom leptospiroze kao i dužine hospitalizacije i dana do postavljanja dijagnoze*

Parameter *Parametar*	Mild form/*Lakši oblik* n=34; n (%)	Severe form/*Teži oblik* n=11; n (%)	p value *p–vrednost*
Leukocytes (x10^9)/*Leukociti*	9.05 (6.76-13.15)	11.11 (9.33-17.6)	0.162
Hemoglobin (g/L)/*Hemoglobin*	129.5 (118.0-136.25)	98.0 (90.0-119.0)	0.00
Hematocrit/*Hematokrit*	**0.37 (0.35-0.39)**	**0.29 (0.28-0.34)**	**0.00**
Platelets (x$10^{9)}$/*Trombociti*	**79.5 (38.4-203.5)**	**52.0 (32.0-374.0)**	**0.937**
CRP (mg/L)/*C-reaktivni protein*	158.,0 (83.82-193.85)	80.4 (13.6-142.0)	0.042
Fibrinogen (g/L)	6.18 (5.33-7.99)	4.68 (3.95-8.89)	0.297
PCT (ng/mL)	3.08 (0.67-8.04)	3.74 (1.36-28.55)	0.621
ALT (U/L)	70.5 (48.25-150.75)	82.0 (44.0-138.0)	0.741
AST (U/L)	59.0 (43.75-113.0)	105.0 (33.0-149.0)	0.468
GGT (U/L)	114 (65-238)	64.0 (43.0-103.0)	0.042
ALP (U/L)	97 (71.25-140.50)	132.0 (75.0-195.5)	0.189
LDH (U/L)	433 (237-619.25)	606.0 (292.5-850.5)	0.369
Total bilirubin (μmol/L)/*Ukupni bilirubin*	**55.55 (17.0-147.97)**	**204.6 (100.0-282.0)**	**0.009**
Direct bilirubin (μmol/L)/*Direktni bilirubin*	**30.35 (6.67-111.7)**	**170.0 (69.0-259.8)**	**0.006**
CPK (U/L)	321.0 (149.0-749.0)	410.0 (87.0-1798.0)	0.983
PT (sec)	1.020 (0.935-1.117)	1.030 (0.900-1.210)	0.751
Urea (mmol/L)	**10.35 (6.75-15.30)**	**23.90 (15.90-39.00)**	**0.001**
Creatinine (mmol/L)/*Kreatinin*	**126.0 (99.75-247.75)**	**353.0 (176.0-722.0)**	**0.007**
Sodium (mmol/L)/*Natrijum*	138.5 (135.75-142.0)	136.0 (133.0-141.0)	0.213
Potassium (mmol/L)/*Kalijum*	3.80 (3.49-4.17)	3.90 (3.20-4.20)	0.781
Chloride (mmol/L)/*Hlorid*	105.0 (101.0-110.0)	103.0 (95.0-110.0)	0.475
Days to diagnosis (day)/*Dani do postavljanja dijagnoze*	5.0 (4.0-8.0)	7.0 (5.0-8.25)	0.228
Length of hospitalization (day)/*Dužina hospitalizacije*	14.5 (11.0-21.0)	17.0 (8.0-25.0)	0.874

Table 3. Comparison of scoring systems as predictors of the severity of clinical presentation of patients with leptospirosis
Tabela 3. *Međusobno poređenje skoring sistema kao prediktore težine kliničke slike obolelih od leptospiroze*

	AUC ROC curve *AUC ROC kriva*	p value *p–vrednost*	95%CI *95%CI*	Optimal cut-off *Optimalni presek*	Sensitivity *Senzitivnost*	Specificity *Specifičnost*
SOFA	**0.996**	**<0.001**	0.914-1.000	>9	100%	97.37%
qSOFA	0.538	0.757	0.383-0.687	–	–	–
SIRS	0.509	0.940	0.356-0.661	–	–	–
SPiRO	**0.836**	**<0.001**	0.696-0.930	>1	71.43	81.58
QuickLepto	**0.855**	**<0.001**	0.718-0.942	>3	57.14	97.37



Graph 1. AUC ROC curves of observed scoring systems
Grafikon 1. *AUC ROC krive posmatranih skoring sistema*

were male (44/45, 97.8%), with only one female patient (1/45, 2.2%).

According to the criteria mentioned, 11 patients (24.4%) had a severe form of the disease, while 34 patients (75.6%) had a milder form. Hemodialysis was required in 6 patients (13.3%), blood transfusion in 8 patients (17.8%), intensive care unit treatment and mechanical ventilation support in 3 patients (6.7%), and vasoactive support in 1 patient (2.2%). There were 2 recorded deaths (4.4%).

A positive epidemiological survey was present in 9 out of 11 patients (81.8%) with a severe form of leptospirosis, and in 28 out of 34 patients (82.4%) with a milder form (p=0.968). Exposure factors were similar between groups, with fishing (16/34 patients (47.1%) with mild form and 5/11 patients (45.5%) with severe form) and swimming in stagnant water (8/34 patients (23.5%) with mild form and 2/11 patients (18.2%) with severe form) being the most common. Other risk factors, such as professional exposure in agriculture (2/34 mild form and 0/11 severe form) and animal husbandry (2/34 mild form and 1/11 severe form) were less prevalent. No statistically significant difference was found in the severity of the clinical picture concerning exposure (p=0.552).

Patients with severe leptospirosis were slightly older than those with a milder form, but this difference was not statistically significant (p=0.285). There was no statistically significant difference in comorbidities (diabetes mellitus, arterial hypertension and other comorbidities) between patients with mild and severe forms of leptospirosis **(Table 1).**

Analyzing clinical symptoms at admission, oliguria was more common in patients with severe leptospirosis (p=0.044), while the other symptoms did not show statistical significance **(Table 1).**

Although not statistically significant, the highest percentage of severe disease (3/5 patients, 60.0%) was caused by Leptospira Australis and Leptospira Harggio. Conversely, Leptospira grippotyphosa led to only a mild disease (7/7 patients, 100.0%) (**Table 1**).

Patients with severe leptospirosis had statistically significantly higher values of urea (p=0.001), creatinine (p=0.007), total bilirubin (p=0.009) and direct bilirubin (p=0.006), and statistically significantly lower values of hemoglobin (p=0.00) and hematocrit (p =0.00) compared to patients with mild leptospirosis (**Table 2)**.

There was no statistically significant difference in the length of hospitalization or the days from hospitalization to diagnosis between patients with mild and severe disease **(Table 2).**

To identify the best predictor of disease severity in leptospirosis, five different scoring systems (SOFA score, qSOFA score, SIRS, SPiRO score, and QuickLepto score) were compared **(Table 3).**

The SOFA score, SPiRO score, and QuickLepto score were statistically significant predictors of severe leptospirosis, whereas qSOFA and SIRS were not.

Comparing the AUC ROC values **(Graph 1)** between the SOFA, SPiRO, and QuickLepto scores showed that the SOFA score had the highest AUC ROC value, making it a statistically significantly better predictor than the SPiRO score (p=0.036). Although the SOFA score had a larger AUC ROC, the difference compared to the QuickLepto score was not statistically significant (p=0.074). Additionally, there was no statistically significant difference between the QuickLepto score and SPiRO scores (p=0.725).

Discussion

Leptospirosis is a globally prevalent zoonosis, posing significant challenges, particularly in underdeveloped countries [14]. While most patients exhibit asymptomatic or mild form, a minority experience severe immune responses, leading to cytokine storms and multiorgan dysfunction [2]. Given the similarities in pathophysiology and clinical mani-

festations with sepsis, the SIRS criteria and SOFA score (including qSOFA) are commonly used to predict the severity of leptospirosis. Recent studies have focused on developing new scoring systems to enable rapid diagnosis and prognosis of leptospirosis, and to determine the need for intensive care.

In our study, patients were categorized into two groups: those with mild forms (not requiring intensive care) and those with severe forms. Our findings indicated no statistically significant difference in age, comorbidities, length of hospitalization, and the causative Leptospira serotype between the groups. However, patients with severe forms had statistically significantly lower hemoglobin and hematocrit values and higher levels of urea, creatinine, direct and indirect bilirubin. Oliguria was also more common in severe cases. These observations are consistent with a study in Turkey [15], which found that SIRS positive patients (with severe leptospirosis) had statistically significantly higher leukocyte ($p=0.002$) and serum creatinine ($p<0.001$) levels, that vomiting ($p=0.046$) and abdominal pain were significantly more frequent ($p= 0.025$), and more frequent changes on chest X-ray ($p=0.003$). Different clinical manifestations of the disease may be a consequence of the different sample and different representation of serotypes, considering that different serotypes of Leptospira cause different clinical presentations [16].

Our results demonstrated that the SOFA score is a superior predictor of disease severity compared to the SIRS criteria and the qSOFA score ($p <0.001$). This aligns with other studies favoring the SOFA score over SIRS criteria [17–21] for predicting severe outcomes. On the other hand, some studies underscore the sensitivity of SIRS criteria [22, 23]. Our results are supported by the fact that, besides infection and sepsis, many non-infectious processes (e.g. pancreatitis, ischemia, multiple trauma, hemorrhagic shock) [25] can lead to systemic inflammatory response syndrome [24], making the SIRS criteria rather non-specific scoring system.

The SPiRO score, another recent scoring system, has shown promise as a predictor of severe leptospirosis. Smith and colleagues [7] conducted a study comparing the SPiRO score to the qSOFA score, finding that the SPiRO score was a statistically significantly better predictor of the severity of leptospirosis ($p=0.003$). The SPiRO score is also supported by numerous studies identifying hypotension, oliguria, and abnormal lung findings as predictors of severe leptospirosis [25–28]. Our research corroborates these findings, demonstrating that the SPiRO score is a statistically significantly superior tool for predicting severe clinical presentations compared to the qSOFA score. However, it did not outperform the SOFA score, which, based on our results, remains the best scoring system for predicting the severity clinical presentations of patients with leptospirosis.

The QuickLepto score is another emerging tool for predicting severe leptospirosis. Our findings indicated that the qLepto score is a better predictor than qSOFA score and SIRS criteria, though not statistically significantly different from the SOFA score ($p=0.074$) or SPiRO score ($p=0.725$). A similar study was conducted in March 2023 [8], comparing the newly developed LeptoScore and qLepto score with widely used scoring systems like SPiRO and qSOFA. Their results indicated that the SPiRO and qSOFA scores have low specificity and sensitivity for leptospirosis patients, making their performance inferior to LeptoScore and qLepto score.

While these studies suggest that SPiRO and qLepto scores are advantageous for predicting the severity of leptospirosis, our research found the SOFA score to be superior. The practical application of the SPiRO and qLepto scores remains noteworthy. Both scoring systems, particularly the SPiRO score, rely on clinical criteria that can be assessed upon patient admission. This is especially useful in rural areas where leptospirosis is more prevalent and laboratory diagnostics are limited. Furthermore, the availability of radiological methods and the expertise required for interpreting these findings are often lacking in such areas, making the SPiRO and qLepto scores highly valuable for quick and effective patient assessment.

A limitation of our study is its retrospective nature, leading to some missing patient information. Additionally, leptospirosis is not widespread in Serbia, resulting in a small sample size.

Currently, several scoring systems can predict the severity of leptospirosis quickly and easily based on criteria available during hospitalization. While different studies favor different systems, their use is crucial in managing and treating patients, particularly in resource-limited areas where the disease is prevalent.

Conclusion

Although the Sequential Organ Failure Assessment score proved to be the best predictor of leptospirosis severity, the **S**ystolic blood **P**ressure, **R**espiratory auscultation abnormalities, **O**liguria and the QuickLepto scores also have practical significance. These scores rely on clinical criteria that can be assessed upon admission, making them particularly useful in underdeveloped regions where leptospirosis is widespread.

References

1. Sethi S, Sharma N, Kakkar N, Taneja J, Chatterjee SS, Banga SS, et al. Increasing trends of leptospirosis in northern India: a clinico-epidemiological study. PLoS Negl Trop Dis. 2010;4(1):e579.

2. Cagliero J, Villanueva SYAM, Matsui M. Leptospirosis pathophysiology: into the storm of cytokines. Front Cell Infect Microbiol. 2018;8:204.

3. Mijailović Ž, Čanović P, Gajović O. Weilov sindrom u toku leptospirozne infekcije - prikaz jednog bolesnika. Med Pregl. 2007;60(9-10):493-6.

4. Bharti AR, Nally JE, Ricaldi JN, Matthias MA, Diaz MM, Lovett MA, et al. Leptospirosis: a zoonotic disease of global importance. Lancet Infect Dis. 2003;3(12):757-71.

5. Pongpan S, Thanatrakolsri P, Vittaporn S, Khamnuan P, Daraswang P. Prognostic factors for leptospirosis infection severity. Trop Med Infect Dis. 2023;8(2):112.

6. Velissaris D, Karanikolas M, Flaris N, Fligou F, Marangos M, Filos KS. Commonly used severity scores are not good predictors of mortality in sepsis from severe leptospirosis: a series of ten patients. Crit Care Res Pract. 2012;2012:532376.

7. Smith S, Kennedy BJ, Dermedgoglou A, Poulgrain SS, Paavola MP, Minto TL, et al. A simple score to predict severe leptospirosis. PLoS Negl Trop Dis. 2019;13(2):e0007205.

8. Galdino GS, de Sandes-Freitas TV, de Andrade LGM, Adamian CMC, Meneses GC, da Silva Junior GB, et al. Development and validation of a simple machine learning tool to predict mortality in leptospirosis. Sci Rep. 2023;13(1):4506.

9. Hochedez P, Theodose R, Olive C, Bourhy P, Hurtel G, Vignier R, et al. Factors associated with severe leptospirosis, Martinique, 2010-2013. Emerg Infect Dis. 2015;21(12):2221-4.

10. ICD-9-CM Official Guidelines for Coding and Reporting

11. ICD-9-CM Official guidelines for coding and reporting effective October 1, 2011 [Internet]. 2012 [cited 2017 Feb 14]. Available from: http://www.cdc.gov/nchs/data/icd/icd9cm_guidelines_2011.pdf

12. Tai HCH, Yeh CC, Chen YA, Hsu CC, Chen JH, Chen WL, et al. Utilization of systemic inflammatory response syndrome criteria in predicting mortality among geriatric patients with influenza in the emergency department. BMC Infect Dis. 2019;19(1):639.

13. de Grooth HJ, Geenen IL, Girbes AR, Vincent JL, Parienti JJ, Oudemans-van Straaten HM. SOFA and mortality endpoints in randomized controlled trials: a systematic review and meta-regression analysis. Crit Care. 2017;21(1):38.

14. Marik PE, Taeb AM. SIRS, qSOFA and new sepsis definition. J Thorac Dis. 2017;9(4):943-5.

15. Victoriano AF, Smythe LD, Gloriani-Barzaga N, Cavinta LL, Kasai T, Limpakarnjanarat K, et al. Leptospirosis in the Asia Pacific region. BMC Infect Dis. 2009;9:147.

16. Yilmaz H, Turhan V, Yasar KK, Hatipoglu M, Sunbul M, Leblebicioglu H. Characteristics of leptospirosis with systemic inflammatory response syndrome: a multicenter study. Ann Clin Microbiol Antimicrob. 2015;14:54.

17. Pappas G, Papadimitriou P, Siozopoulou V, Christou L, Akritidis N. The globalization of leptospirosis: worldwide incidence trends. Int J Infect Dis. 2008;12(4):351-7.

18. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016;315(8):801-10.

19. Williams JM, Greenslade JH, McKenzie JV, Chu K, Brown AFT, Lipman J. Systemic inflammatory response syndrome, quick sequential organ function assessment, and organ dysfunction: insights from a prospective database of ED patients with infection. Chest. 2017;151(3):586-96.

20. Wester AL, Dunlop O, Melby KK, Dahle UR, Wyller TB. Age-related differences in symptoms, diagnosis and prognosis of bacteremia. BMC Infect Dis. 2013;13:346.

21. Zhang W, Zheng Y, Feng X, Chen M, Kang Y. Systemic inflammatory response syndrome in Sepis-3: a retrospective study. BMC Infect Dis. 2019;19(1):139.

22. Seymour CW, Liu VX, Iwashyna TJ, Brunkhorst FM, Rea TD, Scherag A, et al. Incorrect data. JAMA. 2016;315(20):2237. Erratum for: JAMA 2016;315(8):762-74.

23. Rosa RG, Moraes RB, Lisboa TC, Schunemann DP, Teixeira C. Does SOFA predict outcomes better than SIRS in Brazilian ICU patients with suspected infection? A retrospective cohort study. Braz J Infect Dis. 2017;21(6):665-9.

24. Solligård E, Damås JK. SOFA criteria predict infection-related in- hospital mortality in ICU patients better than SIRS criteria and the qSOFA score. Evid Based Med. 2017;22(6):211.

25. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest. 1992;101(6):1644-55.

26. Ko AI, Galvao Reis M, Ribeiro Dourado CM, Johnson WD Jr, Riley LW. Urban epidemic of severe leptospirosis in Brazil. Salvador Leptospirosis Study Group. Lancet. 1999;354 (9181):820-5.

27. Panaphut T, Domrongkitchaiporn S, Thinkamrop B. Prognostic factors of death in leptospirosis: a prospective cohort study in Khon Kaen, Thailand. Int J Infect Dis. 2002; 6(1):52-9.

28. Covic A, Goldsmith DJ, Gusbeth-Tatomir P, Seica A, Covic M. A retrospective 5-year study in Moldova of acute renal failure due to leptospirosis: 58 cases and a review of the literature. Nephrol Dial Transplant. 2003;18(6):1128-34.

29. Papa A, Theoharidou D, Antoniadis A. Pulmonary involvement and leptospirosis, Greece. Emerg Infect Dis. 2009; 15(5):834-5.

Rad je primljen 15. V 2024.
Recenziran 2. VII 2024.
Prihvaćen za štampu 2. VII 2024.
BIBLID.0025-8105:(2024):LXXVII:3-4:88-93.

Subotica General Hospital, Subotica

Original study
Originalni naučni rad
UDK 618.19-006.6:615.277.03
https://doi.org/10.2298/MPNS2404094B

USE OF CYCLIN-DEPENDENT KINASE 4 AND 6 INHIBITORS IN TREATING METASTATIC BREAST CANCER – A YEAR-LONG EXPERIENCE OF SUBOTICA GENERAL HOSPITAL IN PATIENT FOLLOW-UP

PRIMENA INHIBITORA CIKLIN-ZAVISNIH KINAZA 4 I 6 U LEČENJU METASTATSKOG KARCINOMA DOJKE – JEDNOGODIŠNJE ISKUSTVO U PRAĆENJU PACIJENATA OPŠTE BOLNICE SUBOTICA

Teodora BRDAR ZELEN, Marija JOVIŠEVIĆ and Anja PRICA

Summary

Introduction. According to GLOBOCAN data from 2020, breast cancer ranks first in the number of newly diagnosed malignancies. The treatment of advanced, hormone-positive breast cancer has evolved with the use of cyclin-dependent kinase 4 and 6 inhibitors in first- and second-line treatment for metastatic, hormone-positive, HER2-negative breast cancers, in combination with endocrine therapy. As of May 31, 2022, these drugs have become available in the Republic of Serbia. This paper aims to present a one-year experience of a secondary health center in monitoring patients using the treatments. **Material and Methods.** The data analysis included patients treated with cyclin-dependent kinase 4 and 6 inhibitors from June 1, 2022, to June 1, 2023, at General Hospital Subotica. The analysis covered demographic data, disease presentation, previous therapies, drug usage, side effects, duration, and therapy outcomes. Patients were categorized into two groups based on age (<60 and >60 years) and by the nature of their disease (relapsed or initially metastatic). **Results.** A total of 43 patients were treated with cyclin-dependent kinase 4 and 6 inhibitors: 23 (53.5%) in the first line and 20 (46.5%) in the second line. The median therapy duration was eight cycles for patients younger than 60 years. A good therapeutic response was observed in 53.5% of patients. Patients younger than 60 years with late relapse exhibited statistically significantly better treatment outcomes compared to those older than 60 years (p=0.04). The most common site of metastases was the bones (51%, 22 patients), with half of these patients showing a good therapeutic response. **Conclusion.** Although the observed period is short, ongoing monitoring and further research are planned to share experiences on the use of these drugs.

Key words: Breast Neoplasms; Neoplasm Metastasis; Cyclin-Dependent Kinase Inhibitor Proteins; Antineoplastic Agents, Hormonal; Treatment Outcome

ORCID NUMBER
Teodora Brdar Zelen 0000-0001-9802-1720
Marija Jovišević 0009-0002-0339-3121

Sažetak

Uvod. Prema podacima GLOBOCAN iz 2020. godine, karcinom dojke je prvi po broju novodijagnostikovanih slučajeva i čini 11,7% svih maligniteta. Lečenje uznapredovalog, hormonpozitivnog karcinoma dojke je promenjeno primenom inhibitora ciklin-zavisnih kinaza 4 i 6 u prvoj i drugoj liniji metastatskih, hormon-pozitivnih, Her2 negativnih karcinoma dojke u kombinaciji sa endokrinom terapijom. Od 31. 5. 2022. godine ovi lekovi su dostupni u Republici Srbiji. Cilj rada je prikazivanje jednogodišnjeg iskustva sekundarnog zdravstvenog centra u praćenju pacijenata koji ih koriste. **Materijal i metode.** Analiza podataka obuhvatila je pacijente lečene inhibitorima ciklin-zavisnih kinaza 4 i 6 u periodu od 1. 6. 2022. do 1. 6. 2023. godine u Opštoj bolnici Subotica. Analizirani su demografski podaci, prezentacija bolesti, prethodna terapija, primena navedenih lekova, neželjena dejstva, dužina trajanja i ishod terapije. Pacijente smo podelili prema starosti u dve grupe (< 60 i > 60 godina), a potom i u odnosu na relaps ili inicijalno metastatsku bolest. **Rezultati.** Ukupno 43 pacijenta su lečena inhibitorima ciklin-zavisnih kinaza 4 i 6; u prvoj liniji njih 23 (53,5%), a u drugoj 20 (46,5%) pacijenata. Medijana dužine trajanja terapije od osam ciklusa zabeležena je kod pacijenata mlađih od 60 godina. Dobar terapijski odgovor zabeležen je kod 53,5% pacijenata. Pacijenti mlađi od 60 godina sa kasnim relapsom imaju statistički značajno bolje ishode lečenja u poređenju sa pacijentima starijim od 60 godina (p = 0,04). Najučestalija lokalizacija metastaza su kosti (51%, 22 pacijenta); polovina ovih pacijenata ima dobar terapijski odgovor. **Zaključak.** Posmatrani period je kratak te se planira dalje praćenje i istraživanje u cilju razmene iskustava o primeni ovih lekova.

Ključne reči: karcinom dojke; metastaze; inhibitori ciklin zavisne kinaze; hormonska antineoplastična terapija; ishod lečenja

Anja Prica 0009-0000-8409-6609

Introduction

According to the 2020 Global Cancer Statistics (GLOBOCAN), breast cancer has surpassed lung cancer in terms of the number of newly diagnosed cases, with 2.3 million new cases, accounting for 11.7% of all malignancies. Breast cancer also ranks first in mortality among women [1]. In 2021, approximately 4,500

Corresponding Author: Teodora Brdar Zelen, Opšta bolnica Subotica, 24000 Subotica, Izvorska 3, E-mail: brdarteodora@gmail.com

Abbreviations

HR+	– hormone receptor positive
ER	– estrogen receptor
PgR	– progesterone receptor
Her2	– human epidermal growth factor 2
DFS	– disease free survival
CDK4/6 inhibitors	– cyclin dependent kinase 4 and 6
PFS	– progression free survival
iDFS	– invasive disease free survival
RFZO	– Republic Health Insurance Fund
AI	– aromatase inhibitors
CTCAE	– Common Terminology Criteria for Adverse Events
CR	– complete response
PR	– partial response
SD	– stabile disease
PD	– progressive disease

new cases of breast cancer were diagnosed in the Republic of Serbia, making it is the most frequent malignancy among women in the country [2]. **Figure 1** illustrates the global distribution of similar cases.

Hormone-positive breast cancer constitutes about 75% of all breast cancer cases [3]. Patients with hormone receptor-positive (HR+) breast cancer, characterized by estrogen receptor (ER) and progesterone receptor (PgR) positivity, generally have better survival rates compared to other types of breast cancer, such as triple-negative or HER2-positive breast cancer. This improved survival is largely due to the effective use of endocrine therapy, which is employed in neoadjuvant, adjuvant, and metastatic stages of the disease. Adjuvant endocrine therapy can reduce the risk of disease relapse by approximately 50% [4]. However, there remains a risk of relapse even after a prolonged disease free survival (DFS) period. Consequently, diagnostic tests such as OncotypeDX and Mammaprint have been developed to predict which patients at a higher risk of relapse and to aid in the decision-making process regarding adjuvant chemotherapy [5].

Despite advancements in early detection and treatment of breast cancer, which have led to decreased mortality rates, there is still a need for new treatment methods and the identification of new predictive and prognostic factors [6].

Figure 1. Most commonly diagnosed malignant disease per country
Slika 1*. Najčešće dijagnostikovano maligno oboljenje u zemljama sveta*

The treatment landscape for advanced, hormone-positive breast cancer has undergone significant changes following the PALOMA-2, MONALEESA-2, MONALEESA-7, and MONARCH-3 studies. These studies led to the approval of palbociclib, ribociclib, and abemaciclib for first-line use in metastatic, hormone-positive, HER-2 negative breast cancer in combination with endocrine therapy. These drugs are CDK4/6 inhibitors that work by inhibiting the transition of cells from the G1 phase to the S phase of the cell cycle [7].

The PALOMA-3, MONARCH-2, and MONALEESA-3 studies are placebo-controlled, randomized phase III trials that investigated the efficacy of CDK4/6 inhibitors in combination with fulvestrant in postmenopausal women who had progressed on previous endocrine therapy. All these studies demonstrated a significant prolongation of progression free survival (PFS) [8]. Encouraged by the results in metastatic disease, researchers have also explored the effect of these drugs in the earlier stages of the disease. However, the PALLAS and PENELOPE B studies, which examined the adjuvant use of palbociclib in combination with endocrine therapy, did not show a significant prolongation of invasive disease free survival (iDFS) compared to adjuvant endocrine therapy alone, and thus, these drugs have not been adopted for adjuvant treatment [9]. Conversely, abemaciclib was approved for adjuvant use with endocrine therapy following the results of the monarchE study in October 2021 [10].

Ongoing studies continue to investigate the use of CDK4/6 inhibitors across various stages of the disease, in combination with different endocrine therapies, and alongside anti-HER2 therapy in HR+/HER2-positive breast cancers [11].

As of May 31, 2022, in the Republic of Serbia, the Republic Health Insurance Fund (RFZO) has approved the use of CDK4/6 inhibitors, specifically palbociclib and ribociclib, for the treatment of hormone receptor-positive and HER2-negative advanced or metastatic breast cancer. These drugs can be used as initial endocrine therapy in combination with an aromatase inhibitor (AI) or in the second line in combination with fulvestrant for patients who have previously received endocrine therapy. The decision to use these drugs is made by three doctors in tertiary health institutions where the medications are dispensed [12].

Material and Methods

To present a one-year experience in the follow-up of patients who received CDK4/6 inhibitors at the oncology center, patient data were collected using the electronic hospital information system and analyzed using Microsoft Excel. The research was approved by the ethics committee of the Subotica General Hospital. The observation period spanned from June 1, 2022 to June 1, 2023.

The data analysis encompassed demographic characteristics, previous treatments, application of CDK4/6 inhibitors, side effects according to the Common Terminology Criteria for Adverse Events (CTCAE), and duration of therapy. Disease outcomes were assessed

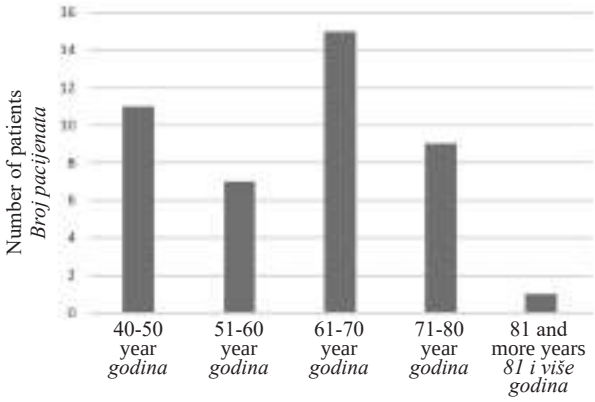
based on clinical, radiological, and laboratory findings and categorized as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). The results were presented in tabular and graphical formats, and statistical processing included the application of the Chi-square test.

The study utilized sources from verified professional literature on established knowledge about hormone-positive breast cancer and its treatment, as well as data from recent research studies, scientific works, and international guidelines. This approach aimed to unify and compare these sources with our own experience.

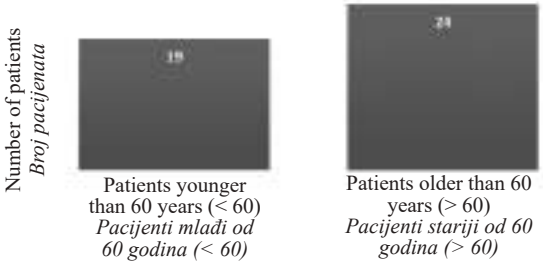
Results

During the observed period, 43 patients treated with CDK4/6 inhibitors under the new RFZO indication were monitored at Subotica General Hospital. Among these patients, one was male, and 42 were female. The median age was 62 years, ranging from 40 to 84 years. The age distribution of patients is illustrated in **Graph 1,** which divides them into two groups: those younger than 60 years (<60) and those older than 60 years (>60) **(Graph 2).**

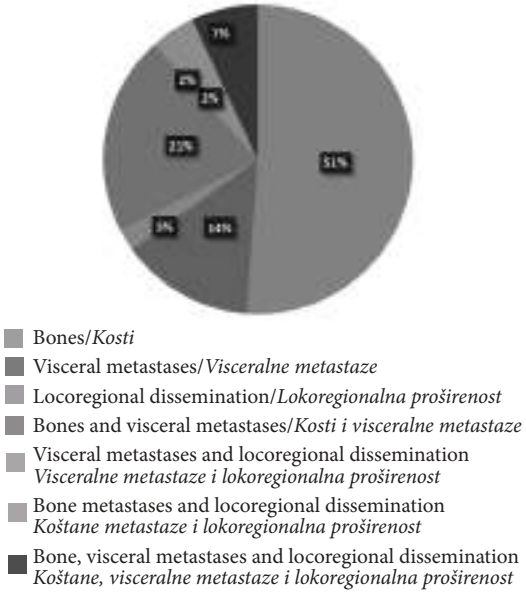
Out of the total number of patients, 29 (67.4%) experienced a relapse of the disease, while 14 (32.6%) were initially diagnosed and treated as having metastatic disease. An early relapse was noted in 16 (37.2%) patients, whereas 13 (30.2%) had a late relapse.



Graph 1. Age structure of patients treated with CDK4/6 inhibitors
Grafikon 1. *Starosna struktura pacijenata lečenih CDK4/6 inhibitorima*



Graph 2. Groups of patients according to age
Grafikon 2. *Grupe pacijenata prema godinama starosti*



Graph 3. Metastatic sites and their frequency
Grafikon 3. *Lokalizacije metastaza i njihova zastupljenost*

Graph 3 shows the localization of metastases, revealing that bone metastases were the most common, occurring in 22 patients (51%). Tamoxifen and anastrozole were the most frequently used adjuvant therapies among our patients.

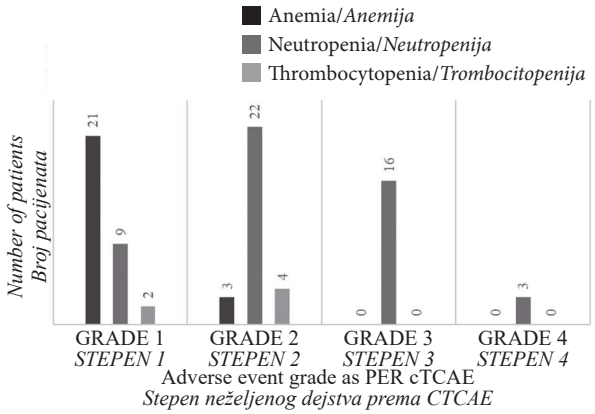
In the first line of metastatic disease, an aromatase inhibitor (anastrozole or letrozole) was used as monotherapy by 10 patients. CDK4/6 inhibitors were not initially represented in Serbia. Twelve patients in each group received chemotherapy and/or palliative radiation for metastatic disease, and of the 12 patients with bone metastases, 10 (83.3%) began treatment of advanced disease with chemotherapy.

In the first line of metastatic disease, 23 patients (53.5%) were treated with CDK4/6 inhibitors, while 20 patients (46.5%) received this therapy as a second line. The patients were nearly evenly split between ribociclib (21 patients, 48.8%) and palbociclib (22 patients, 51.2%). In combination with CDK4/6 inhibitors, aromatase inhibitors were used in 23 patients (53.5%) for first-line treatment, and fulvestrant was used in 20 patients (46.5%) for second-line treatment).

The duration of therapy expressed in months (cycles) was from 4 to 12. In the first line of treatment, the median duration was 7 cycles, while in the second line, it was 6 cycle. Patients younger than 60 years had a median duration of therapy of 8 cycles, longer in the first line (8 cycles) compared to the second line (6 cycles).

Hematological toxicity was the most common side effect **(Graph 4).**

Grade II neutropenia occurred in 22 patients (51.2%), while anemia, present in 21 patients (48.8%), was grade I, and no patients required blood transfusion. Hepatotoxicity was observed in 3 patients (9.3%), manifesting as elevated liver aminotransferases or transaminases, with values tripled



Graph 4. Frequency of hematological toxicity during CDK4/6 inhibitors treatment
Grafikon 4*. Zastupljenost hematološke toksičnosti kod primene CDK4/6 inhibitora*

in 2 patients and quadrupled in 1 patient. After recommended symptomatic therapy, the values returned to acceptable ranges, allowing therapy continuation without further complications. Cardiac toxicity, manifested by QTc interval prolongation, was recorded in 2 patients (4.6%). Due to side effects, the drug dose was reduced for the first time in 9 patients (21%) and for the second time in 2 patients (4.6%), while in 2 patients, the treatment was initiated at a lower dose of CDK4/6 inhibitors due to age and comorbidities. Adverse drug reactions did not lead to therapy discontinuation.

A good therapeutic response (CR, PR and SD) was recorded in 23 patients (53.5%). A complete response to therapy was noted in two patients younger than 60 years. Treatment outcomes by patient groups, in relation to early or late relapse or initially metastatic disease, are shown in **Table 1.** Patients younger than 60 years with late relapse had statistically significantly better treatment outcomes compared to patients older than 60 years (p=0.04). Patients with bone metastases had a good therapeutic response in 50% of cases. Those with bone metastases combined with other metastasis localizations had a good therapeutic response in 54% of cases.

The localization of metastases, line of treatment, and reduction of the drug dose did not have a statistically significant effect on the treatment outcomes with CDK4/6 inhibitors in our patients.

Discussion

In recent years, numerous studies have evaluated the use of CDK4/6 inhibitors in clinical practice, comparing the results with randomized clinical trials that lead to their approval for breast cancer treatment. A study conducted in Brazil included 67.6% of patients disease relapse, and 55.6% received a CKD4/6 inhibitor as first-line treatment for metastatic disease. The most common site of metastases was the bones, in 83.8% of cases, similar to our data [13].

In Germany, after CDK4/6 inhibitors became available, the use of chemotherapy decreased from 42% to 27% over two years [14]. According to our data, a large number of patients still initiated treatment with chemotherapy for metastatic disease, even in the absence of a visceral crisis.

In the study by Knudsen et al., letrozole was the predominant endocrine therapy used, with other aromatise inhibitors (AIs) being less common [15]. In contrast, anastrozole was the first choice of AIs for our patients. Our data indicate that both available CDK4/6 inhibitors, ribociclib and palbociclib, were equally used, whereas in a study conducted in four centers in Germany, approximately 72% of patients used palbociclib. Germany recommendations from 2021, based on data from the MONALEESA-7 study, favor ribociclib for premenopausal patients when combined with AI [16]. The Hellenic Cooperative Oncology Group reported that 82.5% of patients were treated with palbociclib in combination with endocrine therapy [17], and researchers from Asia shared that 95% of their patients were treated with palbociclib [18].

In a multicenter German study, the dose of the drug was reduced in about 20% of patients, with hematological toxicity, primarily neutropenia, being the most common side effect is [16]. Our data also similarly showed hematological toxicity as the prime side effect.

Table 1. Treatment outcomes
Tabela 1. *Ishodi lečenja pacijenata*

Patient group *Grupa pacijenata*	Treatment outcome/*Ishod lečenja*				
	CR	PR	SD	PD	∑ N
Early relapse < 60/*Rani relaps < 60 N*	0	2	3	5	10
Early relapse > 60/*Rani relaps < 60 N*	0	1	2	3	6
Late relapse < 60*/*Kasni relaps < 60* N*	2	3	1	0	6
Late relapse > 60*/*Kasni realps > 60* N*	0	1	1	5	7
Initially metastatic < 60/*Inicijalno metastatski < 60 N*	0	0	1	2	3
Initially metastatic > 60/*Inicijalno metastatski > 60 N*	0	5	1	5	11
∑ N	2	12	9	20	43

N – number of patients/*N – broj pacijenata*
* p=0.04

In an Asian study, almost 50% of patients required a dose reduction, which did not affect PFS [18]. In Brazil, nearly half of the patients required dose reduction due to side effects, mainly grade III or IV neutropenia [13]. According to our experience, CDK4/6 inhibitors proved to be quite safe, and a systematic review of the literature indicates preservation of the quality of life and positive trend in pain control, similar to when applying only endocrine therapy [19]. Fradley et al. showed that cardiovascular side effects occur in a quarter of patients [20], suggesting the need for more intensive monitoring of cardiovascular function in patients treated with CDK4/6 inhibitors.

Nadia Harbeck and colleagues conducted a systematic review of literature published in the period from 2015 to 2019 on the use of CDK4/6 inhibitors in treating metastatic, hormone-positive breast cancer. The majority of studies (79 out of 114) included patients treated with palbociclib, with approximately half of the studies conducted in the United States. The mean or median follow-up in studies reporting PFS and OS ranged from 6 to 24.4 months. Median PFS was 13.3 months with the use of AI and palbociclib, and 5.8 months with the use of palbociclib and fulvestrant. Most patients who had stable disease after six months of treatment were those treated with palbociclib and AI, regardless of the therapy line [21]. Our data similarly indicate that stable disease or progression occurs at similar rates, irrespective of the choice of CDK4/6 inhibitor and endocrine therapy.

In one study, the mean treatment with ribociclib and AI in any treatment line was 4.2 months [22]. The median treatment duration in studies ranges from 1.8 to 19 months for ribociclib + AI, and 3.9 to 15.8 months for palbociclib + AI [21].

In all lines of treatment, in the Brazilian study found that patients treated with ribociclib had the longest PFS (28 months), a statistically significant difference compared to those treated with palbociclib (14 months) and abemaciclib (6 months) (p=0.002). No statistically significant difference was observed in the first line of treatment [13]. This is one of the few studies comparing individual CDK4/6 inhibitors, indicating a need for more such studies to provide clearer insights.

Conclusion

We are confident in the continued use of both drugs equally in treating metastatic, hormone-positive breast cancer. It is imperative to reduce and limit the use of chemotherapy in favor of these targeted therapies. The use of CDK4/6 inhibitors has proven to be safe, and we have gained sufficient confidence in managing their side effects. However, the observed period in our study is relatively short. Thus, ongoing monitoring and exchange of experiences are necessary to ensure optimal treatment and care for patients.

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-49.

2. Institute of Public Health of Serbia "Dr Milan Jovanović Batut". Department for Prevention and Control of Noncommunicable Diseases. Malignant tumours in Republic of Serbia 2021. Serbian Cancer Registry. Belgrade: Institute of Public Health of Serbia "Dr Milan Jovanović Batut"; 2023.

3. Spring LM, Gupta A, Reynolds KL, Gadd MA, Ellisen LW, Isakoff SJ, et al. Neoadjuvant endocrine therapy for estrogen receptor-positive breast cancer: a systematic review and meta-analysis. JAMA Oncol. 2016;2(11):1477-86.

4. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005;365(9472):1687-717.

5. Albain KS, Paik S, van't Veer L. Prediction of adjuvant chemotherapy benefit in endocrine responsive, early breast cancer using multigene assays. Breast. 2009;18(Suppl 3):S141-5.

6. Smolarz B, Nowak AZ, Romanowicz H. Breast cancer – epidemiology, classification, pathogenesis and treatment (review of literature). Cancers (Basel). 2022;14(10):2569.

7. Shah M, Nunes MR, Stearns V. CDK4/6 inhibitors: game changers in the management of hormone receptor–positive advanced breast cancer? Oncology (Williston Park). 2018;32(5):216-22.

8. Iorfida M, Mazza M, Munzone E. Fulvestrant in combination with CDK4/6 inhibitors for HER2- metastatic breast cancers: current perspectives. Breast Cancer (Dove Med Press). 2020;12:45-56.

9. Pernas S, Tolaney SM, Winer EP, Goel S. CDK4/6 inhibition in breast cancer: current practice and future directions. Ther Adv Med Oncol. 2018;10:1758835918786451.

10. Harbeck N, Rastogi P, Martin M, Tolaney SM, Shao ZM, Fasching PA, et al. Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: updated efficacy and Ki-67 analysis from the monarchE study. Ann Oncol. 2021;32(12):1571-81.

11. Clinicaltrials.gov [database on the Internet]. Bethesda: National Library of Medicine. 2000- [cited 2023 Oct 13]. Available from: https://clinicaltrials.gov/

12. Lista C. Lekovi sa posebnim režimom izdavanja [Internet]. 2022 [cited 2023 Oct 13]. Available from: https://rfzo.rs/download/pravilnici/lekovi/C%20Lista_primena%20od%2031.05.2022.pdf

13. Queiroz MM, Sacardo KP, Ribeiro MF, Gadotti LL, Saddi R, Oliveira LJC, et al. Real-world treatment outcomes in HR+ HER2- metastatic breast cancer patients treated with CDK4/6 inhibitors: results from a reference center in Brazil. Cancer Treat Res Commun. 2023;35:100683.

14. Schneeweiss A, Ettl J, Lüftner D, Beckmann MW, Belleville E, Fasching PA, et al. Initial experience with CDK4/6 inhibitor-based therapies compared to antihormone monotherapies in routine clinical use in patients with hormone receptor positive, HER2 negative breast cancer - data from the PRAEGNANT research network for the first 2 years of drug availability in Germany. Breast. 2020;54:88-95.

15. Knudsen ES, Schultz E, Hamilton D, Attwood K, Edge S, O'Connor T, et al. Real-world experience with CDK4/6 inhibitors for metastatic HR+/HER2- breast cancer at a single cancer center. Oncologist. 2022;27(8):646-54.

16. Müller C, Kiver V, Solomayer EF, Wagenpfeil G, Neeb C, Blohmer JU, et al. CDK4/6 inhibitors in advanced HR+/HER2 - breast cancer: a multicenter real-world data analysis. Breast Care (Basel). 2023;18(1):31-41.

17. Fountzilas E, Koliou GA, Vozikis A, Rapti V, Nikolakopoulos A, Boutis A, et al. Real-world clinical outcome and toxicity data and economic aspects in patients with advanced breast cancer treated with cyclin-dependent kinase 4/6 (CDK4/6) inhibitors combined with endocrine therapy: the experience of the Hellenic Cooperative Oncology Group. ESMO Open. 2020;5(4):e000774.

18. Low JL, Lim E, Bharwani L, Wong A, Wong K, Ow S, et al. Real-world outcomes from use of CDK4/6 inhibitors in the management of advanced/metastatic breast cancer in Asia. Ther Adv Med Oncol. 2022;14:17588359221139678.

19. Di Lauro V, Barchiesi G, Martorana F, Zucchini G, Muratore M, Fontanella C, et al. Health-related quality of life in breast cancer patients treated with CDK4/6 inhibitors: a systematic review. ESMO Open. 2022;7(6):100629.

20. Fradley MG, Nguyen NHK, Madnick D, Chen Y, DeMichele A, Makhlin I, et al. Adverse cardiovascular events associated with cyclin-dependent kinase 4/6 inhibitors in patients with metastatic breast cancer. J Am Heart Assoc. 2023;12(12):e029361.

21. Harbeck N, Bartlett M, Spurden D, Hooper B, Zhan L, Rosta E, et al. CDK4/6 inhibitors in HR+/HER2- advanced/metastatic breast cancer: a systematic literature review of real-world evidence studies. Future Oncol. 2021;17(16):2107-22.

22. Wöckel A, Decker T, Fasching PA, Jackisch C, Luftner D, Marme F, et al. Real-world effectiveness of ribociclib + aromatase inhibitor, or endocrine monotherapy, or chemotherapy as first-line treatment in postmenopausal women with HR-positive, HER2-negative locally advanced or metastatic breast cancer: baseline data from the RIBANNA study. J Clin Oncol. 2019;37(15 Suppl):e12520.

Rad je primljen 27. XII 2023.
Recenziran 2. VII 2024.
Prihvaćen za štampu 2. VII 2024.
BIBLID.0025-8105:(2024):LXXVII:3-4:94-99.

Rehabilitation Clinic "Wellness studio Laser", Vrbas[1]
Oncology Institute of Vojvodina, Sremska Kamenica[2]
University of Novi Sad, Faculty of Medicine Novi Sad, Department for Oncology[3]
University Clinical Center of Vojvodina, Novi Sad
Clinic for Gynecology and Obstetrics[4]
University Clinical Center of Vojvodina, Novi Sad, Clinic for Neurosurgery[5]
Academy of Vocational Studies, Department for Medical, Business and Technological Studies, Šabac[6]

Original study
Originalni naučni rad
UDK 616-006.6-085.38.065:616-001-052
https://doi.org/10.2298/MPNS2404100P

ASSESSING FALL RISKS IN ONCOLOGY PATIENTS UNDERGOING CHEMOTHERAPY

PROCENA RIZIKA OD PADA ONKOLOŠKIH PACIJENATA KOJI PRIMAJU HEMIOTERAPIJU

Dušica PEROVIĆ[1], Svetlana POPOVIĆ PETROVIĆ[2,3], Jovana RODIĆ[4], Dušan RODIĆ[5] and Katarina PAVIĆ[6]

Summary

Introduction. The adverse side effects of therapy, combined with cancer symptoms, can significantly impact the functional ability of patients. By assessing fall risks in patients undergoing chemotherapy and implementing preventive interventions, we can enhance the quality of life of these individuals. The study aimed to identify risk factors and evaluate the risk of falls in oncology patients receiving chemotherapy at a Day Hospital. **Material and Methods.** The study was conducted at the General Hospital in Vrbas and the Oncology Institute of Vojvodina. Patients were divided into two age groups. The instruments used for assessment included the Morse Fall Scale, Timed Up and Go Test, Berg Balance Scale, and Mini-Mental State Examination. The collected data were statistically analyzed. **Results.** The first group of patients had an average age below 65, while the second group's average age was above 65. Both groups had a higher portion of female patients. There were significant differences in cancer localization: the first group primarily had breast cancer, whereas the second group had a higher prevalence of colon cancer. Older patients took longer to complete the Timed Up and Go Test. In the older group, age was significantly associated with Timed Up and Go Test and Berg Balance Scale scores. Additionally, there was a notable correlation between Mini-Mental State Examination scores and Berg Balance Scale scores. **Conclusion.** Age, reduced physical ability and balance, and cognitive deficits are significant risk factors for falls in older oncology patients receiving chemotherapy in the Day Hospital setting.

Key words: Accidental Falls; Risk Assessment; Medical Oncology; Drug Therapy; Postural Balance; Cognition

ORCID NUMBER
Dušica Perović 0000-0002-8206-351X
Svetlana Popović Petrović 0000-0001-9637-2017
Jovana Rodić 0009-0006-0669-771X

Sažetak

Uvod. Neželjena dejstva terapije sa simptomima maligne bolesti mogu da utiču na funkcionalnu sposobnost pacijenata. Procenom rizika od pada pacijenata koji primaju hemioterapiju i odabirom preventivnih intervencija može se uticati na poboljšanje kvaliteta života. Cilj studije je identifikacija faktora i procena rizika od pada onkoloških pacijenata koji primaju hemioterapiju u okviru dnevne bolnice. **Materijal i metode.** Istraživanje po tipu studije preseka je sprovedeno u Opštoj bolnici Vrbas i na Institutu za onkologiju Vojvodine. Pacijenti su bili podeljeni u dve starosone grupe. Primenjeni instrumenti su: Morzeova skala padova, Ustani i hodaj test, Bergova skala balansa i Mini-mental skala. Podaci su statistički obrađeni. **Rezultati.** Prva grupa pacijenata imala je manju prosečnu starost, a druga grupa veću od 65 godina. U obe grupe bilo je više pacijenata ženskog pola. Grupe su se statistički značajno razlikovale u lokalizaciji karcinoma. U prvoj grupi najveći broj njih imao je dijagnozu karcinoma dojke, a u drugoj grupi veći broj ispitanika imao je dijagnozu karcinoma debelog creva. Statistički značajne razlike utvrđene su na Ustani i hodaj testu (starijim osobama je potrebno više vremena za obavljanje aktivnosti u testu). U starijoj grupi ispitanika postoji statistički značajna veza starosti sa skorovima na Ustani i hodaj testu i Bergovoj skali balansa. U starijoj grupi ispitanika beleži se statistički značajna korelacija između skorova na Mini-mental testu i Bergovoj skali balansa. **Zaključak.** Godine starosti, lošije fizičko postignuće, lošija ravnoteža i deficit u kognitivnom statusu su faktori rizika za pad kod starijih onkoloških pacijenata koji primaju hemioterapiju u okviru dnevne bolnice.

Ključne reči: akcidentalni padovi; procena rizika; onkologija; hemoterapija; posturalni balans; kognicija

Dušan Rodić 0009-0007-2911-6217
Katarina Pavić 0000-0002-3413-5312

Introduction

With the ageing population, there is an anticipated increase in the frequency of malignant diseases [1]. By 2030, the incidence of cancer in the older population is expected to reach 67% [2]. Advances in science and technology have led to the development of novel diagnostic and therapeutic modalities in oncology, result-

Corresponding Author: Dušica Perović, Ambulanta za rehabilitaciju "Wellness Studio Laser", 21460 Vrbas, Ive Lole Ribara 9c, E-mail: 74dusica@gmail.com, svetlana.popovic-petrovic@mf.uns.ac.rs

Abbreviations

CRF – cancer related fatigue
CGA – Comprehensive Geriatric Assessment
EORTC – European Organisation for Research and Treatment of Cancer
MFS – Morse Fall Scale
TUG – Timed Up and Go Test
BBS – Berg Balance Scale
MMSE – Mini-Mental State Examination
SPSS – Statistical Package for the Social Sciences
MAHC – Missouri Alliance for Home Care

ing in complete recovery or prolonged survival for many patients with malignant neoplasms. However, the adverse side effects of these therapeutic modalities, particularly chemotherapy (such as polyneuropathy, joint pain, muscle pain, and cancer related fatigue (CRF)), combined with the symptoms of the malignancy itself, can significantly impact the overall condition and functional ability of patients. This includes muscle strength, activities of daily living and self-care, balance, gait, and cognitive functions, thereby increasing the risk of falls, especially in the elderly [3]. Falls are the leading cause of unintentional injuries. While definitions of falls vary, they commonly describe unintended incidents not caused by loss of consciousness or external force. Falls account for 40% of all deaths from injuries and 50% of urgent hospitalizations in individuals over 65 years of age. Additionally, 20% of these patients succumb to fall-related injuries within a year. Falls can lead to post-fall syndrome, characterized by loss of independence, immobilization, dependency, confusion, and depression, which further limit everyday activities [4]. The frequency of falls served as a measure of healthcare quality in both healthcare institutions and home environments. Insight into the likelihood of falls can be gained from various factors: anamnesis, disease history (primary disease and comorbidities), medication types, therapeutic modalities for the primary disease, type of cytostatic used and their side effects, socio-demographic data (age, gender), occupation, social status, living conditions, hobbies, lifestyle, etc. [5]. Although many studies have investigated the quality of life in oncology patients, there is limited knowledge about the frequency of falls in this population. Timely assessment of fall risk in oncology patients receiving chemotherapy and the implementation of specific preventive interventions can significantly impact and improve their quality of life. Numerous studies indicate that female gender, physical impairment and subsequent functional decline, depression, and cognitive impairment all increase the risk for falls [6]. Research suggests that a comprehensive geriatric assessment (CGA) can enhance the quality of care for individuals with carcinoma [7]. The European Organisation for Research and Treatment of Cancer (EORTC) recommends implementing some form of CGA in all elderly patients undergoing chemotherapy [8]. Based on the obtained results, fall prevention in oncology patients must include rehabilitation modalities whose effectiveness has been scientifically confirmed [9]. The aim of this study was to determine whether age, reduced physical ability, poor balance, and cognitive deficits in oncology patients receiving chemotherapy in the Day Hospital setting represent risk factors for falls.

Material and Methods

The study was conducted at the Day Hospital of the Department of Oncology at the General Hospital in Vrbas and the Day Hospital of the Oncology Institute of Vojvodina in Sremska Kamenica. This cross-sectional study included patients over 50 years of age, divided into two groups: one group aged 50-64 and another group aged 65 and older. All participants had a diagnosis of malignant neoplasm of various localizations and had received at least three cycles of chemotherapy at the time of the study. Data from the patients' medical records (name, gender, age, diagnosis, comorbidity) were utilized. Exclusion criteria included patients younger than 50, those with secondary deposits, and those with comorbidities such as epilepsy, ischemic heart diseases, and obstructive lung diseases. Participants received an introductory letter and a consent form. Ethical approval was obtained from the Ethics Commission of the Oncology Institute of Vojvodina in Sremska Kamenica and the General Hospital in Vrbas. Patient interviews, conducted at the end of a chemotherapy cycle, confirmed the data from medical records and assessed the patients' functional status.

Tools used for fall risk assessment

Morse Fall Scale (MFS): This scale assesses six variables influencing the likelihood of falls: history of falls, comorbidity, need for assistance in walking, intravenous therapy, gait, and mental status. Scores range from 0 to 125, with higher scores indicating higher risk for falls. Timed Up and Go test (TUG): This test measures the time a patient takes to stand up from a sitting position with their back leaned against a chair, walk three meters in their usual way of walking, return to the chair, and sit down again. Results reflect motor abilities, and specifically: 1-9 seconds (patient independent and ambulatory); 10-19 seconds (patient mostly independent); 20-29 seconds (patient with varied mobility); >30 seconds (diminished mobility). Berg Balance Scale (BBS): This scale assesses balance through tasks scored from 0 (cannot perform) to 4 (can perform without difficulty), with a maximum score of 56. Interpretation of the total score, based on the three-point Likert-type scale, defines three levels of fall risk: high risk (0-20 points), moderate risk (21-40 points), and low risk (41-56 points). Mini-Mental State Examination (MMSE): Initially designed to assess dementia severity, this scale is now a screening tool for cognitive status. It includes eleven tasks evaluating orientation in time and space, short term verbal memory, attention, delayed recall of verbal material, ability to name objects, ability to follow verbal or written instructions, sentence structure, and graphomotor skills (copying a drawing). The total scores categorize cognitive deficit levels, as follows: 25-30 (no cognitive deficit), 20-24

(mild cognitive deficit), 11-19 (moderate cognitive deficit), and 0-10 (profound cognitive deficit). Lower scores are indicative of higher cognitive deficit levels.

Descriptive statistics, including measures of central tendency (mean) and variability (standard deviation), as well as frequency measures for specific variables were used. Inferential statistics tested the significance of the hypotheses using the Chi-square test, Mann-Whitney U test, and Spearman's rank correlation coefficient. Statistical analysis was performed using statistic package for social sciences SPSS 20.0.

Results

The average age in the first group of patients was M=56.65 (SD=4.08), while the second, older group had

Table 1. Basic demographic and clinical characteristics of the sample with regard to age
Tabela 1. *Osnovna demografska i klinička obeležja uzorka u odnosu na starost*

Parameter *Parametar*	50-64 years/*godina* (n=34) number/*broj* (%)	≥ 65 years/*godina* (n=17) number/*broj* (%)	χ^2	p/*p*
Age/*Starost*				
$\overline{X}\overline{X}$+SD	56.65+4.08	70.41+4.37		
Gender/*Pol*				
Men/*Muškarci*	6 (17.6%)	5 (29.4%)	0.927	0.336
Women/*Žene*	28 (82.4%)	12 (70.6%)		
Cancer localization/*Lokalizacija karcinoma*				
Breast/*Dojka*	24 (70.6%)	6 (35.3%)		
Colon/*Debelo crevo*	8 (23.5%)	9 (52.9%)		
Lung/*Pluća*	0 (0%)	2 (11.8%)	10.341	**0.035**
Stomach/*Želudac*	1 (2.9%)	0 (0%)		
Uterus/*Materica*	1 (2.9%)	0 (0%)		

χ^2-Chi-square test/χ^2-*Hi-Kvadrat test*

Table 2. Distribution of categories on clinical scales with regard to age
Tabela 2. *Distribucija kategorija korišćenih kliničkih skala u odnosu na starost*

Parameter *Parametar*	50-64 years/*godina* (n=34) number/*broj* (%)	≥ 65 years/*godina* (n=17) number/*broj* (%)	χ^2	p/*p*
Morse fall scale of MFS/*Morseova skala za procenu rizika za pad – MFS*				
0 – 24 = no risk of falls/*Nema rizika od pada*	32 (94.1%)	13 (76.5%)		
25 – 45 = low to moderate risk of falls *Nizak do umeren rizik od pada*	2 (5.9%)	3 (17.6%)	4.000	0.135
>46 = high risk of falls/*Visok rizik od pada*	0 (0%)	1 (5.9%)		
The Timed Up and Go test – TUG/*Test „Ustani i hodaj" – TUG*				
< 10 s = independent in walking/*Samostalan u kretanju*	31 (91.2%)	13 (76.5%)		
10– 19 s = mostly independent in walking *Uglavnom nezavisan u kretanju*	3 (8.8%)	4 (23.5%)	2.070	0.150
20 – 29 s = varied mobility/*Promenljiva pokretljivost*	0 (0%)	0 (0%)		
>30 s = diminished mobility/*Smanjena pokretljvost*	0 (0%)	0 (0%)		
Berg Balance Scale – BBS/*Bergova Skala Balansa – BBS*				
High risk of falls/*Visok stepen rizika od pada*	0 (0%)	0 (0%)		
Moderate risk of falls/*Srednji stepen rizika od pada*	0 (0%)	0 (0%)	-	-
Low risk of falls/*Nizak stepen rizika od pada*	34 (100%)	17 (100%)		
Mini mental state examination – MMSE/*Mini-mental test – MMSE*				
18 – 25 = cognitive dysfunction, dementia can be diagnosed *Kognitivna disfunkcija, može se dijagnostikovati demencija*	6 (17.6%)	5 (29.4%)		
26 – 28 = borderline cognitive dysfunction *Granična kognitivna disfunkcija*	15 (44.1%)	6 (35.3%)	0.968	0.616
29 – 30 = normal mental status/*Normalan mentalni status*	13 (38.2%)	6 (35.3%)		

χ^2-Chi-square test/χ^2-*Hi-kvadrat test*

Table 3. Differences in average achievement on clinical scales between the two age groups
Tabela 3. *Razlike u prosečnom postignuću na kliničkim skalama između dve starosne grupe*

Parameter *Parametar*	50-64 years/*godina* (n=34)		≥ 65 years/*godina* (n=17)		U/*U*	p/*p*
	Med	$\overline{X}\overline{X}$+SD	Med	$\overline{X}\overline{X}$+SD		
MFS	0.00	7.21 ± 8.54	15.00	17.06 ± 23.39	223.5	0.147
TUG	8.00	7.94±1.43	9.00	8.76 ± 1.25	183.0	**0.029***
BBS	54.00	54.59 ± 1.05	55.00	54.12 ± 1.73	264.0	0.603
MMSE	28.00	27.32 ± 2.46	28.00	26.76 ± 2.66	249.5	0.425

Legend/*Legenda*: MFS – Morse fall scale/*Morseova skala za procenu rizika za pad*; TUG – Timed Up and Go Test/*Test „Ustani i hodaj";* BBS – Berg Balance Scale/*Bergova Skala Balansa*; MMSE – Mini mental state examination/*Mini-mental test*; x – mean/*aritmetička sredina*; Med – median/*medijana;* SD – standard deviation/*standardna devijacija;* U – Mann-Whitney U-test/Men Vitnijev U-test*;*
*significant/*značajan*

Table 4. Correlation between the results on clinical scales and age in two subsamples
Tabela 4. *Korelacija postignuća na kliničkim skalama i starosti u dva poduzorka*

	50-64 years/*godina* (n=34)	≥ 65 years/*godina* (n=17)
	Age/*Starost*	Age/*Starost*
MFS	0.257	0.073
TUG	0.054	0.522*
BBS	-0.024	-0.549*
MMSE	-0.126	-0.289

Legend/*Legenda*: MFS – Morse fall scale/*Morseova skala za procenu rizika za pad*; TUG – Timed Up and Go Test/*Test „Ustani i hodaj";* BBS – Berg Balance Scale/*Bergova Skala Balansa*; MMSE – Mini mental state examination/*Mini-mental test*;
*Spearman's rank correlation coefficient; p < 0.05; **p < 0.01;/*Spirmanov test rang korelacije*; *p < 0.05; **p < 0.01*

an average of M=70.41(SD=4.37). Gender distribution analysis using the Chi-square test revealed no statistically significant difference between groups (p>0.05), indicating both groups had significantly more female than male participants. The two groups showed significant differences in cancer localization (p=0.035). In the 50-64 age group, breast cancer was more prevalent, whereas in the older group, colon cancer was more common. Additionally, participants over 65 included cases of breast cancer and lung cancer, while the younger age group had instances of colon, uterine, and stomach cancers **(Table 1)**. Chi-square tests applied to clinical scales assessing motor, physical, and cognitive abilities (MFS, TUG, BBS, MMSE) showed no statistically significant difference in category distribution between the groups. Specifically, MFS results indicated that most participants had no or low to moderate risk for falls. TUG analysis revealed most patients in both groups were independent in walking. BBS results showed a low risk for falls, with no balance disorder. MMSE test indicated most participants had normal cognitive status or borderline cognitive dysfunction **(Table 2)**. The Mann-Whitney U test indicated no significant differences in average values on clinical scales between the study groups, except for the TUG test, where older patients had higher average scores (p=0.029), suggesting they required more time to perform the test activities **(Table 3)**. Correlation analysis demonstrated that in participants over 65, there was a statistically significant negative relationship between age and measures of physical and motor functioning (TUG and BBS test). This negative correlation implies that higher scores on one dimension were linked to lower scores on the other, indicating that older participants took more time on the TUG test, reflecting poorer functioning, and had lower BBS scores, indicating poorer balance **(Table 4)**. Intercorrelation analysis of the clinical scales revealed several significant correla-

Table 5. Intercorrelations between clinical scales in two independent age samples
Tabela 5. *Interkorelacije primenjenih kliničkih skala nezavisno u dva starosna poduzorka*

	50-64 years/*godina* (n=34)				≥ 65 years/*godina* (n=17)			
	MFS	TUG	BBS	MMSE	MFS	TUG	BBS	MMSE
MFS	1	0.198	- 0.370**	0.097	1	0.018	-0.241	0.092
TUG		1	-.297*	-0.238		1	-0.259	-0.247
BBS			1	0.369**			1	0.449**
MMSE				1				1

Legend/*Legenda*: MFS – Morse fall scale/*Morseova skala za procenu rizika za pad*; TUG – Timed Up and Go Test/*Test „Ustani i hodaj";* BBS – Berg Balance Scale/*Bergova Skala Balansa*; MMSE – Mini mental state examination/*Mini-mental test*;
* Spearman's rank correlation coefficient; p < 0.05; **p < 0.01/* *Spirmanov test rang korelacije; p < 0.05; **p< 0.01;*

tions in both age groups. In participants aged 50-64, there was a statistically significant negative correlation between scores on the BBS, MFS and TUG scales. This suggests that better balance, as measured by the BBS scale, was associated with a lower risk for falls as measured by the MFS scale and shorter time to complete the TUG test, indicating greater walking independence. Additionally, a statistically significant positive correlation was found between MMSE and BBS scores in the younger age group, indicating that better cognitive function was associated with better balance. In the group aged 65 and older, there was a statistically significant moderate positive correlation between MMSE and BBS scores, similar in the younger group, indicating that better cognitive performance was linked to better balance **(Table 5)**.

Discussion

In patients suffering from carcinoma, a key step in the assessing fall risk is documenting their fall history. A previous fall increases the likelihood of subsequent fall by fourfold [5]. The total score on the MFS test indicates fall probability and identifies risk factors, but does not provide guidance on preventing falls. For patients who have already fallen, further assessment using the TUG test is necessary [10]. The TUG test, which evaluates the time taken to rise from a chair, walk and return, helps in understanding a patient's fall risk. Difficulty maintaining balance on one leg, as assessed by the BBS, indicates a predisposition to fall-related injuries. The MMSE test identifies patients with cognitive impairments, which can contribute to falls [11]. Previous studies have shown that age 65 and older is a significant risk factor for falls, justifying the assessment of gait and related variables to predict falls [12]. In our study, participants over 65 exhibited a significant relationship between age and physical/motor functioning. Older patients in this group took longer to complete the TUG test, indicating poorer functioning, and scored lower on the BBS test, indicating poorer balance. Similar studies have confirmed a correlation between MMSE results and the occurrence of falls [12]. In our own study, there was a statistically significant moderate positive correlation between MMSE and BBS scores in participants over 65, suggesting that poorer cognitive performance is associated with poorer balance. MMSE results can be influenced by factors such as education level, fear, stress, anxiety, depression, and illness adaptation mechanisms, which were not considered in this study. We recommend including specific psychological testing in fall risk assessment to understand the impact of psychological factors on cognitive and functional abilities. Additionally, the MMSE and other test results can be affected by CRF, which was not formally screened for in our patients but was indicated by patient-reported symptoms. The CGA tests are typically used for the geriatric population (over 65), but this study included a control group aged 50-64. In this younger group, there was a statistically significant negative correlation of moderate intensity between BBS, MFS, and TUG scores, indicating that better balance is associated with a lower risk of falls and greater mobility independence. Additionally, there was a statistically significant positive correlation between MMSE and BBS scores, indicating that better cognitive function is associated with better balance. The study validated the use of fall risk assessment instruments in both age groups but lacked comparison with age-matched individuals without carcinoma, which would help determine the sensitivity of these instruments in cancer patients undergoing chemotherapy. Future research should investigate whether oncology patients have a higher fall risk compared to their non-cancer counterparts.

The WHO's global report on fall prevention in the elderly highlights female gender as a risk factor for falls [4]. However, a 2007 study found no gender-based difference in risk fall assessment [12]. Our study's gender ratio was unbalanced, with more female participants, which could influence carcinoma frequency and fall risk assessments. The sample was heterogeneous regarding cancer type and treatment phase, and the sample size was small. A larger sample would help validate the hypothesis that gender is a risk factor for falls. Patients with cancers other than breast and colon often do not receive chemotherapy in day hospital setting, making our results less generalizable to other cancer types (brain, cervix, pancreas, kidneys, etc.). This raises the question of whether screening instruments should be modified or new ones developed to assess fall risk based on cancer localizations and treatment modalities. EORTC recommends concerning CGA instruments for all elderly chemotherapy patients, but we used the MFS due to day hospital conditions.

None of the tests included questions on external fall risk factors related to the patient's environment, such as living and working conditions or home hazards (e.g., carpets, slippery surfaces, stairs, elevators, handrails, wheelchair ramps, pets, toilet and bed adaptability, etc.) [13]. These external factors, as reported by patients, often contribute to falls. Standardizing screening instruments to assess environmental conditions could help prevent falls in oncology patients at home. The Missouri Alliance for Home Care's 10 (MAHC-10) – Fall Risk Assessment Tool could partially address environmental differences [14].

Although chemotherapy is known to increase fall risk, our data suggest that its side effects may not directly cause falls but rather contribute indirectly by affecting cognitive status. Further research should examine specific side effects of each chemotherapy agent. Four main obstacles hinder progress in geriatric oncology: lack of consensus on a comprehensive geriatric oncology assessment standard, lack of standardized patient risk classification, insufficient information on the psychometric properties of assessment tools, and poor quality of patient and clinician/researcher reports. These issued are crucial for assessing study results, making it essential to adequately report details and outcomes in future studies [15].

Conclusion

Age is a significant risk factor for falls in oncology patients receiving chemotherapy in the Day Hospital setting.

Poorer physical ability and balance are risk factors for falls in elderly oncology patients undergoing chemotherapy in the Day Hospital setting.

In elderly oncology patients receiving chemotherapy in the Day Hospital setting, cognitive deficits are positively associated with balance deficits, which represent a fall risk factor.

In oncology patients receiving chemotherapy in the Day Hospital setting, better balance is associated with better functional abilities, greater mobility independence, and reduced risk for falls.

References

1. Martinov-Cvejin M, Grujić V, Šušnjević S, Kvrgić S, Arsić M, Ač-Nikolić E. Health of the population of Vojvodina. Med Pregl. 2007;60(11-12):559-63.

2. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020;396(10258):1204-22.

3. Institut za onkologiju i radiologiju Srbije. O malignim bolestima: opšte informacije [Internet]. [cited 2023 Dec 14]. Available from: http://www.ncrc.ac.rs/o-karcinomu/

4. World Health Organization. WHO global report on falls prevention in older age [Internet]. 2008 [cited 2023 Dec 13]. Available from: https://www.who.int/publications/i/item/9789241563536

5. Kuhnow J, Hoben M, Weeks LE, Barber B, Estabrooks CA. Factors associated with falls in Canadian long term care homes: a retrospective cohort study. Can Geriatr J. 2022;25(4):328-35.

6. Montero-Odasso M, van der Velde N, Martin FC, Petrovic M, Tan MP, Ryg J, et al. World guidelines for falls prevention and management for older adults: a global initiative. Age Ageing. 2022;51(9):afac205.

7. Giger AW, Ditzel HM, Jørgensen TL, Ditzel HJ, Mohammadnejad A, Ewertz M, et al. Predictive value of geriatric oncology screening and geriatric assessment of older patients with cancer: a randomized clinical trial protocol (PROGNOSIS-RCT). J Geriatr Oncol. 2022;13(1):116-23.

8. Mahmoud AM, Biello F, Maggiora PM, Bruna R, Burrafato G, Cappelli M, et al. A randomized clinical study on the impact of Comprehensive Geriatric Assessment (CGA) based interventions on the quality of life of elderly, frail, onco-hematologic patients candidate to anticancer therapy: protocol of the ONCO-Aging study. BMC Geriatr. 2021;21(1):320.

9. Liu-Ambrose T, Davis JC, Best JR, Dian L, Madden K, Cook W, et al. Effect of a home-based exercise program on subsequent falls among community-dwelling high-risk older adults after a fall: a randomized clinical trial. JAMA. 2019;321(21):2092-100.

10. Overcash JA, Rivera HR Jr. Physical performance evaluation of older cancer patients: a preliminary study. Crit Rev Oncol Hematol. 2008;68(3):233-41.

11. Guo X, Pei J, Ma Y, Cui Y, Guo J, Wei Y, et al. Cognitive frailty as a predictor of future falls in older adults: a systematic review and meta-analysis. J Am Med Dir Assoc. 2023;24(1):38-47.

12. Overcash J. Prediction of falls in older adults with cancer: a preliminary study. Oncol Nurs Forum. 2007;34(2):341-6.

13. Holley S. A look at the problem of falls among people with cancer. Clin J Oncol Nurs. 2002;6(4):193-7.

14. Missouri Alliance for Home Care. MAHC 10 - fall risk assessment tool [Internet]. [cited 2023 Dec 13] Available from: https://www.homecaremissouri.org/projects/falls/documents/Oct2012FINALValidatedFallriskassessmenttool.pdf

15. Puts MT, Santos B, Hardt J, Monette J, Girre V, Atenafu EG, et al. An update on a systematic review of the use of geriatric assessment for older adults in oncology. Ann Oncol. 2014;25(2):307-15.

Rad je primljen 28. VI 2024.
Recenziran 10. VII 2024.
Prihvaćen za štampu 10. VII 2024.
BIBLID.0025-8105:(2024):LXXVII:3-4:100-105.

Children and Youth Health Care Institute of Vojvodina, Pediatric Surgery Clinic,
Department of Pediatric Anesthesia, Intensive Care and Pain Therapy, Novi Sad[1]
University of Novi Sad, Faculty of Medicine Novi Sad[2]
University Clinical Center of Vojvodina, Novi Sad,
Department of Laboratory Medicine[3]
Oncology Institute of Vojvodina, Sremska Kamenica, Department of Nuclear Medicine[4]

Original study
Originalni naučni rad
UDK 616.441-008.64:616-008.9
https://doi.org/10.2298/MPNS2404106T

CALCIUM AND MAGNESIUM LEVELS IN PATIENTS WITH PRIMARY HYPOTHYROIDISM

NIVOI KALCIJUMA I MAGNEZIJUMA KOD PACIJENATA SA PRIMARNIM HIPOTIREOIDIZMOM

Dragan TURANJANIN[1,2], Romana MIJOVIĆ[2,3], Ivana STARČEVIĆ[2,4] and Vanja TATALOVIĆ[2]

Summary

Introduction. The prevalence of Hashimoto's thyroiditis in the general population, along with the potential impact of altered calcium and magnesium concentrations, provided the impetus for this research. The objective of **o**ur study was to compare calcium and magnesium levels in newly diagnosed hypothyroid patients with those in patients undergoing thyrosubstitution therapy. **Material and Methods.** The study included three groups: patients newly diagnosed with hypothyroidism, patients with hypothyroidism on thyrosubstitution therapy, and a control group of euthyroid individuals matched for age and gender. We measured the concentrations of free triiodothyronine, free thyroxine, thyroid-stimulating hormone, thyroid peroxidase antibodies, thyroglobulin antibodies, total calcium, ionized calcium, magnesium, and phosphorus for all participants. **Results.** Newly diagnosed hypothyroid patients exhibited statistically significantly lower levels of free triiodothyronine, free thyroxine, calcium, and magnesium, and statistically significantly higher thyroid-stimulating hormone levels compared to both patients on thyrosubstitution therapy and euthyroid participants ($p<0.01$ for all comparisons). Additionally, total and ionized calcium, as well as magnesium levels, were found to be negatively correlated with thyroid-stimulating hormone levels ($p<0.05$ for all) and positively correlated with free triiodothyronine and free thyroxine levels ($p<0.05$ for all) in the newly diagnosed hypothyroid group. **Conclusion.** The observed associations between magnesium and calcium levels with thyroid function markers underscore the importance of evaluating the statuses of these elements in patients with primary hypothyroidism.

Key words: Hypothyroidism; Hashimoto Disease; Thyroiditis; Magnesium; Calcium; Blood; Thyroid Hormones

Sažetak

Uvod. Znanje o učestalosti Hašimotovog tireoiditisa u opštoj populaciji, kao i razumevanje potencijalnih posledica uzrokovanih promenama u koncentracijama kalcijuma i magnezijuma, inspirisalo je ideju za ovo istraživanje. Cilj našeg istraživanja bilo je upoređivanje nivoa kalcijuma i magnezijuma između pacijenata sa novodijagnostikovanim hipotireoidizmom i pacijenata na tireosupstitucionoj terapiji. **Materijal i metode.** Naše istraživanje obuhvatilo je tri grupe: pacijente sa novodijagnostikovanim hipotireoidizmom, pacijente sa hipotireoidizmom na tireosupstitucionoj terapiji i kontrolnu grupu eutireoidnih pacijenata, uparenih po uzrastu i polu. Merili smo koncentracije slobodnog trijodotironina, slobodnog tiroksina, tireostimulišućeg hormona, antitela na tireoidnu peroksidazu, antitela na tiroglobulin, ukupnog kalcijuma, jonizovanog kalcijuma, magnezijuma i fosfora kod svih učesnika. **Rezultati.** Ustanovili smo statistički značajno niže nivoe slobodnog trijodotironina, slobodnog tiroksina, kalcijuma i magnezijuma, kao i statistički značajno više nivoe tireostimulišućeg hormona kod pacijenata sa novodijagnostikovanim hipotireoidizmom u poređenju sa pacijentima na tireosupstitucionoj terapiji i eutireoidnim učesnicima ($p < 0,01$ za sva poređenja). Dodatno, nivoi ukupnog i jonskog kalcijuma, kao i nivo magnezijuma bili su u negativnoj korelaciji sa nivoima tireostimulišućeg hormona ($p < 0,05$ za sva merenja) i pozitivnoj korelaciji sa nivoima slobodnog trijodotironina i slobodnog tiroksina ($p < 0,05$ za sva merenja) u grupi pacijenata sa novodijagnostikovanim hipotireozomom. **Zaključak**. Povezanost nivoa magnezijuma i kalcijuma sa pokazateljima funkcije štitaste žlezde ističe važnost procene stanja ovih elemenata kod pacijenata sa primarnim hipotireoidizmom.

Ključne reči: hipotireoidizam; Hašimotova tireoiditis; tireoiditis; magnezijum; kalcijum; krv; tireoidni hormoni

ORCID NUMBER
Dragan Turanjanin 0009-0002-9638-0935
Romana Mijović 0000-0002-4034-1585
Ivana Starčević 0009-0003-6748-2286
Vanja Tatalović 0009-0008-1942-706X

Introduction

Primary hypothyroidism is characterized by decreased levels of free thyroxine (fT4) and increased levels of thyroid-stimulating hormone (TSH) in the blood. Elevated TSH and reduced levels of thyroxine (T4) and triiodothyronine (T3) are crucial laboratory indicators of early thyroid gland dysfunction [1]. The clinical manifestations of thyroid function deficiency depend on the patient's age, comorbidities, and the rate

Corresponding Author: Dragan Turanjanin, Institut za zdravstvenu zaštitu dece i omladine Vojvodine, 21000 Novi Sad, Hajduk Veljkova 10, E-mail: dturanjanin@icloud.com, romana.mijovic@mf.uns.ac.rs

Abbreviations

TSH – thyroid-stimulating hormone
T4 – thyroxine
T3 – triiodothyronine
TgAb – thyroglobulin antibodies
TPOAb – thyroid peroxidase antibodies
fT4 – free-thyroxine
fT3 – free-triiodothyronine

of hypothyroidism progression [2]. However, the absence of symptoms does not exclude hypothyroidism. Diagnosis is, therefore, established based on laboratory findings that indicate dysfunction of the hypothalamic-pituitary-thyroid axis [3].

Hashimoto's thyroiditis, or chronic lymphocytic thyroiditis, is the most common form of primary hypothyroidism. It is an autoimmune disorder marked by inflammation of the thyroid gland [4, 5]. In Hashimoto's thyroiditis, the presence of autoantibodies, such as thyroglobulin antibodies (TgAb) and thyroid peroxidase antibodies (TPOAb), signifies the destruction of thyrocytes and the initiation of an autoimmune process within the thyroid gland [4]. The autoimmune response against thyroid tissue in Hashimoto's thyroiditis is explained by two main pathophysiological mechanisms. The first involves antibody-mediated cell destruction and T-cell-stimulated cytotoxicity, while the second, more recently recognized mechanism involves cellular apoptosis [6]. In vitro studies have demonstrated high expression of pro-apoptotic molecules such as FasL, Fas, and Bax in thyrocytes [7]. Moreover, the stability of the redox system is crucial for protection against autoimmune triggers [8]. Imbalance in the redox system leads to increased production of reactive oxygen species (ROS), reactive nitrogen species (RNS), and reactive sulfides (RS) within cells [8, 9]. Accumulation of ROS results in oxidative stress, causing DNA damage and the accumulation of single-stranded DNA (ssDNA) and double-stranded DNA (dsDNA) [10, 11]. These forms of DNA can trigger autoimmune responses by inducing interferon genes and production of interferon gamma (IFN-γ), thereby initiating autoimmunity and inflammation [11]. Notably, the activity of the redox system is inversely correlated with the concentrations of anti-TPO antibodies and anti-TG antibodies, indicating that higher antioxidant capacity is associated with lower levels of autoantibodies [8].

Thyroid hormones have widespread effects on the metabolism of carbohydrates, fats, proteins, electrolytes, and minerals [12–15]. They also influence renal blood flow, glomerular filtration rate, tubular reabsorption, and mineral excretion, directly affecting the metabolism of calcium, magnesium, and phosphorus [16].

In hypothyroidism, there is a reduced mobilization of calcium from bone cells, leading to decreased total blood calcium levels [13]. This reduction prompts an increase in calcitonin, which enhances tubular reabsorption of phosphates, further lowering total blood calcium levels by increasing urinary excretion [17]. Hyperphosphatemia is also commonly observed in hypothyroidism, with several studies reporting low total calcium levels and elevated phosphate levels [18–20]. However, some studies suggest that both calcium and phosphate levels may remain within the normal reference range in hypothyroid patients [21].

Regarding magnesium levels in hypothyroidism, the evidence is inconsistent. Magnesium plays a key role in activating adenyl cyclase and cyclic 3',5'-nucleotide phosphodiesterase. Since thyroid hormones exert their effects via cAMP, magnesium ions may influence the thyroid gland response to stimulating hormones [22]. Magnesium is also an important protective cation, though the precise mechanism by which it influences the body's antioxidant capacity is not yet fully understood. Recent studies, however, suggest a beneficial role of magnesium in this context [23, 24]. Thyroid hormones play a crucial role in mitochondrial function, where magnesium is essential for oxidative phosphorylation as a component of complex V [24]. It also opposes atherosclerosis, reduces blood pressure, and promotes coronary vasodilation. Consequently, hypomagnesemia is linked to conditions such as arrhythmias, hypertension, and coronary vasospasm [25]. Some researchers have attributed hypomagnesemia in hypothyroidism to increased renal excretion of magnesium [26, 27]. Conversely, other studies have reported hypermagnesemia in hypothyroidism, potentially due to reduced urinary excretion of magnesium. Research by Jones et al. and McCaffrey and Quamme indicated that urinary magnesium excretion is decreased in hypothyroidism. They also suggested that magnesium elimination through feces is enhanced compared to euthyroid individuals, and the availability of magnesium for exchange between intracellular and extracellular spaces is reduced [28, 29].

Although changes in magnesium and calcium concentrations can be subtle, they may have significant long-term repercussion on cardiovascular function [30].

Given the prevalence of Hashimoto's thyroiditis in the general population, and the possible consequences of altered calcium and magnesium concentrations, we aimed to investigate the levels of calcium and magnesium and their relationship to thyroid function status indicators in affected patients.

The aim of this study was to assess the serum levels of calcium and magnesium in patients newly diagnosed with hypothyroidism and in those undergoing thyroid replacement therapy.

Material and Methods

The study was designed as a retrospective cross-sectional analysis and received approval by the Ethics Committee of the Clinical Center of Vojvodina. Data were sourced from the database of the Center for Laboratory Medicine at the Clinical Center of Vojvodina, covering patients referred to the Department from January 2020 to December 2020.

Based on the inclusion criteria, data were obtained from 72 patients of both genders diagnosed with primary autoimmune hypothyroidism, specifically Hashimoto's thyroiditis. These patients were divided into two groups of 36 individuals each. The first group included newly diagnosed hypothyroid patients who had

not yet initiated L-thyroxine therapy. The second group consisted of patients with hypothyroidism already undergoing L-thyroxine replacement therapy, with an average duration of 38 months. A control group of 30 clinically and biochemically healthy individuals was also included, matched for gender and age with the other two groups.

Exclusion criteria encompassed individuals younger than 18 years, pregnant women, patients with concurrent malignant diseases or other autoimmune disorders, those with liver insufficiency, terminal kidney failure, patients on thyroid suppressive therapy, and those taking supplements that could affect calcium, magnesium, or phosphorus levels.

For all enrolled patients, data on blood levels of free-triiodothyronine (fT3), free-thyroxine (fT4), TSH, TPOAb, TgAb, total and ionized calcium, magnesium, and phosphorus were extracted from their medical records for analysis.

Serum levels of fT3, fT4, TSH, TPOAb, and TgAb were determined using the chemiluminescence method on an automated Alinity analyzer (Abbott Diagnostics).

The concentrations of total calcium, magnesium, and phosphorus were measured using an automated Architect c8000 analyzer (Abbott Diagnostics), while ionized calcium levels were assessed using an AVL 910 analyzer (Roche Diagnostics).

Data were presented as absolute and relative numbers for descriptive variables, and as mean values with standard deviations for numeric variables with a normal distribution, as assessed by the Kolmogorov-Smirnov test.

Statistical comparisons of the analyzed variables were performed using the Student's t-test for continuous variables and the χ^2 test for categorical variables. Pearson correlation analysis was employed to evaluate the relationships between the studied parameters, with statistical significance set at a p-value <0.05. All statistical analyses were conducted using MedCalc software, version 9.2.0.1.

Results

The initial analysis focused on evaluating the gender distribution and age structure across the examined groups. As presented in **Table 1**, no statistically significant differences were observed.

As shown in **Table 2**, patients with newly diagnosed hypothyroidism had statistically significantly lower mean values of fT3, fT4, total calcium (Ca), and magnesium (Mg) compared to both patients on thyrosubstitution therapy and the control group ($p<0.01$ for all comparisons). Additionally, the mean TSH level was statistically significantly higher in newly diagnosed hypothyroid patients compared to both the treated group and the control group ($p < 0.01$ for all comparisons). Newly diagnosed hypothyroid patients also exhibited significantly lower levels of ionized calcium compared to the control group ($p=0.009$), with a borderline difference compared to the thyrosubstitution therapy group ($p=0.055$). Magnesium levels were significantly lower in newly diagnosed hypothyroid patients than in both the treated hypothyroid group and the control group ($p<0.01$ for both). In contrast, phosphorus levels were significantly higher in newly diagnosed hypothyroid patients compared to those undergoing thyroid replacement therapy ($p=0.009$). No statistically significant differences were observed between the group on thyroid replacement therapy and the control group in terms of thyroid hormones and electrolyte levels.

No statistically significant difference was found in the concentrations of TPOAb and TgAb between newly diagnosed hypothyroid patients and those on thyroid replacement therapy. However, both TPOAb and TgAb levels were significantly elevated in patients with hypothyroidism compared to the control group.

Table 3 presents the correlations between the concentrations of total Ca, Ca^{++}, Mg and P with TSH levels in patients newly diagnosed with hypothyroidism. Statistically significant negative correlation was observed between THS levels and the concentrations of total Ca, $Ca^{++}$and Mg levels in this patient. In contrast, no significant correlation was found between phosphorus levels and TSH.

Table 4 displays the correlations between the concentrations of total Ca, Ca^{++}, Mg, and P levels with the levels of fT3 in patients with newly diagnosed hypothyroidism. The data show a statistically significant positive correlation between fT3 levels and concentrations of both total and ionized Ca. Additionally, Mg levels also demonstrated a statistically significant correlation with fT3.

Table 1. Demographic data of the patients in relation to the examined groups
Tabela 1. *Demografski podaci pacijenata u odnosu na ispitivane*

Parameter *Parametar*	Group I Hypothyroidism *Grupa I Hipotireoidizam*	Group II Thyros. Therapy *Grupa II Tireosupst. terapija*	Control group *Kontrolna grupa*	p	p*	p**
Male/*Muško*	11 (31)	10 (28)	9 (30)	NS	NS	NS
Female/*Žensko*	25 (69)	26 (72)	21 (70)	NS	NS	NS
Age/*Godine*	54.58±11.38	54.86±9.60	50.93±11.06	NS	NS	NS

Legend: Data is shown as $\overline{X}$ ± SD or n (%); NS - not significant/*Legenda: Podaci su prikazani kao $\overline{X}$± SD ili n (%); NS – nije značajno*
p – Statistical significance between Group 1 (Newly diagnosed hypothyroidism) and Group II (thyrosubstitution therapy)/*Statistička značajnost između Grupe I (Novodijagnostikovani hipotireoidizam) i Grupe II (tireosupstituciona terapija)*
*p** – Statistical significance between Group I (newly diagnosed hypothyroidism) and control group (CG)/*Statistička značajnost između Grupe I (novodijagnostikovani hipotireoidizam) i kontrolne grupe (CG)*
*p*** – Statistical significance between group II (thyrosubstitution therapy) and the control group (CG)/*Statistička značajnost između Grupe II (tirosupstituciona terapija) i kontrolne grupe (CG)*

Table 2. Comparison of biochemical parameters between the examined groups and the control group
Tabela 2. *Komparacija biohemijskih parametara između ispitivanih grupa i kontrolne grupe*

Parameter *Parametar*	Group I Hypothyroidism *Grupa I Hipotireoidizam*	Group II Thyros. Therapy *Grupa II Tireosupst. terapija*	Control group *Kontrolna grupa*	p	p*	p**
fT_3 (pmo/l)	3.47±0.97	4.50±0.60	4.86±0.39	0.000	0.000	NS
fT_4 (pmo/l)	9.15±1.69	11.90±1.70	12.61±2.30	0.000	0.000	NS
TSH (mIU/l)	14.34±16.80	2.30±1.08	2.23±0.97	0.000	0.000	NS
TPO At (IU/l)	499.70±243.91	374.68±137.90	3.75±1.15	NS	0.000	0.000
Tg At (IU/l)	106.23±23.92	91.05±48.03	3.72±1.29	NS	0.000	0.000
Ca (mmol/l)	2.21±0.13	2.35±0.09	2.37±0.11	0.000	0.000	NS
Ca^{++}(mmol/l)	1.11±0.08	1.14±0.04	1.16±0.07	0.055	0.009	NS
Mg (mmol/l)	0.76±0.08	0.82±0.06	0.83±0.04	0.002	0.000	NS
P (mmol/l)	1.19±0.12	1.11±0.12	1.14±0.04	0.009	0.053	NS

Legend: Data is shown as X ± SD; fT_3 - free triiodothyronine; fT_4 - free thyroxine; TSH - thyroid-stimulating hormone; Ca - Calcium; Ca^{++} - ionized calcium; Mg - magnesium; P - phosphorus; NS - not significant
Legenda: Podaci su prikazani kao X ± SD; fT3 – slobodan trijodtironin; fT4 – slobodan tiroksin; TSH – tireostimulišući hormon; Ca – kalcijum; Ca^{++} – jonizovani kalcijum; Mg – magnezijum; P – fosfor; NS – nije značajno
p – Statistical significance between Group 1 (Newly diagnosed hypothyroidism) and Group II (thyrosubstitution therapy)/*Statistička značajnost između Grupe I (Novodijagnostikovani hipotireoidizam) i Grupe II (tireosupstituciona terapija)*
p* – Statistical significance between Group I (newly diagnosed hypothyroidism) and control group (CG)/*Statistička značajnost između Grupe I (novodijagnostikovani hipotireoidizam) i kontrolne grupe (CG)*
p** – Statistical significance between group II (thyrosubstitution therapy) and the control group (CG)/*Statistička značajnost između Grupe II (tirosupstituciona terapija) i kontrolne grupe (CG)*

Table 3. Correlations of examined parameters with TSH level in group of patients with newly diagnosed hypothyroidism
Tabela 3. *Korelacije ispitivanih parametara sa nivoom TSH u grupi pacijenta sa novootkrivenim hipotireoidizmom*

Parameter/*Parametar*	r/*r*	p/*p*
Ca (mmol/l)	-0.389	0.019
Ca^{++}(mmol/l)	-0.440	0.007
Mg (mmol/l)	-0.349	0.037
P (mmol/l)	-0.129	0.452

Legend: Ca – calcium; Ca^{++} – ionized calcium; Mg – magnesium; P – phosphorus
Legenda: Ca – kalcijum; Ca^{++} – jonizovani kalcijum; Mg – magnezijum; P – fosfor

Table 4. Correlations of the examined parameters with fT3 level in the newly diagnosed hypothyroid group
Tabela 4. *Korelacija ispitivanih parametara sa nivoom fT3 u grupi novodijagnostikovanog hipotireoidizma*

Parameter/*Parametar*	r/*r*	p/*p*
Ca (mmol/l)	0.422	0.010
Ca^{++}(mmol/l)	0.480	0.003
Mg (mmol/l)	0.413	0.012
P (mmol/l)	0.074	0.669

Legend: Ca – calcium; Ca^{++} – ionized calcium; Mg – magnesium; P – phosphorus
Legenda: Ca – kalcijum; Ca^{++} – jonizovani kalcijum; Mg – magnezijum; P – fosfor

Table 5. Correlations of the examined parameters with fT4 level in group of patients with newly diagnosed hypothyroidism
Tabela 5. *Korelacije ispitivanih parametara sa nivoom fT4 u grupi pacijenata sa novodijagnostikovanim hipotireoidizmom*

Parameter/*Parametar*	r/*r*	p/*p*
Ca (mmol/l)	0.355	0.034
Ca^{++}(mmol/l)	0.420	0.011
Mg (mmol/l)	0.473	0.004
P (mmol/l)	0.099	0.566

Legend: Ca – calcium; Ca^{++} – ionized calcium; Mg – magnesium; P – phosphorus
Legenda: Ca – kalcijum; Ca^{++} – jonizovani kalcijum; Mg – magnezijum; P – fosfor

Table 5 outlines the correlations between the concentrations of total Ca, Ca^{++}, Mg, and P with fT4 levels in the group of patients with newly diagnosed hypothyroidism. The results indicate a statistically significant positive correlation between fT4 levels and the concentrations of total Ca, Ca^{++}, and Mg. However, no significant correlation was observed between phosphorus levels and fT4 in this patient group.

Discussion

The values of the hypothalamic-pituitary-thyroid axis hormones in our study revealed statistically significant differences across the examined groups. Patients with newly diagnosed hypothyroidism had statistically lower levels of fT3, fT4 and TSH (fT_3: 3.47±0.97, fT_4: 9.15±1.69, TSH: 14.34±16.80) compared to those on thyroid substitution therapy (fT_3: 4.50±0.60, fT_4: 11.90±1.70, TSH: 2.30±1.08) and the control group (fT_3: 4.86±0.39, fT_4: 12.61±2.30, TSH: 2.23±0.97) ($p<0.01$ for all). These findings are consistent with the results of Kevitha et al. [31] and Shivakumar et al. [32]. High TSH levels in patients with newly diagnosed hypothyroidism, compared to euthyroid states, represent a compensatory response to insufficient secretion of thyroid hormones, which, as expected, are significantly lower.

The literature shows conflicting results regarding the concentrations of calcium ions, magnesium, and phosphorus in patients diagnosed with hypothyroidism. Furthermore, the underlying metabolic mechanisms causing these changes are not completely understood. Similar uncertainties persist regarding the electrolyte concentrations in this patient population.

Our study found that patients with newly diagnosed hypothyroidism had significantly lower concentrations of total calcium (2.21±0.13 vs. 2.35±0.09, p=0.000) and magnesium (0.76±0.08 vs. 0.82±0.06, p=0.002) compared to those on thyrosubstitution therapy and the control group (calcium: 2.21±0.13 vs. 2.37±0.11, p=0.000; magnesium: 0.76±0.08 vs. 0.83±0.04, p=0.000). Ionized calcium levels were also significantly lower in newly diagnosed hypothyroid patients compared to the control group (p=0.009). Phosphorus levels were significantly higher in newly diagnosed hypothyroid patients compared to those on thyrosubstitution therapy (1.19±0.12 vs. 1.11±0.12, p=0.009).

Our findings align with those of Saxena et al. [33], who reported significantly lower total calcium and higher phosphorus concentrations in hypothyroid patients. Similar results on total calcium and magnesium concentrations were observed in studies by Kaur et al. [34], Murgod and Soans [13], and other authors [20, 32, 35]. However, Shivakumar et al. [32] found lower phosphorus levels and higher calcium and magnesium levels, differing from our results and those of other studies.

Hypocalcemia in hypothyroidism may result from reduced thyroid hormone action on the mobilization of intracellular calcium and potassium from bone tissue [13]. This leads to increased calcitonin levels, promoting tubular phosphate reabsorption and enhancing calcium excretion through urine [24]. Hyperphosphatemia exacerbates the risk of hypocalcemia by maintaining the constant product of phosphorus and calcium concentrations, whereby elevated phosphorus levels lead to decreased total calcium levels to uphold this balance. Jones et al. [28] found that hypothyroidism is associated with increased urinary and fecal excretion of calcium, contributing to lower serum calcium levels. Studying laboratory rats, McCaffrey and Quamme [36], found that, despite hypocalcemia, there was elevated urinary excretion of calcium that was not responsive to blood calcium concentrations, suggesting dysregulation in renal calcium handling. Almost equal values of total and ionized calcium (2.35±0.09 vs. 2.37±0.11; 1.14±0.04 vs. 1.16±0.07), and phosphorus (1.11±0.12 vs. 1.14±0.04) in the group of patients undergoing thyroid replacement therapy and the euthyroid patients point out to the effect of thyroid hormones on metabolism of the above minerals.

Our study found significantly lower magnesium levels in newly diagnosed hypothyroid patients compared to those on thyroid replacement therapy (0.76±0.08 vs. 0.82±0.06, $p<0.002$) and controls (0.76±0.08 vs. 0.83±0.04, p=0.000). Mean serum magnesium levels across all groups (0.75-0.85 mmol/l) fall within a range that poses a high risk of magnesium deficiency, a condition affecting 20% of the Vojvodina population [37]. Magnesium levels in newly diagnosed hypothyroid patients are at the lower end of this range, suggesting a higher prevalence of deficiency in this subgroup.

Several studies have reported higher magnesium levels in hypothyroid patients [13, 32, 34], contrary to our findings. A comprehensive meta-analysis [38] concluded that magnesium concentrations do not statistically significantly differ between hypothyroid patients and the general healthy population. It highlighted considerable heterogeneity in the type, duration, and treatment of hypothyroidism across studies.

Some researchers link hypomagnesemia in hypothyroidism to increased renal magnesium excretion [26, 27], while others associate hypermagnesemia with urinary magnesium retention [28, 29]. It is suggested that hypothyroidism may elevate fecal magnesium excretion, which could explain the lower magnesium levels in newly diagnosed patients [28]. However, our study's limitation in measuring magnesium excretion fractions in urine and feces precludes definitive determination of this mechanism.

Our study also demonstrated significant negative correlations between total calcium, ionized calcium, and magnesium levels with TSH and positive correlations with fT3 and fT4 levels in newly diagnosed hypothyroid patients. Phosphorus did not show statistically significant correlations with any hormone in our study. Similar correlations between electrolyte levels and TSH have been reported by other studies [13, 20, 31, 32].

Stridevi et al. [35] found a significant negative correlation between TSH and total calcium but no significant correlation between TSH and magnesium or

phosphorus, unlike our study which found a correlation between magnesium and TSH. Un Nisa et al. [39] also reported significant negative correlations between magnesium and TSH, and significant positive correlations between magnesium and fT3 and fT4.

According to Wang et al. [40], lower serum magnesium levels (≤0.55 mmol/l) are linked with significantly higher rates of TPOAb positivity, TgAb prevalence, Hashimoto's thyroiditis, and clinically evident hypothyroidism, suggesting that low magnesium significantly increases the risk of thyroid hypofunction. Low serum magnesium levels may reduce immune tolerance and activate immune cells abnormally. Additionally, magnesium serves as a coenzyme in antioxidant pathways, including glutathione synthesis, which may diminish cellular antioxidant responses and promote accumulation of free radicals, leading to oxidative stress and tissue damage. Epidemiological studies have linked inadequate magnesium intake with several chronic inflammatory conditions and elevated serum C-reactive protein levels [39].

Considering our findings and those of other studies, it is important to monitor magnesium status in patients with Hashimoto's hypothyroidism, as low magnesium levels may exacerbate chronic inflammation in the thyroid. Furthermore, magnesium deficiency is linked to increased cardiovascular and metabolic risks. Hypothyroid patients often experience impaired quality of life, particularly in physical, vitality, and mental health domains [41–44]. Magnesium supplementation in deficient patients with primary autoimmune hypothyroidism may potentially support thyroid function and reduce cardiovascular and metabolic risks associated with the condition.

Conclusion

Our research demonstrates that total and ionized calcium, as well as magnesium levels, are significantly lower in patients with newly diagnosed hypothyroidism compared to those on thyroid replacement therapy and euthyroid controls. Conversely, phosphorus levels are significantly higher in newly diagnosed hypothyroid patients compared to those receiving thyroid replacement therapy. Additionally, we found that serum calcium and magnesium levels show significant negative correlations with thyroid-stimulating hormone (THS) levels and positive correlations with free-triiodothyronine (fT3) and free-thyroxine (fT4) levels in newly diagnosed hypothyroid patients. These findings highlight the critical association between magnesium and calcium levels and thyroid gland function, emphasizing the importance of assessing these elements in patients with primary autoimmune hypothyroidism. Regular monitoring and management of calcium and magnesium levels are crucial in hypothyroid patients, as dysregulation of these electrolytes may lead to suboptimal control of the underlying disease and negatively impact the quality of life. Correcting any deficiencies in these electrolytes could be essential for improving patient outcomes and overall health.

References

1. Wilson SA, Stem LA, Bruehlman RD. Hypothyroidism: diagnosis and treatment. Am Fam Physician. 2021;103(10):605-13.
2. Goichot B, Caron P, Landron F, Bouée S. Clinical presentation of hyperthyroidism in a large representative sample of outpatients in France: relationships with age, aetiology and hormonal parameters. Clin Endocrinol (Oxf). 2016;84(3):445-51.
3. Chakera AJ, Pearce SH, Vaidya B. Treatment for primary hypothyroidism: current approaches and future possibilities. Drug Des Devel Ther. 2012;6:1-11.
4. Stošić Z, Borota R. Osnovi kliničke patofiziologije. Novi Sad: Medicinski fakultet Novi Sad; 2020.
5. Ross DS. Subclinical hypothyroidism. In: Werner SC, Ingbar SH, Braverman LE, Utiger RD. Werner & Ingbar's the thyroid: a fundamental and clinical text. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2005. p. 1070-85.
6. Chen S, Fazle Akbar SM, Zhen Z, Luo Y, Deng L, Huang H, et al. Analysis of expression of Fas, FasL, and Bcl-2 in the pathogenesis of autoimmune thyroid disorders. Cell Mol Immunol. 2004;1(3):224-8.
7. Zhang Y, Ji Q, Zhang W. Expression of apoptosis-related proteins in Hashimoto's thyroiditis and its pathological significance. Zhonghua Yi Xue Za Zhi. 2001;81(7):432-4.
8. Ates I, Yilmaz FM, Altay M, Yilmaz N, Berker D, Güler S. The relationship between oxidative stress and autoimmunity in Hashimoto's thyroiditis. Eur J Endocrinol. 2015;173(6):791-9.
9. Theofilopoulos AN, Kono DH, Baccala R. The multiple pathways to autoimmunity. Nat Immunol. 2017;18(7):716-24.
10. Birben E, Sahiner UM, Sackesen C, Erzurum S, Kalayci O. Oxidative stress and antioxidant defense. World Allergy Organ J. 2012;5(1):9-19.
11. Brzostek-Racine S, Gordon C, Van Scoy S, Reich NC. The DNA damage response induces IFN. J Immunol. 2011;187(10):5336-45.
12. Čaparević Z, Bojković G, Stojanović Dragoš Lj, Ilić V. Dyslipidemia and subclinical hypothyroidism. Med Pregl. 2003;56 (5-6):276-80.
13. Murgod R, Soans G. Changes in electrolyte and lipid profile in hypothyroidism. International Journal of Life Science and Pharma Research. 2012;2(3):185-94.
14. Pearce EN. Hypothyroidism and dyslipidemia: modern concepts and approaches. Curr Cardiol Rep. 2004;6(6):451-6.
15. Susanna TY, Sagayaraj A, Shashidhar KN, Gomathi M, Mahesh V. A correlative study of thyroid profile and mineral status in patients with hypothyroidism – a hospital-based case control study. Asian Journal of Pharmaceutical and Clinical Research. 2016;9(3):292-4.
16. Gohel MG, Shah AM, Shah AM, Makadia JS. A study of serum calcium, magnesium and phosphorus level in hypothyroidism patients. International Journal of Medical and Health Sciences. 2014;3(4):308-12.
17. Alcalde AI, Sarasa M, Raldua D, Aramayona J, Morales R, Biber J, et al. Role of thyroid hormone in regulation of phosphate transport in young and aged rats. Endocrinology. 1999;140(4):1544-51.
18. Al-Tonsi AA, Abdel-Gayoum AA, Saad M. The secondary dyslipidemia and deranged serum phosphate concentration in thyroid disorders. Exp Mol Pathol. 2004;76(2):182-7.

19. Kavitha MM, Pujar S, Hiremath CS, Prasad S, Mahanthesh. Evaluation of serum electrolytes in hypothyroid patients. Medpulse - International Medical Journal. 2014;1(8):393-5.

20. Bharti A, Shrestha S, Rai R, Singh MK. Assessment of serum minerals and electrolytes in thyroid patients. International Journal of Advances in Scientific Research. 2015;1(6):259-63.

21. Sabuncu T, Aksoy N, Arikan E, Ugur B, Tasan E, Hatemi H. Early changes in parameters of bone and mineral metabolism during therapy for hyper- and hypothyroidism. Endocr Res. 2001;27(1-2):203-13.

22. Erdal M, Sahin M, Hasimi A, Uckaya G, Kutlu M, Saglam K. Trace element levels in Hashimoto thyroiditis patients with subclinical hypothyroidism. Biol Trace Elem Res. 2008;123(1-3):1-7.

23. Zheltova AA, Kharitonova MV, Iezhitsa IN, Spasov AA. Magnesium deficiency and oxidative stress: an update. Biomedicine (Taipei). 2016;6(4):20.

24. Jamilian M, Mirhosseini N, Eslahi M, Bahmani F, Shokrpour M, Chamani M, et al. The effects of magnesium-zinc-calcium-vitamin D co-supplementation on biomarkers of inflammation, oxidative stress, and pregnancy outcomes in gestational diabetes. BMC Pregnancy Childbirth. 2019;19(1):107.

25. Barbour RL, Altura BM, Reiner SD, Dowd TL, Gupta RK, Wu F, et al. Influence of Mg2+ on cardiac performance, intracellular free Mg2+ and pH in perfused hearts as assessed with 31P nuclear magnetic resonance spectroscopy. Magnes Trace Elem. 1991;10(2-4):99-116.

26. Salvatore D, Davies TF, Schlumberger MJ, Hay ID, Larsen PR. Thyroid physiology and diagnostic of patients with thyroid disorders. In: Melmed S, Polonsky KS, Larsen PR, Kronenberg H, editors. Williams textbook of endocrinology. 13th ed. Philadelphia: Elsevir; 2016.

27. Suneel B, Nagendra DR, Aparna RR, Balakrishna D, Naidu JN. Mineral status in thyroid disorders (hypo and hyper). Int J Appl Biol Pharm. 2011;2(4):423-9.

28. Jones JE, Desper PC, Shane SR, Flink EB. Magnesium metabolism in hyperthyroidism and hypothyroidism. J Clin Invest. 1966;45(6):891-900.

29. Rizek JE, Dimick A, Wallach S. Plasma and erythrocyte magnesium in thyroid disease. J Clin Endocrinol Metab. 1965;25(3):350-8.

30. Ford HC, Crooke MJ, Murphy CE. Disturbances of calcium and magnesium metabolism occur in most hyperthyroid patients. Clin Biochem. 1989;22(5):373-6.

31. Kavitha MM, Chandrashekharyya SH, Kashinakunti SV, Sunitha H, Neela BM, Ratna S. Alteration in levels of serum calcium, phosphorus and magnesium in patients of hypothyroidism. Int J Biol Med Res. 2014;5(4):4594-6.

32. Shivakumar, Bhargavi SK, Prasad Naidu M. Study of serum calcium, magnesium and phosphorus levels in hypothyroidism. Scholars International Journal of Biochemistry. 2020;3(2):22-6.

33. Saxena S, Srivastava PC, Katyal R, Das B, Pannu SJ. Evaluation of mineral status in hypothyroidism in a tertiary care centre. Int J Res Med Sci. 2020;8(2):667-71.

34. Kaur J, Ahmad N, Gupta A. Changes in the electrolyte profile of patients having hypothyroidism. J Med Sci Clin Res. 2014;2(4):633-7.

35. Sridevi D, Dambal AA, Sidrah, Challa AS, Padaki SK. A study of serum magnesium, calcium and phosphorus in hypothyroidism. International Journal of Clinical Biochemistry and Research. 2016;3(2):236-9.

36. McCaffrey C, Quamme GA. Effects of thyroid status on renal calcium and magnesium handling. Can J Comp Med. 1984;48(1):51-7.

37. Čabarkapa V, Đerić M, Todorović M, Sudji J, Ilinčić B, Trifu A, et al. Hypomagnesemia in adults of northern Serbia: prevalence, nutritional risk factors, and associated comorbidities. Magnes Res. 2019;32(1):25-36.

38. Talebi S, Ghaedi E, Sadeghi E, Mohammadi H, Hadi A, Clark CCT, et al. Trace element status and hypothyroidism: a systematic review and meta-analysis. Biol Trace Elem Res. 2020;197(1):1-14.

39. un Nisa F, Mumtaz A, Ikram Ullah M, Atif M, Sami W. Determination of serum zinc and magnesium levels in patients with hypothyroidism. Trace Elements and Electrolytes. 2014;31(2):43-7.

40. Wang K, Wei H, Zhang W, Li Z, Ding L, Yu T, et al. Severely low serum magnesium is associated with increased risks of positive anti-thyroglobulin antibody and hypothyroidism: a cross-sectional study. Sci Rep. 2018;8(1):9904.

41. Saravanan P, Chau WF, Roberts N, Vedhara K, Greenwood R, Dayan CM. Psychological well-being in patients on 'adequate' doses of l-thyroxine: results of a large, controlled community-based questionnaire study. Clin Endocrinol (Oxf). 2002;57(5):577-85.

42. Wekking EM, Appelhof BC, Fliers E, Schene AH, Huyser J, Tijssen JG, et al. Cognitive functioning and well-being in euthyroid patients on thyroxine replacement therapy for primary hypothyroidism. Eur J Endocrinol. 2005;153(6):747-53.

43. Samuels MH, Schuff KG, Carlson NE, Carello P, Janowsky JS. Health status, psychological symptoms, mood, and cognition in L-thyroxine-treated hypothyroid subjects. Thyroid. 2007;17(3):249-58.

44. Sikjaer T, Moser E, Rolighed L, Underbjerg L, Bislev LS, Mosekilde L, et al. Concurrent hypoparathyroidism is associated with impaired physical function and quality of life in hypothyroidism. J Bone Miner Res. 2016;31(7):1440-8.

Rad je primljen 12. VII 2024.
Recenziran 14. VIII 2024.
Prihvaćen za štampu 14. VIII 2024.
BIBLID.0025-8105:(2024):LXXVII:3-4:106-112.

University Clinical Center of Vojvodina, Novi Sad[1]
University in Novi Sad, Faculty of Medicine Novi Sad[2]

Original study
Originalni naučni rad
UDK 616.14-005.6:616-008.855
https://doi.org/10.2298/MPNS2404113J

DIFFERENCES IN FIBRINOLYTIC PROFILE BETWEEN PATIENTS WITH DIFFERENT LOCALIZATIONS AND TYPES OF VENOUS THROMBOSIS

RAZLIKE U FIBRINOLIZNOM PROFILU IZMEĐU PACIJENATA SA RAZLIČITIM LOKALIZACIJAMA I TIPOVIMA VENSKIH TROMBOZA

Marija JOZING[1], Stevan TUBIĆ[1], Simona IKONOV[1] and Biljana VUČKOVIĆ[1,2]

Summary

Introduction. The role of the fibrinolytic system in venous thrombosis remains incompletely understood. This study aimed to evaluate the effectiveness of the fibrinolytic system in patients with various types and locations of venous thrombosis compared to healthy controls. **Material and Methods.** The study included 100 patients with venous thrombosis and 100 healthy controls. Patients were stratified based on the type of venous thrombosis (spontaneous vs. provoked) and the location (distal, proximal, and atypical). Global fibrinolytic activity was assessed using euglobulin clot lysis time, while specific fibrinolytic components measured included plasminogen, tissue plasminogen activator, thrombin-activatable fibrinolysis inhibitor, and plasminogen activator inhibitor-1. **Results.** Patients with isolated distal and provoked venous thrombosis exhibited significantly prolonged euglobulin clot lysis time compared to healthy controls (218.3 ± 41.1 vs. 185.6 ± 42.3 min, p=0.001; 208.2 ± 48.5 min vs. 185.6 ± 42.3 min, p=0.018, respectively). Patients with provoked venous thrombosis demonstrated higher plasminogen (127.1 ± 27.7 vs. 117.1 ± 24.5%, p=0.044) and tissue plasminogen activator levels (20.0 ± 11.1 vs. 16.8 ± 8.1 ng/ml, p=0.042) compared to controls. Thrombin-activatable fibrinolysis inhibitor levels were significantly elevated in patients with both provoked (19.9 ± 4.0 vs. 17.1 ± 4.3 ng/ml, p=0.000) and spontaneous venous thrombosis (19.5 ± 6.0 vs. 17.1 ± 4.3 ng/ml, p=0.02), as well as in cases of isolated distal (20.7 ± 5.0 vs. 17.1 ± 4.3 ng/ml, p=0.001) and proximal (19.4 ± 5.3 vs. 17.1 ± 4.3 ng/ml, p=0.013) venous thrombosis when compared to healthy controls. **Conclusion.** The study reveals significant variations in the fibrinolytic process across different types and anatomical locations of venous thrombosis compared to healthy individuals.

Key words: Venous Thrombosis; Fibrinolysis; Plasminogen; Carboxypeptidase B2; Risk Factors

Sažetak

Uvod. Uloga fibrinolize u venskoj trombozi još uvek nije razjašnjena. Cilj studije je ispitivanje razlika u globalnoj funkcionalnosti fibrinoliznog mehanizma i njegovim pojedinačnim komponentama između pacijenata sa različitim tipovima i lokalizacijama venskih tromboza i zdravih osoba. **Materijal i metode.** Uzorak je obuhvatio 100 pacijenata sa venskom trombozom i 100 zdravih kontrola. Pacijenti su grupisani u odnosu na tip venske tromboze (spontana ili provocirana) i u odnosu na lokalizaciju (distalna, proksimalna i atipična). Euglobulinsko vreme lize koaguluma korišteno je za procenu globalne fibrinolizne funkcionalnosti, a određivane su i koncentracije plazminogena, tkivnog aktivatora plazminogena, trombinom aktiviranog fibrinoliznog inhibitora i inhibitora aktivatora plazminogena-1. **Rezultati.** Pacijenti sa izolovanom distalnom i sa provociranom venskom trombozom imaju značajno duže euglobulinsko vreme lize koaguluma u poređenju sa kontrolama (218,3 ± 41,1 vs. 185,6 ± 42,3 min, p = 0,001 i 208,2 ± 48,5 vs. 185,6 ± 42,3 min, p = 0,018). Pacijenti sa provociranom venskom trombozom imaju više nivoe plazminogena (127,1 ± 27,7 vs. 117,1 ± 24,5%, p = 0,044) i tkivnog aktivatora plazminogena (20 ± 11,1 vs. 16,8 ± 8,1 ng/ml, p = 0,042) u poređenju sa kontrolama. Trombinom aktivirani fibrinolizni inhibitor je značajno viši kod provociranih (19,9 ± 4 vs. 17,1 ± 4,3 ng/ml, p = 0,000), spontanih (19,5 ± 6 vs. 17,1 ± 4,3 ng/ml, p = 0,023), izolovanih distalnih (20,7 ± 5 vs. 17,1 ± 4,3 ng/ml, p = 0,001) i proksimalnih venskih tromboza (19,4 ± 5,3 vs. 17,1 ± 4,3 ng/ml, p = 0,013) u poređenju sa kontrolama. **Zaključak.** Postoje značajne razlike u fibrinoliznom mehanizmu između bolesnika sa različitim tipovima i lokalizacijama venskih tromboza u poređenju sa zdravim osobama.

Ključne reči: venska tromboza; fibrinoliza; plazminogen; trombinom aktivirani fibrinolizni inhibitor; faktori rizika

ORCID NUMBER
Marija Jozing 0009-0009-6503-9145
Stevan Tubić 0009-0004-1931-6643
Simona Ikonov 0009-0005-7889-6630
Biljana Vučković 0000-0001-6018-1219

Introduction

Thrombosis is defined as the formation of a blood clot within a blood vessel, arising from an imbalance among procoagulant, anticoagulant, and fibrinolytic factors. The balanced function of the hemostatic system ensures that blood remains in a liquid state, allows for clot formation in response to injury, and prevents excessive clotting through three primary mechanisms: primary hemostasis, coagula-

Corresponding Author: Marija Jozing, Univerzitetski klinički centar Vojvodine,
21000 Novi Sad, Hajduk Veljkova 1-7, E-mail: marijajozing05@gmail.com, biljana.vuckovic@mf.uns.ac.rs

Abbreviations

VT – venous thrombosis
ECLT – euglobulin clot lysis time
t-PA – tissue plasminogen activator
TAFI – thrombin activatable fibrinolytic inhibitor
PAI-1 – plasminogen activator inhibitor – 1
u-PA – urokinase plasminogen activator
PI – plasmin inhibitor
PAI-2 – plasminogen activator inhibitor – 2
DVT – deep venous thrombosis
FV – factor V
CT – computed tomography
BMI – body mass index

tion, and fibrinolysis [1]. The fibrinolytic system, which is the final phase of the hemostatic process, plays a crucial role in breaking down fibrin and preventing the formation of fibrin cloths within circulation. The process involves a complex interplay of numerous factors. Central to fibrinolysis is plasmin, an enzyme that circulates in its inactive form, plasminogen. The conversion of plasminogen to plasmin is mediated by plasminogen activators, including tissue plasminogen activator (t-PA) and urokinase-type plasminogen activator (u-PA). Plasmin's proteolytic action involves cleaving arginine and lysine bonds within fibrin and fibrinogen molecules, leading to the generation of degradation products, such as fragments X, Y, D, and E [2]. Notably, several inhibitors regulate plasmin activity, including antiplasmin (PI), plasminogen activator inhibitor-1 (PAI-1), plasminogen activator inhibitor-2 (PAI-2), and thrombin-activatable fibrinolysis inhibitor (TAFI), which collectively prevent excessive fibrin breakdown [3].

The pathogenesis of thrombosis can be explained by Virchow's triad, which comprises three interrelated factors: alterations in the vessel wall, altered blood flow, and changes in blood composition. Among these, altered blood flow and blood composition are the most significant contributors to the development of venous thrombosis [4].Venous thrombosis typically presents as deep vein thrombosis (DVT) of the lower extremities or as a pulmonary embolism, although it can also affect other veins less frequently. Venous thromboses are categorized based on etiology into spontaneous and provoked types, and based on location, into distal, proximal, and atypical localizations.

The incidence of venous thrombosis is approximately 2 per 1,000 individuals per year in the general population, driven by a combination of genetic and acquired risk factors. In Europe, the annual incidence is around 108 per 100,000 individuals, while in the United States, approximately 250,000 new cases are reported annually among whites and 78 per 100,000 among African Americans [6]. The prevalence of venous thrombosis is similar between males and females, but a slightly higher incidence is observed in younger women, largely associated with hormone therapy, pregnancy, and the puerperium. The incidence also increases with age, from 1 per 100,000 annually in children to 1 per 100 annually in older adults [7]. It is important to note that approximately one-third of patients will experience a recurrence of thrombosis within 10 years of their initial episode. The risk of recurrence is highest within the first 6 to 12 months, particularly in men and following idiopathic thrombosis. The mortality rate associated with venous thrombosis ranges from 1% in the younger individuals to 20% in older patients, with the highest rates observed in those with malignancies, predominantly due to pulmonary embolism [8, 9].

As noted, a range of genetic and acquired risk factors contribute to the onset of venous thrombotic events. Common acquired risk factors include advanced age, prolonged immobilization, pregnancy and puerperium, surgical procedures and trauma, malignancy, antiphospholipid syndrome, long-distance travel, lifestyle factors, and hormone therapy. Key hereditary risk factors encompass deficiencies in natural anticoagulants (protein C, protein S, and antithrombin), Factor V Leiden mutation, prothrombin gene mutation G20210A, fibrinogen γ-chain gene mutation, and an increased risk in individuals with non-O blood types [10–12].

While it is established that reduced fibrinolytic activity plays a role in thrombosis onset, many questions remain regarding the specific contributions of individual fibrinolytic factors in venous thrombosis and the overall role of the fibrinolytic system in different types and localizations of venous thrombotic disease.

This study aims to investigate the fibrinolytic system in patients with various types and locations of venous thrombosis and to compare these parameters with those in a healthy population.

Material and Methods

Between January 2022 and January 2024, the Clinical Center of Vojvodina conducted a study involving 100 patients, aged 18 to 88 years, who were newly diagnosed with venous thrombosis. The diagnosis of deep vein thrombosis was confirmed through Doppler ultrasonography, while pulmonary embolism was diagnosed using CT pulmonary angiography. Additionally, a control group of 100 individuals, aged 19 to 87 years, with no prior history of venous thrombosis, was selected. All participants provided written informed consent, and the study protocol was approved by the Medical Ethics Committee of the Clinical Center of Vojvodina in Novi Sad, Serbia.

To be eligible for inclusion in the study, participants had to be enrolled at least three months after their thrombosis diagnosis and at least two months after discontinuing anticoagulation therapy. They completed a standardized questionnaire that captured potential risk factors for venous thrombosis. The overall function of the fibrinolytic system was assessed using euglobulin clot lysis time (ECLT), with values between 120 and 240 minutes considered indicative of normal fibrinolytic activity, and values exceeding 240 minutes indicating reduced

fibrinolytic activity. Levels of TAFI and t-PA were measured using the ELISA method, while PAI-1 concentrations were determined using the chromogenic substrate method.

Out of the 176 patients initially considered for the study, 6 were excluded due to liver and kidney disease, 18 due to acute illness, 21 due to diagnosed malignancy, 12 due to the use of medications affecting the hemostatic mechanism, and 5 due to pregnancy at the time of diagnosis or within the preceding three months. Ultimately, 100 of the remaining 114 patients agreed to participate in the study. The control group also consisted of 100 participants who met the study's inclusion criteria after applying similar exclusion criteria.

All data were analyzed using SPSS software for Windows, version 24.0 (SPSS, Chicago, IL, USA). Descriptive statistics were used to summarize the characteristics of the study participants. To evaluate the statistical significance of differences in continuous variables, we employed the Student's t-test or the Mann-Whitney U test. Correlations were assessed using Pearson's linear correlation coefficient and Spearman's rank correlation coefficient. A P-value of less than 0.05 considered statistically significant.

Results

A total of 200 participants were included in the study after applying exclusion criteria, with 100 in the patient group and 100 in the control group**.**

The basic characteristics of the participants are summarized in **Table 1**. The patient group included 100 individuals, comprising 48 men and 52 women, with a mean age of 52 years. The control group also included 100 participants, with 51 men and 49 women, and a mean age of 50 years. Patients with venous thrombosis had a slightly higher BMI compared to the control group. Traditional risk factors for venous thrombosis were more common among patients (44%) than among controls (15%). Additionally, the patient group exhibited higher rates of obesity (22% vs. 16%), smoking (31% vs. 24%), hypertension (41% vs. 29%), hyperlipoproteinemia (69% vs. 54%), and hyperLp(a) lipoproteinemia (20% vs. 12%) compared to healthy controls.

Table 2 presents the characteristics of the patient group in terms of the type and location of venous thrombosis. Proximal venous thrombosis was observed in 63% of patients, with nearly equal distribution between left-sided and right-sided cases (49% vs. 51%). Distal venous thrombosis was found in 29% of patients, with a higher prevalence on the left side (59% vs. 41%). Thrombosis in atypical locations was seen in 8% of patients, including thrombosis in the deep veins of the arms (7 patients) and in the central retinal vein (1 patient).

Regarding the type of venous thrombosis, 56% of patients had spontaneous venous thrombosis, while 44% had provoked venous thrombosis: 11% following surgical interventions, 27% due to plaster immobilization, 25% resulting from trauma, 23% occurring during pregnancy, and 14% associated with hormone therapy.

The results of global fibrinolytic system functionality testing demonstrated that patients with deep vein thrombosis had significantly prolonged euglobulin clot lysis times compared to the control group (204.3±51.2 min. vs. 185.6±42.3 min; p=0.01), as shown in **Graph 1.**

Patients with isolated distal venous thrombosis had significantly longer ECLT compared to the control group (218.3±41.1 minutes vs. 185.6±42.3 minutes; p=0.001). In contrast, there were no significant differences in fibrinolytic activity between patients with proximal venous thrombosis and healthy controls (194.7±54.0 minutes vs. 185.6±42.3 minutes; p=0.44).

Table 1. Clinical characteristics of the participants
Tabela 1. *Kliničke karakteristike ispitanika*

Patients/*Pacijenti* (n=100)		Controls/*Kontrole* (n=100)
General characteristics/*Opšte karakteristike*		
Male/*Muškarci*	48 (48)	51 (51)
Age, years/*Starost, godine*	52 (19-88)	50 (19-87)
Body mass index, kg/m²/*Indeks telesne mase, kg/m²*	27 (17-39)	26 (18-37)
Classical venous thrombosis risk factors†/*Klasični faktori rizika za nastanak venske tromboze†*		
Present/*Prisutni*	44 (44)	15 (15)
Absent/*Odsutni*	56 (56)	85 (85)
Arterial cardiovascular risk factors/*Klasični faktori rizika za nastanak arterijske tromboze*		
Obesity/*Gojaznost*	22 (22)	16 (16)
Smoking/*Pušenje*	31 (31)	24 (24)
Hypertension/*Hipertenzija*	41 (41)	29 (29)
Hyperlipoproteinemia/*Hiperlipoproteinemija*	69 (69)	54 (54)
HyperLp(a) lipoproteinemia/*HiperLp(a) lipoproteinemija*	20 (20)	12 (12)

†Classical risk factors include surgery, malignancy, immobility, trauma, plaster cast, immobilization, use of hormonal therapy, oral contraceptive therapy, long trips/*†Klasični faktori rizika uključuju hirurške intervencije, malignitet, nepokretnost, traumu, gipsanu imobilizaciju,upotrebu hormonskih preparata i duža putovanja*
Values are n (%) unless otherwise indicated/*Vrednosti su n (%) osim ako nije drugačije naznačeno*

Table 2. Characteristics of the patient group in relation to the type and localization of venous thrombosis
Tabela 2. *Karakteristike grupe bolesnika u odnosu na vrstu i lokalizaciju venske tromboze*

Localization of venous thrombosis/*Lokalizacija venske tromboze*			
Proximal venous thrombosis *Proksimalna venska tromboza*	63 (63)	Right-sided/*Desnostrana* Left-sided/*Levostrana*	32 (51) 31 (49)
Distal venous thrombosis *Distalna venska tromboza*	29 (29)	Right-sided/*Desnostrana* Left-sided/*Levostrana*	12 (41) 17 (59)
Atypical thrombosis localization *Atipično lokalizovana tromboza*	8 (8)	Deep veins of the arms/*Duboke vene ruku* Central retinal vein/*Centralna vena retine*	7 (88) 1 (12)
Type of venous thrombosis/*Tip venske tromboze*			
Provoked venous thrombosis *Provocirana venska tromboza*	44 (44)	Surgical interventions/*Hirurške intervencije*	5 (11)
		Plaster immobilization/*Gipsana imobilizacija*	12 (27)
		Trauma/*Povreda*	11 (25)
		Pregnancy/*Trudnoća*	10 (23)
		Hormone therapy/*Hormonska terapija*	6 (14)
Spontaneous venous thrombosis/*Spontana venska tromboza*	56 (56)		

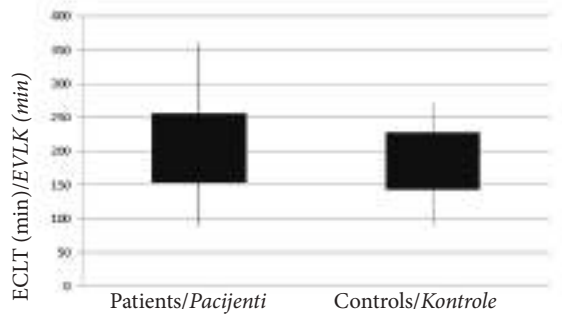
Table 3. Differences in global fibrinolytic mechanism functionality between individual subgroups of patients with venous thrombosis and healthy participants
Tabela 3. *Poređenje globalne funkcionalnosti fibrinoliznog mehanizma između različitih podgrupa bolesnika i zdravih ispitanika*

Euglobulin clot lysis time/*Euglobulinsko vreme lize koaguluma*	SV±SD	Range/*Raspon*	p/*p*
Patients/*Pacijenti*	204.3±51.2	90-360	0.01
Controls/*Kontrole*	185.6±42.3	90-270	
Patients – distal VT/*Pacijenti – distalna VT*	218.3±41.1	140-310	0.00
Controls/*Kontrole*	185.6±42.3	90-270	
Patients – proximal VT/*Pacijenti – proksimalna VT*	194.7±54.0	90-360	0.44
Controls/*Kontrole*	185.6±42.3	90-270	
Patients – atypical localization of VT/*Pacijenti – VT atipične lokalizacije*	229.4±46.2	160-310	0.01
Controls/*Kontrole*	185.6±42.3	90-270	
Patients – provoked VT/*Pacijenti – provocirana VT*	208.2±48.5	130-320	0.02
Controls/*Kontrole*	185.6±42.3	90-270	
Patients – spontaneous VT/*Pacijenti – spontana VT*	201.3±53.5	90-360	0.07
Controls/*Kontrole*	185.6±42.3	90-270	

Legend: VT – venous thrombosis/*Legenda*: *VT – venska tromboza*

Patients with atypical thrombosis locations had notably longer ECLT compared to controls (229.4±46.2 minutes vs. 194.7±54.0 minutes; p=0.01). Those with provoked venous thrombosis also exhibited significantly higher ECLT values compared to healthy controls (208.2±48.5 minutes vs. 185.6±42.3 minutes; p=0.02). However, no significant differences were found between patients with spontaneous thrombosis and the control group (201.3±53.5 minutes vs. 185.6±42.3 minutes; p=0.07) **(Table 3).**

A significant difference in euglobulin clot lysis time (ECLT) was observed among subgroups based on the localization of the venous thrombotic process (distal DVT 218.3 ± 41.1 minutes vs. proximal DVT 194.7 ± 54.0 minutes vs. rare localization DVT 229.4 ± 46.2 minutes; p=0.02). Patients with thrombosis in rare locations of deep venous thrombosis had the



Graph 1. Comparison of global fibrinolytic activity between patients and controls
Grafikon 1. *Poređenje globalne funkcionalnosti fibrinoliznog mehanizma između bolesnika i kontrola*

Table 4. Comparison of global fibrinolytic system functionality between different subgroups of patients
Tabela 4. *Poređenje globalne funkcionalnosti fibrinoliznog mehanizma između različitih podgrupa bolesnika*

Euglobulin clot lysis times/*Euglobulinsko vreme lize koaguluma*			
	SV±SD	Range/*Raspon*	p/*p*
Patients – distal VT/*Pacijenti – distalna VT*	218.3±41.1	140-310	
Patients – proximal VT/*Pacijenti – proksimalna VT*	194.7±54.0	90-360	**0.02**
Patients – atypical localizationof VT/*Pacijenti – VT atipične lokalizacije*	229.4±46.2	160-310	
Patients – provoked VT/*Pacijenti – provocirana VT*	208.2±48.5	130-320	0.66
Patients – spontaneous VT/*Pacijenti – spontana VT*	201.3±53.5	90-360	
Patients – isolated VT/*Pacijenti – izolovana VT*	205.2±51.3	90-360	0.39
Patients – pulmonary thromboembolism/*Pacijenti – plućna tromboembolija*	176.7±49.3	120-210	

Legend: VT - venous thrombosis; *Legenda*: *VT – venska tromboza*

longest ECLT, while those with proximal deep vein thrombosis had the shortest. No significant differences in global fibrinolytic mechanism functionality were found when comparing patients with provoked deep vein thrombosis to those with primary deep vein thrombosis (208.2 ± 48.5 minutes vs. 201.3 ± 53.5 minutes; p=0.66), or when comparing patients with isolated deep vein thrombosis to those with pulmonary thromboembolism (205.2 ± 51.3 minutes vs. 176.7 ± 49.3 minutes; p=0.39) **(Table 4).**

The detailed results of the comparisons of plasminogen, t-PA, PAI-1, and TAFI concentrations between different patient subgroups and the control group are presented in **Table 5**. Patients with provoked deep vein thrombosis had significantly higher plasminogen levels compared to controls (127.1 ± 27.7% vs. 117.1 ± 24.5%; p=0.04). They also had significantly higher t-PA concentrations compared to the control group (20.0 ± 11.1 ng/ml vs. 16.8 ± 8.1 ng/ml; p=0.04). Regarding TAFI concentrations, patients with both distal deep vein thrombosis (20.7 ± 5.0 ng/ml vs. 17.1 ± 4.3 ng/ml; p=0.00) and proximal deep vein thrombosis (19.4 ± 5.3 ng/ml vs. 17.1 ± 4.3 ng/ml; p=0.01) had significantly elevated levels compared to controls. Similarly, patients with provoked deep vein thrombosis exhibited higher TAFI concentrations than healthy individuals (19.9 ± 4.0 ng/ml vs. 17.1 ± 4.3 ng/ml; p=0.00), as did those

Table 5. Comparison of plasminogen, t-PA, PAI-1, and TAFI concentrations between subgroups of patients and controls
Tabela 5. *Poređenje koncentracije plazminogena, t-PA, PAI-1, TAFI između bolesničkih podgrupa i kontrola*

	Plasminogen *Plazminogen* (%)		t-PA (ng/ml)		PAI-1 (ng/ml)		TAFI (ng/ml)	
	SV±SD	p/*p*	SV±SD	p/*p*	SV±SD	p/*p*	SV±SD	p/*p*
Patients DDVT/*Pacijenti DDVT*	129.9±29.7	0.06	18.6±8.4	0.27	5.4±2.7	0.89	20.7±5.0	0.00
Controls/*Kontrole*	117.1±24.5		16.8±8.1		5.4±2.7		17.1±4.3	
Patients PDVT/*Pacijenti PDVT*	121.3±24.7	0.43	18.3±9.8	0.17	5.0±2.9	0.10	19.4±5.3	0.01
Controls/*Kontrole*	117.1±24.5		16.8±8.1		5.4±2.7		17.1±4.3	
Patients ALDVT/*Pacijenti ALDVT*	122.6±38.0	0.51	21.7±15.3	0.51	6.0±2.6	0.48	18.6±4.6	0.38
Controls/*Kontrole*	117.1±24.5		16.8±8.1		5.4±2.7		17.1±4.3	
Patients PRDVT/*Pacijenti PRDVT*	127.1±27.7	0.04	20.0±11.1	0.04	5.5±3.0	0.83	20.0±4.0	0.00
Controls/*Kontrole*	117.1±24.5		16.8±8.1		5.4±2.7		17.1±4.3	
Patients SDVT/*Pacijenti SDVT*	121.4±27.1	0.55	17.6±8.8	0.49	5.0±2.6	0.16	19.5±6.0	0.02
Controls/*Kontrole*	117.1±24.5		16.8±8.1		5.4±2.7		17.1±4.3	
Patients DDVT/*Pacijenti DDVT*	129.9±29.7		18.6±8.4		5.4±2.7		20.7±5.0	
Patients PDVT/*Pacijenti PDVT*	121.3±24.7	0.41	18.3±9.8	0.94	5.0±2.9	0.28	19.4±5.3	0.32
Patients ALDVT/*Pacijenti ALDVT*	122.6±38.0		21.7±15.3		6.0±2.6		18.6±4.6	
Patients PRDVT/*Pacijenti PRDVT*	127.1±27.7	0.16	20.0±11.1	0.37	5.5±3.0	0.31	19.9±4.0	0.34
Patients SDVT/*Pacijenti SDVT*	121.4±27.1		17.6±8.8		5.0±2.6		19.5±6.0	
Patients IDVT/*Pacijenti IDVT*	123.3±27.3	0.15	18.7±10.0	0.98	5.2±2.8	0.26	19.7±5.2	0.94
Patients PTE/*Pacijenti PTE*	142.0±27.2		17.1±7.6		6.6±1.8		18.9±1.9	

Legend/Legenda: DDVT – distal deep venous thrombosis/*DDVT – distalna tromboza dubokih vena;* PDVT – proximal deep venous thrombosis/*PDVT – proksimalna tromboza dubokih vena;* ALDVT – atypical localization deep venous thrombosis/*ALDVT – atipična lokalizacija tromboze dubokih vena;* PRDVT – provoked deep venous thrombosis/*PRDVT – provocirana tromboza dubokih vena*; SPDVT – spontaneous deep venous thrombosis/SPDVT – spontana tromboza dubokih vena; IDVT – isolated deep venous thrombosis/ IDVT – izolovana tromboza dubokih vena; PTE – pulmonary thromboembolism/PTE – plućna tromboembolija

with primary deep vein thrombosis (19.5 ± 6.0 ng/ml vs. 17.1 ± 4.3 ng/ml; p=0.02).

Discussion

The role of fibrinolysis in the pathophysiological mechanism underlying thrombosis formation is an evolving area of research with numerous aspects not fully understood. This study aimed to evaluate the functionality of the fibrinolytic system and its components in patients with various types and locations of VT compared to a healthy control group. In our cohort, 63% of patients had proximal venous thrombosis, while isolated distal venous thrombosis was present in 29% of cases, as aligning with the findings of other studies in this field [14–19]. Similar to the study by Ouriel et al., which reported a left-sided to right-side ratio of 1.3:1 for distal deep vein thrombosis [20], our study found a ratio of 1.4:1 favoring left-sided localization. However, we did not observe this difference in cases of proximal deep vein thrombosis. In our study, 56% of patients had spontaneous venous thrombosis, while 44% had provoked venous thrombosis. This classification is clinically significant, as evidence suggests that the risk of recurrent venous thromboembolism after 3-6 months of anticoagulant therapy is approximately 50% lower in patients with provoked thrombosis compared to those with spontaneous deep vein thrombosis.

Our analysis of the fibrinolytic system's global functionality demonstrated that patients with deep vein thrombosis had significantly prolonged ECLT, indicating reduced fibrinolytic activity compared to healthy participants. The first study to investigate the association between decreased fibrinolytic activity and venous thrombosis was published in 1991, concluding that the evidence for this link was inconclusive [22]. However, the authors noted that while reduced fibrinolytic activity may not predict venous thromboembolism overall, there is likely an association between suppressed fibrinolysis and postoperative venous thrombosis.

When we compared the fibrinolytic system's functionality between specific patient subgroups and the control group, we found no significant difference in ECLT between patients with proximal deep vein thrombosis and healthy controls. However, this difference became apparent when comparing patients with isolated distal venous thrombosis to healthy participants. A comparative analysis of the fibrinolytic system's functionality among patients with different localizations of deep vein thrombosis revealed significant differences in ECLT, with a notable prolongation of ECLT in patients with isolated distal deep vein thrombosis compared to those with proximal thrombotic localization. Additionally, we found that patients with thrombosis in rare locations had the longest ECLT. Given that thrombosis in rare locations is often accompanied by inflammation, increased PAI-1 activity during inflammation may explain these findings [23].

When examining differences in fibrinolytic mechanism functionality, as indicated by ECLT, between patients with provoked venous thrombosis and control participants, and between patients with spontaneous thrombosis and controls, we found that patients with provoked venous thrombosis had significantly higher ECLT values compared to controls. In contrast, there was no significant difference in ECLT between patients with spontaneous thrombosis and healthy participants. A comparative analysis between patients with provoked venous thrombosis and those with spontaneous deep vein thrombosis revealed no significant differences in fibrinolytic mechanism's functionality. Trauma is among the primary triggers of provoked venous thrombosis, as it leads to the release of PAI-1 from the damaged endothelium, potentially suppressing overall fibrinolytic activity [24]. Following the assessment of the overall functionality of the fibrinolytic mechanism, we further analyzed data on specific components of this system. Our findings indicated no substantial differences in plasminogen levels between patients with venous thrombosis and healthy participants, consistent with most of the existing literature. Indeed, aside from a few isolated case reports, there is limited evidence linking plasminogen deficiency to venous thrombosis. A comprehensive population-based case-control study by Okamoto et al. found comparable prevalence rates of plasminogen deficiency among venous thrombosis patients and healthy controls [25]. Subsequent analysis, which stratified patients into various subgroups and compared plasminogen levels with those of healthy controls, revealed no significant differences in patients with isolated distal deep vein thrombosis, proximal thrombosis, atypical venous thrombosis localization, or spontaneous deep vein thrombosis compared to the control group. However, our findings indicate that patients with provoked deep vein thrombosis had significantly elevated plasminogen concentrations compared to healthy individuals.

When comparing t-PA concentrations between all patients and controls, no statistically significant difference was observed, which aligns with most reports in the literature. A case-control study within the Physicians' Health Study cohort, which included 55 patients and controls and followed them for five years, concluded that circulating t-PA levels do not predict venous thrombosis [26]. However, similar to plasminogen, our study showed that after classifying patients and analyzing the comparison of t-PA levels between different patient subgroups and healthy individuals, patients with provoked deep vein thrombosis had significantly higher t-PA concentrations compared to healthy participants.

According to our study results, patients with venous thrombosis did not differ from healthy participants in terms of PAI-1 concentration. Similar results were obtained when comparing individual patient subgroups and healthy participants regarding this fibrinolysis inhibitor level. Other authors also believe that circulating PAI-1 levels do not influence the risk of venous thrombosis. The Physicians' Health Study did not find differences in PAI-1 levels at the study's start between participants who developed venous thrombosis and those who did not. These results were confirmed by a

grouped case-control study from the LITE cohort [27], which included 308 patients and 640 controls, and by a cohort study by Crowther et al. [28], which found no connection between PAI-1 activity or antigen levels and recurrent venous thromboembolism. However, some studies have reported higher PAI-1 antigen or activity levels in patients with recurrent venous thrombosis compared to healthy controls [27, 29, 30].

In contrast to the findings related to other fibrinolysis parameters, our analysis of TAFI concentration revealed that patients with venous thrombosis had significantly elevated levels of this fibrinolysis inhibitor compared to individuals without a history of venous thrombosis. Similar results were observed when comparing TAFI concentrations among various patient subgroups categorized by the type and location of venous thrombosis, in comparison to healthy controls. These findings are consistent with other studies suggesting a direct correlation between TAFI levels and the occurrence of venous thrombosis. For example, a case-control study conducted by Verdu et al. [31], involving 60 patients and 62 controls, reported a fourfold increase in the risk of deep vein thrombosis among participants whose TAFI levels exceeded the 90th percentile.

Conclusion

In conclusion, our results demonstrate that patients with isolated distal deep vein thrombosis and those with provoked deep vein thrombosis show a markedly reduced fibrinolytic potential compared to healthy individuals. Levels of tissue plasminogen activator antigen and plasminogen are significantly elevated in patients with provoked venous thrombosis compared to healthy controls, while plasminogen activator inhibitor-1 concentrations remain similar between these groups. No significant differences in any specific fibrinolytic factor were observed between patients with primary deep vein thrombosis and healthy individuals. However, thrombin-activatable fibrinolytic inhibitor levels are significantly increased in patients with both provoked and spontaneous deep vein thrombosis, as well as in those with isolated distal and proximal deep vein thrombosis, compared to healthy controls. These results underscore notable variations in the fibrinolytic system's functionality depending on the types and locations of venous thrombosis. This information provides a robust foundation for re-evaluating venous thrombosis risk and opens avenues for exploring potential new therapeutic strategies.

References

1. Colman RW, Clowes AW, George JN, Goldhaber SZ, Marder VJ. Overwiew of hemostasis. In: Colman RW, Clowes AW, Goldhaber SZ, Marder VJ, George JN, editors. Hemostasis and thrombosis: basic principles and clinical practice. 5th ed. Philadelphia: Lippincot Williams & Wilkins; 2006.

2. Wu G, Quek AJ, Caradoc-Davies TT, Ekkel SM, Mazzitelli B, Whisstock JC, et al. Structural studies of plasmin inhibition. Biochem Soc Trans. 2019;47(2):541-57.

3. Bouma BN, Meijers JC. New insights into factors affecting clot stability: a role for thrombin activatable fibrinolysis inhibitor (TAFI; plasma procarboxypeptidase B, plasma procarboxypeptidase U, procarboxypeptidase R). Semin Hematol. 2004;41(1 Suppl):13-9.

4. Virchow R. Phlogose und Thrombose im Gefäßsystem; Gesammelte Abhandlungen zur Wissenschaftlichen Medizin. Frankfurt: Staatsdruckerei; 1856.

5. Baylis RA, Smith NL, Klarin D, Fukaya E. Epidemiology and genetics of venous thromboembolism and chronic venous disease. Circ Res. 2021;128(12):1988-2002.

6. Heit JA. Predicting the risk of venous thromboembolism recurrence. Am J Hematol. 2012;87 Suppl 1:S63-7.

7. Han J, van HylckamaVlieg A, Rosendaal FR. Genomic science of risk prediction for venous thromboembolic disease: convenient clarification or compounding complexity. J Thromb Haemost. 2023;21(12):3292-303.

8. Eck RJ, Hulshof L, Wiersema R, Thio CHL, Hiemstra B, van den Oever NCG, et al. Incidence, prognostic factors, and outcomes of venous thromboembolism in critically ill patients: data from two prospective cohort studies. Crit Care. 2021;25(1):27.

9. Folsom AR, Tang W, Hong CP, Rosamond WD, Lane JA, Cushman M, et al. Prediction of venous thromboembolism incidence in the general adult population using two published genetic risk scores. PLoS One. 2023;18(1):e0280657.

10. Ocak G, Vossen CY, Verduijn M, Dekker FW, Rosendaal FR, Cannegieter SC, et al. Risk of venous thrombosis in patients with major illnesses results from the MEGA study. J Thromb Haemost. 2013;11(1):116-23.

11. Morow GB, Mutch NJ. Past, present, and future perspectives of plasminogen activator inhibitor 1 (PAI-1). Semin Thromb Hemost. 2023;49(03):305-13.

12. Kovač M, Miković Ž, Mandić V, Radojković D, Đorđević V, Mitić G. Clinical characteristics of first venous thrombosis among women under and over 45 years of age. Med Pregl. 2014;67(9-10):328-33.

13. Đorđević V, Gvozdenov M, Pruner I, Kovač M, Tomć B, Stanković M, et al. The prevalence of PAI-1 4G/5G polymorphism in women with fetal loss: first data for a Serbian population. J Med Biochem. 2014;33(2):203-7.

14. Stevens SM, Elliot CG, Chan KJ, Egger MJ, Ahmed KM. Withholding anticoagulation after a negative result on duplex ultrasonography for suspected symptomatic deep vein thrombosis. Ann Intern Med. 2004;140(12):985-91.

15. Fang MC, Reynolds K, Fan D, Prasad PA, Sung SH, Portugal C, et al. Clinical outcomes of direct oral anticoagulants vs warfarin for extended treatment of venous thromboembolism. JAMA Netw Open. 2023;6(8):e2328033.

16. Obi AT, Henke PK, Wakefield TW. Pathogenesis and new insights into acute and chronic venous thrombosis. In: Gloviczki P, Dalsing MC, editors. Handbook of venous and lymphatic disorders. 5th ed. Boca Raton: CRPC Press; 2024.

17. Peng J, Feng B, Ren W, Jiang S, Wu C, Hu Z, et al. Incidence and risk factors of isolated calf muscular venous thrombosis after tibial plateau fractures surgery. BMC Musculoskelet Disord. 2023;24(1):625.

18. Bernardi E, Camporese G, Buller HR, Siragusa S, Imberti D, BerchioA, et al. Serial 2-pointultrasonography plus D-dimer vs whole-leg color-coded Doppler ultrasonography for diagnosing suspected symptomatic deep vein thrombosis: a randomized controlled trial. JAMA. 2008;300(14):1653-9.

19. Oger E. Incidence of venous thromboembolism: a community-based study in Western France. Thromb Haemost. 2000;83(5): 657-60.

20. Ouriel K, Green RM, Greenberg RK, Clair DG. The anatomy of deep vein thrombosis of the lower extremity. J Vasc Surg. 2000;31(5):895-900.

21. White RH, Murin S, Wun T, Danielsen B. Recurrent venous thromboembolism after surgery: provoked versus unprovoked thromboembolism. J Thromb Haemost. 2010;8(5):987-97.

22. Prins MH, Hirsh J. A critical review of the evidence supporting a relationship between impaired fibrinolytic activity and venous thromboembolism. Arch Intern Med. 1991;151(9):1721-31.

23. Ding J, Song B, Xie X, Li X, Chen Z, Wang Z, et al. Inflammation in cerebral venous thrombosis. Front Immunol. 2022;13: 833490.

24. Hayakawa M, Tsuchida T, Honma Y, Mizugaki A, Ooyasu T, Yoshida T, et al. Fibrinolytic system activation immediately following trauma was quickly and intensely suppressed in a rat model of severe blunt trauma. Sci Rep. 2021;11(1):20283.

25. Okamoto A, Sakata T, Mannami T, Baba S, Katayama Y, Matsuo H, et al. Population-based distribution of plasminogen activity and estimated prevalence and relevance to thrombotic diseases of plasminogen deficiency in the Japanese: the Suita Study. J Thromb Haemost. 2003;1(11):2397-403.

26. Ridker PM, Vaughan DE, Stampfer MJ, Manson JE, Shen C, Newcomer LM, et al. Baseline fibrinolytic state and the risk of future venous thrombosis. A prospective study of endogenous tissue-type plasminogen activator and plasminogen activator-inhibitor. Circulation. 1992;85(5):1822-7.

27. Sartori MT, Wiman B, Vettore S, Dazzi F, Girolami A, Patrassi GM. 4G/5G polymorphism of PAI-1 gene promoter and fibrinolytic capacity in patients with deep vein thrombosis. Thromb Haemost. 1998;80(6):956-60.

28. Crowther MA, Roberts J, Roberts R, Johnston M, Stevens P, Skingley P, et al. Fibrinolytic variables in patients with recurrent venous thrombosis: a prospective cohort study. Thromb Haemost. 2001;85(3):390-4.

29. Swiatkiewicz A, Jurkowski P, Kotschy M, Ciecireski M, Jawień A. Level of antithrombin III, protein C, protein S and other selected parameters of coagulation and fibrinolysis in the blood of the patients with recurrent deep venous thrombosis. Med Sci Monit. 2002;8(4):CR263-8.

30. Bombeli T, Jutzi M, De Conno E, Seifert B, Fehr J. In patients with deep-vein thrombosis elevated levels of factor VIII correlate only with von Willebrand factor but not other endothelial cell-derived coagulation and fibrinolysis proteins. Blood Coagul Fibrinolysis. 2002;13(7):577-81.

31. Verdu J, Marco P, Benlloch S, Sanchez J, Lucas J. Thrombin activatable fibrinolysis inhibitor (TAFI) polymorphisms and plasma TAFI levels measured with an ELISA insensitive to isoforms in patients with venous thromboembolic disease (VTD). Thromb Haemost. 2006;95(3):585-6.

Rad je primljen 11. VII 2024.
Recenziran 6. VII 2024.
Prihvaćen za štampu 24. VIII 2024.
BIBLID.0025-8105:(2024):LXXVII:3-4:113-120.

CASE REPORTS
PRIKAZI SLUČAJEVA

University Clinical Center of Vojvodina, Novi Sad
Vascular and Endovascular Surgery Clinic[1]
University of Novi Sad, Faculty of Medicine Novi Sad[2]

Case report
Prikaz slučaja
UDK 616.136-007.64+616.61-007.274]-089
https://doi.org/10.2298/MPNS2404121P

OPEN SURGICAL REPAIR OF ABDOMINAL AORTIC ANEURYSM IN ASSOCIATION WITH HORSESHOE KIDNEY – CASE REPORT

OTVORENO HIRURŠKO LEČENJE ANEURIZME ABDOMINALNE AORTE UDRUŽENE SA POTKOVIČASTIM BUBREGOM – PRIKAZ SLUČAJA

Katarina PETROVIĆ[1], Vladimir MANOJLOVIĆ[1,2] and Nikola BATINIĆ[1,2]

Summary

Introduction. Horseshoe kidney is a congenital anomaly in which both kidneys are fused across the midline. An aneurysm is a permanent, irreversible localized dilatation of a blood vessel, at least 1.5 times its normal diameter. The concomitant occurrence of an abdominal aortic aneurysm and a horseshoe kidney is rare, appearing in only 0.12% of patients with a previously diagnosed abdominal aortic aneurysm. The management of an abdominal aortic aneurysm in the presence of a horseshoe kidney poses a unique challenge for surgeons due to the close proximity of the kidneys and the variations in the vascularization of the horseshoe kidney. **Case Report.** We present two cases of abdominal aortic aneurysm in patients with a horseshoe kidney, with vascularization types I and II, successfully treated using a transperitoneal surgical approach without sectioning the isthmus. **Conclusion.** Given the variability in treatment options for these conditions, every case must be evaluated individually to determine the best therapeutic approach for the patient.

Key words: Aortic Aneurysm, Abdominal; Fused Kidney; Surgical Procedures, Operative; Risk Factors; Treatment Outcome

Sažetak

Uvod. Potkovičast bubreg podrazumeva anomaliju fuzije bubrega, kod koje su bubrezi međusobno spojeni. Aneurizma predstavlja trajno, ireverzibilno i lokalizovano proširenje krvnog suda, gde je dijametar krvnog suda uvećan bar za 50% u odnosu na normalan dijametar. Konkomitanto prisustvo aneurizme abdominalne aorte i potkovičastog bubrega pojavljuje se u oko 0,12% pacijenata sa prethodno dijagnostikovanom abdominalnom aneurizmom. Zbog bliskih prostornih odnosa između aneurizme abdominalne aorte i potkovičastog bubrega, kao i varijabilne vaskularizacije, operacija istih predstavlja poseban izazov za hirurge. **Prikaz slučaja.** Predstavljamo 2 slučaja pacijenata sa istovremenim prisustvom aneurizme abdominalne aorte i potkovičastog bubrega, sa vaskualrizacijom tip I i II, koji su bili uspešno tretirani operativnim lečenjem, transperitonelanim pristupom, bez sekcije istmusa. **Zaključak.** S obzirom na različite opcije u terapijskom pristupu pacijentima sa gore navedenim dijagnozama, svaki slučaj mora biti evaluiran ponaosob kako bi se najbolja opcija odbarala za svakog pacijenta.

Ključne reči: aneurizma abdominalne aorte; potkovičasti bubreg; operativne hirurške procedure; faktori rizika; ishod lečenja

ORCID NUMBER
Katarina Petrović 0009-0003-8265-2394
Vladimir Manojlović 0000-0002-7998-2371
Nikola Batinić 0000-0003-2109-9479

Introduction

Horseshoe kidney (HSK) is the most common congenital fusion defect of the kidney, occurring in approximately 0.25% of the population [1]. HSK involves the fusion of both kidneys across the midline, joined by an isthmus composed of either renal parenchyma or fibrous tissue [2]. An aneurysm is a permanent, irreversible localized dilatation of a vessel, with its diameter being at least 1.5 times larger than the expected normal diameter [3]. The concomitant presence of an abdominal aortic aneurysm (AAA) and HSK is rare, occurring in only 0.12% of patients with a previously diagnosed AAA [4]. The management of AAA associated with HSK presents a unique challenge for surgeons due to the close proximity of the kidneys and the variations in the vascularization of the HSK [5]. We present two patients with the coexistence of AAA and HSK treated by open surgical repair using a transperitoneal approach without sectioning the isthmus.

Case Report

First case: A 69-year-old man with a history of hypertension and hyperlipidemia was referred to our clinic for an asymptomatic AAA. The patient had no

Corresponding Author: Katarina Petrović, UKCV – Klinika za vaskularnu i endovaskularnu hirurgiju, 21000 Novi Sad, Hajduk Veljkova 1-7, E-mail: katarinapetrovic1802@gmail.com, vladimir.manojlovic@mf.uns.ac.rs

Abbreviations

HSK – Horseshoe kidney
AAA – abdominal aortic aneurysm
COPD – chronic obstructive pulmonary disease
CKD – chronic kidney disease
CTA – computed tomography angiography
ICU – intensive care unit

family history of aneurysm or renal malformations. Computed tomography angiography (CTA) revealed a 69 mm infrarenal AAA associated to a HSK, with an isthmus lying anterior to the aneurysm. Two main renal arteries were detected, as well as one isthmic branch arising directly from the aorta, classified as Type 2 of HSK **(Figure 1)**. The preoperative serum creatinine level was 75 μmol/L. The surgery was performed through a xyphopubic laparotomy. Transperitoneal dissection revealed the aortic aneurysm with its upper third shielded by the isthmus of the HSK. The infrarenal aorta, isthmus of HSK, common iliac arteries, and two renal arteries, as well as isthmic branch, were dissected. The two renal arteries and the isthmus were controlled by silastic vessel loops. After systemic heparinization, an aortic clamp was placed below both renal arteries, yet proximal to the isthmus of the HSK and the isthmic branch. The aneurysm sac was opened longitudinally, and a 16 mm Dacron graft was sutured. The proximal anastomosis was made right below the HSK, and the isthmus was gently pulled upward with a vessel loop. The proximal anastomosis was placed below the isthmic branch, so no reimplantation was needed. The operation took approximately two hours. The estimated amount of blood collected in the Cell Saver was 950 mL, of which 633 ml were autotransfused during the operation. On the third postoperative day, the patient was transferred from the ICU to the vascular surgery department. He was discharged on the fifth postoperative day without any intraoperative or postoperative complications. The postoperative serum creatinine level was 78 μmol/L.

Second case: A 67-year-old man with a history of hypertension, COPD, mitral, pulmonary, and tricuspid valve insufficiency, as well as CKD stage 2 and right hydronephrosis, was referred to our clinic for an asymptomatic AAA. CTA revealed a 54 mm

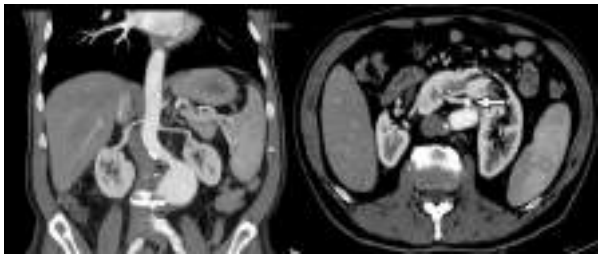


Figure 1. Computed tomography angiography depicting two renal arteries and an abdominal aortic aneurysm. White arrow indicates the isthmic branch.
Slika 1. *Kompjuterizovana tomografska angiografija sa prikazom aneurizme abdominalne aorte i obe renalne arterije. Bela strelica pokazuje istmičnu granu.*

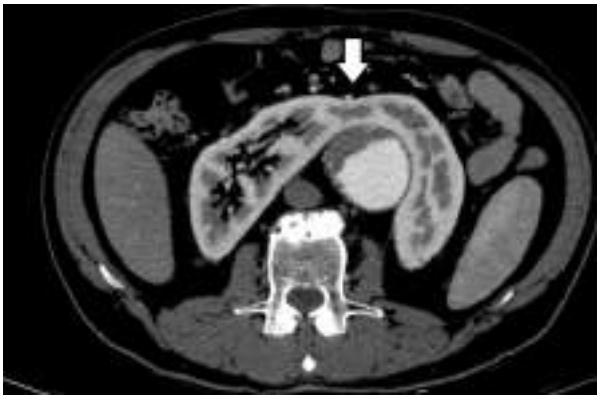


Figure 2. Computed tomography angiography depicting horseshoe kidney and abdominal aortic aneurysm. White arrow indicates the isthmus.
Slika 2. *Kompjuterizovana tomografska angiografija prikazuje potkovičast bubreg i aneurizmu abdominalne aorte. Bela strelica pokazuje istmus potkovičastog bubrega.*

AAA and a 29 mm aneurysm of left common iliac artery. The CTA also showed a horseshoe kidney with the isthmus extended over the AAA, as well as right renal hydronephrosis and a ureteral calculus **(Figure 2)**. Two renal arteries were found, classified as Type I. The initial creatinine level was 95 μmol/L. The patient had no family history of aneurysm or renal malformations. The surgery was performed through a xyphopubic laparotomy. Transperitoneal dissection revealed the aortic aneurysm with the isthmus of the HSK lying over it. The infrarenal aorta, isthmus of the HSK, and common iliac arteries were dissected. After systemic heparinization, an aortic clamp was placed interrenally, with the right renal artery beneath the clamp and the left one above. The proximal part of the aneurysm sac, proximal to the HSK, was opened longitudinally, and a 16x8 mm Dacron bifurcation graft was sutured proximally. The clamp was then transferred to the graft, and the right renal ischemia lasted for 18 minutes. Then graft was placed under the isthmus, and an aneurysmectomy was performed on the lower part of aneurysm sac. Regarding the left common lilac artery aneurysm, distal anastomoses were performed on both common iliac arteries **(Figure 3)**. The operation took approximately three hours and twenty minutes. The estimated amount of blood collected in the Cell Saver was 900 mL, with 350 ml autotransfused during the operation. On the third postoperative day, the patient was transferred from the ICU to the vascular surgery department. He was discharged on the fifth postoperative day without any intraoperative or postoperative complications. The postoperative serum creatinine level was 93 μmol/L.

Discussion

When treating a patient with concomitant AAA and Horseshoe kidney, three main decisions must be made: the type of abdominal exposure to reach the aneurysm, whether to preserve or divide the renal

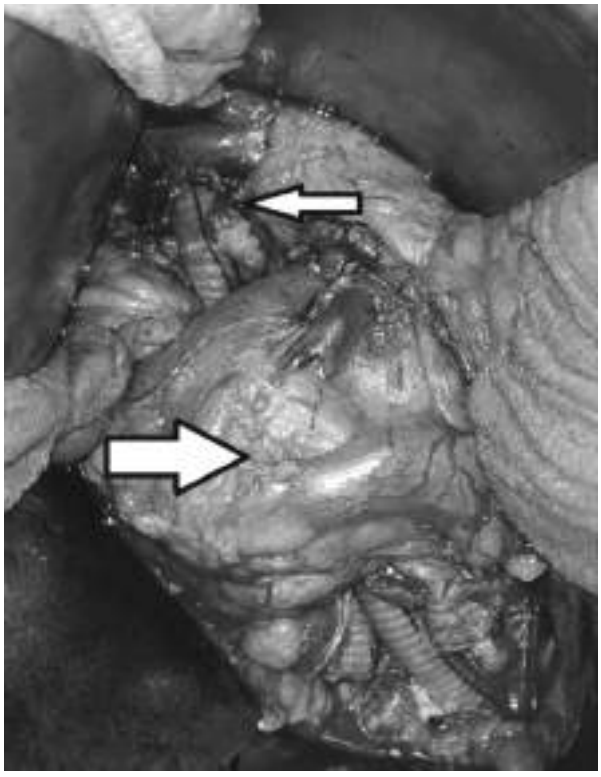


Figure 3. Y-shaped Dacron graft placed under the isthmus (upper white arrow). Horseshoe kidney (lower white arrow).
Slika 3. *Dakron bufurkaciona proteza pozicionirana ispod istmusa potkovičastog bubrega (prva bela strelica). Potkovičast bubreg (druga bela strelica).*

isthmus, and whether to ligate or salvage accessory renal arteries. HSK vascularization is prone to variations, simplified by the classification system proposed by Eisendrath et al. in 1925, which includes five types. Type I refers to the presence of one renal artery on each side of the HSK. Type II demonstrates an auxiliary aortic branch to the renal isthmus in addition to type I. Type III adds one more renal artery to each side of Type II. Type IV refers to the presence of two renal arteries on each side, with one or more originating from iliac arteries or the isthmus branch. Type V refers to the presence of multiple renal arteries arising from the aorta, mesenteric arteries, and iliac arteries [6]. One of our patients belonged to type I, with no auxiliary arteries found on CTA or intraoperatively. The other patient was type II, where an auxiliary isthmic branch was seen on CTA and intraoperatively. Since the proximal anastomosis was made right below the isthmic branch, no reimplantation was needed, and the isthmic branch was preserved. Minimal collateralization between renal segments and asymmetric blood supply mean that ligation of one or more aberrant or accessory renal arteries can result in ischemic necrosis of the kidney [7]. In some cases, accessory renal arteries supplying up to 32% of the total parenchyma can be occluded in patients with normal renal function during EVAR [8]. During open surgery, accessory renal arteries larger than 3 mm in diameter should be preserved or reimplanted [9, 10]. When deciding between open or endovascular aneurysm repair, the pros and cons of each approach must be considered. We chose the open technique in both cases due to inadequate anatomy for EVAR. The advantages of the transperitoneal approach include better exposure, access to aneurysm sac, renal isthmus, ureters, and both iliac arteries. The disadvantages include a higher risk of iatrogenic injury to the isthmus. While the retroperitoneal approach avoids contact with urinary tract and renal isthmus, it often provides inadequate exposure to iliac arteries, especially the right one. However, it offers better exposure to auxiliary renal arteries and easier reimplantation when needed. In both cases, we chose the transperitoneal approach. In the first case, the isthmic branch arose from the anterior surface of abdominal aorta, making the transperitoneal approach satisfactory. The isthmic branch did not need reimplantation. In the second case, there were no supplementary renal arteries that required reimplantation, and better exposure to the iliac arteries was needed due to their aneurysmatic degeneration, making the transperitoneal approach favorable [6]. The section of the isthmus was avoided in both cases to prevent complications such as urinary tract injury, retroperitoneal infection, bleeding, and renal ischemia [11]. Although there are cases in the literature where the isthmus was divided for better exposure and then sutured, resulting in uncomplicated outcomes, the risk of complications remains [9, 12].

Conclusion

Abdominal aortic aneurysm with concomitant horseshoe kidney remains a challenge for vascular surgeons. In both cases, we chose transperitoneal approach without sectioning the isthmus or reimplanting auxiliary renal arteries. In one cases, an auxiliary renal artery was preserved. Given the variability in treating these conditions, each case must be evaluated individually to determine the best therapeutic options for each patient.

References

1. Kirkpatrick JJ, Leslie SW. Horseshoe kidney. In: StatPearls [Internet]. Treasure Island: StatPearls Publishing; 2023 [updated 2023 May 30; cited 2024 Jun 1]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK431105

2. Schiappacasse G, Aguirre J, Soffia P, Silva CS, Zilleruelo N. CT findings of the main pathological conditions associated with horseshoe kidneys. Br J Radiol. 2015;88(1045):20140456.

3. Batinić N, Koković T, Nikolić D, Manojlović V, Till V, Budinski S. The impact of abdominal aortic aneurysm diameter on the outcome of endovascular aortic repair. Med Pregl. 2021;74(11-12):347-53.

4. Davidović L, Marković M, Ilic N, Koncar I, Kostić D, Simić D, et al. Repair of abdominal aortic aneurysms in the presence of the horseshoe kidney. Int Angiol. 2011;30(6):534-40.

5. Bounssir A, Bakkali T, Taghi H, Sefiani Y, Lekehal B. Best strategy in managing the association of horse-shoe-kidney and abdominal aortic aneurysm: case report. Int J Surg Case Rep. 2020;75:11-5.

6. Sachsamanis G, Charisis N, Maltezos K, Galyfos G, Papapetrou A, Tsiliggiris V, et al. Management and therapeutic options for abdominal aortic aneurysm coexistent with horseshoe kidney. J Vasc Surg. 2019;69(4):1257-67.

7. O'Hara PJ, Hakaim AG, Hertzer NR, Krajewski LP, Cox GS, Beven EG. Surgical management of aortic aneurysm and coexistent horseshoe kidney: review of a 31-year experience. J Vasc Surg. 1993;17(5):940-7. Erratum in: J Vasc Surg. 1993;18(4):586.

8. Handa K, Sakamoto T, Kakizawa Y, Kitahara M, Fukui S, Shirakawa Y, et al. Endovascular aneurysm repair for a patient with horseshoe kidney and the importance of watershed sign and volumetry by preoperative contrast-enhanced computed tomography. Ann Vasc Dis. 2021;14(4):396-9.

9. Christoforou P, Kapoulas K, Bekos C. Open surgical repair of abdominal aortic aneurysm and horseshoe kidney: a strange relationship. Int J Surg Case Rep. 2022;93:106971.

10. Davidovic LB, Markovic M, Kostic D, Zlatanovic P, Mutavdzic P, Cvetic V. Open repair of ruptured abdominal aortic aneurysm with associated horseshoe kidney. Int Angiol. 2018;37(6):471-8.

11. De Caridi G, Massara M, Greco M, Mastrojeni C, Serra R, Salomone I, et al. Surgical treatment of a voluminous infrarenal abdominal aortic aneurysm with horseshoe kidney: tips and tricks. Ann Vasc Dis. 2015;8(4):324-7.

12. McIlhenny C, Scott RN. Abdominal aortic aneurysm in association with horseshoe kidney. Eur J Vasc Endovasc Surg. 2002;23(6):556-8.

Rad je primljen 3. VI 2024.
Recenziran 11. VI 2024.
Prihvaćen za štampu 21. VI 2024.
BIBLID.0025-8105:(2024):LXXVII:3-4:121-124.

Health Center "Novi Sad", Novi Sad
Occupational Health Service

Case report
Prikaz slučaja
UDK 616.47-006.55-07
https://doi.org/10.2298/MPNS2404125P

THE SIGNIFICANCE OF EARLY DETECTION OF PARATHYROID ADENOMA

ZNAČAJ RANOG OTKRIVANJA ADENOMA PARATIREOIDNE ŽLEZDE

Eva STOJKOVIĆ and Tanja STEFANOVIĆ

Summary
Introduction. Parathyroid adenoma is the leading cause of primary hyperparathyroidism in 85% of cases, followed by multiglandular hyperplasia (15%) and parathyroid carcinoma (1%). Clinical complications can manifest in the bones, gastrointestinal tract, kidneys, heart, and can also lead to mental disorders and altered consciousness, including coma. Surgical intervention is the primary treatment for primary hyperparathyroidism. However, for patients who do not meet the criteria for surgery or choose to avoid it, medical management is provided. **Case Report.** A 52-year-old female patient presented in late 2019 with a visible, firm, irregular mass above the right clavicle. Initial bone marker tests raised suspicion of a parathyroid adenoma. The COVID-19 pandemic caused delays in further specialized examinations and postponed surgical treatment. The referring physician scheduled a parathyroid scintigraphy while awaiting an endocrinologist's evaluation. Surgery was eventually performed in March 2023. Despite consistently elevated parathyroid hormone and ionized calcium levels, the patient avoided potential complications due to continuous monitoring by her referring physician. **Conclusion.** Early diagnosis of parathyroid adenoma reduces the risk of complications and improves the quality of life for patients.
Key words: Parathyroid Neoplasms; Adenoma; Early Diagnosis; Hyperparathyroidism; Calcinosis

ORCID NUMBER
Eva Stojković 0000-0002-0737-3163

Sažetak
Uvod. Adenom paratireoidne žlezde je najčešći uzrok primarnog hiperparatireoidizma u 85% slučajeva, zatim multiglandularna hiperplazija (15%) i karcinom paratireoidne žlezde (1%). Kliničke komplikacije mogu nastati na kostima, gastrointestinalnom traktu, bubrezima, srcu, kao i psihički poremećaji i poremećaji svesti do kome. Lečenje primarnog hiperparatireodizma je operativno, a kod bolesnika koji ne ispunjavaju kriterijume za operativno lečenje, ili ga bolesnik ne želi, sprovodi se medikamentno lečenje. **Prikaz slučaja.** Pacijentkinja, starosti 52 godine javlja se krajem 2019. godine zbog vidljive, tvrde, nepravilne promene iznad desne ključne kosti. Urađeni su prvo koštani markeri i postavljena sumnja na adenom paratireoidne žlezde. Zbog pandemije COVID-19 u jeku, otežani su dalji specijalistički pregledi i odloženo operativno lečenje. Izabrani lekar sam zakazuje scintigrafiju paratireoidnih žlezda, čekajući mišljenje endokrinologa. Operacija je urađena u martu 2023. godine, a dotle je stanje pacijentkinje pratio izabrani lekar i uprkos konstantno povišenim vrednostima parathormona i jonizovanog kalcijuma, prevenirane su moguće brojne komplikacije adenoma. **Zaključak.** Rano postavljena dijagnoza adenoma paratireoidne žlezde omogućava smanjene nastanka komplikacija, a tako i poboljšava kvalitet života pacijenata obolelih od adenoma paratireoidnih žlezda.
Ključne reči: paratireoidne neoplazme; adenomi; rana dijagnoza; hiperparatireoidizam; kalcifikacija

Tanja Stefanović 0009-0001-3464-2779

Introduction

Primary hyperparathyroidism (HPT) is an endocrinological disorder characterized by increased secretion of parathyroid hormone (PTH) from one or more of the parathyroid glands, which are typically four in number [1]. This condition is more prevalent in women and is most commonly caused by adenomas (80-85%), with hyperplasia accounting for 10-15%, and carcinoma being a rare cause (<1%) [2]. PTH plays a crucial role in regulating calcium metabolism, which is essential for blood clotting, bone mineralization, nerve function, muscle contractions, and various enzymatic reactions.

Parathyroid adenomas are usually localized in the neck, but in up to 5% of cases, they can be ectopic. Ectopic adeno-mas may be found in the mediastinum, thymus, retropharyngeal space, submaxillary region, thyroid gland, and carotid sheath [3]. Over 90% of adenomas occur sporadically, with rare occurrences in familial hyperparathyroidism (hyperparathyroid jaw tumor syndrome) or as part of multiple endocrine neoplasia types I and II [4].

Common complications of adenomas include osteoporosis, nephrolithiasis, gastrointestinal ulcers, pancreatitis, cholelithiasis, hypertension, and heart diseases. Early diagnosis is crucial for effective management.

Case Report

A 52-year-old perimenopausal female patient, newly diagnosed with well-controlled hypertension, presented to her primary care physician in Novem-

Corresponding author: Tanja Stefanović, Dom zdravlja Novi Sad, Služba zdravstvene zaštite radnika, 21000 Novi Sad, Bulevar cara Lazara 75, E-mail: tanjastefanovic.ns@gmail.com

Abbreviations

HPT – hyperparathyroidism
PTH – parathyroid hormone
ALP – alkaline phosphatase
fT4 – free thyroxine
TSH – thyroid-stimulating hormone
25(OH)D – 25-hydroxy vitamin D
CT – computed tomography
PET/CT – positron emission tomography/computed tomography

ber 2019. She expressed concern about a palpable change above her right clavicle and reported feeling fatigued but denied other symptoms. She had a 20-year history of smoking 10 cigarettes per day, did not consume alcohol, and had no known medications or food allergies. Her mother had hypothyroidism.

On physical examination, a firm, painless mass with unclear borders and irregular shape measuring up to 1.5 cm was noted above the right clavicle, closer to the midline. Calcification was suspected and the thyroid gland was not palpable.

Initial differential diagnosis included requesting bone metabolism markers and a chest X-ray. Laboratory results were as follows: N-TACT PTH – 203.0 pg/ml (14.5-87.1 pg/ml); 25-hydroxy vitamin D (25(OH) D) – 27 nmol/l (35-120 nmol/l); crossLaps - 1,217 g/L (556-1008 g/l); total procollagen type 1 fragments – 86 ng/ml (16.3-73.9 ng/ml); alkaline phosphatase (ALP) – 93 IU/L (35-105 IU/L); ionized calcium – 2.89 mmol/L (1.00-1.35 mmol/L); inorganic phosphorus – 0.8 mmol/L (2.5-4.5 mmol/L). Both free thyroxine (fT4) and thyroid-stimulating hormone (TSH) were within reference ranges. The right clavicle X-ray showed no abnormalities. An ultrasound of the neck and upper abdomen, including the kidneys, was planned to evaluate the parathyroid adenoma, but it was delayed due to scheduling constraints.

The patient subsequently examined by an endocrinologist, who included an adenoma of the lower right parathyroid gland in the differential diagnosis. A parathyroid gland scintigraphy was requested, which the primary care physician independently arranged due to the COVID-19 pandemic and limited availability of specialist consultations.

Scintigraphy performed in February 2020 revealed a focal change in the neck and mediastinal region, suggesting an adenoma or hyperplasia of the lower right parathyroid gland. Ultrasonography indicated a separate focal change with hypo/anechoic echotexture measuring 0.8 x 1 x 1.2 cm in the lower pole and posterior right lobe of the thyroid gland, consistent with the scintigraphically isolated change. X-rays of the long bones, heart, and lungs, as well as abdominal and kidney ultrasounds, were normal. No subsequent damage was observed.

Six months post-diagnosis, follow-up laboratory tests showed: fT4 – 10.4 nmol/L (9.0-19.0 nmol/L); TSH – 0.83 mU/L (0.35-4.94 mU/L);); carcinoembryonic antigen – 0.4 ng/L (< 5 ng/ml); N-TACT-PTH – 176.0 pg/mL (14.5-87.1 pg/l); 25(OH)D total – 54 nmol/L (35-120 nmol/L); ionized calcium – 1.66 mmol/L (1.00-1.35 mmol/L); ALP – 105 IU/L (35-105 IU/L).

One year after the adenoma's discovery, the patient contracted a mild COVID-19 infection with respiratory symptoms and fever.

The patient continued to be monitored by her primary care physician, with periodic laboratory tests showing consistently elevated ionized calcium levels and PTH levels. She was prescribed oral vitamin D drops (2,500 IU/day) due to deficiency (25(OH)D total) and atorvastatin tablets (20 mg) for high cholesterol (high-density lipoprotein – 1.77 mmol/L (>1.5 mmol/L), low-density lipoprotein – 4.6 mmol/L (<3.5 mmol/L)) and an atherosclerosis index of 2.4 (<3.0).

Despite the ongoing COVID-19 pandemic, the patient waited over three years for surgical treatment. In March 2023, she underwent surgery at the University Clinical Center of Vojvodina, Clinic of Abdominal and Endocrine Surgery, where the right lower parathyroid gland was removed without complications. Histopathological examination confirmed a parathyroid adenoma measuring 0.8 x 1 cm. Postoperatively, PTH and ionized calcium levels normalized.

An osteodensitometry indicated preserved bone mineral density, with a follow-up scheduled for two years later. Chewable tablets containing calcium (500 mg) and cholecalciferol (400 IU) replaced the oral vitamin D drops. The change above the right clavicle was smaller upon inspection and palpation, and follow-up abdominal and kidney ultrasounds were normal. The patient remains in good overall condition and will continue to be monitored by her primary care physician.

Discussion

Visualizing parathyroid glands can be achieved through ultrasonography, scintigraphy, and computed tomography (CT). Scintigraphy and CT are particularly useful for diagnosing patients with ectopic parathyroid adenomas or suspected metastatic disease [5]. If ultrasonography or scintigraphy results are inconclusive, additional imaging modalities such as single-photon emission computed tomography, positron emission tomography/computed tomography (PET/CT), or Magnetic Resonance Imaging of the neck may be necessary. One potential cause of HPT is multiple endocrine neoplasia, which must be ruled out. [18F] F-choline PET)/CT is highly sensitive for detecting small parathyroid adenomas and accurately determining their location [6]. Although adenomas are most commonly localized in the neck, ectopic locations can present a significant diagnostic challenge [7].

As described, the coexistence of thyroid and parathyroid adenomas during the surgical treatment of nodular goiter underscores the importance of visualizing the parathyroid glands in preoperative preparation for successful management [8]. In this case study, a 52-year-old woman presented with generalized fatigue and a visible, palpable mass on the right side of the neck. Surgical exploration revealed a 7.7 g parathyroid adenoma, whereas adenomas typically weigh around 1 g. The uniqueness of this case lies in the fact that the adenoma was palpable as a neck mass, while the initial ultrasound suggested a thyroid nodule [9]. A review of

the literature identified 57 cases (44 in women) of spontaneous hemorrhage from parathyroid adenomas. In such cases, clinical assessment is crucial for detecting urgent conditions that may require intubation, tracheostomy, or neck exploration [10].

Detailed genomic analysis has revealed various signaling pathways, including numerous genes and proteins implicated in adenoma development. Further studies are needed to enhance our understanding of the pathogenesis of parathyroid adenomas and identify new histological biomarkers that can predict recurrence in other parathyroid glands [11].

Delayed diagnosis and treatment of parathyroid adenoma, indicated by consistently elevated serum calcium levels, significantly increases the risk of osteoporosis and secondary fractures [12].

The goal of treating asymptomatic adenoma is to prevent lesions in target organs, whereas symptomatic adenomas require timely treatment to reverse the resulting lesions.

Conclusion

The approach to managing a patient with suspected parathyroid adenoma must be comprehensive and individualized. Due to the detailed examination, the unusual localization of the observed calcification, and the immediate suspicion of a parathyroid adenoma, which was subsequently confirmed, further complications were prevented. The patient is currently in good overall condition, without nephrolithiasis, significant atherosclerotic changes, or other complications commonly associated with hyperparathyroidism, thanks to preventive measures and early detection and management.

Despite the challenges posed by the COVID-19 pandemic and the delayed surgical treatment, early diagnosis remains crucial, particularly in primary healthcare settings.

References

1. Khan AA, Hanley DA, Rizzoli R, Bollerslev J, Young JE, Rejnmark L, et al. Primary hyperparathyroidism: review and recommendations on evaluation, diagnosis, and management. A Canadian and international consensus. Osteoporos Int. 2017;28(1):1-19.

2. Bilezikian JP, Bandeira L, Khan A, Cusano NE. Hyperparathyroidism. Lancet. 2018;391(10116):168-78.

3. Di Bisceglie M, Voltolini L, Paladini P, Cacchiareli M, Vella A, Gotti G. Ectopic parathyroid adenoma. Two cases treated with video-assisted thoracoscopic surgery. Scand Cardiovasc J. 1998;32(1):51-2.

4. Cetani F, Pardi E, Banti C, Collecchi P, Viacava P, Borsari S, et al. Beta-catenin activation is not involved in sporadic parathyroid carcinomas and adenomas. Endocr Relat Cancer. 2010;17(1):1-6.

5. Buzejić M, Slijepčević N, Živaljević V, Zorić G, Odalović B, Taušanović K, et al. Prikaz slučaja karcinoma paratiroidne žlezde kod pacijenata sa hroničnom bubrežnom insuficijencijom. Medicinski glasnik Specijalne bolnice za bolesti štitne žlezde i bolesti metabolizma " Zlatibor". 2019;24(75):7-14.

6. Giovanella L, Bacigalupo L, Treglia G, Picardo A. Will 18F-fluorocholine PET/CT replace other methods of preoperative parathyroid imaging? Endocrine. 2021;71(2):285-97.

.7. Hakim Tawil JA, Flórez A, Sanabria MC, Palau M, Santivañez JJ. Submandibular ectopic parathyroid adenoma: a case report. Ear Nose Throat J. 2023:1455613231177193.

8. Bojković G, Čaparević Z, Stojanović Dragoš Lj, Lalošević ĐJ, Stojanović M. Parathyroid gland adenoma: case report. Med Pregl. 2003;56(7-8):377-80.

9. Al-Hasan MS, Mekhaimar M, El Ansari W, Daraweesh, Abdelaal A. Giant parathyroid adenoma: a case report and review of the literature. J Med Case Rep. 2019;13(1):332.

10. Familiari M, Di Santo D, Galli A, Danè G, Giordano L, Mellone R, et al. Spontaneous extracapsular parathyroid adenoma hemorrhage: when surgery is required? Endocrine. 2022;75(2):575-82.

11. Chorti A, Cheva A, Chatzikyriakidou A, Achilla C, Boulogeorgou K, Despoina K, et al. Sporadic parathyroid adenoma: an updated review of molecular genetics. Front Endocrinol (Lausanne). 2023;14:1180211.

12. Johnson NA, Tublin ME, Ogilvie JB. Parathyroid imaging: technique and role in the preoperative evaluation of primary hyperparathyroidism. AJR Am J Roentgenol. 2007;188(6):1706-15.

Rad je primljen 14. VI 2024.
Recenziran 9. VII 2024.
Prihvaćen za štampu 9. VII 2024.
BIBLID.0025-8105:(2024):LXXVII:3-4:125-127.

SEMINAR FOR PHYSICIANS
SEMINAR ZA LEKARE U PRAKSI

University of Novi Sad, Faculty of Medicine Novi Sad[1]
University Clinical Center of Vojvodina, Novi Sad
Clinic of Anesthesia and Intensive Care[2]
University of Niš, Faculty of Medicine, Niš[3]

Seminar for physicians
Seminar za lekare u praksi
UDK 616.1-089.163/.168
https://doi.org/10.2298/MPNS2404129M

FRAILTY IN VASCULAR SURGERY

SLABOST U VASKULARNOJ HIRURGIJI

Danijela MILENKOVIĆ[1,2], Teodora TUBIĆ[1,2], Sanja VICKOVIĆ[1,2], Gordana JOVANOVIĆ[1,2], Nataša NESTOROV[2] and Lazar STOŠIĆ[3]

Summary

Introduction. Frailty manifests as diminished physical capacity and heightened susceptibility to stressors, significantly increasing the risk of adverse health outcomes, functional decline, and mortality. **Measurement of frailty.** Despite its clinical significance, there is currently no universally accepted tool for routine frailty assessment in clinical practice. Frailty has emerged as an independent predictor of postoperative outcomes across various surgical disciplines, including general surgery, colorectal surgery, oncology, cardiac surgery, and urology. The modified frailty index is commonly utilized in research to quantify frailty and assess its impact on surgical outcomes. **Frailty in vascular surgery.** Approximately 39% of patients undergoing vascular surgery are estimated to be frail. Frail individuals identified face nearly triple the risk of complications such as postoperative myocardial infarction, stroke, renal failure, and graft/prosthesis/flap failure. Studies consistently report higher postoperative mortality rates among patients with higher modified frailty index scores. Assessing frailty remains a complex task for anesthesiologist and surgeons during preoperative evaluations. **Conclusion.** Early identification of frailty in vascular surgery patients is crucial given their advanced age and numerous concurrent health conditions. Optimizing preoperative management tailored to frail patients can potentially reduce complications and mortality rates.

Key words: Frailty; Vascular Surgical Procedures; Risk Factors; Risk Assessment; Mortality; Postoperative Complications; Anesthesiology

ORCID NUMBER
Danijela Milenković 0009-0000-4325-5730
Teodora Tubić 0000-0001-8094-4607

Sažetak

Uvod. Slabost je stanje koje se karakteriše smanjenom fiziološkom rezervom i povećanom osetljivošću na stresore, što dovodi do povećanog rizika od loših zdravstvenih ishoda, invaliditeta i smrti. **Merenje slabosti.** Još uvek ne postoje standardizovane mere za procenu i kvantifikaciju slabosti, koje bi se svakodnevno koristile u kliničkoj praksi. Slabost se pokazala kao nezavisni faktor rizika za predviđanje neželjenih postoperativnih ishoda kod pacijenata koji su podvrgnuti velikim hirurškim zahvatima, uključujući opšte, kolorektalne, onkološke, kardijalne i urološke procedure. Većina studija koje analiziraju uticaj slabosti na postoperativne ishode koriste modifikovani indeks slabosti. **Slabost u vaskularnoj hirurgiji.** Procenjeno je da je oko 39% pacijenata koji su podvrgnuti vaskularnoj hirurgiji slabo. Slabi pacijenti imaju oko tri puta veći rizik od komplikacija, kao što su postoperativni infarkt miokarda, moždani udar, progresivna bubrežna insuficijencija i otkazivanje grafta, proteze ili flapa. Rezultati studija ukazuju na veći postoperativni mortalitet posle različitih vaskularnih intervencija, kod kojih je veća vrednost modifikovanog indeksa slabosti. Tokom preoperativne pripreme, procena slabosti predstavlja težak zadatak za anesteziologa i hirurga. **Zaključak.** Identifikacija slabog pacijenta preoperativno u vaskularnoj hirurgiji je izuzetno važna, zbog godina starosti i brojnih komorbiditeta ove grupe pacijenata. Na taj način se može optimizovati preoperativno stanje pacijenta i napraviti bolji plan lečenja, sa ciljem smanjenja broja komplikacija, kao i mortaliteta.

Ključne reči: slabost; vaskularne hirurške procedure; faktori rizika; procena rizika; mortalitet; postoperaticne komplikacije; anesteziologija

Gordana Jovanović 0000-0003-4899-4748
Sanja Vicković 0000-0002-2153-3135
Lazar Stošić 0009-0001-5829-7121

Introduction

The precise definition of frailty is continuously evolving, yet it is commonly understood as a condition marked by reduced physiological capacity and increased susceptibility to stressors, leading to a heightened risk of negative health outcomes, disability, and mortality [1]. Frailty is characterized by a reduction in physiological reserves, resulting in increased vulnerability, distinct from the normal aging process [2]. Frail

Corresponding Author: Danijela Milenković, UKCV - Klinika za anesteziju i intenzivnu terapiju,
21000 Novi Sad, Hajduk Veljkova 1-7, E-mail: danijelamilenkovic95@hotmail.com, teodora.tubic@mf.uns.ac.rs

Abbreviations
mFI – modified frailty index

individuals typically exhibit deficits in nutrition, endurance, mobility, physical strength, stability, and cognitive function [3]. This systematic review aims to explore the concept of frailty and the utilization of frailty indices in patients undergoing vascular surgery.

Measurement of frailty

The concept of frailty was first introduced by Vapuel in 1979 [4]. Initially applied to the geriatric population, it has since been incorporated into clinical practice across various domains. Despite its widespread recognition, there is currently no universally accepted tool for routine frailty assessment in clinical settings. Two primary models have been proposed to quantify frailty. The first is the physical phenotype model introduced by Fried et al., which is based on five criteria: unintentional weight loss, feelings of exhaustion, diminished grip strength, reduced gait speed, and low levels of physical activity [2, 5]. An individual is diagnosed as frail if they meet at least three of these criteria; meeting one or two criteria indicates a pre-frail state, which predisposes the individual to progression towards frailty [6]. The second model is the deficit accumulation approach, which views frailty as the cumulative burden of various symptoms, diseases, conditions, and disabilities [7]. The "acquired deficit" model quantitatively assesses frailty based on a 70-item list of patient deficits, with frailty represented by the sum of the deficits [8].

Rockwood et al. proposed the frailty index, a model suggesting that frailty is a multidimensional risk condition marked by the aggregation of diverse health-related deficits. The severity of frailty depends on the quantity rather than the specific nature of these deficits. This model includes various health domains, such as cognitive impairment, functional impairments, psychosocial vulnerabilities, geriatric syndromes, and medical comorbidities [3].

In 2011, Obei et al. introduced the modified frailty index (mFI) [9]. The mFI was derived from the Canadian Study of Health and Aging Frailty Index by matching its 70 variables to 11 comorbidity and deficit variables from the American College of Surgeons' National Surgery Quality and Improvement Project [10]. The mFI consists of 11 variables, with ach criterion assigned one point. The index is calculated by summing the points and dividing by the total number of variables, which is 11. Most studies examining the influence of frailty on post-surgical outcomes utilize the mFI due to its reliance on easily identifiable patient characteristics, which can be gathered through straightforward history taking and physical examination [3].

Frailty in various surgeries

As the general population ages, there is an increasing need for surgery among older adults, particularly due to the prevalence of certain diseases. Surgical procedures and the administration of anesthesia impose significant physiological and psychological stressors on the body [11]. Increasing evidence suggests that frailty holds substantial prognostic value for various surgical procedures. Recent findings indicate that frailty independently serves as a risk factor for forecasting postoperative outcomes among patients undergoing major surgical, including general, colorectal, oncologic, cardiac, and urologic procedures [12].

Frailty frequently correlates with an extended postoperative recovery period, leading to unplanned intensive care unit admissions, prolonged hospital stays, and discharge to skilled care facilities. It is also significantly associated with a higher likelihood of complications following surgery. Frail surgical patients experience more adverse events, ranging from wound infections to mortality. The increased incidence of wound complications in frail patients may be due to their limited physiological reserves, predisposing them to surgical wound issues such as infections [3]. These complications contribute to higher health care costs. Therefore, identifying frailty before surgery is crucial for planning perioperative care [8].

Frailty in vascular surgery

Given that vascular surgery patients primarily comprise older adults with numerous physical disabilities and chronic diseases, considering frailty is particularly significant [13]. The prevalence of vascular disease is closely associated with increased age: 2% among individuals aged 40 to 50 years, 3.5% in those 51–60 years old, 7.1% in 61–70 years old, 13.0% in 71–80 years old, 22.3% in 81–90 years old, and 32.5% in 91–100 years old [14]. With continuous advancements in surgical techniques and minimally invasive technology, the demand for vascular surgical interventions among the elderly is expected to rise [15]. Consequently, the growing prevalence of frailty among elderly patients undergoing vascular and endovascular surgery necessitates the integration of frailty assessments both before and after surgery to improve patient outcomes [16].

Approximately 39% of vascular surgery patients are estimated to be frail [17]. Frail patients have an approximately threefold increased risk of complication, including postoperative myocardial infarction, stroke, progressive renal failure, and graft/prosthesis/flap failure. Ischemic cerebrovascular disease, with its high mortality rate, is the leading cause of disability among neurological diseases, and stroke ranks as the third leading cause of death in developed countries, following heart disease and cancer [18]. Patients scoring between 0.54 and 0.63 on the mFI face a notably increased risk of mortality and complications [19].

Studies consistently suggest higher postoperative mortality rates for patients with higher mFI scores undergoing various vascular procedures. Significant associations have been established between frailty and increased mortality at 30 days, 90 days, 1 year, and 5

years, with the strongest evidence for 30-day mortality [16]. Notably, frailty has emerged as an independent predictor of postoperative morbidity and mortality, with a greater effect size than age alone. Although older age is a major risk factor for poor surgical outcomes, frailty can also develop in younger age groups and might be overlooked if assessments are restricted only to geriatric patients. Using an mFI >0.2 cut-off to define frailty, 20% of those under 65 years and 24% of those aged 65 years or older were classified as frail [12].

Discussion

The majority of preoperative risk assessment for patients with aortic aneurysms and other vascular conditions primarily focus on cardiac risk, often neglecting to consider physiological reserve. A decline in physiologic reserve may be associated with a reduced ability to recover from the stresses of significant surgical procedures [12]. Assessing frailty preoperatively is a challenging task for anesthesiologists and surgeons [8]. Thorough preoperative patient assessment is correlated with decreased hospitalization duration and a reduced risk of postoperative complications. Despite the established role of patient frailty as a predictive risk factor of poor outcomes, the absence of an efficient gold standard to objectively quantify frailty limits its utility as a preoperative risk assessment tool [20]. The mFI was created to facilitate a broader application of assessing patient frailty [21]. Furthermore, Karam et al. found the mFI was the best predictor of mortality compared to other pre-existing comorbidities among vascular surgery patients [22].

Anesthesia and surgical stress contribute to various postoperative complications, such as atelectasis, pneumonia, myocardial injury, acute kidney injury, and postoperative delirium [23], with a significantly elevated risk observed in patients with frailty [8]. Since several elements of the mFI are variable risk factors that can be influenced preoperatively, a multidisciplinary approach involving experts from different specialties is essential to address and correct these factors. Clinicians can optimize outcomes for frail patients through preoperative conditioning, nutrition, and pharmacological therapy [16].

Frailty assessment can aid clinicians and patients in making informed decisions. Medical treatments often need to be tailored to elderly patients due to age-related physiological decline and presence of comorbidities, which can alter the risk-to-benefit analysis. Researchers indicate that frailty assessments can assist physicians in making more accurate predictions and conducting risk-to-benefit analyses. Additionally, these assessments help patients understanding their greater risk of mortality if they are frail, allowing them to make more informed decisions about their treatment [24].

Moreover, frailty is an independent risk factor for increased healthcare costs due to the heightened level of care required for frail patients, which includes greater caregiver involvement, management of postoperative complications, and often prolonged hospital stay [8].

Conclusion

Frailty plays a crucial role in predicting and guiding the management of vascular and endovascular surgery patients throughout the pre-, peri-, and postoperative periods. Identifying frail patients preoperatively is essential due to the advanced age and numerous comorbidities often present in this group. Early identification allows for optimization of the patients' preoperative condition and the development of a more effective treatment plan, ultimately aiming to reduce complications and mortality rates.

References

1. Robinson TN, Eiseman B, Wallace JI, Church SD, McFann KK, Pfister SM, et al. Redefining geriatric preoperative assessment using frailty, disability and co-morbidity. Ann Surg. 2009;250(3): 449-55.

2. Chimukangara M, Frelich MJ, Bosler ME, Rein LE, Szabo A, Gould JC. The impact of frailty on outcomes of paraesophageal hernia repair. J Surg Res. 2016;202(2):259-66.

3. Panayi AC, Orkaby AR, Sakthivel D, Endo Y, Varon D, Roh D, et al. Impact of frailty on outcomes in surgical patients: a systematic review and meta-analysis. Am J Surg. 2019;218(2):393-400.

4. Vaupel JW, Manton KG, Stallard E. The impact of heterogeneity in individual frailty on the dynamics of mortality. Demography. 1979;16(3):439-54.

5. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56(3):M146-56.

6. Wleklik M, Czapla M, Denfeld Q, Przybylski R, Reczuch K, Uchmanowicz I. The how and why of assessing frailty syndrome in cardiac surgery. Adv Clin Exp Med. 2022;31(10):1061-4.

7. Lachmann R, Stelmach-Mardas M, Bergmann MM, Bernigau W, Weber D, Pischon T, et al. The accumulation of deficits approach to describe frailty. PLoS One. 2019;14(10):e0223449.

8. Jin Z, Rismany J, Gidicsin C, Bergese SD. Frailty: the perioperative and anesthesia challenges of an emerging pandemic. J Anesth. 2023;37(4):624-40.

9. Obeid NM, Azuh O, Reddy S. Predictors of critical care-related complications in colectomy patients using the National Surgical Quality Improvement Program: exploring frailty and aggressive laparoscopic approaches. J Trauma Acute Care Surg. 2012;72(4):878-83.

10. Wahl TS, Graham LA, Hawn MT, Richman J, Hollis RH, Jones CE, et al. Association of the Modified Frailty Index with 30-day surgical readmission. JAMA Surg. 2017;152(8):749-57.

11. Turrentine FE, Wang H, Simpson VB, Jones RS. Surgical risk factors, morbidity, and mortality in elderly patients. J Am Coll Surg. 2006;203(6):865-77.

12. Arya S, Kim SI, Duwayri Y, Brewster LP, Veeraswamy R, Salam A, et al. Frailty increases the risk of 30-day mortality, morbidity, and failure to rescue after elective abdominal aortic

aneurysm repair independent of age and comorbidities. J Vasc Surg. 2015;61(2):324-31.

13. Drudi LM, Ades M, Landry T, Gill HL, Grenon SM, Steinmetz OK, et al. Scoping review of frailty in vascular surgery. J Vasc Surg. 2019;69(6):1989-98.e2.

14. Savji N, Rockman CB, Skolnick AH, Guo Y, Adelman MA, Riles T, et al. Association between advanced age and vascular disease in different arterial territories: a population database of over 3.6 million subjects. J Am Coll Cardiol. 2013;61(16):1736-43.

15. Chowdhury MM, Ambler GK, Al Zuhir N, Walker A, Atkins ER, Winterbottom A, et al. Morphometric assessment as a predictor of outcome in older vascular surgery patients. Ann Vasc Surg. 2018;47:90-7.

16. Koh BJ, Lee Q, Wee IJ, Syn N, Lee KS, Jie Ng J, et al. Frailty scoring in vascular and endovascular surgery: a systematic review. Vasc Med. 2022;27(3):302-7.

17. Pandit V, Zeeshan M, Nelson PR, Hamidi M, Jhajj S, Lee A, et al. Frailty syndrome in patients with carotid disease: simplifying how we calculate frailty. Ann Vasc Surg. 2020;62:159-65.

18. Budinski S, Manojlović V, Budakov N, Batinić N, Pejaković Budinski M, Stojić M. Endovascular revascularization of carotid artery stenosis. Med Pregl. 2020;73(11-12):351-6.

19. Ali TZ, Lehman EB, Aziz F. Modified Frailty Index can be used to predict adverse outcomes and mortality after lower extremity bypass surgery. Ann Vasc Surg. 2018;46:168-77.

20. Ehlert BA, Najafian A, Orion KC, Malas MB, Black JH 3rd, Abularrage CJ. Validation of a modified Frailty Index to predict mortality in vascular surgery patients. J Vasc Surg. 2016; 63(6):1595-601.e2.

21. Velanovich V, Antoine H, Swartz A, Peters D, Rubinfeld I. Accumulating deficits model of frailty and postoperative mortality and morbidity: its application to a national database. J Surg Res. 2013;183(1):104-10.

22. Karam J, Tsiouris A, Shepard A, Velanovich V, Rubinfeld I. Simplified Frailty Index to predict adverse outcomes and mortality in vascular surgery patients. Ann Vasc Surg. 2013;27(7):904-8.

23. Ferraris VA, Bolanos M, Martin JT, Mahan A, Saha SP. Identification of patients with postoperative complications who are at risk for failure to rescue. JAMA Surg. 2014;149(11):1103-8.

24. Makary MA, Segev DL, Pronovost PJ, Syin D, Badeen-Roche K, Patel P, et al. Frailty as a predictor of surgical outcomes in older patients. J Am Coll Surg. 2010;210(6):901-8.

Rad je primljen 1. VI 2024.
Recenziran 14. VII 2024.
Prihvaćen za štampu 14. VII 2024.
BIBLID.0025-8105:(2024):LXXVII:3-4:129-132.

CONGRESS REPORTS
IZVEŠTAJI SA STRUČNIH SASTANAKA

Report from the European Congress of Anesthesiologists
Izveštaj sa Evropskog kongresa anesteziologa u Minhenu

The European Congress of Anesthesiologists took place from May 25-27, 2024, in Munich. Euroanaesthesia is one of the most prominent and influential annual congresses in anesthesiology and intensive care medicine. With participants from over 100 countries and more than 130 exhibitors, the event serves as a vital international platform for advancing knowledge and showcasing cutting-edge techniques. It fosters collaboration and networking opportunities among a broad, global audience.

The scientific sessions were organized in a variety of formats to accommodate different learning preferences, promoting active engagement. Many sessions featured thematic units focused on intensive care medicine. The workshop program offered a blend of hands-on training and innovative educational approaches. Delegates had the opportunity to develop both technical and non-technical skills through interactive workshops and simulation-based sessions.

A notable highlight was the introduction of HoloLens, a groundbreaking technology that uses Windows 10 to create three-dimensional holograms in a controlled environment. HoloLens represents an advanced form of augmented and enhanced reality, utilizing special glasses to visualize 3D models. This wireless device, equipped with a display, battery, built-in audio, and 3D capabilities, is poised to revolutionize medical practices. By wearing these holographic glasses, can minimize patient contact time and reduce the number of doctors required on-site.

HoloLens 2 was notably deployed in COVID-19 “red zones”, where it greatly improved communication among medical teams during the pandemic. The device is powered by multiple high-performance computers - one generates image, while another uses laser technology to create holograms.

Additionally, in March 2024, Microsoft unveiled the Mesh platform for mixed reality, which enables individuals in various locations to collaborate using 3D holographic devices. These devices include HoloLens 2, VR headsets, smartphones, tablets, and computers. The benefits of holographic technology have been well-documented: more efficient use of human resources, enhanced communication across different locations, and improved outcomes in medical procedures.

Evropski kongres anesteziologa održan je 25–27. maja 2024. u Minhenu. Euroanestezija je jedan od najvažnijih i najuticajnijih godišnjih kongresa u anesteziologiji i intenzivnoj medicini. Sa istorijom međunarodnih učesnika sa više od 100 zemalja i preko 130 izlagača, Euroanestezija je međunarodna platforma za unapređenje znanja, pregled inovativnih tehnika. Omogućava saradnju i umrežavanje sa velikom međunarodnom publikom.

Naučne sesije su bile dizajnirane u različitim formatima koji odgovaraju različitim stilovima edukacije u cilju olakšanja aktivnog učenja. Posebni formati su bili sa tematskim celinama iz intenzivne medicine. Program radionica je omogućio kombinaciju iskustava praktične obuke i inovativnih pristupa medicinskom obrazovanju. Delegati su imali mogućnost da razviju tehničke i netehničke veštine kroz praktične radionice i simulacione sesije.

Predstavljen je Hololens – revolucija u tehnologiji koja koristi Windows 10 da bi stvorila trodimenzionalne holograme u bliskom okruženju. Hololens je vrsta napredne forme proširene i poboljšane realnosti koja upotrebljava specijalne naočare da bi videla 3D modele. To je bežični uređaj koji se sastoji od displeja, baterije, ugrađene audio podrške i 3D podrške. Pomoću hologramskih naočara moguće je smanjiti vreme provedeno sa pacijentom, broj lekara čije prisustvo je neophodno. Na primer u vreme vizite dovoljno je prisustvo jednog lekara, ostali imaju kompletnu vizuelizaciju. Hololens 2 naočare su korišćene i u crvenoj kovid zoni što je značajno olakšalo komunikaciju između medicinskih stručnjaka i osoblja tokom pandemije. Te naočare imaju više moćnih kompjutera jedan kreira sliku, drugi laserski kreira holograme.

Takođe je istaknuto da je Microsoft u martu ove godine prikazao i meš platformu za pomešanu realnost. Ova platforma ljudima na različitim lokacijama omogućava da se pridruže 3D holografskim različitim uređajima. To uključuje HoloLens2, različite VR kacige, telefone, tablete i računare. Verifikovane su prednosti holografskih uređaja: racionalizacija ljudskih resursa, poboljšana komunikacija uz sugestije sa različitih lokacija i bolji rezultati tokom različitih medicinskih procedura.

Dr Milica Gojković

CIP - Каталогизација у публикацији
Библиотека Матице српске, Нови Сад

61:061(497.113)

MEDICINSKI pregled : časopis Društva lekara Vojvodine Srpskog lekarskog društva = Medical review : journal of the Society of physicians of Vojvodina of the Medical Society of Serbia / glavni i odgovorni urednik Radmila Matijević. – God. 1, br. 1 (1948)- . – Novi Sad : Društvo lekara Vojvodine Srpskog lekarskog društva, 1948- (Novi Sad : Feljton). – 28 cm

Dvomesečno. – Drugo izdanje na drugom nedijumu: Medicinski pregled (Online) = ISSN 1820-7383

ISSN 0025-8105 = Medicinski pregled

COBISS.SR-ID 3138306

COBISS.SR-ID 331773959

UPUTSTVO ZA AUTORE

Časopis ***Medicinski pregled*** objavljuje radove koji prethodno nisu objavljeni niti poslati u drugi časopis. U Časopisu mogu biti objavljeni radovi iz različitih oblasti biomedicine, koji su namenjeni lekarima različitih specijalnosti.

Od 1. januara 2013. godine *Medicinski pregled* je počeo da koristi usluge *e-Ur* − Elektronskog uređivanja časopisa. Svi korisnici sistema − autori, recenzenti i urednici, moraju biti registrovani korisnici sa jednom elektronskom adresom.

Korisnici časopisa treba da se registruju na adresi:
http://aseestant.ceon.rs/index.php/medpreg/user/register

Prijava rada treba da se učini na adresi:
http://aseestant.ceon.rs/index.php/medpreg/

U postupku prijave neophodno je da se pošalje saglasnost i izjava autora i svih koautora da rad nije delimično ili u celini objavljen ili prihvaćen za štampu u drugom časopisu.

Elektronsko uređivanje časopisa obezbeđuje korišćenje sistema *CrossCheck*, koji prijavljene radove automatski proverava na plagijarizam i autoplagijarizam. Autori ne bi smeli da pošalju isti rad u više časopisa istovremeno. Ukoliko se to desi, glavni urednik časopisa *Medicinski pregled* ima pravo da rad vrati autorima bez prethodnog slanja rada na recenziju; da odbije štampanje rada; da se obrati urednicima drugih časopisa u koje je rad poslat ili da se obrati direktoru ustanove u kojoj su autori rada zaposleni.

Primaju se samo radovi koji su napisani na engleskom jeziku, uz sažetak rada i naslov rada koji treba da budu napisani na engleskom i srpskom jeziku.

Radove koji su pristigli u časopis *Medicinski pregled* pregleda jedan ili više članova Uređivačkog odbora Časopisa. Oni radovi koji su napisani prema pravilima Časopisa šalju se na anonimnu recenziju kod najmanje dva recenzenta, stručnjaka iz odgovarajuće oblasti biomedicine. Načinjene recenzije radova pregleda glavni urednik ili članovi Uređivačkog odbora i one nisu garancija da će rad biti prihvaćen za štampu. Materijal koji je pristigao u časopis ostaje poverljiv dok se rad nalazi na recenziji, a identitet autora i recenzenata su zaštićeni, osim u slučaju ako oni odluče drugačije.

U časopisu *Medicinski pregled* objavljuju se: uvodnici, originalni članci, prethodna ili kratka saopštenja, pregledni članci, stručni članci, prikazi slučajeva, članci iz istorije medicine i drugi članci.

1. Uvodnici – do 5 strana. Sadrže mišljenja ili diskusiju o posebno značajnoj temi za Časopis, kao i o podacima koji su štampani u ovom ili nekom drugom časopisu. Obično ih piše jedan autor po pozivu.

2. Originalni članci – do 12 strana. Predstavljaju rezultate istraživanja autora rada i njihovo tumačenje. Istraživanje treba da bude obrađeno i izloženo na način da se može ponoviti, a analiza rezultata i zaključci jasni da bi se mogli proveriti.

3. Pregledni članci – do 10 strana. Predstavljaju sistematsko, sveobuhvatno i kritičko izlaganje problema na osnovu analiziranih i diskutovanih podataka iz literature, a koji oslikavaju postojeću situaciju u određenom području istraživanja. Literatura koja se koristi u radu mora da sadrži najmanje 5 radova autora članka iz uže naučne oblasti koja je opisana u radu.

4. Prethodna ili kratka saopštenja – do 4 strane. Sadrže izuzetno važne naučne rezultate koje bi trebalo objaviti u što kraćem vremenu. Ne moraju da sadrže detaljan opis metodologije rada i rezultata, ali moraju da imaju sva poglavlja kao originalni članci u sažetoj formi.

5. Stručni članci – do 10 strana. Odnose se na proveru ili prikaz prethodnog istraživanja i predstavljaju koristan izvor za širenje znanja i prilagođavanja originalnog istraživanja potrebama postojeće nauke i prakse.

6. Prikazi slučajeva – do 6 strana. Opisuju retke slučajeve iz prakse. Slični su stručnim člancima. U ovim radovima prikazuju se neuobičajeni oblici i tokovi oboljenja, neočekivane reakcije na primenjenu terapiju, primene novih dijagnostičkih procedura ili retke i nove bolesti.

7. Članci iz istorije medicine – do 10 strana. Ovi članci opisuju događaje iz prošlosti sa ciljem da omoguće očuvanje medicinske i zdravstvene kulture. Imaju karakter stručnih članaka.

8. Ostali članci – U časopisu Medicinski pregled objavljuju se feljtoni, prikazi knjiga, izvodi iz strane literature, izveštaji sa kongresa i stručnih sastanaka, saopštenja o radu pojedinih zdravstvenih organizacija, podružnica i sekcija, saopštenja Uredništva, pisma Uredništvu, novosti u medicini, pitanja i odgovori, stručne i staleške vesti i članci napisani u znak sećanja (*In memoriam).*

Priprema rukopisa

Kompletan rukopis, uključujući tekst rada, sve priloge i propratno pismo, treba poslati na elektronsku adresu koja je prethodno navedena.

Propratno pismo:

– mora da sadrži izjavu svih autora da se radi o originalnom radu koji prethodno nije objavljen niti prihvaćen za štampu u drugim časopisima;

– autori svojim potpisom preuzimaju odgovornost da rad ispunjava sve postavljene uslove i da ne postoji sukob interesa i

– autor mora navesti kategoriju članka (originalni rad, pregleni rad, prethodno saopštenje, stručni rad, prikaz slučaja, rad iz istorije medicine, itd.).

Rukopis

Opšta uputstva

Tekst rada treba da bude napisan u programu *Microsoft Word* za *Windows*, na A4 formatu stranice (sve četiri margine 2,5 cm), proreda 1,5 (isto važi i za tabele), fontom *Times New Roman*, veličinom slova 12 *pt*. Neophodno je koristiti međunarodni sistem mernih jedinica (*SI*), uz izuzetak temperature (° *C*) i krvnog pritiska (*mmHg*).

Rukopis treba da sadrži sledeće elemente:

1. Naslovna strana

Naslovna strana treba da sadrži: kratak i sažet naslov rada, bez skraćenica, skraćeni naslov rada (do 40 karaktera), imena i prezimena autora (ne više od 6) i afilijacije svih autora. Na dnu strane treba da piše ime, prezime i titula autora zaduženog za korespondenciju, njena/njegova adresa, elektronska adresa, broj telefona i faksa.

2. Sažetak

Sažetak ne može da sadrži više od 250 reči niti skraćenice. Treba da bude strukturisan, kratak i sažet, sa jasnim pregledom problema istraživanja, ciljevima, metodama, značajnim rezultatima i zaključcima.

Sažetak originalnih i stručnih članaka treba da sadrži uvod (sa ciljevima istraživanja), materijale i metode, rezultate i zaključak.

Sažetak prikaza slučaja treba da sadrži uvod, prikaz slučaja i zaključak.

Sažetak preglednih članaka treba da sadrži Uvod, podnaslove koji odgovaraju istima u tekstu i Zaključak.

Navesti do 10 ključnih reči ispod sažetka. One su pomoć prilikom indeksiranja, ali autorove ključne reči mogu biti izmenjene u skladu sa odgovarajućim deskriptorima, odnosno terminima iz *Medical Subject Headings, MeSH.*

Sažetak treba da bude napisan na srpskom i engleskom jeziku. Sažetak na srpskom jeziku trebalo bi da predstavlja prevod sažetka na engleskom, što podrazumeva da sadrži jednake delove.

3. Tekst članka

Originalni rad treba da sadrži sledeća poglavlja: Uvod (sa jasno definisanim ciljevima istraživanja), Materijal i metode, Rezultati, Diskusija, Zaključak, spisak skraćenica (ukoliko su

korišćene u tekstu). Nije neophodno da se u posebnom poglavlju rada napiše zahvalnica onima koji su pomogli da se istraživanje uradi, kao i da se rad napiše.

Prikaz slučaja treba da sadrži sledeća poglavlja: Uvod (sa jasno definisanim ciljevima), Prikaz slučaja, Diskusija i Zaključak.

Uvod

U poglavlju Uvod potrebno je jasno definisati predmet istraživanja (prirodu i značaj istraživanja), navesti značajne navode literature i jasno definisati ciljeve istraživanja i hipoteze.

Materijal i metode

Materijal i metode rada treba da sadrže podatke o vrsti studije (prospektivna/retrospektivna, uslove za uključivanje i ograničenja studije, trajanje istraživanja, demografske podatke, period praćenja). Detaljno treba opisati statističke metode da bi čitaoci rada mogli da provere iznesene rezultate.

Rezultati

Rezultati predstavljaju detaljan prikaz podataka koji su dobijeni istraživanjem. Sve tabele, grafikoni, sheme i slike moraju biti citirani u tekstu rada i označeni brojevima po redosledu njihovog navođenja.

Diskusija

Diskusija treba da bude koncizna, jasna i da predstavlja tumačenje i poređenje rezultata studije sa relevantnim studijama koje su objavljene u domaćoj i međunarodnoj literaturi. U poglavlju Diskusija potrebno je naglasiti da li su postavljene hipoteze potvrđene ili nisu, kao i istaknuti značaj i nedostatke istraživanja.

Zaključak

Zaključci moraju proisteći isključivo iz rezultata istraživanja rada; treba izbegavati uopštene i nepotrebne zaključke. Zaključci koji su navedeni u tekstu rada moraju biti u saglasnosti sa zaključcima iz Sažetka.

4. Literatura

Potrebno je da se literatura numeriše arapskim brojevima redosledom kojim je u tekstu navedena u parentezama; izbegavati nepotrebno velik broj navoda literature. Časopise bi trebalo navoditi u skraćenom obliku koji se koristi u *Index Medicus* (*http://www.nlm.nih.gov/tsd/serials/lji.html*). Pri citiranju literature koristiti Vankuverski sistem. Potrebno je da se navedu svi autori rada, osim ukoliko je broj autora veći od šest. U tom slučaju napisati imena prvih šest autora praćeno sa *et al*.

Primeri pravilnog navođenja literature nalaze se u nastavku.

Radovi u časopisima

∗ Standardni rad

Ginsberg JS, Bates SM. Management of venous thromboembolism during pregnancy. J Thromb Haemost 2003;1:1435-42.

∗ Organizacija kao autor

Diabetes Prevention Program Research Group. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. Hypertension 2002;40(5):679-86.

∗ Bez autora

21st century heart solution may have a sting in the tail. BMJ. 2002;325(7357):184.

∗ Volumen sa suplementom

Magni F, Rossoni G, Berti F. BN-52021 protects guinea pig from heart anaphylaxix. Pharmacol Res Commun 1988;20 Suppl 5:75-8.

∗ Sveska sa suplementom

Gardos G, Cole JO, Haskell D, Marby D, Pame SS, Moore P. The natural history of tardive dyskinesia. J Clin Psychopharmacol 1988;8(4 Suppl):31S-37S.

∗ Sažetak u časopisu

Fuhrman SA, Joiner KA. Binding of the third component of complement C3 by Toxoplasma gondi [abstract]. Clin Res 1987;35:475A.

Knjige i druge monografije

∗ Jedan ili više autora

Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

∗ Urednik (urednici) kao autor (autori)

Danset J, Colombani J, eds. Histocompatibility testing 1972. Copenhagen: Munksgaard, 1973:12-8.

∗ Poglavlje u knjizi

Weinstein L, Shwartz MN. Pathologic properties of invading microorganisms. In: Soderman WA Jr, Soderman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: Saunders; 1974. p. 457-72.

∗ Zbornik radova sa kongresa

Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer; 2002. p. 182-91.

∗ Disertacija

Borkowski MM. Infant sleep and feeding: a telephone survey of Hispanic Americans [dissertation]. Mount Pleasant (MI): Central Michigan University; 2002.

Elektronski materijal

∗ Članak iz časopisa u elektronskom formatu

Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [Internet]. 2002 Jun [cited 2002 Aug 12];102(6):[about 1 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htmArticle

∗ Monografija u elektronskom formatu

CDI, clinical dermatology illustrated [monograph on CD-ROM]. Reevs JRT, Maibach H. CMEA Multimedia Group, producers. 2nd ed. Version 2.0. San Diego:CMEA;1995.

∗ Kompjuterska datoteka

Hemodynamics III: the ups and downs of hemodynamics [computer program]. Version 2.2. Orlando (FL): Computerized Educational Systems; 1993.

5. Prilozi (tabele, grafikoni, sheme i slike)

BROJ PRILOGA NE SME BITI VEĆI OD ŠEST!

Tabele, grafikoni, sheme i slike se postavljaju kao posebni dokumenti.

– Tabele i grafikone bi trebalo pripremiti u formatu koji je kompatibilan programu u kojem je napisan tekst rada. Slike bi trebalo poslati u jednom od sledećih oblika: *JPG, GIF, TIFF, EPS*.

– Svaki prilog mora biti obeležen arapskim brojem prema redosledu po kojem se navodi u tekstu rada.

– Naslovi, tekst u tabelama, grafikonima, shemama i legende slika bi trebalo da budu napisani na srpskom i engleskom jeziku.

– Nestandardne priloge označiti u fusnoti uz korišćenje sledećih simbola: *, †, ‡, §, | |, ¶, **, † †, ‡ ‡ .

– U legendi slika trebalo bi napisati korišćeno uveličanje okulara i objektiva mikroskopa. Svaka fotografija treba da ima vidljivu skalu.

– Ako su tabele, grafikoni, sheme ili slike već objavljene, navesti originalni izvor i priložiti pisano odobrenje autora za njihovo korišćenje.

– Svi prilozi će biti štampani kao crno-bele slike. Ukoliko autori žele da se prilozi štampaju u boji, obavezno treba da plate dodatne troškove.

6. Dodatne obaveze

AUTORI I SVI KOAUTORI RADA OBAVEZNO TREBA DA PLATE GODIŠNJU PRETPLATU ZA ČASOPIS *MEDICINSKI PREGLED*. U PROTIVNOM, RAD NEĆE BITI ŠTAMPAN U ČASOPISU.

INFORMATION FOR AUTHORS

Medical Review publishes papers (previously neither published in nor submitted to any other journals) from various fields of biomedicine intended for broad circles of doctors.

Since January 1th, 2013 the Medical Review has been using the service e-Ur: Electronic Journal Editing. All users of the Registration system, i.e. authors, reviewers, and editors have to be registered users with only one e-mail address. Registration should be made on the web address:

http://aseestant.ceon.rs/index.php/medpreg/user/register.

Manuscript submission should be made on the web address:

http://aseestant.ceon.rs/index.php/medpreg/

A supplementary file, with the statement that the paper has not been submitted or accepted for publication elsewhere and a consent signed by all authors, have to be enclosed with the manuscript.

Authors may not send the same manuscript to more than one journal concurrently. If this occurs, the Editor may return the paper without reviewing it, reject the paper, contact the Editor of the other journal(s) in question and/or contact the author's employers.

Papers should be written in English language, with an abstract and title page in English, as well as in Serbian language.

All papers submitted to ***Medical Review*** are seen by one or more members of the Editorial Board. Suitable articles are sent to at least two experts to be reviewed, thier reports are returned to the assigned member of the Editorial Board and the Editor. Revision of an article gives no guarantee of acceptance and in some cases revised articles are rejected if the improvements are not sufficient or new issues have arisen. Material submitted to *the Journal* remains confidential while being reviewed and peer-reviewers' identities are protected unless they elect to lose anonymity.

Medical Review publishes the following types of articles: editorials, original studies, preliminary reports, review articles, professional articles, case reports, articles from history of medicine and other types of publications.

1. Editorials – up to 5 pages – convey opinions or discussions on a subject relevant for the Journal. Editorials are commonly written by one author by invitation.

2. Original studies – up to 12 pages – present the authors' own investigations and their interpretations. They should contain data which could be the basis to check the obtained results and reproduce the investigative procedure.

3. Review articles – up to 10 pages – provide a condensed, comprehensive and critical review of a problem on the basis of the published material being analyzed and discussed, reflecting the current situation in one area of research. Papers of this type will be accepted for publication provided that the authors confirm their expertise in the relevant area by citing at least 5 self-citations.

4. Preliminary reports – up to 4 pages – contain scientific results of significant importance requiring urgent publishing; however, it need not provide detailed description for repeating the obtained results. It presents new scientific data without a detailed explanation of methods and results. It contains all parts of an original study in an abridged form.

5. Professional articles – up to 10 pages – examine or reproduce previous investigation and represent a valuable source of knowledge and adaption of original investigations for the needs of current science and practice.

6. Case reports – up to 6 pages – deal with rare casuistry from practice important for doctors in direct charge of patients and are similar to professional articles. They emphasize unusual characteristics and course of a disease, unexpected reactions to a therapy, application of new diagnostic procedures and describe a rare or new disease.

7. History of medicine – up to 10 pages – deals with history with the aim of providing continuity of medical and health care culture. They have the character of professional articles.

8. Other types of publications – The journal also publishes feuilletons, book reviews, extracts from foreign literature, reports from congresses and professional meetings, communications on activities of certain medical institutions, branches and sections, announcements of the Editorial Board, letters to the Editorial Board, novelties in medicine, questions and answers, professional and vocational news and In memoriam.

Preparation of the manuscript

The complete manuscript, including the text, all supplementary material and covering letter, is to be sent to the web address above.

The covering letter:

– It must contain the proof given by the author that the paper represents an original work that it has neither been previously published in other journals nor is under consideration to be published in other journals.

– It must confirm that all the authors meet criteria set for the authorship of the paper, that they agree completely with the text and that there is no conflict of interest.

– It must state the type of the paper submitted (an original study, a review article, a preliminary report, a professional article, a case report, history of medicine).

The manuscript:

General instructions.

Use Microsoft Word for Windows to type the text. The text must be typed in font *Times New Roman*, page format A4, space 1.5 (for tables as well), margins set to 2.5 cm and font size 12pt. All measurements should be reported in the metric system of the International System of Units – SI. Temperature should be expressed in Celsius degrees (°C) and pressure in mmHg.

The manuscript should contain the following elements:

1. The title page.

The title page should contain a concise and clear title of the paper, without abbreviations, then a short title (up to 40 characters), full names and surnames of the authors (not more than 6) indexed by numbers corresponding to those given in the heading along with the full name and place of the institutions they work for. Contact information including the academic degree(s), full address, e-mail and number of phone or fax of the corresponding author (the author responsible for correspondence) are to be given at the bottom of this page.

2. Summary.

The summary should contain up to 250 words, without abbreviations, with the precise review of problems, objectives, methods, important results and conclusions. It should be structured into the paragraphs as follows:

– Original and professional papers should have the introduction (with the objective of the paper), materials and methods, results and conclusion

– Case reports should have the introduction, case report and conclusion

– Review papers should have the introduction, subtitles corresponding to those in the paper and conclusion.

The authors should provide up to 10 keywords below the summary. These keywords will assist indexers in cross-indexing the article and will be published with the summary, but the authors' keywords could be changed in accordance with the list of Medical Subject Headings, MeSH of the American National Medical Library.

The summary should be written in both languages, English as well as Serbian. The summary in Serbian language should be the translation of the summary in English; therefore, it has to contain the same paragraphs.

3. The text of the paper.

The text of original studies must contain the following: introduction (with the clearly defined objective of the study), materials and methods, results, discussion, conclusion, list of abbreviations (if used in the text) and not necessarily, the acknowledgment mentioning those who have helped in the investigation and preparation of the paper.

The text of a case report should contain the following: introduction (with clearly defined objective of the study), case report, discussion and conclusion.

Introduction contains clearly defined problem dealt with in the study (its nature and importance), with the relevant references and clearly defined objective of the investigation and hypothesis.

Material and Methods should contain data on design of the study (prospective/retrospective, eligibility and exclusion criteria, duration, demographic data, follow-up period). Statistical methods applied should be clear and described in details.

Results give a detailed review of data obtained during the study. All tables, graphs, schemes and figures must be cited in the text and numbered consecutively in the order of their first citation in the text.

Discussion should be concise and clear, interpreting the basic findings of the study in comparison with the results of relevant studies published in international and national literature. It should be stated whether the hypothesis has been confirmed or denied. Merits and demerits of the study should be mentioned.

Conclusion must deny or confirm the attitude towards the 0based solely on the author's own results, corroborating them. Avoid generalized and unnecessary conclusions. Conclusions in the text must be in accordance with those given in the summary.

4. References are to be given in the text under Arabic numerals in parentheses consecutively in the order of their first citation. Avoid a large number of citations in the text. The title of journals should be abbreviated according to the style used in Index Medicus (http://www.nlm.nih.gov/tsd/serials/lji.html). Apply Vancouver Group's Criteria, which define the order of data and punctuation marks separating them. Examples of correct forms of references are given below. List all authors, but if the number exceeds six, give the names of six authors followed by 'et al'.

Articles in journals

∗ *A standard article*

Ginsberg JS, Bates SM. Management of venous thromboembolism during pregnancy. J Thromb Haemost 2003;1:1435-42.

∗ *An organization as the author*

Diabetes Prevention Program Research Group. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. Hypertension 2002;40(5):679-86.

∗ *No author given*

21st century heart solution may have a sting in the tail. BMJ. 2002;325(7357):184.

∗ *A volume with supplement*

Magni F, Rossoni G, Berti F. BN-52021 protects guinea pig from heart anaphylaxix. Pharmacol Res Commun 1988;20 Suppl 5:75-8.

∗ *An issue with supplement*

Gardos G, Cole JO, Haskell D, Marby D, Pame SS, Moore P. The natural history of tardive dyskinesia. J Clin Psychopharmacol 1988;8(4 Suppl):31S-37S.

∗ *A summary in a journal*

Fuhrman SA, Joiner KA. Binding of the third component of complement C3 by Toxoplasma gondi [abstract]. Clin Res 1987;35:475A.

Books and other monographs

∗ *One or more authors*

Murray PR, Rosenthal KS, Kobayashi GS, Pfaller MA. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

∗ *Editor(s) as author(s)*

Danset J, Colombani J, eds. Histocompatibility testing 1972. Copenhagen: Munksgaard, 1973:12-8.

∗ *A chapter in a book*

Weinstein L, Shwartz MN. Pathologic properties of invading microorganisms. In: Soderman WA Jr, Soderman WA, eds. Pathologic physiology: mechanisms of disease. Philadelphia: Saunders; 1974. p. 457-72.

∗ *A conference paper*

Christensen S, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer; 2002. p. 182-91.

∗ *A dissertation and theses*

Borkowski MM. Infant sleep and feeding: a telephone survey of Hispanic Americans [dissertation]. Mount Pleasant (MI): Central Michigan University; 2002.

Electronic material

∗ *A journal article in electronic format*

Abood S. Quality improvement initiative in nursing homes: the ANA acts in an advisory role. Am J Nurs [Internet]. 2002 Jun [cited 2002 Aug 12];102(6):[about 1 p.]. Available from: http://www.nursingworld.org/AJN/2002/june/Wawatch.htmArticle

∗ *Monographs in electronic format*

CDI, clinical dermatology illustrated [monograph on CD-ROM]. Reevs JRT, Maibach H. CMEA Multimedia Group, producers. 2nd ed. Version 2.0. San Diego:CMEA;1995.

∗ *A computer file*

Hemodynamics III: the ups and downs of hemodynamics [computer program]. Version 2.2. Orlando (FL): Computerized Educational Systems; 1993.

5. Attachments (tables, graphs, schemes and photographs).

THE MAXIMUM NUMBER OF ATTACHMENTS ALLOWED IS SIX!

– Tables, graphs, schemes and photographs are to be submitted as separate documents, on separate pages.

– Tables and graphs are to be prepared in the format compatible with Microsoft Word for Windows programme. Photographs are to be prepared in JPG, GIF, TIFF, EPS or similar format.

– Each attachment must be numbered by Arabic numerals consecutively in the order of their appearance in the text

– The title, text in tables, graphs, schemes and legends must be given in both Serbian and English languages.

– Explain all non-standard abbreviations in footnotes using the following symbols *, †, ‡, §, | |, ¶, **, † †, ‡ ‡ .

– State the type of color used and microscope magnification in the legends of photomicrographs. Photomicrographs should have internal scale markers.

– If a table, graph, scheme or figure has been previously published, acknowledge the original source and submit written permission from the copyright holder to reproduce it.

– All attachments will be printed in black and white. If the authors wish to have the attachments in color, they will have to pay additional cost.

6. Additional requirements

SHOULD THE AUTHOR AND ALL CO-AUTHORS FAIL TO PAY THE SUBSCRIPTION FOR MEDICAL REVIEW, THEIR PAPER WILL NOT BE PUBLISHED.