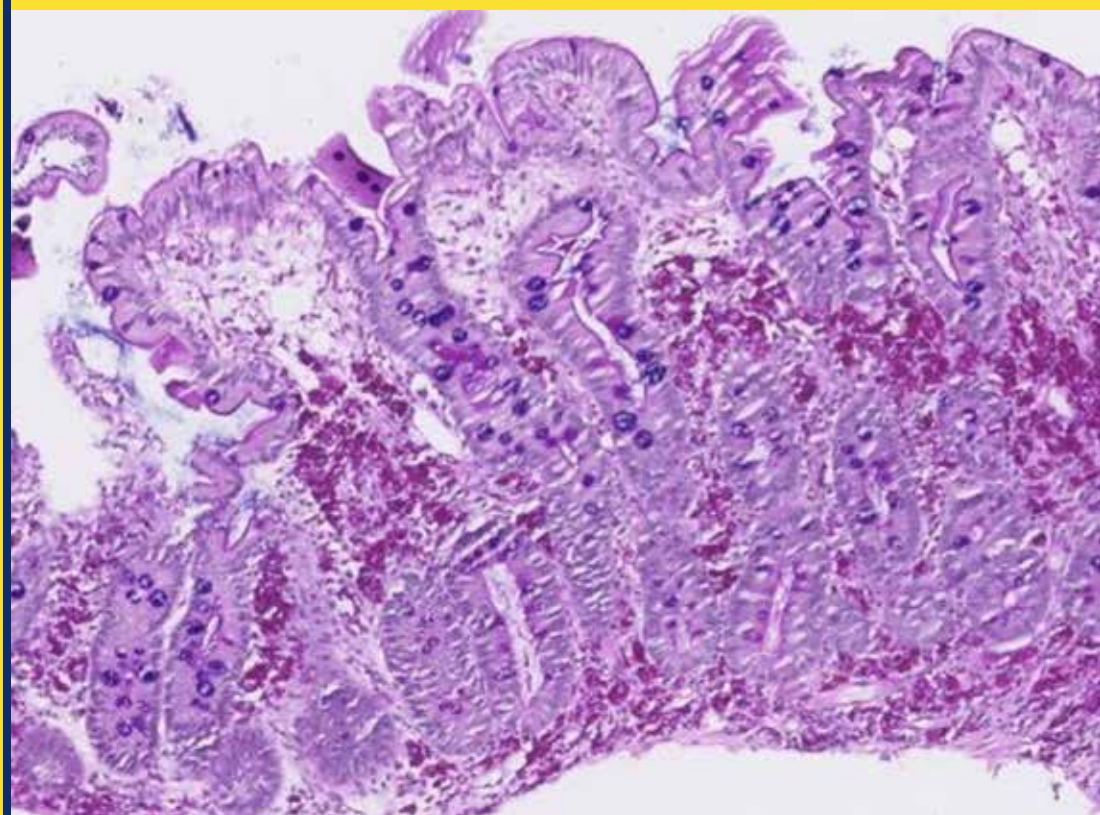
Volume
19
02/2026

amb

ACTA MEDICO-BIOTECHNICA



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Reference:
1. ARGOS® Biometer User Manual, Sept. 2024
2. Tamaoki A, Kojima T, Hasegawa A, et al. Clinical evaluation of a new swept-source optical coherence biometer that uses individual refractive indices to measure axial length in cataract patients. Ophthalmic Res. 2019;19:1-13.
3. Shammas HJ, Ortiz S, Shammas MC, et al. Biometry measurements using a new large-coherence-length swept-source optical coherence tomographer. J Cataract Refract Surg. 2016;42:50-61.
4. Hussaindeen JR, Mariom EG, Arunachalam S, et al. Comparison of axial length using a new swept-source optical coherence tomography-based biometer. PLoS ONE. December 2018.
5. ZEISS IOLMaster 700 510k Submission 2015.
6. VERION Reference Unit User Manual Part I 2019.
7. Whang W, Yoo Y, Kang M, et al. Predictive accuracy of partial coherence interferometry and swept-source optical coherence tomography for intraocular lens power calculation. Sci Rep. 2018;8(1):13732.
8. Shammas HJ, Shammas MC, Jivrajka RV, Cooke DL, Potvin R. Effects on IOL power calculation and expected clinical outcomes of axial lengthmeasurements based on multiple vs single refractive indices. Clin Ophthalmol. 2020;14:1511-1519.
9. Woodard L, Wenthold R, Hsiao C-W. Time and motion study demonstrating the value preposition for Argos®. June 2020.

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PM-SI-2025-6-4008
06/2025

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Univerza v Mariboru, Medicinska fakulteta
University of Maribor, Faculty of Medicine

Založnik / Publisher

Univerza v Mariboru / University of Maribor
Univerzitetna založba / University Press
Slomškov trg 15, 2000 Maribor, Slovenija
https://press.um.si, zalozba@um.si

Izdajatelj / Issued by

Univerza v Mariboru, Medicinska fakulteta
University of Maribor, Faculty of Medicine

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Tisk / Printed by

Tiskarna Silveco, d.o.o.

Naklada / Number of copies

500 izvodov

Dostopno na / available at

https://journals.um.si/index.php/amb

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Izid publikacije je finančno podprla ARIS iz sredstev državnega proračuna iz naslova razpisa za sofinanciranje domačih znanstvenih periodičnih publikacij.

Lektoriranje / Language Editing

Prevekso d.o.o.
International Science Editing, Ireland.

Oblikovanje / Design

Tabula, Tadej Kajzer s.p.

Slika na naslovnici / Cover illustration

(stran 69 / page 69)

ISSN tiskana izdaja: 1855-5640
ISSN elektronska izdaja: 1855-7988

ISSN Print Edition: 1855-5640
ISSN E-Edition: 1855-7988

SPLOŠNE INFORMACIJE

ISSN tiskana izdaja: 1855–5640
ISSN elektronska izdaja: 1855–7988

Internetna stran:

https://journals.um.si/index.php/amb

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ISSN Print Edition: 1855–5640
ISSN E–Edition: 1855–7988

Journal Homepage:

https://journals.um.si/index.php/amb

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Acta medico–biotechnica is the official journal of the Faculty of Medicine, University of Maribor in Slovenia. This scientific–professional journal contains material of interest to a wider readership covering the medical and biotechnical fields.

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Prvo poglavje je napisano, prihodnost je pred nami: prva generacija študentov farmacije v Mariboru

Pred letom dni je vzpostavitev enovitega magistrskega študijskega programa Farmacija na Univerzi v Mariboru pomenila pomemben mejnik po dolgem in zahtevnem procesu njegove priprave. Dolgotrajno strateško načrtovanje, medinstitucionalno sodelovanje in vztrajnost so omogočili njegovo uresničitev. Oktobra 2025 je prva generacija študentov farmacije vstopila v predavalnice Medicinske fakultete ter Fakultete za kemijo in kemijsko tehnologijo Univerze v Mariboru, s čimer je začela pisati novo poglavje v zgodovini farmacevtskega izobraževanja v Sloveniji. Danes, po zaključenem prvem letu izvajanja programa, ko je v študijske klopi sedla že druga generacija, imamo priložnost, da se ozremo na doseženo, ter hkrati usmerimo pogled v prihodnost.

V ospredju prvega leta so bili študenti prve generacije, ki so vstopili v nov študijski program brez izkušenj predhodnih generacij, ustaljenih praks in starejših kolegov, na katere bi se lahko oprli. Zato so bili prav oni prvi, ki so neposredno spoznavali značilnosti, zahteve in začetne izzive študijskega programa. Prehod iz srednješolskega v univerzitetno okolje je bil za številne študente zahteven, hkrati pa je tudi izvajalcem programa ponudil dragocen vpogled v področja, ki jih je mogoče pri nadaljnjem izvajanju programa še izboljšati. Ob zaključku prvega študijskega leta je večina generacije napredovala v drugi letnik, pridobljene izkušnje pa so in bodo pomembno prispevale k nadaljnjemu prilagajanju in kakovostnemu razvoju programa.

Prvo leto izvajanja je namreč prineslo številne izzive tudi institucijama, ki študijski program izvajata skupaj. Njegova interdisciplinarna zasnova, ki povezuje Medicinsko fakulteto ter Fakulteto za kemijo in kemijsko tehnologijo, predstavlja eno največjih prednosti, hkrati pa prinaša precejšnjo organizacijsko zahtevnost. Študenti so se morali prilagoditi študiju na dveh fakultetah, vključno s praktičnimi izzivi prehajanja

The First Chapter Is Written, the Future Lies Ahead: The First Generation of Pharmacy Students in Maribor

One year ago, the establishment of the Integrated Master's Programme in Pharmacy at the University of Maribor marked an important milestone following a long and demanding preparation process. Long-term strategic planning, interinstitutional cooperation, and perseverance made its implementation possible. In October 2025, the first generation of pharmacy students entered the lecture halls of the Faculty of Medicine and the Faculty of Chemistry and Chemical Engineering of the University of Maribor, thereby opening a new chapter in the history of pharmaceutical education in Slovenia. Today, following completion of the programme's first year, with the second generation of students already enrolled, we have an opportunity to reflect on what has been achieved while also looking ahead.

At the centre of the first year were the students of the pioneering generation, who entered a new study programme without the experience of previous cohorts, established practices, or senior students on whom they could rely. They were therefore the first to encounter its characteristics, demands, and initial challenges directly. The transition from secondary school to university-level study proved demanding for many students, but also provided the programme's teaching staff with valuable insights into areas in which the programme could be further improved. By the end of the first year, the majority of the cohort had progressed to the second year, and the experience gained will make an important contribution to the continued refinement and improvement of the programme.

The first year of implementation also brought numerous challenges for the two institutions jointly responsible for delivering the programme. Its interdisciplinary structure, linking the Faculty of Medicine and the Faculty of

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med lokacijama. Pedagoški sodelavci so vložili veliko truda v pripravo in usklajevanje novih učnih vsebin, strokovne službe pa so se soočale z zahtevno nalogo vključevanja novega programa v obstoječe akademske in administrativne procese. Priprava urnikov, zagotavljanje laboratorijskih prostorov, prostorske omejitve in usklajevanje pedagoških obveznosti so dejavniki, ki so zahtevali stalno pozornost, še posebej ob infrastrukturnih omejitvah, s katerimi se soočata obe strani. Vse rešitve niso bile optimalne že od začetka, vendar so posamezni izzivi omogočili sprotno prilagajanje in izboljševanje izvedbe. Ravno pripravljenost na poslušanje, prilagajanje in sodelovanje so omogočili, da smo študijsko izkušnjo lahko izboljševali tudi skozi študijsko leto.

Za temi prizadevanji stoji skupnost predanih visokošolskih učiteljev, raziskovalcev, tehničnih sodelavcev in sodelavcev strokovnih služb. Kakovost študijskega programa ni odvisna zgolj od njegove vsebinske zasnove, temveč tudi od ljudi, ki le tega izvajajo. Veseli nas, da pri implementaciji sodelujejo visoko usposobljeni in predani strokovnjaki, mdr. tudi mednarodno priznani raziskovalci, katerih znanstvene in strokovne izkušnje bogatijo pedagoški proces, ter tudi študentom približujejo sodobni razvoj farmacije. Njihova vloga presega tako predavanja kot preverjanje znanja, saj vključuje mentorstvo, spodbujanje radovednosti ter razvijanje strokovne integritete, ki jo pričakujemo od bodočih farmacevtov.

Medtem ko je prva generacija zaključevala prvi letnik, so intenzivno potekale priprave že na naslednjo stopnjo študija. Drugi letnik prinaša več strokovnih farmacevtskih predmetov, ki se na Univerzi v Mariboru izvajajo prvič, med njimi Farmacevtsko kemijo na Fakulteti za kemijo in kemijsko tehnologijo ter Farmacevtsko tehnologijo na Medicinski fakulteti. Njihova vzpostavitev je zahtevala obsežna vlaganja v učna gradiva, laboratorijske vaje, kadre in infrastrukturo. Zaposlili smo nove pedagoške in strokovne sodelavce, dodatni strokovnjaki so pridobili ustrezne habilitacije, laboratorije pa smo opremili s sodobnimi instrumenti in učno opremo. Ta vlaganja ustvarjajo pogoje za praktično izobraževanje, v okviru katerega bodo študenti razvijali ključne laboratorijske spretnosti, ter tudi farmacevtske znanosti spoznavali še skozi praktično delo. Hkrati predstavljajo dolgoročno

Chemistry and Chemical Engineering, represents one of its greatest strengths, while at the same time introducing considerable organisational complexity. Students had to adapt to studying at two faculties, including the practical challenges of moving between locations. Teaching staff invested substantial effort in preparing and coordinating new course content. At the same time, administrative and professional services faced the demanding task of integrating the new programme into existing academic and administrative processes. Timetabling, the provision of laboratory facilities, spatial constraints, and the coordination of teaching responsibilities required continuous attention, particularly given the infrastructural limitations faced by both faculties. Not all solutions were optimal from the outset, but individual challenges enabled ongoing adjustment and improvement of the programme delivery. The willingness to listen, adapt, and cooperate played a key role in improving the student experience throughout the year.

Behind these efforts is a community of dedicated university teachers, researchers, technical staff, and colleagues from professional and administrative services. The quality of a study programme depends not only on its academic content, but also on the people who deliver it. We are pleased that the programme involves highly qualified and committed professionals, including internationally recognised researchers whose scientific and professional experience enriches the teaching process and brings students closer to contemporary developments in pharmacy. Their role extends beyond lectures and assessment to include mentoring, encouraging curiosity, and fostering the professional integrity expected of future pharmacists.

While the first generation was completing its first year, intensive preparations were already underway for the next stage of study. The second year introduces several professional pharmacy courses being taught at the University of Maribor for the first time, including Pharmaceutical Chemistry at the Faculty of Chemistry and Chemical Engineering and Pharmaceutical Technology at the Faculty of Medicine. Establishing these courses required substantial investment in teaching materials, laboratory exercises, personnel, and infrastructure. New teaching and professional staff were recruited, additional experts obtained the necessary academic teaching qualifications, and laboratories

naložbo v razvoj farmacevtskega izobraževanja, raziskovanja in inovacij v Mariboru.

Enako pomembna razsežnost razvoja programa je mednarodno povezovanje. V preteklem letu smo veliko pozornosti namenili krepitvi mednarodnih akademskih mrež, vzpostavljanju in širjenju partnerstev Erasmus+ ter pripravi skupnih evropskih projektnih prijav. S temi dejavnostmi nameravamo ustvariti možnosti za prihodnje izmenjave študentov in zaposlenih, skupne izobraževalne pobude ter raziskovalno sodelovanje. Posebno pozornost smo namenili tudi evropskim pobudam za krepitev inovativnosti in podjetnosti v visokem šolstvu, mdr. pobudi EIT Higher Education Initiative. Čeprav bodo rezultati teh prizadevanj izraziteje vidni šele v prihodnjih letih, gradimo pogoje za mednarodno povezano, znanstveno ambiciozno in na nove tehnološke ter družbene izzive odzivno farmacevtsko izobraževanje že danes.

Pomen razvoja farmacevtskega izobraževanja v Mariboru potrjuje tudi širše strokovno in gospodarsko okolje. Farmacija je področje hitrega znanstvenega in strokovnega razvoja, ki ga pomembno oblikujejo napredek biotehnologije, razvoj bioloških zdravil, personalizirano zdravljenje, napredne proizvodne tehnologije ter vse večji pomen brezšivne skrbi. V Sloveniji so v zadnjih letih opazna obsežna vlaganja v farmacevtski sektor. Družba Sandoz prek Leka v Sloveniji v večletnem obdobju načrtuje naložbe, ki presegajo milijardo evrov, mdr. v velik proizvodni obrat za podobna biološka zdravila v Lendavi. Tudi Novartis nadaljuje vlaganja v napreden razvoj in proizvodnjo zdravil, pri čemer so naložbe tega podjetja v Sloveniji zgolj v letu 2025 dosegle 233 milijonov evrov. Takšne naložbe ne odražajo le rasti farmacevtskega sektorja, temveč tudi dolgoročno potrebo po visoko usposobljenih strokovnjakih, ki bodo prispevali k farmacevtskim inovacijam, proizvodnji, zagotavljanju kakovosti in raziskovanju. Prihodnost farmacije pa seveda sega precej dlje od industrije. Javne in bolnišnične lekarne, klinične farmacevtske storitve ter interdisciplinarni zdravstveni timi vse bolj potrebujejo farmacevte, ki znanstvena spoznanja povezujejo s klinično presojo, komunikacijskimi spretnostmi in strokovno odgovornostjo. Mariborski študijski program povezuje lekarniško, klinično in industrijsko

were equipped with modern instruments and teaching equipment. These investments provide the conditions for practical education, enabling students to develop key laboratory skills and gain a deeper understanding of pharmaceutical sciences through hands-on work. At the same time, they represent a long-term investment in the development of pharmaceutical education, research, and innovation in Maribor.

Internationalisation is an equally important dimension of the programme's development. Over the past year, considerable attention has been devoted to strengthening international academic networks, establishing and expanding Erasmus+ partnerships, and preparing joint European project proposals. These activities are intended to create opportunities for future student and staff mobility, joint educational initiatives, and research collaboration. Particular attention has also been paid to European initiatives that promote innovation and entrepreneurship in higher education, including the European Institute of Innovation and Technology Higher Education Initiative. Although the results of these efforts will become more visible in the coming years, we are already creating the conditions for pharmaceutical education that is internationally connected, scientifically ambitious, and responsive to emerging technological and societal challenges.

The importance of developing pharmaceutical education in Maribor is also reinforced by the broader professional and economic environment. Pharmacy is a field of rapid scientific and professional development, shaped by advances in biotechnology, the development of biological medicines, personalised treatment, advanced manufacturing technologies, and the growing importance of seamless care. In recent years, Slovenia has seen substantial investment in the pharmaceutical sector. Sandoz, through Lek, is planning investments in Slovenia exceeding 1 billion euros over a period of several years, including a major biosimilar manufacturing facility in Lendava. Novartis has likewise continued investing in advanced pharmaceutical development and manufacturing, with its investments in Slovenia reaching 233 million euros in 2025 alone. Such investments reflect not only the growth of the pharmaceutical sector but also the long-term need for highly qualified professionals who will contribute to pharmaceutical innovation, manufacturing, quality assurance, and research.

farmacijo s trdno znanstvenoraziskovalno osnovo. Takšna povezanost ostaja ena njegovih ključnih značilnosti in pomemben prispevek k razvoju farmacevtskega izobraževanja v Sloveniji.

Prihod druge generacije študentov oktobra 2026 pomeni nov korak v razvoju študija farmacije v Mariboru. Novi študenti se vključujejo v okolje, v katerem se že oblikuje akademska skupnost, prva generacija pa postopoma prevzema vlogo starejših kolegov, ki z novimi generacijami deli svoje izkušnje in pomaga soustvarjati tradicije programa. Njihova opažanja in predlogi bodo dragoceni še pri nadaljnjem razvoju programa.

Naše ambicije za prihodnost segajo dlje od uspešne izvedbe petletnega študijskega programa. Želimo razvijati živahno akademsko okolje, v katerem se izobraževanje, raziskovanje, zdravstvo in industrija medsebojno krepijo ter študente spodbujajo h kritičnemu razmišljanju, zastavljanju znanstvenih vprašanj in sodelovanju pri inovacijah. Naš cilj je, da bodo diplomanti pripravljeni ne le izpolnjevati današnja strokovna pričakovanja, temveč prihodnost farmacije zmožni tudi soustvarjati.

Prvi generaciji se zahvaljujemo za zaupanje in pripravljenost, da se skupaj z nami poda na novo pot. Prvo leto izvajanja študijskega programa je prineslo številne izkušnje, ki bodo pomembno izhodišče za njegovo nadaljnje izboljševanje. Na tej osnovi želimo skupaj s prihodnjimi generacijami graditi kakovostno in prepoznavno tradicijo farmacevtskega izobraževanja v Mariboru.

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The future of pharmacy, however, extends far beyond industry. Community and hospital pharmacies, clinical pharmacy services, and interdisciplinary healthcare teams increasingly need pharmacists who can combine scientific knowledge with clinical judgement, communication skills, and professional responsibility. The Maribor programme integrates community, clinical, and industrial pharmacy with a strong scientific and research foundation. This integration remains one of its key characteristics and an important contribution to the development of pharmaceutical education in Slovenia.

The arrival of the second generation of students in October 2026 marks another step in the development of pharmacy studies in Maribor. New students are entering an environment in which an academic community is already beginning to take shape, while the first generation is gradually assuming the role of senior students, sharing their experience and helping to establish the programme's emerging traditions. Their observations and suggestions will also be valuable for the programme's further development.

Our ambitions for the future extend beyond the successful delivery of a 5-year study programme. We aim to develop a vibrant academic environment in which education, research, healthcare, and industry reinforce one another and encourage students to think critically, ask scientific questions, and participate in innovation. Our goal is to prepare graduates not only to meet today's professional expectations, but also to help shape the future of pharmacy.

We thank the first generation for their trust and willingness to embark on this new path together with us. The first year of implementation has provided valuable experience that will serve as an important basis for the programme's continued improvement. On this foundation, together with future generations, we aim to build a high-quality and distinctive tradition of pharmaceutical education in Maribor.

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REFERENCES

1. Maver U, Krajnc I, Takač I, Maver T. Development of Pharmacy Education at the Faculty of Medicine, University of Maribor: A Chronologic Review Leading to the 2025 Accreditation. Acta Medico-Biotechnica. 2025;18(2):11–27. doi:10.18690/actabiomed.295.
2. Government of the Republic of Slovenia. Premier dr. Golob: »Vlagamo v znanje in ta investicija je plod preteklih vlaganj«. 1 July 2025. Official announcement.
3. Novartis. Novartis in Slovenia in 2025: investments, innovation, new technologies and growth in the number of employees. 4 February 2026. Official announcement.
4. European Institute of Innovation and Technology. EIT Higher Education Initiative – Call for Proposals 2025. Programme information.

Primerjava konzervativnega zdravljenja in terapevtske plazmafereze pri zdravljenju hipertrigliceridemičnega akutnega pankreatitisa

A comparison of conservative therapy and therapeutic plasma exchange in the treatment of hypertriglyceridemic acute pancreatitis

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Ključne besede:
akutni pankreatitis, hipertrigliceridemija, terapevtska plazmafereza, konzervativno zdravljenje

Key words:
Acute pancreatitis, hypertriglyceridemia, therapeutic plasma exchange, conservative treatment

Članek prispel / Received
30. 4. 2026
Članek sprejet / Accepted
7. 8. 2026

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Izvleček

Hipertrigliceridemični akutni pankreatitis (HTGP) je podtip akutnega pankreatitisa, ki nastane kot posledica izrazito povišanih serumskih trigliceridov. Najpogosteje se ta pojavlja pri mlajših moških z metabolnimi dejavniki tveganja. Možnosti zdravljenja vključujejo konzervativen pristop, ki obsega post, nadomeščanje tekočin, analgezijo in zdravljenje z inzulinom ali z ali brez nizkomolekularnega heparina, ali pa bolj invazivno metodo terapevtske plazmafereze. Ta pregledni članek obravnava patofiziologijo in klinične značilnosti akutnega HTGP, ter tudi primerja obe terapevtski strategiji s poudarkom na ključnih raziskavah in trenutnih dokazih na tem področju.

Abstract

Hypertriglyceridemic acute pancreatitis (HTGP) is a subtype of acute pancreatitis that is a result of markedly elevated serum triglycerides. HTGP most commonly occurs in younger men with metabolic risk factors. Treatment options include a conservative approach (fasting, fluid replacement, analgesia, and insulin therapy with or without low-molecular-weight heparin) or the more invasive method (therapeutic plasma exchange). This review article discusses the pathophysiology and clinical features of acute HTGP and compares the two therapeutic strategies with an emphasis on key studies and existing evidence.

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INTRODUCTION

Acute pancreatitis (AP) is an acute inflammation of the pancreas that is clinically manifested by characteristic symptoms, elevated lipase and amylase levels, and structural changes of the pancreas noted on imaging studies (1). The incidence of AP is increasing by 2%–5% annually in the United States and most of Europe, especially in the United Kingdom, Ireland, Denmark, Finland, Germany, Italy and Spain. The global incidence of AP ranges from 3–73 cases per 100,000 population per year. Differences in the incidence of AP between countries are most likely due to the regional variation in the prevalence of risk factors. AP affects men slightly more frequently (1, 2). The clinical presentation of AP typically involves sudden-onset, severe pain radiating from the epigastric or periumbilical region to the back, chest, and/or beneath the left costal margin (3). Initially, the pain is dull and mild but pain reaches a peak within 15–30 min. Pain is sometimes relieved by curling the legs towards their torso. Nausea, vomiting, and signs of peritonitis may also occur. The abdomen may be tense with clinical signs of a paralytic ileus (1). In patients with biliary pancreatitis, jaundice, and symptoms, suggest acute cholangitis. In more severe forms of pancreatitis, signs of shock, such as hypotension, may also occur (2). Less commonly, Cullen's sign (periumbilical ecchymosis), Gray-Turner's sign (ecchymosis of the flanks), both of which indicate an advanced form of necrotizing pancreatitis, and Fox's sign (ecchymosis off the upper medial thigh, often following the course of the inguinal ligament) have been reported (4).

Two of the following three criteria are required for diagnosis: characteristic pain; an increase in serum lipase/amylase levels to at least three times the upper limit; and characteristic findings of the pancreas on ultrasound, computed tomography (CT) or contrast-enhanced MRI (2, 4). Upon admission or diagnosis, it is advisable to determine the serum lactate level, which is a sign of severe AP with the development of shock (5-7). Pancreatic edema, cysts, signs of inflammation, and calcifications can be visualized by imaging studies (1, 4). The cause of AP is excessive alcohol consumption (25–35% of patients) or the presence of gallstones (30–60% of patients). The third most frequent cause of AP is hypertriglyceridemia (HTG), which is due to changes in lifestyle, dietary habits, and the increased prevalence of obesity (1, 2). Other causes of AP, such as toxins, metabolic causes, infections, injuries, medications (e.g. salicylates), congenital anomalies, autoimmune disorders, or genetic diseases, are rare. Approximately one-fifth of AP cases are classified as idiopathic acute pancreatitis [IAP] (1, 2).

The complications of AP are classified as local or systemic in accordance with the 2012 Atlantic classification (Table 1). The definition of complications is important for the classification of pancreatitis severity; the modified Marshall score can be used to identify systemic complications (4, 5, 7, 8).

HYPERTRIGLYCERIDEMIC ACUTE PANCREATITIS

Definition, epidemiology, and risk factors

Hypertriglyceridemic acute pancreatitis (HTGP) is a subtype of AP in which elevated triglycerides (TG) the cause of inflammation (8-11). The incidence of HTGP is increasing, coinciding with urbanization, a Western diet (higher proportion of fat, meat, and processed foods), reduced physical activity, and an increased prevalence of obesity, diabetes, and metabolic syndrome (10, 12).

Patients with HTGP are typically younger men with an average age of approximately 40 years, according to epidemiologic studies. Seasonal fluctuations in prevalence are also a characteristic of HTGP with peaks during the winter months and following the festive season due to the consumption of high-calorie foods and alcohol (10, 12).

Serum TG levels must exceed 10 mmol/l to establish a diagnosis of HTGP; clinically, a TG threshold of 11 mmol/l (>1000 mg/dl) is also frequently used. The risk of AP increases even at lower TG concentrations (10, 11).

The causes of HTG are classified as primary and secondary. Primary causes of HTG are less common and mainly involve genetic disorders of lipid metabolism, such as familial combined

Table 1: *Complications of acute pancreatitis according to the 2012 Atlanta classification. GDA – gastroduodenal artery, ARDS – acute respiratory distress syndrome, AKI – acute kidney injury, DIC – disseminated intravascular coagulation (9)*

Local complications	Interstitial edematous pancreatitis	< 4 weeks	Acute peripancreatic fluid collection
		> 4 weeks	Pancreatic pseudocyst
	Necrotizing pancreatitis	< 4 weeks	Acute necrotic fluid collection (ANC)
		> 4 weeks	Walled-off necrosis (WON)
		Infection of necrosis (ANC or WON)	
	Vascular complications	Thrombosis (splenic, portal veins) Pseudoaneurysm (GDA, splenic arteries)	
Systemic complications	ARDS and respiratory failure AKI DIC and other hemostasis impairments Electrolyte impairments (e.g. hypocalcemia)		

hyperlipidemia. Polymorphisms in genes, such as *APOE*, *LPL*, and *APOA5*, are associated with an increased risk of HTGP and a more severe course of the disease. *APOA5* and *LPL* mutations are more common in China than Western cohorts, which can explain the higher prevalence of HTGP (10, 12). Secondary causes, which are presented in Table 2, are more common than primary causes (10, 12).

Pathophysiology

HTGP occurs when the presence of chylomicrons and/or the breakdown of TG into free fatty acids (FFA) triggers lipotoxicity, local inflammation of the pancreas, and damage to distant organs (9, 11). The mechanism underlying the development of HTGP is based on the relationship between lipid metabolism, the inflammatory response, oxidative stress, and an imbalance in the gut microbiota. An excessive number of chylomicrons is formed at TG levels > 10–20 mmol/L, which increases plasma viscosity and causes microcirculatory ischemia in the pancreas. TG lipase hydrolyses triglycerides into FFA, which are toxic to acinar cells and the vascular endothelium in excess, triggering local necrosis, inflammation, and a systemic

Table 2: *Secondary causes of hypertriglyceridemia (10, 12)*

Secondary causes of hypertriglyceridemia	
A diet high in carbohydrates	Excessive alcohol consumption
Obesity	Pregnancy
Diabetes	Medications (estrogen, isotretinoin, beta-blockers)
Hypothyroidism	Acute hepatitis
Chronic renal failure	Systemic lupus erythematosus
Lipodystrophy	Ileal bypass surgery
Glycogen storage diseases	Stress
Monoclonal gammopathies	
AIDS: protease inhibitors	
Sepsis	

inflammatory response (9, 11, 13). FFA activate the NF-ϰB signaling pathway, leading to the release of pro-inflammatory cytokines, such as IL-6 and TNF-α, and consequently accelerated tissue damage and organ failure. Studies have shown that IL-6 levels in HTGP are up to 3 times higher than in AP with other etiologies (10-13). Genetic predispositions, such as mutations in the lipoprotein lipase gene, also have a significant role in the development of HTGP (10, 12). Another important factor in the development of HTGP is gut microbiota dysfunction, particularly a reduced presence of *Bacteroides uniformis*, which decreases taurine production and increases the release of IL-17 and the formation of neutrophil extracellular traps (NETs). Consequently, gut microbiota dysfunction leads to further activation of the NF-ϰB signaling pathway and additional damage to the pancreas. Taurine supplementation or colonization with B. *uniformis* represents a potential new therapeutic target. Ferroptosis, a specific form of cell death caused by lipid peroxidation and oxidative stress, is also thought to play an important role in the development of HTGP. The use of ferroptosis inhibitors, such as liproxstatin, has reduced pancreatic damage in experimental models, which also represents a promising therapeutic target (8, 10, 12). The pathophysiology of HTGP is presented in Figure 1.

Treatment of hypertriglyceridemic pancreatitis

Treatment of HTGP involves fasting, pain relief, fluid replacement, and lipid-lowering therapy (9, 11). Insulin and low-molecular-weight heparin (LMWH) are indicated for the further management of HTGP because insulin and LMWH stimulate lipoprotein lipase activity and the breakdown of chylomicrons.

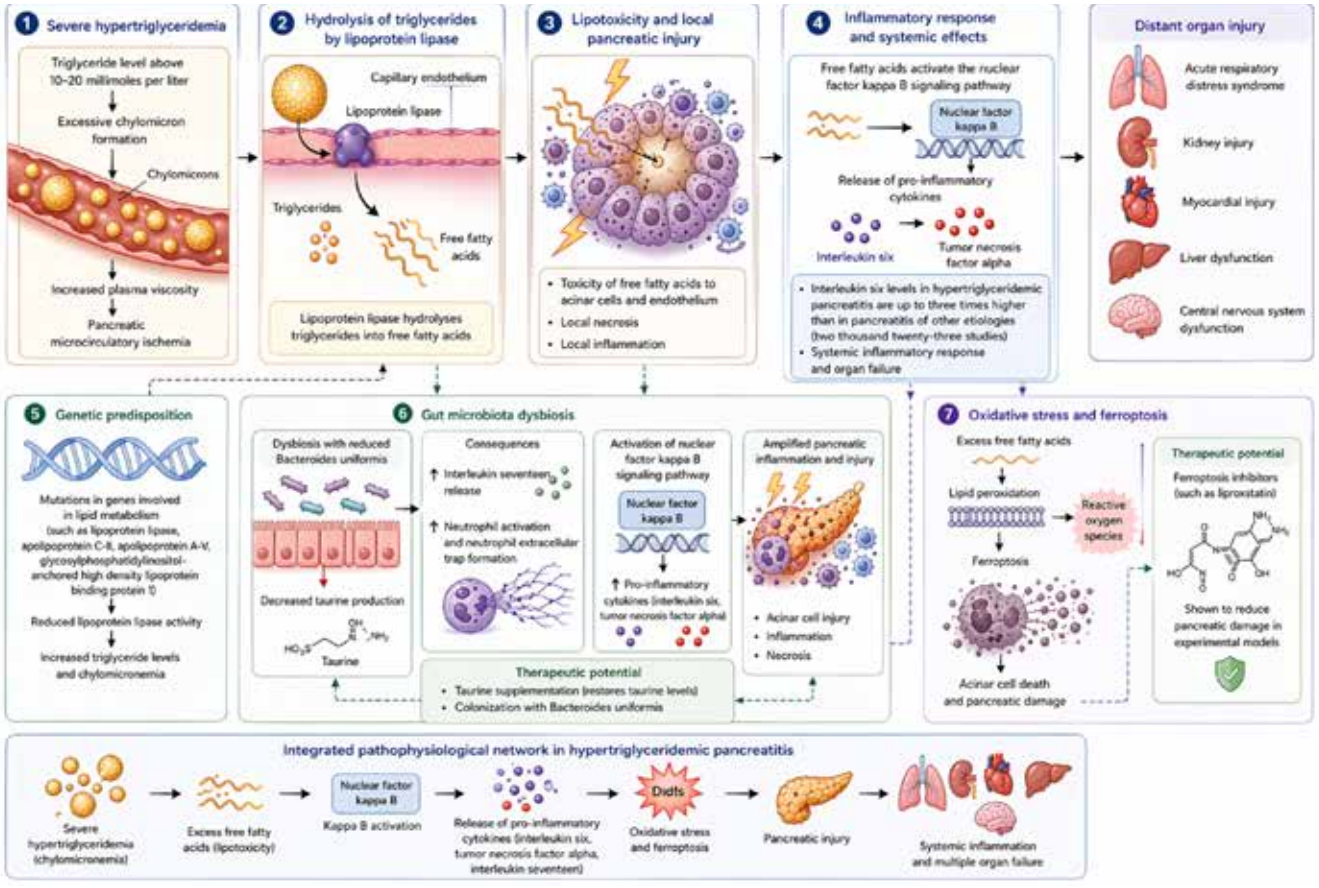

Figure 1. *Pathophysiology of hypertriglyceridemia-induced acute pancreatitis (9-13).*

However, close monitoring for hypoglycemia or bleeding is advised when insulin and LMWH are used to treat patients with HTGP (12, 14).

Therapeutic plasma exchange (TPE) facilitates the rapid removal of lipids from plasma and is used in severe cases of HTGP with a baseline TG level > 1000 mg/dL (≈ 11 mmol/L). The American Association for Apheresis classifies severe HTGP as category III, the treatment of which has not been definitively shown to be effective and is used at the clinician's discretion. Despite the efficacy, TPE has not been established as the universal method of choice due to a lack of randomized prospective studies demonstrating superiority over conservative management. Complications of TPE include infections, bleeding, and complications associated with catheter insertion. Furthermore, the method is more expensive and is not available in all healthcare facilities (14). The 2025 revised International Society of Pancreatology (IAP) and European Pancreatic Club (EPC) guidelines are used in Europe and are based on systematic literature reviews and the PICO and GRADE scoring systems. The guidelines emphasize that persistent multi-organ failure (MOF) lasting > 48 h is the most significant risk factor for mortality and recommend early enteral nutrition and treatment in appropriately equipped centers for severe forms of the disease. TPE is not recommended as part of routine treatment but represents only an additional option in severe cases of HTGP where standard treatment is insufficient (13, 15).

The overall goal of treatment for HTGP is to reduce TG levels below 5.6 mmol/L because higher levels are associated with a risk of disease recurrence. Managing metabolic disorders, particularly diabetes, obesity, and alcohol consumption, which influence relapses and complications, is also crucial for long-term outcomes (9, 11).

COMPARISON OF CONSERVATIVE TREATMENT WITH THERAPEUTIC PLASMA EXCHANGE IN HYPERTRIGLYCERIDEMIC ACUTE PANCREATITIS

Comparison of mortality

The results of several cohort studies have not shown statistically significant differences in mortality between patients treated with TPE and patients treated conservatively (14-17). Although lower TG levels were often achieved more rapidly in patients undergoing TPE, this effect did not result in improved survival or a lower incidence of MOF. Fatal outcomes were limited to patients with necrotizing pancreatitis, systemic inflammatory response syndrome (SIRS), and persistent MOF independent of the method chosen to lower TG levels (15-18). It has been reported higher absolute mortality in patient groups in which TPE was used for treatment but without statistical significance, which the authors attributed primarily to the selection of clinically more severely affected patients for this type of treatment (18). In contrast, some studies have suggested a favorable outcome with early initiation of TPE in severe forms of HTGP, while late initiation was associated with a higher risk of MOF (18-20). The most important prognostic factor for outcome in HTGP is the severity of the disease and the duration of MOF, while the use of TPE does not represent an independent factor for survival (14).

Comparison of complications

Complications occur more frequently in HTGP than in AP with other etiologies and in more severe forms of AP (21). No differences were demonstrated in the incidence of systemic HTGP complications in patients treated with conservative management and TPE between the two groups in previous studies (20-22). Similarly, no differences were detected in the incidence of mortality due to systemic complications in the context of MOF (16, 22-24). Wang et al. (20) reported no differences in the rate of improvement in MOF between the groups treated with TPE and conservative management in a cohort study, despite a faster reduction in TG levels in the TPE group. Similar

conclusions were drawn in a cohort study conducted by Amin et al. (22), in which a greater reduction in TG was achieved in the first 3 d in the group treated with TPE, yet no statistically significant changes in systemic complications or mortality were noted between the two groups. Staudacher et al. (16) cited the absence of clinical evidence that a rapid reduction in TG is associated with a better clinical outcome in HTGP as one possible explanation for the comparable outcomes of both treatments, which would account for the comparable efficacy of TPE and conservative management. Shaka et al. (25) described a higher incidence of complications in patients undergoing TPE. However, this finding may be due to a preference for TPE among patients who already had a more severe form of HTGP prior to treatment or who were unresponsive to conservative management (25). Further research is needed to compare the incidence of local complications between treatment modalities.

Length of stay in the intensive care unit

The length of stay in the intensive care unit (ICU) for patients with HTGP is associated with the severity of the clinical presentation, the timeline of treatment initiation, and the presence of complications (16, 17). Most studies investigating TPE or other blood purification methods (17-20), have focused primarily on the rate of TG reduction, the inflammatory response, and the incidence of organ failure, while the length of ICU stay was not defined as an independent outcome. The results indirectly suggested that early and effective treatment may contribute to faster patient stabilization but there is no clear evidence of a reduction in the length of stay in the ICU (16, 17, 19). Krauss et al. (26, 27) reported a median ICU stay of 3 d (range, 2–16 d) in patients treated with TPE, suggesting a shorter ICU stay with timely treatment and the absence of severe complications. At the same time, Wang et al. (16,18) reported a median of 9 d

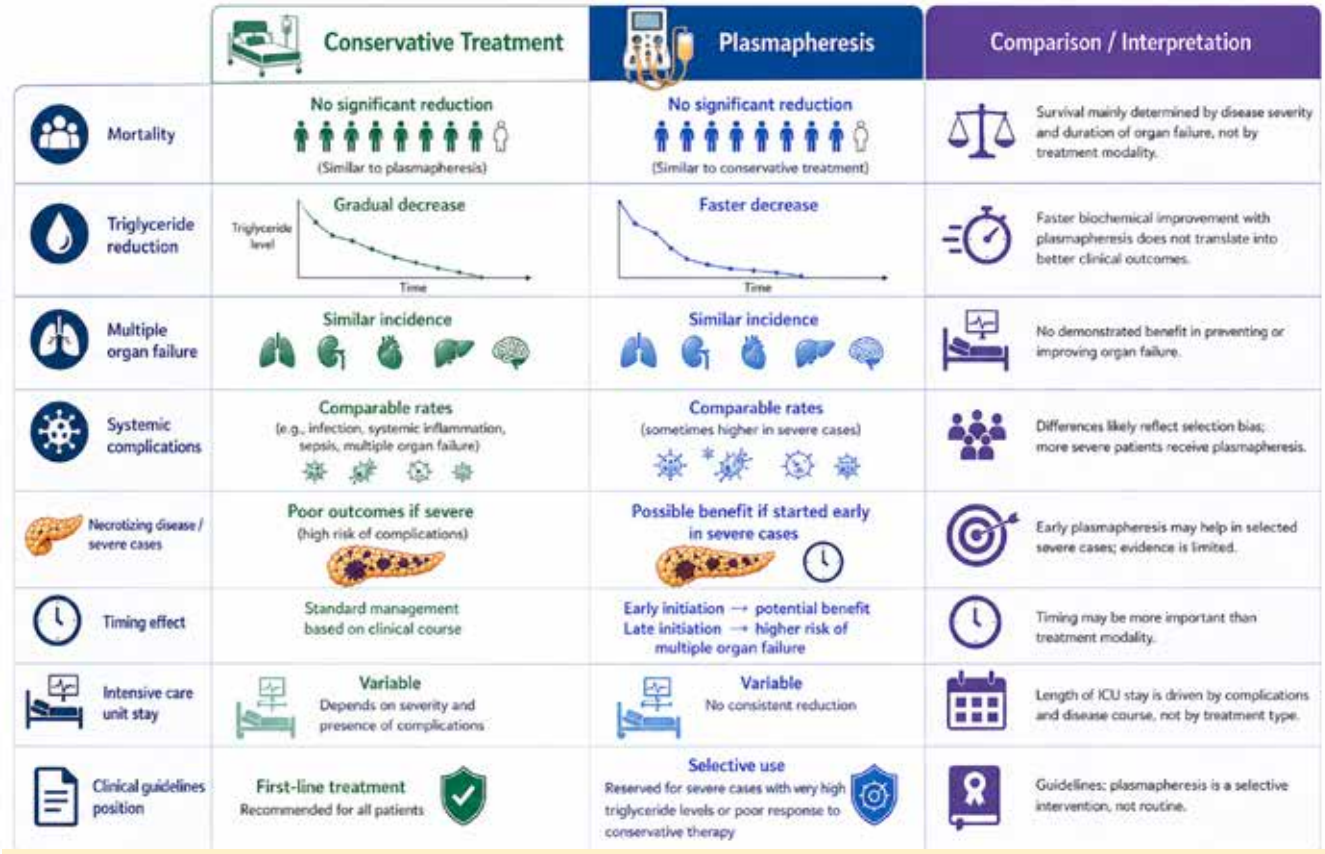

Figure 2. *Comparison between therapeutic plasma exchange (TPE) and conservative management of hypertriglyceridemic acute pancreatitis (16-20).*

with hospitalization extending to 19 d in cases of infection with multidrug-resistant microorganisms, highlighting the significant role of secondary complications. The effect of TPE on the duration of ICU hospitalization has not been demonstrated. According to existing studies, hospitalization is associated with the incidence of complications, the course of the disease, and timely treatment (16, 18). The direct comparison between both treatment approaches is presented in Figure 2.

CONCLUSION

HTGP has recently become an increasingly common cause of AP. The prognosis and course of the disease are primarily influenced by the severity of the condition and the incidence of complications, rather than a reduction in the TG level via TPE. TPE facilitates a rapid reduction in the TG level but current data do not confirm its independent effect on mortality or systemic complications, which is why the cornerstone of HTGP treatment remains a conservative approach. TPE remains a treatment option as a targeted therapy in severe forms of HTGP with very high TG levels.

REFERENCES

1. Tenner S, et al. American College of Gastroenterology Guidelines: Management of Acute Pancreatitis. Am J Gastroenterol. 2024 Mar;119(3):419-437. doi:10.14309/AJG.0000000000002645.
2. Štabuc B, Rihtaršič A. Akutni pankreatitis. Slov J Gastroenterol. 2017;21(1):5-11.
3. Yang AL, McNabb-Baltar J. Hypertriglyceridemia and acute pancreatitis. Pancreatology. 2020 Jul;20(5):795-800. doi:10.1016/j.pan.2020.06.005.
4. Mayer K, et al. Akute Pankreatitis. Anaesthesist. 2014 Mar;63(3):253-263. doi:10.1007/s00101-014-2307-x.
5. Banks PA, et al. Classification of acute pancreatitis-2012: Revision of the Atlanta classification and definitions by international consensus. Gut. 2013 Jan;62(1):102-111. doi:10.1136/gutjnl-2012-302779.
6. Ekart R, et al. Hyperlactatemia in critically ill patients with acute kidney injury treated with renal replacement therapy in the intensive care unit. BMC Nephrol. 2025;26(1):217. doi:10.1186/S12882-025-04149-5.
7. Shu W, et al. Initially elevated arterial lactate as an independent predictor of poor outcomes in severe acute pancreatitis. BMC Gastroenterol. 2020;20(1). doi:10.1186/S12876-020-01268-1.
8. Wang J, et al. Evaluating the efficacy and timing of blood purification modalities in early-stage hyperlipidemic acute pancreatitis treatment. Lipids Health Dis. 2023;22(1):208. doi:10.1186/s12944-023-01968-z.
9. Fan Z, Li J, Wu D. Hypertriglyceridemic pancreatitis: Perspectives from China. Curr Opin Gastroenterol. 2025 Sep;41(5):348-354. doi:10.1097/MOG.0000000000001123.
10. Sarr MG. 2012 revision of the Atlanta classification of acute pancreatitis. Pol Arch Med Wewn. 2013;123(3):118-124. doi:10.20452/pamw.1627.
11. Oppenlander KE, Chadwick C, Carman K. Acute pancreatitis: Rapid evidence review. Am Fam Physician. 2022 Jul;106(1):44-50.
12. Gubensek J. Acute hypertriglyceridemic pancreatitis. Slov J Gastroenterol. 2017;1:62-9.
13. Gubensek J. The role of apheresis and insulin therapy in hypertriglyceridemic acute pancreatitis: a concise review. BMC Gastroenterol. 2023;23(1):341. doi:10.1186/s12876-023-02957-3.
14. Gubensek J, Buturovic-Ponikvar J, Romozi K, Ponikvar R. Factors affecting outcome in acute hypertriglyceridemic pancreatitis treat-

ed with plasma exchange: an observational cohort study. PLoS One. 2014;9(7):e102748. doi:10.1371/journal.pone.0102748.
15. Dichtwald S, Meyer A, Zohar E, Ifrach N, Rotlevi G, Fredman B. Hypertriglyceridemia induced pancreatitis: plasmapheresis or conservative management? J Intensive Care Med. 2022;37(9):1174-8. doi:10.1177/08850666211054365.
16. IAP/APA/EPC/IPC/JPS Working Group. International Association of Pancreatology revised guidelines on acute pancreatitis 2025: supported and endorsed by the American Pancreatic Association, European Pancreatic Club, Indian Pancreas Club, and Japan Pancreas Society. Pancreatology. 2025 Sep;25(6):770-814. doi:10.1016/j.pan.2025.04.020.
17. Staudacher JJ, et al. Plasmapheresis in acute hypertriglyceridemia-induced pancreatitis: The PHIP-JuGa-Study. United European Gastroenterol J. 2025;13(10):2066-74. doi:10.1002/ueg2.70097.
18. Sahin GK, et al. Acute pancreatitis due to hypertriglyceridemia: Plasmapheresis versus medical treatment. Turk J Emerg Med. 2023;23(2):111-118. doi:10.4103/tjem.tjem_276_22.
19. Wang L, et al. Impact of therapeutic plasmapheresis on the duration of organ failure in patients with hypertriglyceridemia-associated acute pancreatitis. Ann Intensive Care. 2024;14(1):57. doi:10.1186/s13613-024-01285-3.
20. Su W, et al. Initiation time of double-filtration plasma apheresis affects the risk of persistent organ failure in hypertriglyceridaemia-induced acute pancreatitis: a retrospective study. Sci Rep. 2023;13(1):13003. doi:10.1038/s41598-023-40287-2.
21. Cao L, et al. Early plasmapheresis among patients with hypertriglyceridemia-associated acute pancreatitis. JAMA Netw Open. 2023;6(6):e2320802. doi:10.1001/jamanetworkopen.2023.20802.
22. Kiss L, et al. The effect of serum triglyceride concentration on the outcome of acute pancreatitis: systematic review and meta-analysis. Sci Rep. 2018;8(1):14096. doi:10.1038/s41598-018-32337-x.
23. Amin N, Carll T, Chela H, Kamran A, Wool GD, Daglilar E. The role of therapeutic plasma exchange in treating hypertriglyceridemia-associated acute pancreatitis: a real-world effectiveness analysis using the TriNetX Global Collaborative Network. J Clin Apher. 2025;40(4):e70053. doi:10.1002/jca.70053.
24. Piko N, Bevc S, Dovžan K, Hussein I, Ekart R. The role of therapeutic plasma exchange in hypertriglyceridemia induced pancreatitis: single-centre experience. Nephrol Dial Transplant. 2025;40(Suppl 3):gfaf116.0756. doi:10.1093/ndt/gfaf116.0756.
25. Shaka H, et al. Plasmapheresis in hypertriglyceridemia-induced acute pancreatitis. Baylor Univ Med Cent Proc. 2022;35(6):768-72. doi:10.1080/08998280.2022.2106531.
26. Huang H, Huang Z, Chen M, Okamoto K. Evaluation of the therapeutic efficiency and efficacy of blood purification in the treatment of severe acute pancreatitis. PLoS One. 2024;19(1):e0296641. doi:10.1371/journal.pone.0296641.
27. Krauß LU, et al. Therapeutic plasma exchange in ICU patients with acute hypertriglyceridemia-induced pancreatitis improves patient outcomes. Dig Dis. 2023;41(4):647-655. doi:10.1159/000529975.

Institucionalne smernice Univerzitetnega kliničnega centra Maribor za uporabo angiotenzina II kot vazopresorja tretjega reda pri bolnikih z distributivnim šokom

University Medical Centre Maribor Institutional Guidelines for the Use of Angiotensin II as a Third-Line Vasopressor in Patients with Distributive Shock

Avtor / Author

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Ključne besede:
distributivni šok, hipotenzija, vazoplegija, vazopresor, angiotenzin II, institucionalne smernice

Key words:
distributive shock; hypotension; vasoplegia; vasopressor; angiotensin II; institutional guidelines

Članek prispel / Received
2. 7. 2026

Članek sprejet / Accepted
9. 9. 2026

Naslov za dopisovanje / Correspondence
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Izvleček

Namen: *Distributivni šok, še posebej septični šok, predstavlja življenje ogrožujoče stanje, za katerega sta značilna huda vazodilatacija in hipotenzija kljub ustreznemu tekočinskemu nadomeščanju in terapiji s konvencionalnimi vazopresorji. Umrljivost zaradi septičnega šoka je visoka. Angiotenzin II je sintetični analog endogenega vazokonstriktorja, ki ga je Ameriška uprava za hrano in zdravila (angl. Food and Drug Administration, FDA) 2017 odobrila za zdravljenje ali septičnega ali drugega distributivnega šoka. Visoka cena angiotenzina II trenutno omejuje njegovo širšo uporabo. Ta dokument vsebuje na dokazih podprta priporočila za ustrezno rabo angiotenzina II pri bolnikih*

Abstract

Purpose: *Distributive shock, particularly septic shock, is a critical medical condition characterized by severe vasodilation and hypotension that persist despite adequate fluid resuscitation and conventional vasopressor therapy. Septic shock is associated with a notably high mortality rate. In 2017, the Food and Drug Administration approved angiotensin II, a synthetic analogue of the endogenous vasoconstrictor, for treating adults with septic shock or other types of distributive shock. The relatively high cost of angiotensin II currently restricts its extensive clinical application. The institutional guidelines presented in this paper provide evidence-based recommendations for the appropriate use of angiotensin II in patients with vasodi-*

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z vazodilatatornim šokom. Opredeljuje kriterije izbire bolnikov, režim odmerjanja, zahteve za spremljanje, varnostne vidike in strategije za ukinjanje zdravila, usmerjene v optimizacijo kliničnega izida.

Metode: *Opravljen je bil pregled trenutno razpoložljive literature ter analiza lastnih kliničnih izkušenj z uporabo angiotenzina II.*

Rezultati: *Raziskava ATHOS-3 je pokazala, da je uporaba angiotenzina II v povprečju pomembno povečala odziv srednjega arterijskega pritiska po treh urah v primerjavi s placebom (69,9 % proti 23,4 %, p = 0.001) in zmanjšala potrebo po kateholaminih ob sprejemljivem varnostnem profilu.*

Kasnejše raziskave iz prakse so potrdile, da pribl. dve tretjini bolnikov hemodinamsko odgovorita na uporabo angiotenzina II, pri čemer odzivni bolniki kažejo zmanjšano 30-dnevno umrljivost.

Zaključek: *Angiotenzin II je namenjen za bolnike z distributivnim šokom, pri katerih vztraja hipotenzija kljub visokim odmerkom konvencionalnih vazopresorjev (noradrenalin ≥ 0,3 mcg/kg/min in vazopresin 0,03 IE/h). Potemtakem ta predstavlja tretji fiziološki mehanizem, ki dopolnjuje terapijo s kateholamini in vazopresinom.*

latory shock. They outline patient selection criteria, dosing regimens, monitoring protocols, safety considerations, and discontinuation strategies for enhancing clinical outcomes.

Methods: *A comprehensive narrative review of the current literature was conducted, and personal clinical experiences with angiotensin II were examined.*

Results: *The ATHOS-3 trial revealed that angiotensin II significantly increased mean arterial pressure response at 3 h compared to placebo (69.9% vs. 23.4%, p = 0.001) and reduced catecholamine requirements while maintaining an acceptable safety profile. Subsequent real-world studies confirmed that approximately two-thirds of patients demonstrate hemodynamic responsiveness to angiotensin II, with responders exhibiting a decrease in 30-day mortality rates.*

Conclusion: *Angiotensin II should be used exclusively for patients with distributive shock who remain hypotensive despite receiving high-dose conventional vasopressors (norepinephrine ≥0.3 μg/kg/min and vasopressin 0.03 IE/h), representing a third physiologic pathway to complement catecholamine and vasopressin therapies.*

INTRODUCTION

Background and Rationale

Distributive shock is the predominant type of shock observed in critical care settings, characterized by peripheral vasodilation, reduced systemic vascular resistance, and hypotension occurrence despite preserved or elevated cardiac output (1,2). The majority of cases of distributive shock are attributed to septic shock, while other etiologies include neurogenic shock, anaphylactic shock, and shock associated with cardiopulmonary bypass (3,4).

Patients with severe vasodilation and persistent hypotension despite receiving high doses of conventional vasopressors show a poor prognosis, with the 30-day all-cause mortality rate exceeding 50% and approaching 100% in patients who require norepinephrine-equivalent doses greater than 1 μg/kg/min (1). Historically, the therapeutic landscape for this condition has been limited to two classes of vasopressors: catecholamines (including norepinephrine, epinephrine, phenylephrine, and dopamine) and vasopressin analogues. Both these classes show narrow therapeutic windows with clinically relevant adverse effects at high doses, including tachyarrhythmias, myocardial ischemia, splanchnic hypoperfusion, and digital ischemia (1,2). The body's physiologic response to hypotension involves the activation of three major systems: the catecholamine system, the vasopressin system, and the renin-angiotensin-aldosterone system (RAAS) (1,5–7). Until recently, therapeutic interventions have primarily targeted the first two systems (8,9).

Recent research has identified angiotensin II, a potent endogenous vasoconstrictor and the primary effector of the RAAS, as a novel therapeutic agent that more closely mimics the body's intrinsic physiologic response to shock (1,10–14).

Mechanism of Action

Angiotensin II exerts its vasopressor effects primarily by binding to angiotensin II type 1 (AT1) receptors located on vascular smooth muscle cells, leading to vasoconstriction and an increase in systemic vascular resistance (5). Angiotensin II also stimulates aldosterone release from the adrenal cortex, which subsequently promotes sodium and water retention and enhances sympathetic nervous system activity. In distributive shock, the RAAS is dysregulated through multiple mechanisms, including downregulation of AT1 receptors by proinflammatory cytokines, excessive nitric oxide production, and increased activity of angiotensin-converting enzyme 2, which degrades angiotensin II (5).

The rationale for therapeutic administration of angiotensin II is based on restoring this deficient physiologic pathway and achieving synergistic effects with catecholamines and vasopressin, potentially allowing the use of lower doses of each agent and consequently reducing the likelihood for associated adverse effects (1,10,13).

Evidence Base

The Food and Drug Administration approved angiotensin II primarily based on the results of the ATHOS-3 (Angiotensin II for the Treatment of High-Output Shock) trial, a multinational, double-blind, randomized, placebo-controlled phase 3 study (1). This trial enrolled 321 patients with vasodilatory shock who received high-dose vasopressors (norepinephrine equivalent >0.2 μg/kg/min). The primary endpoint—mean arterial pressure (MAP) response at 3 h was operationalized as either an increase of ≥10 mmHg or the attainment of MAP ≥75 mmHg without increasing background vasopressors—was successfully reached by 69.9% of angiotensin II-treated patients compared to 23.4% of placebo recipients (odds ratio (OR): 7.95, 95% confidence interval (CI): 4.76–13.3, p = 0.001) (1).

Secondary outcomes indicated a notable enhancement in cardiovascular Sequential Organ Failure Assessment scores at 48 h in the angiotensin II group (-1.75 vs. -1.28, p = 0.01) and a substantial reduction in catecholamine requirements (1). Although the 28-day mortality rate showed a favorable trend (46% vs. 54%, hazard ratio (HR): 0.78, 95% CI: 0.57–1.07), this observation was not statistically significant, probably because the study was underpowered for mortality outcomes (1).

Post-hoc analyses revealed that patients with elevated baseline renin concentrations (exceeding the study median) exhibited a significant reduction in the mortality rate following angiotensin II therapy (50.9% vs. 69.9%, HR: 0.56, 95% CI: 0.35–0.88, p = 0.012) (6). Real-world postmarketing data from 270 patients across five United States tertiary centers confirmed that 67% of patients demonstrated hemodynamic responsiveness, with responders showing a reduction in the 30-day mortality rate (HR: 0.50, 95% CI: 0.35–0.71, p = 0.001) (2). A similar outcome was noted in our retrospective cohort of patients (15).

PATIENT SELECTION CRITERIA

Indications

Angiotensin II is indicated for the management of hypotension in adult patients with distributive shock (14,16,17). Specific clinical scenarios appropriate for the initiation of angiotensin II therapy include the following:

Primary Indication:

- Distributive shock (septic, neurogenic, refractory anaphylactic, post-cardiopulmonary bypass or vasoplegia subsequent to major surgical interventions) accompanied by persistent hypotension
- No significant component of cardiogenic, hemorrhagic, and/or obstructive shock
- Adequate fluid resuscitation
- Receiving norepinephrine equivalent dose ≥0.3 μg/kg/min
- MAP at 65 mmHg or inability to achieve target MAP

Contraindications

Absolute contraindication is known hypersensitivity to angiotensin II or any component of the formulation.

Special Populations

Patients on chronic angiotensin converting enzyme inhibitors (ACEI):

- May show enhanced responsiveness to angiotensin II (18)
- Consider earlier initiation and potentially lower doses
- Monitor for exaggerated blood pressure response

Patients on chronic angiotensin receptor blockers (ARBs):

- May exhibit attenuated responsiveness to angiotensin II (18); however, a previous observational study by Pettit et al. revealed no difference regarding angiotensin II dose and treatment duration between patients receiving ARBs and those not treated with ARBs (19).
- May require higher doses to achieve hemodynamic targets
- Consider alternative vasopressor strategies if the patient shows inadequate response

Patients with acute kidney injury (AKI) receiving renal replacement therapy (RRT):

- Post-hoc analyses suggest potential mortality benefit in AKI patients receiving RRT (20)
- No dose adjustment required for renal dysfunction

DOSING AND ADMINISTRATION

Preparation

Formulation: Angiotensin II is supplied as a sterile solution requiring dilution prior to administration (16,17).

Dilution Instructions:

1. Dilute angiotensin II sterile solution in 250 mL of 0.9% normal saline only.
2. Visually inspect for any particulate matter and discoloration before administration.
3. Discard vial and any unused portion after initial use.

Storage (16,17):

- Undiluted vials: Refrigerate at 2–8°C
- Diluted solution: May be stored at room temperature (20–25°C) or refrigerated (2–8°C)
- Prepared solution: discard after 24 h

Initial Dosing (16,17):

Starting dose: 20 ng/kg/min through continuous intravenous (IV) infusion

Route of Administration:

- Administration through a central venous catheter is recommended and strongly preferred (17).
- Peripheral administration (IV access through the cubital fossa) may be considered if central access is unavailable (21).

Titration Protocol:

1. Assess blood pressure response approximately every 5 min.
2. Titrate by increments of 5–10 ng/kg/min to achieve target MAP every 5 min.
3. Do not exceed the maximum dose of 80 ng/kg/min.
4. Reduce background vasopressor doses during initial titration.
5. Prioritize weaning catecholamines to minimize adverse effects (immunosuppression, arrhythmia, cardiomyocyte injury, or myocardial stress) (17,22–24).
6. Titrate angiotensin II to the lowest effective dose while maintaining hemodynamic stability.
7. Reassess hemodynamic status and vasopressor requirements every 1–2 h.

Duration of Therapy

Standard Duration (1):

- Initial infusion period: Up to 48 h
- May be continued beyond 48 h if clinically indicated (maximum up to 7 days)

Discontinuation Protocol:

1. Begin weaning when underlying shock etiology is being resolved.
2. Reduce dose by decrements of around 5 ng/kg/min every 5–15 min according to blood pressure response (16).
3. If background vasopressor requirements increase to >0.1 µg/kg/min norepinephrine equivalent after discontinuation, consider resuming angiotensin II therapy (1).

MONITORING REQUIREMENTS

Hemodynamic Monitoring

Continuous Monitoring:
- Arterial blood pressure through an arterial line
- Heart rate and cardiac rhythm
- Oxygen saturation

Intermittent Assessment:
- MAP reading every 5 min during initial titration and every 15–30 min thereafter once the patient is stable
- Cardiac output/cardiac index (to be considered)
- Central venous pressure (to be considered)
- Mixed venous oxygen saturation (to be considered)

Laboratory Monitoring

Baseline (Prior to Treatment Initiation):
- Complete blood count
- Comprehensive biochemistry panel (electrolytes, renal function, liver function, and troponin level)
- C-reactive protein, procalcitonin, and interleukin-6 levels in patients with septic shock
- Lactate level
- Arterial blood gas analysis
- Coagulation studies
- Sample for renin concentration measurement to be collected immediately before angiotensin II infusion

Ongoing Monitoring:
- Standard Intensive Care Unit (ICU) laboratory examination
- Renin level measurement at 6 h after the initiation of angiotensin II infusion

Clinical Monitoring

Assessment for Adverse Effects:
- Cardiac: Tachyarrhythmias, atrial fibrillation, ventricular tachycardia, and myocardial ischemia
- Vascular: Digital ischemia, skin mottling, and peripheral cyanosis
- Thrombotic: Clinical signs of deep venous thrombosis or pulmonary embolism, signs of mesenteric ischemia, and signs of cardiac ischemia
- Respiratory: Bronchospasm and worsening oxygenation
- Neurologic: Altered mental status and focal deficits

Organ Perfusion Assessment:
- Urine output (target ≥ 0.5 mL/kg/h)
- Skin perfusion and capillary refill
- Mentation and neurologic status
- Gastrointestinal function (assessment for mesenteric ischemia)

SAFETY CONSIDERATIONS

Adverse Event Profile

The ATHOS-3 trial demonstrated that the safety profile of angiotensin II was comparable with that of placebo, with serious adverse events reported in 60.7% of angiotensin II-treated patients versus 67.1% of placebo-treated patients (1). Distinguishing between adverse effects attributable to the underlying critical illness and those related to angiotensin II therapy poses a considerable challenge.

Common Adverse Events (≥5%):
- Tachyarrhythmias (similar rates to placebo treatment)
- Atrial fibrillation (similar rates to placebo treatment)
- Hyperkalemia (monitor potassium levels closely)
- Thrombocytopenia

Serious Adverse Events of Special Interest:
- Venous and arterial thromboembolic event rates of 12.9% with angiotensin II therapy vs. 5.1% with placebo treatment were reported in the ATHOS-3 trial (1); however, these events occurred very rarely in the angiotensin II therapy group in subsequent observational studies (approximately 1.5%) (2,25).
- Arrhythmias: 10% occurrence rate in postmarketing study (2)

Rare but Serious Events (7):
- Exacerbation of heart failure in patients with left ventricular dysfunction
- Bronchoconstriction in patients with reactive airway disease
- Cerebral hemorrhage (one case reported in a systematic review article)

Drug Interactions

Other Vasopressors:

- Potential synergistic effects with catecholamines and vasopressin (1)
- Allows reduction of catecholamine dose, potentially decreasing toxicity
- No specific drug–drug interactions identified

INTEGRATION INTO VASOPRESSOR ALGORITHM

Recommended Vasopressor Sequence

First-Line Therapy:

Norepinephrine: Initial vasopressor of choice for treating distributive shock. Titrate to MAP ≥65 mmHg.

Second-Line Therapy (if norepinephrine ≥0.2 µg/kg/min): Add vasopressin at the fixed dose of 0.03 units/min.

Third-Line Therapy: Administer angiotensin II if MAP is 65 mmHg despite treatment with norepinephrine equivalent ≥0.3 µg/kg/min.

Combination Therapy Considerations

Angiotensin II is primarily recommended for use in combination with other vasopressors, not as monotherapy. The ATHOS-3 trial enrolled patients receiving a median of 2–3 vasopressors at baseline (1). Optimal combination strategies include the following:

- Angiotensin II + Norepinephrine + Vasopressin: Most frequently used combination, leveraging all three physiologic pathways
- Catecholamine-sparing approach: Use angiotensin II to reduce the doses of norepinephrine/epinephrine, which could minimize tachyarrhythmias, meet myocardial oxygen demand, and attenuate catecholamine-induced immunosuppression.

SPECIAL CLINICAL SCENARIOS

Septic Shock

Septic shock was reported in 91% of patients in the ATHOS-3 trial (1). Angiotensin II is a particularly appropriate treatment agent for septic shock patients with:

- Catecholamine-resistant hypotension;
- Elevated lactate levels with concern for catecholamine-induced tissue hypoperfusion; and
- Tachyarrhythmias limiting catecholamine escalation.

Post-Cardiopulmonary Bypass Vasoplegia

Vasoplegic syndrome following cardiac surgery affects 5–25% of patients and is associated with significant morbidity. Angiotensin II may be considered in post-cardiopulmonary bypass vasoplegia refractory to conventional vasopressors, particularly for patients receiving ACEI, if hyperreninemia is present, or in patients at risk for AKI and de novo atrial fibrillation (17–19), although data are limited to case series and observational studies (13).

Neurogenic Shock

Patients with neurogenic shock due to spinal cord injury, severe traumatic brain injury, or subarachnoidal hemorrhage may respond to angiotensin II therapy, although there is limited evidence. Treatment with angiotensin II could be considered in patients with refractory hypotension despite receiving adequate fluid resuscitation and conventional vasopressors.

AKI

Post-hoc analyses suggest potential benefit in patients with AKI, particularly those receiving RRT (20). Angiotensin II does not require dose adjustment for renal dysfunction and may help maintain renal perfusion pressure (17,26).

QUALITY ASSURANCE AND DOCUMENTATION

Required Documentation

Institutional angiotensin II use form should be completed for each patient receiving angiotensin II therapy.

COST CONSIDERATIONS

Angiotensin II is substantially more expensive than conventional vasopressors. Cost-effectiveness analyses of angiotensin II are limited, and its clinical

benefit compared to traditional agents has not been definitively established (3). Present institutional guidelines aim to balance currently available evidence of clinical benefit versus cost considerations:

- Potential benefits: reduced catecholamine toxicity, improved hemodynamics, and possible mortality benefits in select patients
- Costs: Drug acquisition costs substantially higher than those of norepinephrine, vasopressin, or epinephrine
- Resource utilization: Potential to reduce ICU length of stay if the patient shows more rapid resolution of shock

CONCLUSION

Angiotensin II is a novel therapeutic agent for patients with distributive shock. By targeting the RAAS, angiotensin II provides a third physiologic pathway to restore blood pressure and reduce catecholamine requirements. Evidence from the ATHOS-3 trial and real-world studies demonstrates that angiotensin II offers considerable hemodynamic benefits with an acceptable safety profile. These institutional guidelines provide a framework for appropriate patient selection, dosing, monitoring, and safety management, while considering the current cost of angiotensin II. Future research should focus on identifying biomarkers to predict response, optimal treatment initiation timing, and long-term outcomes to further refine the role of angiotensin II in the management of patients with distributive shock.

REFERENCES

1. Khanna A, English SW, Wang XS, Ham K, Tumlin J, Szerlip H, et al. Angiotensin II for the Treatment of Vasodilatory Shock. N Engl J Med. 2017;377(5):419–30. doi:10.1056/NEJMoa1704154
2. Wieruszewski PM, Wittwer ED, Kashani KB, Brown DR, Butler SO, Clark AM, et al. Angiotensin II Infusion for Shock: A Multicenter Study of Postmarketing Use. Chest. 2020;159(2):596–605. doi:10.1016/j.chest.2020.08.2074
3. Allen JM, Gilbert BW. Angiotensin II: A New Vasopressor for the Treatment of Distributive Shock. Clin Ther. 2019;41(12):2594–610. doi:10.1016/j.clinthera.2019.09.014
4. Chow JH, Abuelkasem E, Sankova S, Henderson RA, Mazzeffi MA, Tanaka KA. Reversal of Vasodilatory Shock: Current Perspectives on Conventional, Rescue, and Emerging Vasoactive Agents for the Treatment of Shock. Anesth Analg. 2020;130(1):15. doi:10.1213/ANE.0000000000004343
5. Senatore F, Balakumar P, Jagadeesh G. Dysregulation of the renin-angiotensin system in septic shock: Mechanistic insights and application of angiotensin II in clinical management. Pharmacol Res. 2021;174:105916. doi:10.1016/j.phrs.2021.105916
6. Bellomo R, Forni LG, Busse LW, McCurdy MT, Ham KR, Boldt DW, et al. Renin and Survival in Patients Given Angiotensin II for Catecholamine-Resistant Vasodilatory Shock. A Clinical Trial. Am J Respir Crit Care Med. 2020;202(9):1253–61. doi:10.1164/rccm.201911-2172OC
7. Busse LW, Wang XS, Chalikonda DM, Finkel KW, Khanna AK, Szerlip HM, et al. Clinical Experience With IV Angiotensin II Administration: A Systematic Review of Safety. Crit Care Med. 2017;45(8):1285–94. doi:10.1097/CCM.0000000000002441
8. Jammer I, Martin P, Wunsch H, Debouche S, Harlet P, Moonesinghe R, et al. Vasopressor use after noncardiac surgery: an international observational study. Br J Anaesth. 2025;135(6):1609–17. doi:10.1016/j.bja.2025.07.034
9. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med. 2021;47(11):1181–247. doi:10.1007/s00134-021-06506-y
10. Kalamar Ž, Gorenjak M, Landoni G, Markota A. Early multimodal vasopressor strategy in septic shock (TRICYCLE)-Study protocol for a randomized controlled clinical trial. PloS One. 2025;20(8):e0331304. doi:10.1371/journal.pone.0331304
11. Bellomo R, Zarbock A, Landoni G. Angiotensin II. Intensive Care Med. 2024;50(2):279–82. doi:10.1007/s00134-023-07290-7
12. Möller Petrun A, Markota A. Angiotensin II—Real-Life Use and Literature Review. Medicina (Mex). 2024;60(9):9. doi:10.3390/medicina60091483
13. Möller Petrun A, Bajec KB. Patofiziologija vazoplegije po kirurškem posegu. Slov Med J. 2025;94(9–10):268–74. doi:10.6016/ZdravVestn.3547
14. Bajec KB, Möller Petrun A. Successful treatment of refractory anaphylactic shock with angiotensin II: A case report. Eur J Anaesthesiol Intensive Care. 2026;5(3):e0104. doi:10.1097/EA9.0000000000000104
15. Möller Petrun A, Gorenjak M, Svenšek F, Matković Lonzarić N, Strdin Košir A, Cvikl Knehtl M, et al. Real-world Experience of Angiotensin II and Renin Usage in Patients With Distributive Shock:A Single-center Descriptive Study. J Cardiothorac Vasc Anesth. 2025;39(12):3359–67. doi:10.1053/j.jvca.2025.08.044
16. Research C for DE and. Drug Trials Snapshots: GIAPREZA. FDA [Internet]. 2019 Sep 2 [cited 2023 Dec 6]. Available from: https://

www.fda.gov/drugs/drug-approvals-and-databases/drug-trials-snapshots-giapreza
17. DailyMed - GIAPREZA- angiotensin ii injection [Internet]. [cited 2026 Mar 31]. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=c265d69a-3efe-4107-9a9e-e6fd3d531c48
18. Leisman DE, Handisides DR, Busse LW, Chappell MC, Chawla LS, Filbin MR, et al. ACE inhibitors and angiotensin receptor blockers differentially alter the response to angiotensin II treatment in vasodilatory shock. Crit Care. 2024;28:130. doi:10.1186/s13054-024-04910-6
19. Pettit N, Benken J, Valdepeñas B, Gandhi N, Alyousef R, Benken S. Angiotensin Receptor Blockade Does Not Decrease Synthetic Angiotensin II (Giapreza®) Effectiveness in Perioperative Hypotension Surrounding Kidney Transplant. Biomedicines. 2025;13(6):1442. doi:10.3390/biomedicines13061442
20. Rodriguez R, Fernandez EM. Role of angiotensin II in treatment of refractory distributive shock. Am J Health-Syst Pharm AJHP Off J Am Soc Health-Syst Pharm. 2019;76(2):101–7. doi:10.1093/ajhp/zxy014
21. Munroe ES, Co IN, Douglas I, Hyzy R, Khan A, Nelson K, et al. Peripheral Vasopressor Use in Early Sepsis-Induced Hypotension. JAMA Netw Open. 2025;8(8):e2529148. doi:10.1001/jamanetworkopen.2025.29148
22. Guarracino F, Habicher M, Treskatsch S, Sander M, Szekely A, Paternoster G, et al. Vasopressor Therapy in Cardiac Surgery-An Experts' Consensus Statement. J Cardiothorac Vasc Anesth. 2021;35(4):1018–29. doi:10.1053/j.jvca.2020.11.032
23. Liu Y, Chen J, Fontes SK, Bautista EN, Cheng Z. Physiological and pathological roles of protein kinase A in the heart. Cardiovasc Res. 2022;118(2):386–98. doi:10.1093/cvr/cvab008
24. Stolk RF, Kox M, Pickkers P. Noradrenaline drives immunosuppression in sepsis: clinical consequences. Intensive Care Med. 2020;46(6):1246–8. doi:10.1007/s00134-020-06025-2
25. Kotani Y, Lezzi M, Murru CP, Khanna AK, Zarbock A, Bellomo R, et al. The Efficacy and Safety of Angiotensin II for Treatment of Vasoplegia in Critically Ill Patients: A Systematic Review. J Cardiothorac Vasc Anesth. 2024;S1053-0770(24)00996-0. doi:10.1053/j.jvca.2024.12.022
26. Tumlin JA, Murugan R, Deane AM, Ostermann M, Busse LW, Ham KR, et al. Outcomes in Patients with Vasodilatory Shock and Renal Replacement Therapy Treated with Intravenous Angiotensin II. Crit Care Med. 2018;46(6):949–57. doi:10.1097/CCM.0000000000003092

Morfološka raznolikost zgornjih centralnih stalnih sekalcev ter njihova povezava z zaznavanjem estetike, funkcije in samozavestjo

Different morphologic shapes of permanent maxillary central incisors and the association with aesthetics perception, self-reported function, and self-esteem

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Ključne besede:
zgornji centralni stalni sekalec, oblika krone, samopodoba, funkcija, estetika

Key words:
maxillary central incisors; crown shapes; self-esteem; function; aesthetics

Članek prispel / Received
14. 2. 2026
Članek sprejet / Accepted
19. 6. 2026

Naslov za dopisovanje / Correspondence
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Izvleček

Namen: *Namen raziskave je bil ugotoviti, katera morfološka oblika zgornjih stalnih centralnih sekalcev prevladuje v Podravski regiji Slovenije, ter tudi oceniti njen vpliv na estetiko, funkcijo in samozavest preiskovancev.*
Metode: *Analizirali smo 184 študijskih modelov, da bi določili najpogostejšo obliko krone zgornjih centralnih stalnih sekalcev. Poleg tega smo podatke zbrali s prilagojenim vprašalnikom, ki ga je izpolnilo 328 anketirancev. Podatke smo analizirali in vrednosti p < 0,05 smo šteli za statistično značilne.*
Rezultati: *Rezultati so pokazali, da je bila najpogostejša oblika krone zgornjih stalnih centralnih sekalcev trikotna (47,3 %); sledile so podolgovata (36,4 %), kvadratna (13,6 %) in ovalna oblika (2,7 %). Med spoloma ni bilo statistično značil-*

Abstract

Purpose: *The aim of the present study was to evaluate which morphologic shape of permanent maxillary central incisors predominates in the Podravska region of Slovenia and the association with aesthetic perception, self-reported function, and self-esteem.*
Methods: *A total of 184 study casts were analyzed to determine the crown shape of permanent maxillary central incisors. Data were also collected about the influence of crown shapes on aesthetics and function using a modified questionnaire, which was completed by 328 respondents. Data were analyzed and P-values < 0.05 were considered statistically significant.*
Results: *The most frequent maxillary central incisor crown shapes were triangular (46.7%), followed by elongated (35.9%), square (14.1%), and ovoid (3.3%) without a statistically signifi-*

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nih razlik. Podolgovata oblika zgornjega centralnega stalnega sekalca je bila med vsemi štirimi morfološkimi oblikami ocenjena kot estetsko najbolj privlačna. Večina udeležencev (99,1 %) je menila, da imajo zobje vpliv na samopodobo. 190 (57,9 %) preiskovancev je bilo v ortodontski obravnavi, pri čemer se jih je 46 % za zdravljenje odločilo zaradi okrnjene estetike in funkcije. Večina anketirancev (93,9 %) je zanikala težave z izraščanjem zgornjih centralnih sekalcev v otroštvu. Deset (3 %) udeležencev je imelo govorne motnje zaradi nepravilnega položaja zgornjih centralnih sekalcev, od tega jih je šest obiskovalo logopeda. Križni griz je bil med ponujenimi možnostmi najmanj estetski položaj sekalcev, pri čemer je bila razlika statistično značilna.

Zaključki: *Razumevanje morfologije zgornjih stalnih centralnih sekalcev lahko prispeva k uspešnejši obravnavi na področju restavrativnega zobozdravstva, ortodontije in protetike ter doprinese k izboljšanju videza zob, njihove funkcije in estetske podobe obraza.*

cant difference between sexes. The elongated maxillary central incisor ranked the most liked out of all four morphologic shapes. Most of the participants (99.1 %) believed that teeth have an impact on self-esteem. Overall, 190 (57.9%) participants had undergone orthodontic treatment, 46% of who were due to compromised aesthetics and function. Most of the respondents (93.9%) denied having problems with maxillary central incisor eruption during childhood. Ten (3%) participants had speech disorders due to the incorrect position of the maxillary central incisors, six of who were required to see a speech therapist. The crossbite was the least liked position of the incisor among the selected options with a statistically significant difference (p = 0.001).

Conclusions: *Understanding the morphology of permanent maxillary central incisors is important for pediatric and restorative dentistry. For orthodontists who provide optimal treatment planning, understanding the morphology of permanent maxillary central incisors may be useful to achieve improved dental appearance, function, and facial aesthetic.*

INTRODUCTION

The maxillary central incisor is positioned along the median plane, making the maxillary central incisor the most visible tooth, and as a result the maxillary central incisor has a key role in facial and smile aesthetics (1). The maxillary central incisor erupts, on average, between 7 and 8 years of age (1, 2) and root development is completed by 10 years of age (1). When a primary tooth is lost, the permanent tooth is at the eruption point and in the proper position to replace its predecessor (1,3). There may be delays in the eruption of the permanent maxillary central incisor due to various factors (4-6).

The shape of the permanent maxillary central incisor varies, often reflecting the shape of the face (7, 8). Some researchers have reported that tooth size and shape vary based on ethnicity, sex, and dietary habits (9). Indeed, some researchers have even identified differences among individuals of the same ethnicity (10-12). Williams classified maxillary central incisor dental crowns into three basic shapes: square; ovoid; and triangular (13). Over the ensuing years, various classifications of maxillary central incisor dental crowns have been reported (14). One of the maxillary central incisor dental crowns was developed by Gašperšič et al. (7), who added an elongated shape to the Williams classification.

The chisel-shaped form of incisors has a crucial role in functions, such as cutting or tearing food, supporting the lips, and facilitating speech [voice formation] (7, 15). The absence of a permanent maxillary central incisor significantly affects facial aesthetics as well as function, speech, and psychological well-being due to the specific location of the incisor (16-19). When a speech error is identified alongside a morphologic dental irregularity, further treatment involving a speech therapist and an orthodontist is required (20, 21). Dental developmental anomalies, such as a palatal pit, palatocervical groove, and talon cusp, can

be present in the maxillary central incisor (1, 22-26). The permanent maxillary central incisor has an important role in aesthetics and function, as well as phonetics and psychosocial well-being. Therefore, the aim of this study was to determine which morphologic shape of the maxillary central incisor predominates in the Podravska region of Slovenia, as well as the potential impact of dental appearance on self-esteem. In addition, we determined whether individuals had undergone orthodontic treatment, and if so, the reasons for orthodontic treatment. Furthermore, we were also interested in understanding individual's aesthetic perception regarding various morphologic shapes of the permanent maxillary central incisor as well as different positions of the permanent maxillary central incisor in the dental arch. Furthermore, we determined whether individuals had experienced issues with eruption of the permanent maxillary central incisors, speech difficulties, or had visited a speech therapist.

MATERIALS AND METHODS

The present study was reviewed and approved by the Institutional Review Board of Community Healthcare Centre Maribor (No. 02/010/03-12/01/24) and conducted between 1 October 2023 and 20 October 2025 in accordance with the Declaration of Helsinki at the Orthodontic Department of Community Healthcare Centre Maribor. The material for the present study included records collected by examining consecutive study casts and using a modified questionnaire (Table 1).

Study casts

The study casts of 200 patients who were treated in the Orthodontic Department of the Community Healthcare Centre were reviewed. Study casts were consecutively selected based on the availability of records and fulfillment of inclusion criteria. The inclusion criteria were fully erupted permanent central incisors and high-quality study casts that allowed for determining the shape of the maxillary central incisors. The exclusion criteria were anomalies in the oral cavity (for example, hypodontia, cleft lip/palate, or any syndrome) that could affect the shape and size of the maxillary central incisor, fillings (restorations), and enamel striping or abrasion, as well as impacted or previous loss of a maxillary central incisor due to trauma, caries, or periodontal disease. Of these 200 study casts, five were excluded because of poor quality, 10 were excluded because the first maxillary central incisors were not fully erupted, and one was excluded because of maxillary lateral incisor hypodontia. Thus, a total of 184 study cases were included in the current study (Figure 1).

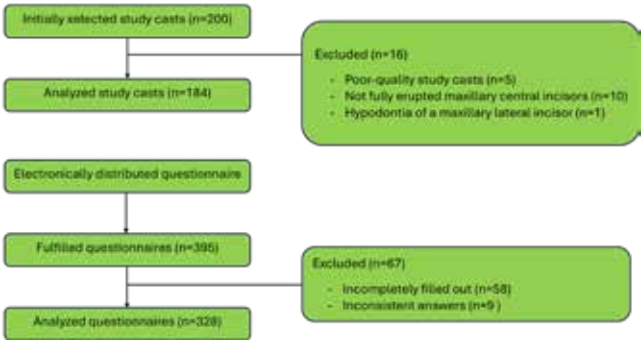

Figure 1. *Flow chart.*

The crown shapes of the maxillary central incisors were classified as square, elongated, ovoid, and triangular by a single examiner (Figure 2). Prior to analysis, the examiner re-evaluated 30 randomly selected study casts after a 2-week interval.

A square maxillary central incisor (Figure 2a) has nearly parallel mesial proximal surfaces with a mesio-incisal angle that is an approximate right angle. Both maxillary central incisors have a proximal contact surface which is longer by one-half the length of the crown. The cervical line is wide and shaped like the letter 'U'. The incisal edge is straight and has a wider mesiodistal distance than the ovoid shape. The width and length of the crown are similar.

An elongated maxillary central incisor (Figure 2b) appears similar to the square shape, except the proximal surfaces are longer.

An ovoid maxillary central incisor (Figure 2c) has

Table 1. *Modified questionnaire*

Question	Answer
1. Gender Please mark one variable	
male	
female	
2. Age Please mark one variable	
20 – 30 years	
30 – 40 years	
40 – 50 years	
50 – 60 years	
3. Status Please mark one variable	
Students of dental/general medicine	
Professionals in dentistry	
Laypersons	
4. What's your opinion about central incisors shape? Answers were given on a 4-point visual analogue scale (VAS) ranging: 1 (most liked), 2 (more like), 3 (liked), 4 (least liked). Please mark one grade on the scale	
square	
elongated	
ovoid	
triangular	
5. Do you think teeth play a role in a person's self – esteem? Please mark one variable	
Yes	
No	
6. Have you ever been in orthodontic treatment? Please mark one variable	
Yes	
No	
No, but I would want to.	
If you answered yes, what was the reason? Please mark one variable	

Question	Answer
Compromised aesthetics (positional irregularities of teeth)	
Incorrect bite	
Compromised function	
I do not remember	
7. Question for dentists: What is the most common reason to referring patient to an orthodontist? Please mark one variable	
Positional irregularities of teeth	
Incorrect bite	
Compromised function	
At the request of parents	
8. What is your opinion on different teeth positions? Answers were given on a 4-point visual analogue scale (VAS) ranging 1 (most liked), 2 (more like), 3 (liked), 4 (least liked) Please mark one grade on the scale	
crowding	
diastema mediana	
cross bite	
spacing	
9. Did you have any issues with the eruption of permanent upper central incisors during childhood?	
Yes	
No	
10. Did you have any problems with speech due to incorrect position of incisors?	
Yes	
No	
11. If you answered yes, did you visit a speech therapist? **Please mark one variable**	
Yes	
No	

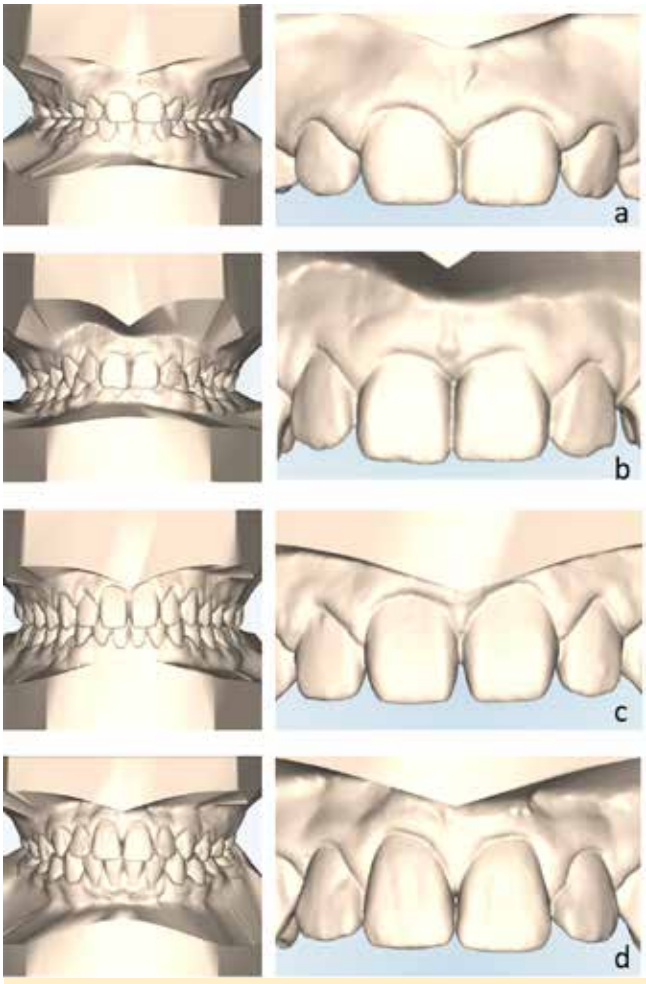

Figure 2. *Various crown morphologies evaluated as square (a), elongated (b), ovoid (c), and triangular (d).*

rounded mesial and distal proximal surfaces. The proximal contact surface is short and in the middle of the proximal surface. Therefore, a triangle usually appears below the contact of the two central incisors. The cervical line is shaped like the letter 'U', which is like the square-shaped maxillary central incisor but more ovoid.

A triangular maxillary central incisor (Figure 2d) has mesial and distal proximal surfaces that converge cervically. The proximal contact surface of both maxillary central incisors is approximately one-half the length of the crown near the incisal edge. Therefore, the interdental papilla is located more incisal than the other shapes. The cervical line is shorter than the incisal edge and slightly V-shaped. The mesial and distal incisal angles are slightly sharp.

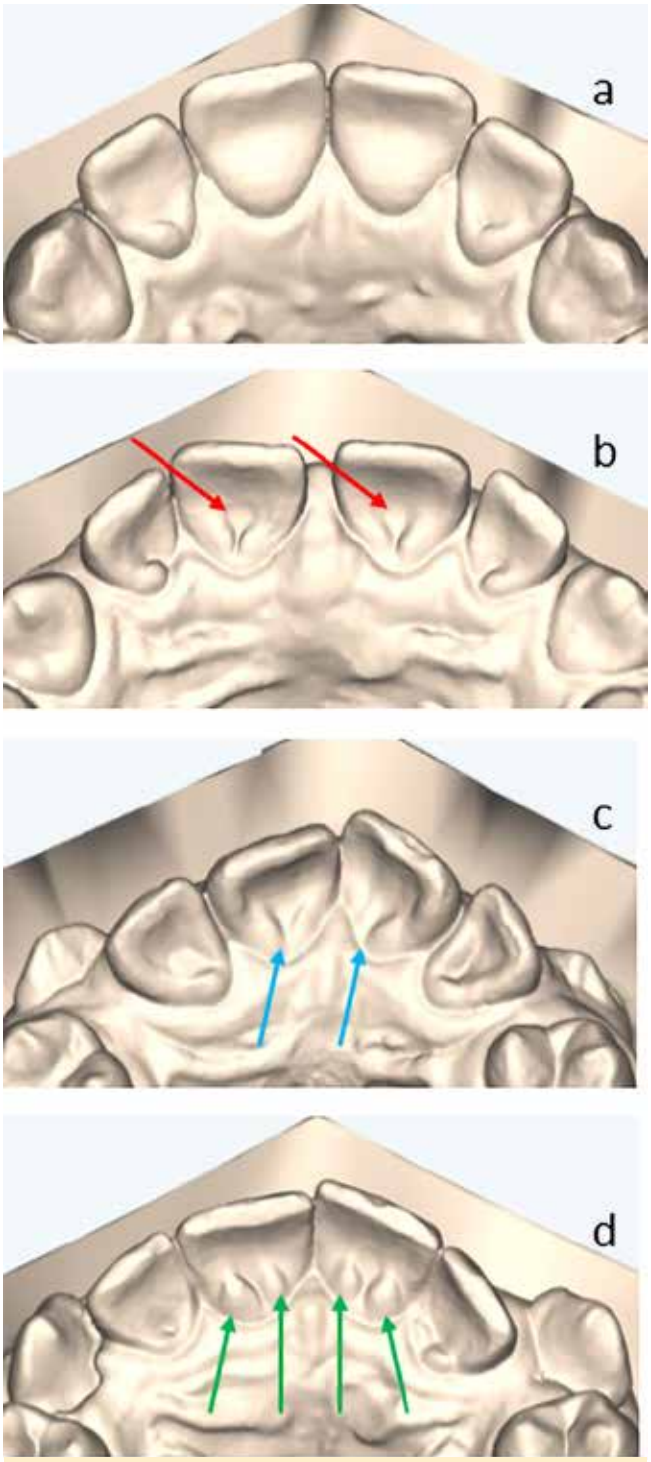

Figure 3. *Normal palatal surface (a), palatal pit [red arrows (b)], palatocervical groove [blue arrows (c)], and palatal tubercule [green arrows (d)].*

We also analyzed palatal surface as normal (Figure 3a) with a palatal pit, palatocervical grove, and double palatal tubercules. The palatal pit (Figure 3b) is

situated in the deep palatal fossa on the incisal surface of the cingulum. The palatocervical grove (Figure 3c) extends from the palatal pit, across the cingulum, and may extend up on the root. Double palatal tubercules (Figure 3d) extend in the cingulum area.

Modified questionnaire

Data on the aesthetic perception of different permanent maxillary central incisor shapes, as well as the potential impact of dental appearance on an individual's self-esteem, problems with maxillary central incisor eruption and possible orthodontic treatment were collected through the use of a modified questionnaire. The modified questionnaire was developed based on previously published studies (15) and adapted for the purposes of the current study. The questionnaire was distributed electronically across Slovenia via social media platforms (e.g., Facebook), e-mail, and WhatsApp. Participants were recruited using a convenience sampling method among three study groups in Slovenia, as follows: dental/general medicine students; professionals working in the field of dentistry; and laypersons. Laypersons were defined as individuals without formal dental education and were invited through general online networks. A total of 395 respondents completed the questionnaire, of whom 67 were excluded due to incomplete or inconsistent responses (Figure 1). Therefore, although the study casts originated from the Podravska region, the questionnaire sample represents a wider Slovenian population. A flowchart illustrating the study sample is presented in Figure 1.

Statistical Analysis

Intra-examiner reliability was assessed using a paired t-test. The recorded data were entered into a spread sheet in Microsoft Office Excel 2007. Descriptive statistics were expressed as frequencies and percentages for categorical variables, while ordinal variables obtained from the visual analogue scale were summarized as medians and interquartile ranges. The association between categorical variables was analyzed using a chi-square (χ^2) test of independence. Fisher's exact test was applied in cases in which the expected frequencies were < 5. Visual analogue scale score comparisons between the two independent groups were performed using the Mann-Whitney U test, whereas comparisons among three independent groups were analyzed using the Kruskal-Wallis test. The significance level was set at a $P < 0.05$.

RESULTS

Study casts

Intra-examiner reliability analysis showed no statistically significant difference detected in the crown shape. Of the 200 examined study casts, 184 fulfilled the selection criteria (Table 2). Of the 184 study casts, 87 were from males (47.3 %) and 97 were from females (52.7 %). The distribution of different maxillary central incisor crown shapes according to sex is presented in Table 2. The triangular shape was most frequent (47.3 %), followed by elongated (36.4 %), square (13.6 %), and ovoid shapes (2.7 %) in both sexes. There was no statistically significant association between crown shape distribution and sex ($x2 = 3.37$, $P = 0.338$).

Table 3 presents the distribution of different palatal structures according to sex. There was no statistically significant association between different palatal structures and sex (Fisher's exact test, $P = 0.850$).

Table 2. *The distribution of different crown shapes of permanent maxillary central incisors by sex.*

Shape / Sex	Square n (%)	Elongated n (%)	Ovoid n (%)	Triangular n (%)	Total n (%)
Male	24 (6.5)	62 (16.8)	2 (0.5)	86 (23.4)	174 (47.3)
Female	26 (7.1)	72 (19.6)	8 (2.2)	88 (23.9)	194 (52.7)
Total	50 (13.6)	134 (36.4)	10 (2.7)	174 (47.3)	368 (100)

Table 3. *The distribution of different structures on palatal surface by sex.*

Patatal structures / Gender	Palatal pit n (5)	Palatocervical groove n (%)	Double palatal cusp n (%)	Total n (%)
Male	4 (1.1)	3 (0.8)	1 (0.3)	8 (2.2)
Female	5 (1.4)	3 (0.8)	3 (0.8)	11 (3.0)
Total	9 (2.5)	6 (1.6)	4 (1.1)	19 (5.2)

Table 4. *The distribution of status (profession), sex, and age (years) of the study participants.*

Status	Age / Sex	20 – 30 n (%)	30 – 40 n (%)	40 – 50 n (%)	50 – 60 n (%)	total n (%)
Students	M	31 (9.4)	0 (0)	0 (0)	0 (0)	31 (9.4)
	F	100 (30.5)	0 (0)	0 (0)	0 (0)	100 (30.5)
Professionals in dentistry	M	1 (0.3)	13 (4.0)	9 (2.7)	8 (2.4)	31 (9.4)
	F	10 (3.0)	53 (16.2)	28 (8.5)	26 (8.0)	117 (35.7)
Laypersons	M	16 (4.9)	1 (0.3)	0 (0)	0 (0)	17 (5.2)
	F	20 (6.2)	5 (1.5)	4 (1.2)	3 (0.9)	32 (9.8)
Total		178 (54.3)	72 (21.9)	41 (12.5)	37 (11.3)	328 (100)

Legend: M: male; F: female.

Modified questionnaire

A total of 395 respondents (participants) completed the modified questionnaire; 67 were excluded due to incomplete or inconsistent responses. The final sample consisted of 328 participants.

The distribution of participants by profession, sex, and age is presented in Table 4. No significant association was detected between sex and age distribution (χ^2 = 2.36, P = 0.50) or between sex and professional status (χ^2 = 3.62, P = 0.16). However, a significant association was detected between age and professional status (χ^2 = 268.4, P < 0.001).

Participants were asked to evaluate photographs of four different maxillary central incisor crown shapes using a 4-point VAS, ranging from 1 (most liked) to 4 (least liked). A significant difference existed with respect to the aesthetic perception of tooth shapes (H = 312.5, P < 0.001) with elongated shape most liked and square shape least liked (Table 5). Subgroup analyses according to professional status and sex are presented in Table 6. Square crown shape received the lowest aesthetic evaluations overall. Statistically

Table 5. *The survey respondents' evaluations of the different maxillary central incisor crown shapes.*

Shape	median	IQR
Square	4	3-4
Elongated	2	1-2
Ovoid	3	2-3
Triangular	3	2-3

Legend: IQR: interquartile range

Answers were given on a four-point visual analogue scale (VAS) ranging from 1 (most liked) to 2 (more liked), 3 (liked), and 4 (least liked).

Table 6. *The survey respondents' evaluations of the different maxillary central incisor*

		Shape evaluation on VAS	
Status	**Sex**	**mediana**	**IQR**
Square shape			
Students	M	3	3-4
	F	4	3-4
Professionals in dentistry	M	4	3-4
	F	4	4-4
Laypersons	M	3	2-4
	F	3	1-4
Elongated shape			
Students	M	2	1-2
	F	1	1-2
Professionals in dentistry	M	2	1-3
	F	2	1-2
Laypersons	M	2	1-3
	F	2	1-2
Ovoid shape			
Students	M	2	1-3
	Ž	2	2-3
Professionals in dentistry	M	2	2-3
	Ž	3	2-3
Laypersons	M	2	1-3
	Ž	3	2-3
Triangular shape			
Students	M	3	2-4
	Ž	3	2-3
Professionals in dentistry	M	2	1-3
	Ž	2	1-3
Laypersons	M	3	2-3
	Ž	3	2-4

Legend: M: male, F: female, IQR: interquartile range

Answers were given on a four-point visual analogue scale (VAS) ranging from 1 (most liked) to 2 (more liked), 3 (liked), and 4 (least liked).

significant differences among students, professionals in dentistry, and laypersons were detected for square crown shape evaluations ($H = 18.72$, $P < 0.001$). Significant sex-related differences were also identified ($U = 8373.5$, $P = 0.017$). Elongated crown shape evaluations differed significantly among the examined groups ($H = 6.21$, $P = 0.045$), as well as between males and females ($U = 11674.5$, $P = 0.006$). No statistically significant differences were detected for ovoid crown shape among the examined groups ($H = 2.08$, $P = 0.353$) or between sexes ($U = 8622.0$, $P = 0.082$). Triangular crown shape evaluations revealed statistically significant differences among students, professionals in dentistry, and laypersons ($H = 6.12$, $P = 0.047$). However, no statistically significant sex differences were detected with respect to triangular crown shape ($U = 10169.0$, $P = 0.638$).

Almost all participants (99.1 %) reported that teeth have a role in self-esteem, while only three respondents indicated that teeth have no role in self-esteem.

A total of 190 (57.9 %) participants reported having undergone orthodontic treatment (Table 7). A statistically significant association was detected between sex and orthodontic treatment ($\chi^2 = 6.05$, $P = 0.048$), indicating that females reported orthodontic treatment more frequently than males Compromised aesthetics and function were the most common reason for orthodontic treatment (46%), followed by aesthetic reasons (34%) and impaired function (13%). A small proportion of participants (7%) could not recall the indication for orthodontic treatment. No statistically significant difference was detected for orthodontic treatment between sexes ($\chi^2 = 5.63$, $P = 0.131$).

Twenty respondents (6.1%) reported problems with eruption of the maxillary central incisors in childhood. No statistically significant difference was detected with respect to childhood eruption of the maxillary central incisors according to participant status ($\chi^2 = 0.25$, $P = 0.883$) or sex ($\chi^2 = 1.39$, $P = 0.239$). Ten (3%) respondents reported speech disorders associated with the position of the maxillary central incisors and six required speech therapy.

Of 136 dentists, 78 (57.3 %) acknowledged that the most frequent indication for referring patients to an orthodontist is an incorrect bite (Table 8).

Participants also evaluated different positions of

Table 7. *Results of the question regarding whether the participants underwent orthodontic treatment.*

Status	Sex	Yes n (%)	No n (%)	No, but I would want to be. n (%)	Total n (%)
Students	M	16 (51.6)	12 (38.7)	3 (2.1)	31 (100)
	F	73 (73.0)	22 (22.0)	5 (5.0)	100 (100)
Professionals in dentistry	M	16 (51.6)	12 (38.7)	3 (9.7)	31 (100)
	F	63 (53.8)	47 (40.2)	7 (6.0)	117 (100)
Laypersons	M	5 (29.4)	8 (47.1)	4 (23.5)	17 (100)
	F	17 (53.1)	10 (31.3)	5 (15.6)	32 (100)
Total		190 (57.9)	111 (33.9)	27 (8.2)	328 (100)

Legend: M: male, F: female

Table 8. *The survey respondents' responses to the question regarding the most common reason for referral to an orthodontist.*

Question for dentists: What is the most common reason for referring a patient to an orthodontist?	Results n (%)
Positional irregularities of teeth	41 (30.2)
Incorrect bite	78 (57.3)
Compromised function	12 (8.8)
At the request of parents	5 (3.7)
Total	136 (100)

maxillary central incisors in the dental arch to rank photographs from 1 (most liked) to 4 (least liked). The results are presented in Table 9. Significant differences in aesthetic preference among tooth positions were detected ($H = 340.2$, $P < 0.001$) with crossbite rated least favorably (77.4% selected a rating of 4).

Table 9. *The survey respondents' evaluations of different maxillary central incisor crown positions.*

Teeth position	median	IQR
Crowding	2	2-3
Diastema mediana	3	2-3
Crossbite	4	4-4
Spacing	1	1-1

Legend: IQR: interquartile range

Answers were given on a four-point visual analogue scale (VAS) ranging from 1 (most liked) to 2 (more liked), 3 (liked), and 4 (least liked).

DISCUSSION

The concept of beauty comprises symmetry and harmony, which is expressed through the proportional relationship of the face and teeth. Oral conditions can greatly affect the psychological, social, and functional health of patients. The most visible teeth when smiling are the maxillary central incisors (27). Incisor shape is important in orthodontics for achieving proper tooth contact and intercuspation. For example, an ovoid shape often requires striping of the proximal surface to achieve good proximal contact. The shape of the maxillary central incisor is also of great importance in restorative dentistry and prosthodontics for the aesthetic appearance of a smile.

Although maxillary central incisors shapes have been studied in various ethnic groups over the years (13,

26, 27), no published study has addressed which shape predominates in the Slovenian population. However, one study examined the relationship between the length and width of the face and the length and width of the crown of the maxillary central incisor (8) and another study investigated the frequency of different crown shapes of permanent maxillary lateral incisors (28). In the present study the predominant shape of the permanent maxillary central incisor is triangular (47.3 %), followed by elongated (36.4 %), square (13.6 %), and ovoid (2.7 %). Differences are apparent when comparing the results of the present study with other studies (26, 27). Paranhos et al. [26] reported that the ovoid shape was most common and the triangular shape was least common, which is in contrast to our results. Trigo-Humaran et al. (27) reported that the ovoid shape was least common, which is consistent with the findings in the current study but the square shape was most common, which differs from the results herein. However, if the square and elongated maxillary central incisor shapes were evaluated together in the current study, the results would have been completely aligned with the findings reported by Trigo-Humaran et al. (27). It should be noted that methodologic differences between studies may have influenced the results. Specifically, some studies relied on visual assessment, while other studies used standardized measurements or digital analysis. These methodologic variations limit direct comparability between findings.

Palatal structures, such as a palatal pit and palato-cervical groove, allow plaque accommodation and can lead to caries and periodontal disease (24, 25). A palatal pit may be located between the cingulum and palatal fossa and may be located near the center of the palatocervical groove if that structure is present. These dental anomalies occurred in 2.5 % and 1.5 % of study casts in the present study, respectively. This finding is agreement with a previous study (24). The palatal pit and palatocervical groove more frequently occur in maxillary lateral incisors than maxillary central incisors (1,24, 28).

The extended palatal tubercule has a greater predilection for the maxilla and when located in the cingulum area is associated with occlusal interferences and disharmony (23,25,28, 29). The prevalence of an extended palatal tubercule in the cingulum area was 1.1 % of maxillary central incisors in the present study. This finding is consistent with the results reported by Guven et al. (25). In the literature, we found that the prevalence of an extended palatal tubercule according to the extant literature is less frequent in the maxillary central incisor than the maxillary lateral incisors (22,23,26,28).

The aesthetic appearance of a smile is strongly influenced by the shape, position, and color of the permanent maxillary central incisors (30). The maxillary anterior teeth are the most important factor in achieving an aesthetic smile and crown shape ranks highest of all the various features that contribute to overall attractiveness, as highlighted by Ong et al. (31). Generally, women exhibit rounder and softer tooth forms compared to men, whose teeth are perceived as angular and square, which harmonizes with appearance (3). Heravi et al. (32) reported that the crown shape of the incisors is the main factor influencing aesthetic preferences. Both males and females rated ovoid incisors as the most aesthetic, which is in contrast with the findings in the present study (i.e., elongated maxillary central incisors were rated most aesthetic). Heravi et al. (32) also reported that square-shaped maxillary central incisors are the least aesthetic, which is consistent with the findings in the current study. The aesthetic perception of maxillary central incisors is very important in restorative dentistry, prosthodontic, and orthodontic treatment. Even laypeople can identify characteristics of facial beauty. Anderson et al. (33) reported that dental professionals (orthodontists and restorative dentists) and laypeople share similarities and exhibit differences when considering aesthetic preference in maxillary central incisor shape. Although there was no consensus in preference among laypeople as a group, the preferences differed from orthodontists and restorative dentists. The position of maxillary incisors is also one of the most important factors that people notice when evaluating a smile (34). In the current study the crossbite position was rated as least aesthetic among the examined positions. In the present study tooth color was not evaluated.

Maxillary central incisors were shown to have a significant impact on self-esteem, which is consistent with the results of previous studies (35-37). Badran (35) reported that students who underwent orthodontic treatment had higher self-esteem than students who had not undergone orthodontic treatment, which is consistent with our findings, in which 57.9 % of the study participants had undergone orthodontic treatment and confirmed higher self-esteem.

Hall et al. (38) reported that 75% of the general dentists in the midwestern United States think that patient satisfaction is as important as functional/occlusal results. Di Blasio et al. (39) reported that the most common reason for referring a patient to an orthodontist is dental irregularities as an aesthetic problem. However, in the current study the most common reason was an incorrect bite.

Tuncer et al. (40) reported that the main reason for orthodontic treatment is to achieve better alignment of the teeth and dental aesthetics, while Coyne et al. (41) reported that the functional aspect is more important than aesthetics. Tuominen and Tuominen (42) reported that the main reasons for seeking orthodontic treatment are to improve dental aesthetics and correct occlusion, which agrees with the present study.

Absence or unerupted maxillary central incisors affect occlusion development (6) and smile and facial aesthetics (5, 43), as well as a child's psychological well-being (6). Tan et al. (44) and Aldowsari et al. (45) reported that 1.4% and 3% of maxillary central incisors had delayed eruption, respectively. The incidence of maxillary central incisor impaction was 0.1% in a previous study involving impacted teeth in the Slovenian population (5). In the present study 6% of the participants reported problems with maxillary central incisor eruption. The percentage in the present study was higher because this study included patients who were treated by an orthodontist and had a higher incidence of dental irregularities than the general population.

The production of the /s/ sound is influenced by the position of the maxillary incisors and some irregularities in incisor position may lead to pronunciation disorders (46). Several studies have addressed speech problems associated with missing anterior teeth (17, 47). Riekman et al. (16) reported that the premature loss of all primary maxillary incisors generally did not impact long-term speech development in most children tested between 5.4 and 11.5 years of age. In the present study adolescent respondents reported speech problems due to malposition of the maxillary central incisors, six of who were required to visit a speech therapist. Specific speech difficulties due to tooth positions were not evaluated in our questionnaire. It should be emphasized that the findings related to function and self-esteem are based on self-reported perceptions rather than objective clinical or psychological assessments.

The current study had limitations. Because study casts were from patients treated in an orthodontist in the Podravska region, the findings cannot be generalized to the entire Slovenian population. Although this study may not represent the entire Slovenian population, the results are useful. To obtain a more comprehensive understanding and ensure broader validation, future research should consider expanding this study to include multiple clinics, both in Maribor and other regions across Slovenia. It would also be important to obtain more information on the function of maxillary incisors in speech and the participation of a speech therapist.

The questionnaire, which included specific questions related to dentistry, was a limitation that could easily confuse laypeople with limited knowledge of dentistry.

CONCLUSIONS

The findings regarding the morphology of permanent maxillary central incisors are important to the field of restorative dentistry, prosthodontics, and orthodontics. Such findings can assist in achieving more effective treatment and can contribute to obtaining an improved dental appearance, function, and facial aesthetic.

REFERENCES

1. Bath Balogh M, Fehrenbach MJ. Dental Embryology, Histology, and Anatomy, 2nd ed.; Elsevier: St. Louis, MO, USA, 1997: 209-13.
2. Fekonja A. Evaluation of the eruption of permanent teeth and their association with malocclusion. Clin Exp Den. Res. 2022; 8: 836-42.
3. Nelson SJ, Ash MM Jr. Wheeler's Dental Anatomy, Physiology and Occlusion, 9th ed.; Elsevier: St. Louis, MO, USA, 2010.
4. Manuja N, Nagpal R. Delayed eruption of maxillary permanent central incisors due to bilateral tuberculate supernumerary teeth: Case report. J Dent Child. 2010; 77: 106-10.
5. Fekonja A. Radiographic characteristics of impacted teeth. AMB. 2015; 8: 18-26,
6. Seehra J, Yaqoob O, Patel S, O'Neill J, Bryant C, Noar J, Morris D, Cobourne MT. National clinical guidelines for the management of unerupted maxillary incisors in children. Br Dent J. 2018; 224: 779-85.
7. Gašperšič D, Cvetko E, Potočnik I, Fidler A. Anatomija zob; Medicinska fakulteta: Ljubljana, Slovenia, 2002: 19-22.
8. Dervarič T, Fekonja A. The relationship between the length/width of the face and the length/width of the crown of the permanent upper central incisors. J Clin Med. 2024; 13: 4698.
9. Olsson M, Lindhe J. Periodontal characteristics in individuals with varying form of the upper central incisors. J Clin Periodontol. 1991;18: 78-82.
10. Lavelle CL. Maxillary and mandibular tooth size in different racial groups and in different occlusal categories. Am J Orthod. 1972; 61: 29-37.
11. Doris JM, Bernard BW, Kuftinec MM, Stom D. A biometric study of tooth size and dental crowding. Am J Orthod. 1981;79: 326-36.
12. Gillen RJ, Schwartz RS, Hilton TJ, Evans DB. An analysis of selected normative tooth proportions. Int J Prosthodont. 1994; 7: 410-17.
13. Williams JL. A New Classification of Human Tooth Forms with a Special Reference to a New System of Artificial Teeth, 1st ed.; The Dentisti Supply Co.: New York, NY, USA, 1914: 30-7.
14. Ibrahimagić L, Jerolimov V, Celebić A, Carek V, Baucić I, Zlatarić DK. Relationship between the face and the tooth form. Coll Antropol. 2001; 25: 619-26.
15. Fekonja A. Prevalence of dental developmental anomalies of permanent teeth in children and their influence on esthetics. J Esthet Restor Dent. 2017; 29: 276-83.
16. Riekman GA, el Badrawy HE. Effect of premature loss of primary maxillary incisors on speech. Pediatr Dent. 1985; 7: 119-22.
17. Bankson NW, Byrne MC. The relationship between missing teeth and selected consonant sounds. J Speech Lang Hear Disord. 1962; 27: 341-8.
18. Rodd HD, Barker C, Baker SR, Marshman Z, Robinson PG. Social judgements made by children in relation to visible incisor trauma. Dent Traumatol. 2010; 26: 2-8.
19. Mockutė G, Klimaitė G, Smailienė D. The Morphology of Impacted Maxillary Central Incisors: A Systematic Review. Medicina. 2022; 22: 462.
20. Farčnik F, Ovsenik M, Primožič J. Obravnava nepravilnosti orofacialnega področja s Franklovimi regulatorji funkcije; Zavod Orthos: Medicinska fakulteta: Ljubljana, 2014.
21. Levc, S. Liba laca lak: kako pomagamo otroku do boljšega govora; Ljubljana, 2014.
22. Guttal KS, Naikmasur VG, Bhargava P, Bathi RJ. Frequency of developmental dental anomalies in the Indian population. Eur J Dent. 2010; 4: 263-9.
23. Hattab FN, Yassin OM, al-Nimri KS. Talon cusp in permanent dentition associated with other dental anomalies: Review of literature and reports of seven cases. ASDC J Dent Child. 1996; 63: 368-76.

24. Gaudex Y, Gandillot V, Fontanille I, Bouchard P, Kerner S, Carra MC. Palatal groove associated with periodontal lesions: a systematic review illustrated by a decisional tree for management. BMC Oral Health. 2024; 24: 1037.
25. Guven Y, Kasimoglu Y, Tuna EB, Gencay K, Aktoren O. Prevalence and characteristics of talon cusps in Turkish population. Dent Res J. 2016; 13: 145-50.
26. Paranhos L, Jóias R, Velasco L, Bérzin F, Júnior E. Prevalence of the different maxillary central incisor shapes in individuals with natural normal occlusion. Braz J Oral Sci. 2010; 9: 104-7.
27. Trigo-Humaran MM, Agüero-Romero AB, Lespade M, García-Cuerva JM, Iglesias ME. Central incisors shape and proportions prevalence in Argentinian university students: by visual assessment and a new standardized method. Acta Odontol. Latinoam. 2021; 34: 113-8.
28. Fekonja A. Morphological diversity of permanent maxillary lateral incisors and their impact on aesthetics and function in orthodontically treated patients. Diagnostics 2022; 12: 2759.
29. Gündüz K, Celenk P. Survey of talon cusps in the permanent dentition of a Turkish population. J Contemp Dent Pract. 2008; 9: 84-91.
30. Rifkin R. Facial analysis: a comprehensive approach to treatment planning in aesthetic dentistry. Pract Periodontics Aesthet Dent. 2000; 12. 865-72.
31. Ong E, Brown RA, Richmond S. Peer assessment of dental attractiveness. Am J Orthod Dentofac Orthop. 2006; 130: 163-9.
32. Heravi F, Rashed R, Abachizadeh H. Esthetic preferences for the shape of anterior teeth in a posed smile. Am J Orthod Dentofac Orthop. 2011; 139: 806-14.
33. Anderson Anderson KM, Behrents RG, McKinney T, Buschang PH. Tooth shape preferences in an esthetic smile. Am J Orthod Dentofac Orthoped. 2005; 128: 458-65.
34. McKiernan EX, McKiernan F, Jones ML. Psychological profiles and motives of adults seeking orthodontic treatment. Int J Adult Orthodon Orthognath Surg. 1992; 7: 187-98.
35. Badran SA. The effect of malocclusion and self-perceived aesthetics on the self-esteem of a sample of Jordanian adolescents. Eur J Orthod. 2010; 32: 638-44.
36. Kaur P, Singh S, Mathur A, Makkar DK, Aggarwal VP, Batra M Sharma A, Goyal N. Impact of dental disorders and its influence on self-esteem levels among adolescents. J Clin Diagn Res. 2017; 11: ZC05-ZC08.
37. Amnaie A, Nasiri M, Adib M, Shirvani A. Relationship between self-concept and satisfaction with tooth alignment and demand for orthodontic treatment and professionally determined orthodontic needs. *J Isfahan Dent Sch.* 2012; 8: 1-9.
38. Hall JF, Sohn W, McNamara JA. Why do dentists refer to specific orthodontists? Angle Orthod. 2009; 79: 5-11.
39. Di Blasio M, Vaienti B, Pedrazzi G, Cassi D, Magnifico M, Meneghello S, Di Blasio A. Are the reasons why patients are referred for an orthodontic visit correct? Int J Environ Res Pub Health. 2021; 18: 5201.
40. Tuncer C, Canigur Bavbek N, Balos Tuncer B, Ayhan Bani A, Çelik B. How do patients and parents decide for orthodontic treatment—Effects of malocclusion, personal expectations, education and media. J Clin Pediatr Dent. 2015; 39: 392-9.
41. Coyne R, Woods M, Abrams R. The community and orthodontic care. Part II: Community-perceived importance of correcting various dentofacial anomalies. Part III: Community perception of the importance of orthodontic treatment. Aust Orthod J. 1999; 15: 289-301.
42. Tuominen ML, Tuominen RJ. Factors asso-

ciated with subjective need for orthodontic treatment among Finnish university applicants. Acta Odontol Scand. 1994; 52: 106-10.
43. Cons NC, Jenny J, Kohout FJ. DAI: The dental aesthetic index. Iowa City, Iowa: College of Dentistry, University of Iowa; 1986.
44. Tan C, Ekambaram M, Yiu CKY. Prevalence, characteristic features, and complications associated with the occurrence of unerupted permanent incisors. PLoS One 2018; 13: e0199501.
45. Aldowsari M, Alsaif FS, Alhussain MS, AlMeshary BN, Alosaimi NS, Aldhubayb SM, AlQahtani S. Prevalence of delayed eruption of permanent upper central incisors at a tertiary hospital in Riyadh, Saudi Arabia. Children. 2022; 9: 1781.
46. Mohammed S, Saloom J, Obaid D, Alhuwaizi A. Malocclusion traits and speech disorders. Med J Babylon. 2024; 20: 661-4.
47. Weinberg B. A cephalometric study of normal and defective –s– articulation and variations in incisor dentition. J Speech Hear Res. 1968; 11: 288-300.

Primerjava izhoda zdravljenja bolnikov z akutnim miokardnim infarktom z dvigom veznice ST (STEMI) z bolniki brez dviga veznice ST (NSTEMI)

Treatment outcome of patients with acute ST-elevation myocardial infarction (STEMI) vs. non-ST-elevation myocardial infarction (NSTEMI)

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Ključne besede:
akutni miokardni infarct s trajnim dvigom veznice ST, akutni miokardni infarkt brez trajnega dviga veznice ST, umrljivost, ponovna hospitalizacija, perkutana koronarna intervencija

Key words:
acute myocardial infarction with sustained ST elevation, acute myocardial infarction without sustained ST elevation, mortality, rehospitalization, percutaneous coronary intervention

Članek prispel / Received
1. 4. 2026

Članek sprejet / Accepted
30. 6. 2026

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Izvleček

Namen: *Med miokardnimi infarkti s trajnim dvigom veznice ST (STEMI) in brez trajnega dviga veznice ST (NSTEMI) obstajajo podobnosti in razlike. Namen tega prispevka je primerjava umrljivosti in ponovne hospitalizacije med STEMI in NSTEMI bolniki.*

Metode: *V retrospektivni raziskavi smo primerjali prevalenco osnovnih kliničnih podatkov, zdravljenje in izhod zdravljenja med 491 STEMI in 304 NSTEMI bolniki, sprejetimi od januarja do decembra 2023. Vodilna reperfuzijska strategija je bila primarna perkutana koronarna intervencija (PCI). Izhod zdravljenja je bila hospitalna, 30-dnevna in šest-mesečna umrljivost ter ponovna hospitalizacija v šestih mesecih.*

Rezultati: *NSTEMI bolniki so bili*

Abstract

Purpose: *There are both similarities and differences in the baseline clinical characteristics, treatment strategies, and outcomes between patients with ST-segment elevation myocardial infarction (STEMI) vs. non-ST-segment elevation myocardial infarction (NSTEMI). The purpose of this study was to compare mortality and rehospitalization rates between STEMI and NSTEMI patients.*

Methods: *In this retrospective study, baseline clinical characteristics, treatment strategies, and outcomes were compared among 491 STEMI and 304 NSTEMI patients admitted from January to December 2023. Percutaneous coronary intervention (PCI) was the main reperfusion strategy. Out-*

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statistično značilno starejši z več spremljajočimi boleznimi, STEMI bolniki pa so bili bistveno pogosteje oživljani, ter tudi kadilci z obsežnejšo miokardno nekrozo. Zgodnja PCI (v prvih 24 urah) je bila bistveno pogosteje opravljena pri STEMI (90,6 % v primerjavi s 45,1 %, p < 0,001) kot pri NSTEMI bolnikih, pri vseh pa uvedena ustrezna priporočena antitrombotična terapija. Akutno bolnišnično srčno popuščanje je prevladovalo pri STEMI bolnikih (28,9 % v primerjavi z 20 %, p = 0.02), med STEMI in NSTEMI bolniki pa ni bilo pomembnih razlik v umrljivosti (bolnišnična: 5,5 % v primerjavi s 5,6 %; 30-dnevna: 5,5 % v primerjavi s 4,6 %; šest-mesečna: 6,7 % v primerjavi s 7,2 %). NSTEMI bolniki so bili rehospitalizirani pogosteje.

Zaključki: *NSTEMI bolniki so bili starejši z več spremljajočimi boleznimi, STEMI bolniki pa so imeli večjo miokardno poškodbo z večjo prevalenco akutnega bolnišničnega srčnega popuščanja. Zaradi več zgodnje PCI pri STEMI kot NSTEMI bolnikih, kombinirane z ustrezno farmakološko terapijo, so bile umrljivosti pri STEMI in NSTEMI bolnikih podobne, a z večjim deležem ponovnih hospitalizacij pri NSTEMI bolnikih.*

comes included in-hospital, 30-day, and 6-month mortality rates, as well as rehospitalization rates within 6 months.

Results: *NSTEMI patients were significantly older and had more comorbidities, whereas STEMI patients were more frequently smokers, more frequently required resuscitation, and had more extensive myocardial injury. Early PCI (within the first 24 h) was performed significantly more often for STEMI than NSTEMI patients (90.6% vs. 45.1%, p < 0.001), and all patients received guideline-recommended antithrombotic therapy. Acute in-hospital heart failure was more prevalent in STEMI patients (28.9% vs. 20%, p = 0.02). There were no significant differences in in-hospital, 30-day, and 6-month mortality rates between STEMI and NSTEMI patients (5.5% vs. 5.6%, 5.5% vs. 4.6%, 6.7% vs. 7.2%, respectively). However, NSTEMI patients were more frequently rehospitalized.*

Conclusions: *NSTEMI patients were older and had more comorbidities, whereas STEMI patients had more extensive myocardial injury and a higher prevalence of acute in-hospital heart failure. More frequent use of early PCI in STEMI patients, combined with appropriate pharmacological therapy, may explain the similar mortality rates observed between STEMI and NSTEMI patients, despite a higher rate of rehospitalization rate in NSTEMI patients.*

INTRODUCTION

Acute myocardial infarction (MI) is a major cause of morbidity and mortality worldwide (1). Acute MI denotes the presence of acute myocardial injury, as evidenced by fluctuations in serum troponin levels (2). In addition to clinical presentation with chest pain and/or dyspnea, changes to standard electrocardiographic findings are crucial to distinguish acute ST-segment elevation myocardial infarction (STEMI) from non-ST-segment elevation myocardial infarction (NSTEMI) (2). Both forms of acute MI share many similarities but also exhibit important differences. In both STEMI and NSTEMI, the main symptom of ischemia is chest pain at rest, accompanied by less specific symptoms, such as dyspnea, palpitations, nausea, and abdominal pain. Notably, chest pain is typically more intense and persistent in STEMI than NSTEMI (2-4). Despite the differences in changes to standard electrocardiographic findings, the underlying pathophysiological mechanisms of STEMI and NSTEMI are similar, as both are most commonly caused by thrombus formation on a ruptured, eroded, or inflamed vulnerable atherosclerotic plaque, which results in complete occlusion of a coronary artery in STEMI or near-complete narrowing of the coronary artery lumen in NSTEMI. To a lesser extent, myocardial infarction with non-obstructive

coronary arteries (MINOCA) is most often observed in NSTEMI patients (2-5).

In the developed world, the incidence of MI has decreased over the past two decades, largely due to a reduction in STEMI cases. However, the prevalence of NSTEMI remains high (4-7). Risk factors for STEMI and NSTEMI are largely similar, although NSTEMI patients are generally older and have more comorbidities as compared with STEMI patients (4, 5, 7).

Treatment strategies for STEMI and NSTEMI patients are broadly similar and include early reperfusion therapy with percutaneous coronary intervention (PCI), combined with antithrombotic therapy or, in some cases, surgical revascularization. Primary PCI is the treatment of choice and the highest priority for STEMI patients. Coronary revascularization by PCI is also recommended as early as possible for high-risk NSTEMI patients (3, 4). Over the past decades, significant differences in early and late mortality have been observed between STEMI and NSTEMI patients, as the risk of early mortality is higher, while the risk of long-term mortality is lower in STEMI patients as compared with NSTEMI patients (4, 6, 7).

The aim of this study was to compare baseline characteristics, admission data, treatment strategies, early and late mortality, and rehospitalization rates within 6 months following the acute event between STEMI and NSTEMI patients.

PATIENTS AND METHODS

The cohort of this retrospective, single-center observational study included 795 consecutive patients with acute MI (70.4% men, mean age 66.3 ± 12.2 years) who were admitted to the University Medical Centre Maribor (UKC Maribor) from January to December 2023. UKC Maribor is a tertiary clinical center in northeastern Slovenia that serves as a referral 24/7 regional center for primary PCI in STEMI patients and for high-risk NSTEMI patients, covering a population of approximately 850,000 inhabitants. Patient medical records were retrieved from an electronic database and reviewed based on the International Classification of Diseases (10th Revision) codes I21.0–I21.4 and I21.9, specific for MI. According to established criteria, 491 STEMI patients and 304 NSTEMI patients were identified (2, 3). Baseline admission data included age, sex, comorbidities, out-of-hospital cardiac arrest prior to admission, time to primary PCI in STEMI patients, estimated glomerular filtration rate, high-sensitivity cardiac troponin I levels ≥1000 pg/L, smoking status, positive family history of MI, body mass index (BMI), and lipid profile (total cholesterol, high-density lipoprotein cholesterol, triglycerides, low-density lipoprotein cholesterol).

Treatment of STEMI and NSTEMI patients in 2023 was conducted in accordance with the European Society of Cardiology guidelines for acute coronary syndromes (3). The main reperfusion strategy was primary PCI for STEMI patients and early PCI following coronary angiography for high-risk NSTEMI patients. The treatment data included the use of PCI and/or surgical revascularization, Thrombolysis in Myocardial Infarction grade III flow after PCI, vascular access (radial or femoral), and antithrombotic therapy (3).

STEMI patients were transferred directly to the catheterization laboratory for coronary angiography and primary PCI. After the procedure, patients were monitored in the Coronary Care Unit or Intensive Care Unit for approximately 24 h or longer in case of complications until transfer to the cardiology ward or local hospitals in stable condition (3).

NSTEMI patients were admitted to the Coronary Care Unit and monitored until coronary angiography, with or without PCI, was performed. PCI was carried out based on the decision of the interventional cardiologist. Early PCI was performed for high-risk NSTEMI patients with disease of up to three vessels, potentially in multiple sessions during hospitalization. Surgical revascularization was the most preferred strategy for patients with multivessel coronary artery disease (CAD) (3).

During hospitalization, all complications were recorded. Acute heart failure was classified according to Killip classes II–IV and arrhythmias were categorized as ventricular and/or atrial (3, 8). Acute kidney injury was defined as an increase in serum

creatinine of at least 50% from baseline within the first 48 h (9). In-hospital bacterial infection was defined as the presence of microorganisms in normally sterile body tissues or fluids with or without clinical signs (fever, increased inflammatory markers) or initiation of antibiotic therapy based on strong clinical suspicion (10). Acute bleeding events were defined as Bleeding Academic Research Consortium type 3–5 (11).

Standard pharmacological treatments were recorded, which included acetylsalicylic acid with clopidogrel, ticagrelor, or prasugrel, unfractionated and low-molecular-weight heparin (LMWH), noradrenalin, dobutamin, levosimendan, loop diuretics, and glycoprotein (GP) IIb/IIIa antagonists. Interventions for complications included intra-aortic balloon pump, veno-arterial extracorporeal membrane oxygenation, and mechanical ventilation (3, 12, 13).

Data analysis and endpoints

The compared baseline characteristics between STEMI and NSTEMI patients included admission data, treatments, in-hospital complications, and outcomes, comprising in-hospital, 30-day, and 6-month mortality rates, as well as rehospitalization rates due to heart failure, need for PCI, reinfarction, or bleeding within 6 months.

Ethical approval

The protocol of this retrospective observational study was approved by the Institutional Medical Ethics Committee of the University Medical Centre Maribor (approval UKC-MB-KME-72/24) and conducted in accordance with the Declaration of Helsinki (1996 revision) and its subsequent amendments. The requirement for informed consent was waived due to the retrospective nature of this study. Patient data were protected in accordance with applicable legislation.

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows (version 19; IBM Corporation, Armonk, N.Y., USA). Data are presented as means ± standard deviations or percentages. Group differences were assessed using the two-sided Student's t-test for continuous variables and Fisher's exact test for categorical variables. A probability (p) value < 0.05 was considered statistically significant. Cumulative 6-month survival was estimated using the Kaplan–Meier method, and differences between groups (STEMI vs. NSTEMI) were assessed using the log-rank test.

RESULTS

The baseline characteristics and admission data of all included MI patients, along with comparisons between STEMI and NSTEMI patients, are presented in Table 1. NSTEMI patients were significantly older than STEMI patients and had significantly higher prevalence of comorbidities (arterial hypertension, diabetes, prior MI), whereas STEMI patients had significantly higher prevalences of smoking, family history of MI, prior resuscitation, and admission levels of high-sensitivity cardiac troponin I levels ≥1000 pg/L. There were no significant differences between STEMI and NSTEMI patients in terms of sex, MI location, BMI, lipid profile, or the prevalence of MINOCA.

Treatment data for STEMI and NSTEMI patients are presented in Table 2. Overall, 98% of STEMI patients and 95.4% of NSTEMI patients underwent coronary angiography; however, this difference was borderline significant ($p = 0.053$). Coronary angiography demonstrated occlusion of the culprit epicardial coronary artery in the majority of STEMI cases, whereas high-grade epicardial coronary stenosis was more common in NSTEMI patients.

Among the 11 MINOCA patients (4 with STEMI and 7 with NSTEMI), stenosis of the epicardial coronary arteries was observed in less than half. The underlying mechanisms included atherosclerosis, tortuosity of the coronary arteries, and spontaneous coronary artery dissection in 7, 1, and 3 patients, respectively.

STEMI patients received early PCI (primary PCI) significantly more frequently than NSTEMI patients (92.3% vs. 61.8%, respectively, $p < 0.001$), particularly within the first 24 h of hospitalization (90.6% vs. 45.1%, $p < 0.001$). For STEMI patients, primary PCI was performed within the first 12 h of chest

Table 1. *Baseline characteristics and admission data of patients with MI and comparison between STEMI and NSTEMI subgroups.*

Baseline and admission characteristics	All patients (n = 795)	STEMI patients (n = 491)	NSTEMI patients (n = 304)	p
Men (%)	70.4%	72.3%	67.4%	0.151
Women (%)	29.6%	27.7%	32.6%	0.151
Age (mean ± SD, years)	66.3 ± 12.2	64.4 ± 12.3	69.4 ± 11.2	<0.001
BMI (mean ± SD, kg/m2)	28.6 ± 4.6	28.6 ± 4.4	28.5 ± 4.9	0.844
Anterior MI (%)	46.9%	47%	33.3%	0.689
Age ≥ 65 years (%)	56.4	50.5	65.8	<0.001
AH (%)	59.5%	52.7%	70.4%	<0.001
Prior MI (%)	17.1%	11.2%	26.6%	<0.001
Diabetes (%)	26.2%	23%	31.3%	0.013
Smoking (%)	33.2%	38.8%	24%	<0.001
Prior resuscitation (%)	6,9%	10,8%	0,7%	<0,001
MINOCA (%)	1.4%	0.8%	2.3%	0.116
Killip II-IV ob sprejemu (%)	17.9%	18.9%	16.1%	0.341
Positive family history of MI (%)	10.4%	18.3%	1.9%	<0.001
Admission hs-TnI ≥ 1000 pg/L (%)	48.8	57.4	34.7	<0,001
Total cholesterol (mean ± SD, mmol/L)	4,7 ± 2,0	4,8 ± 2,3	4,6 ± 1,4	0,198
HDL cholesterol (mean ± SD, mmol/L)	1,2 ± 0,4	1,2 ± 0,4	1,23 ± 0,5	0,077
LDL cholesterol (mean ± SD, mmol/L)	3,0 ± 3,5	2,98 ± 1,0	3,0 ± 5,6	0,691
Triglicerides (mean ± SD, mmol/L)	1.8 ± 3.9	1.6 ± 1.8	2.1 ± 5.9	0.067

Abbreviations: STEMI, ST-elevation myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; SD, standard deviation; MI, myocardial infarction; AH, arterial hypertension;; MINOCA, myocardial infarction with non-obstructive coronary arteries; hs-TnI, high-sensitivity Troponin I; HDL, high density lipoprotein; LDL, low density lipoprotein.

Table 2. *Treatment of patients with MI and comparison between STEMI and NSTEMI subgroups.*

Treatments	All patients (n = 795)	STEMI patients (n = 491)	NSTEMI patients (n = 304)	p
Coronary angiography (%)	97%	98%	95.4%	0.053
PCI (%)	80.6	92.3	61.8	<0.001
PCI in the first 24 h (%)	73.2	90.6	45.1	<0.001
Radial access (%)	58.3	52	69.3	<0.001
Femoralni access (%)	41.7	48	30.7	<0.001
Single-vessel CAD (%)	36.6	43.5	24.7	<0.001
Two-vessel CAD (%)	32.7	34.1	30.2	<0.001
Multi-vessel CAD (%)	30.5	22.4	44.4	<0.001
Thrombus aspiration (%)	7.5	9.9	2	<0.001
Balloon angioplasty (%)	77.8	78.2	76.8	0.681
Stenting (%)	89	92.6	81.3	<0.001

Abbreviations: PCI, percutaneous coronary intervention; CAD, coronary artery disease.

Table 3. *In-hospital pharmacological therapy for patients with MI and comparison between STEMI and NSTEMI subgroups.*

In-hospital phramacological therapy (%)	All patients (n = 795)	STEMI patients (n = 491)	NSTEMI patients (n = 304)	p
ASA	97.6%	98.6%	96%	0.031
P_2Y_{12} inhibitor (%)	89.9	95.9	80.3	<0.001
Ticagrelor	58.8%	71.9%	36.9%	<0.001
Prasugrel	10.6%	11.1%	9.7%	0.549
Clopidogrel	22.9%	14.6%	36.9%	<0.001
Statin (%)	89.3%	91.3%	86.1%	0.032
Standard heparin (%)	64.9%	74.9%	45.4	<0.001
LMWH (%)	28.6%	19.9%	42.6%	<0.001
GP IIb/IIIa inhibitors (%)	25.8%	34.8%	11.3%	<0.001
Noradrenalin (%)	13.8%	16.9%	8.9%	0.001
Dobutamin (%)	6.5%	7.1%	5.7%	0.597
Levosimendan (%)	6.5%	9.2%	2.3%	<0.001
Antibiotics (%)	19.9%	21.4%	17.5%	0.201
Diuretics (%)	21.4%	19.2%	2.3%	<0.001
Fondaparinux (%)	8.6%	2.3%	18.9%	<0.001
VA ECMO (%)	0.6%	0.8%	0.3%	0.654
Mechanical ventilation (%)	9.8	11	7.9	0.177
IABP (%)	1.1	1.4	0.7	0.495
CABG (%)	7.4	4.1	12.8	<0.001
CABG or PCI (%)	86.9	94.1	75.3	<0.001

Abbreviations: ASA, acetylsalicylic acid; LMWH, low-molecular weight heparin; GP, glycoprotein; VA ECMO, veno-arterial extra-corporeal membrane oxygenation; IABP, intra-aortic balloon pump; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention.

Table 4. *In-hospital complications of patients with MI and comparison between STEMI and NSTEMI subgroups.*

Hospital complications (%)	All patients (n = 795)	STEMI patients (n = 491)	NSTEMI patients (n = 304)	p
Killip classes ≥ II (%)	25.8	28.9	20.7	0.012
Cardiogenic shock (%)	11.7%	14.1	7.9	0.009
Arrhythmias (%)	31.9	38.5	21.4	<0.001
Hospital infection (%)	20.5	22.8.	14.8.	0.047
Bleeding (%)	8.8	9.2	8.2	0.700
Reinfarction (%)	0.5	0.4	0.7	0.639
In-stent thrombosis (%)	0.6	0.8	0.3	0.654
Acute kidney injury (%)	11.2	11.9	10	0.418
Ejection fraction < 45% (%)	32.9	39	24.3	0.418
Mitral regurgiration (%)	33.2	31.6	35.7	0.290

pain onset in 71.5% of cases, within the first 6 h in 60.6%, and within 3 h in 31.5%. Femoral access was used significantly more often in STEMI patients whereas radial access was more common in NSTEMI patients. Single-vessel CAD predominated in STEMI patients, while multi-vessel CAD was more frequent in NSTEMI patients.

The types of in-hospital pharmacological therapies are presented in Table 3. The use of acetylsalicylic acid, ticagrelor, unfractionated heparin, statins, bail-out therapy with GP IIb/IIIa inhibitors, noradrenalin, levosimendan, and diuretics were applied significantly more frequently for STEMI patients, while NSTEMI patients more frequently received clopidogrel, low-molecular-weight heparin, fondaparinux, and underwent CABG. There were no significant differences in the use of prasugrel, dobutamine, veno-arterial extracorporeal membrane oxygenation, mechanical ventilation, intra-aortic balloon pump, or antibiotics between STEMI and NSTEMI patients.

Hospital complications are presented in Table 4. STEMI patients had a significantly higher incidences of heart failure (Killip class ≥ 2), cardiogenic shock, arrhythmia, and hospital-acquired infection. There were no significant differences in the incidences of bleeding, reinfarction, in-stent thrombosis, acute kidney injury, mitral regurgitation, or ejection fraction <45% between the groups.

The outcome data are presented in Table 5. There were no significant differences in the in-hospital, 30-day, and 6-month mortality rates between STEMI and NSTEMI patients. However, the rehospitalization rate within 6 months was higher in NSTEMI patients. As shown in Figure 1, there was no significant difference in the 6-month survival rates between STEMI and NSTEMI patients (93.3% vs. 92.8%, respectively, log-rank p = 0.789).

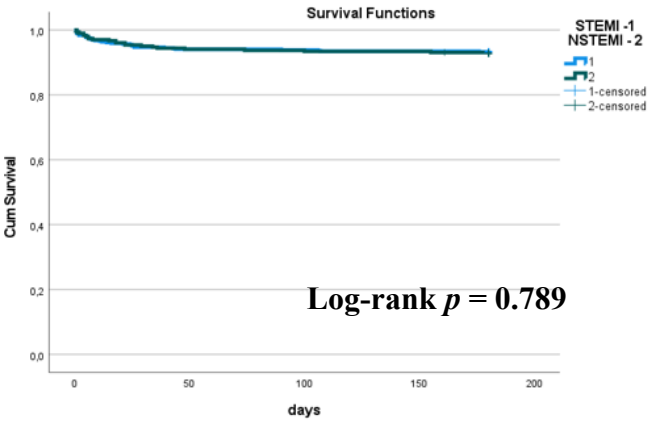

Figure 1. *Six-month survival comparison between STEMI and NSTEMI patients.*

DISCUSSION

Both significant and non-significant differences in the studied characteristics and admission data were observed between STEMI and NSTEMI patients. Among the baseline characteristics and admission data, older age and comorbidities were significantly more prevalent in NSTEMI patients, whereas STEMI patients had higher admission high-sensitivity cardiac troponin I levels ≥1000 pg/L, a higher prevalence of smoking, and more frequent prior resuscitation. Lipid profile, BMI, and the prevalence of heart failure on

Table 5. *Outcome data for patients with MI and comparison between STEMI and NSTEMI subgroups.*

Outcome data	All patients (n = 795)	STEMI patients (n = 491)	NSTEMI patients (n = 304)	p
In-hospital mortality (%)	5.5	5.5	5.6	0.999
30-day mortality (%)	5.2	5.5	4.6	0.624
6-month mortality (%)	6.9	6.7	7.2	0.776
6-month rehospitalization rate (%)	9.1	5	15.5	<0.001
6-month rehospitalization rate or mortality (%)	15.3	11.3	21.5	<0.001

admission were similar between the two groups.
STEMI patients were significantly more likely to be treated with primary PCI within the first 24 h as compared to NSTEMI patients, although coronary angiography was performed within the first 24 h in > 90% of both groups. Femoral access and single-vessel CAD were more common for STEMI patients, whereas multi-vessel CAD, radial access, and CABG were more frequent for NSTEMI patients.
The use of dual antiplatelet therapy, bail-out GP IIb/IIIa inhibitors, and standard heparin was significantly higher in STEMI patients than NSTEMI patients. STEMI patients also more frequently required treatment with noradrenalin, levosimendan, and loop diuretic due to a higher prevalence of in-hospital heart failure, particularly cardiogenic shock. Although no significant differences in mortality were observed between the groups, rehospitalization rates were significantly higher in NSTEMI patients due to heart failure, reinfarction, repeated PCI, or bleeding.
Among all included consecutive acute MI patients, 61.8% had STEMI and 38.2% had NSTEMI. Most studies report a higher prevalence of NSTEMI among acute MI patients (5-7). The lower prevalence of NSTEMI in our cohort may be explained by treatment of NSTEMI patients in smaller local PCI centers in our region, which operate only 8 h per day and 5 days per week.
Our findings confirm previous studies showing that NSTEMI patients are older and have more comorbidities than STEMI patients (5-7). Comorbidities, such as arterial hypertension, diabetes, and prior MI, in NSTEMI patients represent an increased risk of atherosclerosis. STEMI patients, who were on average a few years younger, more frequently had a history of smoking and positive family history of MI.
Although the global prevalence of smoking has declined from 22.7% in 2007 to 17% in 2021, the absolute number of smokers remains high due to population growth (14). According to the World Health Organization, the prevalence of smoking in Slovenia was 17.6% in 2021, despite smoking being banned in public areas since 2007 (15). However, among acute MI patients, 33.2% were smokers and even 38.8% among STEMI patients. The lower prevalence of smoking among older NSTEMI patients likely reflects the implementation of primary and secondary preventive measures.
Regarding the higher proportion of STEMI patients with a family history of MI, our data are consistent with findings of a study of the Danish national registry showing that the number of affected first- and second-degree relatives meaningfully contributes to risk assessment, especially in middle age (16).
The lipid profiles of STEMI and NSTEMI patients were similar. Despite prior MI in 25% and prior PCI in 29.4% of NSTEMI patients, mean low-density lipoprotein cholesterol levels remained well above the recommended target of 1.4–1.8 mmol/L for patients with established atherosclerosis (17).
Our data on PCI use in STEMI patients (>90%), particularly within the first 24 h, are consistent with the European STEMI registry (2021), where primary PCI was used in 83%–97% of cases (18). Although current guidelines recommend performing PCI as soon as possible, only 31.5% of our STEMI patients underwent primary PCI within the first 3 h of chest pain onset, while 45.1% of high-risk NSTEMI patients received early PCI within the first 24 h. High-risk criteria included elevated high-sensitivity cardiac troponin I levels, dynamic ST-segment or T-wave changes, transient ST-segment elevation and a Global Registry of Acute Coronary Events risk score >140 (3). When PCI was not feasible, CABG was performed – 12.8% in NSTEMI versus 4.1% in STEMI patients – to ensure adequate myocardial perfusion. During the initial hospitalization, PCI or CABG was performed for 75.1% of NSTEMI patients, significantly less frequently than for STEMI patients. A 2022 meta-analysis showed that the delayed application of an invasive strategy as compared with standard medical therapy did not significantly affect the hard clinical outcomes of NSTEMI patients (19).
Dual antiplatelet therapy was administered in the majority of both STEMI and NSTEMI patients. Ticagrelor was more commonly used for STEMI patients, whereas clopidogrel was more frequently used for NSTEMI patients due to bleeding or an increased bleeding risk, particularly in older patients

with comorbidities (3). Higher admission levels of high-sensitivity cardiac troponin I levels in STEMI patients reflect more extensive ischemic myocardial injury, which is associated with a higher prevalence of heart failure, including cardiogenic shock, and consequently greater use of noradrenalin, diuretics, and levosimendan (3, 8).

It has long been established that in-hospital heart failure is associated with an increased mortality risk, often due to delays in timely primary PCI for STEMI patients (20). In our cohort of acute MI patients, the incidence of in-hospital acute heart failure was approximately 25%, consistent with reported rates of 7% and 38% in acute coronary syndrome trials (21). Acute heart failure may result from extensive, often anterior-wall myocardial injury. Alternatively, even smaller infarctions can precipitate acute decompensation of chronic heart failure in patients with comorbidities, such as arterial hypertension, previous MI, and type 2 diabetes – particularly in elderly NSTEMI patients (21-23).

Acute heart failure is a major determinant of the mortality of acute MI patients, especially in settings with suboptimal implementation of guideline-directed medical and reperfusion therapies (21,23). In addition to pharmacological therapy, early reperfusion remains crucial, particularly for STEMI patients (3). Despite the high prevalence of acute heart failure in our cohort, the in-hospital and 30-day mortality rates were below 6% due to early PCI and guideline-recommended medical therapy (3, 19, 21-23)

Over the past two decades, the use of reperfusion therapy for both STEMI and NSTEMI has improved in developed countries. In Europe, reperfusion therapy for STEMI patients (primary PCI + intravenous fibrinolysis) increased from 55.8% to 92.7%, and PCI use from 40.4% to 83%–97% (18). In parallel, the in-hospital mortality rate decreased from 7% to 4.4% overall (range, 2.5%–5.9%) in member states and countries affiliated with the European Society of Cardiology (18).

In conclusion, there were both similarities and differences in the studied characteristics and clinical data between STEMI and NSTEMI patients. While the in-hospital, 30-day, and 6-month mortality rates were similar, NSTEMI patients had higher 6-month rehospitalization and combined 6-month rehospitalization/mortality rates. These differences were likely due to older age, greater comorbidity burden, and less likely frequently PCI during the initial hospitalization. NSTEMI patients were significantly older and had more comorbidities, whereas STEMI patients experienced more extensive myocardial injury and higher rates of in-hospital heart failure. However, the higher rate of early PCI and pharmacological therapy resulted in similar mortality data but lower rehospitalization rates for STEMI patients.

STUDY LIMITATIONS

The main limitation of this observational study was the retrospective design, which may have introduced selection and recall biases. Residual confounding could not be entirely excluded. As this was a single-center study, the number of NSTEMI patients was limited, and the findings may not be fully generalizable for this subgroup of acute MI patients. Second, some data were missing, particularly ejection fraction measures and other laboratory parameters, due to early fatalities or early transfers to local hospitals. Nevertheless, these data provide valuable real-world insights into PCI use, pharmacological therapy, in-hospital complications, mortality, and 6-month rehospitalization due to reinfarction, repeat PCI, heart failure, and bleeding in STEMI and NSTEMI patients.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

REFERENCES

1. Bergmark BA, Mathenge N, Merlini PA, Lawrence-Wright MB, Giugliano RP. Acute coronary syndromes. The Lancet. 2022; 399(10332):1347-58. doi: 10.1016/S0140-6736(21)02391-6.
2. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, White HD: the Executive Group on behalf of the Joint European Society of Cardiology (ESC)/American College of Cardiology (ACC)/American Heart Association (AHA)/World Heart Federation (WHF) Task Force for the Universal Definition of Myocardial Infarction Fourth universal definition of myocardial infarction (2018). Eur Heart J. 2019; 40(3):237-69. doi: 10.1093/eurheartj/ehy462.
3. Byrne RA, Rossello X, Coughlan JJ, Barbato E, Berry C, Chieffo A, et al. 2023 ESC Guidelines for the management of acute coronary syndromes. Developed by the task force on the management of acute coronary syndromes of the European Society of Cardiology (ESC). Eur Heart J. 2023;44(38):3720-826. doi: 10.1093/eurheartj/ehad191.44: 3720–826.
4. Mitsis A and Gragnano F. Myocardial Infarction with and without ST-segment Elevation: A Contemporary Reappraisal of Similarities and Differences. Curr Cardiol Rev. 2021;17: e230421189013
5. Montalescot G, Dallongeville J, Van Belle E, Rouanet S, Baulac C, Degrandsart A, and Vicaut E for the OPERA Investigators. STEMI and NSTEMI: are they so different? 1 year outcomes in acute myocardial infarction as defined by the ESC/ACC definition (the OPERA registry). Eur Heart J. 2007;28(12):1409-17. doi: 10.1093/eurheartj/ehm031.
6. Bjarnadóttir S, Aspelund T, Gudmundsson EF, Gudnason V, Andersen K. Why have temporal trends in STEMI and NSTEMI incidence and short-term mortality changed in recent years? A nationwide 35-year cohort study in Iceland. BMJ Open. 2025;15: e087815. doi:10.1136/bmjopen-2024-087815.
7. Hasdai D, Behar S, Wallentin L, Danchin S, Gitt AK, Boersma E, et al. A prospective survey of the characteristics, treatments and outcomes of patients with acute coronary syndromes in Europe and the Mediterranean basin. The Euro Heart Survey of Acute Coronary Syndromes (Euro Heart Survey ACS). Eur Heart J. 2002;23(15):1190–201, https://doi.org/10.1053/euhj.2002.3193
8. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, ta al., ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021;42(36):3599-726. doi: 10.1093/eurheartj/ehab368.
9. Levey AS. Defining AKD: The Spectrum of AKI, AKD, and CKD. Nephron. 2022;146(3):302–5.
10. Calandra T, Cohen J. The international sepsis forum consensus conference on definitions of infection in the intensive care unit. Crit Care Med. 2005;33(7):1538–48.
11. Steg PG, Huber K, Andreotti F, Arnesen H, Atar D, Badimon L, et al. Beeding in acute coronary syndromes and percutaneous coronary interventions: position paper by the Working Group on Thrombosis of the European Society of Cardiology. Eur Heart J. 2011;32(15):1854-64.
12. banez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018;39(2):119-77.
13. Collet J-P, Thiele H, Barbato E, Barthelemy O, Bauersachs J, Bhatt DL, et al. 2020 ESC Guidelines for themanagement of acute coronary syndromes in patients presenting

without persistent ST-segment elevation. The Task Force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J. 2021;42(14):1289-367. doi: 10.1093/eurheartj/ehaa575

14. Global Tobacco rates and Statistics. Available at: https://tobaccoatlas.org/challenges/prevalence
15. ZAKON O SPREMEMBAH IN DOPOLNITVAH ZAKONA O OMEJEVANJU UPORABE TOBAČNIH IZDELKOV (ZOUTI-C). Available at: http://www2.gov.si/zak/Pre_Zak.nsf/2364c45aa6e10646c12566160029fa1c/adcf047674d9b71fc12573020048f6f5?OpenDocument
16. Ranthe MF, Petersen JA, Bundgaard H, Wohlfahrt J, Melbye M, Boyd HA. A Detailed Family History of Myocardial Infarction and Risk of Myocardial Infarction – A Nationwide Cohort Study. PLoS ONE. 2015; 10: e0125896. doi: 10.1371/journal.pone.0125896
17. Mach F, Baigent C, Catapano Al, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). Eur Heart J. 2020;41(1):111-88. doi:10.1093/eurheartj/ehz455.
18. Zeymer U, Ludman P, Danchin N, Kala P, Laroche C, Sadeghi M et al. on behalf of the ACVC EAPCI EORP ACS STEMI investigators group of the ESC. Reperfusion therapies and in-hospital outcomes for ST-elevation myocardial infarction in Europe: the ACVC-EAPCI EORP STEMI Registry of the European Society of Cardiology. Eur Heart J. 2021;42(44):4536–49. doi:10.1093/eurheartj/ehab342
19. Kite TA, Kurmani SA, Bountziouka V, Cooper NJ, Lock ST, Gale CP, et al. Timing of invasive strategy in non-STelevation acute coronary syndrome: a meta-analysis of randomized controlled trials. Eur Heart J. 2022; 43(33):3148–61, https://doi.org/10.1093/eurheartj/ehac213.
20. Steg PG, Dabbous OH, Feldman LJ, Cohen-Solal A, Aumont M-C, López-Sendón J, et al. Determinants and prognostic impact of heart failure complicating acute coronary syndromes: observations from the Global Registry of Acute Coronary Events (GRACE). Circulation.2003;109(4):494–9, https://doi.org/10.1161/01.CIR.0000109691.16944.DA
21. Harrington J, Schuyler Jones W, Udell JA, Hannan K, Bhatt DL, Anker SD, et al. Acute Decompensated Heart Failure in the Setting of Acute Coronary Syndrome. JACC: Heart Failure. 2022;10(6):404-14. doi: 10.1016/j.jchf.2022.02.008.
22. Satya Sai Venkata Jagadeesh K, Shaik T, Mayow A H, Sompalli S, Arsalan M, Chaudhari SS, et al. Factors Associated with the Development of Heart Failure Following Acute Coronary Syndrome: A Systematic Review and Meta-Analysis. Cureus. 2024;16(12): e75999. DOI 10.7759/cureus.75999.
23. Harjola V-P, Parissis J, Bauersachs J, Brunner-La Rocca J-P, Bueno H, Čelutkiene J, et al. Acute coronary syndromes and acute heart failure: a diagnostic dilemma and high-risk combination. A statement from the Acute Heart Failure Committee of the Heart Failure Association of the European Society of Cardiology. Eur Heart J. 2020;22:1298-314. doi:10.1002/ejhf.1831

Sistemska tveganja za varnost v primarnem zdravstvenem varstvu: raziskava z mešanimi metodami

Systemic safety risks in primary healthcare: a mixed-methods study

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Ključne besede:
varnost pacientov, osnovno zdravstveno varstvo, komunikacija, sistemska tveganja, FMEA, simulacijsko učenje

Key words:
patient safety; primary healthcare; communication; systemic risk; FMEA; simulation-based learning

Članek prispel / Received
22. 4. 2026
Članek sprejet / Accepted
9. 9. 2026

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Izvleček

Uvod: *Varnost pacientov v osnovnem zdravstvenem varstvu je vse bolj prepoznana kot sistemski pojav, vendar empirični dokazi še vedno primanjkujejo. Namen raziskave je bil analizirati varnostna tveganja z vidika zdravstvenih delavcev in pacientov ter razviti integrativni konceptualni model varnosti.*

Metode: *Izvedena je bila dvo-stopenjska raziskava z mešanimi metodami v Zdravstvenem domu Ljubljana. Kvantitativni del je vključeval retrospektivno analizo podatkov o prijavljenih varnostnih dogodkih v obdobju 2015–2024 ter proaktivno oceno tveganj z metodo FMEA. Kvalitativni podatki so bili zbrani s strukturiranimi vprašalniki med zdravstvenimi delavci (n = 20) in pacienti (n*

Abstract

Introduction: *Patient safety in primary healthcare is increasingly recognized as a systemic phenomenon, yet empirical evidence is limited. This study aimed to analyse safety risks from the perspectives of healthcare professionals and patients and to develop an integrative conceptual model of safety.*

Methods: *A two-phase mixed-methods study was conducted at Ljubljana Community Health Centre (Ljubljana, Slovenia). Quantitative analysis included retrospective data on reported safety incidents from 2015 to 2024 and proactive risk assessment using Failure Mode and Effects Analysis (FMEA). Qualitative data were obtained through structured questionnaires with*

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= 9), vključno z odprtimi vprašanji, analiziranimi z metodo vsebinske analize.

Rezultati: *Identificiranih je bilo 554 varnostno relevantnih dogodkov, pri čemer so bila organizacijska in procesna tveganja najpogostejša. Komunikacija se je izkazala za osrednje presečno tveganje, ki deluje kot prispevni dejavnik, ranljiv proces in neposreden vir napak. Organizacijska tveganja so pogosta, vendar imajo večinoma zmerne posledice, medtem ko so terapevtska tveganja redkejša, a z večjo klinično težo. Človeška napaka je bila večinoma zaznana kot sekundarni, sistemsko pogojen dejavnik. Pacienti so poročali o visoki zaznani varnosti, vendar bi morebitna napaka pomembno vplivala na zaupanje. Ključni prispevni dejavniki vključujejo časovni pritisk, pomanjkanje kadra, nejasne postopke in komunikacijske izzive.*

Zaključek: *Varnostna tveganja v osnovnem zdravstvenem varstvu so pretežno sistemske narave. Komunikacija, organizacija dela in časovni pritisk predstavljajo ključne vzvode varnosti, simulacije pa obetavno strategijo za proaktivno prepoznavanje in obvladovanje latentnih tveganj.*

healthcare professionals (n = 20) and patients (n = 9), including open-ended questions analysed by content analysis.

Results: *A total of 554 safety-related events were identified; organizational and process-related risks were most frequent. Communication emerged as a central cross-cutting risk, functioning simultaneously as a contributing factor, vulnerable process, and direct source of error. Organizational risks were frequent but generally associated with moderate consequences, whereas therapeutic risks were less frequent but carried higher clinical severity. Human error was predominantly perceived as a secondary, system-dependent factor. Patients reported high perceived safety. However, potential errors were associated with a substantial impact on trust. Key contributing factors included time pressure, staff shortages, unclear procedures, and communication challenges.*

Conclusion: *Safety risks in primary healthcare are predominantly systemic. Communication, organization of work, and time pressure represent key leverage points, while simulation emerges as a promising strategy for proactive identification and mitigation of latent risks.*

INTRODUCTION

Quality and safety of clinical processes in primary healthcare constitute a cornerstone of modern health systems. The primary level of care serves the largest proportion of the population and encompasses a broad spectrum of clinical situations. Primary care represents the first and continuous contact between patients and the healthcare system. Therefore, errors and deficiencies at this level may have long-term and cumulative consequences for individual and population health (1, 2).

Patient safety has evolved into an independent scientific discipline over the past two decades that extends beyond the traditional understanding of clinical quality. The focus has shifted from the individual responsibility of healthcare professionals to systemic factors, organizational culture, and the complexity of healthcare processes. Nevertheless, most empirical research, interventions, and standards remain centred on hospital settings, while primary healthcare continues to be relatively underexplored (3-5).

Patient safety in primary healthcare is a key component of high-quality care. Although outpatient work is less intensive than hospital care, numerous safety risks may affect treatment outcomes, patient satisfaction, and system efficiency. The characteristics of the primary care environment, such as fragmented processes, high staff workload, multiple transitions between levels of care, and reliance on communication and coordination, create a complex network of potential errors and incidents. Safety risks in primary healthcare are multifaceted and extend beyond purely clinical errors. Monitoring and risk assessment should include retrospective data, proactive methods,

individual clinical risk assessments, and measurement of safety climate. A systematic approach and a strong safety culture are essential for reducing adverse events, improving patient safety, and increasing the reliability of care in primary healthcare. Incorporating risk assessment and safety culture analysis enables the identification of priority areas for improvement, leading to better clinical outcomes and a reduction in adverse events.

The most common safety risks in primary healthcare include medication-related errors, communication and coordination challenges, process-related risks, organizational complications, and physical risks to patients (8). Errors in prescribing, dispensing, or administering medications are among the most frequently documented safety risks in primary care. Unclear information about allergies, insufficient verification of drug interactions, and inconsistent work practices contribute to an increased likelihood of errors (1, 8). Transitions between levels of care constitute a systematic source of risk. The absence of consistent documentation during transitions (e.g., hospital discharge to outpatient care) leads to the loss of important information and increases the likelihood of clinical errors (8, 9). Inefficient or non-standardized work processes and insufficient standardization contribute to errors that may not directly result in clinical harm but affect overall quality and safety (8, 10). Although physical injuries occur less frequently in outpatient settings than in hospitals, physical injuries remain a serious source of risk, particularly in relation to falls within clinic premises or among patients with mobility limitations (11).

The aim of this study was to comprehensively analyse the perception of safety risks in primary healthcare from the perspectives of healthcare professionals and patients, to identify key contributory factors, vulnerable processes, and areas of potential error, and to develop an integrative conceptual model of patient safety based on quantitative and qualitative data. The purpose of the study was exploratory and quality-improvement oriented rather than analytical or predictive.

MATERIALS AND METHODS

The situation analysis was conducted as a two-phase mixed-methods study: 1) A retrospective descriptive-analytical study aimed at systematically analysing safety risks in primary healthcare at Ljubljana Community Health Centre [LCHC] (Ljubljana, Slovenia) over an extended time. The study was based on secondary analysis of existing data on reported adverse events and incidents and on the application of a standardized proactive risk analysis method [FMEA] (12); and 2) A qualitative study used structured online questionnaires containing several open-ended questions.

Risk analysis

Data sources

The analysis included data on reported safety risks and incidents at LCHC from 2015 to 2024. The data were derived from internal adverse event and incident reporting records collected within the existing quality assurance and patient safety system. All events documented as safety-relevant during the observed period were included in the analysis, regardless of severity level or outcome.

Risk categorization

The identified risks were classified into the following four thematic domains:

1. physical harm to patients and employees;
2. adverse events related to medication administration;
3. incidents in work processes; and
4. organizational and systemic risks.

For the purposes of this study, a safety risk refers to any condition or circumstance with the potential to cause harm to patients or healthcare professionals. An adverse event is an incident that results in harm to a patient. An incident refers to any unintended event or circumstance that could have or did affect the safety of healthcare delivery, regardless of whether harm occurred. The term "safety-related event" is used as an umbrella term encompassing safety risks, incidents, near misses, and adverse events identified through the institutional reporting system (13). The

classification was based on content analysis of event descriptions and was performed to enable longitudinal comparability and clearer trend analysis.

Quantitative risk analysis

The number of reported risks was calculated for each risk domain for each year of the observed period. Data were analysed using descriptive statistics and absolute frequencies (n) were reported. The quantitative component was designed to provide a descriptive overview of reported safety risks within the institution rather than to test predefined hypotheses. Therefore, descriptive statistics were considered appropriate for the analysis of the complete institutional dataset.

Risk prioritisation was performed using Failure Mode and Effects Analysis (FMEA), which was adapted to the primary healthcare setting and the objectives of this study (12).

In addition to the conventional FMEA dimensions, the assessment incorporated patient impact as a separate criterion to better reflect the potential clinical consequences of safety events in routine primary healthcare practice.

Each identified risk was assessed according to the following four criteria:

- frequency (F), occurrence rate of the risk;
- severity (S), expected seriousness of the consequences should the event occur;
- likelihood (V), probability that the event would recur under similar circumstances; and
- patient impact (P), expected influence of the event on patient care and clinical outcomes.

Each criterion was rated on a five-point scale (1–5). Frequency categories were established using the average annual number of reported events for each risk domain during the study period. The thresholds were determined according to the distribution of reported events within the LCHD to facilitate local risk prioritisation, as follows:

- ≥ 30 events/year (very frequent) = 5;
- 20–29 events/year (frequent) = 4;
- 10–19 events/year (occasional) = 3;
- 5–9 events/year (rare) = 2; and
- < 5 events/year (very rare) = 1.

To prioritise risks, an adapted risk priority number (RPN) was calculated using the following equation: $RPN = (F \times V) + (S \times P)$.

This adapted calculation was developed specifically for the present study to distinguish the clinical severity of an event from its potential impact on patient care, unlike the conventional FMEA approach (14), which typically combines severity, occurrence, and detectability. The modified approach was intended to support local prioritisation of patient safety risks (15) rather than to serve as a validated alternative to the classic FMEA model. The resulting RPN values were used to rank identified risks and to inform the prioritisation of improvement measures within the institution.

Qualitative part

Participants

Two groups of participants were included: 1) healthcare professionals employed in primary healthcare (n = 20); and 2) patients receiving care in primary healthcare (n = 9).

Participation was voluntary and anonymous. All individuals who completed the questionnaire (fully or partially) during the data collection period were included in the analysis.

Research instruments

Data were collected using two structured questionnaires (one for healthcare professionals and one for patients) Both questionnaires included a combination of closed-ended questions (nominal and ordinal variables) and open-ended questions.

The healthcare professional questionnaire included basic demographic data, perception of existing for underreporting, perception of safety culture, and open-ended questions on perceived risks and improvement suggestions. Patient questionnaire included basic demographic data, perception of safety of care, experience with care and communication with healthcare professionals, and perceived risks and suggestions for improvement.

Data collection procedure

The questionnaires were distributed electronically. The participants were informed about the purpose of the study, anonymity of participation, and the

voluntary nature of involvement before completing the questionnaires. No time limit was imposed for completing the questionnaires.

Data analysis

Data were analysed using descriptive statistics. Absolute (n) and relative frequencies (percentages) were calculated for each variable. The results are presented in frequency tables with variables listed in rows and response categories presented with corresponding frequencies and percentages.

Responses to the open-ended questionnaire items were analysed using qualitative content analysis (16). An inductive approach was adopted to identify recurring concepts and themes emerging from participant responses. The unit of analysis consisted of individual meaningful statements or phrases related to patient safety, perceived risks, contributing factors, vulnerable processes, safety events, and proposed improvement measures.

The analysis was performed in several stages. First, all responses were read repeatedly to achieve familiarity with the data. Meaning units relevant to the research aims were then identified and assigned initial descriptive codes. Similar codes were subsequently grouped into broader categories based on conceptual similarity. Finally, the categories were reviewed and refined through iterative comparison with the original data and integrated with the quantitative findings to develop the conceptual framework.

The coding and category development were performed independently by two members of the research team. Differences in coding and category assignment were discussed until consensus was reached. When necessary, the original questionnaire responses were re-examined to ensure that the final categories accurately reflected the views of the participants.

Several procedures were applied to enhance the credibility of the qualitative analysis, including independent coding, iterative review of the coding framework, consensus discussions between researchers, and continuous comparison of the developed categories with the original responses. The integration of qualitative findings with quantitative data provided an additional form of methodologic triangulation, which supported the consistency of the overall interpretation.

Integration of quantitative and qualitative findings

Following separate quantitative and qualitative analyses, findings were integrated using a convergent mixed-methods approach. Categories emerging from qualitative content analysis were compared to quantitative risk domains and synthesised into an integrative conceptual framework describing relationships between contributory factors, vulnerable processes, safety events, and proposed interventions.

Ethical approval and data protection

The study received ethical approval from the National Ethics Committee (No. 0120-481/2025-2711-3). Appropriate technical and organisational measures were implemented, including encryption, anonymisation and pseudonymisation of data, role-based access control, and storage in secure data repositories, to ensure the confidentiality of study participants. Data were managed in accordance with the Findable, Accessible, Interoperable, and Reusable (FAIR) principles and applicable data protection regulations.

RESULTS

Risk analysis

Number of risks by domain and year

Analysis of the aggregated data showed the following distribution of risks across domains (Table 1):

- physical harm (consistently present throughout the entire study period and more pronounced fluctuations between year);
- other risk domains (the highest absolute number of events, indicating a broad range of organizational and process-related risks);
- medication administration (a lower number of events but with high clinical significance); and
- incidents (a moderate number of events, primarily related to disruptions in work processes0.

Table 1: *Safety risks in the Ljubljana Community Health Centre from 2015 to 2024*

Year	Physical threat		Other risk areas		Medication application		Safety incidents		SUM
	N	%	N	%	N	%	N	%	
2016	26	33.3	24	30.8	14	17.9	14	17.9	78
2017	11	14.9	38	51.4	10	13.5	15	20.3	74
2018	25	26.0	42	43.8	16	16.7	13	13.5	96
2019	6	7.2	59	71.1	11	13.3	7	8.4	83
2020	8	17.4	15	32.6	8	17.4	15	32.6	46
2021	7	17.1	20	48.8	5	12.2	9	22.0	41
2022	9	27.3	15	45.5	4	12.1	5	15.2	33
2023	6	18.8	16	50.0	5	15.6	5	15.6	32
2024	9	12.7	43	60.6	10	14.1	9	12.7	71
SUM	107	19.3	272	49.1	83	15.0	92	16.6	554

Table 2: *FMEA risks in the Ljubljana Community Health Centre from 2015 to 2024*

Risk Area	Examples of reported events	Frequency (F)	Severity (S)	Likelihood (V)	Impact on Patient (P)	RPN	Risk Level	Proposed Measures
Physical hazards	Falls, needle-stick injuries, workplace violence	4	3	4	4	28	Critical	Facility improvements, non-slip surfaces, regular inspections, training
Medication administration	Wrong dose, wrong medication, omitted medication	3	5	3	5	30	Critical	Double-checking, standardized procedures, additional training
Incidents	Documentation errors, delayed referrals, workflow disruptions	3	2	3	2	13	Moderate	Process optimization, improved communication
Organizational risks	Staff shortages, scheduling problems, communication failures	2	3	2	3	12	Moderate	Review of work organization, long-term workforce planning

Results of FMEA

The analysis of reported safety risks in the LCHC during the study period (2015–2024) revealed the presence of risks in several content areas. The areas analysed included physical threats to patients and employees, adverse drug administration events, incidents in work processes, and organizational and systemic risks. The number of reported risks varied between years during the study period under review. The largest absolute number of events was recorded in the area of organizational and systemic risks, followed by risks in the area of physical threats, incidents in work processes, and adverse drug administration events. The number of reported events varied between years with higher and lower values detected depending on the individual year and area (Table 2).

Table 3: *Characteristics of healthcare workers*

Variable	Category	Frequency (n)	Share (%)
Your role in the health centre	Management position	7	35
	Physician	6	30
	Nurse / medical technician	6	30
	Other healthcare professional	1	5
Work experience in primary healthcare	> 20 years	9	45
	11–20 years	9	45
	< 5 years	1	5
	5–10 years	1	5

Table 4: *Characteristics of patients*

Variable	Category	Frequency (n)	Share (%)
Gender	Female	8	88.9
	Male	1	11.1
Age group	51–70 years	4	44.4
	31–50 years	3	33.3
	Up to 30 years	2	22.2

Qualitative results

Sample characteristics

The characteristics of study participants are presented in Tables 3 and 4.

Safety perceptions

Qualitative and quantitative data identified communication-related issues across multiple analytical categories, including perceived risks, contributing factors, vulnerable processes, and areas of potential error (Table 5). Organizational risks were frequently identified in the retrospective analysis, whereas therapeutic risks were reported less often but yielded higher FMEA severity scores. Healthcare professionals most often identified time pressure, staff shortages, unclear procedures, and poor internal communication as contributing factors to safety events. Human error was also reported, typically in conjunction with organizational and communication-related factors. Vulnerable processes most frequently included clinical care, medication-related procedures, communication and documentation, and work organization. Participants identified near misses, minor events, and adverse events as relevant types of safety events and proposed measures, including standardization of procedures, improved communication, organizational improvements, increased staffing, and simulation-based training. Patients associated patient safety with clear communication, understanding of instructions, and trust in healthcare professionals.

Table 5: *Integrative coding matrix of security perception in the Ljubljana Community Health Centre*

Analytical Level	Main Category	Key Codes (Summary)	Related Questionnaire Questions	Integrative Meaning
1. PERCEIVED RISKS	Communication risks	Unclear communication, incorrect instructions, information transfer	Perceived risks, areas of errors	Horizontal risk, present across all processes
	Therapeutic risks	Incorrect dosage, polypharmacy, medication administration	Perceived risks, vulnerable processes	Low frequency, high severity
	Organizational risks	Scheduling, waiting, patient triage	Areas of errors	Process triggers of errors
	Violence against staff	Verbal, non-verbal, psychological violence	Perceived risks	Staff safety as a prerequisite for patient safety
2. CONTRIBUTING FACTORS (CAUSES)	Organizational factors	Time pressure, staff shortages	Contributing factors of events	Structural pressure on the system
	Communication factors	Poor internal communication	Contributing factors of events	Amplifier of other risks
	Process factors	Unclear procedures, lack of standardization	Contributing factors of events	Increases variability
	Individual factors	Human error	Contributing factors of events	Secondary, consequential factor
3. VULNERABLE PROCESSES	Clinical processes	Patient management, diagnostics	Vulnerable processes	High complexity
	Therapeutic processes	Prescribing, administration	Vulnerable processes	Critical clinical point
	Communication and documentation	Handovers, records	Vulnerable processes	Key to continuity
	Work organization	Substitutions, workload	Vulnerable processes	Contextual vulnerability
4. AREAS OF POTENTIAL ERRORS	Communication and instructions	Misunderstanding, misinterpretation	Areas of errors	Most common direct source of errors
	Waiting organization	Delays, omissions	Areas of errors	Indirect safety consequences
	Medications	Incorrect use	Areas of errors	High risk of harm
5. EVENTS	Near misses	Near misses	Events	High learning potential
	Minor events	No consequences	Events	Indicate system weaknesses
	Adverse events	Clinical complications	Events	Visible manifestation of risks

Analytical Level	Main Category	Key Codes (Summary)	Related Questionnaire Questions	Integrative Meaning
6. LEARNING MECHANISMS	Simulations	Triage, communication, medications	Simulations	Proactive learning without harm
	Event analysis	Reflection	Multiple questions	Transition from reactive to learning system
7. MEASURES	Standardization	Protocols	Measures	Reducing variability
	Communication	Clear instructions	Measures, patient safety	Key safety lever
	Organization and staffing	More time, more staff	Measures	Reducing system pressure
	Technical and spatial	Equipment, privacy	Measures	Supporting safe communication
8. OUTCOME	Patient safety	Understanding, trust	Patient safety	Final system outcome

DISCUSSION

Summary of main findings

The findings of this study suggest that safety risks in primary healthcare are influenced by a range of organizational and process-related factors. Both quantitative and qualitative data identified communication-related issues across multiple domains, including perceived risks, contributing factors, vulnerable processes, and potential areas of error. Organizational risks were reported more frequently, whereas therapeutic risks occurred less often but were associated with higher FMEA severity scores. These findings suggest that different categories of risk may require different approaches to prioritisation and management.

Comparison to other studies

The findings herein are consistent with previous research findings and suggest that patient safety in primary healthcare is shaped by interactions between organizational, human, and process-related factors rather than by individual errors alone (5, 17).

Communication and information transfer were identified across several domains of the analysis, including perceived risks, contributing factors, vulnerable processes, and potential sources of error. This pattern suggests that communication may represent an important cross-cutting component of patient safety, rather than being limited to a single aspect of care (18).

The communication-related issues identified in this study extended beyond interactions between healthcare professionals and patients to include intra-team communication, handovers, documentation practices, and organizational processes, such as scheduling and waiting-list management. These findings are consistent with previous studies indicating that unclear, incomplete, or poorly coordinated information exchange may contribute to safety incidents, particularly in time-pressured environments (9).

The findings also suggest differences between the frequency and potential impact of different types of risks. Organizational risks, including scheduling, waiting, and patient triage, were more frequently reported, whereas therapeutic risks were less common but received higher severity ratings in the FMEA.

Although this pattern should be interpreted cautiously, the pattern may indicate that prioritising safety improvements should consider both the frequency of events and the potential clinical consequences, which is consistent with the principles of proactive risk assessment (12, 19).

Healthcare professionals rarely described human error as an isolated cause of safety events. Instead, human error is typically discussed together with organizational factors, such as time pressure, staffing shortages, unclear procedures, and communication challenges (20,2 1).

Patients generally reported feeling safe during the most recent healthcare encounter and most did not express concerns about potential errors. At the same time, participants indicated that a safety incident could substantially affect trust in the healthcare institution. Although these findings are based on a small patient sample, the findings suggest that trust may be closely linked to patients' perceptions of communication quality and the clarity of information provided by healthcare professionals (22).

Implications for practice

The integrative analysis suggests that patient safety in primary healthcare is influenced by interactions between organizational factors, communication, clinical processes, and learning from safety events. Participants most frequently proposed interventions aimed at improving communication, standardising procedures, reducing organizational workload, and increasing the time available for patient interactions. Taken together, these findings suggest that improving patient safety may require a combination of organizational, process-related, and communication-focused interventions. Simulation-based education may represent one approach for supporting proactive identification of latent safety risks and strengthening teamwork and communication in a controlled environment.

Given the exploratory nature of this study and the single-centre design, these implications should be interpreted cautiously. Nevertheless, the findings are consistent with current patient safety literature supporting system-oriented approaches to safety improvement (18, 23, 24). Future studies involving multiple healthcare settings and larger samples are needed to confirm these observations and to evaluate the effectiveness of simulation-based interventions in primary healthcare.

Limitations of the study

The findings of this study should be interpreted in light of several limitations. First, the qualitative component included a relatively small number of healthcare professionals (n = 20) and patients (n = 9), which may limit the transferability of the findings to other primary healthcare settings. In particular, the small patient sample requires cautious interpretation of patient perspectives because these views may not reflect the experiences of the broader patient population. Second, participation in the questionnaire was voluntary, introducing the possibility of sampling bias because individuals with a particular interest in patient safety may have been more likely to participate. Third, the study was conducted in a single primary healthcare institution, which may limit the generalisability of the findings to other healthcare organisations with different organisational structures, resources, or safety cultures. Finally, the adapted FMEA approach used in this study was developed to support local risk prioritisation and has not been externally validated. Despite these limitations, the convergence of quantitative and qualitative findings provides a more comprehensive understanding of patient safety risks in the studied setting and offers a basis for future multicentre research.

The retrospective analysis relied on reported safety events, which may underestimate the true occurrence of incidents because reporting systems are susceptible to underreporting and reporting bias.

The modified FMEA approach was developed to support local risk prioritisation and has not been externally validated. Consequently, the calculated risk priority numbers should be interpreted as decision-support measures within the study setting rather than as universally applicable risk estimates.

The quantitative component of the study was designed as a descriptive analysis of all safety-related events reported within the LCHC during the study

period. Because the dataset comprised the complete institutional database of reported events rather than a sample drawn from a larger population, the primary objective was to describe the distribution and characteristics of safety risks rather than to test predefined hypotheses or estimate population parameters. Consequently, descriptive statistics, including absolute frequencies and percentages, were considered the most appropriate analytical approach. Risk prioritisation was subsequently performed using the adapted FMEA methodology to support the identification of areas requiring safety improvement.

CONCLUSION

Patient safety in primary healthcare represents a dynamic outcome of a complex system. Communication, time pressure, and work organization emerge as key levers of safety, while simulation appears as a promising system-level approach for identifying and addressing latent risks. The findings of this study provide an empirical basis for the further development of simulation-based programs aimed at improving the quality and safety of clinical processes in primary healthcare.

REFERENCES

1. Cánovas Zaldúa Y, Martín Martín S, Serraboguña Bret J, Hermosilla Perez E, Redon EC, Rodoreda Noguerola S. Simulated Clinical Stations in Quality and Patient Safety in a Primary Care Setting. Healthcare (Basel, Switzerland). 2025;13(13). doi: 10.3390/healthcare13131501.
2. Panesar SS, deSilva D, Carson-Stevens A, Cresswell KM, Salvilla SA, Slight SP, et al. How safe is primary care? A systematic review. BMJ Qual Saf. 2016;25(7):544–53. doi: 10.1136/bmjqs-2015-004178.
3. Baldovin T, Bassan F, Bertoncello C, Buja A, Cocchio S, Fonzo M, et al. Shaping the future of healthcare: improving quality and safety through integrating simulation into Public Health education. Front Public Health. 2024;12:1446708. doi: 10.3389/fpubh.2024.1446708.
4. Klemenc-Ketis Z, Makivic I, Poplas-Susic A. Safety culture in the primary health care settings based on workers with a leadership role: the psychometric properties of the Slovenian-language version of the safety attitudes questionnaire - short form. BMC Health Serv Res. 2018;18(1):767. doi: 10.1186/s12913-018-3594-8.
5. Simsekler MCE, Qazi A, Ozonoff A. Exploring the role of safety culture dimensions in patient safety using a Bayesian Belief Network model. Safety Sci. 2025;186:106817. doi: https://doi.org/10.1016/j.ssci.2025.106817.
6. Samra R, Bottle A, Aylin P. Monitoring patient safety in primary care: an exploratory study using in-depth semistructured interviews. BMJ Open. 2015;5(9):e008128. doi: 10.1136/bmjopen-2015-008128.
7. Virtič Potočnik T, Klemenc-Ketiš Z. Perception Of Patient Safety Culture At The Primary Care Level: The Case Of The Community Health Centre Ljubljana. Zdr Varst. 2024;63(1):21–9. doi: 10.2478/sjph-2024-0004.
8. Hernan AL, Giles SJ, Carson-Stevens A, Morgan M, Lewis P, Hind J, et al. Nature and type of patient-reported safety incidents in primary care: cross-sectional survey of patients from Australia and England. BMJ Open. 2021;11(4):e042551. doi: 10.1136/bmjopen-2020-042551.
9. Katantha MN, Strametz R, Baluwa MA, Mapulanga P, Chirwa EM. Effective Interprofessional Communication for Patient Safety in Low-Resource Settings: A Concept Analysis. Safety. 2025;11(3):91. doi.

10. Chen H, Huang Y, Yin C, He X, Ison RL, Bell LL, et al. Care coordination and patient safety outcome: a graph-based approach. npj Health Systems. 2025;2(1):15. doi: 10.1038/s44401-025-00020-9.
11. Wåhlin C, Kvarnström S, Öhrn A, Nilsing Strid E. Patient and healthcare worker safety risks and injuries. Learning from incident reporting. European Journal of Physiotherapy. 2020;22(1):44–50. doi: 10.1080/21679169.2018.1549594.
12. El-Awady SMM. Overview of Failure Mode and Effects Analysis (FMEA): A Patient Safety Tool. Glob J Qual Saf Healthc. 2023;6(1):24–6. doi: 10.36401/jqsh-23-x2.
13. WHO. Patient safety incident reporting and learning systems: technical report and guidance. Geneva: WHO; 2020.
14. Vecchia M, Sacchi P, Marvulli LN, Ragazzoni L, Muzzi A, Polo L, et al. Healthcare Application of Failure Mode and Effect Analysis (FMEA): Is There Room in the Infectious Disease Setting? A Scoping Review. Healthcare. 2025;13(1):82. doi.
15. De Haro T, Papay Ramirez L, Garcia Chileme S. A-188 Modal Failure and Effects Analysis, FMEA methodology, as a strategy to increase patient safety. Clinical Chemistry. 2024;70(Supplement_1). doi: 10.1093/clinchem/hvae106.186.
16. Mayring P. Qualitative Content Analysis: A Step-by-Step Guide. London: SAGE Publications; 2021.
17. Rashdan D, Farha RA, Yasin H, Hadi MA. Human factors frameworks in analysis of contributory factors to medication error: A systematic review. Research in Social and Administrative Pharmacy. 2025;21(9):629–52. doi: https://doi.org/10.1016/j.sapharm.2025.04.005.
18. Pacenko CdL, Figueiredo KC, Nunes E, Cruchinho P, Lucas P. Mapping Strategies for Strengthening Safety Culture: A Scoping Review. Healthcare. 2024;12(12):1194. doi.
19. Cui Y, Wang Y, Liu H, Xu S, Zhang X. Exploring the Correlation Between Patient Safety Culture and Adverse Medical Events Using Failure Mode and Effect Analysis (FMEA). Risk Manag Healthc Policy. 2025;18:1367–76. doi: 10.2147/rmhp.S502725.
20. Pereira SCdA, Ribeiro OMPL, Fassarella CS, Santos EJF. The impact of nursing practice environments on patient safety culture in primary health care: a scoping review. BJGP Open. 2024;8(1):BJGPO.2023.0062. doi: 10.3399/bjgpo.2023.0062.
21. Kumah A. Adverse event reporting and patient safety: the role of a just culture. Front Health Serv. 2025;5:1581516. doi: 10.3389/frhs.2025.1581516.
22. Entwistle VA, Quick O. Trust in the context of patient safety problems. Journal of health organization and management. 2006;20(5):397–416. doi: 10.1108/14777260610701786.
23. Ramar K, Oxentenko AS, Dowdy SC. Transforming Health Care Through Quality and Safety. Mayo Clin Proc. 2025;100(8):1385–401. doi: https://doi.org/10.1016/j.mayocp.2025.04.012.
24. Tsamasiotis C, Fiard G, Bouzat P, François P, Fond G, Boyer L, et al. From Reporting to Improving: How Root Cause Analysis in Teams Shape Patient Safety Culture. Risk Manag Healthc Policy. 2024;17:1847–58. doi: 10.2147/rmhp.S466852.

Whipplova bolezen: redka in tiha ubijalka, skrita v vsakdanjosti – prikaz primera

Whipple's Disease: A Rare but Deadly Condition Hidden in Plain Sight – A Case Report

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Ključne besede:
Whipplova bolezen, Tropheryma whipplei, globoka venska tromboza, pljučna hipertenzija, ehokardiografija

Key words:
Whipple's disease, Tropheryma whipplei, deep vein thrombosis, pulmonary hypertension, echocardiography

Članek prispel / Received
21. 8. 2025
Članek sprejet / Accepted
9. 9. 2026

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Izvleček

Namen: *Whipplova bolezen je zelo redka sistemska vnetna bolezen, ki jo povzroča okužba z bakterijo Tropheryma whipplei. Vsako leto je po svetu potrjenih približno 12 novih primerov. Klasična tetrada simptomov je sestavljena iz artralgije, anoreksije, bolečin v trebuhu in driske, vendar lahko atipična manifestacija bolezni zakasni postavitev diagnoze. Diagnostični kriteriji, s katerimi bolezen potrdimo, zahtevajo pozitivne rezultate biopsije sluznice želodca in dvanajstnika. Bolniki se po zdravljenju z antibiotiki pogosto precej hitro izboljšajo; v primeru nezdravljene bolezni pa je le-ta smrtna.*

Poročilo o primeru: *V tem kliničnem primeru obravnavamo 81-letne-*

Abstract

Background: *Whipple's disease, a rare systemic infection caused by the bacterium Tropheryma whipplei, is confirmed annually in approximately 12 new cases worldwide. The classical tetrad of symptoms consists of arthralgia, anorexia, abdominal pain, and diarrhoea; however, atypical manifestations may delay diagnosis.*

Diagnostic criteria require positive results following a stomach and duodenal mucosa biopsy. Patients often improve quite rapidly after antibiotic treatment. However, if left untreated, Whipple's disease is lethal.

Case report: *We present the case of an 81-year-old man with progressive weakness, malnutrition, chron-*

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ga bolnika s progresivno šibkostjo, malnutricijo, kroničnim vnetjem, globoko vensko trombozo in pljučno hipertenzijo brez pljučne embolije. Ehokardiografija je pokazala obremenitev desnega prekata in povečan desni prekat. Z uporabo testiranja s polimerazno verižno reakcijo (PCR) smo dokazali prisotnost Tropheryme whipplei v plevralni tekočini, blatu in slini, prisotnost v bioptatu duodenalne sluznice pa je dokončno potrdila diagnozo. Po zdravljenju s ceftriaksonom intravensko ter dolgotrajnim peroralnim zdravljenjem s sulfametoksazol-trimetoprimom je bolnik doživel izrazito klinično izboljšanje z normalizacijo vnetnih pokazateljev in izboljšanjem fizičnega stanja.

Zaključek: *S tem kliničnim primerom nameravamo izpostaviti Whipplovo bolezen kot eno izmed možnih diagnoz, katero je potrebno upoštevati pri bolnikih s sistemskimi simptomi in atipičnimi kardiovaskularnimi manifestacijami.*

ic inflammation, deep vein thrombosis, and pulmonary hypertension without pulmonary embolism. Echocardiography revealed right ventricular strain and an enlarged right ventricle.

Polymerase chain reaction detected Tropheryma whipplei in pleural fluid, stool, and saliva, while duodenal biopsy confirmed the diagnosis. Following treatment with ceftriaxone and long-term oral trimethoprim-sulfamethoxazole antibiotics, the patient experienced marked clinical improvement with normalization of inflammatory markers and improved functional status.

Conclusion: *This case highlights the importance of considering Whipple's disease in patients with unexplained systemic symptoms and atypical cardiovascular manifestations.*

INTRODUCTION

Whipple's disease (WD) is a rare multisystem infection caused by Tropheryma whipplei (1-6). The prevalence of WD is approximately 3/1,000,000, mainly affecting middle-aged Caucasian men (mean onset 55 years; male:female ratio is about 8:1), and is associated with human leukocyte antigen B27 (1,3,5-7). WD was first described in 1907, and both culture and polymerase chain reaction (PCR) diagnostic methods advanced in the 1990s (1-6). Tropheryma whipplei is detectable not only in duodenal biopsies, but also in saliva, blood, stool, cardiac valves, synovial fluid, cerebrospinal fluid (CSF), brain and multiple organs (1,9). Transmission of the disease is likely by the fecal–oral route via contaminated water (1,6,7,9). Clinically, WD often has two phases: initial arthritis/arthralgia, then (months to years later) abdominal pain, diarrhea, and weight loss (1-4,7,9,10). Other manifestations include fever, lymphadenopathy, pulmonary disease, endocarditis, encephalitis, bacteremia and neurological signs (cognitive impairment, ataxia, supranuclear ophthalmoplegia) (1,6,7). Laboratory tests usually show elevated inflammatory markers (1). Gastrointestinal findings include malabsorption, steatorrhea, malnutrition and muscle wasting (1,3,7).

Cardiac involvement can cause endocarditis, pericarditis, pleuritis, heart failure and has been reported with thrombosis and reversible pulmonary hypertension (PH). Post-mortem studies show cardiovascular involvement in >50% of cases (1,6,12). Initial diagnosis involves noninvasive PCR of stool/saliva samples, invasive biopsies (duodenal, lymph node, valve, CSF) and confirmed with Periodic acid-Schiff (PAS)-positive macrophages and villous atrophy (1,6). WD is treated with intravenous ceftriaxone or penicillin+streptomycin followed by trimethoprim–sulfamethoxazole for ≥12 months; therapy usually leads to rapid improvement, but relapses occur if eradication is inadequate (5-7). Untreated WD is fatal; nutritional support often resolves malnutrition within 2–3 months, although prolonged or higher-dose antibiotics may be required for relapse or complicated organ involvement (5-7). Long-term follow-up is recommended to monitor recurrence and manage

residual neurological or cardiac sequelae (5-7). Early recognition significantly improves outcomes.

CASE REPORT

An 81-year-old man with hypertension, type 2 diabetes, hyperlipidemia, chronic lymphocytic leukemia and previous prostate cancer presented with progressive arthralgias, weight loss, anorexia and immobility. He had a noteworthy history of extensive travel, including a trip to South America four years ago, with frequent visits to Third World countries.

Eight months before admission he developed worsening malaise, productive cough, dyspnea, elevated inflammatory markers and abdominal lymphadenopathy, with intermittent abdominal pain, diarrhea and constipation. On admission (June 2023) he had dyspnea and left leg swelling.

Laboratory tests showed the following: elevated erythrocyte sedimentation rate of 56 mm/h, leukocytes of 19.5 ×109/L, C-reactive protein of 62 mg/L, high-sensitivity troponin of 396 ng/L, D-dimer of 17,243 µg/L, N-terminal-pro-B-type natriuretic peptide (NT-pro-BNP) of 12,385.2 ng/L, hemoglobin of 120 g/L, mild renal impairment and low iron, ferritin, folate and vitamin D. Electrocardiography showed sinus rhythm with right bundle branch block and atrial fibrillation. Venous ultrasound confirmed left iliofemoral deep vein thrombosis (DVT). Computed tomography angiography excluded pulmonary embolism but suggested PH and right pleural effusion. Initial antibiotics (amoxicillin/

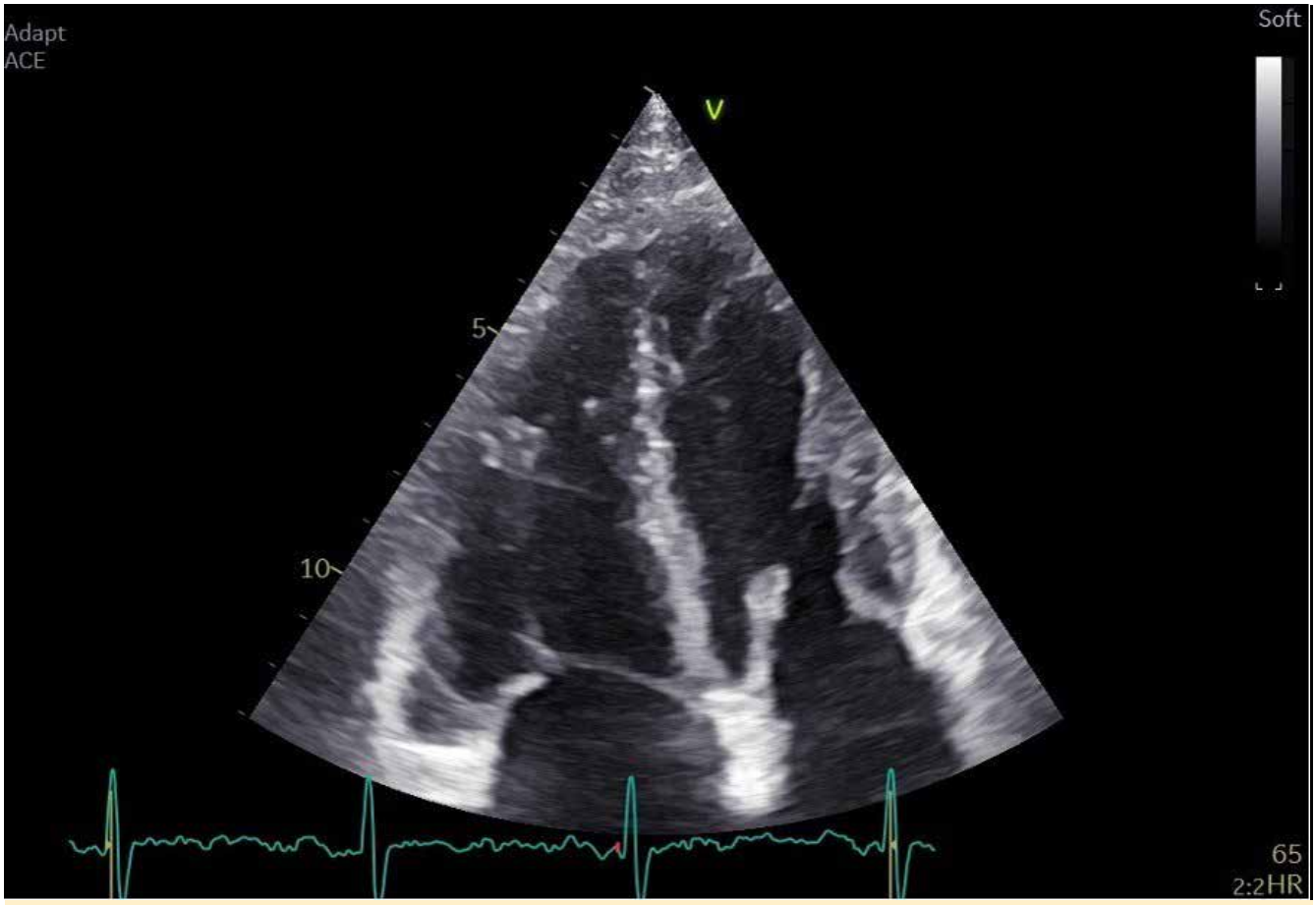

Figure 1. *Four-chamber view with enlarged right ventricle, slightly thickened free wall and weakened systolic function (RVEF 3D 41%, TAPSE 1.3 cm, FAC 29%) in the patient (J.B., 1941)*

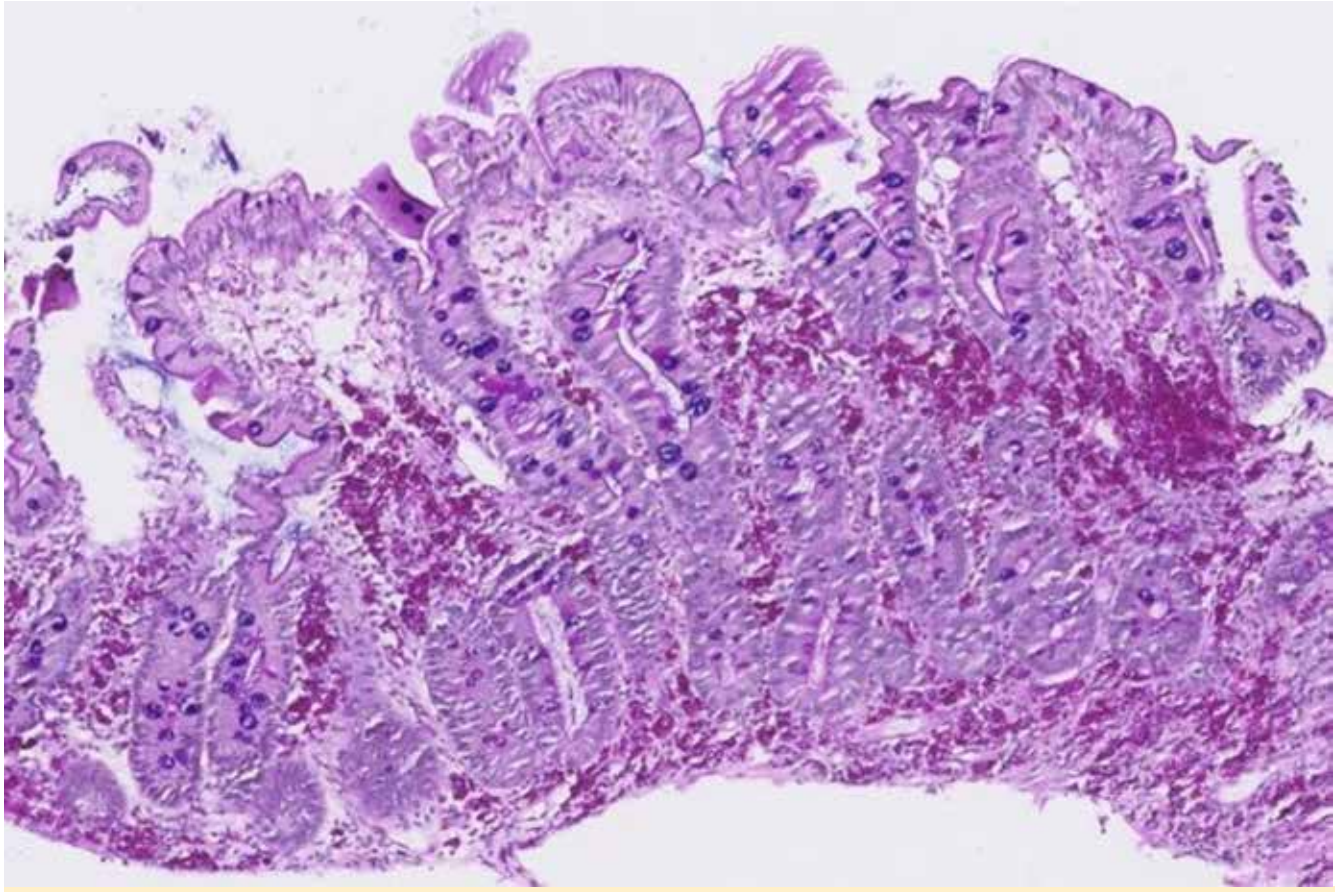

Figure 2. *Histology of duodenum mucosa with changes consistent with Whipple's disease in the patient (J.B.,1941): foamy macrophages are located in the lamina propria with villous atrophy.*

Table 1: *Comparison of laboratory findings on admission and at discharge*

	Laboratory values at admission	Laboratory values upon discharge
Leukocytes (x10^9/L)	19,5	14,5
Haemoglobin (g/L)	120	109
MCV (g/L)	80.5	82.1
Thrombocytes (10^9/L)	175	328
C-reactive protein (mg/L)	62	6
High-sensitivity troponin (ng/L)	396	/
D-dimer (ug/L)	17243	/
NT-pro-BNP (ng/L)	12385,2	803,5
BUN (mmol/L)	18,8	11.7
Creatinine (umol/L)	134	70

clavulanic acid, azithromycin) did not improve the patient's inflammation. Infection and tumor screens were negative. After a fall revealed ischemic infarction, anticoagulation was initially contraindicated; a vena cava filter was placed and low-molecular weight heparin was started once anticoagulation was deemed safe.

Echocardiography demonstrated right ventricular strain, mildly enlarged right ventricle (RV) with reduced systolic function (RV ejection fraction (RVEF) 41%, tricuspid annular plane systolic excursion (TAPSE) 1.3 cm, fractional area change (FAC) 29%, and moderate probable precapillary PH (systolic pulmonary artery pressure (sPAP) 56 mmHg.

Pleural fluid, stool and saliva PCR were positive for Tropheryma whipplei; duodenal biopsy confirmed Whipple's disease (Figure 2).

The patient received intravenous ceftriaxone 2 g/day for 19 days, the vena cava filter was removed, and anticoagulation was switched to apixaban 5 mg twice daily. Physiotherapy improved mobility; and within ten days, the patient could walk with assistance.

On discharge, antibiotics were changed to doxycycline and hydroxychloroquine, and later adjusted to sulfamethoxazole–trimethoprim when available. Follow-up showed improved inflammatory markers and NT-pro-BNP (803.5 ng/L). Four months later the corrected QT interval was prolonged (488 ms), prompting a regimen change (Table 1).

Seven months later, echocardiography revealed persistent moderate PH (sPAP 52 mmHg, mean PAP 30 mmHg) and right ventricular dysfunction (TAPSE 2.1, FAC 29%). LVEF remained normal (LVEF 3D 65%), with moderate diastolic dysfunction. The precise cause of PH remained unclear, although Whipple's disease may have been a contributory factor.

CONCLUSION

Whipple's disease is an uncommon systemic infection with variable manifestations and often delayed diagnosis. Our patient had arthralgia followed by weight loss, malnutrition, abdominal symptoms, chronic inflammation, extensive iliofemoral DVT, and persistent PH without pulmonary embolism. DVT may reflect immobility, systemic inflammation, endothelial activation, and infection-related hypercoagulability. Despite hypertension and diabetes suggesting pre-existing diastolic dysfunction, PH persisted after successful antibiotic therapy, indicating possible pulmonary vascular remodeling, direct pulmonary Tropheryma whipplei involvement, or irreversible vascular change. Stroke was likely cardioembolic due to atrial fibrillation. Diagnosis relied on PCR of pleural fluid, stool, and saliva and duodenal biopsy with PAS-positive macrophages. Early antibiotic treatment (ceftriaxone followed by oral therapy) produced clinical recovery, improved mobility, and reduced inflammatory markers in our case. Whipple's disease, although rare, should be considered in patients with unexplained weight loss, malnutrition, arthralgia, chronic inflammation, and gastrointestinal symptoms. Cardiovascular presentations including DVT and PH can occur and require prompt recognition and prolonged antibiotic therapy.

REFERENCES

1. Dolmans RA, Boel CH, Lacle MM, Kusters JG. Clinical Manifestations, Treatment, and Diagnosis of Tropheryma whipplei Infections. Clin Microbiol Rev. 2017;30(2):529-55.
2. Lopes A, Santos AF, Alvarenga MJ, Mello E Silva A. Whipple's disease: a rare case of malabsorption. BMJ Case Rep. 2018;2018.
3. Turcan S, Tofan-Scutaru L, Istrate V, Tirbu V. Whipple's disease? A case report and discussion. Med Pharm Rep. 2021;94(Suppl No 1):S76-S8.
4. Berent R, Auer J, Lassnig E, von Duvillard SP, Crouse SF, Tuppy H, et al. Whipple's disease: misdiagnosed as sarcoidosis with further tricuspid valve endocarditis and pulmonary embolism - a case report. BMJ Case Rep. 2009;2009.
5. Cardoso J, Gomes L, Santos S, Moreira H, Gomes P, Rua J, et al. Whipple's Disease: A Rare Cause of Malabsorption Syndrome. GE Port J Gastroenterol. 2020;27(4):283-9.
6. Dutly F, Altwegg M. Whipple's disease and "Tropheryma whippelii". Clin Microbiol Rev. 2001;14(3):561-83.
7. Kutlu O, Erhan S, Gökden Y, Kandemir Ö, Tükek T. Whipple's Disease: A Case Report. Med Princ Pract. 2020;29(1):90-3.
8. Biagi F, Balduzzi D, Delvino P, Schiepatti A, Klersy C, Corazza GR. Prevalence of Whipple's disease in north-western Italy. Eur J Clin Microbiol Infect Dis. 2015;34(7):1347-8.
9. Batista M, Santos ML, Silva C, Pereira G, Alves G, Cotter J. Whipple's Disease: A Case Report. Cureus. 2023;15(6):e39963.
10. Aguiar Ferreira A, Gomes P, Curvo-Semedo L, Donato P. Whipple's disease: imaging contribution for a challenging case. BMJ Case Rep. 2020;13(2).
11. Seddon O, Hettiarachchi I. Whipple's endocarditis presenting as ulnar artery aneurysm; if you don't look, you won't find. BMJ Case Rep. 2017;2017.
12. Terrones-Peinador M, Eremiev-Eremiev S, Pigrau-Serrallach C, Solans-Laque R. Recurrent thrombosis as a clinical presentation of Whipple disease. BMJ Case Rep. 2022;15(2).

Hematomukometra kot netipična predstavitev raka endometrija pri ženski po menopavzi

Hematomucometra as an Atypical Presentation of Endometrial Carcinoma in a Postmenopausal Woman

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Ključne besede:
hematomukometra, pomenopavza, rak endometrija, bolečina v trebuhu

Key words:
hematomucometra, postmenopause, endometrial carcinoma, abdominal pain

Članek prispel / Received
25. 11. 2025
Članek sprejet / Accepted
22. 6. 2026

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Izvleček

Namen: *Predstaviti redko in netipično klinično manifestacijo hematomukometre, povezane z rakom endometrija pri ženski po menopavzi.*

Predstavitev primera: *72-letna bolnica po menopavzi je več mesecev navajala bolečine v spodnjem delu trebuha, brez vaginalne krvavitve ali izcedka. Klinični pregled in slikovne preiskave so pokazali 15 cm veliko medenično maso, ki je ustrezala razširjeni maternici z gosto intrauterino vsebino in intraluminalnim izrastkom velikosti do 3 cm. Tumorski označevalci so bili blago povišani, vnetni markerji pa so ostali v mejah referenčnih vrednosti. Eksplorativna laparotomija je razkrila povečano, makroskopsko spremenjeno maternico z videzom »peščene ure«.*

Abstract

Purpose: *To present a rare and atypical clinical manifestation of hematomucometra associated with endometrial carcinoma in a postmenopausal woman.*

Case presentation: *A 72-year-old postmenopausal patient presented with several months of lower abdominal pain without vaginal bleeding or discharge. Clinical examination and imaging revealed a 15 cm pelvic mass corresponding to a distended uterus with dense intrauterine contents and an intraluminal excrescence as large as 3 cm. Tumor markers were mildly elevated, while inflammatory markers remained within reference values. Exploratory laparotomy revealed an enlarged, macroscopically altered*

https://doi.org/10.18690/actabiomed.311, CC BY 4.0
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Evakuiranih je bilo približno 500 mL čokoladno obarvane, viskozne in ne smrdeče vsebine, mikrobiološka analiza pa je pokazala sterilen vzorec. Opravljena je bila totalna abdominalna histerektomija z obojestransko adneksektomijo. Histopatološka preiskava je potrdila endometrioidni adenokarcinom endometrija, slabo diferenciran (stopnje 3), FIGO IC.

Zaključek: *Hematomukometra je lahko netipična predstavitev raka endometrija pri ženskah po menopavzi, tudi ob odsotnosti vaginalne krvavitve ali izcedka. Vztrajajoča bolečina v trebuhu in razširjena maternica zato zahtevata temeljito ginekološko obravnavo.*

uterus with an "hourglass" appearance. Approximately 500 ml of chocolate-colored, viscous, non-fetid content was evacuated and microbiological analysis was sterile. Total abdominal hysterectomy with bilateral adnexectomy was performed. Histopathology confirmed grade 3 endometrioid adenocarcinoma of the endometrium, FIGO Ic.

Conclusion: *Hematomucometra may represent an atypical presentation of endometrial carcinoma in postmenopausal women, even in the absence of vaginal bleeding or discharge. Persistent abdominal pain and uterine distension should therefore prompt thorough gynecological evaluation.*

INTRODUCTION

Hematometra and pyometra are gynecological entities characterized by the accumulation of blood or pus within the uterine cavity, because of impaired or obstructed cervical canal drainage. These conditions are most frequently observed in postmenopausal women, in whom the incidence is approximately 0.2%, whereas in patients with endometrial carcinoma (EC), the incidence ranges between 1.5% and 4%. The clinical presentation is often nonspecific and may include symptoms such as vaginal discharge, bleeding, fever, uterine enlargement, and lower abdominal pain. The frequency of pyometra significantly increases with advanced age, reduced physical activity, urinary incontinence, diabetes mellitus, and poor hygiene[1,2]. Hematomucometra (HMM) is an extremely rare entity involving retention of blood and mucus within the uterine cavity. We report this case because of its atypical clinical presentation in the setting of EC,after having obtained the patient's consent and approval from our hospital's ethics committee.

CASE REPORT

A 72-year-oldpostmenopausal patient (P1), who had been postmenopausal since 50 years of age, was admitted to the emergency department of our gynecology clinic because of several months of severe lower abdominal pain. She had been repeatedly evaluated in emergency settings, but because of her dementia and poor socioeconomic circumstances, which contributed to delayed gynecological and radiological evaluation, no comprehensive workup had been performed. She denied vaginal bleeding or discharge.Significant findings in her medical history included poorly controlled arterial hypertension and type II diabetes mellitus. A physical examination revealed a painful palpable pelvic mass measuring approximately 15 cm in the hypogastrium. A speculum examination showed atrophic upper vaginal walls without secretion, and the external cervical os could not be visualized. A digital rectal examination indicated an enlarged cervix occupying the entire pelvis and a relatively small uterine corpus. Her pap smear was normal, without atypical cells. Because of vaginal semi-occlusion, hysteroscopy or curettage could not be performed. Cervical dilatation under anesthesia was not considered feasible, because of the inability to identify the external cervical os and marked anatomical distortion.

Transvaginal ultrasound demonstrated a cystic mass filled with opalescent material, measuring 11 × 8 cm. No ovaries or free abdominal fluid were visualized. On

admission, uncontrolled type II diabetes mellitus was noted (blood glucose 25.8 mmol/L); consultation with a diabetologist led to administration of rapid-acting insulin, which achieved satisfactory glycemic control. Preoperative laboratory and imaging evaluation were performed. Tumor markers were mildly elevated: CEA, 5.2 µg/L (reference value <3.8); CA-125, 62.7 kIU/L (reference value <35.0). Inflammatory markers (CRP and leukocyte count) remained within reference values. Because the patient was afebrile,preoperative antibiotic therapy was not administered. Multislice computed tomography (MSCT) of the chest, abdomen, and pelvis revealed a relatively well-defined bilobular pelvic mass involving the uterine cavity and cervix; filled with dense, possibly mucinous material; and measuring 15.1 × 8.5 × 19.5 cm. A centrally hypodense intramural lesion (0.8 cm) was noted in the uterine fundus, along with an endoluminal proliferative lesion as large as 3 cm, which was inseparable from the uterine wall. No pelvic or abdominal lymphadenopathy or pathological adnexal findings were observed. The bladder was compressed but intact, with no intraluminal abnormalities. Minimal pelvic free fluid was present (Figure 1). Given the patient's postmenopausal status, tumor markers, MSCT findings, and ASA III classification, an exploratory Joel-Cohen laparotomy was performed. Intraoperatively, an enlarged "hourglass-shaped" uterus was identified, with a softened corpus and a lower uterine segment approximately twice the size of the corpus, with intact perimetrium and normal adnexa. During uterine manipulation, viscous, chocolate-colored, non-fetid contents leaked from the thinned uterine wall; approximately 500 ml was aspirated and sent for microbiological analysis, and was found to be sterile. A total abdominal hysterectomy with bilateral adnexectomy was performed (Figure 2). Postoperative antibiotic therapy with 1 g cefazolin was administered three times daily.

Histopathology confirmed endometrioid adenocarcinoma of the endometrium, G3. The postoperative course was uneventful. The patient was discharged in good general condition with controlled diabetes and referred for further oncological treatment according to histopathological findings.

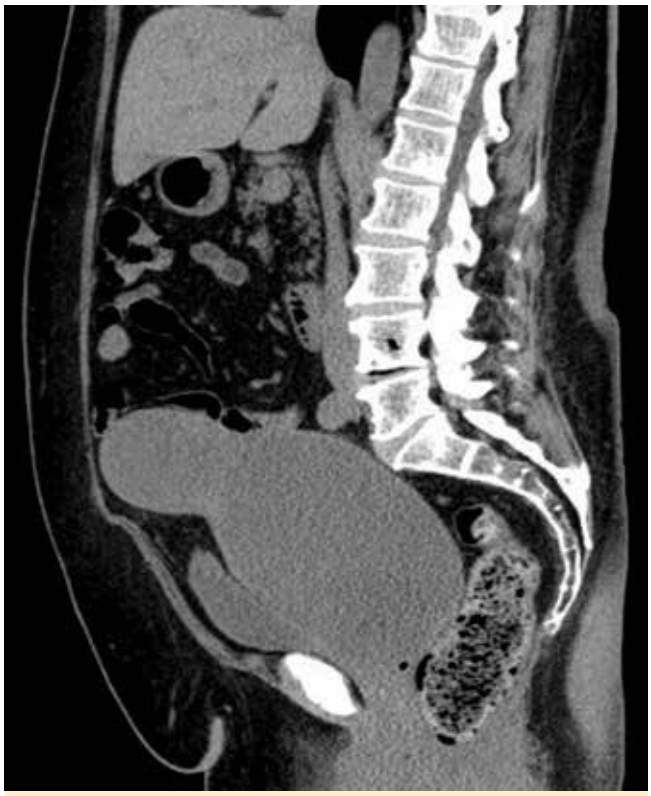

Figure 1. *MSCT scan showing a distended uterus filled with dense content and showinga markedly thinned myometrium.*

DISCUSSION

Prolonged blood retention within the uterine cavity leads to breakdown of hemoglobin into hematin, thus conferring a chocolate-brown appearance. When this blood combines with mucus degeneration, a thick adhesive material, characteristic of HMM, is formed. Although pyometra has been most frequently described in postmenopausal women as pus retention due to necrotic debris, most often secondary to endometrial malignancy, and mucometra is occasionally reported because of mucous secretion of the endometrial glands, HMM represents an unusual combination of hematinized hematometra and mucometra.

These entities all cause uterine distension and intermittent cramping pain, historically described as Simpson's cramps [3,4]. Our patient presented exclusively with prolonged abdominal pain and

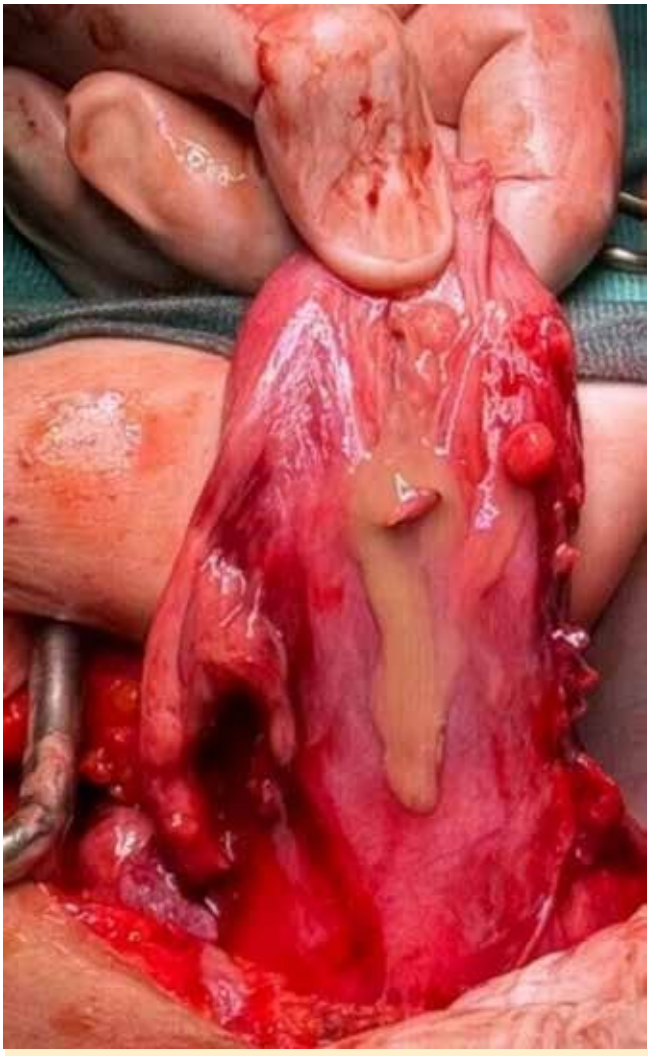

Figure 2. *Intraoperative finding of hematomucometra with chocolate-like content.*

a large palpable pelvic mass, without the typical symptoms of pyometra such as bleeding or purulent discharge. In one retrospective study spanning 8 years, the most common symptoms in women with confirmed pyometra were postmenopausal bleeding (59.2%), vaginal discharge (40.8%), fever (6.6%), and abdominal pain (5.3%) [5]. Another retrospective cohort study in 192 patients found abdominal pain in 49.0% and vaginal discharge in 47.9% of patients [6]. Therefore, our case highlights that HMM can present solely with abdominal pain, thus potentially complicating timely diagnosis. The absence of vaginal bleeding or discharge was probably associated with severe cervical ostium stenosis and the highly viscous nature of the retained intrauterine content.Our patient's laboratory results were within reference limits, except for elevated CA-125 (62.7 kIU/L), a finding also described in the literature. Unlike the case reported by Febriany etal. [2], our patient had inflammatory markers within reference values, thus excluding infection and supporting the diagnosis of non-infectious HMM. Mendoza et al. have described a case of massive pyometra with elevated CA-125 (214 U/ml), in which the rise was attributed to inflammation rather than malignancy[7]. This finding highlights the nonspecific nature of CA-125, particularly in postmenopausal women with pyometra, and the need for histopathological confirmation to establish malignancy. Microbiological analysisof the aspirated uterine content showed no bacterial growth, thereby suggesting a sterile exudate. In a study by Ikeda et al., *Escherichia coli*, *Bacteroides*, and *Peptococcus species* were most common in isolates, whereas no pathogens were identified in 8% of cases, in agreement with our findings [8].

Atypical benign presentations of pyometra and pyosalpinx in postmenopausal women have previously been reported [9]. Histopathology in our patient revealed endometrioid adenocarcinoma of the endometrium, G3, representing an aggressive high-grade form that atypically manifested as prolonged HMM. The dense, viscous nature of the retained content prevented spontaneous evacuation through the vagina. Among malignant tumors associated with intrauterine content retention, EC is most common, and is followed by cervical carcinoma [10].

This case demonstrates an atypical clinical manifestation of HMM, more precisely hematomuco-trachelometra, with a cervix distended to twice the volume of the uterine corpus. The viscous adhesive content produced no discharge but instead caused severe abdominal pain in a postmenopausal patient with EC as the underlying disease.

AUTHOR CONTRIBUTION

All authors read and approved the final version of the manuscript.

DECLARATIONS

The authors declare that they have no competing interests.

ETHICAL STANDARDS

For images or other information within the manuscript which identify patients, consent was obtained from them.

REFERENCES

1. Kerimoglu OS, Pekin A, Yilmaz SAet al. Pyometra in elderly post-menopausal women: a sign of malignity. Eur J Gynaecol Oncol. 2015;36:59zczc-61.
2. Febriany DC, Hameed Sultan MA, Ahmad Sharifuddin Z, Thangavelu AR, Chin C. The dual danger of pyometra and endometrial carcinoma: a case report. Ital J GynaecolObstet. 2024;36:168.
3. Walthall L, Heincelman M. Pyometra: An Atypical Cause of Abdominal Pain. J Investig Med High Impact Case Rep. 2021;9:23247096211022481.
4. Habek D. et al. Textbook of Obstetrics and Gynecology. Medicinska naklada Publisher Zagreb, 2025.
5. Lui MW, Cheung VY, Pun TC. Clinical Significance of Pyometra. J Reprod Med. 2015;60:329zczc-32.
6. Jang S, Jeon M, Mun SJ et al. Clinical characteristics and risk factors for septic shock in patients with pyometra: A retrospective multicentercohort study. J Infect Public Health. 2024;17:862zczc-67.
7. Ortiz Mendoza CM. Giant piometra originating high serum levels of CA-125. Ginecol Obstet Mex. 2009 ;77:445zczc-48.
8. Ikeda M, Takahashi T, Kurachi H. Spontaneous perforation of pyometra: a reportof seven cases and review of the literature. Gynecol Obstet Invest. 2013;75:243zczc-49.
9. Habek D. Pyometra and bilateral pyotuboovarium in an 84-year-old woman. Eur J Obstet Gynecol Reprod Biol. 2005;123:258zczc-60.
10. Tal Bliman Y, Rafaeli Yehudai T, Shiber Y et al. Spontaneous pyometra in postmenopausal women and gynecologic cancer-a preliminary study based on experience of a tertiary medical center. Menopause. 2025;https://doi.org/10.1097/GME.0000000000002600.

Prof. dr. Andraž Stožer, prejemnik nagrade Republike Slovenije na področju šolstva za leto 2026 za izjemne dosežke na področju visokega šolstva.

Full Professor Andraž Stožer, recipient of the Republic of Slovenia Award in the field of education for 2026 for outstanding achievements in higher education.

Foto: Nebojša Tejić/STA.





Ustanovitelji odcepljenega podjetja Univerze v Mariboru EndoVia Therapeutics, ki razvija inovativno platformo za personalizirano zdravljenje raka. Z leve: doc. dr. Marko Milojević, doc. dr. Jan Rožanc in prof. dr. Uroš Maver.

Founders of EndoVia Therapeutics, a University of Maribor spin-off developing an innovative platform for personalized cancer treatment. From left: Assist. Prof. Dr. Marko Milojević, Assist. Prof. Dr. Jan Rožanc, and Prof. Dr. Uroš Maver.

Foto: Arhiv MF UM

University of Maribor
Faculty of Medicine

ACTA MEDICO-BIOTECHNICA

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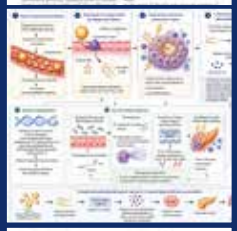

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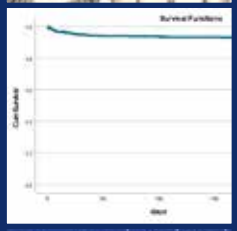

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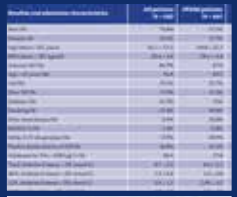

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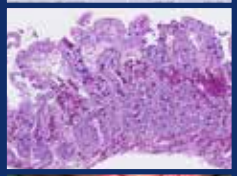

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