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Klinička obilježja bolesnika oboljelih od COVID-19 s plućnom embolijom ili bez nje

Clinical features of COVID-19 hospitalized patients with or without pulmonary embolism

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Sažetak

Cilj: Cilj ovoga istraživanja bio je usporediti demografske, kliničke i laboratorijske karakteristike hospitaliziranih COVID-19 bolesnika s plućnom embolijom i bez nje.

Metode: Provedeno je retrospektivno kohortno istraživanje. Nasumičnim odabirom analizirana je medicinska dokumentacija 100 COVID-19 bolesnika hospitaliziranih u razdoblju od 1.1. do 31.12.2021. godine, 50 bolesnika s plućnom embolijom, te 50 bolesnika bez nje.

Rezultati: Većinu COVID-19 bolesnika činili su muškarci (60%), dok je plućna embolija bila učestalija u žena (57,5%). Medijan dobi bolesnika koji su razvili plućnu emboliju bio je viši u skupini bolesnika s plućnom embolijom, iako bez statistički značajne razlike. Pušenje kao navika bila je češća u osoba s embolijom, iako bez statistički značajne razlike dok su bolesnici bez embolije bili češće cijepljeni protiv COVID-19 u odnosu na one s embolijom, iako bez statistički značajne razlike. U 80% bolesnika bio je prisutan neki od komorbiditeta i to najčešće arterijska hipertenzija (62,5%). Antikoagulacijsku i/ili antiagregacijsku terapiju češće su imali bolesnici u kontrolnoj skupini, ali bez statistički značajne razlike. Leukociti, D-dimeri, trombociti i NT-proBNP bilježili su statistički značajno više vrijednosti u grupi bolesnika s embolijom. Medijan pojave plućne embolije bio je 11 dana od početka simptoma s najčešćim nalazom embolije, utvrđenim CT angiografijom, u segmentalnim ograncima (38%). Mehanička ventilacija češće je korištena u bolesnika s embolijom u kojih je zabilježen i veći broj smrtnih ishoda, iako bez statistički značajne razlike.

Zaključak: Iako su bolesnici s plućnom embolijom bili češće ženskog spola i starije životne dobi, spol i dob nisu se značajno razlikovali među analiziranim skupinama. Bolesnici s plućnom embolijom imali su značajno više vrijednosti D-dimera, leukocita, trombocita i natriuretskog peptida u odnosu na ispitanike koji je nisu razvili. Plućna embolija bila je najčešće lokalizirana u segmentalnim ograncima plućnih arterija. Potreba za mehaničkom ventilacijom, te učestalost smrtnoga ishoda bila je češća u bolesnika s embolijom, ali bez značajne razlike.

Ključne riječi: COVID-19, SARS-CoV-2, plućna embolija

Summary

Aim: This study aimed to compare the demographic, clinical, and laboratory findings of hospitalized COVID-19 patients with and without pulmonary embolism (PE).

Methods: We conducted a retrospective cohort study in which we analyzed medical records of a

hundred randomly selected COVID-19 patients hospitalized from January 1, 2021, until December 31, 2021; half developed pulmonary embolism and half did not, respectively.

Results: Most COVID-19 patients were men (60%), while pulmonary embolism occurred more frequently in female patients (57.5%). The median age of the patients who developed pulmonary embolism was higher in the group of patients with pulmonary embolism, although without a statistically significant difference. Smoking, as a habit, was more common in patients with PE, while patients without PE were more often vaccinated against COVID-19 than those with PE, although without a statistically significant difference. The majority of patients with PE (80%) had some comorbidities, with arterial hypertension being the most common (62.5%). Anticoagulation and/or antiplatelet therapy were more common in the control group, although the difference was not statistically significant. Leukocytes, D-dimers, platelets, and NT-proBNP had statistically significantly higher values in the test group than the controls. A median of 11 days was needed to develop pulmonary embolism, with the most common MSCTA location being the segmental branches (38%). In the group of patients with pulmonary embolism, mechanical ventilation was more commonly needed, and there have been more fatal outcomes, although without a statistically significant difference.

Conclusion: Although patients with pulmonary embolism were more often females and older than the patients without pulmonary embolism, there were no significant differences in sex or age between the analyzed groups. Patients with pulmonary embolism had significantly higher D-dimers, leukocytes, platelets, and NT-proBNP values than patients without pulmonary embolism. The most frequent location of embolism was the segmental branches of pulmonary arteries. The need for mechanical ventilation and the frequency of fatal outcomes were more frequent in patients with embolism but without a significant difference.

Key words: COVID-19, SARS-CoV-2, pulmonary embolism

Uvod

COVID-19 (od engl. *coronavirus disease 2019*) zarazna je bolest uzrokovana virusom SARS-CoV-2 (od engl. *severe acute respiratory syndrome coronavirus 2*). Bolest se iznenadno pojavila u prosincu 2019. godine u gradu Wuhan u Kini, te se vrlo brzo proširila u pandemijskim razmjerima. Radi se o betakoronavirusu koji dijeli 79% svoje genomske sekvence s teškim akutnim respiratornim koronavirusom (SARS-CoV, od engl. *severe acute respiratory syndrome coronavirus*), te 50% s bliskoistočnim respiratornim koronavirusom (MERS-CoV, od engl. *Middle East respiratory syndrome coronavirus*). Do trenutka pisanja ovoga članka (1.02.2024.) u cijelom svijetu zabilježeno je preko 774 milijuna ljudi zaraženih SARS-CoV-2, od kojih je preminulo preko 7.019.000 ljudi (letalitet <1%).¹

Prema zadnjim dostupnim podacima Vlade Republike Hrvatske i Hrvatskog zavoda za javno zdravstvo (HZJZ), u Republici Hrvatskoj do 27.10.2023. zabilježeno je ukupno 1.276.216 SARS-CoV-2 pozitivnih stanovnika, te 18.414 preminulih COVID-19 bolesnika, što čini stopu letaliteta od 1,4%.²

U većini slučajeva radi se o blagoj respiratornoj infekciji sa spontanom izlječenjem, dok je manji broj slučajeva obilježen komplikacijama kao što su tromboembolijske i potrebom za hospitalizacijom.³ Navedene komplikacije čine bitan čimbenik koji doprinosi ukupnom morbiditetu i mortalitetu, a

javljuju se u vidu plućne embolije, duboke venske tromboze, ishemijskog moždanog udara, te srčanog udara.⁴

Rizični čimbenici koji su povezani s lošijim ishodom i višim mortalitetom su: dob >75 godina, muški spol, pretilost 2. stupnja, maligna bolest, krvna grupa A i pušenje. Od simptoma, na lošiji ishod upućuje prisutnost mijalgije, dispneje, mučnine, zimice, te produkcija sputuma.⁵

U dijagnostici infekcije SARS-CoV-2 koriste se tri skupine metoda za detekciju: testovi koji koriste amplifikaciju nukleinskih kiselina (NAAT, od engl. *nucleic acid amplification tests*), imunološke metode koje obuhvaćaju serološke i antigenske testove, te slikovne radiološke metode. Zlatni standard prilikom dijagnostike je reakcija polimerazom nakon obrnutog prepisivanja (RT-PCR, od engl. *reverse transcription polymerase chain reaction*), budući da se radi o RNK-virusu.⁶

Među slikovnim radiološkim metodama najkorištenija je radiografija prsnog koša (RTG) zbog svoje dostupnosti i brzine, ali kada govorimo o osjetljivosti testa onda je računalna tomografija prsišta (CT, od engl. *computed tomography*) na prvom mjestu. Najčešći nalazi na CT-u su zasjenjenje po tipu mliječnog stakla i konsolidacije, obično s multiplim lezijama koje su vidljive već u ranoj fazi blage bolesti i to čak prije pozitivnog RTG nalaza.⁷

U liječenju COVID-19 koriste se brojni modaliteti, te nam istraživanja iz dana u dan donose nove terapijske mogućnosti. Većina slučajeva prezentira se blažom kliničkom slikom, a liječenje

takvih bolesnika je simptomatsko. Kod hospitaliziranih bolesnika s težom kliničkom slikom bolesti visoki je postotak razvoja akutnog respiratornog distress sindroma (ARDS, od engl. *acute respiratory distress syndrome*) koji zahtijeva oksigenoterapiju, dok u kritičnih bolesnika sve više studija ističe važnost izvantjelesne membranske oksigenacije (ECMO, od engl. *extracorporeal membrane oxygenation*) uz visoku stopu otpusta bolesnika iz Jedinice intenzivnog liječenja ili bolnice od 50%.⁸⁻¹⁰

Nadalje, postoji niz farmakoterapijskih opcija od kojih se veliki broj njih još istražuje. Jedna od njih su kortikosteroidi za koje je u RECOVERY studiji pokazano da u slučaju potrebe za umjetnom ventilacijom značajno smanjuju stopu smrtnosti.^{11, 12}

Remdesivir je adenoziński nukleotidni analog za kojeg studije nisu pokazale statistički značajnu razliku u smrtnosti i vremenu ozdravljenja dok se kombinacija nirmatrelvira i ritonavira pokazala kao visoko učinkovita u sprječavanju teških oblika bolesti i smanjenju mortaliteta.^{13, 14}

Plućna embolija u COVID-19

Prema metaanalizi Gong i sur. koja obuhvaća 36 studija s ukupno 10 367 hospitaliziranih bolesnika, incidencija plućne embolije u COVID-19 bolesnika bila je 21%. Incidencija je bila veća u bolesnika hospitaliziranih u Jedinici intenzivnog liječenja (JIL), te je iznosila 26%, dok je kod ostalih hospitaliziranih bolesnika iznosila 17%.¹⁵

Među demografskim činiteljima, na incidenciju najviše utječu muški spol i indeks tjelesne mase veći od 30. Dob i ostali komorbiditeti poput hipertenzije, šećernne bolesti, venske tromboembolije i ostalih nisu pokazali statistički značajni utjecaj na incidenciju. Osobe koje su hospitalizirane u JIL-u i osobe koje su mehanički ventilirane također imaju veći rizik za razvoj plućne embolije, kao i osobe koje na CT-u pokazuju parenhimatozne promjene koje zahvaćaju više od 50% pluća. Od laboratorijskih parametara na plućnu emboliju upućuju visoke vrijednosti D-dimera i leukocita.¹⁶

Dijagnoza plućne embolije predstavlja rizik za primjenu mehaničke ventilacije i za prijam u JIL, dok ne utječe značajno na stopu smrtnosti.¹⁷

Patogeneza plućne embolije u bolesti COVID-19 prilično je kompleksna i nedovoljno istražena. Vjeruje se da je rezultat hiperkoagulabilnosti, aktivacije trombocita i endotelne disfunkcije. Kod COVID-19 bolesnika često nalazimo visoke vrijednosti D-dimera i fibrinogena, ali i minimalne promjene u protrombinskom vremenu (PV) i broju trombocita, što je glavna razlika u odnosu na septičku

koagulopatiju i diseminiranu intravaskularnu koagulaciju. Kako bi ušao u stanicu, SARS-CoV-2 koristi angiotenzin konvertirajući enzim 2 (ACE2, od engl. *angiotensin-converting enzyme 2*) kao svoj receptor na površini endotelne stanice. Time ACE2 gubi svoju funkciju, čime dolazi do smanjene inaktivacije angiotenzina II i smanjene pretvorbe u angiotenzin, što u konačnici rezultira vazokonstrikcijom i smanjenom sintezom dušikovog oksida (NO, od engl. *nitric oxide*). Endotelne stanice normalno luče NO koji sprječava adheziju trombocita i leukocita, migraciju upalnih stanica, proliferaciju glatkih mišićnih stanica unutar zida krvne žile, apoptozu i upalu. Infekcija SARS-CoV-2 interferira s nabrojenim fiziološkim funkcijama, što dovodi do formiranja mikrotromba. Također dolazi i do upalnog i virusnog oštećenja glikokaliksa, što, uz visoke vrijednosti upalnih citokina, umanjuje antitrombotsku komponentu endotelne površine.¹⁸

Bolesnici koji se prezentiraju slikom duboke venske tromboze i imaju rizične čimbenike za tromboemboliju (prethodne tromboze, maligne bolesti, hormonska terapija) su oni koje moramo strogo pratiti, pogotovo ako dođe do iznenadnog pogoršanja respiratornog statusa praćenog hipotenzijom i tahikardijom.¹⁹ Od ostalih simptoma najčešće vidamo dispneju i kašalj, a u laboratorijskim nalazima često imamo nisku saturaciju hemoglobina kisikom, visoki C-reaktivni protein (CRP, od engl. *C-reactive protein*) i leukocite.²⁰ U usporedbi s bolesnicima koji su razvili plućnu emboliju bez dijagnoze COVID-19, bolesnici s COVID-19 i embolijom imaju u prosjeku nižu saturaciju hemoglobina kisikom, brži puls, te više vrijednosti CRP-a i leukocita.²¹ Razina natriuretskog peptida (NT-proBNP, od engl. *N-terminal pro-brain natriuretic peptide*) vrlo je često povišena u bolesnika s COVID-19 bolešću, pri čemu većina dispnoičnih bolesnika ima razine iznad 400 pg/mL. Razine ispod 100 pg/mL u COVID-19 bolesnika imaju visoku negativnu prediktivnu vrijednost za zastoj srca.²²

Inicijalni korak pri sumnji na plućnu emboliju je provjera vrijednosti D-dimera. Naime, zbog svoje visoke negativne prediktivne vrijednosti, normalan nalaz gotovo isključuje plućnu emboliju. Vrijednosti D-dimera 1,001-2,5 mg/L pokazuju omjer izgleda za trombotsku komplikaciju od 3,04, a vrijednosti iznad 2,5 mg/L omjer izgleda od 6,79. Zlatni standard u dijagnostici plućne embolije ostaje višeslojna CT angiografija (MSCTA, od engl. *multislice spiral computed tomographic angiography*) plućne arterije. Dilatacija desne klijetke, McConnel znak ili paradoksalno gibanje septuma na ehokardiografiji također nas mogu uputiti na plućnu emboliju, te, u određenim slučajevima, uz tipičnu kliničku sliku,

mogu biti indikacija za uvođenje antikoagulantne terapije, a isto vrijedi i za nalaz duboke venske tromboze na ultrazvuku (UZV) vena donjih ekstremiteta.²³

Konsenzusa oko liječenja plućne embolije u COVID-19 bolesnika nema. Prema algoritmu Adams i sur., kod dijagnoze plućne embolije, ukoliko ne postoje kontraindikacije, odlučujemo se za antikoagulantnu terapiju i to najčešće nefrakcioniranim ili niskomolekularnim heparinom. Ako se radi o masivnoj plućnoj emboliji s opterećenjem desne klijetke i rizikom za njezinu rupturu ili ishemijsku miokarda, preporučuje se perkutana kateterska tromboliza. Kod hemodinamske nestabilnosti, i ako nema kontraindikacija, dolazi u obzir i sistemska trombolitička terapija. Ukoliko bolesnik ipak nije kandidat za takvu terapiju, provodi se otvorena ili perkutana trombektomija.²⁴

Spomenimo još i cijepljenje kao najučinkovitiji način za prevenciju teških oblika COVID-19, pa tako i razvoja tromboembolijskih komplikacija. Metaanaliza Zheng i sur. pokazala je kako je u potpuno cijepljenih osoba učinkovitost cjepiva protiv teških oblika bolesti, hospitalizacije i smrtnog ishoda veća od 89%, a zaštita protiv same infekcije SARS-CoV-2 iznosi preko 83%.²⁵

Cilj rada

Cilj ovoga istraživanja bio je usporediti demografske, kliničke i laboratorijske karakteristike hospitaliziranih COVID-19 bolesnika s embolijom pluća i bez nje, te utvrditi postoje li statistički značajne razlike među navedenim skupinama. Dobivena saznanja mogla bi biti korisna u izradi budućih smjernica za prevenciju tromboembolijskih incidenata u SARS-CoV-2 infekciji.

Metode rada

Provedeno je retrospektivno kohortno istraživanje bolesnika hospitaliziranih na Klinici za infektologiju Kliničkog bolničkog centra (KBC) Split uslijed COVID-19 bolesti u razdoblju od 1.1. do 31.12.2021. godine.

Nasumičnim odabirom dobiven je uzorak od 100 COVID-19 bolesnika u navedenom razdoblju, 50 onih koji su razvili plućnu emboliju (ispitivana skupina), te 50 onih koji je nisu razvili (kontrolna skupina). Pregledom njihove medicinske dokumentacije prikupljeni su podaci o spolu, dobi, navici pušenja, cijepljenju protiv COVID-19,

komorbiditetima, te kroničnoj terapiji od koje smo posebno analizirali prethodno korištenje antikoagulantne i antiagregacijske terapije. Nadalje, prikupili smo i laboratorijske (CRP, broj leukocita, D-dimere, broj trombocita, PV-udjel, NT-proBNP), te radiološke (RTG, MSCTA) nalaze ispitanika.

Prikupljeni podaci obrađeni su u programskim paketima *Microsoft Office* za obradu teksta, te izradu tabličnih prikaza.

Za statističku analizu prikupljenih podataka korišten je statistički program TIBCO® Statistica™ (verzija 12, TIBCO®, Palo Alto, Kalifornija, Sjedinjene Američke Države). Korištene su metode deskriptivne statistike (medijan i interkvartilni raspon (IQR) za prikaz numeričkih varijabli). Kvalitativne varijable prikazane su kao cijeli broj i postotak. Ispitivanje razlike u numeričkim varijablama provedeno je korištenjem Mann-Whitney testa, dok se za usporedbu frekvencija kvalitativnih varijabli koristio hi-kvadrat (χ^2) test. Razina statističke značajnosti u navedenim testovima postavljena je na $P < 0,05$.

Istraživanje je odobrilo Etičko povjerenstvo KBC-a Split pod brojem 2181-147/01/06/M.S.-22-02, a provedeno je u skladu s etičkim načelima Helsinške deklaracije.

Rezultati

Demografska obilježja ispitanika

Među ispitanicima je bilo 60 (60%) muškaraca i 40 (40%) žena. Od 50 ispitanika s embolijom, njih 27 (54%) bili su muškarci, a 23 (46%) žene. Od ukupnog broja muških ispitanika, njih 45% razvilo je plućnu emboliju, dok je kod žena taj postotak iznosio 57,5%. Iako je veći udio žena imao plućnu emboliju, ispitivanjem nije utvrđena prisutnost statistički značajne razlike u prisutnosti plućne embolije u ovisnosti o spolu ($P=0,22$).

Medijan dobi bolesnika iznosio je 65 (51-80,75) godina u ispitanika koji nisu razvili plućnu emboliju, te 71 (65,75-81) godina u ispitanika koji su je razvili. Razlika nije bila statistički značajna ($P=0,11$).

Većina promatranih bolesnika bili su nepušači (90%). Zastupljenost pušača među bolesnicima kod kojih je dijagnosticirana embolija bila je 2,3 puta veća u odnosu na one bez embolije. Rezultati u Tablici 1 pokazuju da ispitivanjem nije utvrđena prisutnost statistički značajne razlike u zastupljenosti pušača ($P=0,18$).

Tablica 1. Ispitanici prema navici pušenja / **Table 1** Patients according to smoking habit

Pušenje (<i>smoking</i>)	Nije prisutno (<i>not present</i>)		Prisutno (<i>present</i>)		χ^2	P*
	N	%	N	%		
Embolija (<i>embolism</i>)						
Nije prisutna (<i>not present</i>)	47	94,00	3	6,00	1,78	0,18
Prisutna (<i>present</i>)	43	86,00	7	14,00		

* χ^2 test (*chi-square test*)

Rezultati u Tablici 2 pokazuju da većina ispitanika nije bila cijepljena protiv COVID-19 (90%). Cijepljenje ispitanika bilo je 2,3 puta učestalije među onima u kontrolnoj skupini, u odnosu na promatrane

bolesnike kod kojih je dijagnosticirana embolija, dok ispitivanjem nije utvrđena statistički značajna razlika (P=0,18).

Tablica 2. Ispitanici prema cijepljenju / **Table 2** Patients according to vaccination

Cijepljenje (<i>vaccination</i>)	Nije provedeno (<i>not administered</i>)		Provedeno (<i>administered</i>)		χ^2	P*
	N	%	N	%		
Embolija (<i>embolism</i>)						
Nije prisutna (<i>not present</i>)	43	86,00	7	14,00	1,78	0,18
Prisutna (<i>present</i>)	47	94,00	3	6,00		

* χ^2 test (*chi-square test*)

Kod obje promatrane skupine po 40 (80%) ispitanika imalo je neki od komorbiditeta, te nije bilo razlike između skupina. Najveći broj ispitanika kod obje promatrane skupine imao je dijagnosticiranu arterijsku hipertenziju (62,5%), dok ispitivanjem nije

utvrđena prisutnost statistički značajne razlike u zastupljenosti hipertenzije među promatranim skupinama (P=0,12). Drugi najčešći komorbiditeti među ispitanicima bili su dijabetes (21,25%), hipotireoza (10%) i hiperlipidemija (8,75%) (Tablica 3).

Tablica 3. Lista prethodnih bolesti među ispitanicima / **Table 3** List of previous diseases among the patients

Embolija (<i>embolism</i>)	NE (not present) (N=40)		DA (present) (N=40)	
	N	%	N	%
Prethodna bolest (<i>previous disease</i>)				
Arterijska hipertenzija (<i>arterial hypertension</i>)	28	70,00	22	55,00
Šećerna bolest (<i>diabetes mellitus</i>)	7	17,50	10	25,00
Hipotireoza (<i>hypothyroidism</i>)	4	10,00	4	10,00
Hiperlipidemija (<i>hyperlipidemia</i>)	4	10,00	3	7,50
Prethodna plućna embolija (<i>previous pulmonary embolism</i>)	0	0,00	3	7,50
Benigna hiperplazija prostate (<i>benign prostatic hyperplasia</i>)	3	7,50	1	2,50
Atrijska fibrilacija (<i>atrial fibrillation</i>)	3	7,50	1	2,50
Astma (<i>asthma</i>)	2	5,00	1	2,50
Depresija (<i>depression</i>)	2	5,00	1	2,50
Kronična opstruktivna bolest pluća (<i>chronic obstructive pulmonary disease</i>)	2	5,00	1	2,50
Infarkt miokarda (<i>myocardial infarction</i>)	2	5,00	1	2,50
Multipli mijelom (<i>multiple myeloma</i>)	2	5,00	1	2,50
Kronična bubrežna bolest (<i>chronic kidney disease</i>)	2	5,00	0	0,00
Ishemijska bolest srca (<i>ischemic heart disease</i>)	2	5,00	0	0,00
Azbestoza pluća (<i>asbestosis</i>)	1	2,50	2	5,00
Cerebrovaskularni inzult (<i>cerebrovascular insult</i>)	1	2,50	2	5,00
Gastritis (<i>gastritis</i>)	1	2,50	2	5,00
Glaukom (<i>glaucoma</i>)	1	2,50	2	5,00
Kardiomiopatija (<i>cardiomyopathy</i>)	1	2,50	2	5,00
Totalna endoproteza oba kuka (<i>total endoprosthesis of both hips</i>)	1	2,50	1	2,50
Transplantirani bubreg (<i>transplanted kidney</i>)	1	2,50	1	2,50
Akutni hepatitis B (<i>acute hepatitis B</i>)	1	2,50	0	0,00
Akutni pankreatitis (<i>acute pancreatitis</i>)	1	2,50	0	0,00
Intracerebralno krvarenje (<i>intracerebral haemorrhage</i>)	1	2,50	0	0,00
Kronični bronhitis (<i>chronic bronchitis</i>)	1	2,50	0	0,00

Embolija (embolism)	NE (not present) (N=40)		DA (present) (N=40)	
	N	%	N	%
Prethodna bolest (previous disease)				
Mitralna insuficijencija (<i>mitral insufficiency</i>)	1	2,50	0	0,00
Splenektomija (<i>splenectomy</i>)	1	2,50	0	0,00
Stabilna angina pectoris (<i>stable angina pectoris</i>)	1	2,50	0	0,00
Umjetna mitralna valvula (<i>artificial mitral valve</i>)	1	2,50	0	0,00
Epilepsija (<i>epilepsy</i>)	1	2,50	0	0,00
Giht (<i>gout</i>)	1	2,50	0	0,00
Kronični sinusitis (<i>chronic sinusitis</i>)	1	2,50	0	0,00
Planocelularni karcinom (<i>squamous cell carcinoma</i>)	1	2,50	0	0,00
Subarahnoidalno krvarenje (<i>subarachnoid hemorrhage</i>)	1	2,50	0	0,00
Neuralgija trigeminusa (<i>trigeminal neuralgia</i>)	0	0,00	1	2,50
Artroza kuca (<i>coxarthrosis</i>)	0	0,00	1	2,50
Psorijaza (<i>psoriasis</i>)	0	0,00	1	2,50
Blok lijeve grane (<i>left bundle branch block</i>)	0	0,00	1	2,50
Kronična disekcija torakalne aorte (<i>chronic thoracic aortic dissection</i>)	0	0,00	1	2,50
Alergijski rinitis (<i>allergic rhinitis</i>)	0	0,00	1	2,50
Gastroezofagealna refluksna bolest (<i>gastroesophageal reflux disease</i>)	0	0,00	1	2,50
Tranzitorna ishemijska ataka (<i>transient ischemic attack</i>)	0	0,00	1	2,50

Kroničnu terapiju uzimalo je 73% bolesnika i to njih 35 (70%) u ispitnoj, te 38 (76%) u kontrolnoj skupini, a ispitivanjem nije utvrđena prisutnost statistički značajne razlike ($P=0,49$). Rezultati u tablici 4 pokazuju da je kod obje promatrane skupine

najčešća kronična terapija bila antihipertenzivna s prevalencijom od 73,97%, dok uspoređivanjem obiju skupina nije utvrđena prisutnost statistički značajne razlike ($P=0,579$).

Tablica 4. Lijekovi ispitanika prema skupinama / **Table 4** Patients' medicine according to groups

Embolija (embolism)	NE (not present) (N=38)		DA (present) (N=35)	
	N	%	N	%
Kronična terapija (chronic therapy)				
Antihipertenzivi (<i>antihypertensives</i>)	29	76,32	25	71,43
Antiagregacijska terapija (<i>antiplatelet therapy</i>)	9	23,68	5	14,29
Antidijabetici (<i>antidiabetics</i>)	7	18,42	8	22,86
Antilipemici (<i>antilipemics</i>)	6	15,79	8	22,86
Inhibitori protonske pumpe (<i>proton pump inhibitors</i>)	6	15,79	6	17,14
Levotiroksin (<i>levothyroxine</i>)	4	10,53	5	14,29
Antikoagulacijska terapija (<i>anticoagulant therapy</i>)	3	7,89	2	5,71
Terapija za BHP (<i>therapy for BHP</i>)	3	7,89	0	0,00
Vitamin D (<i>vitamin D</i>)	2	5,26	2	5,71
Terapija za giht (<i>therapy for gout</i>)	2	5,26	2	5,71
Kortikosteroidi (<i>corticosteroids</i>)	2	5,26	1	2,86
Antidepresivi (<i>antidepressants</i>)	2	5,26	1	2,86
Terapija za astmu/KOPB (<i>asthma/COPD therapy</i>)	1	2,63	2	5,71
Željezo (<i>iron therapy</i>)	1	2,63	1	2,86
Kapi za glaukom (<i>eye drops for glaucoma</i>)	1	2,63	1	2,86
Citostatici (<i>cytostatics</i>)	1	2,63	1	2,86
Antipsihotici (<i>antipsychotics</i>)	1	2,63	1	2,86
Oralni hormonski kontraceptivi (<i>oral hormonal contraceptives</i>)	1	2,63	0	0,00
Antiepileptici (<i>antiepileptics</i>)	1	2,63	0	0,00
Nitrati (<i>nitrates</i>)	1	2,63	0	0,00
Antihistaminici (<i>antihistamines</i>)	0	0,00	2	5,71

*BHP – benigna hiperplazija prostate (*benign prostatic hyperplasia*); KOPB (COPD) – kronična opstruktivna plućna bolest (*chronic obstructive pulmonary disease*)

Rezultati u tablici 5 pokazuju da je među bolesnicima kod kojih nije dijagnosticirana plućna embolija učestalije primijenjena antikoagulacijska/antiagregacijska terapija u odnosu na bolesnike kod kojih je dijagnosticirana embolija, dok ispitivanjem

nije utvrđena prisutnost statistički značajne razlike ($P=0,29$). Kao antiagregacijsku terapiju većina bolesnika koristila je acetilsalicilnu kiselinu, dok se kod antikoagulacijske terapije radilo o varfarinu ili novim oralnim antikoagulansima (NOAK).

Tablica 5. Ispitanici prema terapiji (antikoagulacijska/antiagregacijska) / **Table 5** Patients according to therapy (anticoagulant/antiplatelet therapy)

Antikoagulacijska/antiagregacijska terapija (anticoagulant/antiplatelet therapy)	Korištena (used)		Nije korištena (not used)		χ^2	P*
	N	%	N	%		
Embolijska (embolism)						
Nije prisutna (not present)	11	22,00	39	78,00	1,08	0,29
Prisutna (present)	7	14,00	43	86,00		

* χ^2 test (chi-square test)

Laboratorijska obilježja ispitanika

Medijan CRP-a bio je za 22,25 mg/L veći među bolesnicima u kojih je dijagnosticirana plućna embolija u odnosu na one kod kojih plućna embolija nije dijagnosticirana (97 prema 74,75 mg/L), bez statistički značajne razlike ($P=0,80$).

Medijan broja leukocita bio je za $5,15 \times 10^9/L$ veći u bolesnika u kojih je dijagnosticirana plućna embolija u odnosu na one u kontrolnoj skupini ($12,35 \times 10^9/L$ prema $7,2 \times 10^9/L$), što je bilo statistički značajno ($p < 0,01$).

Vrijednost medijana D-dimera bila je za 19,53 mg/L veća kod bolesnika kod kojih je dijagnosticirana plućna embolija u odnosu na one kod kojih plućna embolija nije dijagnosticirana (20,56

prema 1,03 mg/L), što se također pokazalo statistički značajnim ($P < 0,01$).

Broj trombocita također se značajno razlikovao u dvije analizirane skupine. U bolesnika bez embolije medijan je bio $207,5 \times 10^9/L$, dok je u bolesnika s embolijom bio značajno veći - $301,5 \times 10^9/L$ ($P < 0,01$).

Medijan PV udjela u bolesnika u kojih nije dijagnosticirana embolija bio je za 0,21 veći u odnosu na bolesnike u kojih je dijagnosticirana plućna embolija, što nije bilo na razini statističke značajnosti ($P > 0,05$).

Medijan razine NT-proBNP bio je značajno veći (926 pg/mL) u bolesnika u kojih je dijagnosticirana plućna embolija u odnosu na one u kojih plućna embolija nije dijagnosticirana (353 pg/mL), a razlika se pokazala i statistički značajnom ($P < 0,01$) (Tablica 6).

Tablica 6. Laboratorijske vrijednosti ispitanika / **Table 6** Patients' laboratory values

Embolijska (embolism)	NE (not present) (N=50)		DA (present) (N=50)		z	P*
	M		M			
CRP (mg/L)	74,75		97		0,25	0,802
LEUKOCITI (leukocytes) ($10^9/L$)	7,2		12,35		3,82	0,0001
D-DIMERI (D-dimer) (mg/L)	1,03		20,56		3,35	0,0007
TROMBOCITI (thrombocytes) ($10^9/L$)	207,5		301,5		3,26	0,001
PV-udjel (prothrombin time percentage)	1,26		1,05		1,06	0,289
NT-proBNP (pg/mL)	353		926		3,07	0,002

*Mann-Whitney test

Radiološke karakteristike

Rezultati u tablici 7 pokazuju najčešće nalaze na RTG-u pluća. Inhomogena infiltrativna zasjenjenja bila su najčešći nalaz s prevalencijom od 54% kod osoba koje su razvile plućnu emboliju, odnosno 66% kod osoba koje je nisu razvile. Intersticijski infiltrati

s retikularnim crtežom slijede s prevalencijom od 22%, odnosno 14% u osoba koje jesu, odnosno nisu razvile plućnu emboliju. Dvadeset posto bolesnika s plućnom embolijom nije imalo nikakvih infiltrativnih i zastojnih promjena, dok je taj postotak u osoba bez embolije bio 14%.

Plućna embolija zabilježena je na nalazu MSCTA, te su tablično uneseni podaci najproksimalnijeg

tromba u plućnom stablu. Najčešća lokalizacija embolije bila je na području segmentalnih ogranaka s incidencijom od 38%. Slijedi je zahvaćenost lobarnih ogranaka u 32% slučajeva. Najproksimalniju emboliju unutar stabla plućne arterije i glavnih

plućnih arterija razvilo je 28% bolesnika, dok su subsegmentalni ogranaci bili zahvaćeni u 2% slučajeva (Tablica 8).

Medijan dana od početka simptoma do nastupa plućne embolije iznosio je 11 (10-14).

Tablica 7. Nalazi RTG pluća / **Table 7** Chest X-ray findings

Embolija (<i>embolism</i>)	DA (<i>present</i>)		NE (<i>not present</i>)	
	N	%	N	%
RTG PLUĆA (<i>chest X-ray</i>)				
Inhomogena infiltrativna zasjenjenja (<i>inhomogeneous infiltrative shadows</i>)	27	54,00	33	66,00
Intersticijski infiltrati (<i>interstitial infiltrates</i>)	11	22,00	7	14,00
Bez infiltrativnih i zastojnih promjena (<i>without infiltrative and stagnant changes</i>)	10	20,00	7	14,00
Grublji plućni crtež (<i>coarse lung markings</i>)	1	2,00	0	0,00
Kondenzirani areali plućnog parenhima (<i>condensed areas of lung parenchyma</i>)	1	2,00	0	0,00
Pleuralni izljev (<i>pleural effusion</i>)	0	0,00	2	4,00
Pleuralni plakovi (<i>pleural plaques</i>)	0	0,00	1	2,00

Tablica 8. Nalaz MSCTA u bolesnika s plućnom embolijom / **Table 8** MSCTA finding in patients with pulmonary embolism

MSCTA – lokalizacija najproksimalnijeg tromba (<i>MSCTA - localization of the most proximal thrombus</i>)	N	%
Segmentalni ogranaci (<i>segmental branches</i>)	19	38,00
Lobarni ogranaci (<i>lobar branches</i>)	16	32,00
Stablo plućne arterije s glavnim plućnim arterijama (<i>pulmonary trunk with main pulmonary arteries</i>)	14	28,00
Subsegmentalni ogranaci (<i>subsegmental branches</i>)	1	2,00

*MSCTA - od engl. *multislice spiral computed tomographic angiography*

Ishodi

Mehanička ventilacija bila je 1,67 puta učestalije korištena u bolesnika u kojih je dijagnosticirana plućna embolija u odnosu na one u kontrolnoj skupini, a ispitivanjem nije utvrđena prisutnost statistički značajne razlike ($P=0,27$) (Tablica 9). U

obje promatrane skupine (ispitivana i kontrolna) veći broj ispitanika imao je pozitivan ishod liječenja (89%). Ipak, smrtni ishod zabilježen je u 11 bolesnika, te je bio 1,75 puta učestaliji među bolesnicima u kojih je dijagnosticirana plućna embolija u odnosu na one iz kontrolne skupine, bez statistički značajne razlike (Tablica 10).

Tablica 9. Ispitanici prema mehaničkoj ventilaciji / **Table 9** Patients according to mechanical ventilation

Mehanička ventilacija (<i>mechanical ventilation</i>)	Korištena (<i>used</i>)		Nije korištena (<i>not used</i>)		χ^2	P*
	N	%	N	%		
Nije prisutna (<i>not present</i>)	44	88,00	6	12,00	1,19	0,275
Prisutna (<i>present</i>)	40	80,00	10	20,00		

* χ^2 test (*chi-square test*)

Tablica 10. Ispitanici prema ishodu liječenja / **Table 10** Patients according to treatment outcome

Smrtni ishod (<i>fatal outcome</i>)	Nije prisutna (<i>not present</i>)		Prisutna (<i>present</i>)		χ^2	P*
	N	%	N	%		
Nije prisutna (<i>not present</i>)	46	90,00	4	8,00	0,92	0,338
Prisutna (<i>present</i>)	43	86,00	7	14,00		

* χ^2 test (*chi-square test*)

Rasprava

U našem istraživanju žene su češće razvile plućnu emboliju u sklopu COVID-19, dok nešto starija životna dob nije bila značajan činitelj za razvoj plućne embolije. Metaanaliza Gomez i sur. koja je obuhvatila gotovo 6000 bolesnika, za razliku od našeg istraživanja, pokazala je veći rizik embolije u pripadnika muškog spola s omjerom izgleda od 1,59, dok starija dob također nije predstavljala statistički značajan rizični čimbenik za plućnu emboliju.¹⁷

Većinu ispitanika u našoj studiji činili su nepušači. Promatrajući samo pušače, njihova zastupljenost među bolesnicima s plućnom embolijom bila je oko dva puta veća nego u onih bez embolije, iako bez statističke značajnosti. Studija Riyahi i sur. koja je obuhvatila 413 COVID-19 bolesnika također prikazuje pušenje kao rizični čimbenik za emboliju.²⁶

Procijepljenost ispitivane populacije iznosila je svega 10%. Cijepljenih ispitanika bilo je dva puta više u kontrolnoj nego u ispitivanoj skupini. Istraživanje Law i sur. prikazuje incidenciju plućne embolije u cijepljenih i necijepljenih kroz tri različite virusne varijante. Relativni rizik za plućnu emboliju u COVID-19 bolesnika iznosio je 3,89 za necijepljene kod Omicron varijante, dok je taj rizik kod Delta varijante bio 3,2.²⁷

Rezultati su pokazali kako je 80% ispitanika imalo neki od komorbiditeta, te nije bilo statistički značajne razlike između skupina. Najčešće prisutne bolesti bile su arterijska hipertenzija, šećerna bolest, hipotireoza i hiperlipidemija. Studija Budimir Mršić i sur. promatrala je rizične čimbenike za emboliju u COVID-19 i definirala sljedeće komorbiditete kao najučestalije u bolesnika s plućnom embolijom: arterijsku hipertenziju (43,58%), diabetes mellitus (14,10%) i prisutnost karcinoma (12,82%). Većina ispitanika imala je prisutan barem jedan komorbiditet (82,06%).²⁸

Nadalje, ustanovljeno je da je 73% bolesnika uzimalo neki oblik kronične terapije. Među najčešće korištenim lijekovima kod osoba s razvijenom plućnom embolijom nalazili su se antihipertenzivi (71,43%), antidijabetici (22,86%) i antilipemici (22,86%). Osamnaest posto COVID-19 bolesnika uzimalo je antiagregacijsku i/ili antikoagulacijsku terapiju, s tim da je 1,57 puta bila češće korištena u kontrolnoj grupi koja nije razvila plućnu emboliju. Iako rezultat nije statistički značajan, u praksi često nailazimo na profilaktičko davanje antikoagulansa COVID-19 bolesnicima. U metaanalizi Kamel i sur. dokazano je da terapijske, ali i profilaktičke doze antikoagulansa smanjuju mortalitet u osoba s bolešću COVID-19 i rizikom za plućnu emboliju. Kronična

antikoagulantna terapija nije se pokazala statistički značajnom u smanjenju mortaliteta, ali ima tendenciju smanjenja incidencije plućne embolije u COVID-19 bolesnika.²⁹ Promatrajući laboratorijske nalaze pokazali smo da su sljedeći parametri u bolesnika s plućnom embolijom bili statistički značajno različiti u odnosu na kontrolnu skupinu: veći broj leukocita, viša koncentracija D-dimera, veći broj trombocita, te viša koncentracija NT-proBNP-a. Metaanaliza Wu i sur. također pokazuje više vrijednosti leukocita, te D-dimera u osoba s embolijom u sklopu COVID-19, kao i više vrijednosti APTV-a i fibrinogena, što odgovara općem upalnom zbivanju, ali i prokoagulantnom stanju.³⁰ Razina NT-proBNP-a odražava stupanj miokardijalne ozljede pod utjecajem SARS-CoV-2 infekcije, te stupanj hemodinamskog stresa miokarda, te stoga ima bitnu ulogu u dijagnozi i liječenju srčanog zatajenja. Dakle, više vrijednosti NT-proBNP-a povezane su s težom kliničkom slikom i većim mortalitetom. U studiji Caro-Codon i sur. analizirana je grupa od 396 osoba oboljelih od COVID-19, te su u 48,5% bolesnika pokazane povišene vrijednosti NT-proBNP-a.³¹ Vrijednosti PV-a promatrane su u studiji Tang i sur. u 183 bolesnika, te su, za razliku od naše studije, zabilježene više vrijednosti kod preminulih bolesnika, što je bilo povezano s težom kliničkom slikom i većom stopom tromboembolijskih komplikacija. Srednja vrijednost PV-a u bolesnika sa smrtnim ishodom iznosila je 1,19 (1,10-1,25), a ukupna smrtnost 11,47%.³²

U našem istraživanju pokazali smo da su glavni nalazi na RTG-u pluća inhomogena infiltrativna zasjenjenja (60%) i retikularni intersticijski crtež (18%), dok 17% bolesnika nije imalo nikakvih infiltrativnih i/ili zastoynih promjena. Prema istraživanju Martinez Comorro i sur. 80% hospitaliziranih bolesnika imalo je neki od pozitivnih nalaza na RTG-u. Najčešće se radilo o retikularnom crtežu, zasjenjenju po tipu mliječnog stakla ili konsolidacijama s multifokalnom distribucijom. Negativan nalaz tipičan je za početni stadij bolesti, te ne isključuje infekciju. Atipični nalazi koji su se javljali u 3% bolesnika su lobarna konsolidacija, čvorovi, milijarni rasap, kavitacija i pleuralni izljev.³³ Nalazi na RTG-u kod plućne embolije dosta su nespecifični i suptilni, te se kreću od kardiomegalije, povećane plućne arterije, atelektaza, konsolidacija do smanjenog plućnog vaskularnog crteža. Iz tog razloga RTG pluća ne koristi se rutinski za dijagnozu plućne embolije u COVID-19 bolesnika.³⁴

Analizirajući lokalizaciju najproksimalnijeg tromba u plućnom stablu na MSCTA, pokazali smo kako je 38% njih bilo u segmentalnim, 32% u lobarnim, 28% u centralnim, te 2% u

subsegmentalnim ograncima. U istraživanju Poyiadji i sur. također je provedena navedena analiza, te je pokazano kako se u 51% slučajeva najproksimalniji tromb nalazio u segmentalnim, u 3% u lobarnim, u 13% u centralnim, te u 5% slučajeva u subsegmentalnim ograncima.⁴ Medijan nastupa plućne embolije u našem istraživanju bio je 11 (10-14) dana od početka simptoma, dok je primjerice u studiji Ameri i sur. bio 15 (9-24) dana.³⁵

U našem istraživanju također smo ustanovili da je mehanička ventilacija češće korištena u bolesnika u kojih je dijagnosticirana embolija u odnosu na bolesnike iz kontrolne skupine. Isto tako smrtni ishod bio je češći u bolesnika s embolijom, iako razlika nije bila statistički značajna. U metaanalizi Gomez i sur. uočavamo veći rizik za mehaničku ventilaciju, kao i veći rizik za primitak u JIL bolesnika s plućnom embolijom kao i u našem istraživanju, te također nije dokazana statistički značajna razlika u mortalitetu između ispitne i kontrolne skupine.¹⁷

Zaključak

Iako su bolesnici s COVID-19 i plućnom embolijom bili češće ženskoga spola, starije životne dobi i s češćim komorbiditetima od COVID-19 bolesnika bez plućne embolije, dob, spol, te veći broj komorbiditeta nisu se statistički značajno razlikovali među skupinama. Antiagregacijska i/ili antikoagulacijska terapija kao kronična terapija također se nije pokazala statistički značajno manje prisutnom u COVID-19 bolesnika s plućnom embolijom. COVID-19 bolesnici s plućnom embolijom imali su značajno više vrijednosti D-dimera, trombocita, leukocita, te natriuretskog peptida u odnosu na COVID-19 bolesnike bez plućne embolije, što nije vrijedilo za razlike u vrijednostima CRP-a i PV-a. Veći je broj umjetno ventiliranih i umrlih bio u COVID-19 bolesnika s plućnom embolijom, najčešće lokaliziranu u segmentalnim ograncima plućne arterije, iako bez statistički značajne razlike između skupina.

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Psychometric properties of the Croatian version of the Non-motor Symptoms Scale in Parkinson's disease

Psihometrijska svojstva hrvatske verzije „Non-motor Symptoms Scale“ skale kod bolesnika oboljelih od Parkinsonove bolesti

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Summary

Objectives: The objective was to evaluate the psychometric properties of the Croatian version of the Non-Motor Symptoms Scale (NMSS), a tool to assess non-motor symptoms (NMSs) in Parkinson's disease (PD).

Methods: A cross-cultural adaptation of the NMSS into Croatian and a psychometric analysis of the translated version of the NMSS was carried out in PD patients. NMSS includes nine domains: cardiovascular, sleep/fatigue, mood/cognition, perceptual problems/hallucinations, attention/memory, gastrointestinal tract, urinary, sexual function and miscellaneous. The quality of data was descriptively analysed, and Cronbach's alpha coefficient assessed internal consistency. Pearson correlations were performed on the nine domains. The level of significance was set to $p < 0.05$.

Results: 76 PD patients were assessed (mean age 68.4 ± 9.6 years; 45% women; mean length of disease 8.7 ± 4.6 years). Mean NMSS score was 110.68 ± 58.76 , where the more common NMSs in PD patients were related to the following domains: mood/cognition (22.86 %), sleep/fatigue (19.74 %), sexual function (13.65 %) and urinary (11.58 %). Cronbach's alpha for the NMSS total score was 0.92 (range for domains: 0.48-0.96). Total NMSS score was highly correlated with each of the nine domains (Pearson correlation range: 0.45-0.82).

Conclusions: The Croatian version of NMSS can be considered a comprehensive and helpful measure for NMSs in Croatian-speaking PD patients.

Key words: Croatia, Parkinson's disease, non-motor symptoms, Non-Motor Symptoms Scale

Sažetak

Cilj: Cilj ovoga rada bio je evaluirati psihometrijska svojstva hrvatske verzije 'Non-motor Symptoms Scale' skale, pomagala koje se koristi u procjeni nemotoričkih simptoma kod bolesnika oboljelih od Parkinsonove bolesti.

Metode: Međukulturalna adaptacija 'Non-motor Symptoms Scale' skale na hrvatski jezik i

psihometrijska analiza prevedene verzije navedene skale, vršila se na bolesnicima oboljelim od Parkinsonove bolesti. 'Non-motor Symptoms Scale' skala uključuje devet domena: kardiovaskularni sustav, spavanje/umor, raspoloženje/spoznaja, vidljivi problemi/halucinacije, pažnja/memorijska, gastrointestinalni trakt, urinarni tegobe, seksualna funkcija i domena razno. Podaci su opisno analizirani, a unutarnja dosljednost procijenjena je pomoću Cronbach alpha koeficijenta. Pearsonove korelacije primijenjene su na svih devet domena, a razina značajnosti postavljena je na $p < 0,05$.

Rezultati: U istraživanje je ukupno bilo uključeno 76 bolesnika koji boluju od Parkinsonove bolesti (prosječna starost $68,4 \pm 9,6$ godina, 45 % žene, prosječno trajanje bolesti $8,7 \pm 4,6$ godina). Srednja vrijednost ukupnog rezultata 'Non-motor Symptoms Scale' skale iznosila je $110,68 \pm 58,76$, pri čemu su češći nemotorički simptomi bili povezani sa sljedećim domenama: raspoloženje/spoznaja (22,86 %), spavanje/umor (19,74 %), seksualna funkcija (13,65 %) i urinarni tegobe (11,58 %). Cronbach alpha koeficijent za ukupni rezultat 'Non-motor Symptoms Scale' skale iznosio je 0,92 (raspon za domene od 0,48 do 0,96). Ukupni rezultat 'Non-motor Symptoms Scale' bio je visoko povezan sa svih devet domena (Pearsonova korelacija bila je u rasponu od 0,45 do 0,82).

Zaključak: Hrvatska verzija 'Non-motor Symptoms Scale' skale može se smatrati sveobuhvatnim i korisnim instrumentom koji pomaže mjerenje nemotoričkih simptoma kod bolesnika koji boluju od Parkinsonove bolesti na hrvatskom govornom području.

Ključne riječi: Hrvatska, nemotorički simptomi, 'Non-Motor Symptoms Scale' skala, Parkinsonova bolest

Introduction

Parkinson's disease (PD) is a progressive neurological disorder which is characterized by a dopamine deficiency that is associated with tremor, rigidity, bradykinesia and gait problems. In the last decade, PD has been also recognized as implying non-dopaminergic dysfunction and non-motor symptoms (NMSs) which appear at all stages of disorder¹ and have a notable impact on PD patients' health and quality of life.²⁻⁵ NMSs mainly consider neuropsychiatric symptoms, sleep disorders, autonomic dysfunction, gastrointestinal symptoms and sensory symptoms.⁶ NMSs associated with PD are sadly often under-recognized and remain untreated in the early stages of the disease. The exact prevalence and severity of non-motor symptoms in early PD (before initiation of antiparkinsonian drugs) remains unclear.⁷

In order to respond to the need for quantification of PD symptoms, various instruments have been recently developed and validated to assess and advance their detection. Several instruments are available for the quantification of motor feature (Unified Parkinson's Disease Rating Scale, UPDRS) and health-related quality of life (Parkinson's Disease Questionnaires - PDQ 8 and 39), but until year 2006, no scale had yet been developed or validated specifically for the assessment of the full range of NMSs observed in PD. In the mentioned year, Chaudhuri et al. developed and validated a self-reported questionnaire for PD patients for NMS (NMSQuest). NMSQuest consisted of 30 common symptoms scored "yes" or "no," and it is designed to provide a quick screen for problematic NMSs for clinical management.⁸

Because NMSQuest is not a rating scale, nor is it intended to evaluate the effect of treatment, Chaudhuri et al. developed and validated the Non-motor Symptoms Scale for PD (NMSS-PD) one year later. That scale has been efficiently used to assess and measure NMSs of PD and it is the most often scale used in clinical practice for assessment of NMSs in PD. NMSS scale was originally designed and validated by Chaudhuri et al. in 2007, on a total of 242 PD patients across centres in the UK, Italy, Germany, USA, and Japan.⁹

NMSS is a specific validated scale in different populations for the screening and the assessment of NMSs. It is a 30-item scale involving 9 domains: Cardiovascular, Sleep/Fatigue, Mood/Cognition, Perceptual problems, Attention/Memory, Gastrointestinal, Urinary, Sexual function and Miscellaneous domain. The items inside of every mentioned domain are assessed for severity (from 0 to 3) and frequency (from 1 to 4) and scored through the multiplication of both values (from 0 to 12). The higher result indicates higher severity and frequency of NMSs, and the maximum score is 360.¹⁰

The objective of this study was to evaluate the psychometric properties of the Croatian version of the NMSS, a tool to assess NMSs in PD.

Participants and methods

Participants

In this research data was analysed on 76 PD patients, which included 34 women and 42 man which underwent neurological care at Clinical Hospital Centre Osijek, Croatia. All the patients were

required to sign a statement of informed consent before we started the research.

Questionnaire procedures

Our research problem was examined using the 30-item NMSS which includes the following nine domains: Cardiovascular, Sleep/Fatigue, Mood/Cognition, Perceptual problems, Attention/Memory, Gastrointestinal, Urinary, Sexual function and Miscellaneous domain.⁹ We received approval from the original author to translate the NMSS into Croatian. In the translation stage, two bilingual researchers with experience in clinical practice independently translated the original tool. In the back-translation stage, another translator who had not previously encountered the original tool translated the Croatian version back into English. Back-translation worked well in avoiding translation errors because a large part of the original language structure was retained. The translated tool was finalized in the final stage. This process required comparing the two versions, and it confirmed that there were no meaningful differences between the original and translated versions. All differences were reviewed and corrected through discussions. The consensus process was repeated to complete the translation if corrections were needed due to the accuracy of translation or cultural differences.

Statistical analysis

The data was descriptively analysed, and Cronbach's alpha coefficient assessed internal consistency. Pearson's correlation coefficient (r) was performed on the nine domains of the NMSS. The level of significance was set to $p < 0.05$.

Results

The mean age was 68.4 ± 9.6 years, and the mean disease duration was 8.7 ± 4.6 years. The highest mean score was measured for the Mood/Cognition domain, while the lowest was found for the Perceptual problems domain. The mean NMSS total score measured 110.68 ± 58.76 , where the more common NMSs in PD patients were related to the following domains: mood/cognition (22.86 %), sleep/fatigue (19.74 %), sexual function (13.65 %) and urinary (11.58 %). Cronbach's alpha coefficient for the NMSS total score using the entire sample was 0.92, indicating high internal consistency. The Cronbach's alpha coefficient ranged from 0.48 for the Miscellaneous domain to 0.96 for the Urinary and Sexual function domains (Table 1).

Table 1 Descriptive statistics and internal consistency of NMSS total score and domain
Tablica 1. Deskriptivna statistika i unutarnja konzistentnost ukupnog rezultata i domene NMSS-a

NMSS	Mean (SD)	Cronbach's alpha
Cardiovascular <i>Kardiovaskularna</i>	5.26 (5.64)	0.73
Sleep/Fatigue <i>Spavaje/umor</i>	21.85 (12.46)	0.78
Mood/Cognition <i>Raspoloženje/spoznaja</i>	25.30 (18.40)	0.93
Perceptual problems <i>Perceptualni problemi</i>	2.72 (4.75)	0.65
Attention/Memory <i>Pažnja/pamćenje</i>	9.24 (8.39)	0.77
Gastrointestinal <i>Gastrointestinalni</i>	6.57 (8.61)	0.86
Urinary/ <i>Urinarni</i>	12.82 (12.34)	0.96
Sexual function <i>Seksualna funkcija</i>	15.11 (9.10)	0.96
Miscellaneous/ <i>razno</i>	11.81 (7.38)	0.48
Total score <i>Ukupni rezultat</i>	110.68 (58.76)	0.92

NMSS: Non-Motor Symptoms Scale; SD: standard deviation
NMSS: Ljestvica nemotornih simptoma; SD: standardna devijacija

The total NMSS score was highly correlated with each of the nine domains, the Pearson's correlation coefficient ranged from 0.45 to 0.82, indicating a strong association with the related construct. The highest correlation was measured for the Attention/Memory domain, while the lowest one was found for the Cardiovascular domain (Table 2).

Table 2 The domains-total NMSS score correlation
Tablica 2. Korelacija domena i ukupnog NMSS rezultata

NMSS	r
Cardiovascular/ <i>Kardiovaskularna</i>	0.45*
Sleep/Fatigue <i>Spavaje/umor</i>	0.71*
Mood/Cognition <i>Raspoloženje/spoznaja</i>	0.76*
Perceptual problems <i>Perceptualni problemi</i>	0.47*
Attention/Memory <i>Pažnja/pamćenje</i>	0.82*
Gastrointestinal <i>Gastrointestinalni</i>	0.67*
Urinary/ <i>Urinarni</i>	0.76*
Sexual function/ <i>Seksualna funkcija</i>	0.74*
Miscellaneous/ <i>Razno</i>	0.64*

NMSS: Non-Motor Symptoms Scale; * - statistically significant at $p < 0.05$
*NMSS: Ljestvica nemotoričkih simptoma; * - statistički značajno pri $p < 0,05$*

Discussion

The aim of this study was to evaluate the psychometric properties of the Croatian version of the NMSS, a tool to assess NMSs in PD patients. The Croatian version of NMSS was earlier translated but it had not been psychometrically validated by Bago Roznakovic et al. in 2017 year on a total of 71 PD patients and 60 healthy participants.¹¹ To the best of our knowledge, this is the second study in Croatia which investigated NMSs for patients with PD in which Croatian version of the NMSS was used for NMSs assessment.

We found most necessary and important to investigate the NMSs of patients suffering from PD because of the mentioned and proved statement that NMSs associated with PD are often very prevalent and severe but for now, they are sadly often under-recognized and remain untreated in early stages of disease.⁷ The secure the right and early treatment of NMSs in patients with PD, it is first necessary to make as complete and as high-quality assessment of their severity and prevalence as possible.

The reason why we chose to translate and validate the Croatian version of the NMSS for the purpose of assessing NMSs of patients suffering from PD rather than use already translated and clinically used questionnaires in Croatia is mainly because the NMSS is the rating scale, it is specifically designed to provide a quick screen for problematic NMSs for clinical management and it can be used for the evaluation of the effect of treatment.⁹ The results of this paper were discussed in connection with published literature in NMSs of patients suffering from PD domain from around 20 years ago until today.

The earlier mentioned translation of the Croatian version of NMSS¹¹, after its original validation by Chaudhuri et al. in 2007⁹ the NMSS was also translated and validated on PD patients from various countries and regions.^{10,12-21}

Back in 2007, Chaudhuri et al. made the first and original validation of NMSS on a total of 242 PD patients across centers in the UK, Italy, Germany, USA, and Japan. The total NMSS score was almost two times lower than the one in our research, measuring 56.46 (40.66). The same result as ours was found in terms of the lowest domain mean score which was measured for the Perceptual problems domain - 1.71 (4.03). The highest score was found for the Sleep/Fatigue domain measuring 12.60 (10.35). In terms of correlation of NMSS domains with a total NMSS score, the correlation coefficient (r) ranged from 0.45 for the Cardiovascular domain to 0.96 for the Mood/Cognition domain. In our research, the

lowest correlation with total NMSS score was also found for the Cardiovascular domain measuring also 0.45, while the highest correlation was found for the Attention/Memory domain ($r = 0.82$). Four domains (Mood/Cognition, Attention/Memory, Urinary, and Sexual function) showed Cronbach's alpha coefficient higher than 0.70 (from 0.71 for the Urinary domain to 0.85 for the Mood/Cognition domain). The other two, the Sleep/Fatigue and Perceptual problems domains reached values around 0.60 and the remaining domains had Cronbach's alpha under the limit, while mean Cronbach's alpha was 0.61.⁹ Those Cronbach's alpha results indicate lower internal consistency reliability than one in our research.

Croatian authors Bago Roznakovic et al. conducted a research about NMSs in de novo PD comparing to normal aging while using the NMSS score. A total of 71 PD patients and 60 healthy participants (control group) completed their study. Significantly higher frequency of NMSs in PD patients was found in Cardiovascular, Sleep/Fatigue, Mood/Cognition, Hallucinations and Attention/Memory when comparing to control group. Most PD patients in their research suffered from sleep/fatigue (97.2 %), mood/cognition (98.6 %) and attention/memory (97.2 %) NMSs. The highest NMSS score was present in the Mood/Cognition domain in PD patients' group (median 14.0), the same as the highest score in our study which was also found for the Mood/Cognition domain measuring 25.30 (18.40). The total NMSS score was higher in the PD group than in the control group indicating that NMS were more serious and frequent among PD patients (median PD 38,00 vs. controls 8,00; $p < 0.001$).¹¹ Both PD patients and the control group total NMSS scores were lower than the one in our research that measured 110.68 (58.76). When investigating the correlation between the total NMSS score and NMSS domains, the highest correlation with total NMSS score was found for the Mood/Cognition domain ($r = 0.785$) and the lowest for the Hallucinations domain ($r = 0.311$). For comparison, the highest correlation with a total NMSS score in our research was found for the Attention/Memory domain ($r = 0.82$), while the second highest was found for the Urinary domain ($r = 0.76$) and also the Mood/Cognition domain ($r = 0.76$). On the other hand, the lowest correlation was found for the Cardiovascular domain ($r = 0.45$).

Martinez-Martin et al. conducted an international study on the psychometric attributes of the NMSS for PD on 411 PD patients 12 centres across 10 countries in America, Asia, and Europe. The total NMSS score measured 57.1 (44.0) was almost two times lower than the one in our study which was measured on

110.68 (58.76). The same as in our research, the highest mean value was measured for the Mood/Cognition domain - 11.2 (14.3) while the lowest was measured for the Cardiovascular domain - 1.8 (3.2), which was the second lowest domain measured in our study. The intraclass correlation coefficient ranged from 0.67 for the Sexual function domain to 0.91 for the Mood/Cognition domain, which is higher correlation with a total NMSS than ours where it ranged from 0.45 to 0.82. In terms of internal consistency reliability, Cronbach's alpha ranged from 0.44 for the Miscellaneous domain to 0.85 for the Mood/Cognition domain.¹⁰ Similar results for Cronbach's alpha are measured in our study (from 0.48 to 0.96), especially for the lowest which was also found for the Miscellaneous domain measuring 0.48.

The validation of the Chinese NMSS for PD was made on a total of 126 PD patients in a study conducted by Wang et al. The highest mean value was measured for the Mood/Cognition domain, the same as in our research, with a result of 8.26 (11.23) while the lowest was measured for the Cardiovascular domain with a result of 0.60 (1.44). The total NMSS score was measured on 31.06 (30.88), which is more than 3 times lower than our total NMSS score. Cronbach's alpha coefficient for the total NMSS was 0.89, which is slightly lower than the one in our research. The Cronbach's alpha coefficients for the 9 NMSS subscales were 0.23, 0.68, 0.90, 0.55, 0.85, 0.54, 0.85, 0.89, and 0.36, respectively. Significant coefficients ($r_s > 0.19$, $P < 0.05$) were found for all 30 items of 9 NMSS domains except item 2 (fainting) in the item-total (corrected) correlation analysis of the NMSS.¹²

The validation of the Korean version of the NMSS for PD was made by Koh et al. on a total of 102 PD patients. The total NMSS score in their research was measured at 43.87 (42.35) with the highest value again for the Mood/Cognition domain - 10.54 (13.41) and the lowest for the Perceptual problems domain - 0.69 (1.99). Those results in terms of the highest and the lowest measured mean value are the same as in our study, but the total NMSS score in our research is still noticeably higher. Cronbach's alpha coefficient for the total NMSS score was 0.742 and each of the nine NMSS domains gave Cronbach's alpha coefficients of ≥ 0.70 . That result is better than the one measured in our study in which the Perceptual problems and Miscellaneous domains did not reach Cronbach's alpha higher than 0.70. Furthermore, the correlations between each domain with the total NMSS score were statistically significant - Spearman's rank correlation coefficient (r_s) ranged from 0.376 for the Cardiovascular domain to 0.806

for the Attention/memory domain.¹³ The results for the best and the worst correlation with total NMSS score was measured for the same NMSS domains in our research.

Carod-Artal and Martinez-Martin made a research on the independent validation of the NMSS for PD in a total of 150 Brazilian patients with PD. The highest measured NMSS domain in their research was also the Mood/Cognition domain - 11.2 (13.7) and the lowest score was measured for the Cardiovascular domain - 1.5 (2.5). The total NMSS score measured 48.9 (36.3)¹⁴ which is still lower than the total NMSS score in our research. Same result for the highest and the lowest value was earlier found in an international [10] and Chinese study.¹² The mean Cronbach's alpha of the NMSS Brazilian version was 0.60, and four domains (Mood/Cognition, Attention/Memory, and Urinary and Sexual function) showed a satisfactory internal consistency and reached a Cronbach's alpha over the standard 0.70.¹⁴ These results are equivalent to those in the original study of validation⁹, and still lower than those from our study.

The evaluation of an Arabic version of the NMSS for PD was made in the research of Sellami et al. on 62 Tunisian PD patients. The mean NMSS score was 82.29 (55.76) which is still lower than the total score in our research. The mean Cronbach's alpha of the NMSS Arabic version was measured at 0.87¹⁵, indicating a high internal consistency reliability, the same as in our study.

Cova et al. made validation of the Italian version of the NMSS for PD on a total of 71 PD patients from Rome (43 patients) and Milano (28 patients). The total NMSS score was 39.76 (31.90), and the highest mean score was measured for the Urinary domain - 7.87 (8.70), which was not the case in earlier research. The lowest mean value was found for the Perceptual problems domain, the same as in the NMSS original validation study⁹, Korean study¹³, and in our study, measuring 0.90 (1.86). In terms of NMSS domains AND total NMSS score correlation, all domains, except the Sexual function domain, showed a statistically significant correlation with the total NMSS score. Internal consistency reliability was adequate, as the Cronbach's alpha coefficient resulted in 0.72 for the total NMSS scale which is slightly worse than in our study (0.79). The Cronbach's alpha coefficients for the 9 NMSS subscales were measured at 0.72, 0.64, 0.68, 0.73, 0.69, 0.69, 0.68, 0.73 and 0.71.¹⁶

Furthermore, two review articles were made on the assessment and use of NMSS for PD, the first back in 2017. by Sauerbier et al.¹⁷ specifically for the Asian population, and the second by Wamelen et al. in 2020.¹⁸ Except earlier mentioned and discussed

studies, Sauerbier et al.¹⁷ in their review additionally included seven studies from China²²⁻²⁸, three from Korea²⁹⁻³¹, one from Singapore³² and one from India³³ in which NMSS was used. Three years later, Wamelen et al.¹⁸ additionally included three studies³⁴⁻³⁶ in their review. Both reviews^{17,18} concluded that the NMSS provided a roadmap for clinical quantification of the NMSs in PD patients and that the NMSS has been validated with acceptable psychometric properties as a reliable and reproducible outcome measures.

Natadidjaja et al. made a validation of the Indonesian version of the NMSS for PD on a total of 70 PD patients in 2023. The mean NMSS total score was 51.86 (44.02) which is still more than two times lower score than the total NMSS score in our research. In terms of correlation of each NMSS domain with total score, all domains were significantly correlated with total score, the same as in our study with the correlation coefficient (r) ranging from 0.506 for the Miscellaneous domain to 0.805 for the Mood/Cognition domain. Cronbach's alpha coefficient for the NMSS total score was 0.853 and Cronbach's alpha coefficients for the 9 NMSS domains were 0.274, 0.565, 0.702, 0.534, 0.806, 0.666, 0.701, 0.814, and 0.146.¹⁹ That result of internal consistency reliability is lower than the one that we measured in our research.

In 2023, Eghlidos et al. made a research on the validation of the Persian version of the NMSS for PD on a total of 186 PD patients from Iran. The total NMSS score was measured on 52.01 (38.54) or also two times lower than the total NMSS score in our study. The lowest mean values were measured for the Perceptual problems domain - 1.30 (4.22), and the highest mean value was measured for the Mood/Cognition domain - 11.77 (12.01)²⁰, same as in the Korean¹³ and our study. The correlation between the NMSS total score and NMSS subscales ranged from the Perceptual problems/Hallucinations domain ($r = 0.40$) to Mood/Cognition domain ($r = 0.79$). The overall Cronbach's alpha of the Persian version of NMSS was 0.84. Three domains (Mood/Cognition, Attention/Memory, and Urinary domain) had good internal consistency (more than 0.7), and two domains (Sleep/Fatigue and Perceptual problems/Hallucinations) showed acceptable value (more than 0.6). The rest of the NMSS domains had values of Cronbach's alpha lower than 0.6.²⁰ Considering those results, the intercorrelation between the total NMSS score and NMSS domains, as well as internal consistency validity is slightly lower than in our study.

Also, in year 2023, Hamdan et al. tested the validity and reliability of NMSS for PD on a total of 35 PD patients in Dr. Soetomo General Hospital,

Surabaya, Indonesia. Internal consistency reliability was performed using Cronbach's alpha coefficient value of > 0.7 for the reliability of the total NMSS score (0.836). Cronbach's alpha coefficients ranged from 0.489 to 0.985, and the highest Cronbach's alpha was measured for the Sexual function domain which was 0.985.²¹ This is similar to the results in the Brazilian¹⁴ and Italian¹⁶ versions of the validation studies, in which Cronbach's alpha coefficient of a total NMSS score was measured on 0.60 and 0.72, with the reliability value of each item ranging from 0.37 and 0.82 and from 0.64 to 0.71, whereas in a study conducted by Martinez et al.¹⁰, the Cronbach's alpha coefficients ranged from 0.44 to 0.85.

Differences and variations of results in earlier cited studies are probably caused by a wide clinical picture and various clinical manifestations of PD, including NMSs. There is no reported data about the significant influence of culture or territorial area on NMSs in PD³⁷, meaning that they are likely triggered by different pathology of PD. Since our results of internal consistency reliability and intercorrelation between separate dimensions of NMSS are pretty high when compared to the ones from cited studies, we think that the differences in the results of those studies have no consequences on the interpretation of the Croatian version of the NMSS in Croatian-speaking PD patients.

Conclusion

According to our results, the total score of NMSS for our participants, and therefore PD symptom severity, was self-estimated at 110.68 (58.76) which is higher than all the total NMSS scores in studies from relevant literature included and discussed in this paper. The highest mean value was measured for Mood/Cognition, while on the other hand, the lowest values were measured for the Perceptual problems domain. Cronbach's alpha ranged from 0.48 to 0.93 and a statistically significant correlation was found between all NMSS domains and the total score when Pearson correlations were performed. Therefore, when looking at the results of internal consistency reliability and intercorrelation between separate dimensions of NMSS, and when comparing them with the relevant studies and relevant literature from this research domain, it can be concluded that the Croatian version of the NMSS can be considered a comprehensive and helpful measure for NMSs in Croatian-speaking PD patients.

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Anemia in Patients with Type 2 Diabetes

Anemija u bolesnika s tipom 2 šećerne bolesti

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Summary

Objectives: The aim of the research is to examine the frequency and types of anemia in patients with type 2 diabetes depending on gender, age, and therapy for the treatment of diabetes mellitus.

Material and methods: The research is a cross-sectional study with historical data. The research used data collected during regular check-ups for patients with type 2 diabetes in primary health care offices in Osijek Health Center from February to June 2022. The collected data were demographic data, data on the duration of diabetes and the used therapy, data on the presence of diabetic nephropathy, fasting glucose values, values of glycosylated hemoglobin, iron, unsaturated and total iron binding capacity, hemoglobin, average erythrocyte volume, average hemoglobin in erythrocyte and average concentration of hemoglobin in erythrocyte.

Results: Anemia was recorded in 19% of the subjects and was usually normocytic normochromic, characterized as mild or moderate. Etiologically, the most prevalent were anemia of chronic disease and mixed anemia. The average age of patients with anemia was 12 years higher than those without anemia. Normocytic normochromic and hypochromic anemia occurred statistically significantly more often in elderly patients, as did mixed anemia. No difference was observed in the frequency of anemia regarding the treatment of diabetes with monotherapy or combined therapy. A significantly higher frequency of anemia was observed in patients who used sulfonylurea derivatives. The first 5 years of metformin treatment were significantly associated with the onset of anemia of chronic disease, and treatment lasting longer than 10 years with the onset of mixed anemia.

Conclusion: Regular screening is essential as a part of routine controls because patients with type 2 diabetes have a high incidence of anemia. This is especially significant for elderly individuals with renal insufficiency and poor disease control, as well as for patients receiving sulfonylurea derivative treatment.

Keywords: Anemia, Type 2 Diabetes mellitus, Diabetic complications, Metformin, Sulfonylurea Derivatives

Sažetak

Cilj istraživanja: Cilj istraživanja jest ispitati učestalost i vrste anemija kod osoba s tipom 2 šećerne bolesti ovisno o spolu, dobi i terapiji za liječenje tipa 2 šećerne bolesti.

Ispitanici i metode: Istraživanje je ustrojeno kao presječno s povijesnim podacima koji su prikupljeni u ambulantom primarne zdravstvene zaštite u Domu zdravlja Osijek od veljače do lipnja 2022. Godine,

pri redovitim kontrolama bolesnika s tipom 2 šećerne bolesti. Prikupljeni su demografski podaci, podaci o trajanju šećerne bolesti i terapiji, podaci o prisutnosti dijabetičke nefropatije, vrijednosti glukoze natašte, vrijednosti glikoliziranog hemoglobina, željeza, nezasićenog i ukupnog kapaciteta vezanja željeza, hemoglobina, prosječnog volumena eritrocita i prosječnog hemoglobina u eritrocitu te prosječne koncentracije hemoglobina u eritrocitu.

Rezultati: U 19 % ispitanika zabilježena je anemija, najčešće normocitna normokromna, karakterizirana kao blaga ili umjerena. Etiološki su najzastupljenije anemija kronične bolesti i miješana anemija. Prosječna dob osoba s anemijom 12 je godina veća od prosječne dobi osoba bez anemije. Normocitna normokromna i hipokromna anemija statistički značajnije su se češće pojavljivale u osoba starije životne dobi, kao i miješana anemija. Nije uočena razlika u učestalosti anemije s obzirom na liječenje tipa 2 šećerne bolesti monoterapijom ili kombiniranom dijabetološkom terapijom. U osoba koje su koristile derivate sulfonilureje uočena je značajno veća učestalost anemije. Prvih pet godina liječenja metforminom značajno je povezano s nastankom anemije kronične bolesti, a liječenje koje traje dulje od 10 godina s nastankom miješane anemije.

Zaključak: Zbog visoke incidencije anemije u osoba s tipom 2 šećerne bolesti potrebno je vršiti probir u sklopu redovitih kontrola, a posebice u osoba starije životne dobi s bubrežnom insuficijencijom te lošom kontrolom bolesti, kao i u osoba liječenih derivatima sulfonilureje.

Ključne riječi: anemija, šećerna bolest tip 2, komplikacije šećerne bolesti, metformin, derivati sulfonilureje

Introduction

Diabetes mellitus (DM) with vascular complications is one of the main causes of death worldwide.¹ The number of people between the ages of 20 and 79 who were diagnosed with DM increased from 285 million in 2009 to 463 million in 2019, accounting for 95% of patients with type 2 diabetes mellitus (T2DM), according to the 2022 International Diabetes Federation (IDF) reports.² Globally, the number of adults with DM is predicted to rise to 783 million by the year 2045, which is posing a serious threat to public health.^{3,4} Poor control of glycemic status is extremely important for the control of DM, and is associated with the development of complications that impair functional ability, autonomy, and quality of life, eventually also leading to high mortality.⁵

T2DM is a condition that eventually impairs the operation of nearly every organ in the human body. Therefore, the most significant issue for individuals with DM are chronic complications, and the most prevalent are: diabetic nephropathy, retinopathy, neuropathy, diabetic foot, brain stroke, and coronary artery disease causing myocardial infarction.⁶ Anemia can also be one of the many chronic complications of T2DM. According to World Health Organization (WHO) standards, anemia is a common blood condition characterized by a hemoglobin level of less than 130 g/L for males and less than 120 g/L for females. Iron deficiency is the cause of around half of all anemia cases worldwide.⁷ Anemia is known to have a major role in the illness, resulting in symptoms such as low energy, breathlessness, lightheadedness, poor appetite, reduced cognitive function, and ability to work, all of which negatively affect the patient's social life. Because of all the above

mentioned, patients with anemia typically have a worse quality of life, so we can say that anemia is an unwelcome extra burden for diabetic individuals who already have an increased risk of acute and chronic complications.^{8,9}

Anemia is twice as common in patients with T2DM as in non-diabetic patients and has been linked to end-stage renal and cardiovascular diseases (CVD).¹⁰ Moreover, patients with diabetes with lower hemoglobin levels are more likely to require hospitalization.¹¹ DM is considered to be the leading cause of chronic renal disease (CKD) in Western countries, and anemia as a frequent complication of CKD is occurring in almost half of patients with CKD.¹² However, DM is a risk factor for the development of anemia regardless of the presence of CKD, which is confirmed by the NHANES-III study, according to which patients with diabetes have a 1.7 times higher risk of anemia compared to individuals without diabetes with the same degree of renal damage functions.¹³ Anemia is also more frequent in patients with diabetes and normal kidney function and can occur even before the decline of renal function.^{14,15} Patients with diabetes have a higher risk and earlier occurrence of anemia¹⁶ compared to patients with the same degree of kidney damage from other etiologies.

Chronic diseases such as DM are often accompanied by mild to moderate normocytic, normochromic anemia, so this is also the case in patients without CKD. The mentioned type of anemia is considered an anemia of inflammation, and we also call it anemia of a chronic disease. Proinflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- α), and nuclear factor kappa-light-chain-enhancer of activated B cells (NF κ B) play an important role in its development, and hyperglycemia

is directly related to their increased expression. The above is also associated with other complications besides anemia, especially cardiovascular complications.¹⁷ The erythrocyte lifespan in anemia of chronic disease is reduced from 120 to 80 days. This is explained by the fact that the inflammatory process causes the mononuclear phagocytic system to become hyperactive, which causes the early evacuation of circulating red blood cells (RBCs) from the body. Moreover, a decreased bone marrow response to erythropoietin (EPO) and reduced erythropoiesis due to an inadequate iron supply all contribute to anemia.¹⁸

Systemic inflammation, inhibition of EPO release, damage to the renal interstitium, and severe autonomic neuropathy, which results in efferent sympathetic denervation of the kidney, affecting the production of EPO and RBCs, are some of the factors proposed as the cause of the earlier onset of anemia in patients with diabetes. Individuals diagnosed with T2DM often have deficiencies in iron, folate, and/or cyanocobalamin, which can lead to various forms of anemia. Certain medications, including metformin, might additionally hinder the absorption of cyanocobalamin, which could lead to a vitamin B12 deficit; however, research in this area has produced inconsistent findings.¹⁹

Although anemia is a common complication in patients with T2D, it is frequently overlooked and untreated. It can negatively impact the appearance and progression of other diabetes-related complications, which can accelerate the progression of anemia, leading to a vicious cycle.²⁰ In people with T2DM, anemia is considered a robust and independent predictor of an elevated risk for both macrovascular and microvascular complications associated with the disease and therefore must be considered when conducting routine examinations.¹⁶

Our study was intended to determine the type and frequency of anemia in individuals with T2DM and to investigate whether there are any differences regarding age, gender, and therapy used for T2DM treatment.

Respondents and methods

The research was organized as a cross-sectional study with historical data and was conducted in Osijek Health Center, in primary healthcare offices, from February 2022 to June 2022. The research was approved by the Ethics Committee of Osijek Faculty of Medicine, J.J. Strossmayer University in Osijek, and carried out according to the principles of the Declaration of Helsinki. Respondents gave written consent to participate in the research. Data was

collected through regular controls from the database "Central Health Information System of the Republic of Croatia" (CEZIH). The collected data is anonymous. During the research, the following data were collected from the available medical documentation: age, gender, duration of T2DM, the type of drugs used for the treatment of T2DM, the presence of diabetic nephropathy as a complication of diabetes, values of fasting plasma glucose, glycosylated hemoglobin A1c (HbA_{1c}), iron (Fe), unsaturated iron binding capacity (UIBC), total iron binding capacity (TIBC), hemoglobin (Hb), average volume of erythrocytes (MCV), mean erythrocyte hemoglobin (MCH) and mean erythrocyte hemoglobin concentration (MCHC). The value of TIBC was calculated by summing the values of Fe and UIBC. Anemia was defined by reduced hemoglobin values (Hb < 130 g/L for men and Hb < 120 g/L for women). Hemoglobin values were also used to determine the severity of anemia, so severe anemia was defined as Hg < 80 g/L, moderate anemia as hemoglobin values from 80 to 110 g/L, and mild anemia as Hg > 110 g/L.²¹ The values of MCV and MCHC were used for the morphological classification of anemia. Concerning the values of MCV, anemias were divided into macrocytic, in which the MCV is > 97.2, normocytic, with MCV between 83 and 97.2, and microcytic, in which the MCV is < 83. According to the values of MCHC, anemias were divided into hypochromic with MCHC < 320, normochromic with MCHC from 320 to 345, and hyperchromic with MCHC > 345. The etiological classification of anemia into sideropenic anemia, anemia of chronic disease, mixed anemia, anemia of chronic renal insufficiency, and non-specific anemia was also made. Iron values are reduced in sideropenic anemia, anemia of a chronic disease, and mixed anemia. To distinguish sideropenic anemias from the remaining two types, which are characterized by reduced iron values, iron-binding capacity values (UIBC, TIBC) were used. These values are elevated in sideropenic anemia, lowered in anemia of a chronic disease, and in mixed anemia they can be lowered or within the reference values. Transferrin saturation (TSAT) was calculated according to the formula: $TSAT = Fe/TIBC$ to differentiate between anemia of a chronic disease and mixed anemia. Therefore, anemia of chronic disease was determined by decreased iron and TIBC values and normal or slightly decreased TSAT, while in mixed anemia, iron values were decreased, TIBC was decreased or normal, and TSAT was significantly decreased ($TSAT < 10\%$).²² Normocytic or macrocytic anemia, with iron values within the reference intervals and in the presence of diabetic nephropathy, were classified

as anemias of chronic renal disease.²³ The remaining anemias in which no iron deficiency was observed were classified as non-specific anemias.

Categorical data were represented by absolute and relative frequencies. Differences in categorical data were tested with the χ^2 test and, if necessary, Fisher's exact test. The normality of the distribution of numerical variables was tested with the Shapiro-Wilk test. In the case of normal distributions, numerical variables were described by the arithmetic mean and standard deviation and, in other cases, by the median and the interquartile range. Differences of normally distributed numerical variables between two independent groups were tested by Student's t test. In the case of deviations from the normal distribution, the differences in numerical variables between independent groups were tested with the Mann-Whitney U test. All P values are two-sided. The significance level was set at Alpha = 0.05. For statistical analysis we used the statistical program MedCalc® Statistical Software version 20.109 (MedCalc Software Ltd, Ostend, Belgium; <https://www.medcalc.org>; 2022).

Results

Seventy-eight subjects (56% women) with T2DM participated in the research. The median age was 71 years, and 19% had anemia. The median value of HbA_{1c} was 6.95% with an interquartile range of 6.3 to 7.9%, while the median value of fasting blood glucose was 7.7 mmol/L with an interquartile range of 6.5 to 9.3 mmol/L. The median duration of diabetes in the subjects was 8 years. No statistically significant difference was observed in the occurrence of anemia regarding fasting plasma glucose values, HbA_{1c} values, and duration of diabetes (Table 1).

According to the morphological classification, the most common anemias were normocytic normochromic (36.84%) and microcytic hypochromic anemias (21.05%). Considering etiology, the most common were unspecified anemia and anemia of chronic disease in 47.37% of cases. All anemias were mild (46.67%) or moderate (53.33%).

Subjects with anemia were statistically significantly older than those without anemia (Mann-Whitney U test, P = 0.03) (Table 1).

Table 1 Characteristics of the respondents included in the research

Tablica 1. Osnovna obilježja ispitanika uključenih u istraživanje

	Type 2 diabetes/ Tip 2 šećerne bolesti	Subjects without anemia/ Ispitanici bez anemije	Subjects with anemia/ Ispitanici s anemijom	P*
Number of subjects (N, %)/ Broj ispitanika (N, %)	78 (100)	63 (81)	15 (19)	
Age (years)/ Dob (godine)	71 (59 - 78)	66 (59 - 77)	78 (70 - 82)	0,03 [†]
Duration of type 2 diabetes (years)/ Trajanje tipa 2 šećerne bolesti (godine)	8 (4 - 15)	8 (4 - 15)	10 (2,5 - 14,8)	0,97
HbA _{1c} (%)	6,95 (6,3 - 7,9)	7,1 (6,4 - 7,9)	6,5 (5,8 - 7,7)	0,24
Fasting plasma glucose (mmol/L)/ Glukoza u plazmi natašte (mmol/L)	7,7 (6,5 - 9,3)	7,7 (6,6 - 9,3)	7,7 (5,9 - 10,9)	0,89

*Mann-Whitney U test; Bold denotes statistical significance/Podebljano označava statističku značajnost

[†]at the P<0.05 level, higher values are significant in the group of subjects with anemia/†na razini P<0,05 značajne su više vrijednosti u skupini ispitanika s anemijom

Values: age, duration of type 2 diabetes, HbA_{1c} and fasting plasma glucose are expressed as median (interquartile range)/Vrijednosti: dob, trajanje šećerne bolesti tipa 2, HbA_{1c} i glukoze u plazmi natašte iskazane su kao medijan (interkvartilni raspon).

According to the morphological classification, certain types of anemia were also more common in the elderly, namely normocytic hypochromic (Mann-Whitney U test, P = 0.007) and normocytic normochromic anemias (Mann-Whitney U test, P = 0.04). Etiologically, mixed anemia occurred

statistically significantly more in elderly people (Mann-Whitney U test, P = 0.04), while no statistically significant difference in the severity of anemia was found depending on the age of the subjects.

Furthermore, 73.3% of patients with anemia were

women, and although microcytic hypochromic and normocytic normochromic anemia were more common in women, no statistically significant difference was observed in the occurrence of individual morphological types of anemia with regard to gender. Etiologically, all types of anemias were more common in women than in men. However, no statistically significant difference was observed in the occurrence of certain etiological forms of anemia, nor

in the severity of anemia with regard to gender.

55% of subjects in the study used monotherapy for the treatment of T2DM, while the rest used combined antidiabetic therapy, and 27% of them were treated with insulin therapy (Tables 2 and 3). No statistically significant difference was observed in the frequency of anemia among subjects on monotherapy and combined antidiabetic treatment.

Table 2 Types of therapy of type 2 diabetes in respondents included in the research

Tablica 2. Načini liječenja šećerne bolesti tipa 2 u ispitanika uključenih u istraživanje

	Number of subjects (N,%)/Broj ispitanika (N,%)	Total (N,%)/Ukupno (N,%)
Oral therapy/Peroralna terapija	57 (73)	
Insulin therapy/Inzulinska terapija	11 (14)	78 (100)
Combined insulin and oral therapy/Kombinirana inzulinska i peroralna terapija	10 (13)	
Combined therapy/Kombinirana terapija	35 (45)	78 (100)
Monotherapy/Monoterapija	43 (55)	

Table 3 Medicines used in the treatment of type 2 diabetes in respondents included in the research

Tablica 3. Lijekovi korišteni u liječenju šećerne bolesti tipa 2u ispitanika uključenih u istraživanje

	Monotherapy (N,%)/Monoterapija (N,%)	Combined with other therapy (N,%)/Kombinirano s drugom terapijom (N,%)	Total (N,%)/Ukupno (N,%)
Metformin/Metformin	28 (47)	32 (53)	60 (100)
Insulin therapy/Inzulinska terapija	11 (52)	10 (48)	21 (100)
Dipeptidyl peptidase IV Inhibitors /Inhibitori dipeptidil peptidaze IV	2 (7)	25 (93)	27 (100)
Sulfonylurea derivative/Derivati sulfonilureje	2 (25)	6 (75)	8 (100)
Glucagon-Like Peptide-1 Receptor Agonists/Glukagonu sličan peptid-1 receptor agonist	0 (0)	5 (100)	5 (100)
Sodium-glucose Cotransporter-2 Inhibitors/Inhibitori suprijenosnika natrija-glukoze 2	0 (0)	4 (100)	4 (100)

86% of the total number of subjects were treated with oral antidiabetic therapy, and 13% of them had anemia. Most of the subjects were treated with metformin and DPP-4 inhibitors. No statistically significant differences were found in the frequency of anemia depending on using certain types of oral

drugs, except in the case of sulfonylurea derivatives. The frequency of anemia was statistically significantly higher in subjects who used the mentioned drug (Fischer's exact test, $P = 0.01$). Subjects who used sulfonylurea derivatives were mostly treated with combined therapy that included

metformin if it was a dual therapy or metformin and DPP-4 inhibitors if it was a triple therapy. Anemia appeared significantly more often when combined therapy was used, which included sulfonylurea derivatives (Fischer's exact test, $P = 0.02$).

Furthermore, in patients treated with sulfonylurea derivatives, a statistically significant frequency of normocytic normochromic anemia (Fisher's exact test, $P = 0.03$) and non-specific anemia (Fisher's exact test, $P < 0.001$) was observed.

Considering the other therapy used for the treatment of T2DM and whether monotherapy or combined therapy was used in the treatment, no statistically significant differences were observed in the severity of anemia, morphological types of anemia, or etiology of anemia. In subjects treated with metformin, either in monotherapy or as part of combined therapy, no statistically significant differences were observed in the frequency or severity of anemia depending on the length of treatment with metformin. However, normocytic hypochromic anemia occurred statistically significantly more often in subjects in whom metformin was used as antidiabetic therapy for more than 10 years (Fisher's exact test, $P = 0.02$). Looking at the etiological cause of anemia, in subjects who used metformin in therapy for up to 5 years, anemia of chronic disease was statistically significantly more common (Fisher's exact test, $P = 0.04$), and in subjects who used metformin in therapy for longer than 10 years, mixed anemia (Fisher's exact test, $P = 0.02$).

Discussion

In the research that was carried out, the proportion of subjects with anemia, among those suffering from T2DM, was 19%, which is comparable to many other world studies conducted on a similar sample of subjects, with the proportion from 19 to 25%. Some studies showed that the frequency of anemia among patients with T2DM is more than 50%, and the higher incidence may depend on age groups, the severity of T2DM, or the presence of comorbidities in the subjects included in the research. A recent meta-analysis that included almost 20,000 subjects with T2DM worldwide showed that the incidence of anemia is around 27%, and this certainly indicates that anemia is an important public health problem for chronic patients whose health is already impaired by the primary disease, but also frequent complications and comorbidities.^{11,16}

The results show no cases of severe anemia in the subjects, but all could be characterized as mild or moderate, which is following other conducted research in which severe anemia in patients with

T2DM appeared only exceptionally.¹⁷ Furthermore, morphologically, normocytic normochromic anemia was the most prevalent, followed by microcytic hypochromic anemia, and other studies showed similar results.^{24,25} The high prevalence of mild to moderate normocytic anemia could be explained by the anemia of a chronic disease, which can occur in people with T2DM, as shown by other studies.¹⁷ In this study, a part of normocytic anemias could be characterized as anemia of chronic disease, taking into account the etiology, but a part of normocytic anemias due to an unclear etiological cause was recorded as unspecified anemia. The aforementioned is due to the main healthcare institution's laboratory's incapacity to measure additional indicators, like ferritin and TSAT, as part of the routine management of T2DM patients.

Our research did not show statistically significant differences in the frequency of anemias depending on fasting plasma glucose and HbA1c values, although previous studies have shown different results. In some studies, poor glycemic control was associated with a more frequent anemia, while other studies showed lower HbA1c values in people with anemia.^{26,27} Given that anemia resulting from iron deficiency raises HbA1c values regardless of how diabetes is regulated, it is highly likely that the outcomes vary depending on the type of anemia that manifests in subjects.²⁸ On the other hand, hemolytic anemias lead to a drop in HbA1c values due to a shorter life span of erythrocytes and, therefore, the disproportionality of HbA1c values with plasma glucose values.²⁹ Anemias of chronic disease are also known to have a slightly expressed hemolytic component, so they can also lead to lower HbA1c values. If the anemia is mild, its impact on the above values is negligible; nevertheless, if the anemia is severe, it is advisable to proceed with extra caution when interpreting the HbA1c figure, as an incorrect interpretation may result in insufficient diabetes management.³⁰

Furthermore, in our study, the average duration of T2DM in subjects was 11 years, which is in line with research showing that the duration of diabetes longer than 10 years is a risk factor for anemia.¹⁶ It is known that age is a risk factor for the development of anemia, so the results of our study, in which people with anemia and T2DM were significantly older than those without anemia, correspond to other studies conducted so far.³¹ In our analysis, several kinds of anemia—namely, normocytic hypochromic and normocytic normochromic anemia—were also more prevalent in the elderly. Etiologically, mixed anemia showed statistically significant increases in older people. In elderly individuals, normocytic anemia is

most likely the result of the interaction between sideropenic anemia and anemia of chronic disease. It is frequently a complex anemia of mixed multiple etiology, involving, in addition to the conditions listed above, age-dependent renal insufficiency, aging of hematopoietic cells, and androgen insufficiency that otherwise stimulates erythropoiesis, as well as other unavoidably occurring conditions of chronic inflammation.³²

Gastrointestinal symptoms, which can occur as side effects of using metformin, a drug that is still considered the first line of treatment for diabetes but is also used in many other conditions such as prediabetes, insulin resistance, polycystic ovary syndrome, can potentially lead to deficiency absorption of vitamin B12 and consequently the development of megaloblastic anemia.³³ In addition to being a consequence of using metformin therapy, the above can also occur in the case of malnutrition, alcoholism, and other diseases of the gastrointestinal system that inhibit the absorption of vitamin B12, but also in the case of the use of other drugs such as antacids, H₂ receptor antagonists, proton pump inhibitors and many others. Furthermore, the insufficiency of the mentioned vitamin is linked to certain age groups, so it is more common in people over 65 years of age, and it also occurs more often in pregnant women.^{33,34} Among the 60 patients treated with metformin in our study, 12 had anemia, most often normocytic normochromic. Anemia from a chronic condition was the most common cause in the subjects receiving monotherapy; in the remaining patients, the cause was unknown. In our investigation, we found two cases of macrocytic anemia, both treated with metformin; however, we did not find any evidence of a causal relationship between the metformin treatment and the development of the indicated anemia.

In this study, anemia was more common in the first 5 years of treatment with metformin and after 10 years of treatment, but no statistical significance was observed. However, some previous studies have shown that long-term use of metformin can be associated with vitamin B12 deficiency but also with the occurrence of anemia in general, which does not need to be related to the deficiency of vitamin B12.³⁵ Anemia of chronic disease appeared significantly more often in subjects treated with metformin in the first 5 years of treatment and mixed and normocytic hypochromic anemia in subjects in whom the treatment lasted longer than 10 years. It can be concluded that the anemias recorded in the group of subjects treated with metformin in our study are primarily the result of chronic disease and/or iron deficiency. At the same time, cobalamin insufficiency

may be only a secondary factor that contributed to the development. Nonetheless, new research examining the relationship between iron deficiency anemia and metformin use suggests that metformin may have a pleiotropic effect in individuals with T2DM. Specifically, the study demonstrated that metformin had a protective effect on these individuals and that the incidence of such anemia was lower in the group of people treated with metformin across all subgroups, with the protective effect being particularly noticeable in the subset of those over 65 years old.³⁶

In the conducted research, anemia appeared significantly more often in people treated with sulfonylurea derivatives, which is contrary to the results of the A Diabetes Outcome Progression Trial (ADOPT) and The UK Prospective Diabetes Study (UKPDS), which showed that treatment with metformin leads to a more significant decrease in hemoglobin compared to sulfonylurea.^{37,38} Anemias in subjects treated with sulfonylurea were more often normocytic normochromic, non-specific etiology, and mild. Research so far has shown that in the treatment of sulfonylurea derivatives, if anemia occurs, it is mild mainly.³⁹ Aplastic anemia, hemolytic anemia, anemia from acute blood loss, anemia linked to complications like infections, and hemolytic or microangiopathic anemias, in which there is an increased production of erythrocytes, can all be considered differential diagnostic causes of anemia in unspecified anemia in patients treated with sulfonylurea derivatives. Anemia resulting from chronic kidney disease would also be considered in the differential diagnosis; however, as chronic kidney disease was not present in our participants receiving therapy with sulfonylurea derivatives and who had documented anemia, it is ruled out as a possible cause.

Conclusion

Based on the conducted research, it can be concluded that anemia is common in people with T2DM, and in this study, it was recorded in as many as 19% of the total number of subjects and characterized as mild or moderate anemia. Normocytic normochromic anemia is the most common morphological form of anemia, and etiologically, non-specific anemia of chronic disease prevails. The incidence of anemia was higher in older adults, and normocytic normochromic and hypochromic anemia occurred more often in these subjects, while mixed anemia was the most common one regarding etiology. The frequency of anemia did not depend on the gender of the subjects or whether monotherapy or combined therapy was used in the

treatment of T2DM. People who used sulfonylurea derivatives, either as monotherapy or in combination with other therapy, had a higher incidence of anemia, which was characterized as mild, non-specific, normocytic normochromic anemia. Anemia of chronic disease is significantly more common in the first 5 years of metformin used in the treatment of T2DM, while after 10 years of treatment, mixed anemia, morphologically normocytic hypochromic, is the most common. In conclusion, we can say that due to the high incidence of anemia in patients with T2DM, it is necessary to carry out regular screening as part of regular controls, especially in older adults with micro or macroalbuminuria, poor disease control, and reduced transferrin saturation as and in patients treated with sulfonylurea derivatives. Screening is essential at the level of primary health care, with the aim of starting treatment and correcting therapy as early as possible.

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The efficacy and safety of the intracoronary stents at patients with acute stemi: a meta-analysis and systematic review

Učinkovitost i sigurnost intrakoronarnih stentova u bolesnika s akutnim stemi: meta-analiza i sustavni pregled

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Summary

Introduction: This meta-analysis investigates and reevaluates the efficacy and safety of various intracoronary stents after acute ST-elevation myocardial infarction (STEMI).

Methods: PubMed/ScienceDirect databases were systematically searched for Randomized Controlled Trials (RCTs) with outcomes after acute STEMI in relation to stent type. During follow-up, the efficacy outcomes were target lesion revascularization (TLR) and target vessel revascularization (TVR), while the safety outcomes were overall death, cardiac death, myocardial infarction, total in-stent thrombosis (IST) and major adverse cardiovascular events/target vessel failure (MACE/TVF) (the composite of overall/cardiac death, myocardial infarction, TLR and TVR). Stents were classified as bare-metal stent (BMS), drug-eluting stent of the first (DES^{1st}) and second-generation (DES^{2nd}), and biodegradable polymer DES (BP-DES).

Results: We included 31 RCTs, with 17,010 participants (74.6% males), with an average age of 61.2 years. During the average 35-month follow-up, DES are preferred over BMS in reducing the risk of TLR (odds ratio (OR) = 0.47, confidence interval (CI) [0.41-0.54]), TVR (OR = 0.54, CI [0.47-0.61]), overall death (OR = 0.85, CI [0.74-0.99]) and MACE/TVF (OR = 0.61, CI [0.55-0.68]); DES^{2nd} are preferred over DES^{1st} in reducing the risk of myocardial infarction (OR = 0.61, CI [0.39-0.96]), IST (OR = 0.41, CI [0.22-0.73]) and MACE/TVF (OR = 0.70, CI [0.54-0.90]); and, BP-DES are preferred over DES^{2nd} in reducing the risk of TLR (OR = 0.55, CI [0.35-0.86]) and IST (OR = 0.56, CI [0.33-0.96]) (for all $P < 0.05$).

Conclusion: After acute STEMI, DES are superior to BMS in efficacy and safety, DES^{2nd} to DES^{1st} in safety, and BP-DES to DES^{2nd} in efficacy and safety.

Keywords: stents; acute ST-elevation myocardial infarction; outcomes.

Sažetak

Uvod: Ova meta-analiza istražuje i reevaluira učinkovitost i sigurnost različitih intrakoronarnih stentova nakon akutnog infarkta miokarda sa ST-elevacijom (STEMI).

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Metode: Sustavno su pretražene baze podataka PubMed/ScienceDirect za randomizirana kontrolirana ispitivanja (RCT) s ishodima nakon akutnog STEMI u odnosu na vrstu stenta. Tijekom praćenja, ishodi učinkovitosti bili su revaskularizacija ciljne lezije (TLR) i revaskularizacija ciljne žile (TVR), dok su sigurnosni ishodi bili ukupna smrt, srčana smrt, infarkt miokarda, ukupna tromboza u stentu (IST) i glavni štetni kardiovaskularni događaji/zatajenje ciljne žile (MACE/TVF) (kompozit ukupne/srčane smrti, infarkta miokarda, TLR i TVR). Stentovi su klasificirani kao metalni stent (BMS), stent s lijekom prve (DES^{1gen}) i druge generacije (DES^{2gen}) te biorazgradivi polimerni DES (BP-DES).

Rezultati: Uključili smo 31 RCT sa 17.010 sudionika (74,6% muškaraca), prosječne starosti 61,2 godine. Tijekom prosječnog 35-mjesečnog praćenja, DES ima prednost u odnosu na BMS u smanjenju rizika od TLR (omjer izgleda (OR) = 0,47, interval pouzdanosti (CI) [0,41-0,54]), TVR (OR = 0,54, CI [0,47-0,61]), ukupne smrti (OR = 0,85, CI [0,74-0,99]) i MACE/TVF (OR = 0,61, CI [0,55-0,68]); DES^{2gen} imaju prednost u odnosu na DES^{1gen} u smanjenju rizika od infarkta miokarda (OR = 0,61, CI [0,39-0,96]), IST (OR = 0,41, CI [0,22-0,73]) i MACE/TVF (OR = 0,70, CI [0,54-0,90]), dok BP-DES imaju prednost u odnosu na DES^{2gen} u smanjenju rizika od TLR (OR = 0,55, CI [0,35-0,86]) i IST (OR = 0,56, CI [0,33-0,96]) (za sve P<0,05).

Zaključak: Nakon akutnog STEMI-a, DES je superiorniji od BMS-a u djelotvornosti i sigurnosti, DES^{2gen} od DES^{1gen} u sigurnosti, a BP-DES od DES^{2gen} u djelotvornosti i sigurnosti.

Ključne riječi: stentovi; akutni infarkt miokarda sa ST-elevacijom; ishodi.

Introduction

Primary percutaneous coronary intervention (PCI) is the treatment of choice in patients with acute ST-segment elevation myocardial infarction (STEMI).¹ In contrast to subjects with chronic coronary or non-ST-elevation acute coronary syndrome, patients presenting with STEMI carry the highest risk of early and late adverse events after PCI due to heightened platelet activation and the presence of thrombus.²⁻⁴ Due to plaque vulnerability, high clot burden, and persistent inflammation, STEMI patients are predisposed to delayed healing and positive vessel remodeling, which results in high rates of uncovered stent struts and stent malapposition.⁵ As a consequence, the risk of stent thrombosis in STEMI patients is the highest among coronary artery disease patients.^{2,6}

Compared to angioplasty, bare-metal stents (BMS) have shown the benefit in reducing the risk of reocclusion of the ischemia-related artery and the need for repeated revascularization.⁷ But, the main limitation of these devices is in-stent thrombosis (IST), which is present in more than 20% of subjects with STEMI.⁸

According to the current guidelines, a new generation of drug-eluting stents (DES) are preferred over BMS (Class of Recommendation I, Level of Evidence: A).¹ A new DES generation, with more biocompatible durable polymers or biodegradable polymers, were developed to reduce the increased risk of stent thrombosis observed with first-generation DES (DES^{1st}).

In the STEMI population, biolimus biodegradable polymer DES (BP-DES) has shown improved clinical outcomes compared with BMS and DES^{1st}.^{9,10} The

high lipophilicity of biolimus may facilitate rapid drug distribution and potentiate local drug effects in lipidic lesions in patients with STEMI.¹¹

Conversely, the safety of BP-DES compared with durable polymer DES has been questioned in several meta-analyses.^{12,13}

This meta-analysis aimed to investigate and reevaluate the safety and efficacy of different generations of stents in patients with acute STEMI treated with primary PCI.

Methods

Data sources

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and MetaAnalyses (PRISMA) statement.¹³

PubMed and ScienceDirect databases were systematically searched for studies (Randomized Controlled Trials, RCTs) that reported adverse outcomes in relation to stent type in patients with acute STEMI. Multiple queries using the following keywords were performed: drug-eluting stent or bare-metal stent or biodegradable stent or bioresorbable stent or durable stent or uncoated stent or everolimus eluting stent or zotarolimus-eluting stent or sirolimus eluting stent or paclitaxel eluting stent and ST segment elevation myocardial infarction or ST segment elevation acute coronary syndrome or STEMI and primary PCI.

Eligibility criteria

Studies fulfilling the eligibility criteria were included in the analysis. The selection process was performed according to the PRISMA statement

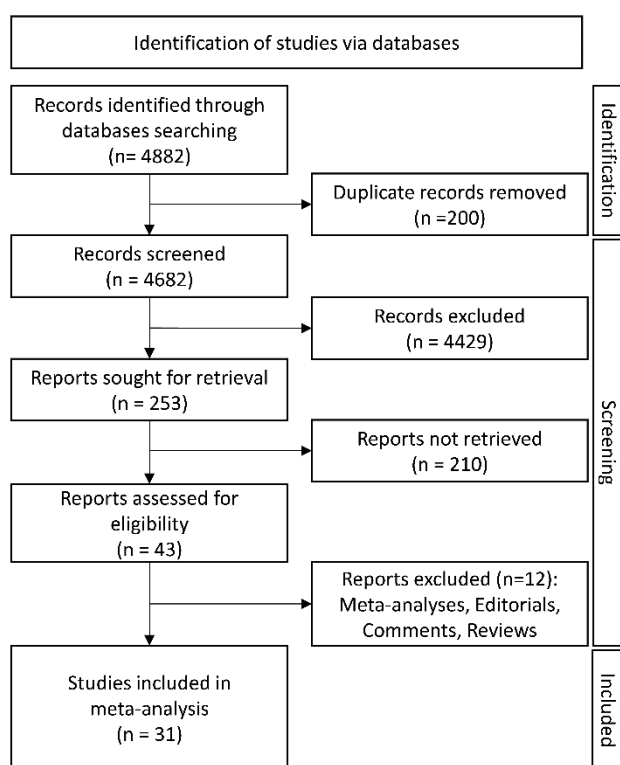
(Figure 1).¹⁴

Figure 1 Flow diagram of the study (according to the PRISMA* statement).

Slika 1. Dijagram toka studije (prema izjavi PRISMA*).

*PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

PRISMA, Preferirane stavke izvještavanja za sustavne preglede i meta-analize.

In brief, eligible studies had to meet the following criteria: (1) RCTs; (2) included only patients with acute STEMI; (3) related to the association between stents type and outcomes; (4) minimum 6-month follow-up; (5) published in English or other language which can be translated for the purpose of sufficient data extraction. The range of time for the years of the included studies was not limited. Studies were excluded if they were abstracts, editorials, comments, other meta-analyses, or literature reviews. The titles and abstracts of the retrieved studies were screened independently according to the above criteria by two researchers. The full texts of the potentially relevant studies were then obtained and strictly assessed. Disagreements were resolved by discussion with the other researchers.

Data extraction and synthesis

Data extraction was conducted by two researchers separately. Discrepancies were resolved by discussion with the other researchers. The following

data were extracted from each eligible study: the first author or the name of the RCT, the enrollment period, the study population, stent type, symptom-to-balloon time, dual antiplatelet treatment (DAPT) duration, GP IIb/IIIa treatment, and follow-up maximum duration. During follow-up, the efficacy outcomes were target lesion revascularization (TLR) and target vessel revascularization (TVR), while the safety outcomes included overall death, cardiac death, myocardial infarction, total IST (probable/definite) and major adverse cardiovascular events/target vessel failure (MACE/TVF) (the composite of overall/cardiac death, myocardial infarction, TLR, and TVR). Stents were classified as follows:

- a) BMS;
- b) DES^{1st} (sirolimus/paclitaxel (SES/PES)) and second-generation (DES^{2nd}) (everolimus/zotarolimus (EES/ZES)); and,
- c) BP-DES.

Statistical analysis

A meta-analysis was performed to calculate the odds ratio (OR) and associated 95% confidence interval [CI]. The I-squared statistic test was used to test for the heterogeneity across studies. If no evidence of heterogeneity was presented (I-squared<50%, $P>0.05$), a fixed effect model was used. Otherwise, a random effect model was adopted. The publication bias was evaluated by funnel plots and the Egger's linear regression test, which was considered positive in case of $P<0.05$. For comparison between the groups, we used a chi-squared test with values presented as the absolute number and percentage. The probability value $P<0.05$ was considered statistically significant. All statistical analyses were performed using MedCalc software (12.7.0.0. for Windows).

Results

Study characteristics

We identified 4,882 studies through the Pubmed and ScienceDirect databases (Figure 1); after screening and exclusion, this meta-analysis finally included 31 studies (RCTs)¹⁵⁻⁴⁵ enrolled in the period 2002-2018 (10 single-center), with 17,010 participants (74.6% males), average aged 61.2 years; 21 studies investigated various relationships between DES and BMS, four studies among DES^{1st} generation, six studies between DES^{2nd} and DES^{1st}, and two studies between BP-DES and DES devices. Other RCTs characteristics are presented in Table 1. The average follow-up duration was 35 months.

Table 1 The list of RCT's* which evaluate the efficacy and safety according to stent type during 35-month follow-up after acute STEMI (31 studies, 17,010 patients)
 Tablica 1. Popis RCT-ova* koji procjenjuju učinkovitost i sigurnost prema vrsti stenta tijekom 35-mjesečnog praćenja nakon akutnog STEMI-a (31 studija, 17.010 bolesnika)

Author/Trial <i>Autor/Pokus</i>	Enrollment period <i>Razdoblje upisa</i>	Design <i>Dizajn</i>	Patients <i>Bolesnici</i>	Age (years) <i>Starost</i>	Males (%) <i>Muškarci</i>	Stents <i>Stentovi</i>	Symptom-to-balloon <i>Simptom do balona</i>	DAPT (months) <i>mjeseci</i>	GP IIB/IIIa (%)	Efficacy and safety outcomes of the interest [#] <i>Ishodi učinkovitosti i sigurnosti od interesa[#]</i>	Follow-up (months) <i>Pregled (mjeseci)</i>
BASKET [15], 2009	2002-2003	Single-center, RCT, superiority <i>Jednocentrično, RCT, superiornost</i>	210	62.1	80.0	DES ^{1st} (SES, PES) <i>vrs</i> BMS	-	6	-	IST, death, myocardial infarction <i>IST, smrt, infarkt miokarda</i>	36
BIOSTEMI [16], 2023	2016-2018	Multicenter, RCT, superiority <i>Multicentrično, RCT, superiornost</i>	1300	62.7	76.0	BP-DES <i>vrs</i> DES ^{2nd} (EES)	-	≥12	-	TVF (the composite of cardiac death, myocardial infarction, TVR), overall/cardiac death, myocardial infarction, TLR, TVR, IST <i>TVF (kompozitni pokazatelj srčane smrti, infarkta miokarda, TVR), ukupna/srčana smrt, infarkt miokarda, TLR, TVR, IST</i>	60
COMFORTABLE-AMI [17], 2019	2009-2011	Multicenter, RCT, superiority <i>Multicentrično, RCT, superiornost</i>	1157	60.6	79.4	BP-DES <i>vrs</i> BMS	<12h	≥12	48.0 <i>vrs</i> 45.7	MACE (the composite of cardiac death, myocardial infarction and TLR), overall/cardiac death, myocardial infarction, TLR, TVR, IST <i>MACE (kompozitni pokazatelj srčane smrti, infarkta miokarda, TVR), ukupna/srčana smrt, infarkt miokarda, TLR, TVR, IST</i>	60
COMPARE [18], USPOREDBA 2012	2007-2008	Single-center, RCT, superiority <i>Jednocentrično,</i>	452	-	-	DES ^{2nd} (EES) <i>vrs</i>	-	12	-	MACE (the composite of overall death, myocardial infarction and TVR),	24

Author/Trial <i>Autor/Pokus</i>	Enrollment period <i>Razdoblje upisa</i>	Design <i>Dizajn</i>	Patients <i>Bolesnici</i>	Age (years) <i>Starost</i>	Males (%) <i>Muškarci</i>	Stents <i>Stentovi</i>	Symptom- to-balloon <i>Simptom do balona</i>	DAPT (months) <i>mjeseci</i>	GP IIb/IIIa (%)	Efficacy and safety outcomes of the interest [#] <i>Ishodi učinkovitosti i sigurnosti od interesa[#]</i>	Follow- up (months) <i>Pregled (mjeseci)</i>
		<i>RCT, superiornost</i>				DES ^{1st} (PES)				overall/cardiac death, myocardial infarction, TLR, TVR, IST <i>MACE (kompozitni pokazatelj srčane smrti, infarkta miokarda, TVR), ukupna/srčana smrt, infarkt miokarda, TLR, TVR, IST</i>	
DEBATER [19], 2012 <i>DEBATAR</i>	2006-2008	Single-center, RCT, superiority <i>Jednocentrično, RCT, superiornost</i>	907	60.5	76.5	DES ^{1st} (SES) <i>vrs</i> BMS	<12h	≥1 for BMS and ≥6-12 for DES	54 <i>vrs</i> 55	MACE (the composite of death, myocardial infarction, stroke, repeat revascularization, and bleeding), overall death, TVR, IST <i>MACE (kombinacija smrti, infarkta miokarda, moždanog udara, ponovljene revaskularizacije i krvarenja), ukupna smrt, TVR, IST</i>	12
DEDICATION [20], 2013 <i>POSVETA</i>	2005-2006	Multicenter, RCT, superiority <i>Multicentrično, RCT, superiornost</i>	626	62.5	73.5	DES ^{1st} (SES, PES) and DES ^{2nd} (ZES) <i>vrs</i> BMS	<12h	12	97 <i>vrs</i> 96	MACE (the composite of cardiac death, myocardial infarction and TLR), overall/cardiac death, myocardial infarction, TLR, TVR, IST <i>MACE (kompozitni pokazatelj srčane smrti, infarkta miokarda, TVR), ukupna/srčana smrt, infarkt miokarda, TLR, TVR, IST</i>	60
Diaz et al. [21], 2007	2004-2006	Single-center, RCT, superiority <i>Jednocentrično,</i>	114	64.5	79.2	DES ^{1st} (SES) <i>vrs</i>	<12h	≥1 for BMS and ≥9 for	100 <i>vrs</i> 100	MACE (the composite of cardiac death, myocardial infarction and TLR), cardiac	12

Author/Trial <i>Autor/Pokus</i>	Enrollment period <i>Razdoblje upisa</i>	Design <i>Dizajn</i>	Patients <i>Bolesnici</i>	Age (years) <i>Starost</i>	Males (%) <i>Muškarci</i>	Stents <i>Stentovi</i>	Symptom- to-balloon <i>Simptom do balona</i>	DAPT (months) <i>mjeseci</i>	GP IIb/IIIa (%)	Efficacy and safety outcomes of the interest [#] <i>Ishodi učinkovitosti i sigurnosti od interesa[#]</i>	Follow- up (months) <i>Pregled (mjeseci)</i>
		<i>RCT, superiornost</i>				BMS		DES		death, IST, TLR <i>MACE (kompozitni pokazatelj srčane smrti, infarkta miokarda i TLR-a), srčana smrt, IST, TLR</i>	
EXAMINATION- EXTEND [22], 2021 <i>PRODUŽETAK ISPITIVANJA</i>	2008-2010	Multicenter, RCT, superiority <i>Multicentrično, RCT, superiornost</i>	1498	61.2	82.6	DES ^{2nd} (EES) <i>vrs</i> BMS	<1 2h	12	53.3 <i>vrs</i> 51.5	MACE (the composite of all- cause death, myocardial infarction, revascularization), overall/cardiac death, myocardial infarction, TLR, TVR, IST <i>MACE (kompozitni pokazatelj srčane smrti, infarkta miokarda, TVR), ukupna/srčana smrt, infarkt miokarda, TLR, TVR, IST</i>	120
Gao et al. [23], 2007	January 2005- December 2005	Single-center, RCT, superiority <i>Jednocentrično, RCT, superiornost</i>	156	58.8	80.8	DES ^{1st} (SES) <i>vrs</i> BMS	-	9-12	-	MACE (the composite of overall death, myocardial infarction, TLR, TVR, IST), overall death, TVR <i>MACE (kompozitni pokazatelj ukupne smrti, infarkta miokarda, TLR-a, TVR-a, IST- a), ukupna smrt, TVR</i>	6
HORIZONS-AMI [24], 2010	2005-2007	Multicenter, RCT, superiority <i>Multicentrično, RCT, superiornost</i>	3006	59.6	76.5	DES ^{1st} (PES) <i>vrs</i> BMS	<12h	≥6	52.0 <i>vrs</i> 51.5	MACE (the composite of death, myocardial infarction, stroke, IST), overall/cardiac death, myocardial infarction, TLR, TVR, IST <i>MACE (kompozitni pokazatelj srčane smrti, infarkta miokarda, TVR), ukupna/srčana smrt, infarkt</i>	24

Author/Trial <i>Autor/Pokus</i>	Enrollment period <i>Razdoblje upisa</i>	Design <i>Dizajn</i>	Patients <i>Bolesnici</i>	Age (years) <i>Starost</i>	Males (%) <i>Muškarci</i>	Stents <i>Stentovi</i>	Symptom-to-balloon <i>Simptom do balona</i>	DAPT (months) <i>mjeseci</i>	GP IIb/IIIa (%)	Efficacy and safety outcomes of the interest [#] <i>Ishodi učinkovitosti i sigurnosti od interesa[#]</i>	Follow-up (months) <i>Pregled (mjeseci)</i>
<i>miokarda, TLR, TVR, IST</i>											
Juwana et al. [25], 2009	2005-2007	Single-center, RCT, superiority <i>Jednocentrično, RCT, superiornost</i>	397	61.0	72.0	DES ^{1st} (PES) <i>vrs</i> DES ^{1st} (SES)	-	≥6	33 <i>vrs</i> 28	MACE (the composite of overall death, myocardial infarction, TVR), overall death, myocardial infarction, TVR, IST <i>MACE (kompozitni pokazatelj srčane smrti, infarkta miokarda, TVR), ukupna/srčana smrt, infarkt miokarda, TLR, TVR, IST</i>	12
KOMER-AMI [26], 2011	2006-2008	Multicenter, RCT, superiority <i>Multicentrično, RCT, superiornost</i>	611	59.8	78.9	DES ^{1st} (PES) <i>vrs</i> DES ^{1st} (SES) <i>vrs</i> DES ^{2nd} (ZES)	-	12	-	MACE (the composite of cardiac death, myocardial infarction and TLR), IST <i>MACE (kombinacija srčane smrti, infarkta miokarda i TLR-a), IST</i>	18
MASTER [27], 2019	2013-2015	Multicenter, RCT, superiority <i>Multicentrično, RCT, superiornost</i>	500	61.0	80.6	DES ^{1st} (SES) <i>vrs</i> BMS	<12h	-	26.1 <i>vrs</i> 18.2	TVF (the composite of cardiac death, myocardial infarction, and TVR), all-cause/cardiac death, myocardial infarction, TLR, TVR, IST <i>TVF (kompozit srčane smrti, infarkta miokarda i TVR-a), smrt od svih uzroka/srčana smrt, infarkt miokarda, TLR, TVR, IST</i>	12
MISSION [28], 2012	2004-2006	Single-center, RCT, superiority <i>Jednocentrično,</i>	310	59.2	77.8	DES ^{1st} (SES) <i>vrs</i>	<12h	12	100 <i>vrs</i> 100	TVF (the composite of cardiac death, myocardial infarction, TVR), overall/cardiac death,	60

Author/Trial <i>Autor/Pokus</i>	Enrollment period <i>Razdoblje upisa</i>	Design <i>Dizajn</i>	Patients <i>Bolesnici</i>	Age (years) <i>Starost</i>	Males (%) <i>Muškarci</i>	Stents <i>Stentovi</i>	Symptom- to-balloon <i>Simptom do balona</i>	DAPT (months) <i>mjeseci</i>	GP IIb/IIIa (%)	Efficacy and safety outcomes of the interest [#] <i>Ishodi učinkovitosti i sigurnosti od interesa[#]</i>	Follow- up (months) <i>Pregled (mjeseci)</i>
		<i>RCT, superiornost</i>				BMS				myocardial infarction, TLR, TVR, IST <i>TVF (kompozitni pokazatelj srčane smrti, infarkta miokarda, TVR), ukupna/srčana smrt, infarkt miokarda, TLR, TVR, IST</i>	
MULTI- STRATEGY [29,30], 2008/2013	2004-2007	Multicenter, RCT, superiority <i>Multicentrično, RCT, superiornost</i>	744/736	63.9	75.9	DES ^{1st} (SES) <i>vrs</i> BMS	<12h	≥3	100 <i>vrs</i> 100	MACE (the composite of overall death, myocardial infarction and TVR), overall death, myocardial infarction, TLR, TVR, IST <i>MACE (kompozitni pokazatelj ukupne smrti, infarkta miokarda i TVR-a), ukupna smrt, infarkt miokarda, TLR, TVR, IST</i>	36
PASEO [31], 2009	2003-2005	Single-center, RCT, superiority <i>Jednocentrično, RCT, superiornost</i>	270	62.3	70.4	DES ^{1st} (SES) <i>vrs</i> DES ^{1st} (PES) <i>vrs</i> BMS	<12h	6	100 <i>vrs</i> 100 <i>vrs</i> 100	MACE (the composite of death, myocardial infarction and TLR), myocardial infarction, TLR, IST, cardiac death <i>MACE (kompozit smrti, infarkta miokarda i TLR-a), infarkt miokarda, TLR, IST, srčana smrt</i>	24
PASSION [32,33], 2006/2011	2003-2004	Multicenter, RCT, superiority <i>Multicentrično, RCT, superiornost</i>	619	61.0	76.0	DES ^{1st} (PES) <i>vrs</i> BMS	<12h	≥6	73.2 <i>vrs</i> 74.4	MACE (the composite of cardiac death, myocardial infarction, TLR), overall/cardiac death, myocardial infarction, IST, TLR <i>MACE (kompozit smrti,</i>	60

Author/Trial <i>Autor/Pokus</i>	Enrollment period <i>Razdoblje upisa</i>	Design <i>Dizajn</i>	Patients <i>Bolesnici</i>	Age (years) <i>Starost</i>	Males (%) <i>Muškarci</i>	Stents <i>Stentovi</i>	Symptom-to-balloon <i>Simptom do balona</i>	DAPT (months) <i>mjeseci</i>	GP IIb/IIIa (%)	Efficacy and safety outcomes of the interest [#] <i>Ishodi učinkovitosti i sigurnosti od interesa[#]</i>	Follow-up (months) <i>Pregled (mjeseci)</i>
										<i>infarkta miokarda i TLR-), ukupna smrt, infarkt miokarda, IST, TLR, TVR</i>	
RACES-MI [34], 2016	2007-2009	Single-center, RCT, superiority <i>Jednocentrično, RCT, superiornost</i>	500	59.0	64.8	DES ^{2nd} (EES) <i>vrs</i> DES ^{1st} (SES)		≥12	54.4 <i>vrs</i> 42.4	MACE (the composite cardiac death, myocardial infarction, IST, TVR), cardiac death, myocardial infarction, TVR, IST <i>MACE (kompozit smrti, infarkta miokarda i TLR), ukupna smrt, infarkt miokarda, IST, TLR, TVR</i>	84
RESOLVE [35], 2014	2005-2010	Multicenter, RCT, superiority <i>Multicentrično, RCT, superiornost</i>	1,271	64.0	79.1	BP-DES <i>vrs</i> DES ^{1st} (SES)	<12h	≥12	76.0 <i>vrs</i> 74.0	MACE (the composite of all-cause death, myocardial infarction, TLR), overall/cardiac death, myocardial infarction, TLR, IST <i>MACE (kompozitni pokazatelj srčane smrti, infarkta miokarda, TVR), ukupna/srčana smrt, infarkt miokarda, TLR, TVR, IST</i>	12
SELECTION [36], 2007	2004-2005	Multicenter, RCT, superiority <i>Multicentrično, RCT, superiornost</i>	80	60.7	82.5	DES ^{1st} (PES) <i>vrs</i> BMS	<12h	9	100 <i>vrs</i> 100	MACE (the composite of death, myocardial infarction and TLR), overall death, myocardial infarction, IST, TLR, TVR <i>MACE (kompozit smrti, infarkta miokarda i TLR-a), ukupna smrt, infarkt miokarda, IST, TLR, TVR</i>	7

Author/Trial <i>Autor/Pokus</i>	Enrollment period <i>Razdoblje upisa</i>	Design <i>Dizajn</i>	Patients <i>Bolesnici</i>	Age (years) <i>Starost</i>	Males (%) <i>Muškarci</i>	Stents <i>Stentovi</i>	Symptom- to-balloon <i>Simptom do balona</i>	DAPT (months) <i>mjeseci</i>	GP IIb/IIIa (%)	Efficacy and safety outcomes of the interest [#] <i>Ishodi učinkovitosti i sigurnosti od interesa[#]</i>	Follow- up (months) <i>Pregled (mjeseci)</i>
SESAMI [37], 2010	2003-2006	Single-center, RCT, superiority <i>Jednocentrično, RCT, superiornost</i>	320	62.5	80.0	DES ^{1st} (SES) <i>vrs</i> BMS	<12h	-	77.4 <i>vrs</i> 73.7	MACE (the composite of death, myocardial infarction, CABG, and TLR), death, TLR, TVR and TVF (the composite of TVR, myocardial infarction and cardiac death), IST <i>MACE (kompozit smrti, infarkta miokarda, CABG-a i TLR-a), smrt, TLR, TVR i TVF (kompozit TVR-a, infarkta miokarda i srčane smrti), IST</i>	36
SEZE [38], 2012	2007-2009	Multicenter, RCT, superiority <i>Multicentrično, RCT, superiornost</i>	122	60.9	80.9	DES ^{2nd} (ZES) <i>vrs</i> DES ^{1st} (SES)	<12h	≥12	11.7 <i>vrs</i> 13.1	MACE (the composite of cardiac death, myocardial infarction, TVR), overall/cardiac death, myocardial infarction, TLR, TVR, IST <i>MACE (kompozitni pokazatelj srčane smrti, infarkta miokarda, TVR), ukupna/srčana smrt, infarkt miokarda, TLR, TVR, IST</i>	12
STRATEGY [39- 41], 2005/2007/ 2009	2003-2004	Multicenter, RCT, superiority <i>Multicentrično, RCT, superiornost</i>	175	62.5	73	DES ^{1st} (SES) <i>vrs</i> BMS	-	≥3	100 <i>vrs</i> 100	MACE (the composite of death, myocardial infarction, stroke and TLR), death, myocardial infarction, TLR, TVR, IST <i>MACE (kompozit smrti, infarkta miokarda, moždanog udara i TLR smrt, infarkt miokarda, TLR, TVR, IST</i>	60
TYPHOON [42,43],	2003-2005	Multicenter,	712	59.3	78.4	DES ^{1st}	<12h	≥6	69.3	TVF (the composite of cardiac	48

Author/Trial <i>Autor/Pokus</i>	Enrollment period <i>Razdoblje upisa</i>	Design <i>Dizajn</i>	Patients <i>Bolesnici</i>	Age (years) <i>Starost</i>	Males (%) <i>Muškarci</i>	Stents <i>Stentovi</i>	Symptom-to-balloon <i>Simptom do balona</i>	DAPT (months) <i>mjeseci</i>	GP IIb/IIIa (%)	Efficacy and safety outcomes of the interest [#] <i>Ishodi učinkovitosti i sigurnosti od interesa[#]</i>	Follow-up (months) <i>Pregled (mjeseci)</i>
2006/2011		RCT, superiority <i>Multicentrično, RCT, superiornost</i>				(SES) <i>vrs</i> BMS			<i>vrs</i> 73.7	death, myocardial infarction, TVR), overall/cardiac death, myocardial infarction, IST, TLR, TVR <i>TVF (kompozitni pokazatelj srčane smrti, infarkta miokarda, TVR), ukupna/srčana smrt, infarkt miokarda, TLR, TVR, IST</i>	
XAMI [44], 2012	2008-2009	Multicenter, RCT, superiority <i>Multicentrično, RCT, superiornost</i>	625	61.6	74.1	DES ^{2nd} (EES) <i>vrs</i> DES ^{1st} (SES)	<12h	≥12	74.5 <i>vrs</i> 77.8	MACE (the composite of cardiac death, myocardial infarction, TVR), overall/cardiac death, myocardial infarction, TLR, TVR, IST <i>MACE (kompozitni pokazatelj srčane smrti, infarkta miokarda, TVR), ukupna/srčana smrt, infarkt miokarda, TLR, TVR, IST</i>	12
ZEST-AMI [45], 2009	2006-2007	Multicenter, RCT, superiority <i>Multicentrično, RCT, superiornost</i>	328	59.6	82.3	DES ^{2nd} (ZES) <i>vrs</i> DES ^{1st} (SES) <i>vrs</i> DES ^{1st} (PES)	<12h	≥12	18.5 <i>vrs</i> 20.9 <i>vrs</i> 20.0	MACE (the composite of overall death, myocardial infarction and TVR), overall/cardiac death, TVR, IST <i>MACE (kompozitni pokazatelj ukupne smrti, infarkta miokarda i TVR-a), ukupna/srčana smrt, TVR, IST</i>	12

*Abbreviations: BMS, bare-metal stent; BP-DES, biodegradable polymer drug-eluting stent; EES, everolimus-eluting stent; IST, in-stent thrombosis; MACE, major adverse cardiovascular events; PES, paclitaxel-eluting stent; RCT, randomized controlled trial; SES, sirolimus-eluting stent; STEMI, ST-elevation myocardial infarction; TLF, target lesion failure; TLR, target lesion revascularization; TVF, Target vessel failure; TVR, target vessel revascularization; ZES, zotarolimus-eluting stent. Kratice: BMS, stent od golog metala; BP-DES, biorazgradivi polimerni stent koji otpušta lijek; EES, stent koji otpušta everolimus; IST, tromboza u stentu; MACE, veći štetni kardiovaskularni događaji; PES, stent koji otpušta paklitaksel; RCT, randomizirano kontrolirano ispitivanje; SES, stent koji otpušta sirolimus; STEMI, infarkt miokarda s elevacijom ST linije; TLF, neuspjeh ciljne lezije; TLR, revaskularizacija ciljne lezije; TVF, neuspjeh ciljne žile; TVR, revaskularizacija ciljne žile; ZES, stent koji otpušta zotarolimus #Efficacy parameters: TLR and TVR. Safety parameters: myocardial infarction, IST, overall death, cardiac death, MACE/TVF. #Parametri učinkovitosti: TLR i TVR. Parametri sigurnosti: infarkt miokarda, IST, ukupna smrt, smrt od srčanih bolesti, MACE/TVF.

Study results

- a) Myocardial infarction: DES were not superior to BMS (14 studies, no publication bias, fixed OR=0.88, CI [0.74-1.05], $P=0.162$); DES^{2nd} were superior to DES^{1st} due to EES (3 studies, publication bias, fixed OR=0.61, CI [0.39-0.96], $P=0.033$); and, BP-DES were not superior to DES^{2nd} (2 studies, publication bias, fixed OR=0.89, CI [0.60-1.32], $P=0.554$) (Table 2, Fig. 2). There were no significant differences among DES^{1st} generation of stents (PES/SES) (2 studies, publication bias, fixed OR=0.90, CI [0.39-2.08], $P=0.806$);
- b) TLR: DES were superior to BMS (14 studies, publication bias), mainly due to SES (fixed OR=0.39, CI [0.30-0.51], $P=0.000$); DES^{2nd} were not superior to DES^{1st} (4 studies, no publication bias, random OR=1.05, CI [0.29-3.80], $P=0.939$); and, BP-DES were superior to DES^{2nd} (2 studies, publication bias, fixed OR=0.55, CI [0.35-0.86], $P=0.000$) (Table 2, Fig. 2). There were no significant differences among DES^{1st} generation of stents (PES/SES) (2 studies, publication bias, fixed OR=1.64, CI [0.52-5.11], $P=0.398$);
- c) TVR: DES were superior to BMS (13 studies, publication bias), mainly due to SES (fixed OR=0.45, CI [0.36-0.56], $P=0.000$); and, DES^{2nd} were superior to DES^{1st} due to EES (3 studies, no publication bias, random OR=0.52, CI [0.33-0.80], $P=0.003$) (Table 2, Fig. 2). There was only one study for comparison between the BP-DES and DES^{2nd}, and the meta-analysis was not possible. There were no significant differences among DES^{1st} generation of stents (PES/SES) (2 studies, publication bias, fixed OR=1.25, CI [0.63-2.45], $P=0.634$);
- d) IST: DES were not superior to BMS (17 studies, no publication bias, fixed OR=0.86, CI [0.71-1.05], $P=0.133$); DES^{2nd} were superior to DES^{1st} due to EES (2 studies, publication bias, fixed OR=0.34, CI [0.17-0.71], $P=0.004$); and, BP-DES were superior to DES^{2nd} (2 studies, publication bias, fixed OR=0.50, CI [0.27-0.92], $P=0.027$) (Table 2, Fig. 2). There were no significant differences among DES^{1st} generation of stents (PES/SES) (4 studies, no publication bias, fixed OR=0.90, CI [0.37-2.19], $P=0.822$);
- e) Overall death: DES were superior to BMS (13 studies, no publication bias), mainly due to EES (fixed OR=0.77, CI [0.60-0.98], $P=0.048$); DES^{2nd} were not superior to DES^{1st} (4 studies, no publication bias, fixed OR=0.74, CI [0.39-1.38], $P=0.340$); and, BP-DES were not superior to DES^{2nd} (2 studies, publication bias, fixed OR=0.96, CI [0.71-1.29], $P=0.771$) (Table 2, Fig. 2). There were no significant differences among DES^{1st} generation of stents (PES/SES) (2 studies, publication bias, fixed OR=0.46, CI [0.16-1.29], $P=0.139$);
- f) Cardiac death: DES were not superior to BMS (12 studies, no publication bias, fixed OR=0.94, CI [0.79-1.13], $P=0.512$); DES^{2nd} were not superior to DES^{1st} (5 studies, no publication bias, fixed OR=0.70, CI [0.44-1.11], $P=0.125$); and, BP-DES were not superior to DES^{2nd} (2 studies, publication bias, fixed OR=0.91, CI [0.65-1.26], $P=0.562$) (Table 2, Fig. 2). There were no significant differences among DES^{1st} generation of stents (PES/SES) (2 studies, publication bias, fixed OR=0.86, CI [0.29-2.53], $P=0.784$); and,
- g) MACE/TVF: DES were superior to BMS (15 studies, publication bias), mainly due to SES (fixed OR=0.53, CI [0.45-0.63], $P=0.000$); DES^{2nd} were superior to DES^{1st} due to EES (3 studies, no publication bias, fixed OR=0.55, CI [0.41-0.74], $P=0.000$); BP-DES were not superior to DES^{2nd} (2 studies, publication bias, fixed OR=0.81, CI [0.63-1.03], $P=0.078$) (Table 2, Fig. 2). There were no significant differences among DES^{1st} generation of stents (PES/SES) (4 studies, no publication bias, fixed OR=1.15, CI [0.77-1.71], $P=0.509$).

Discussion

This meta-analysis brings updated data about the influence of various stents on outcomes after acute STEMI treated with primary PCI. According to our results, DES are preferred over BMS in reducing the risk of TLR, TVR, overall death, and MACE/TVF, mainly due to SES and EES; DES^{2nd} over DES^{1st} in reducing the risk of myocardial infarction, IST, and MACE/TVF due to EES; and BP-DES over DES^{2nd} in reducing the risk of TLR and IST.

In the previous meta-analysis, DES were superior to BMS concerning long-term efficacy, while second-generation DES were superior to first-generation DES in reducing IST.⁴⁶ Other meta-analyses revealed improvements in outcomes with the evolution from BMS to first-generation and second-generation DES, with the most favorable safety and efficacy was with DES-EES.^{47,48} DES versus BMS was associated with a substantial decrease in the risk of TVR without compromising safety; DES-EES had the added advantage of a substantial reduction in the risk of IST when compared with first-generation DES and BMS with no increase in very late IST.⁴⁹

Table 2 Differences between stents in outcomes during 35-month follow-up after acute STEMI* (31 studies, 17,010 patients)

Tablica 2. Razlike između stentova u ishodima tijekom 35-mjesečnog praćenja nakon akutnog STEMI* (31 studija, 17.010 bolesnika)

<i>OUTCOMES[#]</i> <i>ISHODI</i>	<i>Myocardial infarction</i> <i>OR [CI]</i>	<i>TLR</i> <i>OR [CI]</i>	<i>TVR</i> <i>OR [CI]</i>	<i>IST</i> <i>OR [CI]</i>	<i>Overall death</i> <i>OR [CI]</i>	<i>Cardiac death</i> <i>OR [CI]</i>	<i>MACE/TVF</i> <i>OR [CI]</i>
DES/BMS	0.88 [0.74-1.05]	0.47 [0.41-0.54]	0.54 [0.47-0.61]	0.86 [0.71-1.05]	0.85 [0.74-0.99]	0.94 [0.79-1.13]	0.61 [0.55-0.68]
SES/BMS	0.82 [0.58-1.15]	0.39 [0.30-0.51]	0.45 [0.36-0.56]	0.76 [0.46-1.25]	0.83 [0.62-1.11]	0.77 [0.53-1.12]	0.53 [0.45-0.63]
PES/BMS	1.23 [0.37-4.10]	0.54 [0.43-0.67]	0.50 [0.25-0.99]	1.00 [0.69-1.44]	0.76 [0.55-1.06]	0.77 [0.55-1.08]	0.40 [0.16-1.02]
EES/BMS	0.88 [0.57-1.36]	0.62 [0.42-0.93]	0.73 [0.53-1.02]	0.72 [0.40-1.31]	0.77 [0.60-0.98]	1.06 [0.77-1.47]	0.77 [0.62-0.95]
BP-DES/BMS	0.67 [0.44-1.04]	0.44 [0.28-0.69]	0.55 [0.37-0.83]	0.67 [0.39-1.16]	0.95 [0.63-1.43]	0.88 [0.52-1.49]	0.54 [0.37-0.79]
DES^{1st}/DES^{1st} (PES/SES)	0.90 [0.39-2.08]	1.64 [0.52-5.11]	1.25 [0.63-2.45]	0.90 [0.37-2.19]	0.46 [0.16-1.29]	0.86 [0.29-2.53]	1.15 [0.77-1.71]
DES^{2nd}/DES^{1st}	0.61 [0.39-0.96]	1.05 [0.29-3.80]	0.72 [0.38-1.37]	0.41 [0.22-0.73]	0.74 [0.39-1.38]	0.70 [0.40-1.21]	0.70 [0.54-0.90]
ZES/DES ^{1st}	-	2.22 [0.89-5.50]	1.56 [0.85-2.87]	0.54 [0.20-1.48]	1.09 [0.31-3.87]	0.28 [0.03-2.39]	1.25 [0.79-1.98]
EES/DES ^{1st}	0.61 [0.39-0.96]	0.50 [0.08-2.94]	0.52 [0.33-0.80]	0.34 [0.17-0.71]	0.65 [0.32-1.33]	0.76 [0.43-1.36]	0.55 [0.41-0.74]
BP-DES/DES^{2nd}	0.89 [0.60-1.32]	0.55 [0.35-0.86]	-	0.50 [0.27-0.92]	0.96 [0.71-1.29]	0.91 [0.65-1.26]	0.81 [0.63-1.03]

*Abbreviations: BMS, bare-metal stent; BP-DES, biodegradable polymer drug-eluting stent; CI, confidence interval; EES, everolimus-eluting stent; IST, in-stent thrombosis; MACE/TVF, major adverse cardiovascular events/target vessel failure; OR, odds ratio; PES, paclitaxel-eluting stent; RCT, randomized controlled trial; SES, sirolimus-eluting stent; STEMI, ST-elevation myocardial infarction; TLR, target lesion revascularization; TVR, target vessel revascularization; ZES, zotarolimus-eluting stent.

Kratice: BMS, metalni stent; BP-DES, biorazgradivi polimerni stent koji otpušta lijek; CI, interval pouzdanosti; EES, stent koji otpušta everolimus; IST, tromboza u stentu; MACE/TVF, glavni štetni kardiovaskularni događaji/zatajenje ciljne žile; OR, omjer šansi; PES, stent koji otpušta paklitaksel; RCT, randomizirano kontrolirano ispitivanje; SES, stent koji otpušta sirolimus; STEMI, infarkt miokarda sa ST-elevacijom; TLR, revaskularizacija ciljne lezije; TVR, revaskularizacija ciljne žile; ZES, stent koji otpušta zotarolimus

[#]Efficacy parameters: TLR and TVR. Safety parameters: myocardial infarction, IST, overall death, cardiac death, MACE/TVF.

Parametri učinkovitosti: TLR i TVR. Parametri sigurnosti: infarkt miokarda, IST, ukupna smrt, srčana smrt, MACE/TVF.

Significant values are marked in bold (P<0.05).

Značajne vrijednosti označene su podebljano (P<0,05).

Myocardial infarction - DES/BMS, 0.88 (0.74-1.05) (NS)
 Myocardial infarction - DES2nd/DES1st, 0.61 (0.39-0.96) (P<0.05)
 Myocardial infarction - BP-DES/DES2nd, 0.89 (0.60-1.32) (NS)
 TLR - DES/BMS, 0.47 (0.41-0.54) (P<0.05)
 TLR - DES2nd/DES1st, 1.05 (0.29-3.80) (NS)
 TLR - BP-DES/DES2nd, 0.55 (0.35-0.86) (P<0.05)
 TVR - DES/BMS, 0.54 (0.47-0.61) (P<0.05)
 TVR - DES2nd/DES1st, 0.72 (0.38-1.37) (NS)
 IST - DES/BMS, 0.86 (0.71-1.05) (NS)
 IST - DES2nd/DES1st, 0.41 (0.22-0.73) (P<0.05)
 IST - BP-DES/DES2nd, 0.56 (0.33-0.96) (P<0.05)
 Overall death - DES/BMS, 0.85 (0.74-0.99) (P<0.05)
 Overall death - DES2nd/DES1st, 0.74 (0.39-1.38) (NS)
 Overall death - BP-DES/DES2nd, 0.96 (0.71-1.29) (NS)
 Cardiac death - DES/BMS, 0.94 (0.79-1.13) (NS)
 Cardiac death - DES2nd/DES1st, 0.70 (0.40-1.21) (NS)
 Cardiac death - BP-DES/DES2nd, 0.91 (0.65-1.26) (NS)
 MACE/TVF - DES/BMS, 0.61 (0.55-0.68) (P<0.05)
 MACE/TVF - DES2nd/DES1st, 0.70 (0.54-0.90) (P<0.05)
 MACE/TVF - BP-DES/DES2nd, 0.81 (0.63-1.03) (NS)

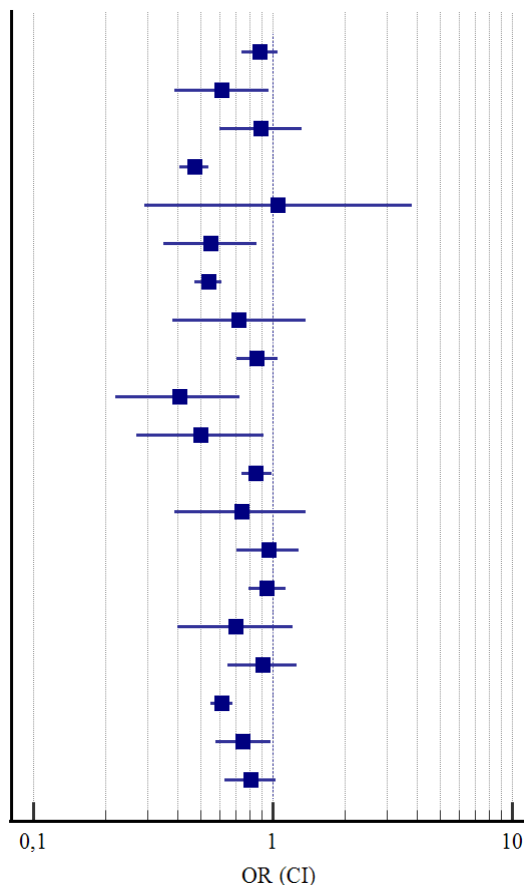


Figure 2 Forest plot with differences between stents in outcomes during 35-month follow-up after acute STEMI* (31 studies, 17,010 patients)

*Abbreviations: BMS, bare-metal stent; BP-DES, biodegradable polymer drug-eluting stent; CI, confidence interval; EES, everolimus-eluting stent; IST, in-stent thrombosis; MACE/TVF, major adverse cardiovascular events/target vessel failure; NS, non-significant; OR, odds ratio; PES, paclitaxel-eluting stent; RCT, randomized controlled trial; SES, sirolimus-eluting stent; STEMI, ST-elevation myocardial infarction; TLR, target lesion revascularization; TVR, target vessel revascularization, ZES, zotarolimus-eluting stent.

#Efficacy parameters: TLR and TVR. Safety parameters: myocardial infarction, IST, overall death, cardiac death, MACE/TVF.

Significant values with $P < 0.05$.

DES or BMS in STEMI patients

In most RCTs, the implantation of DES (including BP-DES) resulted in more favorable short and long-term outcomes, with the lower rates of MACE, reduction of repeat revascularization (TVR/TLR) and low incidence of acute/subacute IST; DES demonstrated confirmed superiority in combined patient and device-oriented composite endpoints compared with BMS, with no safety concerns.^{17,19,21-24,27,29-31,36,37,39-43} Some RCTs reported an increased rate of late IST and a trend to more related clinical events (cardiac mortality) in patients treated with DES, while in the other trials, no significant difference in MACE was observed.^{15,20,28,32,33} Taken together, our meta-analysis of these RCTs revealed efficacy and safety of DES over BMS, mainly due to

EES and SES.

BMS is a small, tubular, wire-mesh device that is pre-loaded in a collapsed form onto a catheter balloon, threaded to the narrowed section of the artery, and expanded within the vessel. Once expanded, the BMS acts as a mechanical scaffold, reducing elastic recoil and maintaining post-treatment vessel patency. BMS generally results in extremely favourable initial clinical results; however, re-narrowing of the treated artery is commonly observed in 20–30% of patients. This re-narrowing of the treated artery is due to in-stent restenosis (ISR).⁵⁰ To deal with this ISR, a repeat procedure of angiography needs to be performed, and despite extensive research, no therapy consistently prevents this difficult problem. With antiproliferative drugs released slowly, the use of DES interrupts the smooth

muscle cell cycle and thus their proliferation and can significantly reduce ISR.

First or second-generation DES in STEMI patients

DES-EES are superior to DES-PES and DES-SES in terms of safety and efficacy.^{18,34} DES-EES are noninferior to DES-SES, and superiority for MACE was suggested.⁴⁴ According to the other trials, the use of DES-ZES had similar rates of MACE, cardiac death, and recurrent MI at long-term follow-up as compared with DES-PES and DES-SES.²⁶ Also, compared to DES-SES, DES-ZES was associated with significantly higher in-stent late lumen loss at 9-month angiographic follow-up, although there was no significant difference in 1-year clinical outcomes.³⁸ In the ZEST-AMI trial, the efficacy and safety of the three different DESs (ZES, SES, and PES) showed similar, acceptable results in the treatment of STEMI.⁴⁵ Finally, DES-SES results in less late luminal loss compared with DES-PES. However, these benefits did not translate into a significant decrease in major adverse cardiac events at 1-year follow-up.²⁵ Taken together, our meta-analysis of these RCTs revealed the safety of DES^{2nd} over DES^{1st} due to EES. First-generation DES, such as SES and PES, have improved coronary intervention results by improving early results and reducing the risk of restenosis. But, there is presently debate on the safety of first-generation DES regarding late IST, especially after discontinuing dual antiplatelet therapy.⁵⁰ Thus, second-generation DES such as ZES and EES have been introduced with promising anti-restenotic efficacy as well as long-term safety. They differ from the first-generation stents concerning the antiproliferative agent, the polymer layer, and the stent frame.

BP-DES or DES in STEMI patients

BP-DES was proven superior to DES-EES concerning target lesion failure at 5 years of follow-up. The difference was driven by a numerically lower risk for ischaemia-driven TLR.¹⁶ In the RESOLVE trial, the use of BP-DES was associated with noninferior 1-year rates of MACE compared with DES-SES.³⁵ In our meta-analysis of these studies, BP-DES is superior to DES^{2nd} in efficacy and safety.

Recent refinements of newer generation DES involve the reduction of strut thickness of the metallic stent platform and using biodegradable polymers as a carrier for the antiproliferative substance. These improvements in stent design mitigate arterial injury, inflammation, and thrombogenicity, facilitate

endothelialization, and reduce neointimal hyperplasia.^{16,50}

Study limitations

The main limitation of this study was the small number of studies that evaluate the influence of biodegradable stents on outcomes and consequent publication bias, so further investigations will be necessary. The second limitation is the usage of GPIIb/IIIa inhibitors and duration of DAPT, which varies across the trials. Third, as with any meta-analysis, our report shares the limitations of the original RCTs. Fourth, follow-up data for some studies are limited to 6 months, while for others, they are limited to 120 months. Therefore, whether the observed differences would remain constant, increase, or diminish with more extended follow-up is unknown. Finally, some endpoints (e.g., MACE, TVF, overall/cardiac death) were based on study-specific definitions, which were not uniform across trials, a limitation inherent in most cardiovascular meta-analyses.

Conclusion

In conclusion, DES devices are superior to BMS, as well as BP-DES to the older generation of DES, in terms of efficacy and safety, and should be preferred in everyday clinical practice according to the judgment of an interventional cardiologist.

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Provode li zdravstveni djelatnici preporuke koje propisuju bolesnicima?

Do healthcare professionals follow recommendations prescribed to patients?

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Sažetak

Kardiovaskularne bolesti (KVB) glavni su uzrok preuranjene smrtnosti i rastućih troškova zdravstvene skrbi. Opterećenje KVB koje se može pripisati promjenjivim čimbenicima rizika nastavlja rasti na globalnoj razini. Cilj nam je bio istražiti prisutnost čimbenika rizika za nastanak KVB među zdravstvenim djelatnicima, njihovu učestalost i povezanost sociodemografskih čimbenika rizika za nastanak KVB.

Ispitanici i metode: Tijekom siječnja i veljače 2023. provedeno je presječno istraživanje u koje su uključena 224 zdravstvena radnika. Kao instrument istraživanja korišteni su anonimni anketni upitnici: sociodemografski upitnik, upitnik za procjenu životnoga stila (eng. Simple Lifestyle Indicator Questionnaire, SLIQ) i upitnik o prakticanju i pridržavanju mediteranskog načina prehrane (eng. Prevention with mediterranean diet, PREDIMED). Razlike u kontinuiranim varijablama s obzirom na dvije nezavisne skupine testirane su Mann Whitney U testom, a između tri i više skupina Kruskal Wallisovim testom. Povezanost je ocijenjena Spearmanovim koeficijentom korelacije Rho. Razina značajnosti postavljena je na Alpha (α) = 0,05.

Rezultati: Nepravilne prehrambene navike iskazane nepridržavanjem uputa mediteranske prehrane, te prekomjerna tjelesna težina i pušenje, najviše su negativno zastupljeni čimbenici rizika za razvoj kardiovaskularnih bolesti. Prisutna je niska zastupljenost bolesti srca i krvnih žila među zdravstvenim djelatnicima. Prema ukupnom broju bodova u SLIQ, ispitivana skupina zdravstvenih djelatnika procjenjuje srednje zdrave životne navike, a prema ukupnom broju bodova u PREDIMED upitniku, nisko je pridržavanje mediteranske prehrane. Nema statistički značajne razlike s obzirom na spol u procjeni životnih navika i u pridržavanju mediteranske prehrane. Mlađi liječnici imaju zdravije životne navike, a među njima je i statistički značajno umjereno pridržavanje preporuka mediteranske prehrane u odnosu na sve ostale ispitanike.

Zaključak: Provedenim istraživanjem uočeno je da zdravstveni djelatnici imaju umjeren rizik od razvoja kardiovaskularnih bolesti. Obzirom na umjereno pridržavanje zdravih stilova života i prehrambenih preporuka, ključno je razvijati i provoditi programe usmjerene na promicanje zdravijeg ponašanja zdravstvenih djelatnika.

Ključne riječi: kardiovaskularne bolesti, mediteranska prehrana, rizični čimbenici, životne navike

Summary

Cardiovascular diseases (CVD) are the leading cause of premature mortality and increasing healthcare costs. The burden of CVD attributable to modifiable risk factors continues to rise globally. We aimed to investigate the presence of risk factors for CVD among healthcare professionals, their prevalence, and the association of sociodemographic risk factors with the development of CVD.

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Participants and Methods: A cross-sectional study was conducted in January and February 2023, including 224 healthcare workers. Anonymous survey questionnaires were used as research instruments: a sociodemographic questionnaire, the Simple Lifestyle Indicator Questionnaire (SLIQ), and the Prevention with Mediterranean Diet (PREDIMED) Questionnaire. The differences in continuous variables between the two independent groups were tested using the Mann-Whitney U test, and the differences among three or more groups were tested using the Kruskal-Wallis test. The correlation was assessed with Spearman's Rho correlation coefficient, with the significance level set at Alpha (α) = 0.05.

Results: Lack of adherence to Mediterranean dietary guidelines, excess body weight, and smoking were the most prevalent risk factors for the development of cardiovascular diseases. There was a low prevalence of heart and vascular diseases among healthcare workers. Based on the overall SLIQ score, the studied group of healthcare workers was evaluated as having moderately healthy lifestyle habits, while adherence to the Mediterranean diet was found to be low according to the overall PREDIMED score. There was no statistically significant difference in lifestyle habits or adherence to the Mediterranean diet based on gender. Younger physicians exhibited healthier lifestyle habits and adhered moderately to the recommendations of the Mediterranean diet compared to other respondents.

Conclusion: This study found that healthcare professionals have a moderate risk of developing cardiovascular diseases. Given the moderate adherence to healthy lifestyle and dietary recommendations, it is essential to develop and implement programs aimed at promoting healthier behaviors among healthcare professionals.

Keywords: cardiovascular diseases, Mediterranean diet, risk factors, lifestyle habits

Uvod

Kardiovaskularne bolesti (KVB) vodeći su uzrok morbiditeta i mortaliteta, te predstavljaju značajan javnozdravstveni problem u cijelom svijetu. Višestruki rizični čimbenici za njihov nastanak posljedica su genetske sklonosti i djelovanja okoline, odnosno životnog stila suvremenog čovjeka (pušenje, prehrana, fizička neaktivnost, pretjerana konzumacija alkohola), te bolesti kao što su hipertenzija, dijabetes i dislipidemija.¹ Moderno, industrijski razvijeno društvo nameće i rizično profesionalno okruženje koje pridonosi razvoju KVB.

Radni procesi i radna okolina u kojima se odvija zdravstvena skrb za bolesnike, zahtjevni su za provođenje zdravih životnih stilova. Zdravstveni djelatnici su pod većim rizikom za razvoj bolesti nezdravih životnih stilova, te za pogoršanje kroničnih bolesti. U usporedbi s općom populacijom, oni imaju veći rizik za bolest koronarnih arterija, šećernu bolest, pretilost, mišićno-koštane ozljede i obolijevanje od nekih tumora. Naime, smjenski rad i rad u dežurstvima, prekobrojni radni sati, nepromjenjivo radno vrijeme, prvenstveno narušavaju cirkadijalni ritam. Svakodnevno zbrinjavanje životno ugroženih ili kronično bolesnih ljudi, te nastojanje profesionalaca za održanjem zdravlja i izlječenjem bolesti, izvori su kroničnog stresa. Uz veliki broj sati provedenih na poslu vezana je i tjelesna neaktivnost koja, uz konzumaciju kalorične hrane u zamjenu za nedostatak sna, povećava rizik od prehranjenosti/pretilosti.²

Iako se od njih očekuje da promoviraju zdrav životni stil i preventivne mjere za bolesnike, zdravstveni djelatnici često zanemaruju vlastito

zdravlje zbog prirode svoga posla.^{3,4} Narušeno zdravlje među liječnicima i drugim zdravstvenim osobljem ima potencijalni negativni učinak i na bolesnike, povećava rizik za medicinsku pogrešku, smanjenu opreznost i nepovoljan ishod liječenja za bolesnike. Liječnici koji provode zdrave životne stilove, češće će svojim bolesnicima savjetovati isto, a i bolesnici su suradljiviji u prihvaćanju savjeta, te više stječu povjerenje.² Stoga bi zdravstvenim djelatnicima vlastito zdravlje trebalo biti prioritet.

Cilj ovoga rada bio je istražiti prisutnost rizičnih čimbenika (prehrana, stanje uhranjenosti, pušenje, konzumacija alkohola, tjelesna aktivnost) za nastanak kardiovaskularnih bolesti među zdravstvenim djelatnicima, te utvrditi povezanost sa sociodemografskim čimbenicima i profesionalnim okruženjem.

Ispitanici i metode

U istraživanju je sudjelovalo 224 zdravstvena djelatnika različitih biomedicinskih usmjerenja s područja zapadnog dijela Brodsko-posavske županije. Istraživanje je provedeno tijekom siječnja i veljače 2023. godine. Ispitanici su regrutirani prema zdravstvenom usmjerenju, a svaki od njih je potvrdio suglasnost za anonimno sudjelovanje u istraživanju. Kao instrument istraživanja korišteni su anonimni anketni upitnici koji su distribuirani putem neinstitucijskih društvenih mreža:

Prvi upitnik sadržavao je sociodemografske podatke, pitanja o uvjetima rada, obiteljskoj anamnezi, prisutnosti kardiovaskularnih bolesti i rizičnih čimbenika za kardiovaskularne bolesti.

Drugi upitnik sadržavao je 12 pitanja za procjenu

životnoga stila (eng. Simple lifestyle indicator questionnaire, SLIQ).⁵ Uпитnik se sastojao od pitanja o načinu života obuhvaćenih iz pet kategorija: prehrana, tjelesna aktivnost, alkohol, pušenje i stres. Ovaj sustav omogućuje brzu procjenu općega zdravlja na temelju više aspekata. SLIQ sustav ocjenjivanja zasniva se na različitim komponentama zdravlja, gdje svaka komponenta dobije ocjenu 0, 1 ili 2 temeljem odgovora na pitanja koja se odnose na tu komponentu. Zbroj ocjena svih komponenti daje ukupni SLIQ rezultat koji može biti u rasponu od 0 do 10. Ukoliko je ukupna ocjena 0 do 4, životni stil je označen kao nezdrav, ukupna ocjena od 5 do 7 - srednje zdravi životni stil, a ukupna ocjena 8 do 10 - zdravi životni stil.⁵

Treći upitnik sadržavao je 14 pitanja o prakticiranju i pridržavanju mediteranskog načina prehrane (eng. Prevention with mediterranean diet, PREDIMED). Rezultati upitnika se zbrajaju. Raspon pridržavanja uputa mediteranske prehrane prikazan je brojevima 0 – 14 i označava razinu niskog (≤ 5), umjerenog (6 – 9) i visokog (≥ 10) pridržavanja uputa.^{6,7}

Statističke metode

Kategorički podaci predstavljeni su apsolutnim i relativnim frekvencijama. Razlika u kategoričkim varijablama testirala se Fisherovim egzaktnim testom. Normalnost raspodjele numeričkih varijabli testirana je Shapiro - Wilkovim testom, a zbog razdiobe koja ne slijedi normalnu, podaci su opisani medijanom i interkvartilnim rasponom. Razlike u kontinuiranim varijablama s obzirom na dvije nezavisne skupine testirane su Mann Whitney U testom (Hodges Lehmannova razlika medijana, uz 95% raspon pouzdanosti razlike), a između tri i više skupina Kruskal Wallisovim testom (post hoc Conover). Povezanost je ocijenjena Spearmanovim koeficijentom korelacije Rho. Unutarnja pouzdanost skala prikazana je koeficijentom Cronbach Alpha. Sve P vrijednosti su dvostrane. Razina značajnosti je postavljena na Alpha (α) = 0,05. Za analizu podataka korišten je statistički program MedCalc® Statistical Software version 20.218 (MedCalc Software Ltd, Ostend, Belgium; <https://www.medcalc.org>; 2023) i SPSS ver. 23 (IBM Corp. Released 2015. IBM SPSS, Ver. 23.0. Armonk, NY: IBM Corp.).

Rezultati

Obilježja bolesnika

Istraživanje je provedeno na 224 zdravstvena djelatnika, od kojih je 188 (83,9 %) žena. S obzirom na razinu obrazovanja, najviše je medicinskih sestara

i to srednje stručne spreme, njih 59 (26,3 %). U bolnici radi 174 (77,7 %) ispitanika, a s obzirom na radno vrijeme 108 (48,2 %) ih radi u smjenama (Tablica 1).

Tablica 1. Osnovna obilježja ispitanika

Table 1 Demographics

	Broj ispitanika (%) number of respondents
Spol/gender	
Muškarci/men	36 (16,1)
Žene/women	188 (83,9)
Razina obrazovanja/ education level	
Liječnik specijalist /Physician specialist	6 (2,7)
Liječnik specijalizant/Resident physician	49 (21,9)
Medicinska sestra srednje stručne spreme Nurse with secondary education	59 (26,3)
Medicinska sestra više stručne spreme Nurse with college education	41 (18,3)
Medicinska sestra visoke stručne spreme Nurse with university education	31 (13,8)
Ing. med. radiologije /radiology engineer	15 (6,7)
Fizioterapeutski tehničar/ Technician physiotherapist	7 (3,1)
Magistar farmacije/ farmaceutski tehničar Pharmacist graduate /pharmacist high school	12 (5,4)
Medicinsko – biokemijski lab. tehničar Medical biochemical lab technician	4 (1,8)
Mjesto rada /working place	
Bolnica/hospital	174 (77,7)
Dom zdravlja/health institute	33 (14,7)
Ljekarna/pharmacy	12 (5,4)
Zdravstvena njega u kući Home health care	5 (2,2)
Radno vrijeme / work hours	
Redovno (7 – 15 h) 7 regular	97 (43,3)
Smjenski rad /work in shifts	108 (48,2)
Dežurstva / work on duty	19 (8,5)

Medijan dobi ispitanika je 31 godina, u rasponu od 20 do najviše 64 godine (Tablica 2).

Prema vrijednostima indeksa tjelesne mase, 134 (59,8 %) ih je normalne uhranjenosti, prekomjernu

tjelesnu masu ima 56 (25 %) ispitanika, dok je pretilo njih 27 (12,1 %).

Od neke bolesti srca i krvnih žila boluje 20 (8,9 %) ispitanika. U obitelji kardiovaskularnu bolest navodi 120 (53,6 %) ispitanika (Tablica 3).

Tablica 2. Dob ispitanika, te mjere sredine tjelesne mase i visine, te indeksa tjelesne mase
Table 2 Age of the subjects, and measurements of body mass and height, and body mass index

	Medijan (interkvartilni raspon) Median (interquartile range)	Raspon od najniže do najviše vrijednosti Range from lowest to highest value
Dob (godine) /age	31 (26 – 40)	20 – 64
Tjelesna visina (cm) /Body height	169 (165 – 174)	152– 194
Tjelesna masa (kg) /Body mass	68 (60 – 79)	51 – 163
Indeks tjelesne mase (kg/m ²) /Body mass index	23,44 (21,48 – 27,08)	17,36 – 37,20

Tablica 3. Učestalost kardiovaskularnih bolesti kod ispitanika u obitelji, kao i rizičnih čimbenika
Table 3 Frequency of cardiovascular diseases in respondents and in the family, as well as risk factors

	Broj (%) ispitanika Number of respondents
Boluju od neke vrste bolesti srca i krvnih žila They suffer from some type of heart and blood vessel disease	20 (8,9)
Koje bolesti /Which diseases	
Koronarna bolest / Coronary disease	2 / 20
Srčano zatajenje (popuštanje) / Heart failure	1 / 20
Periferna arterijska bolest /Peripheral artery disease	2 / 20
Ostalo / Other	15 / 20
Boluje li itko u obitelji od kardiovaskularnih bolesti Does anyone in the family suffer from cardiovascular disease	
Da/Yes	120 (53,6)
Ne/No	93 (41,5)
Ne znam /I do not know	7 (3,1)
Imaju li šećernu bolest / Do they have diabetes	
Ne /no	211 (94,2)

	Broj (%) ispitanika Number of respondents
Šećerna bolest tip 1 / diabetes type 1	1 (0,4)
Šećerna bolest tip 2 / diabetes type 2	4 (1,8)
Imaju li povišene masnoće u krvi (kolesterol i trigliceridi) Do they have elevated blood fats (cholesterol and triglycerides)	
Da/yes	36 (16)
Ne/no	168 (75)
Ne znam /I do not know	18 (8)
Imaju arterijsku hipertenziju / having arterial hypertension	26 (11,6)
Liječe se od maligne bolesti / being treated for malignant disease	5 (2,2)

Istraživanjem znanja o kardiovaskularnim rizicima, od ukupnoga broja ispitanika, njih 184 (82,1 %) navelo je da su rizični čimbenici za razvoj kardiovaskularnih bolesti tjelesna neaktivnost, prehrana, stres, pušenje, prekomjerna tjelesna masa i nasljeđe.

Unutarnja pouzdanost cijele skale SLIQ je Cronbach Alpha od 0,814, što znači da je upitnik dobar alat za procjenu životnih navika na našem uzorku. Prema ovom upitniku zelenu salatu dva do tri puta tjedno konzumira 98 (43,8 %) ispitanika, voće njih 71 (31,7 %), a žitarice bogate vlaknima njih 67 (29,9). Laganom tjelesnom aktivnošću (1 – 3 puta tjedno) bavi se 92 (41,1 %) ispitanika, a snažnom tjelesnom aktivnošću ne bavi se 136 (60,7 %) ispitanika.

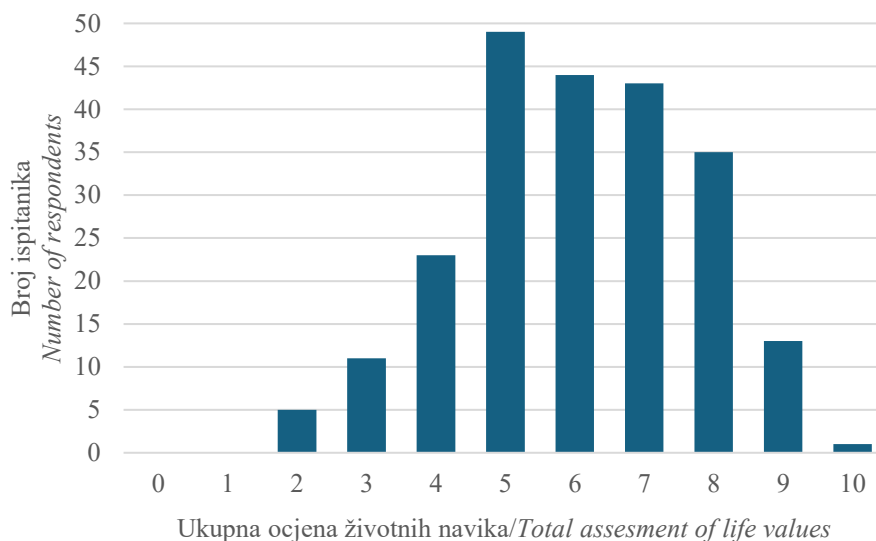
Vino i ostali alkohol konzumiraju do 5 puta tjedno, a pivo do 6 puta tjedno.

Aktivnih pušača je 67 (29,9 %), a od nepušača, njih 68 (30,4 %) je nekad pušilo, a 101 (45,1 %) nije nikada pušilo.

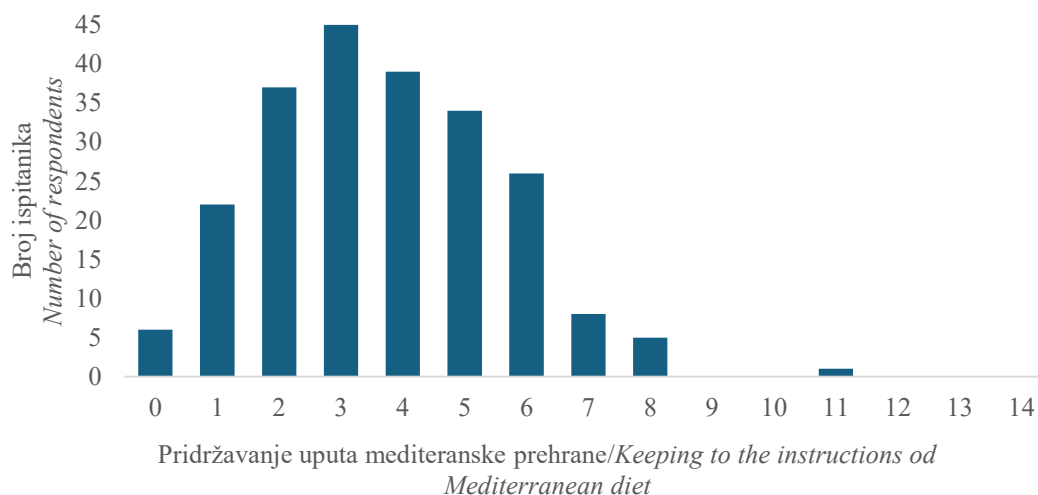
Na skali od 1 do 6 procijenili smo razinu stresa, te uočavamo da je za 11 (4,9 %) ispitanika razina stresa u svakodnevnom životu vrlo jaka, dok za 19 (8,5 %) ispitanika nema izloženosti stresu.

Ukupni broj bodova u SLIQ upitniku je u rasponu od 0 do 10. Viša ocjena povezana je sa zdravijim načinom života. Na ovom uzorku medijan SLIQ skale je 6 (interkvartilnog raspona od 5 do 7) u rasponu od najmanje 2 do najviše 10 (Slika 1).

Procjena pridržavanja mediteranske prehrane učinjena je primjenom PREDIMED upitnika, unutarnje pouzdanosti skale Cronbach Alpha od 0,690. Mogući raspon cijele skale je od 0 do 14, a medijan ocjene pridržavanja mediteranske prehrane na ovom uzorku je 4 (interkvartilnog raspona od 2 do 5), u rasponu od najmanje 0 do najviše 11 (Slika 2).



Slika 1. Raspodjela ispitanika prema ocjeni Upitnika za procjenu životnih navika (Simple lifestyle indicator questionnaire, SLIQ)
 Figure 1 Distribution of respondents according to the rating of life habits (Simple lifestyle indicator questionnaire, SLIQ)



Slika 2. Raspodjela ispitanika prema pridržavanju uputa za mediteransku prehranu
 Figure 2 Distribution of respondents according to adherence to the Mediterranean diet guidelines

S obzirom na broj bodova, uočavamo da je kod najvećeg broja ispitanika prisutno nisko pridržavanje preporuka - kod 183 (81,7 %) ispitanika, umjereno kod njih 40 (17,9 %), a visoku razinu pridržavanja bilježimo kod samo jednog (0,4 %) ispitanika. Ukoliko ispitanike dijelimo samo prema tome pridržavaju li se ili ne mediteranske prehrane (pridržavanje je broj bodova ≥ 8), pridržava ih se samo 6 (2,7 %), a ne pridržava 218 (97,3 %) ispitanika.

Povezanost životnih navika i pridržavanja uputa o mediteranskoj prehrani u odnosu na opća obilježja

Analizom povezanosti spola s ocjenom skale

životnih navika i s pridržavanjem preporuka za mediteransku prehranu, nije uočena razlika s obzirom na spol.

Spearmanovim koeficijentom korelacije ocijenili smo povezanost dobi s ocjenom životnih navika i ocjenom pridržavanja preporuka mediteranske prehrane. Stariji ispitanici imaju lošije životne navike ($Rho = -0,214$ $P = 0,001$), dok nema značajne povezanosti dobi s ocjenom pridržavanja preporuka mediteranske prehrane ($Rho = -0,093$ $P = 0,17$).

Specijalizanti imaju značajno bolje životne navike u odnosu na sve ostale skupine prema razini obrazovanja, osim u odnosu na skupinu liječnika specijalista (Kruskal Wallis test, $P < 0,001$) (Tablica

4). Liječnici specijalizanti se značajno više umjereno odnose na sve ostale ispitanike (Fisherov egzakti pridržavaju preporuka za mediteransku prehranu u test, $P < 0,001$) (Tablica 4).

Tablica 4. Ocjena životnih navika i pridržavanja preporuka za mediteransku prehranu s obzirom na razinu obrazovanja

Table 4 Assessment of life habits with regard to the level of education

	Medijan (interkvartilni raspon) median (interquartile range)						
	Liječnik specijalist <i>Physician specialist</i> (n = 6)	Liječnik specijalizant <i>Resident physician</i> (n = 49)	Medicinska sestra SSS ^a <i>Nurse sec. school</i> (n = 59)	Medicinska sestra VŠŠ ^b <i>Nurse higher. school</i> (n = 41)	Medicinska sestra VSS ^γ <i>Nurse univ degree</i> (n = 31)	Ostali zdravstveni radnici ^δ <i>Other health care workers</i> (n = 38)	<i>P*</i>
Ocjena životnih navika / Assessment of life habits							
Ukupna ocjena <i>Total grades Life habits scale</i>	6 (5 – 8)	7 (6 – 8)	6 (5 – 7)	6 (5 – 7)	6 (5 – 7)	6 (5 – 7)	<0,001 [†]
Pridržavanja preporuka za mediteransku prehranu / Adhering to Mediterranean diet recommendations							
Nisko pridržavanje <i>Low adhering (≤ 5)</i>	6 (100)	29 (59)	56 (95)	36 (88)	27 (87)	29 (76,3)	<0,001
Umjereno pridržavanja <i>Moderate adhering (6 – 9)</i>	0	19 (39)	3 (5)	5 (12)	4 (13)	9 (24)	
Visoka razina pridržavanja <i>High level of adhering (≥ 10)</i>	0	1 (2)	0	0	0	0	
Ukupno/ <i>Total</i>	6 (100)	49 (100)	59 (100)	41 (100)	31 (100)	38 (100)	

*Kruskal Wallis test (post hoc Conover)

**Fisherov egzakti test

[†]na razini $P < 0,05$ značajno su najbolje znanje pokazali liječnici specijalizanti u odnosu na sve ostale skupine, osim na skupinu liječnika specijalista

^δing.med. radiologije, fizioterapeutski tehničar, farmaceut, farmaceutski tehničar, med. biokemijski laboratorijski tehničar

^aSSS, srednja stručna sprema

^bVŠŠ, viša stručna sprema

^γVSS, visoka stručna sprema

Rasprava

Istraživanje je imalo za cilj ispitati prisutnost čimbenika rizika od kardiovaskularnih bolesti (KVB) među zdravstvenim djelatnicima, njihovu prevalenciju i korelaciju sa sociodemografskim čimbenicima. Sudionici istraživanja su pretežno osobe ženskog spola, mlađe životne dobi, najčešće zaposleni u bolničkim zdravstvenim ustanovama, a gotova polovina njih izvršava svoje radne obveze kroz smjenski rad.

Prosječna visina i težina bili su 169 cm, odnosno 68 kg, s medijanom ITM od 23,44 kg/m². Rezultati ovoga istraživanja su u korelaciji s ITM među korejskim, te engleskim zdravstvenim djelatnicima.^{8,9} Većina sudionika je normalne tjelesne težine (59,8%), dok ih je 25% s prekomjernom tjelesnom težinom, a njih 12,1% je pretilo, što ukazuje na značajan udio u riziku od KVB. U ovom ispitivanom uzroku svih zdravstvenih radnika, udio ispitanika s prekomjernom tjelesnom težinom/pretilošću niži je u odnosu na rezultate istraživanja u Europi i Aziji.^{10,11}

Visoka je, međutim, zastupljenost djelatnika s prekomjernom tjelesnom težinom/pretilošću u sestrinskoj profesiji, u odnosu na druge zdravstvene djelatnike, što pokazuje naše istraživanje, ali i druga istraživanja u Hrvatskoj i u inozemnim istraživačkim centrima.^{12,13}

U osobnoj anamnezi samo je 8,9% ispitanika izjavilo da ima KVB, dok je njih 53,6% imalo KVB u obiteljskoj povijesti. Uz to, 2,2% njih imalo je dijabetes, 16% hiperlipidemiju, a 11,6% hipertenziju. Malezijska studija koja je uključivala 23 bolnice diljem države, pokazala je prevalenciju dijabetesa, hipertenzije i/ili hiperlipidemije od 5,3% među zdravstvenim djelatnicima.¹⁴

U Framingham Heart Study prepoznati su hipertenzija, pušenje, tjelesna neaktivnost i pretilost kao čimbenici rizika za razvoj KVB.¹⁵ Znanje ispitanika o rizicima za kardiovaskularne bolesti u ovom istraživanju je zadovoljavajuće. Većina (82,1%) je prepoznala tjelesnu neaktivnost, lošu prehranu, pušenje, stres i genetske predispozicije kao čimbenike koji pridonose KVB. Bihevioralna psihologija pokazuje kako samo znanje čovjeka ne dovodi nužno i do promjene ponašanja. Ovo se može posebno odnositi na zdravstvene djelatnike koji sudjeluju u promociji zdravih životnih navika i stilova. Medicinske sestre pokazuju visoki stupanj nesuradljivosti/neprovođenja javnozdravstvenih smjernica o tjelesnoj aktivnosti i prehrani, unatoč tome što je sastavni dio njihovih radnih uloga savjetovanje o prehrani i tjelesnoj aktivnosti. I sami liječnici prepoznaju dobrobiti tjelesne aktivnosti i prehrane, ali manje od 25% njih provodi ove aktivnosti.²

Pokazatelj životnoga stila povezan s rizikom za razvoj KVB, mjereno je pomoću upitnika SLIQ (upitnik za procjenu životnoga stila) koji obuhvaća pet kategorija (prehrana, tjelesna aktivnost, konzumiranje alkohola, pušenje i stres). U domeni tjelesne aktivnosti, snažnom tjelesnom aktivnošću poput brzog trčanja, teškog rada u vrtu ili treninga s utezima (teretana) ne bavi se 136 (60,6 %) ispitanika. Najzastupljenija je umjerena tjelesna aktivnost 1 – 3 puta tjedno, koju prakticira (33,9 %) ispitanika. Među studentima sestrinstva u saveznoj državi Bihar, 41 (27,2 %) ispitanik 1 – 3 puta tjedno bavi se laganom tjelesnom aktivnošću, dok se snažnom tjelesnom aktivnošću ne bavi 70 (46,4 %) ispitanika.¹⁶

Konzumacija vina, piva i ostalog alkohola tijekom tjedna ukazuje na to da se pivo konzumira i do šest puta tjedno, dok se vino i ostali alkohol konzumira do pet puta tjedno. Istraživanje provedeno među medicinskim sestrama i liječnicima u Španjolskoj ukazuje na to da se alkohol konzumira više od četiri puta tjedno među 208 (11,9 %) ispitanika.¹⁷

U domeni pušenja, 67 (29,9 %) ispitanika aktivno puši, 68 (30,4 %) ispitanika nekada je pušilo, dok 101 (45,1 %) ispitanik nikada nije pušio. Pušenje je visoko zastupljeno u ispitivanoj populaciji. Istraživanje provedeno u Kanadi 2020. godine među zdravstvenim djelatnicima prikazuje kako 83 (92,2 %) ispitanika nikada nije pušilo, dok samo 5 (5,6 %) ispitanika puši svakodnevno.¹⁸ Francuski zdravstveni djelatnici 2020. godine, poput Kanadskih, imaju nižu zastupljenost pušenja, pa tako 557 (79,3 %) ispitanika nikada nije pušilo, a njih 145 (20,7 %) puši.¹⁹

Izloženost stresu i pokretači stresa često su proučavani u različitim istraživanjima, pa tako zdravstveni djelatnici navode kako je posao najčešći izvor stresa, potom obitelj i osobno zdravlje. U domeni stresa, za samo 11 (4,9 %) ispitanika razina stresa u životu vrlo je jaka, dok 19 (8,5 %) ispitanika nema izloženost stresu. Najviše ispitanika, njih 68 (30,4 %) procijenilo je razinu stresa kao umjerenu.²⁰ Tijekom pandemije bolesti COVID – 19, među osam europskih država (Njemačka, Ujedinjeno Kraljevstvo, Španjolska, Francuska, Portugal, Austrija, Italija i Švicarska) razina stresa za zdravstvene djelatnike u najvećem broju, kod njih 356 (59 %), bila je normalna/blaga, dok je 87 ispitanika (14 %) bilo umjereno pod stresom. Rezultati su bili ohrabrujući, pokazujući kako su se zdravstveni djelatnici bili spremni dobro nositi s pandemijom.²¹

Iz pet kategorija SLIQ upitnika proizlaze rezultati o nezdravom, srednje zdravom i zdravom načinu života. Ukupni rezultat životnoga stila bio je 6, što ukazuje na umjereno zdrav način života sa srednje prisutnim rizikom za KVB. Naši rezultati u skladu su s malobrojnim istraživanjima o rizicima za KVB među zdravstvenim djelatnicima. Naime, koristeći isti upitnik uočeno je kako i malezijski zdravstveni djelatnici imaju srednje zdravi način života.²² Istraživanja provedena u Čileu i Izraelu potvrđuju kako je način života i prevalencija rizika za KVB bolesti jednaka za zdravstvene djelatnike kao i za opću populaciju.^{23,24}

Prakticiranje mediteranske prehrane u općoj populaciji pokazuje vrlo široke različitosti s obzirom na geografsku lokaciju i klimatsko podneblje, ali i mediteranske zemlje pokazuju umjereno pridržavanje ovog tradicionalnog načina prehrane.^{25,26} Zdravstveni djelatnici u našem istraživanju ne pridržavaju se mediteranskog načina prehrane (97,3%). Istraživanja pokazuju kako se samo jedna petina studenata medicine koji studiraju u Dalmaciji (Split), pridržava mediteranskog načina prehrane.⁸ Budući da zastupljenost mediteranskog načina prehrane ovisi i o geografskom položaju, jedan od argumenata koji objašnjava ovako loše rezultate je i provođenje

istraživanja u kontinentalnom dijelu Hrvatske (Slavonija). Istraživanja u općoj populaciji iznose puno bolje rezultate, pa se tako u Italiji 76% ispitanika opće populacije pridržava mediteranske prehrane (ima ukupnu ocjenu iznad osam).²⁷

Analizom korelacije životnih navika i pridržavanja mediteranskog načina prehrane, stariji ispitanici imaju lošije životne navike, dok liječnici specijalizanti imaju bolje životne navike i više provode mediteransku prehranu ($P < 0,001$). Nedostaje istraživanja koja uspoređuju životne stilove u odnosu na dob ispitanika, a primjena preventivnih programa i promocija zdravih navika donose suprotne rezultate za različite dobne skupine.²⁸ Uočava se kako je primjena preventivnih mjera koje uključuje modernu tehnologiju, više prihvaćena u mlađim dobnim skupinama.²⁹

Nekoliko je ograničenja istraživanja. Kao prvo, upitnici su distribuirani online, putem društvene mreže. Virtualnom načinu komunikacije sklonije su osobe mlađe životne dobi koje i prevladavaju u istraživanju. Stoga istraživanje prikazuje životne stilove mlađih zdravstvenih djelatnika. Zdravstveni djelatnici su većinom iz sekundarne bolničke zdravstvene ustanove, dok imamo malo sudionika iz primarne zdravstvene zaštite, a nemamo podatke za javno zdravstvo ili tercijarnu zdravstvenu zaštitu. U sljedećim istraživanjima trebalo bi pristupiti i starijim zdravstvenim djelatnicima, te uključiti zdravstvene ustanove iz različitih područja Hrvatske s ciljem pornije analize dobne i regionalne pripadnosti na životne stilove. Istraživanje je provedeno kao presjek trenutne populacije, te ne možemo iznositi zaključke o uzročnoj povezanosti.

Možemo zaključiti kako zdravstveni djelatnici u cjelini imaju nisku razinu pridržavanja i konzumiranja namirnica iz mediteranske prehrane. Rezultati su zapravo negativni, uzimajući u obzir obrazovanje ispitanika, edukaciju i istaknutu ulogu u skrbi među bolesnicima i poticanju na zdrav način života. Mlađe generacije zdravstvenih djelatnika, te mlađi liječnici pokazuju pozitivan trend u poboljšanju životnih navika i prehrane, i oni mogu biti nositelji promjena među zdravstvenim djelatnicima.

Provedenim istraživanjem uočeno je kako zdravstveni djelatnici imaju umjeren rizik od razvoja kardiovaskularnih bolesti, prvenstveno zbog čimbenika povezanih s načinom života. Obzirom na umjerenost pridržavanje zdravih stilova života i prehranbenih preporuka, ključno je razvijati i provoditi programe usmjerene na promicanje zdravijeg ponašanja zdravstvenih djelatnika, čime se djeluje na osobno zdravlje i poboljšava skrb koja se pruža bolesnicima.

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Epidemiološki pokazatelji mentalnoga zdravlja u dječjoj i adolescentnoj psihijatriji tijekom pandemije COVID-19

Epidemiological Indicators of Mental Health in Child and Adolescent Psychiatry during the COVID-19 pandemic

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Sažetak

Razdoblje pandemije COVID-19 imalo je duboki i široki utjecaj na djecu i adolescente te se posebno odrazilo na njihovo mentalno zdravlje. Cilj ovoga preglednog rada bio je prikazati epidemiološke podatke o prevalenciji i incidenciji najčešćih mentalnih poremećaja u dječjoj i adolescentnoj psihijatriji tijekom pandemije COVID-19. Pretražene su baze podataka PubMed, Google Scholar, APA PsycInfo i SpringerLink, a koristili smo i podatke Hrvatskog zavoda za javno zdravstvo. Uključena su 23 izvora. Prevalencije depresije i anksioznosti kretale su se od 11–27% i 18,3–49,5%, posttraumatskog stresnog poremećaja od 15,5–60,3%, a psihosomatskih smetnji od 30,5–48,7%. Opservirana incidencija anoreksije nervoze ili atipične anoreksije nervoze bila je 40,6, dok je prevalencija bulimije nervoze bila 0,07%. Prevalencija poremećaja ponašanja u ovom radu iznosi 21,72% i 29,70%, a poremećaja pažnje s hiperaktivnošću 14,10% i 10,5%. Opservirana je prevalencija samoozljeđivanja u Hrvatskoj od 29,1%, dok je incidencija u drugoj europskoj državi bila za 38,4% veća od očekivane. Opserviran je porast incidencije suicidalnih ideja i pokušaja suicida na europskoj razini. Incidencija pokušaja suicida bila je 38,4 i 40,5. U Hrvatskoj je opservirana prevalencija suicidalnih ideja u rasponu od 30,6–38%, pokušaja suicida od 6,5% i 15,6%, a stopa izvršenih suicida je bila 7,4/100 000. Prikazana je prevalencija ovisnosti o videoigramama koja se kreće od 2,3–29,4%, dok se prevalencija upotrebe sredstava ovisnosti smanjila u odnosu na pretpandemijsko vrijeme. Ovaj rad prikazuje porast epidemioloških pokazatelja vezanih uz mentalno zdravlje djece i adolescenata tijekom COVID-19 pandemije, što ukazuje na potrebu za daljnjim istraživanjima i jačanjem javnozdravstvenih strategija u cilju pravovremenih intervencija u području mentalnoga zdravlja ove populacije.

Ključne riječi: epidemiologija, dječja i adolescentna psihijatrija, COVID-19, mentalno zdravlje

Summary

The COVID-19 pandemic has had a profound and widespread impact on children and adolescents, particularly affecting their mental health. The aim of this paper was to present epidemiological data on the prevalence and incidence of the most common mental disorders in child and adolescent psychiatry during the COVID-19 pandemic. Databases such as PubMed, Google Scholar, APA PsycInfo, and SpringerLink were searched, and data from the Croatian Institute of Public Health were also utilized. A total of 23 sources were included. Prevalence of depression and anxiety ranged from 11–27% and 18.3–49.5%, and prevalence of post-traumatic stress disorder and psychosomatic symptoms ranged from 15.5–60.3% and 30.5–48.7%, respectively. The observed incidence of anorexia nervosa or atypical anorexia nervosa was 40.6, while the

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prevalence of bulimia nervosa was 0.07%. The prevalence of conduct disorders in this study was 21.72% and 29.70%, while the prevalence of attention deficit and hyperactivity disorder was 14.10% and 10.5%. The observed prevalence of self-harm in Croatia was 29.1%, while the incidence in another country in Europe was 38.4% higher than expected. An increase in suicidal ideations and attempts has been observed across Europe. The incidence of suicide attempts was 38.4 and 40.5. In Croatia, the prevalence of suicidal ideation ranged from 30.6–38%, suicide attempts of 6.5% and 15.6%, and the suicide rate was 7.4 per 100,000. The prevalence of video game addiction ranged between 2.3% and 29.4%, while the prevalence of substance abuse decreased compared to pre-pandemic levels. This paper demonstrates an increase in epidemiological indicators of children's and adolescents' health disorders during the COVID-19 pandemic, highlighting the need for further research and strengthening public health strategies to ensure timely interventions in the mental health of this population.

Key words: Epidemiology, Child and Adolescent Psychiatry, COVID-19, Mental Health

Uvod

Razdoblje pandemije COVID-19 uzrokovalo je široke i duboke poremećaje u svakodnevnom životu djece i adolescenata diljem svijeta, ostavljajući fizičke, psihološke, obrazovne, razvojne, ponašajne i socijalne posljedice¹, a prema podacima Fonda ujedinjenih naroda za djecu, ova bi pandemija na mentalno zdravlje djece i adolescenata mogla imati posljedice koje će se vidjeti godinama kasnije.² Navedeno se ponajviše pripisuje uvođenju restriktivnih mjera u vidu zatvaranja škola, uvođenja karantena, socijalnog distanciranja i smanjenja vršnjačke interakcije, kao i nošenja zaštitnih maski na javnim mjestima.³⁻⁷ Može se smatrati da je psihička reakcija nastala kao rezultat procesa koji je spajajući nesvjesne elemente i fantaziju sa svjesnim mislima naglašavao „mračnu stranu“ pandemije virusa.⁸ Prvi slučajevi zaraze virusom Sars-CoV-2 zabilježeni su u Kini (Wuhan) u prosincu 2019. godine, a službeni početak pandemije proglasila je Svjetska zdravstvena organizacija (engl. World Health Organization) u ožujku 2020. godine.⁹ Pandemija je službeno završena 5. svibnja, 2023. godine kada je Svjetska zdravstvena organizacija proglasila kraj hitne faze pandemije.¹⁰ Prema podacima Svjetske zdravstvene organizacije od virusa Sars-Cov-2 do srpnja 2024. godine u svijetu je oboljelo preko 775 milijuna ljudi, od čega je umrlo 7 milijuna¹¹, pri čemu se smatra da djeca i adolescenti mlađi od 20 godina čine otprilike 21% od ukupnog broja oboljelih, uz stopu smrtnosti manju od 0,4%.¹²

Uzimajući u obzir navedeno, kao i opserviran povećan broj slučajeva u kliničkoj praksi autora, cilj ovoga preglednog rada bio je prikazati epidemiološke podatke o prevalenciji i incidenciji najčešćih mentalnih poremećaja kod djece i adolescenata tijekom pandemije COVID-19.

Do sada objavljeni pregledi literature vezani uz ovo područje¹³⁻¹⁶ obuhvatili su studije objavljene od

2020.–2024. godine, pri čemu najkasnije objavljeni rad datira iz 2024. godine.¹⁴ Prema našim saznanjima ovo je prvi pregledni rad na području Hrvatske koji predstavlja epidemiološke podatke o najčešćim psihijatrijskim entitetima kod djece i adolescenata tijekom pandemije COVID-19. Smatramo da doprinosi i do sada objavljenim svjetskim publikacijama s obzirom na to da obuhvaća studije objavljene od 2020.–2025. godine te pruža klinički osvrt koji je važan za praktični rad stručnjaka u području mentalnoga zdravlja djece i adolescenata.

Metodologija

Izvršeno je pretraživanje baza podataka PubMed, Google Scholar, APA PsycInfo i SpringerLink s ciljem pronalazanja znanstvenih, stručnih i preglednih radova na temu COVID-19 i mentalno zdravlje, uz pretraživanje ključnih riječi "epidemiology", AND "COVID-19", AND "mental health", AND "child and adolescent psychiatry" OR "anxiety", OR "depression", OR "PTSD", OR "conduct disorders", OR "psychosomatic disorders", OR, "eating disorders", OR "self-harm", OR "suicide", OR "addictions"; uz kriterij dobi od 3–19 godina, a godine objave 2020.–2025.

Rezultati

Pretraživanjem baza podataka PubMed, Google Scholar, APA PsycInfo i SpringerLink pronađeno je devet presječnih istraživanja, dvije longitudinalne studije, četiri retrospektivne studije, jedna komparativna studija, tri sustavna pregleda literature, dvije meta-analize i jedan sustavni pregled literature s meta-analizom, a koristili smo i jednu referencu HZJZ. Prikazani su podaci za razdoblje od 2020.–2023. godine. Rezultate prikazujemo opisno i u tablici 1.

Tablica 1. Epidemiološki pokazatelji mentalnoga zdravlja kod djece i adolescenata tijekom COVID-19 pandemije.
 Table 1 Epidemiological indicators of mental health in children and adolescents during the COVID-19 pandemic

Prvi autor/ First author	Godina objave/ Year of Publication	Vrsta studije/ Type of Study	Broj ispitanika/ Number of participants	Broj uklju- čenih studija/ Number of Studies included	Razdoblje promatranja/ Observation period	Dob/ Age	Rezultati/ Results
Racine ¹⁷	2021	Meta-analiza/ Meta-analysis	80.879	29	1/2020 - 3/2021	4,1-17,6	Prevalencija depresije/ <i>The prevalence of depression</i> 25,2% Prevalencija anksioznosti/ <i>The prevalence of anxiety</i> 20,5%
Panchal ¹⁸	2021	Sustavni pregled literature/ Systematic review	54.999	61	3/2020.- 4/2021	11-19	Prevalencija depresije/ <i>The prevalence of depression</i> 27%
Alizadeh ¹⁹	2023	Meta-analiza i sustavni pregled literature/ Meta-analysis and Systematic Review	329.159	43	1/2020.- 12/2022	≤18	Prevalencija depresije; anksioznosti; posttraumatskog stresnog poremećaja/ <i>The prevalence of depression; anxiety; post- traumatic stress disorder, respectively</i> Globalno/ <i>Globally</i> : 23 %; 26%; 23% Sjeverna Amerika/ <i>North America</i> : 35,4%, - , - Srednja i Južna Amerika/ <i>Central and South America</i> -, 18,3%, 60,3%

Prvi autor/ First author	Godina objave/ Year of Publication	Vrsta studije/ Type of Study	Broj ispitanika/ Number of participants	Broj uklju- čenih studija/ Number of Studies included	Razdoblje promatranja/ Observation period	Dob/ Age	Rezultati/ Results
							Europa/Europe: 12,2%, 43,2%, 40,5%
							Istočna Azija/East Asia: -, -, 15,5 %
Ajduković ²⁰	2022	Presječno istraživanje/ Cross-sectional study	1.096	-	2016, 2021	≈14-16	Prevalencija depresije/The prevalence of depression 20,6% Prevalencija anksioznosti/The prevalence of anxiety 33%
Ravens- Sieberer ²¹	2022	Longitudinalna studija (u tri vala)/ Longitudinal study (in three waves)	2.097	-	5-6/2020 (val 1) 12/2020.- 1/2021 (val 2) 9-10/2021 (Val 3)	7-17	Prevalencija depresije; anksioznosti/The prevalence of depression; anxiety val 1 (Wave 1) 11%; 24% val 2 (Wave 2) 15%, 30% val 3 (Wave 3) 11%, 27% Prevalencija glavobolja; bolova u trbuhu/The prevalence of headaches; abdominal pain val 3 (Wave 3): 48,7%; 39,2%
Durđević ²²	2022	Sustavni pregled literature/ Systematic review	52.797	27	1-10/2020	6-19	Prevalencija anksioznosti/The prevalence of anxiety 49,5%

Prvi autor/ First author	Godina objave/ Year of Publication	Vrsta studije/ Type of Study	Broj ispitanika/ Number of participants	Broj uklju- čenih studija/ Number of Studies included	Razdoblje promatranja/ Observation period	Dob/ Age	Rezultati/ Results
Yang ²³	2022	Meta-analiza/ Meta-analysis	17.385	10	1/2020.-5/2021	<18	Prevalencija posttraumatskog stresnog poremećaja/ <i>The prevalence of post-traumatic stress disorder</i> Ukupno/ <i>Total</i> : 28,15% SAD/ <i>USA</i> : 50.8% Kina/ <i>China</i> : 19,61% Italija/ <i>Italy</i> : 50,08%
Gómez- Restrepo ²⁴	2023	Presječno istraživanje/ Cross-sectional study	657	-	10/2021-3/2022	12-18	Prevalencija posttraumatskog stresnog poremećaja/ <i>The prevalence of post-traumatic stress disorder</i> 22,3 %
Ravens- Sieberer ²⁵	2021	Longitudinalna studija (u dva vala)/ Longitudinal study (in two waves)	1.923	-	5-6/2020 (val 1) 12/2020-1/2021 (val 2)	7-17	Prevalencija glavobolja; bolova u trbuhu/ <i>The prevalence of headaches; abdominal pain</i> val 1 (<i>Wave 1</i>): 40,5%; 30,5% val 2 (<i>Wave 2</i>): 46,4%; 36,4%
Trafford ²⁶	2023	Retrospektivna studija/ Retrospective study	9.184.712		1/2010-3/2022	10-24 Izabrana dobna skupina/ Selected age group: 13-16	Incidencija poremećaja hranjenja u djevojčica veća od očekivane za: <i>The incidence of eating disorders in girls was higher than expected by:</i> 42,4% Incidencija samoozljeđivanja u djevojčica veća od očekivane za/ <i>The incidence of self-harm in girls was higher than expected by:</i> 38,4%
Agostino ²⁷	2021	Presječno istraživanje/ Cross- sectional study	1.883 (Klinički uzorak/ Clinical sample)	-	1/2015.-2/2020	.13.8-16.9	Incidencija anoreksije nervoze ili atipične anoreksije nervoze/ <i>The incidence of anorexia nervosa or atypical anorexia nervosa</i> 40,6 Broj mjesečnih hospitalizacija/ <i>The number of</i>

Prvi autor/ First author	Godina objave/ Year of Publication	Vrsta studije/ Type of Study	Broj ispitanika/ Number of participants	Broj uklju- čenih studija/ Number of Studies included	Razdoblje promatranja/ Observation period	Dob/ Age	Rezultati/ Results
							monthly hospitalizations 20
Leickert ²⁸	2025	Retrospektivna studija (komparativna)/ <i>Retrospective study (comparative)</i>	565.499	-	1/2018-3/2020 4/2020-12/2021	10-17.9	Prevalencija bulimije nervoze/ <i>The prevalence of bulimia nervosa</i> 0.07%
Mallik ²⁹	2021	Presječno istraživanje/ <i>Cross-sectional study</i>	552	-	6-8/2020	4-17	Prevalencija poremećaja ponašanja; poremećaja pažnje s hiperaktivnošću/ <i>The prevalence of conduct disorder; attention deficit and hyperactivity disorder</i> 29,70%; 14,10%
Al-Mamun ³⁰	2024	Presječno istraživanje/ <i>Cross-sectional study</i>	1.496		2022	12-14	Prevalencija poremećaja ponašanja/ <i>The prevalence of the conduct disorder</i> 21,72%
Danielson ³¹	2024	Presječno istraživanje/ <i>Cross-sectional study</i>	45.169	-	2022	3-17	Prevalencija poremećaja pažnje s hiperaktivnošću / <i>The prevalence of attention deficit and hyperactivity disorder</i> 10,5%
Cousien ³²	2021	Presječno istraživanje/ <i>Cross-sectional study</i>	830 (Klinički uzorak/ <i>Clinical sample</i>)	-	1/2010- 4/2021	Prosječna dob/ <i>Mean age</i> 13.5	Incidencija pokušaja suicida/ <i>The incidence of suicide attempts</i> 9-10/2020: 38,4 11-12/2020: 40,5
Moscoco ³³	2024	Retrospektivna studija/ <i>Retrospective study</i>	2.833 (Klinički uzorak/ <i>Clinical sample</i>)	-	1/2018-12/2021	Prosječna dob/ <i>Mean age</i> 15.1	Primijećen porast incidencije pokušaja suicida 6-10 mjeseci nakon početka pandemije, ovisno o državi/ <i>An increase in the incidence of suicide attempts observed was 6 to 10 months after the start of the pandemic, depending on the country</i>

Prvi autor/ First author	Godina objave/ Year of Publication	Vrsta studije/ Type of Study	Broj ispitanika/ Number of participants	Broj uklju- čenih studija/ Number of Studies included	Razdoblje promatranja/ Observation period	Dob/ Age	Rezultati/ Results
García Fernandez ³⁴	2023	Retrospektivna studija/ <i>Retrospective study</i>	138 (Klinički uzorak/ <i>Clinical sample</i>)	-	1/2018-12/2021	8-17	Prevalencija suicidalnih misli ili pokušaja/ <i>The prevalence of suicidal thoughts or attempts</i> 31,1%
HZJZ ³⁵	2023	-	-	-	2022	15-19	Stopa izvršenih suicida/ <i>The suicide death rate</i> 7,4/100 000
Paradžik ³⁶	2022	Presječno istraživanje/ <i>Cross-sectional study</i>	2428 djece i adolescenata, od kojih je 447 izvještavalo o suicidalnom ponašanju/ <i>A total of 2428 children and adolescents participated in the study, of whom 447 reported suicidal behavior.</i> (Klinički uzorak/ <i>Clinical sample</i>)	-	2019 i/ and 2020	8-19	Udio suicidalnih ideja/ <i>The proportion of suicidal thoughts</i> 5/2020 - 32,8% 8/2020 - 30,6% 9/2020 - 38% Udio suicidalnih pripremnih aktivnosti/ <i>The proportion of suicidal preparatory actions</i> 5/2020 - 25% 9/2020 - 17,7% 11/2020 - 20,6% Udio pokušaja suicida/ <i>The proportion of suicide attempts</i> 5/2020 - 15,6% 8/2020 - 6,5%
Rezo- Bagarić ³⁷	2023	Komparativna studija/ <i>Comparative study</i>	622	-	2016/2021	14-17	Prevalencija samoozljeđivanja/ <i>The prevalence of self-harm</i> 29,1%
Han ³⁹	2022	Sustavni pregled literature/ <i>Systematic review</i>	Nepoznato/ <i>Unknown</i>	18	6/2020-2/2022	<19	Prevalencija ovisnosti o videoigrama/ <i>The prevalence of video game disorder</i> 2,3% - 29,4%

Depresija

Studija autorice Racine i suradnika, provedena je u razdoblju od siječnja 2020. do ožujka 2021. godine te je uključila 29 studija, a rezultati su pokazali prevalenciju depresivnih simptoma od 25,2%.¹⁷ Studija autorice Panchal i suradnika, objavljena 2021. godine, obuhvatila je 61 studiju, a rezultati su pokazali prevalenciju teške depresije od 27%.¹⁸ Studija autorice Alizadeh i suradnika, provedena u razdoblju od siječnja 2020. do prosinca 2022. godine, prikazala je ukupnu globalnu prevalenciju depresije od 23%, pri čemu je najveća prevalencija procijenjena u Sjevernoj Americi (35,4%), a najniža u Europi (12,2%).¹⁹ Istraživanje autorica Ajduković i Kožljan, provedeno na uzorku od 1.096 učenika srednjih škola grada Zagreba, pokazalo je prevalenciju ozbiljnih i vrlo ozbiljnih simptoma depresije od 20,6%.²⁰ Studija autorice Ravens-Sieberer i suradnika, provedena u tri vala na uzorku od 2.097 ispitanika (svibanj–lipanj 2020., prosinac 2020.–siječanj 2021., rujn 2021.–listopad 2021.), ukazala je na prevalenciju depresivnih simptoma od: 11% (Val 1), 15% (Val 2) i 11% (Val 3).²¹

Anksioznost

Studija autorice Racine i suradnika, objavljena 2021. godine, ukazala je na prevalenciju anksioznih simptoma od 20,5%.¹⁷ Studija autorice Alizadeh i suradnika, objavljena 2023. godine pokazala je ukupnu globalnu prevalenciju anksioznosti od 26%, pri čemu je najveća zabilježena u Europi (43,2%), a najniža u Srednjoj i Južnoj Americi (18,3%).¹⁹ Autorice Ajduković i Kožljan, u studiji objavljenoj 2022. godine, pokazale su da je 2021. godine prevalencija anksioznosti bila 33,0%.²⁰ Studija autorice Ravens-Sieberer i suradnika, objavljena 2022. godine, pokazala je prevalenciju anksioznosti od 24% u Valu 1, 30% u Valu 2 i 27% u Valu 3.²¹ Istraživanje autorice Đurđević i suradnika uključilo je 27 studija, u razdoblju između siječnja i listopada 2020. godine, a pokazalo je da je prevalencija simptoma anksioznosti tijekom pandemije iznosila 49,5%.²²

Posttraumatski stresni poremećaj (PTSP)

Studija autorice Alizadeh i suradnika je, uz globalnu prevalenciju depresije i anksioznosti, istraživala i prevalenciju PTSP-a tijekom pandemije COVID-19. Ukupna prevalencija PTSP-a procijenjena je na 23%, uz zabilježene regionalne razlike: Južna i Srednja Amerika (60,3%), Europa (40,5%) i Istočne Azija (15,5 %).¹⁹ Studija Yanga i

suradnika, objavljena 2022. godine, obuhvatila je 10 studija u razdoblju od siječnja 2020. do svibnja 2021. godine, a prikazana je ukupna prevalencija od 28,15%, uz razlike ovisno o geografskoj lokaciji: 19,61% (Kina), 50,8% (SAD) i 50,08% (Italija).²³ Istraživanje Gómez-Restrepoa i suradnika, provedeno od listopada 2021. do ožujka 2022. godine na uzorku od 657 ispitanika ukazalo je na prevalenciju vjerojatnog PTSP-a od 22,3%.²⁴

Psihosomatika

Studija autorice Ravens-Sieberer i suradnika, provedena tijekom pandemije u dva vala (svibanj–lipanj 2020. godine i prosinac 2020.–siječanj 2021. godine) na uzorku od 1.923 ispitanika, zabilježila je prevalenciju psihosomatskih tegoba poput glavobolja: 46,4% u valu 2, 40,5% u valu 1, te bolova u trbuhu: 36,4% u valu 2, 30,5% u valu 1.²⁵ Druga studija istih autora, obuhvatila je 2.097 ispitanika u tri vala (svibanj–lipanj 2020. godine, prosinac 2020.–siječanj 2021. godine, rujn 2021.–listopad 2021. godine). U valu 3 prevalencija bolova u trbuhu bila je 39,2%, a glavobolja 48,7%.²¹

Poremećaji hranjenja

Studija Trafforda i suradnika objavljena 2023. godine, provedena je na uzorku od 9.184.712 ispitanika u razdoblju promatranja od siječnja 2010. do ožujka 2022. godine.²⁶ Za potrebe rada izdvojili smo skupinu djevojčica u dobi od 13–16 godina, za koje je opservirana incidencija bila 42,4% veća od očekivane.²⁶ Istraživanje autorice Agostino i suradnika provedeno na kliničkom uzorku od 1.883 ispitanika, obuhvatilo je podatke iz razdoblja od siječnja 2015. do veljače 2020. godine. Rezultati su pokazali da je incidencija anoreksije nervoze (AN) ili atipične anoreksije nervoze (AAN) tijekom pandemije bila 40,6, dok je broj mjesečnih hospitalizacija bio 20,0.²⁷ Studija autorice Leickert i suradnika, objavljena 2025. godine obuhvatila je uzorak od 565.499 ispitanika u dva razdoblja: siječanj 2018. do ožujka 2020. godine i travanj 2020. do prosinca 2021. godine. Pokazana je prevalencija bulimije nervoze od 0,07%.²⁸

Poremećaji ponašanja i poremećaj pažnje s hiperaktivnošću

Istraživanje Mallika i autorice Radwan provedeno u razdoblju od lipnja do kolovoza 2020. godine, pokazalo je prevalenciju poremećaja ponašanja od 29,70% te prevalenciju poremećaja pažnje s hiperaktivnošću (ADHD) od 14,10%.²⁹ Istraživanje

Al-Mamuna i suradnika, objavljeno 2024. godine, provedeno na uzorku od 1.496 ispitanika pokazalo je prevalenciju poremećaja ponašanja od 21,72%.³⁰ Istraživanje autorice Danielson i suradnika provedeno je na uzorku od 45.169 ispitanika tijekom 2022. godine te je pokazalo prevalenciju ADHD-a od 10,5%.³¹

Suicidalnost i samoozljeđivanje

Istraživanje Trafforda i suradnika objavljeno 2023. godine pokazalo je incidenciju samoozljeđivanja za 38,4% višu od očekivane kod djevojaka u dobi od 13-16 godina.²⁶ Istraživanje Cousiena i suradnika provedeno na kliničkom uzorku od 830 ispitanika u razdoblju od siječnja 2010. do travnja 2021. godine, ukazalo je na incidenciju pokušaja suicida od 38,4 (u rujnu i listopadu 2020. godine) i 40,5 (početak studenog do prosinca 2020. godine).³² Studija autorice Moscoso i suradnika, objavljena 2024. godine obuhvatila je klinički uzorak od 2.833 ispitanika i ukazala na porast u incidenciji pokušaja suicida 6 do 10 mjeseci nakon početka pandemije, ovisno o državi.³³ Studija autorice Gárcie-Fernandez i suradnika provedena na kliničkom uzorku od 138 ispitanika u razdoblju od siječnja 2018. do prosinca 2021. godine, pokazala je prevalenciju suicidalnih misli ili pokušaja suicida od 31,1%.³⁴ U Republici Hrvatskoj, prema podacima Hrvatskog zavoda za javno zdravstvo, u 2022. godini je zabilježena stopa izvršenih suicida od 7,4/100 000 u dobnoj skupini od 15-19 godina.³⁵ Istraživanje autorice Paradžik i suradnika objavljeno 2022. godine provedeno je na kliničkom uzorku od 2428 ispitanika, pri čemu je njih 447 izvještavalo o suicidalnom ponašanju.³⁶ Istraživanje je ukazalo na veći udio suicidalnih ideja, suicidalnih pripremnih aktivnosti i suicidalnih pokušaja 2020. godine. Udio suicidalnih ideja za svibanj, kolovoz i rujan 2020. godine bio je redom: 32,8%, 30,6% i 38,0%. Udio suicidalnih pripremnih aktivnosti za svibanj, rujan i studeni 2020. godine bio je redom: 25,0%, 17,7% i 20,6%. Tijekom svibnja i kolovoza 2020. godine udio pokušaja suicida bio je 15,6% i 6,5%.³⁶ Istraživanje autorice Rezo-Bagarić i suradnika provedeno na uzorku od 269 ispitanika 2016. godine i 353 ispitanika 2021. godine, pokazalo je da je prevalencija nesuicidalnog samoozljeđivanja tijekom pandemije bila 29,1%.³⁷

Ovisnosti

Podaci vezani uz konzumaciju droga, alkohola i cigareta u populaciji mlađoj od 18 godina tijekom pandemije su oskudni i nekonzistentni.

Studija autorice Biagioni i suradnika objavljena 2023. godine, provedena na uzorku od 6.027 ispitanika pokazala je da je prevalencija upotrebe svih sredstava ovisnosti pala u odnosu na pretpandemijsko vrijeme, to jest 2016. godinu, a od svih ispitivanih sredstava najviše mladih je konzumiralo alkohol.³⁸ Istraživanje Hana i suradnika objavljeno 2022. godine ukazalo je na porast prevalencije ovisnosti o videoigrama, a procijenjeno je da se kretala između 2,3% i 29,4%.³⁹

Rasprava

Trend porasta učestalosti psihičkih poremećaja kod djece i adolescenata bilježi se od početka ovog tisućljeća⁴⁰⁻⁴³, a pogoršanje mentalnoga zdravlja mladih na globalnoj razini dodatno je uzrokovala pandemija COVID-19, što je vidljivo prema statističkim pokazateljima.^{17-27, 29-37, 39}

Rezultati prikazani u ovom radu pokazali su da je prevalencija depresije u uključenim studijama obuhvatila raspon od 11–27%.¹⁷⁻²¹ Ukupna globalna prevalencija iznosila je 23%¹⁹, dok je u pretpandemijsko vrijeme bila 2,6%.⁴³ Pokazana prevalencija u Hrvatskoj bila je 20,6%²⁰ u odnosu na pretpandemijskih 15% i 21,3%.^{20,44} Prikazani rezultati pokazali su i povećanu prevalenciju anksioznosti u rasponu od 18,3–49,5%^{17,19-22}, što je više u odnosu na razdoblje prije pandemije, kada se opća prevalencija kretala od 9,4–11,4%.⁴⁵ Ukupna globalna prevalencija anksioznosti tijekom pandemije bila je 26%¹⁹, dok je prije pandemije iznosila 6,5%.⁴³ Prevalencija anksioznosti u Hrvatskoj iznosi 33,0%, a u pretpandemijsko vrijeme bila je 13,4%.²⁰ Značajan porast prevalencije navedenih poremećaja se u kontekstu ove pandemije može objasniti utjecajem restriktivnih mjera poput zatvaranja škola^{6,7}, oslabljenom funkcijom "sadržavanja" (engl. containment) majki^{46,47} te osjećajem krivnje koji je bio izražen kod djece koja su strahovala da virusom ne zaraze starije članove obitelji.⁴⁸ Nalazi iz literature su već od ranije ukazivali na povezanost između osjećaja krivnje i depresije.⁴⁹ U prikazanim rezultatima prevalencija PTSP-a iznosi 15,5–60,3%^{19,23,24}, što je više u odnosu na pretpandemijsko vrijeme kada se bilježila prevalencija od 1,3%-8% (50) i 15,9%.⁵¹ Kao rizični čimbenici za nastanak PTSP-a kod djece i adolescenata navode se prethodno traumatsko iskustvo, postojeće psihijatrijske teškoće, preboljeni teži oblik COVID-19 infekcije i gubitak bliskih osoba zbog COVID-19.^{52,53} Prikazali smo prevalenciju psihosomatskih smetnji u rasponu od 30,5–48,7%^{21,25}, što je više u odnosu na pretpandemijske podatke od 21,3% i 28,3%^{21,25}, a porast se djelomično

može objasniti izraženom kognitivnom opterećenošću (tj. brigom), pri čemu briga o obiteljskim financijama ima naj snažniju povezanost s psihosomatskim smetnjama.⁵⁴ Prikazani rezultati vezani uz poremećaje hranjenja pokazali su da je u odnosu na pretpandemijsko vrijeme incidencija AN ili AAN porasla s 24,5 na 40,6 tijekom pandemije²⁷, dok se prevalencija bulimije nervoze smanjila s pretpandemijskih 0,09% na 0,07%.²⁸ Postavlja se pitanje je li uzrok potonjem veći broj neprepoznatih slučajeva ili su tijekom pandemije određeni slučajevi BN naposljetku zadovoljili dijagnostičke kriterije za AN.²⁸ Broj mjesečnih hospitalizacija zbog AN ili AAN porastao je s pretpandemijskih 7,5 na 20,0²⁷, a u literaturi je pokazano da na težinu simptoma posebno utječe aleksitimija⁵⁵ koja se definira kao deficit u emocionalnom procesiranju, a odnosi se na nesposobnost prepoznavanja emocija i nemogućnost razlikovanja emocija i tjelesnih senzacija.⁵⁶ Rezultati prikazani u ovom radu pokazali su prevalenciju poremećaja ponašanja od 29,70% i 21,72%^{29,30}, što je više u odnosu na pretpandemijsko vrijeme, kada je prevalencija iznosila 15,80% i 3,1%^{29,57}, a ukupna globalna prevalencija bila procijenjena na 5,7%.⁴³ Važan je podatak da je u Hrvatskoj (KBC Rijeka) ukupan broj hospitalizacija u 2021. i 2022. godini porastao za 14%, pri čemu je najčešće postavljena dijagnoza bila poremećaj ponašanja.⁵⁸ Porast učestalosti poremećaja ponašanja tijekom pandemije u literaturi je povezan s emocionalnom opterećenošću roditelja i strogim roditeljskim stilom.⁵⁹ U ovom radu prikazali smo prevalenciju ADHD-a tijekom pandemije od 14,10% i 10,5%^{29,31}, u odnosu na 4,90% i 8,9% prije pandemije.^{29,31} Ukupna globalna prevalencija ADHD-a prije pandemije iznosila je 3,4%.⁴³

Prikazani rezultati ukazuju na značajan porast suicidalnih ponašanja i samoozljeđivanja.^{26,32-37} U pretpandemijskom razdoblju zabilježena je prevalencija samoozljeđivanja od 17–17,7%.^{37,60}, što je manje u odnosu na prikazane rezultate koji su pokazali prevalenciju od 29,1%³⁷, a treba napomenuti i incidenciju za 38,4% veću od očekivane.²⁶ Pokušaji suicida su značajno porasli, što je vidljivo iz toga što je incidencija prije pandemije bila 12,2 i 22,5³², a tijekom pandemije 38,4 i 40,5.³² Rezultati domaćih autora provedeni na kliničkom uzorku, potvrđuju globalni trend porasta.³⁶ Pokazano je da je stopa izvršenih suicida u RH u 2022. godini bila 7,4/100 000 u dobnoj skupini od 15–19 godina³⁵, dok je za istu dobnu skupinu u 2018. godini zabilježena stopa od 4,8/100 000.⁶¹ Poznato je da su u pretpandemijsko vrijeme suicidalna ponašanja bila javnozdravstveni problem i vodeći uzrok smrtnosti mladih, a uzrok se promatrao kroz prizmu konstitucionalnih čimbenika,

osobnih iskustava i precipitirajućih stresnih događaja.⁶²

Osvrnuli smo se na to da je tijekom pandemije došlo do smanjenja uporabe sredstava ovisnosti u odnosu na pretpandemijsko razdoblje³⁸, pri čemu izdvajamo da je prevalencija uporabe alkohola iznosila 43,1%, u odnosu na pretpandemijskih 63,8% (38). Navedeni pad može se pripisati smanjenoj dostupnosti supstanci i ograničenim vršnjačkim druženjima uslijed mjera izolacije⁶³, dok vrijeme provedeno u kućanstvu može imati dvojaki učinak jer permisivni roditeljski stil i obiteljska disfunkcionalnost mogu potaknuti uzimanje sredstava ovisnosti.⁶³ Prevalencija ovisnosti o videoigramu je u prikazanim rezultatima varirala između 2,3% i 29,4%³⁹, što je značajan porast u odnosu na razdoblje prije pandemije kada je iznosila 1,2-9%.⁶⁴ Porast možemo pokušati objasniti tim što je virtualna stvarnost, pod izgovorom održavanja komunikacije, kapilarno prodrlo u sve sfere života.^{39,65}

Iako epidemiološki pokazatelji prije pandemije govore o porastu dijela psihopatoloških smetnji mladih⁴⁰⁻⁴³, konsenzus struke je da je ova pandemija nedvojbeno pridonijela daljnjem rastu tih podataka, što potvrđuju rezultati prikazanih sustavnih pregleda i meta-analitičkih studija.^{17-19,22,23,39} Pandemija COVID-19 predstavlja značajan kronični stresor te se može tumačiti kao kolektivni traumatski događaj^{66,67}, a poznato je da i ostale velike ljudske katastrofe poput globalnih pandemija, prirodnih katastrofa, ratnih sukoba, socijalnih kriza, mogu izazvati duboke emocionalne traume u društvu, što se osobito odnosi na djecu i adolescente.⁶⁸⁻⁷⁰ Pandemije su karakterizirane naglim i iznenadnim izbijanjem te odsustvom pripreme za njihovo upravljanje, a iako se njihov utjecaj često promatra kroz prizmu somatske medicine, naglasak bi trebalo staviti na mentalno zdravlje.⁷⁰ Prevalencija anksioznosti i depresije kod mladih zahvaćenih pandemijom ebole bila je 36,33% za anksioznost, te 56,94% i 87,32% za depresiju^{71,72}, dok je prevalencija PTSP-a bila 44,42%⁷², što ukazuje na ozbiljnu ugroženost mentalnoga zdravlja u ebolom zahvaćenim područjima.^{71,72} Iako su ovi rezultati promjenjivi u odnosu na naše rezultate vezane uz anksioznost, depresiju i PTSP¹⁷⁻²⁴, važno je napomenuti da niti jedna naša studija nije obuhvaćala uzorak afričke djece i mladih, što upućuje na pitanje regionalnih razlika i kulturološkog utjecaja na prevalenciju ovih poremećaja.^{19,73} U ovom radu je vidljivo da su tijekom COVID-19 pandemije bile izražene regionalne razlike u prevalenciji psihičkih poremećaja. Najviša prevalencija depresije u tom razdoblju zabilježena je u Sjevernoj Americi (35,4%), a najniža u Europi (12,2%). Najviša prevalencija

anksioznosti bila je u Europi (43,2%), najniža u Srednjoj i Južnoj Americi (18,3%), a što se tiče PTSP-a, najviša procijenjena prevalencija bila je u Srednjoj i Južnoj Americi (60,3%), a najniža u Istočnoj Aziji (15,5%).¹⁹ Razlike se mogu promatrati kroz prizmu socioekonomskog statusa, rasnih karakteristika i stigmatizacije vezane uz mentalne poremećaje.^{19,74-76}

COVID-19 pandemiju jedinstvenom su činili elementi nekontroliranosti i dugotrajnost, pri čemu ju posljednje razlikuje od stresora kao što su prirodne katastrofe.^{65,77} Pokazano je da prevalencija depresije kod djece i adolescenata nakon prirodnih katastrofa varira od 2–69%⁷⁸, a prevalencija PTSP-a nakon poplava i potresa od 19,2–30%⁷⁹, što pokazuje da je mentalno zdravlje ove skupine ugroženo nakon prirodnih katastrofa, kao i tijekom pandemije COVID-19. U kontekstu prevalencije mentalnih poremećaja je, osim navedenoga, potrebno uzeti u obzir utjecaj ratova i drugih fenomena (80). Pokazano je da ratovi uzrokuju prevalenciju PTSP-a od 47%, depresije 43% i anksioznosti 27%⁸¹, a povišenu prevalenciju ovih poremećaja nalazimo i kod djece u izbjeglištvu, kako slijedi redom: 40%, 21% i 10%.⁸² U Hrvatskoj je 1991. provedeno istraživanje koje je obuhvatilo lokalnu djecu i izbjeglice, te je pokazano da su obje grupe imale veću učestalost depresivnih simptoma u odnosu na djecu iste dobi prije rata.⁸³

Učinci traumatskih događaja (pandemija, rat, prirodne katastrofe, izbjeglištvo) na mentalno zdravlje mogu trajati godinama, a najčešće uključuju anksioznost, depresiju i PTSP.⁸¹⁻⁸³ Ako ova stanja budu potiskivana, neprorađena i neliječena, može doći do transgeneracijske traume, odnosno prenošenja psihotraume na buduće generacije potomaka različitim tipovima prijenosa.^{84,85}

Pandemija COVID-19 bila je višeznačna egzistencijalna ugroza, kako za pojedince, tako i za grupne i međugrupne odnose⁶⁵, a njezin negativni utjecaj zrcalio se, osim u porastu broja oboljelih, koji je primijećen kliničkim iskustvom autora, i u negativnim učincima pokazanim u epidemiološkim pokazateljima.^{17-27,29-37,39} Razvijanje i poboljšanje usluga za unaprjeđenje ranog prepoznavanja i učinkovitoga liječenja mentalnih poremećaja u djece, prioritet je javnog zdravstva, a studije o epidemiološkim pokazateljima su važne, kako bi se osiguralo da potrebe budu zadovoljene.⁸⁶ Ključno je poznavati epidemiološke pokazatelje i razumjeti dugoročne učinke pandemije, kako bi se planirale javnozdravstvene strategije, a u svrhu osnaživanja zdravstvenih kapaciteta potrebnih za zbrinjavanje djece i adolescenata s poteškoćama mentalnoga zdravlja.^{18,86-89}

Zaključak

Tijekom pandemije COVID-19 zabilježen je porast učestalosti poteškoća vezanih uz mentalno zdravlje djece i adolescenata. Povećala se učestalost depresivnih poremećaja, anksioznih poremećaja, psihosomatskih smetnji, poremećaja ponašanja, te ADHD-a. Od poremećaja hranjenja povećao se broj slučajeva anoreksije nervoze i atipične anoreksije nervoze, dok se smanjila prevalencija bulimije nervoze. Prikazan je porast učestalosti samoozljeđivanja, suicidalnih ideja i pokušaja, a za Republiku Hrvatsku prikazujemo i porast stope izvršenih suicida. Od bolesti ovisnosti u porastu je prevalencija ovisnosti o videoigrama. Iako je trend porasta zabilježen u pretpandemijsko vrijeme, neosporno je da je pandemija COVID-19 dovela do pogoršanja mentalnoga zdravlja mladih na globalnoj razini. S obzirom na to da je pandemija uvedenim zabranama bitno utjecala na način suočavanja sa stresom na individualnoj i grupnoj razini, te da je svojom dugotrajnošću i nepredvidivošću izazivala strahove, ne samo kod djece i adolescenata, nego i kod onih koji su trebali ublažavati te strahove (roditelji, učitelji, bake i djedovi), bilo je očekivano da će se pojaviti negativni efekti vezani uz epidemiološke pokazatelje mentalnoga zdravlja djece i adolescenata. Sukladno epidemiološkim pokazateljima opravdano je planirati povećanje zdravstvenih kapaciteta potrebnih za pružanje skrbi u području mentalnoga zdravlja ove populacije.

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Znanja i mišljenja među studentima Sestrinstva o rizičnim čimbenicima za nastanak neplodnosti

Knowledge and attitude of Nursing students about risk factors of infertility

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Sažetak

Uvod: Neplodnost je bolest ženskog i/ili muškog reproduktivnog sustava, a ukoliko postoje preklapanja, imamo udruženi čimbenik neplodnosti. Definirana je kao neuspjeh u postizanju trudnoće nakon dvanaest mjeseci nezaštićenih redovitih spolnih odnosa i predstavlja značajan javnozdravstveni problem za parove u reproduktivnoj dobi diljem cijeloga svijeta. Cilj ovoga istraživanja bio je ispitati razinu znanja i mišljenja studenata prijediplomskog Studija sestrinstva o rizičnim čimbenicima za nastanak neplodnosti.

Ispitanici i metode: U presječno istraživanje provedeno u svibnju 2023. godine bilo je uključeno 70 studenata prijediplomskog Studija sestrinstva s Fakulteta za dentalnu medicinu i zdravstvo Osijek, od kojih je 77,1% ženskog spola, uz podjednaku raspodjelu studenata po godini studiranja. Istraživanje je provedeno s pomoću anonimnog anketnog upitnika upotrebom internetske značajke „Google obrasci.“ Upitnik je sadržavao 21 pitanje o općim podacima ispitanika te specifičnim podacima o životnom stilu ispitanika, budućoj reprodukciji te njihovu znanju i mišljenju o rizičnim čimbenicima koji dovode do neplodnosti.

Rezultati: Statistički obrađeni podaci ispitanika pokazali su zadovoljavajuću razinu znanja studenata o rizičnim čimbenicima za nastanak neplodnosti. Rezultati nisu ukazali na statistički značajnu razliku u godini studija ispitanika te čimbenicima rizika koji dovode do neplodnosti.

Zaključak: Studenti prijediplomskog Studija sestrinstva imaju zadovoljavajuću razinu znanja o čimbenicima rizika koji dovode do neplodnosti, ali studenti treće godine studija nisu pokazali višu razinu znanja od ostalih studenata. Veći dio studenata ima životni stil u skladu sa svojim znanjima o čimbenicima rizika za neplodnost. Saznanja svakako treba dalje nadopunjavati te kontinuirano procjenjivati utjecaj čimbenika rizika za nastanak neplodnosti, budući da isti mijenjaju obrasce pojavljivanja neplodnosti.

Ključne riječi: neplodnost; čimbenici rizika; studenti, sestrinstvo

Summary

Introduction: Infertility is a disease of the female and/or male reproductive system and if there is an overlap then there is a combined infertility factor. It is defined as the failure to achieve pregnancy after twelve months of regular unprotected intercourse and represents a significant public health problem for couples of reproductive ages throughout the world. The aim of the study was to examine the level of knowledge and opinions of undergraduate nursing students about risk factors for the occurrence of infertility.

Subjects and methods: In this cross-sectional study conducted in May 2023, 70 undergraduate nursing students from Osijek Dental Medicine and Health Faculty were included, of whom 77.1% were female,

with an equal distribution of students by year of study. The research was conducted using an anonymous survey questionnaire using the Internet feature "Google Forms." The questionnaire contained 21 questions about the respondents' general data and specific data about the respondents' lifestyle, future reproduction, and their knowledge and opinions about risk factors that lead to infertility.

Results: Statistically analyzed data of the respondents showed a satisfactory level of knowledge of the students about risk factors for the occurrence of infertility. The results did not indicate a statistically significant difference in the year of study of the respondents and the risk factors that lead to infertility.

Conclusion: Nursing undergraduate students had a satisfactory level of knowledge about risk factors that lead to infertility, but third-year students did not show a higher level of knowledge than other students. Most of the students had a lifestyle in accordance with their knowledge of risk factors for infertility. Knowledge should certainly be supplemented further, and the impact of risk factors for the occurrence of infertility should be continuously assessed, since they change the patterns of infertility occurrence.

Keywords: infertility; risk factors; students, nursing

Uvod

Neplodnost je bolest ženskog, muškog, ili oba reproduktivna sustava, definirana kao neuspjeh u postizanju trudnoće nakon dvanaest mjeseci redovitih nezaštićenih spolnih odnosa.¹ Veliki je javnozdravstveni problem za parove u reproduktivnoj dobi² te ima štetan psihološki i socijalni utjecaj na oboljele, njihove obitelji i cijelo društvo.^{3,4} Pod pojmom primarne neplodnosti podrazumijeva se da žena nikada nije zatrudnjela, unatoč redovitim spolnim odnosima bez zaštite, tijekom godine dana. Sekundarna neplodnost podrazumijeva nemogućnost postizanja trudnoće nakon barem jedne uspješne trudnoće.⁵ Najčešći uzroci ženske neplodnosti su oštećeni jajovodi, izostanak ovulacije, endometrioza i viša životna dob žene u kojoj žena pokušava zatrudnjeti. Promjenjivi čimbenici rizika koji dovode do neplodnosti su pušenje, konzumacija alkohola, tjelesna aktivnost, pothranjenost i pretilost.⁶⁻⁹ Rezultati istraživanja pokazali su da žene koje puše imaju povećan rizik od izvanmaternične trudnoće, neuspješne implantacije, dismenoreje i oligomenoreje i 54% više poteškoća pri ostvarivanju trudnoće.¹⁰⁻¹² Rezultati istraživanja pokazali su da pušenje može biti neovisni čimbenik neplodnosti. Pušenje je povezano sa značajnim poremećajima hormonalnog statusa žene kojega karakterizira niža razina estrogena i progesterona te više razine androgenih hormona.¹⁰ Žene koje puše češće su izložene i drugim rizicima koji su uzročno-posljedično povezani s neplodnošću i vaginalnim infekcijama. Holly i suradnici utvrdili su visok stupanj mutagenosti u cervikalnome obrisku žena koje puše.¹³ Pušenje kod muškaraca djeluje na broj, pokretljivost i morfologiju spermija.^{11,14} Uspješnost izvantjelesne oplodnje kod žena koje aktivno puše 30 % je smanjena u odnosu na žene koje ne konzumiraju duhanske proizvode.¹² Prekomjerni unos alkohola kod žena rezultira povećanjem razine folikulostimulirajućeg i luteinizirajućeg hormona te

estrogena, pojavom dismenoreje i amenoreje, te niže vjerojatnosti začeća za 50%.⁸ Kronična konzumacija alkohola kod muškaraca značajno smanjuje razinu testosterona, što može dovesti do impotencije. Istovremeno dolazi do smanjenja broja i pokretljivosti spermija i sterilnosti.^{8,15,16} Visok intenzitet tjelesne aktivnosti rezultira hormonalnim promjenama, te posljedično nepovoljno utječe na reproduktivni sustav žene, osobito kod sportašica. Tjelesna aktivnost prilagođena potrebama i mogućnostima pojedinca smanjuje rizik za neplodnost te poboljšava perfuziju ženskog reproduktivnog sustava.^{17,18} Pothranjenost i pretilost negativno utječu na reproduktivni sustav oba spola.^{8,14} Žene čiji je indeks tjelesne mase ispod 17 imaju povećan rizik od neplodnosti, dok pretilost rezultira povećanom razinom leptina u serumu, što narušava ovulaciju.^{18,19} Zbog manjka masnog tkiva smanjena je pretvorba androgena u estrogene, kao i razina neuropeptida koji utječu na sekreciju GnRH. Manjak leptina kao posljedica manjka masnog tkiva, utječe na lučenje gonadotropina i na smanjenje razine kortikotropin oslobađajućeg hormona (CRH), adrenokortikotropnog hormona (ACTH) i kortizola, tireotropnog hormona (TSH) i hormona štitnjače.²⁰ Debljina je vrlo često povezana sa sindromom policističnih jajnika koji mogu biti razlog anovulacijskih ciklusa. Kod žena s policističnim jajnicima opažamo niže postotke trudnoća, poremećaj odnosa androgena i estrogena, povišenu proizvodnju muških spolnih hormona i pojačano izlučivanje inzulina. Visceralna debljina sudjeluje u glavnim patofiziološkim procesima vezanim uz sintezu adipokina, što dovodi do inzulinske rezistencije.^{21,22} U muškaraca je povezana sa smanjenom koncentracijom, kvalitetom i brojem spermija.²³ U nepromjenjive rizične čimbenike koji dovode do neplodnosti ubrajamo dob, bolesti, uključujući spolno prenosive bolesti. Neliječene spolno prenosive bolesti čiji su uzročnici *Chlamydia trachomatis* (klamidija), *Neisseria gonorrhoeae* (gonoreja), *Mycoplasma*

genitalium i parazit *Trichomonas vaginalis* (trihomonijaza) uzrokuju neplodnost.²⁴ Neplodnost može nastati kao posljedica operativnih zahvata, kao i ozljeda organa reproduktivnog sustava.^{7,25,26} Hipogonadotropni hipogonadizam, cistična fibroza, hiperprolaktinemija i autoimune bolesti, stanja su koja mogu u oba spola rezultirati neplodnošću.²⁷ Posljednjih trideset godina, osobito u zapadnim zemljama, javlja se trend odgađanja pokušaja trudnoće u starijoj dobi. Smanjenje ženske plodnosti počinje nakon 25. godine, a izrazito smanjenje plodnosti javlja se nakon 35. godine života.²⁸ Kod muškaraca se nakon 40. godine života javlja pad razine volumena sjemena i pokretljivosti te se posljedično smanjuje plodnost.^{29,30} Cilj ovoga istraživanja bio je ispitati razinu znanja i mišljenje studenata prijediplomskog Studija sestrinstva o rizičnim čimbenicima za nastanak neplodnosti. Pretpostavilo se da će studenti prve godine prijediplomskog Studija sestrinstva pokazati najmanju razinu znanja o rizičnim čimbenicima za nastanak neplodnosti. Neophodno je podizanje razine znanja o neplodnosti među studentima zdravstvenih fakulteta, kao mogućih budućih sudionika u liječenju iste.

Ispitanici i metode

Provedeno presječno istraživanje obuhvatilo je redovite studente prijediplomskog sveučilišnog Studija sestrinstva Fakulteta za dentalnu medicinu i zdravstvo Osijek. Istraživanju je pristupilo 70 od 83 studenata prve, druge i treće godine. Istraživanje je provedeno u svibnju 2023. godine. S obzirom na to da je istraživanje provedeno na ispitanicima koji su studenti Fakulteta za dentalnu medicinu i zdravstvo Osijek, a prema hodogramu Etičkog povjerenstva Fakulteta za dentalnu medicinu i zdravstvo Osijek, nije bilo potrebe za ishođenjem odobrenja istoga.

Istraživanje je provedeno anonimnim anketnim upitnikom koji je kreiran na mrežnim stranicama i proveden u trajanju od 5 do 10 minuta. Pitanja iz anketnog upitnika pisana su prema primjeru javno dostupnog, besplatnog te CC BY licencom pokrivenog upitnika.³¹ Upitnik je sadržavao 21 pitanje s ponuđenim odgovorima, od kojih je trebalo zaokružiti samo jedan. Sadržaj pitanja odnosio se na opće podatke ispitanika (spol, dob, godina studija, ima li ispitanik dijete) te specifične podatke o životnom stilu (puši li ispitanik cigarete, konzumira li alkohol, upražnjava li tjelesnu aktivnost, pridaje li značaj uravnoteženoj prehrani), o budućoj reprodukciji (želi li ispitanik u budućnosti imati dijete, u kojoj dobi želi posljednje dijete), o znanju i mišljenju o dobi u kojoj dolazi do smanjenja ženske

plodnosti.

Statističke metode

Analiza podataka prikupljenih anketnim upitnikom izvršena je s pomoću MS Excel (inačica 2016 MSO - verzija 2308,16.0.16731.20052, 32-bitna verzija, Microsoft, Redmond, Washington SAD) i MedCalc (inačica 22.009, MedCalc Software Ltd, Ostend, Belgija) za Windows program. Deskriptivne statističke metode upotrebljavane su za opis distribucije istraživanih varijabli, a aritmetičkom sredinom i standardnom devijacijom za normalno distribuirane varijable iskazane su srednje vrijednosti kontinuiranih varijabli. Raspodjelom učestalosti i udjelom po određenim grupama prikazani su nominalni pokazatelji. Upotrebom χ^2 -testa utvrđene su razlike proporcija između dvaju neovisnih uzoraka te je Pearsonov koeficijent korelacije upotrebljavan za ispitivanje korelacije varijabli. Za određivanje značajnosti razlika utvrđenih statističkim testiranjem upotrebljavana je razina $P < 0,05$.

Rezultati

Provedeno istraživanje uključilo je ukupno 70 studenata prijediplomskog Studija sestrinstva od kojih je 77,1% ženskog i 22,9% muškog spola, te podjednake raspodjele po godini studiranja. Značajno veći broj ispitanih studenata bio je u dobi od 18-23 godine, njih 94,3%, dok je starijih od 23 godine bilo 5,7%. Analizirajući životne navike ispitanika istraživanje je pokazalo kako većina nisu pušači, njih 68,6%, dok alkohol konzumira njih 74,3%. Tjelesnom aktivnošću bavi se 55,7% ispitanika, od kojih samo njih 28,6 % više puta tjedno. Važnost uravnoteženoj prehrani pridaje 88,6 % ispitanika, od kojih njih 60% samo ponekad. Promatrajući raspodjelu ispitanika s obzirom na buduću reprodukciju, uočeno je da većina ispitanika, njih 74,3%, želi imati djecu/još djece. Od ispitanika koji su potvrdno odgovorili na pitanje o budućoj reprodukciji, njih 83% želi imati od dvoje do petero djece. Značajno veći dio ispitanika, njih 72,3% želi imati prvo dijete između 25. i 30. godine života, 45,45% ispitanika želi imati dijete između 31. i 35. godine, a samo jedna osoba izrazila je želju za posljednjim djetetom nakon 35. godine života.

Analizirajući raspodjelu ispitanika s obzirom na znanja i mišljenja o ženskoj plodnosti, primjetno je kako najveći broj ispitanika, njih 62,9%, smatra da su žene najplodnije između 20. i 24. godine života. Pitajući o dobi žene kada dolazi do smanjenja plodnosti, 42,9% ispitanika smatra da je to u rasponu od 35. do 39. godine života. Većina ispitanika, njih

58,6%, smatra kako konzumacija alkohola smanjuje plodnost žena i muškarca, Značajno veći broj ispitanika, njih 82,9%, smatra kako pušenje smanjuje plodnost kod oba spola, dok 72,9% ispitanika vjeruje kako redovita tjelesna aktivnost povećava plodnost obaju spolova. Gotovo svi ispitanici, njih 97,1%, tvrde da pretilost i pothranjenost smanjuju plodnost žena i muškaraca.

U tablici 1. prikazan je međuodnos godine studija

te znanja i mišljenja o dobi kada su žene najplodnije. Ispitanici treće godine nisu pokazali veću razinu znanja od studenata prve i druge godine studija.

Promatrajući raspodjelu studenta po godini studiranja, s obzirom na pokazano znanje i mišljenje o utjecaju konzumacije alkohola na plodnost žene i muškarca, nije utvrđena statistički značajna razlika. (Tablica 2.)

Tablica 1. Međuodnos godine studija te znanja i mišljenja o dobi kada su žene najplodnije

Table 1 Correlation between years of study and knowledge and opinions about the age when women are most fertile

		Godina studija Year of study			Ukupno Total	P*	r§
		1.	2.	3.			
Dob za koju studenti smatraju da su žene najplodnije	< 20	N (%)	1 (4,55)	0 (0)	1 (4,17)	2 (2,86)	0,46 0,27
	20-24	N (%)	14 (63,63)	13 (54,17)	17 (70,83)	44 (62,86)	
	25-29	N (%)	6 (27,27)	11 (45,83)	6 (25)	23 (32,85)	
	30-34	N (%)	1 (4,55)	0 (0)	0 (0)	1 (1,43)	
Ukupno Total		N (%)	22 (100)	24 (100)	24 (100)	70 (100)	

N- broj ispitanika * χ^2 -test; § Pearsonov koeficijent korelacije

N- number of subjects * χ^2 -test; § Pearson correlation coefficient

Tablica 2. Međuodnos godine studija te znanja i mišljenja o utjecaju konzumacije alkohola na plodnost
Table 2 Correlation between years of study and knowledge and opinions about the influence of alcohol consumption on fertility

		Godina studija Year of study			Ukupno Total	p*	r§
		1.	2.	3.			
Mišljenje o utjecaju konzumacije alkohola na plodnost žena i muškarca	Povećava Increases	N (%)	0 (0)	0 (0)	0 (0)	0,61 0,12	
	Ne utječe Does not affect	N (%)	0 (0)	0 (0)	0 (0)		
Opinion on the influence of alcohol consumption on female and male fertility	Česta konzumacija smanjuje, povremena ne utječe Frequent consumption reduces it occasional consumption does not affect it	N (%)	10 (45,45)	11 (45,83)	8 (33,33)	0,61 0,12	
	Smanjuje Decreases	N (%)	12 (54,55)	13 (54,17)	16 (66,67)		41 (58,57)
Ukupno Total		N (%)	22 (100)	24 (100)	24 (100)	70 (100)	

N- broj ispitanika * χ^2 -test; § Pearsonov koeficijent korelacije

N- number of subjects * χ^2 -test; § Pearson correlation coefficient

Promatrajući raspodjelu studenta po godini studiranja, s obzirom na pokazano znanje i mišljenje o utjecaju pušenja cigareta na plodnost žene i muškarca, nije utvrđena statistički značajna razlika. (Tablica 3.)

Analizom raspodjele studenta po godini studiranja, s obzirom na pokazano znanje i mišljenje o utjecaju redovitog bavljenja tjelesnom aktivnošću na plodnost žene i muškarca, nije utvrđena statistički značajna razlika. (Tablica 4.)

Tablica 3. Međuodnos godine studija te znanja i mišljenja o utjecaju pušenja cigareta na plodnost
Table 3 Correlation between years of study and knowledge and opinions about the impact of cigarette smoking on fertility

		N	Godina studija Year of study			Ukupno Total	P*	r§
			1.	2.	3.			
Mišljenje o utjecaju pušenja cigareta na plodnost žena i muškarca Opinion on the influence of cigarette smoking on female and male fertility	Povećava Increases	N (%)	0 (0)	0 (0)	0 (0)	0 (0)	0,74	0,09
	Ne utječe Does not affect	N (%)	0 (0)	0 (0)	0 (0)	0 (0)		
	>20 /dan smanjuje <20/dan ne utječe >20 /day reduces <20/day does not affect	N (%)	4 (18,18)	5 (20,83)	3 (12,5)	12 (17,14)		
	Smanjuje Decreases	N (%)	18 (81,82)	19 (79,17)	21 (87,5)	58 (82,86)		
Ukupno Total		N (%)	22 (100)	24 (100)	24 (100)	70 (100)		

N- broj ispitanika * χ^2 -test; § Pearsonov koeficijent korelacije
N- number of subjects * χ^2 -test; § Pearson correlation coefficient

Tablica 4. Međuodnos godine studija te znanja i mišljenja o utjecaju redovitog bavljenja tjelesnim aktivnostima na plodnost
Table 4 Correlation between years of study and knowledge and opinions about the impact of regular physical activity on fertility

		N	Godina studija Year of study			Ukupno Total	P*	r§
			1.	2.	3.			
Mišljenje o utjecaju redovitog bavljenja tjelesnom aktivnošću na plodnost žena i muškarca Opinion on the influence of regular physical activity on female and male fertility	Povećava Increases	N (%)	18 (81,81)	18 (75)	15 (62,5)	51 (72,86)	0,59	0,19
	Ne utječe Does not affect	N (%)	4 (18,18)	5 (20,83)	8 (33,3)	17 (24,29)		
	Smanjuje Decreases	N (%)	0 (0)	1 (4,17)	1 (4,17)	2 (2,86)		
Ukupno Total		N (%)	22 (100)	24 (100)	24 (100)	70 (100)		

N- broj ispitanika * χ^2 -test; § pearsonov koeficijent korelacije
N- number of subjects * χ^2 -test; § pearson correlation coefficient

U tablici 5. i tablici 6. prikazana je raspodjela studenta po godini studiranja s obzirom na pokazano

znanje i mišljenje o utjecaju pretilosti i pothranjenosti na plodnost žene i muškarca te o utjecaju zdrave i uravnotežene prehrane na plodnost oba spola.

Tablica 5. Međudnos godine studija te znanja i mišljenja o utjecaju pretilosti i pothranjenosti na plodnost
 Table 5 Correlation between year of study and knowledge and opinion about the influence of obesity and malnutrition on fertility

		N	Godina studija Year of study			Ukupno Total	p*	r§
			1.	2.	3.			
Mišljenje o utjecaju pretilosti i pothranjenosti na plodnost žena i muškarca <i>Opinion on the influence of obesity and malnutrition on female and male fertility</i>	Povećava <i>Increases</i>	N (%)	0 (0)	0 (0)	0 (0)	0 (0)	0,58	0,12
	Ne utječe <i>Does not affect</i>	N (%)	1 (4,55)	1 (4,17)	0 (0)	2 (2,86)		
	Smanjuje <i>Decreases</i>	N (%)	21 (95,45)	23 (95,83)	24 (100)	68 (97,14)		
Ukupno <i>Total</i>		N (%)	22 (100)	24 (100)	24 (100)	70 (100)		

N- broj ispitanika * χ^2 -test; § pearsonov koeficijent korelacije
 N- number of subjects * χ^2 -test; § pearson correlation coefficient

Tablica 6. Međudnos godine studija te znanja i mišljenja o utjecaju zdrave i uravnotežene prehrane na plodnost
 Table 6 Correlation between years of study and knowledge and opinions about the influence of a healthy and balanced diet on fertility

		N	Godina studija Year of study			Ukupno Total	p*	r§
			1.	2.	3.			
Mišljenje o utjecaju zdrave i uravnotežene prehrane na plodnost žene i muškarca <i>Opinion on the influence of a healthy and balanced diet on female and male fertility</i>	Povećava <i>Increases</i>	N (%)	22 (100)	21 (87,5)	19 (79,17)	62 (88,57)	0,13	0,30
	Ne utječe <i>Does not affect</i>	N (%)	0 (0)	3 (12,5)	3 (12,5)	6 (8,57)		
	Smanjuje <i>Decreases</i>	N (%)	0 (0)	0 (0)	2 (8,33)	2 (2,86)		
Ukupno <i>Total</i>		N (%)	22 (100)	24 (100)	24 (100)	70 (100)		

N- broj ispitanika * χ^2 -test; § Pearsonov koeficijent korelacije
 N- number of subjects * χ^2 -test; § Pearson correlation coefficient

Rasprava

Istraživanju je pristupilo 70, od mogućih 83 redovnih studenata prijediplomskog Studija sestrištva Osijek s Fakulteta za dentalnu medicinu i zdravstvo Osijek. Raspodjela ispitanika po godini studiranja bila je podjednaka. Ženskog je spola 77,1% ispitanika, što odgovara konstanti da su u Republici Hrvatskoj studenti ženskoga spola više zastupljeni nego studenti muškoga spola.³² Najveći broj ispitanika u dobi je od 20. do 21. godine života, njih 32%, a najmanji je broj ispitanika koji imaju više od 23 godine, njih 4%. Samo 1,4% ispitanika ima dijete, dok preostalih 98,6% nema djecu.

Analizom raspodjele ispitanika s obzirom na godinu studija te znanja i mišljenja o dobi kada su žene najplodnije, najveći postotak studenata točno je

odredio dob kada su žene najplodnije i kada dolazi do smanjenja njihove plodnosti. Nije utvrđena statistički značajna razlika uz prisutan slabo izražen pozitivan međudnos.

Zanimljivo je usporediti dobivene rezultate s istraživanjima slične tematike provedenima u drugim zemljama. Prema austrijskoj studiji koja je uspoređivala svijest o plodnosti studenata medicine i ostalih studenata koji nisu u području medicine i zdravstva, studenti medicine imali su veću svijest, ali svejedno nisko znanje, o utjecaju dobi na plodnost žene.³¹ Također, istraživanje provedeno među ukrajinskim studentima pokazuje slične rezultate.³³

Kada je riječ o varijablama „godina studija“ i „utjecaj konzumacije alkohola na plodnost žena i muškarca“ te „godina studija“ i „utjecaj pušenja cigareta na plodnost žena i muškarca“, značajna

statistička razlika u navedenim međuodnosima nije utvrđena. Rezultati istraživanja provedenog u Bangladešu, čiji su ispitanici bili studenti medicine i zdravstveni radnici, prepoznali su pušenje cigareta te konzumaciju alkohola kao rizične čimbenike za nastanak neplodnosti, ali su unatoč toga pokazali nisku razinu znanja o neplodnosti općenito i njezinim čimbenicima rizika.³⁴ Prema istraživanju provedenom u Poljskoj, studentice medicinskog i nemedicinskog fakulteta znale su prepoznati ranije spomenute čimbenike rizika koji dovode do neplodnosti, što se može pripisati općem znanju, jer su pušenje cigareta i konzumacija alkohola dobro prepoznati rizični čimbenici za brojne kronične bolesti.³⁵

Ispitivanjem međuodnosa varijabli „godina studija“ i „utjecaj redovitog bavljenja tjelesnom aktivnošću na plodnost žena i muškarca,“ „godina studija“ i „utjecaj pretilosti i pothranjenosti na plodnost žena i muškarca“ te „godina studija“ i „utjecaj zdrave i uravnotežene prehrane na plodnost žena i muškarca“, nisu ustanovljene statistički značajne razlike te je u sva tri slučaja izražen slab pozitivan međuodnos. Osvrćući se na ranije spomenuto istraživanje u Poljskoj, studentice nisu znale prepoznati sve spomenute varijable kao rizične čimbenike za neplodnost, neovisno o tome jesu li sa sveučilišta medicinskih znanosti ili nekog drugog, nemedicinskog studija.³⁵ S druge strane, jedno istraživanje provedeno u Kanadi ispitalo je znanje 3345 žena u dobi od 20 do 50 godina, te je njih čak 66,2% tvrdilo kako je pretilost jedan od čimbenika rizika koji dovode do neplodnosti.³⁶

U ovome istraživanju izdvojeni su neki čimbenici rizika prisutni kod ispitanika koji su kontradiktorni s njihovim pokazanim znanjem. Od ukupnog broja ispitanika, njih 31,4% su pušači. Budući da 72,3% ispitanika želi imati prvo dijete između 25. i 30. godine života, ispitana je dob u kojoj pušači žele imati posljednje dijete. Njih 45,45% želi imati dijete između 31. i 35. godine, a samo jedna osoba izrazila je želju za posljednjim djetetom nakon 35. godine života, kada dolazi do izrazitog smanjenja plodnosti kod žena. Uz to, ispitano je i znanje pušača o utjecaju pušenja na plodnost. Većina pušača, njih 68,18%, svjesna je toga da pušenje smanjuje plodnost žena i muškarca, dok preostalih 31,82% misli da pušenje smanjuje plodnost obaju spolova samo ako puše više od dvadeset cigareta dnevno.

Jedno od pitanja iz podataka o životom stilu ispitanika bilo je i pitanje „Bavite li se nekom tjelesnom aktivnošću?“ Većina ispitanika, njih 65,7%, bavi se nekom tjelesnom aktivnošću barem nekoliko puta mjesečno, 28,6% njih bavi se tjelesnom aktivnošću više puta tjedno, a preostalih 34,3%

ispitanika ne bavi se nikakvom tjelesnom aktivnošću, te je ispitano njihovo znanje o utjecaju bavljenja tjelesnim aktivnostima na plodnost žene i muškarca. Veći broj ispitanika (62,5%) zna da redovito bavljenje tjelesnim aktivnostima povećava plodnost žene i muškarca, iako se oni sami ne bave tjelesnim aktivnostima. 33,33% ispitanika tvrdi kako tjelesna aktivnost ne utječe na plodnost žena i muškarca, a 4,17% vjeruje da redovito bavljenje tjelesnim aktivnostima smanjuje plodnost obaju spolova, što ukazuje na nedovoljno znanje.

Postoji nekoliko ograničenja ovoga istraživanja. Najveće je ograničenje mali broj ispitanika studenata Studija sestrinstva na jednom fakultetu u Republici Hrvatskoj. Da bi se rezultati mogli generalizirati potrebno je provesti jednako istraživanje i na drugim studijima Sestrinstva unutar Republike Hrvatske. Drugo je ograničenje veći broj ispitanika ženskoga spola, što je bilo očekivano s obzirom na to da Studij sestrinstva i dalje upisuju u većem postotku žene, a ženska dominacija prisutna je i na Sveučilištu Josipa Jurja Strossmayera u Osijeku već dulji niz godina.

Zaključak

Provedenim istraživanjem pomoću dobivenih rezultata može se zaključiti kako je razina znanja studenata prijediplomskog Studija sestrinstva o rizičnim čimbenicima za nastanak neplodnosti zadovoljavajuća. Ne postoji statistički značajna razlika u godini studija ispitanika u odnosu na njihovo znanje i mišljenje o čimbenicima rizika za nastanak neplodnosti. Studenti treće godine nisu pokazali višu razinu znanja od ostalih studenata. Većina studenata ima razvijene životne navike u skladu sa svojim znanjima o čimbenicima rizika koji dovode do neplodnosti. Sukladno navedenom, saznanja o istraživanim varijablama svakako treba dalje nadopunjavati te kontinuirano procjenjivati utjecaj čimbenika rizika za nastanak neplodnosti. Istraživanje je značajno jer može pomoći u pronalaženju novih preventivnih mogućnosti, što ukazuje na potrebu dodatne edukacije studenata kroz određene kolegije. U tom smislu nužno je, uz nastavnike i javnozdravstvene djelatnike, u edukaciju uključiti i nutricioniste, te nevladine udruge koje se bave ovim problemom. Naime, samo zajedničkim naporima i djelovanjem nastavnika, kliničara, javnozdravstvenih djelatnika, nutricionista, te osoba koje se suočavaju s problemom neplodnosti, mogu se očekivati pozitivne promjene koje će znatno unaprijediti zdravstveno stanje i kvalitetu života.

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Uloga hitnog medicinskog transporta u zbrinjavanju infarkta miokarda sa ST elevacijom

The role of emergency medical transportation in the management of ST-elevation myocardial infarction

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Sažetak

Cilj: Ishemijska bolest srca, uključujući infarkt miokarda s elevacijom ST segmenta (STEMI, engl. ST elevation myocardial infarction), predstavlja vodeći uzrok prerane smrti u svijetu, pa tako i u Hrvatskoj. Hitna uspostava protoka krvi u zahvaćenoj koronarnoj arteriji temelj je liječenja, a ključni element u postizanju toga cilja je hitan medicinski transport bolesnika do najbližeg centra za invazivnu kardiologiju. Stoga je cilj ovoga istraživanja bio utvrditi osnovne demografske i epidemiološke odlike bolesnika sa STEMI podvrgnutih hitnoj intervenciji timova Zavoda za hitnu medicinu (ZZHM) Zadarske županije.

Bolesnici i metode: Proveli smo retrospektivnu analizu podataka iz medicinske dokumentacije u pismohrani ZZHM Zadarske županije, koja je obuhvatila 820 bolesnika s dijagnozom STEMI, transportiranih vozilom ZZHM u razdoblju od 01.06.2015. do 31.12.2023. godine. Analizirali smo dob i spol bolesnika, temeljne vitalne parametre (krvni tlak, frekvencija bila i zasićenost periferne krvi kisikom), vrijeme proteklo od poziva do dolaska bolesnika u bolnicu i podatke o preživljavanju bolesnika. U ovom istraživanju koristili smo program Statistica verzija 14.1.0.8 (Cloud Software Inc.). Za opis podataka koristili smo deskriptivnu statistiku, Kolmogorov-Smirnovljevi test i neparametrijske testove. Vremenski niz analizirali smo korištenjem linearnog trenda. Statističku značajnost procijenili smo na razini $p \leq 0,05$, uz 95%-tne granice pouzdanosti.

Rezultati: Utvrdili smo kako se STEMI češće javlja kod muškaraca, posebice poslije 50-te godine života. Žene s dijagnozom STEMI starije su od muškaraca (73 u odnosu na 65 godina). U ispitivanom razdoblju bilježi se kontinuirani porast broja transporta zbog STEMI od oko 10%. Unatoč tome, vrijeme proteklo od poziva do izlaska na teren je u 50,86% slučajeva manje od 10 minuta, a 97% prijevoza obavljeno je unutar 120 minuta. Stopa preživljenja u ispitivanom razdoblju iznosila je 99,27%.

Zaključak: Kontinuirani porast broja transporta bolesnika sa STEMI ukazuje na nužnost daljnjeg strateškog planiranja i razvoja organizacije Zavoda za hitnu medicinu Zadarske županije, kao i na potrebu za jačanjem javnozdravstvenih preventivnih aktivnosti. Većina bolesnika transportirana je u bolnicu u zadovoljavajućim vremenskim okvirima, uz visoku stopu preživljenja.

Ključne riječi: hitan medicinski transport, infarkt miokarda, ST elevacija

Summary

Objectives: Ischemic heart disease, including ST-segment elevation myocardial infarction (STEMI), is a leading cause of premature death worldwide, including in Croatia. Urgent restoration of blood flow in the affected coronary artery is the cornerstone of treatment, and a key element in achieving this goal is the rapid medical transport of patients to the nearest invasive cardiology center. Therefore, this study aimed to

determine the basic demographic and epidemiological characteristics of patients with STEMI who underwent emergency intervention by teams of the Emergency Medical Service (EMS) of Zadar County.

Patients and methods: We conducted a retrospective analysis of data from the EMS registry of Zadar County, including 820 patients diagnosed with STEMI who were transported by EMS vehicles between June 1, 2015, and December 31, 2023. The analysis included patients' age and sex, key vital parameters (blood pressure, heart rate, and peripheral oxygen saturation), the time elapsed from the emergency call to hospital arrival, and patient survival outcomes. We used Statistica software, version 14.1.0.8 (Cloud Software Inc.), for data processing. Descriptive statistics were applied, along with the Kolmogorov-Smirnov test and non-parametric tests. Time trends were analyzed using a linear trend model. Statistical significance was assessed at $p \leq 0.05$, with 95% confidence intervals.

Results: STEMI was more common in men, particularly after age 50. Women diagnosed with STEMI were older than men (73 vs. 65 years). During the study period, we observed a continuous increase of approximately 10% in the number of STEMI-related transports. Despite this, the time from emergency call to field dispatch was under 10 minutes in 50.86% of cases, and 97% of transports were completed within 120 minutes. The overall survival rate during the study period was 99.27%.

Conclusion: The continuous increase in the number of STEMI patient transports highlights the need for further strategic planning and organizational development of Zadar County EMS, as well as the importance of strengthening public health prevention efforts. Crucially, however, despite the challenges, the majority of patients were transported to the hospital within a satisfactory timeframe and had a high survival rate. Indeed, transportation is one of the key elements in reducing mortality and ensuring optimal treatment of STEMI patients.

Keywords: Emergency medical transport, myocardial infarction, ST elevation

Uvod

Kardiovaskularne bolesti najčešći su uzrok hospitalizacije i smrti u Republici Hrvatskoj, a među njima vodeće mjesto pripada ishemijskoj bolesti srca s udjelom od 12,2% u ukupnom mortalitetu u 2022. godini.¹ Jedna od njezinih najčešćih prezentacija je akutni infarkt miokarda s elevacijom ST segmenta (STEMI, od engl. ST elevation myocardial infarction), uzrokovan potpunom i naglom okluzijom koronarne arterije.² Patofiziološki mehanizam STEMI temelji se na rupturi aterosklerotskog plaka s posljedičnim stvaranjem intraluminalnog tromba koji uzrokuje akutnu okluziju zahvaćene koronarne arterije.³ Koronarna okluzija dulja od 20 minuta rezultira nepovratnim oštećenjem kardiomiocita, a gotovo polovina miokarda koji se potencijalno može spasiti gubi se unutar prvog sata.^{4,5} Opseg smrti stanica miokarda ovisi o opskrbnom području miokarda začepljene arterije, trajanju okluzije i prisutnosti kolateralne cirkulacije.⁶ Bez pravodobne reperfuzije dolazi do ireverzibilnog oštećenja srčanog mišića, čime se povećava rizik od akutnih komplikacija, poput poremećaja srčanog ritma, tromboembolijskih i mehaničkih komplikacija, kao što su ruptura slobodne stijenke ventrikula, papilarnog mišića, interventrikularnog septuma ili razvoj kardiogenog šoka.⁷ S obzirom na brze intervencije, kliničke smjernice stručnih društava ističu potrebu za hitnim transportom bolesnika sa STEMI u ustanove koje omogućuju brzo izvođenje perkutane koronarne intervencije (PCI).

Zadarska županija je priobalna županija koja

povezuje sjeverni i južni dio Republike Hrvatske. Ukupna površina županije je 7.276 km², sa 116 otoka, od kojih je 17 naseljenih, a prema posljednjem popisu stanovništva iz 2021. godine, na području Županije živi 159.766 stanovnika.^{8,9} Zavod za hitnu medicinu (ZZHM) Zadarske županije ima ukupno 11 timova u 9 ispostava za akutno zbrinjavanje bolesnika na čitavom teritoriju županije.

Cilj ovoga istraživanja bio je utvrditi osnovne demografske i epidemiološke odlike bolesnika sa STEMI kao indikacije za hitan medicinski prijevoz vozilom ZZHM Zadarske županije u Opću bolnicu Zadar.

Bolesnici i metode

Bolesnici

Istraživanjem smo obuhvatili 820 bolesnika s dijagnozom STEMI postavljenom od strane timova ZZHM Zadarske županije, koji su prevezeni vozilom ZZHM u Opću bolnicu Zadar, u razdoblju od 01.06.2015. do 31.12.2023. godine.

Podatke smo prikupili retrospektivno, pretraživanjem medicinske dokumentacije u pismohrani ZZHM Zadarske županije. Nisu uključeni bolesnici s drugim uzrocima boli u prsima, bolesnici koji su preminuli prije dolaska tima ZZHM te bolesnici prevezeni osobnim vozilima.

U bazu podataka izrađenu u programu Microsoft Excel unijeli smo podatke o dobi, spolu, vremenu proteklom od pojave boli do poziva upućenog ZZHM, vremenu proteklom od poziva bolesnika do

dolaska tima ZZHM, vremenu proteklom od mjesta prihvata bolesnika do predaje bolesnika hitnoj službi OB Zadar te podatke o vrijednostima arterijskog tlaka, zasićenosti periferne krvi kisikom, frekvenciji bila te konačno, o preživljenju ili smrtnom ishodu bolesnika u razdoblju od poziva ZZHM do prijma u hitnu službu OB Zadar.

Statistička analiza podataka

U statističkoj obradi primijenjena je opisna statistika. Pravilnost raspodjele testirana je Kolgomorov-Smirnovim testom. U slučaju pravilne raspodjele kvantitativni pokazatelji su prikazani kao srednja vrijednost i standardna devijacija (SV±SD), dok su u slučaju nepravilne raspodjele prikazani kao medijani i interkvartilni rasponi. Kvalitativni pokazatelji su prikazani kao postoci i učestalosti. Za usporedbu pravilno raspodijeljenih kvantitativnih vrijednosti korišten je Studentov t-test, a u slučaju nepravilne raspodjele Mann-Whitney U test; pri usporedbi kvalitativnih pokazatelja korišten je hi-kvadrat test. Prikupljene podatke analizirali smo u vremenskom nizu od devet godina, izračunom jednadžbe linearnog trenda.

Tablica 1. Temeljni podaci o bolesnicima
Table 1 Baseline characteristics of patients

	Broj uzoraka <i>Number of examples</i>	Srednja vrijednost <i>Mean value</i>	Medijan <i>Median</i>	Min <i>Min</i>	Maks <i>Max</i>	Standardna devijacija <i>Standard Deviation</i>	Interkvartilni raspon <i>Interquartile range</i>
Dob (godine) <i>Age (years)</i>	814	68,48	68	23	95	12,29	18
Puls (otk/min) <i>Pulse (beats/min)</i>	781	86,05	83	23	220	24,88	31
Sistolički tlak (mmHg) <i>Systolic blood pressure (mmHg)</i>	758	136,90	140	50	280	1,16	45
Dijastolički tlak (mmHg) <i>Diastolic blood pressure (mmHg)</i>	758	80,22	80	30	151	17,05	20
Saturacija kisika (%) <i>Oxygen saturation (%)</i>	781	94,82	97	54	100	6,44	4
	Žene <i>Women</i>	Muškarci <i>Men</i>	Žene <i>Women</i> (%)	Muškarci <i>Men</i> (%)			
Spol <i>Gender</i>	325	492	39,63	60			

U obradi podataka koristili smo program Statistica verzija 14.1.0.8 (Cloud Software Inc.). Statističku značajnost procijenili smo na razini $p \leq 0,05$.

Rezultati su prikazani tekstualno ili grafički.

Etički aspekt istraživanja

Istraživanje je odobrilo Etičko povjerenstvo ZZHM Zadarske županije (Odluka od 13.11.2023.). Tijekom i nakon istraživanja štitili smo prava i osobne podatke ispitanika u skladu s važećim zakonskim propisima Republike Hrvatske te odrednicama Helsinške deklaracije (1964. – 2013.). Sve podatke smo povjerljivo i pod šifrom unijeli u bazu podataka u koju su uvid imali samo autori istraživanja.

Rezultati

U razdoblju od 01.06.2015. do 31.12.2023. 820 bolesnika s dijagnozom STEMI vozilom je ZZHM Zadarske županije prevezeno u Opću bolnicu Zadar. Od navedenoga broja šest (0,7%) bolesnika je preminulo tijekom transporta, dok su ostali bolesnici dovedeni živi u bolnicu.

Temeljni demografski i klinički podaci o bolesnicima navedeni su u Tablici 1.

Životna dob poznata je za 814 ispitanika s obzirom na neadekvatnost unesenih podataka u medicinsku dokumentaciju, a 764 (94%) bolesnika imalo je više

od 50 godina. Podjela bolesnika prema dobnim skupinama prikazana je u Tablici 2.

Tablica 2. Dobne skupine bolesnika
Table 2 Age groups of patients

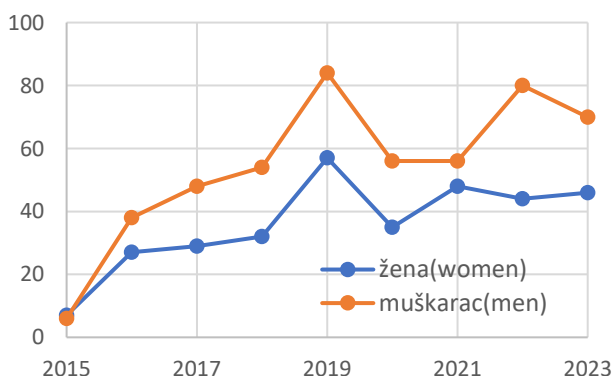
Dob (godine) Age (years)	Ukupan broj bolesnika Total number of patients	Postotak Percentage	Broj muškaraca Number of men	Broj žena Number of women
Do 50 Up to 50	50	6,14	41	9
Od 50 do 70 From 50 to 70	385	47,29	287	98
Od 70 do 90 From 70 to 90	361	44,34	158	203
Preko 90 Over 90	18	2,21	5	13

Žene su bile statistički značajno starije od muškaraca (Tablica 3).

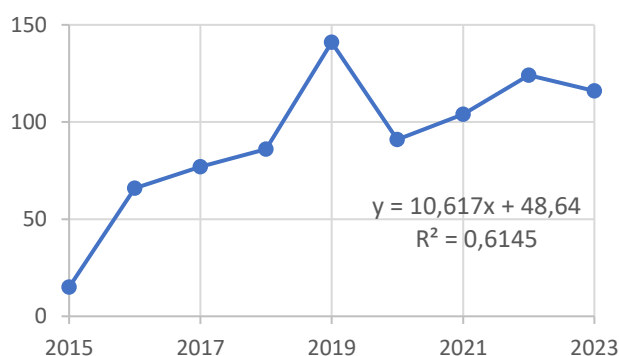
Tablica 3. Usporedba dobi muškaraca i žena
Table 3 Comparison of the age of men and women

Dob (godine) Age (years)	Srednja vrijednost Mean value	Mod Mod	Medijan Median	Raspon Range	Donja kvartila Lower quartile	Gornja kvartila Upper quartile	Mann-Whitneyev U	P vrijednost P value
Žene Women	73,69	80	76	56	67	83	46311	< 0,001
Muškarci Men	65,05	68	65	72	57	73		

Na slici 1 prikazan je broj prijevoza prema spolu u razdoblju od devet godina. Ističe se gotovo stalan porast broja transporta vozilima ZZHM. Izuzetak čini 2020. godina u kojoj je započela pandemija COVID-19. Također, veći je broj muškaraca u odnosu na žene. Broj prijevoza tijekom devetogodišnjeg razdoblja za cijelu skupinu bolesnika prikazan je na slici 2. Iz linijskog dijagrama vidi se povećanje od 11 prijevoza godišnje (jednadžba linearnog trenda $y=10,62x+48,64$; $R^2>0,6$, $p=0,012$).



Slika 1. Broj prijevoza u odnosu na spol tijekom promatranog razdoblja
Figure 1 Number of transports by gender during the observed period



Slika 2. Prikaz broja prijevoza po godinama
Figure 2 Display of the number of transports by year

Vrijeme proteklo od poziva do izlaska na teren izmjereno je za ukupno 465 intervencija (Tablica 4). Vrijeme kraće od 10 minuta zabilježeno je u 237 (50,86%) prijevoza. Analizom podataka od 2015. do 2023. godine nije uočen značajan trend promjena navedenog pokazatelja ($p=0,631$).

Tablica 4. Podaci za vrijeme proteklo od poziva do izlaska na teren

Table 4 Data on the time elapsed from the call to field dispatch

	Broj bolesnika (N=465)			
	Number of patients (N=465)			
	Medijan Median value	Min Min	Maks Max	Interkvartilni raspon Interquartile range
Vrijeme od poziva do izlaska na teren (minute) Time from call to field dispatch (minutes)	10	0	88	13

Vrijeme proteklo od poziva do dolaska u bolnicu izmjereno je za 819 intervencija (Tablica 5). Prosječno vrijeme iznosilo je 50,53 minute. Ukupno je 795 (97,07%) prijevoza obavljeno unutar 120 minuta. Gledajući po godinama u razdoblju od 2015.-2023. nije bilo značajnih promjena ($p=0,086$).

Tablica 5. Podaci za vrijeme proteklo od poziva do dolaska u bolnicu

Table 5 Data on time elapsed from the call to arrival at the hospital

	Broj bolesnika (N=819)			
	Number of patients (N=819)			
	Medijan Median value	Min Min	Maks Max	Interkvartilni raspon Interquartile range
Vrijeme od poziva do dolaska u bolnicu (minute) Time from call to arrival at the hospital (minutes)	44	2	351	35

Rasprava

Našim istraživanjem utvrdili smo da je gotovo 94% ispitanika bilo starije od 50 godina, dok je njihova prosječna dob iznosila 68,48 godina. Ovi

rezultati su u skladu s prethodnim istraživanjima koja ukazuju na porast učestalosti STEMI s porastom životne dobi, poput studije Tumminello i suradnika.¹⁰ Od ukupnog broja ispitanika, 60% su činili muškarci, što potvrđuje već poznatu činjenicu o većoj učestalosti infarkta miokarda u muškaraca u usporedbi sa ženama.¹¹ Prosječna dob ispitanika u ovom istraživanju značajno se razlikovala među spolovima. Žene su u prosjeku bile starije (73 godine) u odnosu na muškarce (65 godina). Ovi rezultati odgovaraju istraživanju Kuehnemunda i suradnika iz 2021. godine.¹² Tome doprinosi činjenica kako su muškarci skloniji rizičnijem ponašanju i imaju veći kardiovaskularni rizik od žena.¹³ Pored toga, utvrđeno je da estrogen štiti žene u generativnoj dobi od kardiovaskularnih bolesti, odnosno da smanjenje razine estrogena u postmenopauzi, pored promjena u građi i morfologiji tijela, povećava i oksidativni stres u tijelu žena te izaziva porast tjelesne mase i pojavu pretilosti s posljedičnim porastom učestalosti infarkta miokarda, što je potaklo primjenu estrogenske terapije u postmenopauzi u svrhu smanjenja kardiovaskularnog rizika.^{14,15}

Pravovremena reperfuzijska terapija osnova je u liječenju STEMI. U bolesnika liječenih primarnom perkutanom koronarnom intervencijom (PCI), uz primjenu medikamentozne terapije u skladu s kliničkim smjernicama, desetogodišnja stopa mortaliteta je samo 2% viša u usporedbi s općom populacijom.¹⁶ Ovi podaci dodatno naglašavaju važnost hitnog transporta bolesnika do najbliže ustanove za invazivnu kardiologiju. U našem istraživanju medijan vremena proteklog od zaprimanja hitnog poziva do polaska medicinskog tima prema bolesniku iznosio je 10 minuta. Nacionalni institut za zdravlje Ujedinjenog Kraljevstva postavio je ambiciozne ciljeve za hitne intervencije, te bi po njihovom mišljenju vrijeme intervencije trebalo uslijediti unutar sedam minuta.¹⁷ Europska istraživanja dodatno ističu kako svaka minuta zakašnjenja kod srčanog aresta smanjuje stopu preživljavanja za oko 5%.¹⁸

Ipak, unatoč jasno definiranim ciljevima, autori naglašavaju da britanske hitne službe nisu uspjele dostići ove preporuke. Štoviše, vrijeme reakcije značajno se pogoršalo nakon pandemije COVID-19. Primjerice, prosječno vrijeme odgovora na hitne pozive druge kategorije, poput moždanog udara, u lipnju 2022. godine iznosilo je 51 minutu, iako je cilj bio 18 minuta.¹⁷ U našem istraživanju nisu zabilježena značajnija odstupanja vremena reakcije timova Zavoda za hitnu medicinu. Ipak, valja istaknuti da su podaci o vremenu izlaska na teren zabilježeni u tek nešto više od polovine intervencija, što upućuje na potrebu poboljšanja ažurnosti unosa

podataka u medicinsku dokumentaciju te važnost dosljednog dokumentiranja svih hitnih intervencija. Pored toga, maksimalno zabilježeno vrijeme izlaska na teren od 88 minuta upućuje na potrebu detaljnije analize svake pojedine intervencije, s ciljem daljnjeg unapređenja kvalitete zdravstvene skrbi. Ipak, treba uzeti u obzir da se prikupljeni podaci odnose na čitavo područje Zadarske županije, bez odvajanja urbanih i ruralnih sredina. Stoga bi u budućim istraživanjima bilo korisno posebno analizirati podatke za grad Zadar i okolna područja, kako bi se dobila preciznija slika učinkovitosti intervencija. Posebice je važno kako se vrijeme intervencije nije pogoršavalo, odnosno značajno mijenjalo tijekom analiziranog razdoblja, unatoč kontinuiranom povećanju broja hitnih medicinskih poziva zbog STEMI (godišnji porast iznosio je oko 10%). Tijekom pandemijskih godina 2020. i 2021. zabilježen je očekivani pad broja prijevoza bolesnika sa STEMI, vjerojatno zbog zdravstvenih posljedica same pandemije, dodatnog straha od zaraze i posljedičnih promjena u organizaciji zdravstvenoga sustava.

Vrijeme do dolaska u bolnicu, što je ključan čimbenik za uspješnost liječenja STEMI, u prosjeku je iznosilo 50,53 minute. U čak 97% slučajeva prijevoz je obavljen unutar 120 minuta, što je unutar preporučenog vremenskog okvira za hitne intervencije kod STEMI bolesnika, prema smjernicama Europskog kardiološkog društva.¹⁹ Pri tome ipak treba uzeti u obzir i geografska obilježja ispitivanog područja te ograničen broj timova hitne medicine. Iako smjernice stručnih društava u svoje preporuke uvrštavaju i mogućnost prijevoza bolesnika do najbližeg centra za invazivnu kardiologiju osobnim prijevozom, treba reći kako istraživanje Alghamdi i suradnika nije pokazalo značajne razlike u vremenu transporta između prijevoza privatnim vozilima i vozilom hitne medicinske pomoći.²⁰ Međutim, transport ambulantnim vozilom značajno je skratio vrijeme do prvog kontakta bolesnika s osobljem bolničke hitne medicinske službe. Osim toga važno je istaknuti i veću razinu sigurnosti bolesnika u odnosu na prijevoz osobnim vozilom, budući da su tijekom transporta bolesnici pod stalnim nadzorom medicinskog tima. Timovi u vozilu prate vitalne parametre te pružaju osnovnu medicinsku skrb, a u pojedinim slučajevima provode i dodatne intervencije, uključujući farmakološko liječenje. Naše istraživanje pokazalo je kako su prosječne vrijednosti osnovnih vitalnih parametara zadovoljavajuće (prosječni puls iznosio je 86/min, prosječni sistolički tlak 136 mmHg, dijastolički tlak 80 mmHg, a saturacija kisika 94%). Bolesnici koji i u daljnjem tretmanu tijekom PCI ostanu stabilni, rijetko razvijaju komplikacije koje

zahtijevaju dulju medicinsku skrb u jedinicama intenzivnog liječenja. Time se smanjuje pritisak na intenzivne odjele i smanjuju troškovi liječenja.²¹ Ipak, činjenica je kako akutno koronarno zbivanje može biti obilježeno i značajnim komplikacijama u prehospitalnom tijeku zbrinjavanja bolesnika, poput srčanog zastoja, električne ili hemodinamske nestabilnosti s razvojem kardiogenog šoka.²² Tijekom ispitivanog razdoblja stopa preživljenja bolesnika sa STEMI-jem bila je izuzetno visoka, iznoseći 99,27%, uz zabilježenih samo šest smrtnih slučajeva. Iako u prikazanim podacima nije uključena analiza kretanja stope smrtnosti kroz vrijeme, već samo kumulativni ishod, činjenica da je smrtnost ostala vrlo niskog postotka sugerira stabilnu i visoku razinu učinkovitosti sustava. Analiza hrvatske mreže za primarnu perkutanu koronarnu intervenciju pokazala je da se stope smrtnosti nisu značajno mijenjale tijekom sedmogodišnjeg razdoblja, što ukazuje na održavanje visoke kvalitete skrbi, u čemu posebno značajnu ulogu ima ZZHM.²³ Brza aktivacija timova i terenska evaluacija, te žuran, ali istovremeno organiziran i siguran transport bolesnika u odgovarajuću zdravstvenu ustanovu, ključni su čimbenici koji doprinose povoljnim ishodima.

Ograničenja ove studije su prvenstveno u tome što retrospektivna analiza nosi sa sobom rizik od nepotpunih ili netočnih podataka, budući da su informacije prikupljene iz medicinske dokumentacije. To je osobito izraženo u kontekstu bilježenja vremena proteklog od hitnog poziva do izlaska medicinskog tima na teren, gdje su registrirane značajne manjkavosti u evidenciji. Također, postoje varijacije u bilježenju kliničkih podataka od strane različitih medicinskih timova. Osim toga, istraživanje je provedeno isključivo na populaciji jedne županije, bez posebne analize razlika između urbanog (gradskog) i ruralnog (okolnog) područja. Ova činjenica može ograničiti mogućnost generalizacije rezultata na druge regije.

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Dermoidna cista nosa: prikaz bolesnika

Dermoid cyst of the nose: Case report

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Sažetak

U radu smo prikazali dijagnostički i terapijski postupak kod dermoidne ciste nosa, rijetke kongenitalne anomalije. Prikazan je dječak kod kojega je u dobi od pet godina postavljena dijagnoza kongenitalne ciste nosa koja se klinički očitovala kao mekotkivna masa s fistulnim otvorom na sredini vanjskog nosa. Magnetskom rezonancijom isključili smo intrakranijalnu lokalizaciju ciste i utvrdili da je cista smještena ispod nosnih kostiju. Metoda izbora u liječenju ovakvih bolesnika je kompletna kirurška ekscizija. Kod našeg bolesnika za kirurški pristup koristili smo obrnuti T rez koji pruža dobar pristup uz zadovoljavajući estetski rezultat. Dvije godine nakon operacije nalaz je uredan, bez znakova recidiva bolesti.

Ključne riječi: dermoidna cista, dijagnostika, kirurško liječenje

Summary

In this paper, we present the diagnostic and therapeutic procedure for nasal dermoid cyst, a rare congenital anomaly. We present a boy who was diagnosed with a congenital nasal cyst at the age of five. Clinically, it manifested as a soft tissue mass with fistulous opening in the middle of the external nose. Magnetic resonance imaging ruled out intracranial localization of the cyst and determined that the cyst was located under the nasal bones. The method of choice in the treatment of such patients is complete surgical excision. In our patient, we used an inverted T incision for access, which provided good access, with a satisfactory aesthetic result. Two years after surgery, the patient has a normal finding, with no signs of disease recurrence.

Key words: dermoid cyst, diagnostic, surgical treatment

Uvod

Dermoidna cista nosa rijetka je kongenitalna anomalija ektodermalnog i mezodermalnog porijekla. Pojavljuje se u ranom embrionalnom razdoblju, tijekom razvoja sredine lica protruzijom divertikula tvrde moždane ovojnice kroz kristu gali. Divertikul tijekom razvoja involuira, a ukoliko se to ne dogodi dolazi do nastanka ciste.^{1,2} Većina cista lokalizirana je u predjelu vanjskog nosa kao mekana tvorba s izvodnim otvorom koji se može nalaziti od korijena nosa, pa do kolumele.^{2,3,4,5} U odnosu na njihov

smještaj mogu se razlikovati: površne nosne lezije, koštane lezije, intrakranijalne epiduralne i intrakranijalne duralne lezije.^{3,4,5} Ukoliko dođe do infekcije javiti će se oteklina nosa i sekrecija kroz otvor fistule. U sekretu se nerijetko nalaze dlake, što ukazuje na ektodermalno porijeklo ciste.^{1,2,3,4,5} Većina nazalnih dermoidnih cista dijagnosticira se do treće godine života. Ukoliko nema komplikacija, ciste mogu dugo ostati neotkrivene.^{5,6,7} Patohistološki, radi se o ektodermalnoj inkluziji građenoj od fibrozne kapsule obložene skvamoznim epitelom, koja sadrži privjeske kože, poput dlaka i žljezda lojnica i

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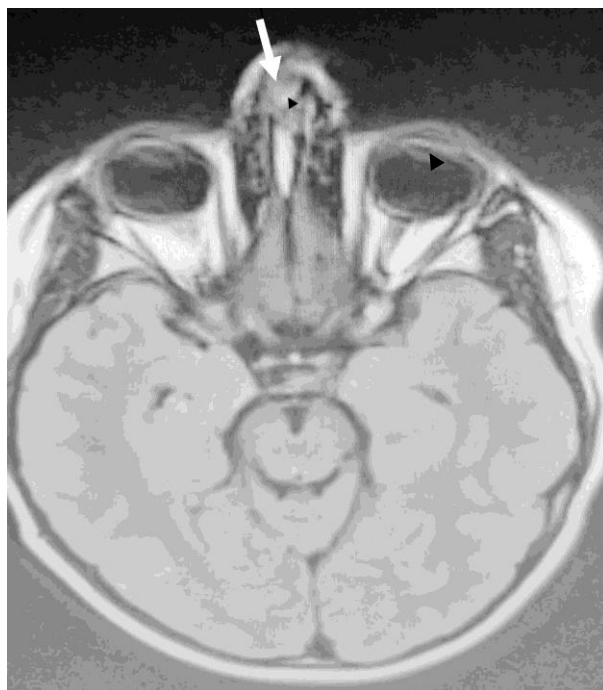
znojnica. Ako sadrži samo skvamozni epitel može se koristiti pojam epidermoidna cista.^{1,2,3,4,5,6,7} Magnetskom rezonancijom ili kompjutoriziranom tomografijom obavezno treba isključiti intrakranijalnu lokalizaciju ciste.^{8,9,10} Smatra se da čak u 12% slučajeva dolazi do intrakranijalnog širenja ciste te pritiska na čeonu režanj velikog mozga.^{5,6,7,8} U diferencijalnoj dijagnozi dolaze u obzir prvenstveno encefalokela, epiduralna cista, neurofibrom, teratom, hemangiom i gliom.^{5,6,7,8} Rana dijagnoza i kirurško liječenje preporučuje se kako bi se izbjegnula lokalna atrofija kosti i širenje nosa usljed pritiska ciste te prevenirale moguće infekcije s intrakranijalnim komplikacijama.^{8,9} Operacija se predlaže u dobi od druge do pete godine života.^{10,11} Svaki kirurški postupak mora omogućiti adekvatan pristup kojim se u cijelosti odstranjuje cista i olakšava rekonstrukcija nastalog defekta. Koristi se više kirurških tehnika, od otvorene rinoplastike, frontalne kraniotomije, endoskopskih pristupa, pa do jednostavne ekscizije i ekstirpacije ciste. Koja će se tehnika koristiti ovisi prvenstveno o lokalizaciji ciste i dobi djeteta.^{10,11,12,13}

Prikaz bolesnika

Dječak u dobi od pet godina dolazi u pratnji roditelja zbog otoka nosa koji se u više navrata povezivao s udarcem u predjelu čela. Prvi put je pregledan u dobi od dvije godine od strane pedijatra, kada je radiološki bio vidljiv otok mekih česti bez prekida kontinuiteta nosnih kostiju. Prema kazivanju roditelja dječak je hiperaktivan, često pada i udara se. Kontrolira se kod psihologa zbog blagog poremećaja iz spektra autizma i poremećaja pozornosti s hiperaktivnošću. Prilikom pregleda prisutan je tjestasti otok sredine čela i korijena nosa s vidljivim otvorom u predjelu sredine vanjskog nosa na koji, prema kazivanju majke, ponekad izlazi sirasti sadržaj u kojem ima i dlaka. Klinički je postavljena dijagnoza kongenitalne ciste nosa s fistulom (Slika 1). Magnetskom rezonancijom potvrđena je cistična struktura ispod nosnih kostiju, bez intrakranijalnog širenja veličine 9×5×6mm, dok se postojanje fistule zbog nemira djeteta nije moglo potvrditi (Slika 2). Prijedlog da se dijete uspava i ponovi pretraga, roditelji nisu prihvatili. Endoskopija nosa u ambulantnim uvjetima nije bila moguća. Roditeljima je predložen i obrazložen operacijski zahvat, kao i moguće kasnije komplikacije vezane uz razvoj vanjskog nosa. Nakon pristanka roditelja, u općoj anesteziji sondirana je fistula.

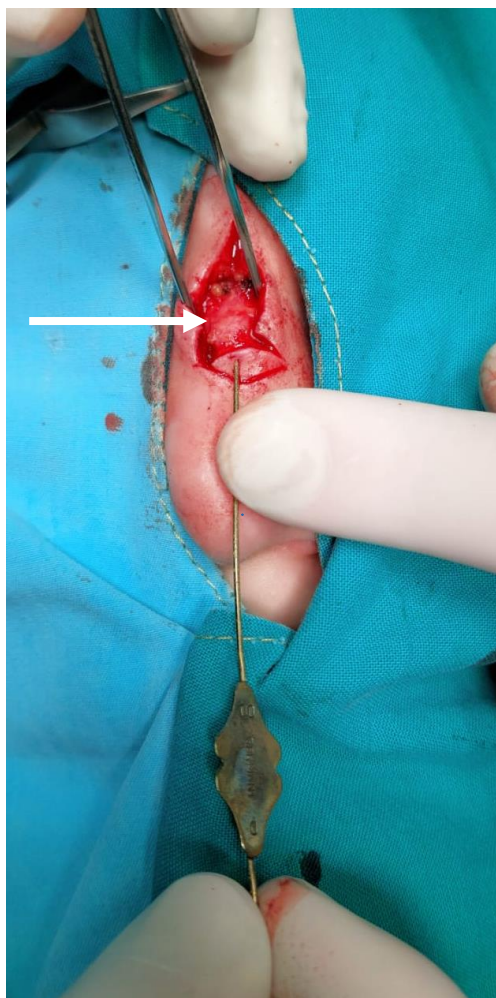


Slika 1. Zaokružen fistulni otvor na sredini nosa
Figure 1 Rounded fistula opening in the middle of the nose



Slika 2. Magnetska rezonancija- strelica pokazuje cistu lokaliziranu ispod nosnih kostiju
Figure 2 Magnetic resonance-the arrow shows a cyst localised under the nasal bones

Pomoću tanke sonde ušli smo cijelom dužinom, oko 15mm, u fistulni kanal (Slika 3).



Slika 3. Strelica pokazuje „ispreparirani“ fistulni kanal koji vodi ispod nosnih kostiju
Figure 3 The arrow shows a “prepared” fistula channel leading under the nasal bones

Na koži dorzuma nosa napravili smo obrnuti T rez čiji je horizontalni krak uključivao otvor fistule. Fistula je završavala defektom nosnih kostiju ispod kojih se nalazio prostor ispunjen bjelkastim, sirastim sadržajem i nakupinom dlaka. Oštrom kiretom pažljivo smo očistili epitel koji je oblagao šupljinu te endoskopom utvrdili da nema komunikacije s unutrašnjošću nosa. Širina otvora između nosnih kostiju bila je oko 4mm te ga nismo zatvarali osteotomijom (Slika 4). Patohistološki nalaz potvrdio je da se radi o sadržaju ektodermalne ciste s adneksima. Dječak redovito dolazi na kontrole svakih šest mjeseci. Tijekom dvije godine nakon operacijskog zahvata nema znakova recidiva tvorbe. Nos dječaka se proporcionalno razvija, a ožiljak na koži estetski je prihvatljiv.



Slika 4. Koštani defekt nakon odstranjenja ciste
Figure 4 Bone defect after cyst removal

Rasprava

Dermoidna cista nosa najčešća je od svih kongenitalnih anomalija sredine lica.^{1,2,3,4} Javlja se između sedmog i osmog tjedna intrauterinog razvoja kao posljedica defekta neuralne cijevi, kada kroz foramen cekum dura dolazi u kratkotrajni kontakt s ektodermom.^{1,2,3,4,5} Povlačenjem dure ponekad se intrakranijalno može povući i ektoderm, tako da lokacija dermoidne ciste može biti intrakranijalno i ekstrakranijalno.^{1,2,3,4,5} Češće se javljaju kod muškog spola.^{3,4,5,6} Infekcija kao prvi simptom je rijetka a kada se desi nastaje zamjetno zadebljanje u području nosa, popraćeno sekrecijom kroz izlazni otvor.^{5,6,7,8} Dijagnoza bolesti postavlja se kliničkim pregledom. Neki autori tvrde da plač ili pritisak na venu jugularis, tzv. Furstenbergerov test, može dovesti do povećanja ili pulzacije ciste ukoliko postoji intrakranijalna lokalizacija, što je prema našem mišljenju nepouzdan.^{9,10,11,12} Kod bolesnika se preporučuje pregled oftalmologa i neuropedijatra, uz obaveznu endoskopiju nosa, kako bi se isključila

intranazalna lokalizacija tvorbe.^{6,7,8,9,10} Radiološke pretrage potvrđuju konačan smještaj ciste. Kompjutorizirana tomografija i magnetska rezonancija, kao slikovne metode pretrage, imaju svaka svoje mjesto u postavljanju dijagnoze. Defekt kosti prednje lubanjske jame ili među nosnim kostima, bolje će se uočiti na kompjutoriziranoj tomografiji.^{11,12,13,14,15,16} Neki autori rade magnetsku rezonanciju u svim slučajevima, dok ju drugi indiciraju s gadolinijem kao kontrastom samo u slučaju bifidne kriste gali.^{12,13,14,14,15,16} Opće-prihvaćeni postupak liječenja je kompletna kirurška ekscizija, čime se preveniraju komplikacije i recidivi.^{17,18,19} Za kompletnu eksciziju i dobru pristupačnost cisti treba planirati: moguće osteotomije nosnih kostiju, rekonstrukciju nosnih kostiju, reparaciju kribriiformne ploče, te prihvatljiv ožiljak.^{16,17,18,19} Čak i jednostavne subkutane ekscizije koje se nalaze na vršku ili dorzumu nosa, mogu poremetiti njegov estetski izgled.^{14,15,16,17,18,19} Ukoliko se dokaže intrakranijalna ekstenzija ciste, kombinira se intrakranijalni i transnazalni pristup.^{17,18,19} Neki autori rade otvorenu dekortikacijsku rinoplastiku, uz poprečnu eliptičnu eksciziju kože oko otvora fistule, ostavljajući fibrozni trakt vezan uz cistu.^{14,15,16,17,18,19} Dekortikacijska tehnika s pomoćnim rezom oko fistule, prema našem mišljenju, ne pruža bolji pristup, niti ostavlja manji ožiljak. Endoskopski pristup, osobito kod male djece, vrlo je teško izvodiv. Ukoliko prilikom operacije dođe do većeg otvaranja krova nosnih kostiju, indicirane su dodatne osteotomije.^{15,16,17,18,19} U našem slučaju koristili smo obrnuti T -rez s horizontalnim krakom oko otvora fistule, čime smo najbolje mogli prikazati kanal fistule. Umetanjem okulističke sonde u kanal fistule, značajno se olakšava prepariranje istog. Dodatne osteotomije kod našeg bolesnika nismo radili. Kako bi se na vrijeme uočio poremećaj u rastu nosa, potrebno je dugotrajno praćenje, a kod sumnje na recidiv potrebne su kontrolne radiološke pretrage.^{17,18,19}

Zaključak

Kod svakog odebljanja vanjskog nosa djeteta, koje ne prolazi, treba posumnjati na dermoidnu cistu i pažljivo potražiti fistulni otvor na koži. Radi dobi djeteta radiološke pretrage potrebno je raditi u općoj anesteziji. Time se dobivaju kvalitetnije snimke i izbjegava ponavljanje pretrage. Kod ekstrakranijalne lokalizacije ciste pristup obrnutim T rezom je zadovoljavajući.

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The bibliography is quoted:

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Mention all the authors, if there are six or less, if seven or more, then mention the first three and add et al. in the English bibliography.

Soter Na Wasserman SJ, Austebn KF. Cold urticarial: release into the circulation of histamine and eosinophil chemostatic factor of anaphylaxis during cold challenge.

N Engl J Med. 1976;194:687-90.

Čupić V, Čupić N, Dražančić A et al. Neuro-psihološki razvoj nedonoščadi. Liječ Vjesn 1983; 105:343-6.

Web article

Daszak P, Olival KJ, Li H. A strategy to prevent future epidemics similar to the 2019-n CoV outbreak. Bioasafety Health 2020 Accessible at the address: <http://dx.doi.org/10.1016/j.bsheal.2020.01.003> Date accessed: March 22, 2020

Mutual author

The Committee of Enzymes of the Scandinavian Society for Clinical Chemistry and Clinical Physiology. Recommended method for the

determination of gamma glutamyl transferase in blood. Scand J Clin Lab Invest 1967;36:119-25.

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Anonymous. Fetal nicotine poisoning. J Amer Med Ass 1938;110:143-45.

Without author

Coffee drinking and cancer of the pancreas (editorial) Br Med J 1981;283:628.

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News article

Matić-Glažar Đ. Etičke dileme. Novi list 1985. Dec 13;11.

b) books, monographs, proceedings, doctoral or graduate thesis

State the year of the print and the page numbers of the chapter in the book or proceedings citing the quote after the mentioned quote. In case of a doctoral, diploma or similar thesis, except for the year of printing, the page on which the citation is quoted should be written.

One book author

Richeter B. Medicinska parazitologija. 3. izd. Zagreb: Liber, 1982;112-3.

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Zergollen-Čupak Lj, ed. Humanica genetica. Zagreb: Jumena, 1983;17-60.

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Šimurina T. Model predviđanja povraćanja nakon anestezije pri laparoskopskim ginekološkim zahvatima [dorski rad]. Medicinski fakultet Sveučilišta u Zagrebu, 2011;98.

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