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Analiza mortaliteta periferne arterijske bolesti od 2011. do 2020. godine po regijama u Republici Hrvatskoj

Analysis of Mortality from Peripheral Artery Disease from 2011 to 2020 by Region in the Republic of Croatia

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SAŽETAK: Periferna arterijska bolest (PAB), uz ishemijsku bolest srca i moždani udar, među najznačajnijim je dijagnostičkim podskupinama kardiovaskularnih bolesti i jedan od vodećih javnozdravstvenih problema. U Europskoj je uniji tom bolešću zahvaćeno oko 17 milijuna ljudi. Stvarna incidencija i prevalencija višestruko nadmašuju procjene i bolest je nedostatno dijagnosticirana. Republika Hrvatska ima visoko opterećenje i mortalitet od kardiovaskularnih bolesti. Svrha je ovoga rada izračunati i usporediti dobno standardizirane stope moraliteta od PAB-a prema statističkim regijama 2. razine i spolu od 2011. do 2020. godine.

Iz bolničkih informacijskih sustava odabrane su dijagnoze koje se u kliničkoj praksi primjenjuju za kodiranje smrti od PAB-a te za kodiranje interventnih i dijagnostičkih postupaka, a dopunjene su dijagnozama iz drugih istraživanja. Na temelju podataka iz Baze umrlih Hrvatskog zavoda za javno zdravstvo od 2011. do 2020. godine izračunati su proporcionalni mortalitet, postotna promjena za 2020. godinu u odnosu prema 2011. godini i dobno specifične stope na 100 000 stanovnika. U statističkoj analizi primjenjivane su deskriptivne i analitičke statističke metode.

Među 16 799 umrlih bile su 10 352 žene i 6447 muškarca. Dijagnoza I70.9 Generalizirana i nespecificirana ateroskleroza imala je najveći udio – 43,2 %. Najviše dobno standardizirane stope mortaliteta u muškaraca i žena imala je Sjeverna Hrvatska, a najmanje Jadranska Hrvatska. Među regijama postoje značajne razlike dobno standardiziranih stopa mortaliteta u obaju spolova.

Ovo je istraživanje također pokazalo porast trenda od 2018. godine. Kako bi se smanjio mortalitet od PAB-a, potrebno je uložiti napore u prevenciju i ranu dijagnostiku te sustavno prikupljati podatke o kliničkim ishodima liječenja bolesnika.

SUMMARY: Peripheral artery disease (PAD) is, along with ischemic heart disease and stroke, among the most significant diagnostic subgroups of cardiovascular diseases and one of the leading public health issues. Approximately 17 million people are affected by this disease in the European Union. Its real incidence and prevalence are several times higher than the estimates for this disease, and it is insufficiently diagnosed. The Republic of Croatia has a high burden and mortality from cardiovascular diseases. The goal of this analysis was to calculate and compare the age-standardized mortality rates for PAD based on sex and on 2nd level statistical regions in Croatia in the period from 2011 to 2020.

Hospital information systems were searched for diagnoses that are applied for coding death from PAD in clinical practice and for coding interventional and diagnostic procedures, which were also supplemented by diagnoses from other studies. Based on data from the Croatian Institute of Public Health Mortality Database from 2011 to 2020, we calculated proportional mortality, percentage change for 2020 in comparison with 2011, and age-specific rates per 100 000 inhabitants. Statistical analysis used descriptive and analytic statistical methods.

Among the 16 799 people who died, 10 352 were women and 6447 were men. Diagnosis I70.9, Generalized and non-specific atherosclerosis, was the most common at 43.2%. The highest age-standardize mortality rates in men and women were found in Northern Croatia, and the lowest in Adriatic Croatia. There were significant differences between regions in age-standardized mortality rates in both sexes.

This study also showed an increase in the trend since 2018. In order to reduce mortality from PAD, efforts should be invested in prevention and early diagnostics and implementing systematic data collection on clinical outcomes for patient treatment.

KLJUČNE RIJEČI: periferna arterijska bolest, mortalitet, dobno standardizirane stope, Republika Hrvatska.

KEYWORDS: peripheral artery disease, mortality, age-standardized rates, Republic of Croatia.

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Uvod

Pod pojmom periferna arterijska bolest (PAB) razumijevamo bolest krvnih žila smještenih izvan srca i mozga. Najčešće je uzrokuje ateroskleroza, a mnogo rjeđe aneurizma, upala ili udruženo djelovanje prije navedenih patofizioloških procesa.[1] U kliničkoj se praksi ovaj termin primjenjuje za opis kronične aterosklerotske opstruktivne bolesti donjih ekstremiteta.

Periferna arterijska bolest, uz ishemijsku bolest srca (IBS) i moždani udar, jedna je od najznačajnijih dijagnostičkih podskupina kardiovaskularnih bolesti (KVB). Ubraja se u vodeće javnozdravstvene probleme i, prema procjenama, u Europskoj uniji (EU) tom je bolešću zahvaćeno oko 17 milijuna ljudi ili 3,4 % populacije.[2] Opterećenje tom bolešću u porastu je, i od 2000. do 2010. godine njezina se prevalencija u svijetu povećala za 23 %.[3]

Prema epidemiološkim istraživanjima i iskustvima iz kliničke prakse, PAB je u usporedbi s IBS-om nedostatno dijagnosticirana bolest, čija stvarna incidencija i prevalencija u svijetu višestruko nadmašuju procjene.[1,4] Velik broj bolesnika s IBS-om također ima klinički nemanifestnu PAB, koja pogoršava ishode liječenja. Zbog toga se ističu važnost i nužnost probira ovakvih bolesnika tijekom kliničke obradbe.[5,6]

Čimbenici su rizika istovjetni tradicionalnim čimbenicima rizika za druge KVB-e, a najznačajniji su pušenje, dija-

Introduction

The term peripheral artery disease (PAD) denotes the disease of blood vessels outside the heart and the brain. It is most commonly caused by atherosclerosis, and much less frequently by aneurysm, inflammation, or the joint effect of these pathophysiological processes.[1] In clinical practice, the term PAD is used to describe chronic atherosclerotic obstructive diseases of the lower extremities.

Peripheral artery disease is, along with ischemic heart disease (IHD) and stroke, among the most significant diagnostic subgroups of cardiovascular diseases (CVDs). It represents one of the leading public health issues, and it is estimated that approximately 17 million people, i.e. 3.4% of the population, are affected by this disease in the European Union.[2] The burden of this disease is increasing, and its global prevalence has increased by 23% between 2000 and 2010.[3]

Based on epidemiological research and experience from clinical practice, PAD is an insufficiently diagnosed disease in comparison with IHD, and its real incidence and prevalence are several times higher than current estimates.[1,4] A large number of patients with IHD also has clinically non-manifesting PAD, which negatively influences treatment outcomes. Therefore, the importance and necessity of screening such patients during clinical examination have been emphasized.[5,6]

Risk factors are identical to the traditional risk factors for other CVDs, the most important being smoking, diabetes, hyperten-

betes, arterijska hipertenzija i hiperkolesterolemija.[7] Republika Hrvatska je članica Europske unije visoko opterećena kardiovaskularnim morbiditetom i mortalitetom.[8] Sustavna istraživanja koja bi objasnila izrazito visoke vrijednosti epidemioloških pokazatelja nisu provedena, međutim, neupitno je da su one pripisive manjku prevencije, kao i nedostatnoj učinkovitosti zdravstvenih intervencija.[9] Isto tako, teško je procijeniti stvarne učinke medicinskih intervencija jer na razini sekundarne i tercijarne medicinske skrbi nema sustavnog prikupljanja i usporedbe ishoda liječenja zbog nepovezanosti bolničkih informacijskih sustava medicinskih ustanova.[10] Od epidemioloških pokazatelja kojima se može prikazati dinamika kretanja bolesti u populaciji na individualnoj razini sustavno su dostupni samo podatci o uzrocima smrti.

Svrha je ovoga rada usporediti dobno standardizirane stope moraliteta od PAB-a prema statističkim regijama 2. razine (NUTS-2) i spolu u Republici Hrvatskoj od 2011. do 2020. godine.

Materijali i metode

IZVORI I PRIKUPLJANJE PODATAKA

Periferna arterijska bolest u kliničkoj praksi obuhvaća širok spektar dijagnoza i zamijećene su velike razlike unutar i između zemalja. Zbog mogućnosti sustavno pogrešne klasifikacije među bolnicama u smislu odabira dijagnoza i veće kliničke utemeljenosti, dva su liječnika specijalista, interventni radiolog iz Kliničke bolnice Dubrava i internist iz Kliničkog bolničkog centra Zagreb, iz bolničkih informacijskih sustava navedenih ustanova odabrali dijagnoze koje se primjenjuju u kodiranju PAB-a te interventnih i dijagnostičkih postupaka u ovakvih bolesnika.[2,11] Navedene su dijagnoze dopunjene dijagnozama koje su primjenjivane u drugim istraživanjima.[3,12-14]

U konačnici su iz Baze umrlih HZJZ-a za razdoblje od 2011. do 2020. godine dobiveni podatci po petogodišnjim dobnim skupinama od 0 do 85+, spolu i županijama te dijagnoze navedeni u **tablici 1**.

Popis stanovnika po županijama preuzet je s mrežnih stranica Državnog zavoda za statistiku na temelju procjena načinjenih sredinom svake od navedenih godina.[15]

Republika Hrvatska je, prema Nacionalnoj klasifikaciji statističkih regija 2021., podijeljena u četiri NUTS-2 regije: (i) Grad Zagreb, (ii) Sjeverna Hrvatska, (iii) Panonska Hrvatska i (iv) Jadranska **(slika 1)**.[16]

IZRAČUN OPĆIH, DOBNO SPECIFIČNIH I DOBNO STANDARDIZIRANIH STOPA

Za svaku od prethodno navedenih dijagnoza izračunat je proporcionalni mortalitet kao udio umrlih od pojedinih dijagnoza u ukupnome broju umrlih od PAB-a od 2011. do 2020. god. Postotna promjena izračunata je 2020. godine u odnosu prema 2011. godini.

Opće stope za ukupnu populaciju za 2020. god. prikazane su kao ukupan broj umrlih od navedenih dijagnoza na 100 000 stanovnika.[17] Dobno specifične stope primijenjene su za izračun dobno standardiziranih stopa na temelju Revidirane europske standardne populacije (RESP) 2013 tako da su dobno specifične stope (od 0 do 85+) pomnožene s ponderima standardnih populacija. RESP 2013 utemeljena je na projekcijama populacija zemalja članica EU-27 i članica Europskog udruženja, i hypercholesterolemia.[7] The Republic of Croatia is an EU country with a high burden of cardiovascular morbidity and mortality.[8] No systematic studies that would explain the extremely high values of epidemiological indicators have been conducted, but it is clear that these values can be ascribed to a lack of prevention and insufficient effectiveness of healthcare intervetions.[9] It is also difficult to estimate the true effects of medical interventions, since there is a lack of data collection at the secondary and tertiary healthcare levels and a lack of data comparing treatment outcomes due to the lacking interconnectedness of hospital information systems in medical institutions.[10] Of the epidemiological indicators that can be used to show the dynamics of the disease in the population at the individual level, only data on cause of death are systematically available.

The goal of this study was to compare the age-standardized mortality rates due to PAD according to 2nd level statistical regions (NUTS-2) and according to sex in the Republic of Croatia from 2011 to 2020.

Materials and methods

SOURCES AND DATA COLLECTION

In clinical practice, peripheral artery disease encompasses a whole spectrum of diagnosis, and large differences have been observed both within and among different countries. Due to the possibility of misclassification bias among hospitals in the context of choice of diagnosis and in order to achieve higher clinical reliability, two specialist physicians, namely a interventional radiologist from the Dubrava Clinical Hospital and an internist from the Zagreb Clinical Hospital Center, were engaged to examine hospital information systems and choose the diagnoses that are applied in coding PAD and interventional and diagnostic procedures in these patients.[2,11] These diagnoses were supplemented by diagnoses used in other studies.[3,12-14]

Subsequently, the Mortality Database of the Croatian Institute of Public Health was used to collect data for the period from 2011 to 2020, stratified by five-year age groups for patients between the ages of 0 and 85+, by sex, and by county, as shown in **Table 1**.

The population census by county was taken from the webpages of the Croatian Bureau of Statistics based on estimates made at the middle of each of the examined years.[15]

Based on the National Classification of Statistical Regions from 2021, the Republic of Croatia is divided into four NUTS-2 regions: (1) the City of Zagreb, (ii) Northern Croatia, (iii) Pannonian Croatia, and (iv) Adriatic Croatia (**Figure 1**).[16]

CALCULATING GENERAL, AGE-SPECIFIC, AND AGE-STANDARDIZED RATES

For each of the diagnoses listed above, we calculated proportional mortality as the ratio of deaths from individual diagnoses in the total number of PAD deaths from 2011 to 2020. The percentage change was calculated for 2020 in comparison with 2011.

General mortality rates for the total population for 2020 are shown as the total number of deaths from the examined diagnoses per 100 000 inhabitants.[17] Age-specific rates were applied to the calculation of age-standardized rates based on the revised European Standard Population (RESP) from 2013 by multiplying age-specific rates (from age 0 to 85+) with

TABLE 1. Diagnoses used in peripheral artery disease coding and interventional and diagnostic procedures.

E10.5 Insulin-dependent diabetes with peripheral circulatory complications
E10.7 Insulin-dependent diabetes with multiple complications
E11.5 Non-insulin-dependent diabetes mellitus with peripheral circulatory complications
E11.7 Non-insulin-dependent diabetes mellitus, with multiple complications
E13.7 Other specified diabetes, with multiple complications
E14.5 Diabetes mellitus, unspecified, with peripheral circulatory complications
E14.7 Diabetes mellitus, unspecified, with multiple complications
I70.0 Atherosclerosis of the aorta
I70.1 Atherosclerosis of renal artery
I70.2 Atherosclerosis of arteries of limbs
I70.8 Atherosclerosis of other arteries
I70.9 Generalized and unspecified atherosclerosis
I73.9 Disease of peripheral blood vessels, unspecified
I74.2 Embolism and thrombosis of the arteries of the hand
I74.3 Embolism and thrombosis of leg arteries
I74.4 Embolism and thrombosis of arteries of limbs, unspecified
I74.5 Embolism and thrombosis of iliac artery
I74.8 Embolism and thrombosis of other arteries
I74.9 Embolism and thrombosis of unspecified arteries

FIGURE 1. Map of regions and associated counties in Croatia.

ženja slobodne trgovine za razdoblje od 2011. do 2030. godine i podijeljena u petogodišnje dobne skupine, uz iznimku prve dobne skupine s dobnom kategorijom 0, dok je najstarija dobna skupina 95+.[18,19]

STATISTIČKA OBRADA

Za analizu podataka i prikaza mape uporabljen je računalni program za tabličnu pohranu i obradu podataka Microsoft Excel 365 (Microsoft Corporation, Redmond, Washington, SAD). U statističkoj analizi primjenjivane su metode deskriptivne i analitičke statistike. T-test i ANOVA uporabljeni su za usporedbu kontinuiranih varijabli, a kao razina statističke značajnosti uzeta je vrijednost p <0,05. Statističke analize napravljene su primjenom statističkog programa *SPSS Statistics 26* (IBM, Amonk, New York, SAD) i *JASP 0.17.2*.[20]

Rezultati

APSOLUTAN BROJ UMRLIH I PROPORCIONALNI MORTALITET

Od 2011. do 2020. ukupno je od PAB-a umrlo 16 799 osoba, 10 352 žene i 6447 muškarca. Među ukupno umrlima najveći je udio dijagnoze I70.9 Generalizirana i nespecificirana ateroskleroza (43,2 %), nakon čega slijede I70.2 Ateroskleroza arterija udova (14,3 %) i E14.7 Šećerna bolest, nespecificirana, s višestrukim komplikacijama (11,5 %), dok su ostali udjeli prikazani na **slici 2**.

Postotna promjena od 2011. do 2020. za muškarce prema regijama bila je sljedeća: Grad Zagreb 60,71 %, Jadranska Hrvatska 21,43 %, Panonska Hrvatska 20,45 % i Sjeverna Hrvatska 10,94 %. Za žene je ranije navedena postotna promjena iznosila: Grad Zagreb 38,13 %, Jadranska Hrvatska 13,49 %, Panonska Hrvatska 9,17 % i Sjeverna Hrvatska 8,61 % **(slika 3)**.

Omjer najviše i najniže stope za 2020. godinu bio je manji u muškaraca, a iznosio je 1,4 (Grad Zagreb *vs.* Jadranska Hrweighted standard population averages. RESP 2013 is based on population projections for EU-27 member states and members of the European Free Trade Association for the period from 2011 to 2030 and is divided into five-year age groups, with the exception of the first group with the age category of 0, and with the oldest age group being 95+.[18,19]

STATISTICAL ANALYSIS

Data analysis and mapping were performed in the Microsoft Excel 365 computer program for spreadsheeting and data analysis (Microsoft Corporation, Redmond, Washington, USA). Statistical analysis employed descriptive and analytic statistical methods. The T-test and ANOVA were used for comparing continuous variables, and statistical significance was set at p<0.05. Statistical analyses were performed using the SPSS Statistics 26 program (IBM, Amonk, New York, USA) as well as JASP 0.17.2.[20]

Results

ABSOLUTE MORTALITY NUMBERS AND PROPORTIONAL MORTALITY

A total of 16 799 persons died from PAD from 2011 to 2002, of whom 10 352 were women and 6447 were men. Among the total number of deaths, the cause with the highest ratio was I70.9, Generalized and non-specific atherosclerosis (43.2%), followed by I70.2, Atherosclerosis of arteries in the limbs (14.3%), and E14.7, Diabetes, non-specific, with multiple complications (11.5%), with other ratios shown in **Figure 2**.

The percentage change from 2011 to 2020 for men by region was as follows: the City of Zagreb 60.71%, Adriatic Croatia 21.43%, Pannonian Croatia 20.45%, and Northern Croatia 10.94%. For women, this percentage change was: the City of Zagreb 38.13%, Adriatic Croatia 13.49%, Pannonian Croatia 9.17%, and Northern Croatia 8.61% (**Figure 3**).

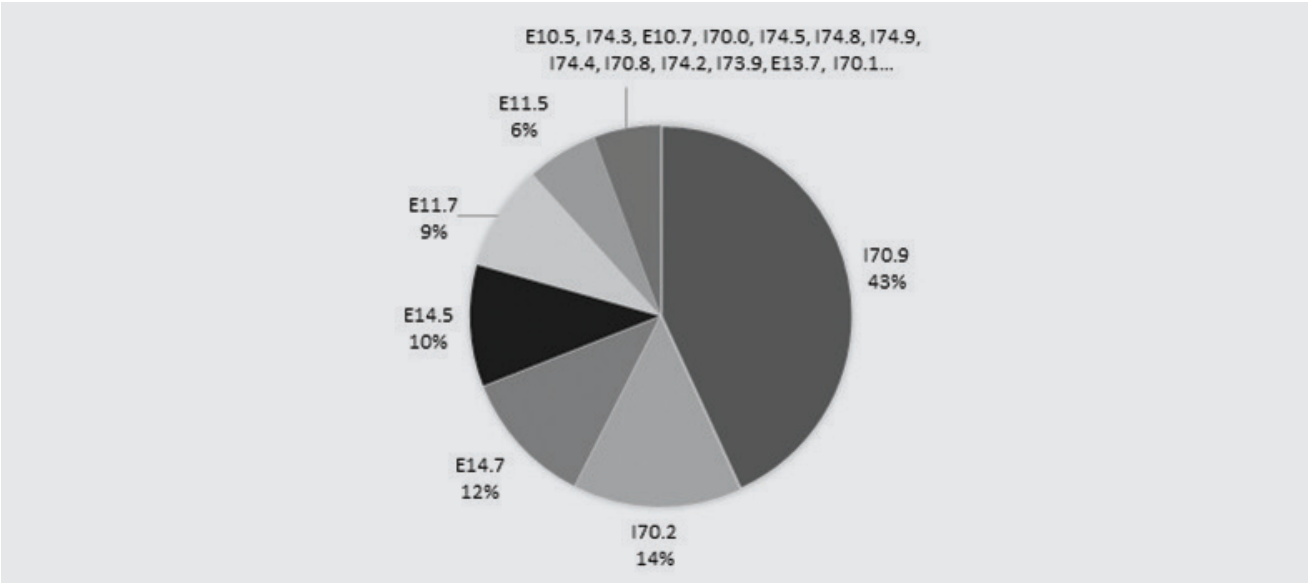

FIGURE 2. Proportional mortality according to the International Classification of disease diagnoses, both sexes, 2011-2020.
M = males; F = females.

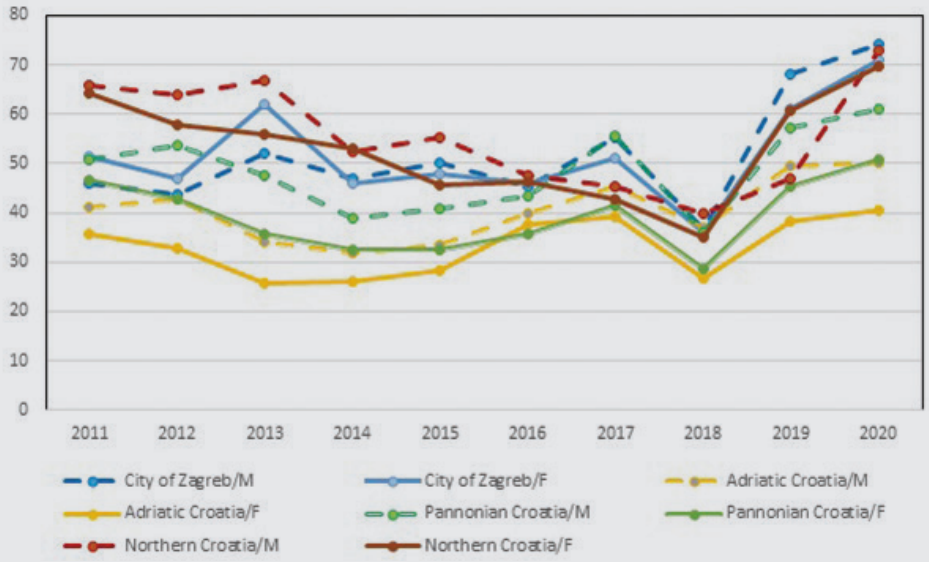

FIGURE 3. Age-standardized rates of peripheral artery disease / 100 000 population (males and females).

vatska), u odnosu prema ženama u kojih je iznosio 1,7 (Grad Zagreb *vs.* Jadranska Hrvatska).

Sjeverna Hrvatska ima najviše dobno standardizirane stope mortaliteta na 100 000 i u muškaraca i u žena – 55,62 i 53,10 **(tablica 2)**. Nakon toga slijede Grad Zagreb, Panonska Hrvatska i Jadranska Hrvatska. Srednje vrijednosti stopa mortaliteta u muškaraca više su za sve NUTS-2 regije, osim kod Grada Zagreba, gdje su više stope zabilježene u žena.

Zamijećene su statistički značajne razlike stopa između muškaraca i žena. U Panonskoj Hrvatskoj muškarci imaju mnogo više stope mortaliteta od žena (p = 0,02), što je slučaj i u Jadranskoj Hrvatskoj (p = 0,01), dok su u Gradu Zagrebu (p = 0,97) i Sjevernoj Hrvatskoj (p = 0,61) stope slične.

Razlike među prosječnim dobno standardiziranim stopama mortaliteta od PAB-a za muškarce su statistički značajne (p < 0,001). Jadranska Hrvatska ima mnogo niže stope od Sjeverne Hrvatske (p < 0,001), dok među ostalim NUTS-2 regijama nema značajnih razlika. U žena su međuregionalne razlike statistički značajne (p < 0,001). Grad Zagreb ima mno-

The ratio between the highest and lowest rates for 2020 was lower in men, i.e. 1.4 (the City of Zagreb vs. Adriatic Croatia), in comparison with women, in whom it was 1.7 (the City of Zagreb vs. Adriatic Croatia).

Northern Croatia had the highest age-standardized mortality rates per 100 000 inhabitants both in men and in women – 55.62 and 53.10 (**Table 2**). It was followed by the City of Zagreb, Pannonian Croatia, and Adriatic Croatia. Mean values for mortality rates in men were higher for all NUTS-2 regions except for the City of Zagreb, where higher rates were observed in women.

We observed statistically significant differences in mortality rates in men and women. In Pannonian Croatia, men had significantly higher mortality rates in comparison with women (p=0.02), which was also the case in Adriatic Croatia (p=0.01), whereas the rates were similar in the City of Zagreb (p=0.97) and in Northern Croatia (p=0.61).

The differences in average age-standardized mortality rates from PAD for men were statistically significant (p<0.001). Adri-

TABLE 2. Age-standardized mortality rates (per 100.000) from peripheral artery disease by region and sex, 2011-2020.

		City of Zagreb	Adriatic Croatia	Pannonian Croatia	Northern Croatia
Men		51.78	40.53	48.52	55.62
	SD	11.44	6.51	8.47	11.11
	Range	36.51 – 74.07	31.86 – 50.14	36.13 – 61.13	39.80 – 73.00
Women		51.94	33.05	39.17	53.10
	SD	10.07	5.87	7.20	10.62
	Range	36.00 – 71.00	25.66 – 40.37	28.65 – 50.81	35.01 – 69.65

SD = standard deviation

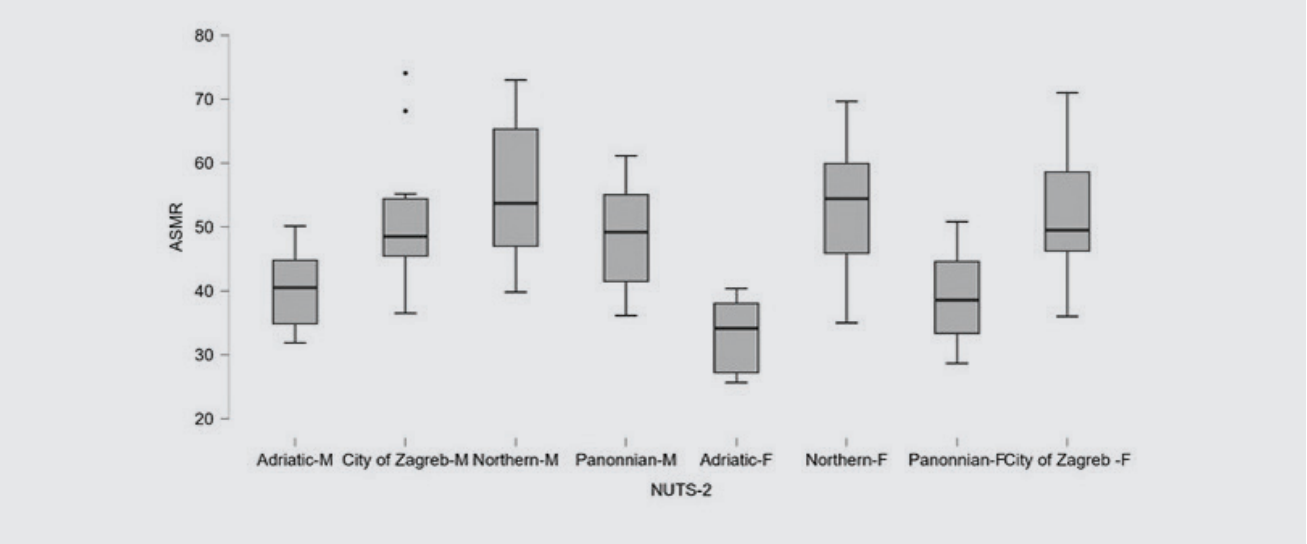

FIGURE 4. Average age-standardized mortality rates from peripheral artery disease 2011-2020 (men and women).
ASMR = age-standardized mortality rates; M = males; F = females

go više stope od Jadranske Hrvatske (p < 0,001) i Panonske Hrvatske (p = 0,01), a slične sa Sjevernom Hrvatskom (p = 0,99). Razlike su statistički značajne između Sjeverne Hrvatske i Jadranske Hrvatske (p < 0,001); Sjeverne Hrvatske i Panonske Hrvatske (p < 0,001) te Jadranske Hrvatske i Panonske Hrvatske (p = 0,04) **(slika 4)**.

Diskusija

U ovom su radu prvi put na nacionalnoj i regionalnoj razini analizirane dobno standardizirane stope mortaliteta od PAB-a i trend od 2011. do 2020. godine. Od 2018. godine mortalitet se u svim NUTS-2 regijama povećao uz znatne regionalne razlike prosječnih stopa mortaliteta po spolu.

Među 16 799 umrlih od PAB-a, najveći proporcionalni mortalitet imale su dijagnoze I70.9 (43,2 %) i I70.2 (14,3 %), nakon čega slijede dijagnoze povezane sa šećernom bolešću, što je objašnjivo velikim aterogenim potencijalom te bolesti **(slika 2)**. Učinci dijabetesa na morbiditet i mortalitet stanovništva neupitno su podcijenjeni i u službenoj statistici i u kliničkoj praksi.[21,22] U svim NUTS-2 regijama postotna promjena mortaliteta u 2020. godini u odnosu prema 2011. godinu za muškarce i žene najveća je u Gradu Zagrebu; 60,71 % i 38,13 %. Što se muškaraca tiče, nakon Grada Zagreba, sa sličnim postotcima slijede Jadranska i Panonska Hrvatska, i u konačnici Sjeverna Hrvatska. U žena je poredak isti, ali su postotna povećanja niža. Porast standardiziranih stopa mortaliteta razvidan je od 2018. godine **(slika 2**, **slika 3)**.

Takav trend porasta zamijećen je i u drugim zemljama EU-a. Naime, od 1990. do 2017. godine sve EU15+ države bilježe porast mortaliteta u žena, a u muškaraca njih čak 16 od ukupno 19. Negativan trend zabilježen je u Italiji (−25,1 %), Portugalu (−1,9 %) i Švedskoj (−0,6 %).[4,23] Etiologija porasta mortaliteta je multifaktorska i, zasigurno, većim dijelom pripisiva samoj dinamici kretanja bolesti u populaciji. Bolja registracija uzroka smrti također je mogla pridonijeti pozitivnom trendu jer su nedostatno prepoznavanje ove bolesti u općoj populaciji i smanjena osviještenost globalan problem. Istraživanja u druatic Croatia had significantly lower rates than Northern Croatia (p<0.001), whereas there were no significant differences between the other NUTS-2 regions. In women, the inter-regional differences were also statistically significant (p<0.001). The City of Zagreb had significantly higher rates than Adriatic Croatia (p<0.001) and Pannonian Croatia (p=0.01), and similar rates as Northern Croatia (p=0.99). The differences were also statistically significant when comparing Northern Croatia and Adriatic Croatia (p<0.001); Northern Croatia and Pannonian Croatia (p<0.001); and Adriatic Croatia and Pannonian Croatia (p=0.04) (**Figure 4**).

Discussion

This study was the first to analyze age-standardized mortality rates due to PAD at the national and regional levels, as well as their trends from 2011 to 2020. Since 2018, mortality has increased in all NUTS-2 regions in Croatia, with significant regional differences in average mortality rates by sex.

Among the 16 799 deaths due to PAD, the highest proportional mortality was for the diagnoses I70.9 (43.2%) and I70.2 (14.3%), followed by diagnoses associated with diabetes, which can be explained by the high atherogenic potential of this disease (**Figure 2**). The effects of diabetes on morbidity and mortality in the population are undoubtably underestimated both in official statistics and in clinical practice.[21,22] Of all NUTS-2 regions, the greatest percentage change in mortality in 2020 in comparison with 2011 for both men and women was found in the City of Zagreb; 60.71% and 38.13%, respectively. For men, the City of Zagreb was followed by Adriatic and Pannonian Croatia with regard to percentage change, with similar percentages, and ultimately also by Northern Croatia. The ranking was the same for women, but the percentage increases were lower. The increase in standardized mortality rates can be observed starting from 2018 (**Figure 2**, **Figure 3**).

This trend of increasing mortality has also been observed in other EU member states. Namely, between 1990 and 2017, all EU15+ countries have had an increase in mortality in women,

gim zemljama upućuju na nedostatno znanje o PAB-u u općoj populaciji i u medicinskih djelatnika, ali u Republici Hrvatskoj slična istraživanja nisu provedena.[5,24]

Rezultati upućuju na velik raspon stopa po spolu i po regijama. Za 2020. godinu omjer najviše i najniže stope mortaliteta u Gradu Zagrebu prema regiji Jadranska Hrvatska upućuje na 40 % veći mortalitet u muškaraca i 70 % u žena. Sjeverna Hrvatska ima najveću prosječnu stopu mortaliteta u obaju spolova. Muškarci, osim u Gradu Zagrebu, imaju više prosječne stope i u svim drugim regijama **(tablica 2)**. Mnogo je viši mortalitet muškaraca u Panonskoj i u Jadranskoj Hrvatskoj, za razliku od Grada Zagreba i Sjeverne Hrvatske, gdje muškarci i žene imaju slične stope **(slika 4)**.

Spol je važan pri postavljanju dijagnoze i terapiji.[25] U žena klinički simptomi često izostaju, zbog čega se bolest često ne dijagnosticira i ne liječi sukladno preporukama.[26] Navedene sustavne pogreške mogu utjecati na ishode istraživanja i svakako ih treba razmotriti pri interpretaciji epidemioloških pokazatelja. Isto tako, unutar istoga spola zamijećene su znatne regionalne razlike mortaliteta. Tako, primjerice, muškarci u Sjevernoj Hrvatskoj mnogo više umiru od muškaraca u Jadranskoj Hrvatskoj, dok su stope mortaliteta među svim ostalim regijama slične. Takvi su rezultati očekivani zbog niže prevalencije čimbenika rizika i protektivnoga kardiovaskularnog učinka mediteranskoga načina života u Jadranskoj Hrvatskoj. Stope mortaliteta u žena slične su između Grada Zagreba i Sjeverne Hrvatske, ali pri usporedbi s Jadranskom i Panonskom Hrvatskom Grad Zagreb ima mnogo više stope. Promatrajući ostale regije, zaključujemo da Sjeverna Hrvatska ima mnogo više stope od Jadranske i Panonske Hrvatske, a Panonska od Jadranske Hrvatske **(slika 4)**. Ovakve su razlike u najvećoj mjeri pripisive čimbenicima rizika i izostanku učinkovite prevencije, premda se ne može isključiti utjecaj boljeg prepoznavanja same bolesti. Naime, nacionalni program prevencije KVB-a iz 2001. godine nije primijenjen u kliničkoj praksi, a naknadno su utvrđene i neusklađenosti kliničke i javnozdravstvene prakse s preporukama koje se primjenjuju u drugim zemljama. Neke su regije, primjerice Jadranska Hrvatska, provele preventivne programe KVB-a koji su mogli smanjiti morbiditet i mortalitet.[27] Treba istaknuti da u hrvatskome zdravstvenom sustavu ne postoje strategije za prevenciju vodećih uzroka lošeg zdravlja kao što su pušenje, visok arterijski tlak i loša prehrana, a koje bi bile implementirane na svim razinama zdravstvene zaštite.[28]

Isto tako, nije provedeno nacionalno istraživanje koje bi kvantificiralo učinak čimbenika rizika na morbiditet, mortalitet i troškove liječenja KVB-a, a agregirani podatci u ovom istraživanju ograničavaju precizno navođenje mogućih uzroka razlika u mortalitetu. Međutim, sva epidemiološka istraživanja naglašavaju izuzetno veliku ulogu prevencije i procjenjuje se da bi se smanjenjem čimbenika rizika spriječilo čak do 80 % KVB-a. Kada se razmatra samo mortalitet od KVB-a, može se reći da je više od polovice pripisivo čimbenicima rizika, dok je preostali udio određen medicinskom skrbi.[29-31] Educiranost i osviještenost opće populacije, kao i medicinskih djelatnika preduvjet je smanjenju visoke prevalencije tradicionalnih čimbenika rizika. Ona je u Hrvatskoj nedostatna u studenata medicine i u općoj populaciji jer samo trećina stanovnika zna da su KVB-i vodeći uzrok smrti.[5,6,32,33] Iako u općoj populaciji nisu provedena istraživanja o poznavanju etiologije PAB-a, valja pretpostaviti da je kao i u drugim zemljama

and an increase in mortality in men was observed in as many as 16 out of 19 of the countries. A negative trend was reported in Italy (-25.1%), Portugal (-1.9%), and Sweden (-0.6%).[4,23] The etiology of the mortality increase is multifactorial, and can certainly be largely ascribed to the dynamics of the disease in the population. Improved registration of causes of death may have also contributed to the positive trend, since inadequate identification of this disease in the general population and reduced awareness represents a global problem. Studies in other countries have indicated inadequate knowledge on PAD in both the general population and in medical professionals, but no such studies have been conducted in the Republic of Croatia.[5,24]

The results of our study indicate a wide spectrum of mortality rates by sex and by region. For 2020, the ratio of the highest and lowest mortality rate in the City of Zagreb in comparison with the Adriatic region indicates a 40% higher mortality in men and a 70% higher rate in women. Northern Croatia has the highest average mortality rate for both sexes. Men, except in the City of Zagreb, have higher average mortality rates in all the other regions (**Table 2**). Mortality was significantly higher in men in Pannonian and Adriatic Croatia in comparison with the City of Zagreb and Northern Croatia, where men and women had similar rates (**Figure 4**).

Sex is a significant factor in diagnosis and therapy selection.[25] In women, the clinical symptoms of PAD are often not present, resulting in failure to diagnose and treat the disease according to recommendations.[26] These systemic errors can influence study outcomes and must be considered when interpreting epidemiological indicators. Furthermore, significant regional differences in mortality were observed within the same sex. For example, men in Northern Croatia had significantly higher mortality than men in Adriatic Croatia, whereas mortality rates were similar among other regions. These results are to be expected due to lower prevalence of risk factors and the protective cardiovascular effect of the Mediterranean lifestyle in Adriatic Croatia. Mortality rates in women were similar in the City of Zagreb and in Northern Croatia, but the City of Zagreb had significantly higher mortality rates in comparison with Adriatic and Pannonian Croatia. When examining other regions, we can conclude that Northern Croatia has significantly higher mortality rates than Adriatic and Pannonian Croatia, and the Pannonian region has higher rates than Adriatic Croatia (**Figure 4**). These differences can be primarily ascribed to risk factors and the lack of effective prevention, although the influence of better identification of the disease itself cannot be excluded. Namely, the national program for the prevention of CVD from 2001 was not applied in clinical practice, and it was also subsequently determined that there were clinical and public health practices that did not match recommendations applied in other countries. Some regions, such as Adriatic Croatia, have implemented preventive programs for CVD that may have reduced morbidity and mortality.[27] It should be emphasized that the Croatian healthcare systems lacks strategies for the prevention of leading causes of poor health such as smoking, high arterial pressure, and poor diet, which would be implemented at all levels of healthcare.[28]

Furthermore, no national studies have been conducted that would quantify the effect of risk factors on morbidity, mortality, and treatment costs for CVD, and aggregated data used in the present study limits the precise determination of the possible causes of differences in mortality. However, all epidemiological studies emphasize the very large role played by prevention, estimating that reducing risk factors would prevent as much as 80% of cardiovascular diseases. When examining mortality form CVD alone, it can be said that more

gim populacijama, znanje o ovoj bolesti lošije u usporedbi s drugim KVB-ima, primjerice IBS-om.[9,34] Čak ni kliničari često nisu osviješteni da smrtnost od PAB-a nadilazi smrtnost od koronarne bolesti srca.[35]

Republika Hrvatska je članica EU-a izrazito opterećena KV čimbenicima rizika. Uz arterijsku hipertenziju okolišni čimbenici rizika, pušenje i rizici povezani s prehranom najviše pridonose mortalitetu i morbiditetu.[9] Pušenje i dijabetes osobito se ističu po važnosti u etiologiji PAB-a. Prevalencija pušenja je 2019. godine u žena bila 32,6 %, a u muškaraca 39,1 %. Od 1990. do 2019. godine prevalencija pušenja smanjena je i u žena i u muškaraca, –11,7 % i –17,6 %, ali negativni je trend u usporedbi sa zemljama srednje Europe mnogo lošiji. U navedenom je razdoblju Poljska smanjila pušenje –17,8 % u žena i čak –40,5 % u muškaraca.[36] Usprkos tomu što regionalne usporedbe nameću i određena ograničenja, slab uspjeh smanjenja prevalencije pušenja u Republici Hrvatskoj neupitno je pripisiv izostanku i nedostatnoj primjeni dokazano učinkovitih metoda kao što su povećanje cijena duhanskih proizvoda, reklamiranje prestanka pušenja u sredstvima informiranja, uvođenje nastavnih materijala o štetnosti pušenja u škole, smanjenje mogućnosti marketinga duhanske industrije, kao i uvođenje socijalnih normi koje pušenje čine neprihvatljivim ponašanjem.[37] Osim pušenja, Republika Hrvatska među članicama EU-a ima najveći udio žena i muškaraca s neregulirano arterijskom hipertenzijom, 38 % i 36 %.[8,38] Opterećenje hipertenzijom je neujednačeno i veće je u kontinentalnim i ruralnim regijama i u osoba s nižim socioekonomskim statusom.[8,39] Uz izrazito visoku prevalenciju dijagnosticirane hipertenzije procjenjuje se da čak šestina bolesnika ima nedijagnosticiranu hipertenziju, čime se ova bolest nameće kao urgentni javnozdravstveni problem. I ovdje je zamjetna regionalna neujednačenost te je udio bolesnika s nedijagnosticiranom hipertenzijom veći u Jadranskoj Hrvatskoj.[40] U Europi bolesnici od PAB-a najčešće imaju kombinaciju više čimbenika rizika koja uključuje hipertenziju, dislipidemiju i povećan opseg struka.[41]

Rizici povezani s prehranom, uz pušenje, najčešći su uzrok mortaliteta i morbiditeta.[42] Prehrambeni obrasci hrvatske populacije sve više nalikuju na zapadnu prehranu zbog gubitka mediteranskog nasljeđa u tranzicijskim procesima. Termin hrvatski paradoks skovan je kako bi se naglasio nerazmjer između stopa mortaliteta od KVB-a nalik na one u zemljama istočne i srednje Europe i pripadnosti grupi mediteranskih zemalja.[43,44] Osim nezdrave prehrane, potrebno je istaknuti i ulogu tjelesne neaktivnosti koja je povezana s pretilošću i povećanim opsegom struka. Prevalencija tjelesne neaktivnosti razlikuje se po spolu, dobi i regijama. Zamijećena je i promjena trenda unatrag dvaju desetljeća i početkom 2000-ih godina gotovo 36 % populacije bilo je fizički neaktivno. Regionalne su razlike bile i tada izražene i, dok je u Gradu Zagrebu fizički neaktivno bilo 85,6 % muškaraca, u Južnoj Hrvatskoj taj je udio iznosio 15 %. Nepovoljna je distribucija po dobi i prevalencija je bila najviša u dobnoj skupini od 18 do 34 god., kada se navike o vježbanju i kretanju najviše stječu, dok je najniža bila u srednjoj dobi u obaju spolova.[45] Desetljeće poslije tjelesno je aktivno bilo 80 % odrasle populacije, više muškarci nego žene, što čini pozitivnu promjenu. Ipak, udio adolescenata koji dosežu razinu tjelesne aktivnosti koju je preporučila Svjetska zdravstvene organizacije i dalje je ostao nizak – 25 %.[46] Usprkos preporukama za tjelesnu aktivnost, sedentarno ponašanje i spavanje iz 2019. godine takav se udio u adolescena-

than half is ascribable to risk factors, with the rest being determined by medical care.[29-31] Education and awareness of the general population and of medical professionals is a precondition for reducing the high prevalence of traditional risk factors. Education is lacking in Croatia, both among medical students and in the general population, since only a third of the population is aware that CVDs are the leading cause of death.[5,6,32,33] Although no studies have been conducted in the general population on knowledge of the etiology of PAD, we may assume that, as in other populations, knowledge on this disease is worse in comparison with other CVDs, such as IHD.[9,34] Even clinicians are often unaware that mortality from PAD surpasses mortality from coronary heart disease.[35]

The Republic of Croatia is an EU member state that is severely burdened by CV risk factors. Along with hypertension, environmental risk factors, smoking, and risks associated with diet are the strongest contributors to mortality and morbidity.[9] Smoking and diabetes are especially important in the etiology of PAD. The prevalence of smoking in 2019 was 32.6% in women and 39.1% in men. From 1990 to 2019, the prevalence of smoking was reduced both in women and in men, by -11.7% and -17.6%, respectively, but the negative trend has been significantly worse in comparison with Central European countries. In the same period, Poland reduced smoking by -17.8% in women and by as much as -40.5% in men.[36] Despite the limitations imposed by regional comparisons, the poor success of reduction in the prevalence of smoking in the Republic of Croatia is undoubtably attributable to the lack and inadequate application of demonstrably effective methods such as increasing the prices of tobacco products, advertising smoking cessation in information-providing media, introducing educational materials about hazardous effect of smoking into schools, reducing the capacity of the tobacco industry to market its products, and introducing social norms that make smoking an unacceptable behavior.[37] Aside from smoking, the Republic of Croatia is the EU member state with the highest ratio of women and men with unregulated hypertension, 38% and 36%, respectively.[8,38] The burden of hypertension is unequally distributed by region, with a higher burden in continental regions and in persons with lower socioeconomic status.[8,39] In addition to the extremely high prevalence of diagnosed hypertension, it is estimated that as many as one sixth of patients have undiagnosed hypertension, which firmly identifies this disease as an urgent public health issue. Regional differences are present as well, with the ratio of patients with undiagnosed hypertension being higher in Adriatic Croatia.[40] In Europe, patients with PAD usually have a combination of multiple risk factors that include hypertension, dyslipidemia, and increased waist circumference.[41]

Risks associated with diet are, along with smoking, the most common causes of mortality and morbidity.[42] The dietary patterns of the Croatian population increasingly resemble Western diet due to the loss of Mediterranean heritage in transitional processes. The term "the Croatian paradox" was coined to emphasize the discrepancy between having CVD mortality rates similar to those in countries of Eastern and Central Europe despite belonging to the group of Mediterranean countries.[43,44] In addition to unhealthy diet, it is important to emphasize the role of physical inactivity, which is associated with obesity and increased waist circumference. The prevalence of physical inactivity differs by sex, age, and region. A trend change was observed two decades ago, and almost 36% of the population was physically inactive at the start of the 2000s. Regional differences were also pronounced at the time, with 85.6% of men being physically inactive in the City of Zagreb, as opposed to 15% in Southern Croatia. The dis-

ta zadržao i 2021. godine, kada je i utvrđeno da samo sustav zdravstva i socijalne skrbi nadzire i prati razinu tjelesne aktivnosti populacije.[47,48] Dokazi o koristi od tjelesne aktivnosti u svrhu smanjenja učestalosti brojnih kroničnih nezaraznih bolesti, uključujući i KVB, nisu upitni.[49] U ovom je istraživanju zamjetna podudarnost razine tjelesne neaktivnosti i stopa smrtnosti od PAB-a u Kontinentalnoj Hrvatskoj i u Gradu Zagrebu nasuprot Jadranskoj Hrvatskoj, međutim, metodološke različitosti ograničavaju procjenu uzročno-posljedične povezanosti. Kohortna bi istraživanja omogućila preciznu kvantifikaciju protektivne uloge tjelesne aktivnosti u morbiditetu i mortalitetu od PAB-a.

Uz dominantnu ulogu čimbenika rizika na morbiditet i mortalitet, svakako ne treba zanemariti podjednako važan utjecaj medicinskih intervencija kod klinički težih oblika PAB-a. U usporedbi sa susjednom Mađarskom koja ima najveću stopu amputacija u Europi, ali i s Njemačkom i Austrijom, RH ima osjetno niže dobno standardizirane stope smrtnosti od PAB-a koje su u razdoblju od 1990. do 2019. u obaju spolova slične europskom prosjeku.[50] Ipak, sustavne analize nije moguće provesti zbog nepostojanja informatičke ujedinjenosti svih razina zdravstvene zaštite koja onemogućuje rutinsku kvantifikaciju broja intervencija po medicinskim ustanovama i praćenje ishoda liječenja, analize troškova i koristi i troškovne učinkovitosti.[51,52] Ipak, zamijećene regionalne razlike u mortalitetu zasigurno su u određenoj mjeri pripisive i razlikama u distribuciji ljudskih i tehnoloških potencijala u specijalističkim granama koje se skrbe za bolesnike s PAB-om, kao što su radiologija i kardiologija te vaskularna kirurgija. Prethodna istraživanja upućuju na regionalne razlike u dostupnosti medicinskih usluga poput vremena čekanja na dijagnostičku obradu kompjutoriziranom tomografijom i magnetnom rezonancijom, ali i u mortalitetu od akutnog i ponavljajućeg infarkta miokarda.[53-56] Također, mortalitet od PAB-a, kao i od akutnoga koronarnog sindroma, pripisiv je prirodnom tijeku bolesti, ali isto tako može biti uzrokovan medicinskim, endovaskularnim ili kirurškim intervencijama, pa je stoga potrebno razlikovati i bilježiti spontane neželjene ishode od neželjenih ishoda povezanih s intervencijama.[57,58]

Ovo istraživanje ima određene prednosti i nedostatke, što se u potonjem slučaju odnosi na ograničenja istraživanja i mogućnost postojanja sustavne pogreške. Najveća je prednost u tome što su ovim istraživanjem prvi put kvantificirane regionalne razlike u mortalitetu od PAB-a. Prema SZO-u, upravo je mortalitetna statistika jedna od najpouzdanijih izvora zdravstvenih podataka. Podatci o mortalitetu su za ocjenu zdravstvenoga stanja stanovništva, kreiranje zdravstvenih politika, evaluaciju nacionalnih zdravstvenih programa te za regionalnu i međunarodnu usporedbu. Autori projekta *Global Burden of Disease* analizirali su kvalitetu mortalitetnih podataka u zemljama članicama EU-a i ocijenili pouzdanost godišnjih procjena uzroka smrti na skali do 5, a Hrvatska je uz čak 14 članica EU-a (Belgija, Bugarska, Češka, Danska, Francuska, Njemačka, Grčka, Luksemburg, Nizozemska, Poljska, Portugal, Rumunjska, Slovenija i Španjolska) ocijenjena ocjenom 4 koja podrazumijeva da je cjelovitost podataka o smrtnosti veća od 65 %.[59]

Uz navedene prednosti postoje brojna ograničenja koja treba razmotriti pri interpretaciji podataka. Kao prvo, metodološki je riječ o opažajnom istraživanju koje po svojem ustroju nudi ograničenu mogućnost dokazivanja uzročno-

tribution by age was unfavorable, and prevalence was highest in the 18-34 age group, which is the period in life where exercise and physical activity habits are predominantly acquired, whereas prevalence was lowest in middle age in both sexes.[45] One decade later, 80% of the adult population was physically active, more so men than women, which represented a positive change. However, the ratio of adolescents who achieved the recommended level of physical activity according the World Health Organization remained low at 25%.[46] Despite the recommendations for physical activity, sedentary behavior, and sleep from 2019, this ratio in adolescents remained the same in 2021, when it was also determined that only the healthcare and social welfare systems follow and monitor the level of physical activity in the population.[47,48] The evidence on the benefits of physical activity for the reduction of the incidence of numerous chronic non-infectious diseases, including CVDs, is beyond doubt.[49] The present study highlights the noticeable correlation between the level of physical inactivity and the mortality rate due to PAD in Continental Croatia and the City of Zagreb in comparison with Adriatic Croatia, although methodological differences limit the assessment of the causal relationship between the two. Cohort studies would allow precise quantification of the protective role of physical activity for PAD-related morbidity and mortality.

In addition to the dominant role of risk factors in morbidity and mortality, it is also important not to neglect the comparably important influence of medical interventions in more clinically severe forms of PAD. In comparison with the neighboring Hungary, which has the highest amputation rate in Europe, as well as in comparison with Germany and Austria, the Republic of Croatia has noticeably lower age-standardized mortality rates due to PAD, which were similar to the European average for both sexes in the period from 1990 to 2019.[50] However, systematic analyses cannot be performed due to the lack of informational interconnectedness between all levels of healthcare, which prevents routine quantification of the number of interventions per medical institution and monitoring treatment outcomes, cost-benefit analyses, and cost-efficiency analyses.[51,52] The observed regional differences in mortality are certainly also partially ascribable to the differences in the distribution of human and technological potential in the specialist branches that provide care for patients with PAD, such as radiology, cardiology, and vascular surgery. Previous studies indicate the existence of regional differences in the availability of medical services, such as differences in waiting times for diagnostic examination using computed tomography (CT) and magnetic resonance (MR) imaging, but also differences in mortality from acute and recurrent myocardial infarction.[53-56] Additionally, the mortality from PAD, as with acute coronary syndrome, is ascribable to the natural course of the disease, but can also be caused by medical, endovascular, or surgical interventions, which necessitates differentiating and recording spontaneous unwanted outcomes as opposed to unwanted outcomes associated with medical interventions.[57,58]

The present study had certain advantages and disadvantages, the latter being the study limitations and the possibility of systemic errors. Its greatest advantage is the fact that this was the first study to quantify the regional differences in PAD-related mortality. According to the WHO, mortality statistics are one of the most reliable sources of scientific data. Mortality data are used for assessing the overall state of health in the population, creating health-related policies, evaluating national healthcare

posljedične povezanosti. Također, izgledno je da je PAB kao uzrok smrti rjeđe dijagnosticirana, primjerice, od IBS-a, iako obje bolesti u podlozi imaju aterosklerotski proces. Uzroci smrti u bolesnika s PAB-om malokad su rezultat same bolesti donjih ekstremiteta i procjenjuje se da svaki drugi oboljeli umire od komplikacija koronarne bolesti, a svaki deseti od komplikacija cerebrovaskularne bolesti.[60] Usporedivost je istraživanja ograničena jer ne postoji jednoznačna primjena MKB dijagnoza u različitim zemljama. Ipak, usprkos manjku usporedivosti na međudržavnoj razini moguća je regionalna usporedivost jer se postojanje sustavnih pogrešaka na regionalnoj razini koje bi dovele do razlika u ishodima istraživanja ne očekuje. Moguće je da je u Gradu Zagrebu zbog većeg broja centara koji provode postupke za liječenje bolesnika s PAB-om poboljšano kodiranje uzroka smrti, ali ne postoje istraživanja koja bi kvantificirala navedena odstupanja po centrima. Periferna arterijska bolest zasigurno se može uvrstiti u skupinu bolesti kod kojih MKB sustav ne odgovara u cijelosti složenosti kliničke slike.[61] S obzirom na klinički tijek bolesti, izglednije je da se dijagnosticiraju klinički teži oblici, dok je najveći broj slučajeva ipak asimptomatski i stoga smanjeno dijagnosticiran.[62]

Zaključno, ovo je istraživanje usprkos agregiranim podatcima i ograničenjima pokazalo znatne regionalne razlike u mortalitetu od PAB-a uz porast trenda od 2018. godine. Sjeverna Hrvatska ima najveći mortalitet za oba spola, dok Jadranska Hrvatska ima najmanji mortalitet. Procjena uzročno-posljedične povezanost otežana je ekološkim dizajnom istraživanja koji je uvjetovan izostankom sustavnoga prikupljanja podataka koji uključuje i ishode liječenja. Ipak, epidemiološka istraživanja ističu ulogu prevencije i rane dijagnostike u smanjenju mortaliteta i učinkovitost je takvoga pristupa neupitna i za oboljele od PAB-a.

programs, and performing regional and international comparisons. The authors of the Global Burden of Disease (GBD) project analyzed the quality of mortality data in EU member states and evaluated the reliability of annual assessments of causes of death on a scale ranging from 1 to 5, with Croatia being among 14 other countries (Belgium, Bulgaria, the Czech Republic, Denmark, France, Germany, Greece, Luxemburg, the Netherlands, Poland, Portugal, Romania, Slovenia, and Spain) that were marked with a score of 4, indicating that the completeness of mortality data was higher than 65%.[59]

Along with these advantages, the present study had numerous limitations that should be considered when interpreting the data. Firstly, from a methodological perspective, this was an observational study, which means that it can provide only limited demonstration of causal relationships. Furthermore, it is likely that PAD is less often diagnosed as a cause of death than for instance IHD, despite both diseases having atherosclerotic processes as the underlying cause. The causes of death in PAD are rarely the direct result of the disease of the lower extremities, and it is estimated that every other patient with this disease dies from complications related to coronary disease, and every tenth patient dies from complications related to cerebrovascular disease.[60] The comparability of this study is limited, as there is no unified application of ICD diagnoses among different countries. However, despite the lack of comparability at the international level, comparisons between regions are possible, since the existence of systemic errors at the regional level that would lead to differences in outcomes is not anticipated. It is possible that the larger number of medical centers performing treatment on patients with PAD in the City of Zagreb has resulted in improved coding of mortality causes, but there are no studies quantifying such discrepancies between centers. Peripheral artery disease can certainly be included in the group of diseases in which the ICD system does not fully represent the complexity of the clinical picture.[61] Given the clinical course of the disease, it is likely that the more severe forms of the disease are diagnosed, while the majority of the cases remains asymptomatic and are thus diagnosed less often.[62]

In conclusion, despite aggregated data and its limitations, this study has shown significant regional differences in mortality due to PAD, with an increasing trend since 2018. Northern Croatia had the highest mortality for both sexes, while Adriatic Croatia had the lowest mortality. Estimating causal relationships is difficult due to the ecological study design, which was the result of the lack of systematic data collection that includes treatment outcomes. However, epidemiological studies emphasize the role of prevention and early diagnostic in the reduction of mortality, and the effectiveness of this approach is undoubtably also applicable to patients with PAD.

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