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CONTENT - СОДРЖИНА

PUBLIC HEALTH

HEALTH AND ECONOMIC BENEFITS OF CYCLING AND SATISFACTION WITH THE CYCLING ENVIRONMENT IN SKOPJE

Jansun Bukovetz[1], Kristina Shuntova[2], Aneta Kostova[1], Mihail Kochubovski[3], Igor Spiroski[3]

[1] *Institute of Public Health of the Republic of North Macedonia, Skopje, Republic of North Macedonia*
[2] *Private Health Institution "D-r Trajkovski", Skopje, Republic of North Macedonia*
[3] *Institute of Public Health of the Republic of North Macedonia; Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Republic of North Macedonia*

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***Correspondence:** Jansun Bukovetz, Institute of Public Health of the Republic of North Macedonia, Skopje.

E-mail: cansun-97@hotmail.com

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Abstract

Walking and cycling provide numerous environmental, health, and societal benefits, improving urban life quality and saving infrastructure costs. These benefits also lead to substantial healthcare cost savings. The aim of this study was to assess the health and economic benefits of cycling and satisfaction with the cycling environment in Skopje. Materials and methods: This study utilized the Health Economic Assessment Tool (HEAT) to quantify the societal economic value of reduced premature mortality due to cycling in Skopje, North Macedonia. A survey of 1,169 participants aged 20-64 was conducted from April to November 2022, with data analyzed using the HEAT model and statistical analysis performed using the chi-square test ($p < 0.05$), with effect size measured by Cramér's V. Results: The total benefit derived from cycling activities of the 1,169 participants for one year was US$471,150 and US$4,955,982 for 10 years. Over ten years, continuing cycling habits would result in nearly 12 prevented premature deaths. The most frequently used route for cycling was in urban zones. Most participants were dissatisfied with the bike lanes in their municipalities ($p < 0.001$). To enhance safety, participants suggested more bike lanes, increased authority intervention on illegal parking, and reduced vehicle speed limits where motor and bicycle traffic intersect. Conclusion: Shifting to active mobility can reduce negative impacts on vulnerable groups, enhancing public health, environmental sustainability, and social well-being. Improving infrastructure and safety should be a priority to make cycling a viable option in Skopje.

ЈАВНО ЗДРАВЈЕ

ЗДРАВСТВЕНО-ЕКОНОМСКИ ПРИДОБИВКИ ОД ВОЗЕЊЕТО ВЕЛОСИПЕД И ЗАДОВОЛСТВО ОД ВЕЛОСИПЕДСКАТА ИНФРАСТРУКТУРА ВО СКОПЈЕ

Џансун Буковец[1], Кристина Шунтова[2], Анета Костова[1], Михаил Кочубовски[3], Игор Спироски[3]

[1] *Институт за јавно здравје на Република Северна Македонија, Скопје, Република Северна Македонија*
[2] *Приватна здравствена установа „Д-р Трајковски", Скопје, Република Северна Македонија*
[3] *Институт за јавно здравје на Република Северна Македонија, Скопје; Медицински факултет, Универзитет „Св. Кирил и Методиј" во Скопје, Република Северна Македонија*

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***Кореспонденција:** Џансун Буковец, Институт за јавно здравје на Република Северна Македонија, Скопје, Република Северна Македонија. E-mail: cansun-97@hotmail.com

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Извадок

Пешачењето и возењето велосипед нудат бројни еколошки, здравствени и општествени придобивки, подобрувајќи го квалитетот на животот во урбаните средини и намалувајќи ги трошоците за инфраструктура. Овие придобивки исто така водат до значајни заштеди во трошоците за здравствена заштита. Целта на ова истражување беше да се проценат здравствените и економските придобивки од возењето велосипед и задоволството од велосипедската инфраструктура во Скопје. Материјали и методи: Во ова истражување се користеше Health Economic Assessment Tool (HEAT) за квантитативно да ја процени економската вредност од намалувањето на предвремената смртност поради возење велосипед во Скопје, Република Северна Македонија. Анкетата беше спроведена кај 1169 испитаници на возраст од 20-64 години од април до ноември 2022 година, а податоците беа анализирани со HEAT алатката, додека статистичката анализа беше извршена со тест на χ^2 ($p < 0,05$), со мерка на ефектот преку Cramér's V. Резултати: Вкупниот бенефит од возењето велосипед на 1169 учесници за една година изнесуваше 471.150 USD, а за 10 години 4.955.982 USD. Продолжувањето на навиките за возењето велосипед во период од десет години ќе резултира со речиси 12 спречени предвремени смртни случаи. Најчесто користениот пат за возењето велосипед беше во урбаните зони. Повеќето учесници не беа задоволни од велосипедските патеки во нивните општини ($p < 0,001$). За да се зголеми безбедноста, жителите предложија повеќе велосипедски патеки, зголемена интервенција на властите за нелегално паркирање и ограничување на брзината на местата каде што се пресекуваат моторниот и велосипедскиот сообраќај. Заклучок: Ориентирањето кон активната мобилност може да ги намали негативните ефекти врз ранливите групи, подобрувајќи го јавното здравје, одржливоста на животната средина и социјалната благосостојба. Подобрувањето на инфраструктурата и безбедноста треба да биде приоритет за да се направи велосипедизмот одржлива опција во Скопје.

Introduction

Skopje is the capital of North Macedonia and covers an area of 1,818 km² with a population of 526,502. The topography of the city is generally flat having gentle slopes from 0.1 to 0.7 degrees, and its continental climate makes it highly suitable for cycling. Short trips (up to 5 km) are a significant part of the urban travel, with cycling being the highest speed mode of transport in such distances. Therefore, Skopje can certainly have a large role to play in becoming a cyclist-friendly city[1]. The total length of the Skopje bicycle network in 2018 was 96 km, the breakdown of which included 15 km of separated bicycle tracks/lanes, 45.5 km of mixed bicycle/pedestrian tracks/lanes, 11.8 km of combined pedestrian-bicycle tracks/lanes, and 20.8 km of recreational roller and bike tracks along the bank. By 2023, the network expanded to 117 km, marking an increase of 21 km over five years (Grad Skopje, 2021)[2]. Comparatively, Belgrade[3] has a 65 km long network of bicycle lanes, Zagreb 270 km[4], Ljubljana 300 km[5] and Copenhagen[6] 546 km long bicycle paths. In larger cities, alternative travel modes such as walking and cycling are more accessible, while smaller cities often lack public transport options. Although walking and cycling may be more time-consuming for longer distances, they are largely unaffected by traffic congestion, unlike driving and public transport. Mid-sized cities generally offer better infrastructure for walking and cycling, which is reflected in higher satisfaction among residents. The findings stress the importance of community planning focused on ensuring safety and comfort for walking and cycling, particularly in areas with limited public transport[7]. Investing in cycling networks can increase cycling rates and has a positive impact on public health by raising physical activity. Despite the fact that it is more expensive to build new cycling paths than to run advertising campaigns, it substantially enhances the safety and attractiveness leading to cycling being an attractive and practical alternative[8]. Health benefits include improvements in quality of life, reductions in all-cause and cardiovascular mortality, and decreased incidence of anxiety, depression, hypertension, hip fractures, and metabolic disorders, such as type 2 diabetes and dementia. In addition to health and environmental benefits, active transport also provides important societal benefits. It is a cheap, space-saving solution for short distances that can alleviate gridlock and improve the robustness of transport infrastructure. Active transport improves urban life quality and results in infrastructure savings[9]. These health benefits also translate into substantial cost savings for healthcare systems. The first attempt to provide estimates for the health and economic advantages of cycling in the Republic of North Macedonia was performed in 2011[10] and for walking in 2021[11]. Economic assessments have become a standard practice in transport planning and public health evaluations. The mean annual benefit for North Macedonia was €45,000 with a sample of 24 people for the mean trip length of 8.64 km back in 2011[11]. Eleven years later, we conducted a follow-up study to assess the health and economic benefits of cycling in Skopje, expanding the analysis to a larger population sample. Additionally, we examined the influence of various cycling environment

factors on cycling behavior. The aim of this study was to assess the health and economic benefits of cycling and satisfaction from the cycling environment in Skopje.

Materials and methods

The Health Economic Assessment Tool (HEAT) is a quantitative tool that has been developed by the London School of Hygiene and Tropical Medicine. It is based on the principles of HEAT for cycling, first published in 2007 and upgraded in 2023. The tool aims to incorporate societal economic value of reduced premature mortality due to cycling and walking into economic appraisals of transport and urban planning interventions. The HEAT model applies a comparative risk assessment approach to calculate the health effects of regular cycling and/or walking in different exposure levels and their variation in specific population over a defined period at national and local level. It also calculates the number of premature deaths in those specific populations over a period by multiplying the mortality rate by the population size and the given period. The tool offers the following impacts to consider in the assessment: physical activity, air pollution, crash risk, and carbon emissions. The study was conducted from April to November 2022 in Skopje, Republic of North Macedonia. We carried out a population survey including 1,169 participants who completed a 35-question questionnaire; the population was aged 20-64 years. As HEAT requires long-term average input on active travel and is affected by several factors such as seasons, time of day, or weather, the tool offers temporal and spatial adjustments. The default setting for the tool is 0%, and we kept that value for the whole study. The physical inactivity-related risks are defined in HEAT by the use of all-cause mortality rates dependent on the age range and selected mode. The default value in our study was 381, the number of deaths over 100,000 inhabitants within the given age range, according to country-level data from the WHO Global Health Observatory. To monetize mortality impacts from physical activity, air pollution and crashes, HEAT uses the Value of statistical life (VSL) that is available in US dollars based on market exchange rates, international dollars, adjusted for purchasing power parity and local currency. Our estimates were done in US dollars based on market exchange rates; the default value of VSL for US dollars was 420,000. HEAT provides economic discounting or inflating for the year in which the assessment is done; again, we used the default discount rate, which for the year 2022 was 5%. The average cycling speed is 14 km/h and provides both default and editable values if the user likes to specify his own. Furthermore, data for average daily travelers, including the count per location, per day, and the distance travelled (in kilometers), were inputted for the assessment.

The analysis was made by utilizing IBM® SPSS® Modeler 16.0. The Chi-square two-sample test was used to determine the association between two groups. A value of $p<0.05$ was used to determine statistical significance. Cramér's V is an effect size measurement for the chi-square test of independence. It measures how strongly two categorical fields are associated (Table 1).

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Table 1. Interpretation of effect size

Effect size (ES)	Interpretation
ES ≤ 0.2	The result is weak. Although the result is statistically significant, the fields are only weakly associated.
0.2 < ES ≤ 0.6	The result is moderate. The fields are moderately associated.
ES > 0.6	The result is strong. The fields are strongly associated.

Results

A total of 1,169 participants (age range 20-64) responded to the questionnaire, in accordance with HEAT-Cycling criteria. The mean age was 37.8 years and the largest percentage (36%) of participants was in the age-range group of 31-40 years. In total, 52.7% of participants were male, 46.8% were female, and 0.5% did not specify the gender. 92.6% of participants declared its ethnicity as Macedonian, other ethnic groups were Albanians, Turks, Serbs, Vlachs, Roma and Bosnians. In addition, 78.1% of participants completed high school, 21.4 secondary and 0.5% elementary school. 85% of participants were categorized as employed; the remaining 15% were students, freelancers, unemployed or retired. In total, 78.5% of participants belonged to the "middle-income household", 13.3% to the "high-income household" and 8.2% to the "low-income household". According to the place of residence, the largest number of participants were from the municipality Aerodrom (25.2%), followed by Karposh (25%) and Centar (18%). Other municipalities included Kisela Voda (11%), Gazi Baba (8.2%), and Gjorche Petrov (8%). Fewer participants were from Butel (2%), Chair (1.7%), Shuto Orizari (0.4%), and Saraj (0.5%).

In Skopje, 1.8% of the population aged 15-79 (the working-age population according to the International Labor Organization and the State Statistical Office, the 2021 census)[12], defined as the working-age population, and used a bicycle as a mode of transportation, representing 4% or 7,759 of individuals who used any form of transportation. On the other hand, in Macedonia, 0.9% or 14,093 of the working-age population used a bicycle, accounting for 2.3% of those who used any form of transportation.

Table 2. Number of residents who used a bicycle for commuting

Municipality	Number of residents who used a bicycle to commute to work or school	Percentage of cyclists by municipality	Percentage of the population aged 15-79, defined as the working-age population, who used a bicycle to commute to work or school
Aerodrom	1,943	25	3.1
Butel	229	3	0.8
Gazi Baba	534	6.9	0.9
Gjorche Petrov	719	9.2	2
Karposh	1,707	22	3.4
Kisela Voda	940	12.1	1.9

Saraj	61	0.8	0.2
Centar	962	12.5	2.7
Chair	602	7.7	1.3
Shuto Orizari	62	0.8	0.3

In the green zone, participants from Aerodrom most often cycled, followed by participants from Karposh. In the urban zone, participants from Karposh most often cycled, followed by participants from Aerodrom. In the industrial zone, participants from Gazi Baba most often cycled, followed by participants from Karposh. In the suburbs, participants from Aerodrom most often cycled, followed by participants from Karposh. In general, the suburbs were the least liked area for cycling (Table 3).

Table 3. The most frequently used route for cycling for all municipalities

	Aerodrom (n)	Butel (n)	Gazi Baba (n)	Gazi Baba (n)	Karposh (n)	Kisela Voda (n)	Saraj (n)	Centar (n)	Chair (n)	Shuto Orizari (n)
Green zone (parks, green spaces, quays, etc.)	207	8	51	53	175	72	3	122	13	2
Urban zone	230	23	73	68	248	105	3	182	15	3
Industrial zone	12	0	14	5	13	10	2	11	1	0
Suburbs of Skopje	59	5	33	25	37	32	3	45	2	3

All analyses revealed a significant relationship between the identified factors.

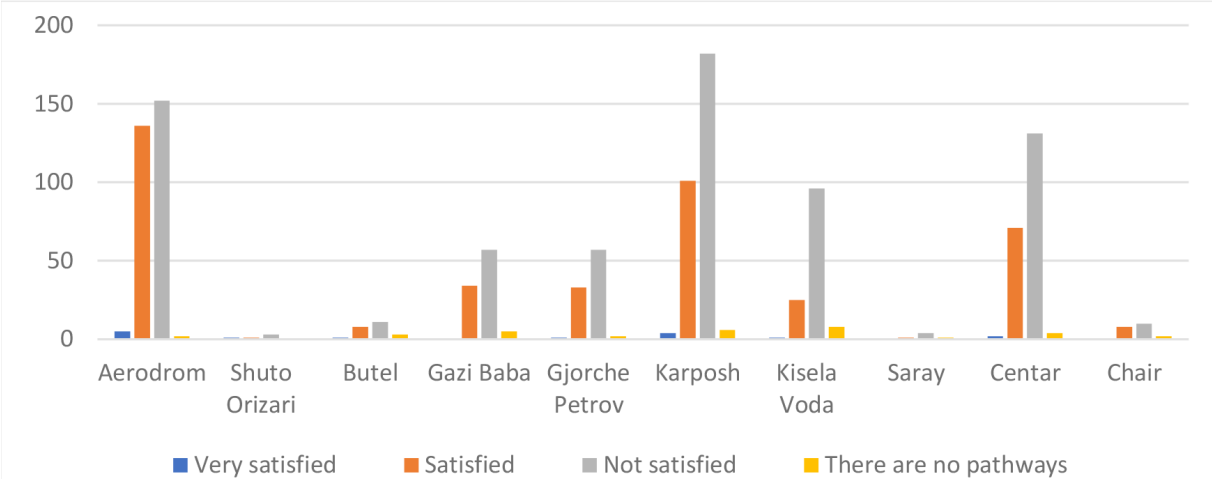
Table 4. Statistical analysis of determinants influencing cycling factors in accordance with the place of residence

Variables	Chi-square	Degree of freedom	*p*-value	Cramér's V
The most common physical obstacles when cycling on a bike lane	148.389	90	0.001	
Satisfaction with bike lanes	76.651	27	0.001	
Appropriately marked and protected construction works on the bike pathways	19.177	9	0.024	0.128
Affect your feeling of safety while cycling	83.049	54	0.007	0.109
Reasons if improved would motivate you to ride a bike	165.343	9	0.001	

When asked, the citizens of Skopje if they were satisfied with the bike lanes in the city, the majority of them gave a negative response. There was a difference between satisfaction with bike lanes in Skopje in relation to place of residence. The most satisfied with the cycling paths were

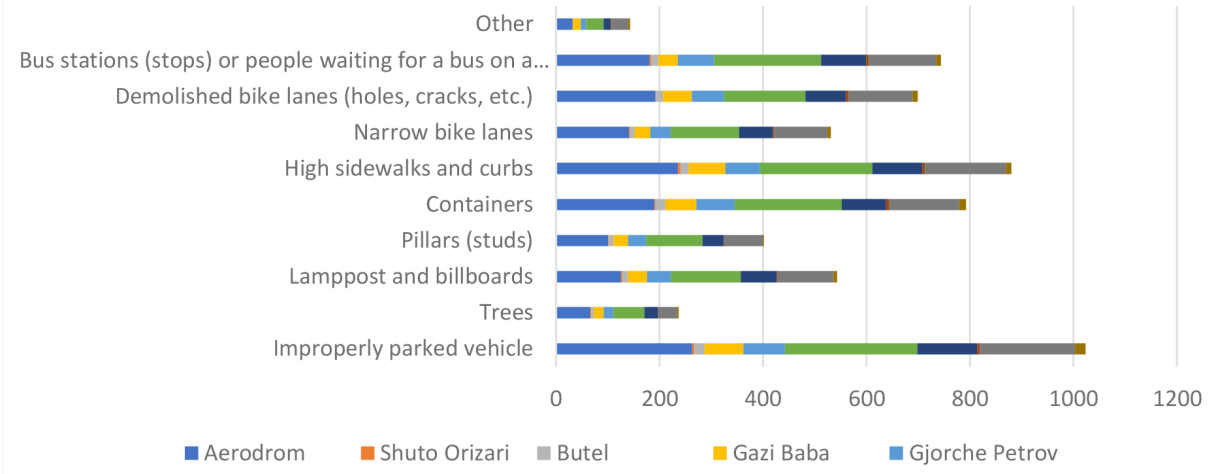
participants from Aerodrom, and the least satisfied were those from Karposh municipality. Participants from municipality of Kisela Voda answered there were no bike lanes in their place of residence (Figure 1).

Figure 1. Level of satisfaction of bike lanes for all municipalities



When asked *"What was the most common physical obstacle when cycling on a bike lane?"*, most participants from Aerodrom and Karposh answered "Improperly parked vehicles". High sidewalks and curbs were the option most participants from Shuto Orizari chose. Participants from Butel complained on improperly parked vehicles as well as containers. Overall, the most common obstacle reported by participants was improperly parked vehicles (up to 87%), followed by high walks and curbs (75%), containers (67%), bus stops or people waiting for the bus (63%) (Figure 2).

Figure 2. Level of satisfaction of bike lanes for all municipalities



A significant number of participants from the municipalities in the city of Skopje answered that construction works on the bike paths were not appropriately marked and protected. Contrary, participants from the municipality of Shuto Orizari answered that construction works on the bike paths were appropriately marked and protected. In percentage terms, 11.2%

of participants from Centar gave a positive answer for the most common physical obstacles when cycling on a bike lane for all municipalities, – followed by 9.17% of participants from Aerodrom, – 7.87% from Karposh and 5.84% from Kisela Voda.

The reasons that affected the feeling of safety when riding a bike were various depending on participants' place of residence. A significantly larger number of participants to the question *"Which of the following would affect your feeling of safety while riding a bike?" answered "More bike lanes". The most frequent suggestion of the participants from the municipality of Aerodrom was to "reduce the speed limit of vehicles"*, followed by the participants of Karposh. *"More studs on pavements"* was the most common answer given by participants from the municipalities of Karposh and Centar. Participants from the municipalities of Aerodrom and Gazi Baba suggested *"Better signalization and more traffic signs"*. Answers such as *"More bike paths," "Higher intervention rate of the authorities regarding illegally parked vehicles," and "Reducing the speed limit of vehicles where motor and bicycle traffic intersect"*, were common implications. Across all municipalities, the most common suggestion given by participants was "More bike lanes", followed by "Greater intervention by authorities regarding illegally parked vehicles", and the third option was *"Reducing the speed limit of vehicles where motor and bicycle traffic intersect"* (Figure 4).

Figure 4. Factors that affect the feeling of safety whilst cycling

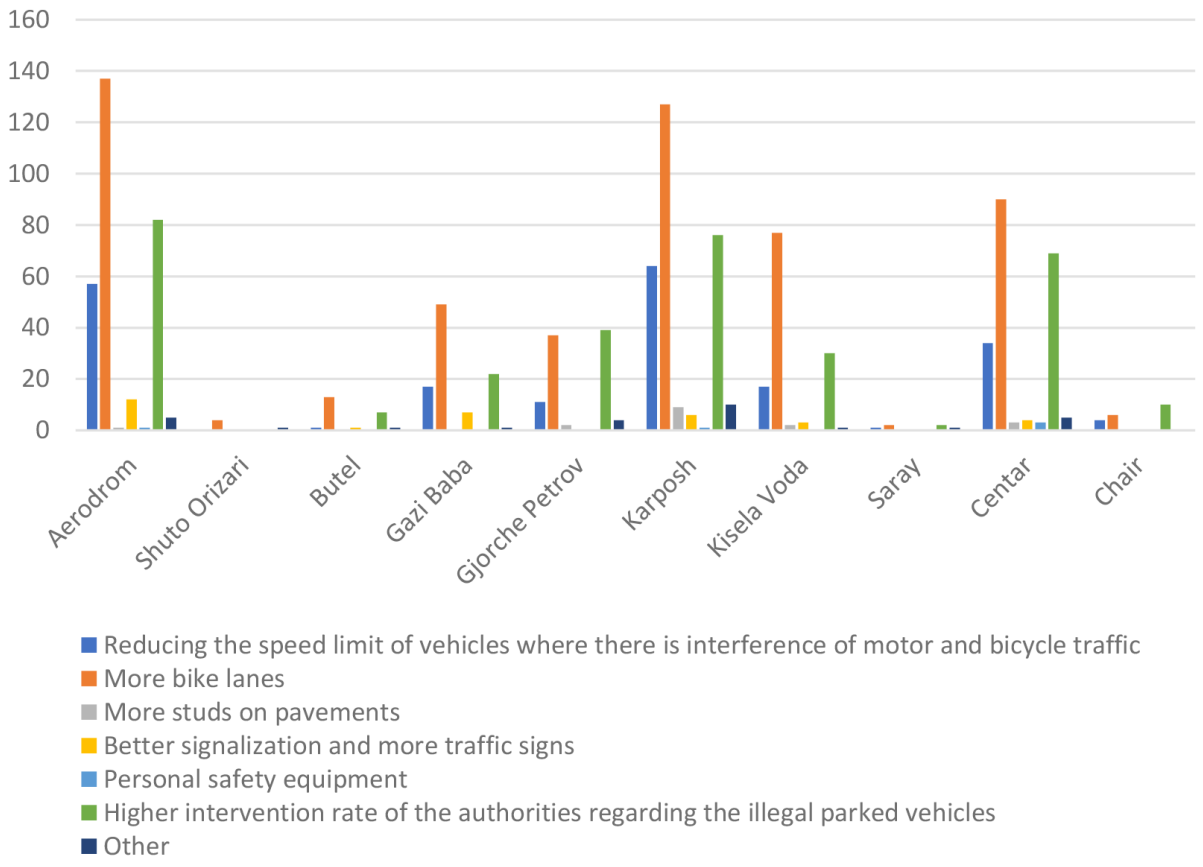


Table 5. Factors that would motivate bike riding if improved

Factor	Number of participants*
Weather	452
Air pollution	483
Traffic safety	688
Not having enough bicycle pathways	618
My colleagues or people close to me do not use bikes; therefore, I do not use it	30
Financial reasons	40
Having more time in the morning	93
Having safe parking lots for bikes	564
If I would have not been physically active enough	23
If I receive subsidies from the workplace	145

*The participants were able to choose more than one answer to this question.

Participants also reported a number of factors that would persuade them to cycle more often in general if they were enhanced. The most significant factor was reduced traffic safety issues as a key motivator identified by 688 participants. It was succeeded by the availability of bicycle pathways (618 participants) and safer bike parking options (564 participants). A total of 483 and 452 participants, respectively, mentioned air pollution and weather as significant considerations influencing their decision to cycle. Other incentives included having more time in the morning (93 participants) and receiving a workplace subsidy (145 participants). When considering financial motives and influence from coworkers or close family members, only 40 and 30 participants, respectively, considered these factors important. The least influential factor was the desire to be more physically active, identified by only 23 participants (Table 4).

Table 6 presents a summarized data of the HEAT evaluation for the distance cycled and the people that cycled that exact amount.

The total benefit derived from the cycling activities of the 1,169 surveyed people for one year was US$495,598, that being adjusted with 5% discount rate for 2022 is US$471,150. A five percent of annual discount rate is a value already suggested by the tool. It can be changed if the country in which the study is conducted has other monetary policies. It should be mentioned that along the discount rate, there is an inflation rate for the years 2024, 2025 and up. A projection over 10 years for the same sample size gives a total of an economic impact of US$4,955,982. At a discounted rate, this becomes US$3,825,166.

In terms of potentially preventable premature mortality, if those 1,169 people continue their habits of cycling over the course of ten years, there would be almost 12 prevented premature deaths. The majority of participants answered they cycled 15 km. If they were to continue cycling the same distance for the upcoming

ten years, (from 2022) there would be 5 prevented premature deaths and the total economic benefit would be US$1,520,000. With a 5 km difference in the entered data, meaning cycling 9 km, 168 people would participate, and over the course of ten years there would be 3 prevented premature deaths, with a total economic impact of US$938,000.

Table 6. Summary of the data analyzed by the HEAT

Amount of km a person cycled	Assessed population	Premature deaths prevented over one year	Premature deaths prevented over 10 years	Total economic value per 1 year (US$)	Total economic impact adjusted for 2022 (US$)	Total economic impact over 10 years (US$)	Total economic impact over 10 adjusted for 2022 (US$)
1 km	49	0.0035	0.035	1,460	1,400	14,600	11,300
2 km	70	0.015	0.15	6,310	6,010	63,100	48,700
3 km	100	0.047	0.47	19,700	18,700	197,000	152,000
4 km	113	0.077	0.77	32,500	31,000	325,000	251,000
5 km	71	0.041	0.41	17,400	16,600	174,000	134,000
6 km	42	0.017	0.17	6,970	6,640	69,700	53,800
7 km	43	0.02	0.2	8,410	8,010	84,100	64,900
8 km	17	0.0031	0.031	1,320	1,250	13,200	10,200
9 km	168	0.29	2.9	121,000	115,000	1,210,000	935,000
10 km	36	0.016	0.16	6,710	6,390	67,100	51,800
11 km	29	0.013	0.13	5,500	5,240	55,000	42,500
12 km	31	0.017	0.17	7,030	6,700	70,300	54,300
13 km	27	0.011	0.11	4,770	4,540	47,700	36,800
14 km	84	0.14	1.4	58,500	55,700	585,000	451,000
15 km	273	0.47	4.7	197,000	187,000	1,970,000	1,520,000
16 km	9	0.0018	0.018	745	710	7,450	5,750
17 km	5	0.0006	0.006	253	241	2,530	1,960
19 km	2	0.000048	0.00048	20	19	202	156
				Σ=495,598	Σ=471,150	Σ=4,955,982	Σ=3,825,166

We also assessed health and economic benefits from cycling in Skopje and municipalities of Skopje. According to the 2021 census, data on transportation modes was collected for individuals aged 15 to 79 (the working population)12. However, since the HEAT tool is calibrated for the 20-64 years, we estimated the population within this age range and used these figures for the analysis, as indicated in the "Assessed Population" column. The average distance between home and workplace, school or university was 5.6 km. Based on these input data,

HEAT estimates that cycling in Skopje and its municipalities annually avert around 2.9 premature deaths valued at an economic benefit of approximately US$1,140,000. Furthermore, if the 4,593 individuals who currently cycle maintain this behavior, ten years of cycling would prevent approximately 29 premature deaths, with an approximate economic impact of US$9,250,000 over a ten-year period.

Table 7. HEAT estimation for the municipalities in Skopje in accordance with the data of the State Statistical Office

Location	Amount of km a person cycled	Assessed population	Premature deaths prevented over one year	Premature deaths prevented over 10 years	Total economic value per 1 year (US$)	Total economic impact adjusted for 2022 value (US$)	Total economic impact over 10 years (US$)	Total economic impact over 10 adjusted for 2022 (US$)
Skopje	5.6km	4593	2.9	29	1,200,000	1,140,000	12,000,000	9,250.000
Aerodrom	5.6km	1150	0.71	7.1	300,000	286,000	3,000,000	2,320,000
Butel	5.6km	135	0.084	0.84	35,200	33,500	352,000	272,000
Gazi Baba	5.6km	316	0.2	2	82,400	78,500	824,000	636,00
Gjorche Petrov	5.6km	434	0.27	2.7	113,000	108,800	1,130,000	874,000
Karposh	5.6km	1010	0.63	6.3	263,000	251,000	2,630,000	2,030,000
Kisela Voda	5.6km	596	0.37	3.7	155,000	148,000	1,550,000	1,200,000
Saraj	5.6km	35	0.022	0.22	9,130	8,690	91,300	70,500
Centar	5.6km	556	0.35	3.5	145.000	138.000	1,450,000	1,120,000
Chair	5.6km	354	0.22	2.2	92,300	87,900	923,000	713,000
Shuto Orizari	5.6km	35	0.022	2.2	9,130	8,690	91,300	70,500

Further, a hypothetical scenario about cycling behavior in North Macedonia was performed. Due to the lack of country-specific data on distances cycled, we used the 5.6 km distance from Skopje as a proxy. If the 8,484 individuals (the population among 20-64 years of the working-age population which used a bicycle) continue their cycling habit for a period of ten years, the prevented mortality would be approximately 53 premature deaths, and, hence, an estimated economic benefit of US$17,100,000.

Discussion

This cross-sectional study gave valuable findings on the health, economic, and environmental factors that influence cycling behavior and satisfaction with cycling infrastructure in the city. The mean age of participants was 37.8 years, indicating that cycling

as a mode of transport is most popular among adults in mid-career years.

Safety concerns remain a key barrier to cycling in Skopje. A desire for more bike lanes was the most-mentioned factor to influence feelings of safety among cyclists and was stated consistently across municipalities. Strong association between place of residence and factors influencing safety perceptions signal regional disparities in cycling conditions and infrastructure. The participants from both Aerodrom and Karposh also identified reduction of the speed limit for vehicles and improvement of traffic regulation as important, again suggesting that safety is a key determinant of cycling. The results thus indicate that practical barriers to cycling, such as reduction of traffic safety problems, availability of bike pathways, and safer possibilities for parking bikes, are important facilitators of more cycling. Interestingly, the relatively low percentage of participants who identified increased physical activity as a motivator may suggest that for most, cycling is more a need or a way of getting around than it is a means to improve health. This is to say that the promotion of cycling will have to be effectively addressed through environmental and infrastructural measures.

The total economic value adjusted for 2022 for one year was US$471,150, and the total economic value adjusted for 10-year as (from 2022) calculated by HEAT was US$3,825,166. These findings underscore the potential of cycling as a public health strategy, reinforcing the role of regular physical activity in reducing health risks. The use of the HEAT tool allowed for a valuable estimation of the economic impact of these health benefits, emphasizing the cost-effectiveness of cycling interventions.

‘In the fight against rising overweight and obesity levels, and unhealthy urban environments, the renaissance of active mobility (cycling and walking as a transport mode) is encouraging’ . According to a study conducted in 2011 on the traffic system in Skopje, cycling is a decreasing mode of transport. In the year of 1981, 4.2% of the total number of trips were assigned to cycling, in 2000 this percentage went much lower (1.9% of the total number of trips), and in 2010 only 1.4% of trips were attained by bike. Municipalities of Shuto Orizari and Saraj do not have bike lanes or paths at all, so they lack bike infrastructure for safe cycling. In addition, these municipalities have a higher percentage of population aged 5-19, which are deprived of safe conditions for cycling. The municipality of Chair, being the most densely populated in Skopje, has only 7.58 km long bicycle lane. Municipalities of Centar, Karposh and Aerodrom, which are municipalities with lowest unemployment rate and highest percentage of high education among the citizens, have the longest bicycle network.

We could not find any data on the average cycling distance on a national level for Macedonia. However, in our

study, the average cycling distance was 8.9 km. The average cycling distance in the Netherlands in the year of 2008 was 4.3 km[14]; this number increased to 6 km[15] just two years later, compared to Finland where the average cycling distance was 14 km in 2010[16]. In Austria, over 40% of car trips are shorter than 10 km, and in Switzerland, more than 60% of commuter distances are under 10 km. In England, more than 50% of trips are 2-3 km[9]. Considering the question *"Unrelated to the reason, how long is your average passed route/tour?"* and that a sizeable number of participants reported using the bike as a mean of recreation, it is understandable that the average cycled distance was slightly higher.

In an Australian study, the most highly reported barriers to riding a bike for transport included not wanting to ride on the road with motor vehicle traffic (56%), concern about collision with a motor vehicle (54%), and motorist aggression (53%)[17]. Another Australian study confirmed that leading barriers to riding a bike was related to riding on the road alongside motor vehicles[18]. According to Fowler *et al.*[19], the two main obstacles to cycling in urban settings are reduced traffic safety concerns and the presence of designated bike lanes. Traffic safety therefore plays a key role in the promotion of active mobility. Perceived lack of safety can have unintended consequences by discouraging physical activity entirely[20]. Safety as expected is an important issue for most bike riders and non-bike riders. In our study, out of 1,169 people, 46.3% answered they would feel safer if there were more bike lanes, while in the study by Engber *et al.*[21] out of 799, 16% answered that more or better cycle paths would make them feel safer.

According to Gössling *et al.*, the most important thing for the cyclists is the clear separation of bicyclists from other forms of traffic. Mixed traffic, particularly when cyclists and motorists share lanes, is generally felt to be the least safe. A main road scenario without a cycle path was rated as "safe" or "rather safe" by just 11%[22] of cyclists. Cycling tracks are perceived as safer than cycling lanes, which in turn are preferred over cycling on the street. Physical separations from the car lane, a greater lane width, and a coloured surface contribute most to a high subjective safety of cycling lanes. On narrower cycling lanes, people experience extensive buffer designs as rather constraining and as impairing their safety. Combining several safety features (i.e. a sufficient demarcation of the left buffer and a coloured surface) is not necessarily beneficial for subjective safety. Our findings are mostly in line with findings on the factors benefitting or impairing objective safety[23].

In our study, among 1,169 participants, there was only 1 prevented premature death over the course of one year and 11 premature deaths prevented over the course of a decade. Cycling increases life expectancy by 0.025 years per year of regular cycling, which corresponds to only 3 hours of cycling per week, or 2,592 km cycled per year[24]. A study conducted in Australia reported a health economic benefit of $1,12 Australian Dollars[25] per kilometer of cycling, due to both the mortality and morbidity decrease resulting from a more active lifestyle. The estimated global cost of physical inactivity to the pub-

lic health care systems for the period 2020-2030 is approximately US$300 billion (or US$27 billion annually) if physical inactivity is not reduced[26]. A scenario-based study done in 17 counties across 5 continents suggests that if only 8% of the world car trips are replaced with bike trips, 18,589 annual premature deaths could be prevented by 2050 in the same population[27].

Authorities frequently cite insufficient resources as a rationale for underinvesting in active mobility infrastructure. However, numerous scientific studies suggest that investments in active mobility not only offer substantial health benefits but also yield significant economic returns. HEAT estimated that the New York City Bike share system could prevent an additional 2 to 3 premature deaths and increase its annual economic benefit from US$18,800,000 to US$28,300,000 due to increased use of bikes[28]. Deenihan *et al.*[29] made a HEAT assessment for Dublin, Ireland, and estimated that over a decade, the economic benefits of cycling the financial benefits infrastructure were in the range between €26,695,000 and €141,222,000 with a 5% discount rate, averaging between €2,669,000 and €14,122,000 annually with its maximised benefits above the seventh year. In comparison, our study estimated financial health benefits of US$3,439,168 (converted from US$3,825,166) over a decade. The public funding of the bicycle infrastructure is often deficient, which is why, Denmark made a comparative analysis of the car versus bike costs. It has shown that a kilometer of cycling costs €0.08 when all factors are taken into account, whereas a kilometer of driving a car costs €0.50. If taking into account social expenses only, every kilometer traveled by bicycle contributes to society €0.16, but every kilometer traveled by automobile incurs expenditures €0.15[24]. Skyannis *et al.* in 2019 HEAT's assessment revealed that for 5,000 cyclists riding 1,830 meters per day, 5 days a week, over 10 years, the economic benefit would be €7,800,000[30]. In our study, only 5.9% of participants reported cycling 2 km, and almost all of them cycled 5 times a week. The total economic benefit for these people was around US$6 000 for 1 year, and in a 10-year projection, that number would amount to approximately US$48,000.

Nowadays, 0.83 million (0.43–1.47) deaths are attributable to low physical activity[31]. It was estimated that in 2021, due to low physical activity, 386 deaths occurred[32]. Gharibzadeh *et al.* conducted a study in Tehran, the capital city of Iran, using HEAT of both walking and cycling modes, and found that switching from non-cycling to cycling for commuting could reduce mortality rates by 18%. If the cycling modal share increases from 1.72% to 2.5%, 5%, or 10%, it could save between 3.39 and 17.93 lives annually and generate economic benefits of €26.7 million to €141.2 million over ten years, with an initial investment of €12 million[33], resulting in highly favorable benefit-cost ratios ranging from 2.22:1 to 11.77:1.

This study has some limitations. Firstly, the reliance on Skopje-specific data to estimate the national impact of cycling introduces potential inaccuracies, as cycling behavior may vary in different regions of North Macedonia. Additionally, assumptions about the average cycling distance and the 5% discount rate may not fully reflect the local economic

conditions, warranting further sensitivity analysis. Furthermore, due to the limitation of the HEAT for the age range 20-64 years, we were unable to calculate the cycling benefits for the entire population that reported cycling at present.

Conclusion

Physical activity benefits are the dominant effects from cycling from a public health perspective. It is from monumental importance that the government, non-profitable organizations, international funds etc. invest in, firstly, quality bike lanes and paths which would be safe enough not only for the cyclists, but also for the pedestrians and motor vehicles, and secondly, policies implemented to promote cycling. Shifting to active mobility can reduce negative impacts on vulnerable groups while enhancing public health, environmental sustainability, and social well-being. Improvements in infrastructure and safety should be paramount in order to make cycling an attractive and viable option in Skopje. It is important to invest in bike lanes, reduce traffic speed in high-traffic areas, and provide a safe place for bicycle parking to improve safety and increase cycling. Further to this, local authorities should extend cycling subsidies, making such finance-available schemes accessible to all citizens, particularly to those from disadvantaged groups. Additionally, it is required to enforce traffic rules that protect the cyclists, to increase public awareness of cycling issues, and to discuss environmental challenges regarding air quality and weather conditions. Finally, the development of cycling-friendly urban spaces, like green pathways and recreational zones will be important in promoting a culture of cycling in the city.

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PUBLIC HEALTH

THE RELATIONSHIP BETWEEN CYCLIST BEHAVIOR, SAFETY MEASURES, AND TRAFFIC ACCIDENTS: A CROSS-SECTIONAL STUDY IN SKOPJE

Jansun Bukovetz[1], Kristina Shuntova[2], Aneta Kostova[1], Gordana Ristovska[3], Danica Stevkovska[4], Sanja Sazdovska[4], Mihail Kochubovski[1]

[1] *Institute of Public Health of the Republic of North Macedonia, Skopje, Republic of North Macedonia*
[2] *Private Health Institution "D-r Trajkovski", Skopje, Republic of North Macedonia*
[3] *Institute of Public Health of the Republic of North Macedonia, Skopje, Republic of North Macedonia; Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Republic of North Macedonia*
[4] *Ministry of Health of the Republic of North Macedonia, Skopje, Republic of North Macedonia*

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***Correspondence:**

Jansun Bukovetz, Institute of Public Health of the Republic of North Macedonia, Skopje, Republic of North Macedonia

Email: cansun-97@hotmail.com

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Abstract

Globally, vulnerable road users - cyclists, pedestrians and motorcyclists – account for more than half of all road traffic injuries. The aim of this paper was to identify the relationship between sociodemographic characteristics, education level, mobile phone and headphone usage, and wearing protective equipment during cycling and involvement in traffic accidents. Materials and methods: A cross-sectional study was conducted via online questionnaire in Skopje, Republic of North Macedonia in 2022. The questionnaire consisted of 35 questions; grouped in four different topics. Data were analyzed with SPSS 16.0. Results: More than half of the participants (59%) did not wear protective equipment during cycling, and 17.7% wore protective equipment always. Mobile phones during cycling were used by 32.5% of participants, regularly or sometimes, and using headphones during cycling was reported by 41%. Usage of protective equipment is highly correlated with a reduced risk of involvement in a traffic accident. Cycling with the use of mobile phones is strongly associated with an increased risk of accidents. The largest percentage of participants who had experienced a traffic accident, did not wear protective equipment. On the other hand, 70% of participants who had not been involved in a traffic accident did not use a mobile phone while cycling. Conclusion: The findings of this study should be implemented in future policies for better public health and traffic safety, emphasizing the use of protective equipment and reducing mobile phone-related distraction. Addressing these aspects can help policymakers improve cyclist safety, reduce traffic accidents, and improve overall road safety.

ЈАВНО ЗДРАВЈЕ

ПОВРЗАНОСТА ПОМЕЃУ НАВИКИТЕ НА ВЕЛОСИПЕДИСТИТЕ, ЗАШТИТНИТЕ МЕРКИ И СООБРАЌАЈНИТЕ НЕЗГОДИ: СТУДИЈА НА ПРЕСЕК ВО СКОПЈЕ

Џансун Буковец[1], Кристина Шунтова[2], Анета Костова[1], Гордана Ристовска[3], Даница Стевковска[4], Сања Саздовска[4], Михаил Кочубовски[3]

[1] *Институт за јавно здравје на Република Северна Македонија, Скопје, Република Северна Македонија*
[2] *Приватна здравствена установа „Д-р Трајковски", Скопје, Република Северна Македонија*
[3] *Институт за јавно здравје на Република Северна Македонија, Скопје, Република Северна Македонија; Медицински факултет, Универзитет „Св. Кирил и Методиј" во Скопје, Република Северна Македонија*
4 *Министерство за здравство на Република Северна Македонија, Скопје, Република Северна Македонија*

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***Кореспонденција:**

Џансун Буковец, Институт за јавно здравје на Република Северна Македонија, Скопје, Република Северна Македонија

Email: cansun-97@hotmail.com

Примено: 13-мај-2025;**Ревидирано:** 15-јул-2025; **Прифатено:** 23-ное-2025; **Објавено:** 30-дек-2025

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Извадок

На глобално ниво, вулнерабилните учесници во сообраќајот - велосипедисти, пешаци и мотоциклисти - сочинуваат повеќе од половина од повредите на учесниците во сообраќајните патни несреќи. Целта на овој труд беше да се идентификува односот помеѓу социодемографските карактеристики, нивото на образование, користењето мобилни телефони и слушалки, како и носењето заштитна опрема за време на возење велосипед и учеството во сообраќајни незгоди. Материјали и методи: Беше спроведена студијата на пресек преку онлајн прашалник во 2022 година во Скопје, Република Северна Македонија. Прашалникот се состоеше од 35 прашања, групирани во четири различни теми. Податоците беа анализирани со SPSS 16.0. Резултати: Повеќе од половина од учесниците (59%) не носеле заштитна опрема за време на возење велосипед, додека 17,7% секогаш носеле заштитна опрема. 32,5% користеле мобилни телефони за време на возење велосипед, редовно или понекогаш, додека 41% користеле слушалки при возење велосипед. Користењето заштитна опрема е силно поврзано со намалена инволвираност во сообраќајни незгоди, додека користењето мобилни телефони во тек на возењето велосипед е силно поврзано со зголемен ризик од незгоди. Најголем процент од учесниците кои имале сообраќајна незгода не носеле заштитна опрема, додека, пак, 70% од учесниците кои немале сообраќајна незгода, не користеле телефон. Заклучок: Резултатите од ова истражување треба да се имплементираат во идни политики за подобро јавно здравје и сообраќајна безбедност, со акцент на користењето заштитна опрема и одвлекување на вниманието со користење мобилни телефони додека се вози велосипед. Обраќањето внимание на овие аспекти може да им помогне на носителите на политики да ја подобрат безбедноста при возење велосипед, да го намалат бројот на сообраќајни незгоди и да придонесат кон општо подобрување на безбедноста на патиштата.

Introduction

Globally, vulnerable road users - cyclists, pedestrians and motorcyclists – account for more than half of all road traffic injuries[1]. The World Health Organization, in its agenda on sustainable development 2030, has set a goal to reduce the number of traffic-related accidents by 50%[2]. Reduction in road traffic fatalities and injuries did not align with the Sustainable Development Goals (SDG) target in United Nations Economic Commission for Europe (UNECE) region[3]. Of the total amount of road traffic fatalities, there were approximately 1.19 million in 2021. Road traffic injury continues to be the leading cause of fatality amongst children and young adults (5-29 years) and the 12th for all ages in 2019[4]. Cycling is highly promoted for having considerable advantages to public health, personal welfare, and the environment[5]. Yet, compared to motor vehicles, cyclists are specifically vulnerable for not having any protective covering. One of the major barriers to boosting cycling, especially for novice or anxious cyclists, is road safety[6]. On the other side, transportation is also causing an increase in road accidents, early deaths, and physical and psychological injuries. This trend increases health care costs and puts additional pressure on public finances. Because of this, scientists, together with police and accident reconstruction experts, are researching possible causes of cyclist-related crashes[7]. A contributing factor to this increasing traffic injury and death rate among pedestrians and bicyclists may be increasing distractions due to mobile phone use. The world population was estimated at 7.9 billion in 2022. From 6.9 billion mobile phone subscriptions in 2014, the number increased to 8.9 billion subscriptions in 2023. More recently, smartphone subscription numbers have overwhelmingly exceeded the numbers of people on earth[8].

Over half of the cyclists (56%) aged 12 to 80 used their phones occasionally while cycling[9]. As mobility in traffic is increasingly associated with use of mobile phones, MP3 players, and similar portable devices, serious road safety issues are raised. These devices are capable of diverting the drivers in several ways (physically, visually cognitively, auditorily). Furthermore, emotionally driven driving behavior induced by the use of such devices can negatively influence driving performance affecting emotional states and mood[10]. Consequently, a distracted cyclist using a phone is at a higher risk of collision, and the resulting accidents can have severe consequences[11]. Bicycle helmets cannot prevent accidents, but they can reduce head injuries[12]. Measures can be directed at the individual cyclist or the cycling environment, and can be focused on pre-event prevention or post-event mitigation[13]. Driving speed is a key to the problem of road traffic injuries in North Macedonia[14].Lower speed limits are appropriate to ensure safety and can better handle high levels of cycling traffic[15]. The largest subgroup of patients who suffered a traumatic brain injury (TBI) were drivers, while smaller subgroups were bicyclists (11%), and this proportion in North Macedonia is 10%[16]. In North Macedo-

nia, children and young people under 24 years old account for 43.6% of all traffic injuries and 26.5% of traffic fatalities, and traffic accidents cause 30-50% of fatal injuries in those aged 5 to 2414.[14] Analysis of bicycle accidents provides for an in-depth investigation of the causes and contributing circumstances of collisions, taking into consideration the drivers, cyclists, vehicles, roadways, and environmental conditions. The conclusions from these investigations assist in providing recommendations for improvements in transportation infrastructure and vehicle safety features[17]. The aim of this paper was to identify the relationship between sociodemographic characteristics, education level, mobile phone and headphone usage, and wearing protective equipment during cycling and involvement in traffic accidents.

Materials and methods

A cross-sectional study was performed from April to November 2022 in Skopje, Republic of North Macedonia. We prepared and distributed an online questionnaire to various social media platforms, in order to reach specific target groups (cycling enthusiasts, people that do sports via riding a bike). At the outset of the questionnaire, participants were informed about the study's objectives and made aware that by completing the questionnaire, they were consenting to take part in the survey. The study was conducted entirely anonymously. Participants were thoroughly briefed on the purpose of the study and provided their voluntary consent to participate. The questionnaire consisted of 35 questions, grouped into four different topics: sociodemographic characteristics, cycling habits, safety and behaviors while cycling, and infrastructure. Data were analyzed with SPSS 16.0. Chi-square test was used to determine the association between two nominal variables. Statistical significance was defined as $p<0.05$.

Results

Demographic characteristics

The questionnaire was completed by 1169 participants with age range from 20 to 64 years; the mean age was 37.8 years. In terms of gender, 52.7% of participants were male, 46.8% were female, and 0.5% did not report their gender. Regarding education level, the majority of participants claimed to have completed a high school as the highest level of education (78.1%), followed by those with secondary school (21.4%), and elementary school (0.5%). According to the place of residence, the largest number of participants were from the municipalities Aerodrom (25.2%), Karposh (25%) and Centar (18%). Other municipalities included Kisela Voda (11%), Gazi Baba (8.2%), and Gjorche Petrov (8%). Fewer participants were from Butel (2%), Chair (1.7%), Shuto Oriz-

Table 1: Characteristics and behavior of study population

	Male (N)	Male (%)	Female (N)	Female (%)	Prefer not to tell the gender (N)	Prefer not to tell the gender (%)	Total (N)	Total (%)
Elementary school	4	0.3	/	/	2	0.17	6	0.50
Secondary school	175	15	74	6.33	1	0.08	250	21.5
High school	437	37.4	473	40.4	3	0.2	913	78
Involvement in traffic accident								
Yes	126	10.7	79	6.8	2	0.17	207	17.7
No	491	42	467	40	4	0.34	962	82.2
Wearing protective equipment during bicycling								
Yes, all the time	134	11.5	64	5.5	2	0.17	200	17.2
Only when I ride out of the bicycle path	165	14.1	89	7.6	/	/	254	21.7
Only when I ride in the city	14	1.2	14	1.2	/		28	2.4
No, I don't	304	26	379	32.4	4	0.34	687	58.7
Phone usage while cycling								
Yes	33	2.8	19	1.6	2	0.17	54	4.6
Sometimes	220	18.8	106	9.06	/	/	326	27.9
No	364	31.1	421	36.1	4	0.34	785	67.5
Headphones usage while cycling								
Yes	103	8.8	101	8.6	3	0.2	207	17.7
Sometimes	166	14.2	104	8.9	/	/	270	23.1
No	348	29.8	341	29.2	3	0.2	692	59.2

ari (0.4%), and Saraj (0.5%).

A total of 207 participants or 17.7% claimed having experienced traffic accidents. Among them, 125 were male, 80 were female and two did not want to specify the gender. Most of the participants involved in traffic accidents were males (60.9 %).

Protective equipment use

The majority of participants (58.7%) reported not wearing protective equipment while cycling, 17.2% of them always wore protective equipment, and 21.7% of them wore protective equipment only when riding bicycles outside of the bicycle path. Fewer participants (2.4%) reported using protective equipment only when cycling within the city.

Regarding wearing protective equipment while cycling, e.g., helmets, , 134 (11.4%) male participants

reported always using protective equipment, whereas 483 (41.3%) reported not using it or using it occasionally. Among female participants, 64 (5.5%) reported always using protective equipment, whereas 482 (41.2%) reported never using it or using it sometimes.

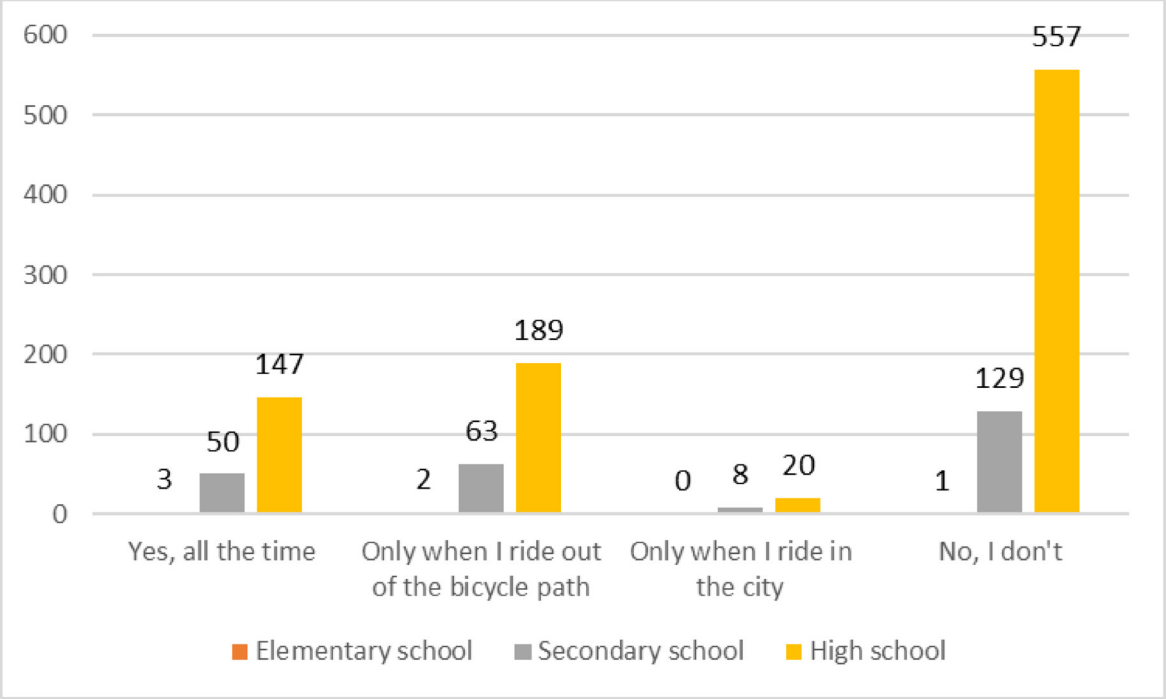

Figure 1: Wearing protective equipment while cycling and education level

61% of cyclists with high school reported never using protective equipment, while 51.6% of cyclists with a secondary school did not use protective equipment. 20% of cyclists with secondary school reported using protective equipment allways, whereas only 16.1% of cyclists with high school education reported always using protective equipment. The Chi-square test was conducted to examine the association between education level and the use of protective equipment. The analysis revealed a significant relationship between these two variables, with a Chi-square value of 13.514, df = 6, and a p-value = 0.036. This indicates a notable association between the level of education and the likelihood of wearing protective equipment. With the increase in education, the wearing of protective equipment has decreased. Out of the total number of participants, the highest percentage of participants with high school (47.6%) responded 'No, I Don't', while 11% of respondents with secondary school responded 'No, I don't' (Figure 1). Specifically, Cramer's V statistic was 0.076, and the p-value was 0.036, reinforcing the significance of this relationship.

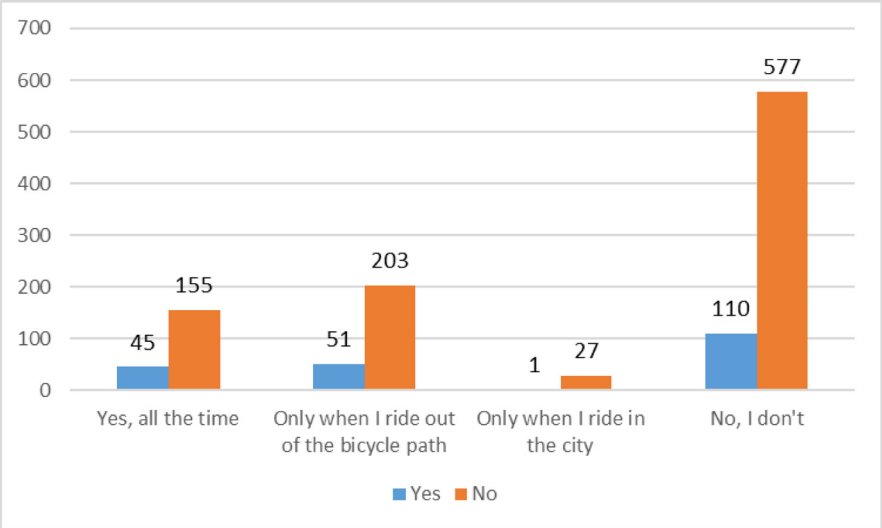

Figure 2: Wearing protective equipment while cycling and having traffic accident

The Chi-square test was conducted to examine the relationship between wearing protective equipment and involvement in a traffic accident. The analysis revealed a significant association between these variables: $\chi^2(3) = 9.328$, df=3, p = 0.025. Cramer's V value of 0.089, with a p-value of 0.025, further supported the association between wearing protective equipment and having a traffic accident. Of the total number of participants who had a traffic accident, the largest percentage did not wear protective equipment (53.1%) (Figure 2).

Phone usage while cycling

The results showed that 34% of participants reported using their phones while cycling, while 67.5% indicated that they did not use their phones during cycling. Among male participants, 253 (21.6%) reported using their phones while cycling (either all the time or sometimes), while 364 males (31.1%) reported not using their phones at all. Among female participants, 125 (10.7%) and 421 (36.1%) did/did not use mobile phone when cycling, respectively.

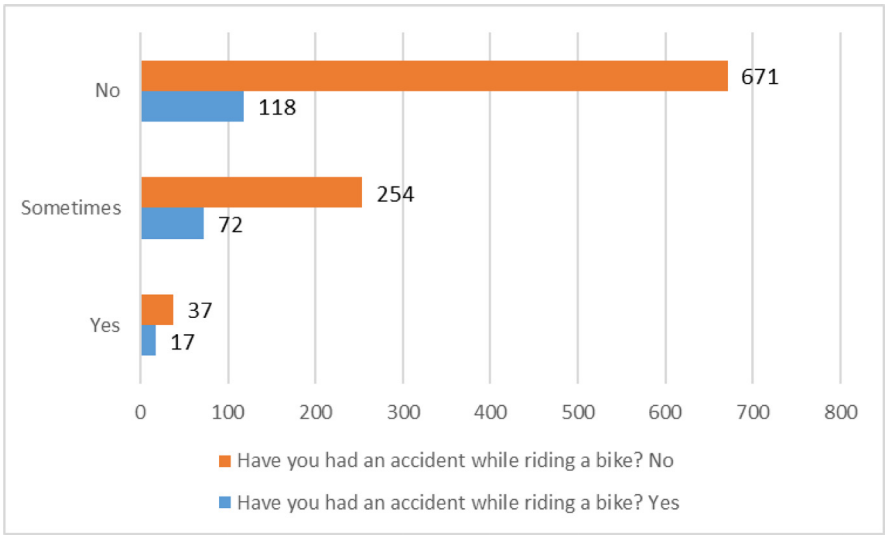

Figure 3: Phone use during cycling and traffic accidents

The Chi-square test was conducted to assess the relationship between phone use while cycling and involvement in traffic accidents. The analysis showed a highly significant association between these variables, with $\chi^2(2) = 15.420$, df=2, $p < 0.001$. This indicates a notable difference in the likelihood of having a traffic accident based on phone use while riding a bike. Cramer's V of 0.115 and a p-value of less than 0.001 confirmed a mild association between phone use and traffic accidents. Of the total number of participants who did not have a traffic accident, 69.8% did not use a phone (Figure 3).

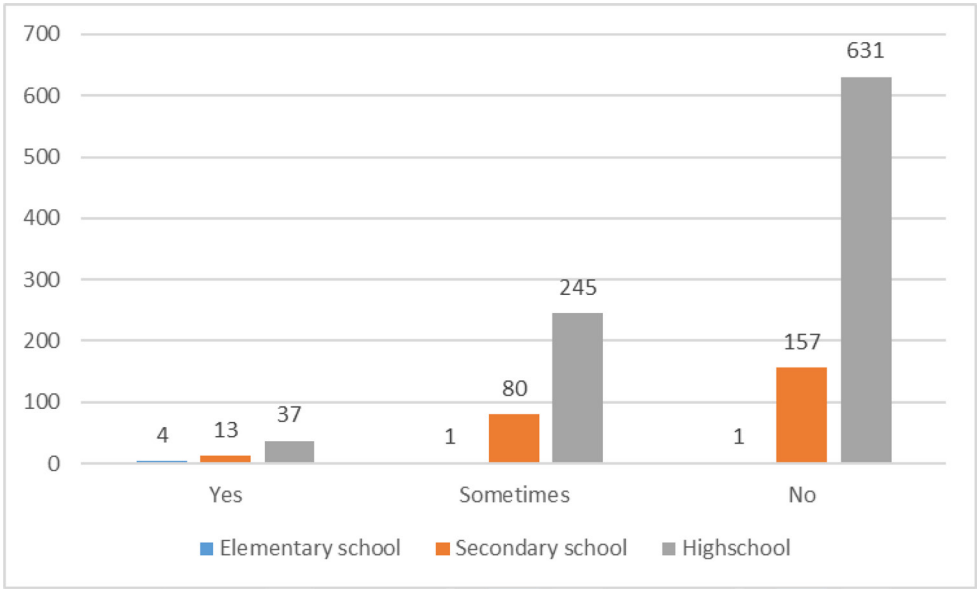

Figure 4: Phone use during cycling and education level

The Chi-square test was used to assess the relationship between education level and the use of a mobile phone while cycling. The analysis revealed a highly significant association between these variables, with a Chi-square: 56.440, df = 4, and $p < 0.001$. This indicates a significant difference in phone usage based on education level, with Cramer's V statistic at 0.155 and a p-value less than 0.001. The results show that the highest proportion of participants with primary education tend to use a phone while cycling. In contrast, individuals with higher education are less likely to carry a phone while riding a bicycle. 32.5% of participants use their mobile phone always or sometimes while riding a bike (Figure 4).

Headphones while cycling

The survey revealed that 40.8% of participants used headphones while cycling, while a majority (59.2%) among those who did not use headphones had not experienced a traffic accident (Figure 5). A total of 269 (23%) male participants reported always or sometimes wearing headphones during cycling, and 348 (29.8%) did not use headphones during cycling. A total of 205 (17.5%) female participants used headphones , and 341 (29.2%) did not use headphones.

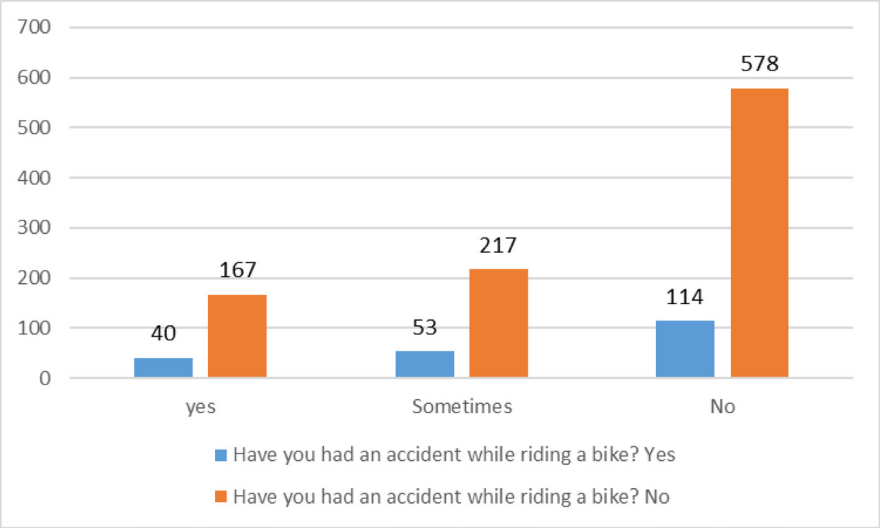

Figure 5: Wearing headphones while cycling and traffic accidents

The Chi-square test was conducted to evaluate the relationship between wearing headphones while riding a bike and experiencing a traffic accident. The results showed non-significant association $\chi^2(2) = 1.778$; df=2, p = 0.411, indicating no significant difference in accident rates based on headphone use.

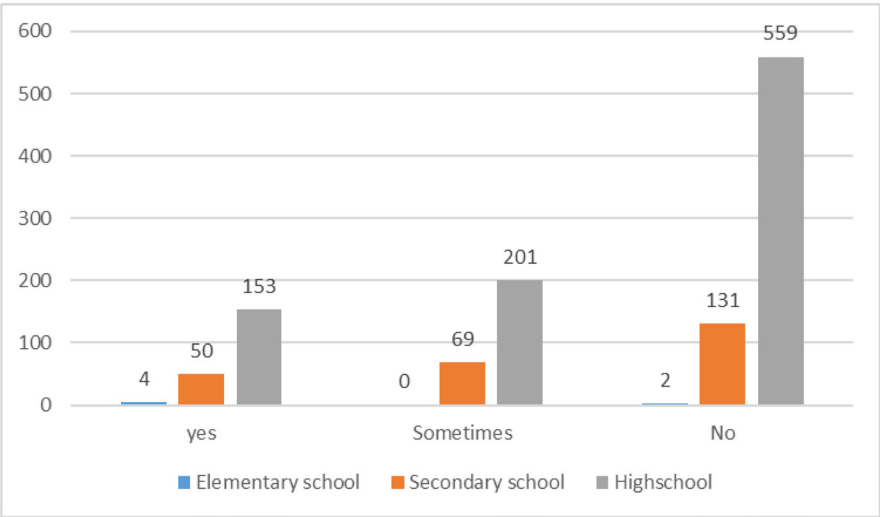

Figure 6: Wearing headphones while cycling and education level

The Chi-square test was conducted to investigate the relationship between education level and the use of headphones while cycling. The analysis revealed a significant association between these variables, with a Chi-square: 20.651, df = 6, p = 0.002. This indicates a notable difference in the use of headphones based on education level, with Cramer's V statistic of 0.094 and a p-value of 0.002. The findings showed that participants with only primary school education were more likely to wear headphones while riding a bicycle, whereas those with a high school degree generally did not use headphones while cycling. 30.3% of participants with high school education used their headphones always or sometimes while riding a bike (Figure 6).

Construction works on bike paths

We found no significant association between construction works on bike paths, which were not appropriately marked and protected and traffic accidents. However, 89.1% of participants reported that bike paths were not appropriately marked and protected (Figure 7). The Chi-square Test was performed to assess the relationship between properly marked and protected construction works (excavations) on bike paths and the occurrence of traffic accidents. The analysis revealed a $\chi^2(1) = 0.738$, with a p-value of 0.390, indicating no significant difference in accident rates related to the presence of well-marked and protected construction sites.

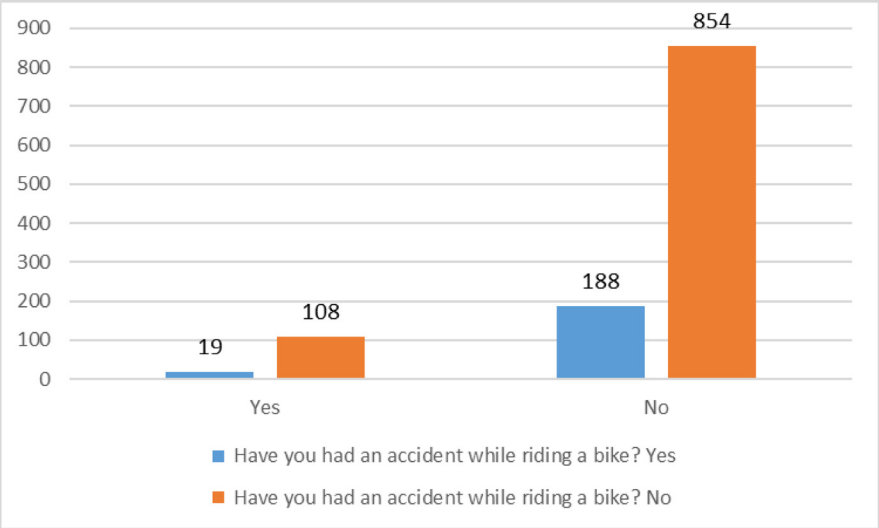

Figure 7: Construction works (excavations) on the bike path and traffic accidents

There was no significant association between properly marked and protected construction works (excavations) on bike paths and the likelihood of traffic accidents. Participants who did not experience a traffic accident generally reported that construction works on bike paths were not adequately marked and protected. Conversely, those who had experienced a traffic accident were more likely to report that these construction sites were not properly marked and protected.

Speed limitation

With regard to the question 'Do you agree with speed limiting on boulevards to be 50 km/h and streets 30 km/h?', 83% said 'Yes' and 17% 'No'.

Table 2: Relationship between education level and support for speed limits on boulevards

	Yes	No	
Elementary school	4	2	Pearson Chi-square = 6.591
Secondary school	197	53	df =3
High school	767	146	p = 0.086

The Chi-square test was conducted to examine the relationship between education level and support for speed limits on boulevards. The results indicated that this relationship was not statistically significant, p = 0.086 (Table 10). This indicated no significant difference in participants' opinions on speed limiting on boulevards based on their level of education.

Discussion

The study investigated the influence of various factors on involvement in a traffic accident and provided many valuable insights into the way different factors contribute towards road safety. More than half of the participants (59%) did not wear protective equipment during cycling, and 17.7% wore protective equipment always. Mobiles during cycling, regularly or sometimes, were used by 32.5% of participants, while 41% used headphones during cycling. The study found that wearing protective equipment significantly reduced the risk of accidents, highlighting its importance for safety. In contrast, mobile phone used while cycling was strongly associated with higher accident rates, indicating the dangers of distractions. However, wearing headphones had little impact on accident involvement.

Construction site conditions on bike paths did not significantly affect accident rates, suggesting that such sites are not major contributors to accidents. The study also found that education level influenced safety practices; individuals with higher education were more likely to use protective equipment, while those with lower education were more prone to using mobile phones while cycling, indicating a potential gap in safety awareness. There is widespread support for stricter speed limits, with many advocating for 50 km/h on boulevards and 30 km/h on streets.

EU cyclists are a unique group in that fatality numbers have remained virtually the same for more than ten years, ranging between 1,800 and 2,100. While the overall number of road fatalities decreased by 34% during this time, the share of cyclist fatalities increased, increasing from 7% in 2011 to 10% in 2020. The highest share of cyclist fatalities - i.e. the number of cyclist fatalities within the total amount of road fatalities - was recorded in the Netherlands, Denmark, Belgium, and Germany, in order from high to less high. The number of cyclist fatalities per million inhabitants is lower in the south and in the north - i.e. Sweden and Finland - of the EU and higher in the EU Member States in between. These observations are at least partly related to the number of bicycle trips and bicycle kilometers traveled in the respective countries, though safe infrastructure also plays a key role as do other factors such as user behavior - one from both cyclists and other road users - and lack of enforcement. In most collisions, cyclists were involved with cars, other cyclists, and pedestrians[18]. According to Evgenikos *et al.*, the actual cycling fatality figures are likely to be higher because police statistics are particularly poor at recording cyclist accidents compared to hospital records and other studies[19].

In the period from 2010 to 2023, 1,176 people died, and 53,817 were injured in traffic accidents in the Republic of North Macedonia. Of these, 6.7% were cyclists. The Skopje Department of Internal Affairs reported that 538

(45.7%) people died, and 35,168 (65.3%) were injured in the city of Skopje[20]. It is intriguing to note that in North Macedonia, bicycles are used for commuting by only 2.3% of the population aged 15-79 years, and by 4% in Skopje[21]. This is much lower compared to the numbers reported in the Netherlands (45%) and Spain (6%)[22].

Distribution of injured and dead citizens in the whole country for the period 2017-2021 year was killed cyclists, motorcyclists and passengers: 119; seriously injured cyclists, motorcyclists and passengers: 1135; slightly injured cyclists, motorcyclists and passengers: 4291. In this period, 69% of men were involved in traffic accidents and 31% of women[22]. From 2010 to 2021, the Skopje Department of Internal Affairs reported 2,073 traffic accidents involving cyclists. Of these incidents, 20 resulted in fatalities, 240 in severe injuries, 1,363 in minor injuries, and 450 involved only property damage. Interestingly, vehicles involved were over 80% private motor vehicles. Finally, in 2020-2021, the municipalities with the highest incidence rate of cycling-related accidents were Centar (98), Karposh (52), Aerodrom (44), and Gazi Baba (37) cases, respectively[21],[23].

UNECE reported that the number of persons injured, of persons killed, and of road traffic accidents in North Macedonia slightly moved in the same direction -8.8%, -32.6%, and -2.8% for the period 2011-2021, respectively[3]. In 2015, Road Traffic Injuries (RTIs) in Macedonia resulted in 4,960 disability-adjusted life years (DALYs), with young males (aged 15-29) being the most affected group. Speeding was the main factor and despite the existence of road safety national strategy, traffic law enforcement was still negligibly poor[24]. By 2017, the RTIs burden had slightly reduced to 4,894 DALYs and still significantly affected young males. Although the Decade of Action for Road Safety was successful compared to a 4-month period "baseline", there was continued necessity for strengthened law enforcement and cross-systematic collaboration[25]. According to Eurocost disability weights, the average disability weight for a temporary cyclist injury is 0.0326. For lifelong injuries, the average DALYs is 8.3. A Norwegian study reported that most injuries were temporary, with very few classified as lifelong. The median disability weight of these injuries was lower than the mean, indicating that while some injuries were more severe, the majority were less serious[26].

Safe infrastructure and understanding some needs of the population will be of importance to encourage safe cycling. In Germany, for instance, the cycling boom is benefiting highly educated people disproportionately, and an approach aimed at addressing this gulf is vital if cycling is to make its full contribution towards sustainability and reduced social inequalities[27]. Infrastructure can reduce the incidence of accidents and stimulate safety feeling among cyclists, as psychological safety is one of the factors supporting and sustaining cycling as a mode of transport[28]. Many authors share the view that human misbehavior accounts for about 85% of the total number of traffic accidents, while poor condition of roads, vehicles defects and other factors account for the remaining 15%[29]. Most studies reported factors of road users' behavior (59.3%) and infrastructure characteristics (57.6%) as relevant causes

of BMV collisions. Notably, 20.3% of these studies mentioned the presence of environmental factors that could be significant causes[30]. Providing adequate space on cycling lanes is a prerequisite for cyclists' subjective safety. Well-designed bike lanes enhance the feeling of safety, while physical demarcation further increases cyclists' perception of safety by a significant margin[31].

A detailed analysis of single bicycle accidents in Denmark showed that the leading causes included skidding on water or ice (60%), inadequate roadway design (24.9%), including things such as kerbstones and road maintenance, and cyclist-related factors such as alcohol use (1.4%), excessive speed (4.6%), and distraction (4.6%)[32]. Similarly, a Finnish study[33] on commuter bicycle crashes found that over 60% were linked to infrastructure issues, such as slippery road surfaces. Shared paths are commonly used in many countries for cycling when dedicated bike paths are not feasible. However, safety concerns are rising, as most accidents on these paths involve falls due to loss of control or collisions with objects and a significant number involve collisions with pedestrians, other cyclists, or motor vehicles at intersections[34]. Barriers related to safety were more commonly reported (31.9% of total bicyclists), compared to barriers related to infrastructure (22.1% of total bicyclists)[35].

Although our research team cannot determine whether the low usage of personal protective equipment among participants (58.7% do not use it) is due to habitual behavior, insufficient awareness, or the observation by Aldred and Woodcock[36] that protective clothing use declines when cycling is perceived as safer, it is evident that the use of bicycle helmets significantly reduces injuries: head injuries by 48%, serious head injuries by 60%, traumatic brain injuries by 53%, facial injuries by 23%, and the overall rate of fatalities or severe injuries by 34%[37]. In the US and Canada, helmet use among adults typically ranges from 30% to 50% in the absence of legal mandates, and slightly over 70% where helmet laws are enforced. Helmets were used on 69% of trips, with usage rates of 76% in Vancouver, where law mandates helmet use, and 59% in Toronto, where it is not. Helmet use was positively correlated with bike light use, longer trip distances, hybrid bike type, and abstinence from alcohol in the six hours prior to the trip, female gender, older age, higher income, and higher education levels. In two of Canada's largest cities, helmets were the most widely used safety equipment[38].

Personal behaviors and habits also play a significant role in enhancing traffic safety. The possible harms of mobile phone distraction are often dismissed. Focusing on nonmotor distracting activities during cycling shifts part of the cyclist's attention and it makes it more difficult to concentrate on the main task of cycling[39]. De Waard *et al.*,[40] in 2010 concluded that telephoning while cycling is associated with decreased speed, impaired peripheral vision, and heightened risk and mental effort ratings. Among various mobile phone activities, text messaging has the most detrimental effect on cycling performance. The reduced accident rate that has been observed in the group of people who are calling by phone may be explained by their slower speed and higher mental workload, which

can help avoid some of the dangerous issues. In a study conducted in Mexico City in 2022, 31.4% of participants used a mobile phone for talking, and 24.2% use did for text messaging while cycling. Additionally, 32.4% reported being involved in a crash or fall. The data indicate that each additional unit of mobile phone talking frequency increases the odds of experiencing a crash or fall by 20% (95% CI: 1.061–1.352)[41]. In Shanghai, China, 50.2% of cyclists had used a mobile phone within one minute prior to their injury. The main analysis indicated that the use of a mobile phone during this one-minute period was related to a threefold likelihood of traffic injury among pedestrians, cyclists, and motorcyclists, with an odds ratio of 3.00, at a 95% confidence interval of 2.04 to 4.42[42]. Moreover, in the case of Spain, an investigation into cyclists' reports on their crashes found that as many as 89.3% out of 25,439 traffic crashes involving cyclists involved associated factors of distraction, including the use of mobile phones[43]. On the contrary, headphones were not correlated with traffic accidents in our survey. A Dutch internet survey found that 39% of the cyclists listened to music at least occasionally and for 55% of the cyclists, at least occasionally, a phone call had been made while cycling[44]. Overall, 22.7% (95% CI: 20.9–24.4%) of all cyclists were engaged in any secondary task; wearing headphones or earphones was most frequently observed (13.1%, 95% CI: 11.7–14.5%)[45]. In the period 2010-2023, speeding accounted for 34.2% of all recorded factors contributing to traffic accidents and retained its position as the leading cause. In the Skopje Department of Internal Affairs, 38.5% of all accidents recorded were due to speeding[21]. The design of the road system and the speed limits set for it must consider the forces the human body can tolerate and survive. In areas where motorized vehicles and vulnerable road users share the same space, such as in residential areas, 30 km/h is the recommended maximum speed limit[46]. Research indicates a significant relationship between reduced speed and lower accident risk and severity. In response, many cities have implemented lower speed limits, such as 30 km/h in residential areas and 50 to 70 km/h on major roads, to enhance safety and encourage cycling and public transit. Despite these safety improvements, comprehensive evaluations are crucial to assess the full impact of such measures. The European Parliament's 2021 endorsement of a 30 km/h limit in residential and high pedestrian zones underscored the importance of thorough assessments to ensure the effectiveness of speed limit changes[47]. Many European cities are adopting 30 km/h speed limits across their road networks. Research from 40 cities, including Brussels, Paris, and Zurich, found that these speed limits significantly enhanced road safety by reducing crash risk and severity—road crashes dropped by 23%, fatalities by 37%, and injuries by 38%. Environmental benefits included an 18% reduction in emissions, a 2.5 dB decrease in noise pollution, and a 7% cut in fuel consumption. Encouraging walking, cycling, and public transit further contributes to safer and more sustainable urban environments[48],[49].

Despite the valuable insights provided by this study, several methodological limitations should be considered. Although the sample size was substantial for an urban population

such as the city of Skopje, the use of a questionnaire-based survey may limit the representativeness of certain subgroups of cyclists, particularly occasional or recreational riders. Furthermore, reliance on self-reported data introduces the potential for recall bias and social desirability bias, especially with regard to behaviors such as mobile phone use, helmet use, and compliance with traffic regulations. Finally, due to the cross-sectional design of the study, the observed relationships should be interpreted as associations rather than causal effects. Future research employing longitudinal designs or objective exposure measures could provide a deeper understanding of causal pathways and strengthen the evidence base.

Conclusion

The findings of this study should be implemented in future policies for better public health and traffic safety, emphasizing the use of protective equipment and mobile phone distraction. We need to design and carry out public awareness campaigns highlighting the advantage of wearing protective equipment. Such campaigns should target all cyclists; however, special emphasis should be placed on lower educational attainment groups as they seem unlikely to make use of protective equipment. In addition, targeted education programs on safe cycling behaviors among children and youth should be introduced. These programs will enhance safety awareness across all education levels. Further development of national regulation in order to introduce more stringent penalties for phone use while cycling, and promote technology solutions that discourage phone usage during cycling. Identification of other contributing factors related to traffic safety at construction sites on the streets can help in the introduction of new measures for enhancement of cyclist safety around these construction areas. Addressing these aspects can help policymakers improve safety while cycling, reduce accidents in traffic flow, and contribute toward overall road safety improvements.

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PUBLIC HEALTH

IMPACT OF NIGHT WORK ON HEALTH AND WORK ABILITY AMONG HEALTHCARE WORKERS

Sasho Stoleski[1], Gjulsever Asani Kuki[2], Dragan Mijakoski[1], Jordan Minov[1], Vesna Velikj Stefanovska[3]

[1] *Institute for Occupational Health of R North Macedonia, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, North Macedonia*

[2] *PHI Military Medical Center, Skopje, North Macedonia*

[3] *Institute of Epidemiology and Biostatistics with Medical Informatics, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, North Macedonia*

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***Correspondence:**

Stoleski Sasho, Institute for Occupational Health of R. North Macedonia - Skopje, R. North Macedonia; Faculty of Medicine, University "Ss. Cyril and Methodius", Skopje, R. North Macedonia

sstoleski@gmail.com

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Abstract

Aim of the study. The study objective was to determine the impact of night work on health and work ability of health workers. Material and methods. This was a cross-sectional study conducted with an anonymous survey questionnaire distributed among 120 health workers employed in PHI CGH „8th September" - Skopje, in the period January-May 2024. The study comprised male and female subjects aged 21 to 62 years, 86.7% of them worked full-time, 60% worked in shifts, 40% worked only in the first shift, while 50% of them also had night shifts. Results. The mean age of examined subjects was 40.9±10.6 years, and the average length of service in the current workplace was 11.8±8.9 years (range 1-42 years). 44.2% of them were active smokers with an average smoking experience of 6.2±9.1 years, while only 2.5% of them drank alcohol daily in an amount greater than one large glass (200 ml) of beer/wine or one small glass (50 ml) of brandy or other strong drink. A significant difference between subjects who worked and those who did not work night shifts was determined for the consumption of alcohol in a larger amount (P=0.030), followed by dissatisfaction with the workplace (P=0.031), as well as in dissatisfaction with life (P=0.042). The majority of subjects believed that psychophysical abilities during and after night work were worse than during day work, 66.6% of them answered that they had difficulties in sleeping after night shifts. The frequency of cardiovascular diseases was significantly higher among subjects who worked night shifts compared to those who did not work (P=0.043), together with the frequency of health conditions that require regular medication at a strictly defined time (P=0.037). The average values of current work ability in subjects who worked night shifts and those who did not work night shifts were similar. Conclusion. The results of the study evidently showed a significant impact of night work on health and well-being as well as on work ability of health workers.

ЈАВНО ЗДРАВЈЕ

ВЛИЈАНИЕ НА НОЌНАТА РАБОТА ВРЗ ЗДРАВЈЕТО И РАБОТНАТА СПОСОБНОСТ КАЈ ЗДРАВСТВЕНИТЕ РАБОТНИЦИ

Сашо Столески[1], Ѓулсевер Асани Куки[2], Драган Мијакоски[1], Јордан Минов[1], Весна Велиќ Стефановска[3]

[1] *Институт за медицина на трудот на Република Северна Македонија, Медицински факултет, Универзитет „Св. Кирил и Методиј" – Скопје, Северна Македонија*

[2] *ЈЗУ Воено медицински центар – Скопје, Северна Македонија*

[3] *Институт за епидемиологија и биостатистика со медицинска информатика, Медицински факултет, Универзитет „Св. Кирил и Методиј"– Скопје, Северна Македонија*

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***Кореспонденција:**

Сашо Столески, Институт за медицина на трудот на Република Северна Македонија, Медицински факултет, Универзитет „Св. Кирил и Методиј" – Скопје, Северна Македонија

sstoleski@gmail.com

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Извадок

Цел на студијата. Целта на студијата беше да се утврди влијанието на ноќната работа врз здравјето и работната способност на здравствените работници. Материјал и методи. Ова беше студија на пресек спроведена со анонимен анкетен прашалник дистрибуиран кај 120 здравствени работници вработени во ЈЗУ ГОБ „8-ми Септември" - Скопје, во периодот јануари-мај 2024 година. Студијата опфати машки и женски испитаници на возраст од 21 до 62 години, 86,7% од нив работеа со полно работно време, 60% работеа во смени, 40% работеа само во прва смена, додека 50% од нив работеа и ноќни смени. Резултати. Просечната возраст на испитаниците беше 40,9 ± 10,6 години, а просечниот стаж на актуелното работно место беше 11,8 ± 8,9 години (опсег 1-42 години). 44,2% од нив беа активни пушачи со просечен пушачки стаж од 6,2 ± 9,1 години, додека само 2,5% од нив консумираа алкохол дневно во количина поголема од една голема чаша (200 мл) пиво/вино или една мала чаша (50 мл) ракија или друг жесток пијалок. Значајна разлика помеѓу испитаниците кои работеа и оние кои не работеа ноќни смени беше утврдена само за консумирање алкохол во поголема количина (P = 0,030), следено со незадоволството од работното место (P = 0,031), како и во незадоволството од животот (P = 0,042). Поголемиот дел од испитаниците сметаа дека психофизичките способности за време и по ноќната работа се полоши отколку за време на дневната работа, а 66,6% од нив одговорија дека имаат тешкотии со спиењето по ноќните смени. Зачестеноста на кардиоваскуларни заболувања беше значително поголема кај испитаниците кои работеле и ноќни смени во споредба со оние кои не работеле (P=0,043), заедно со фреквенцијата на здравствени состојби кои бараат редовна терапија со лекови во строго дефинирано време (P=0,037). Просечните вредности на моменталната работна способност кај испитаниците кои работеле ноќни смени и оние кои не работеле ноќни смени беа слични. Заклучок. Резултатите од студијата евидентно покажаа значително влијание на ноќната работа врз здравјето и благосостојбата, како и врз работната способност на здравствените работници. Здравствените работници треба да бидат свесни за ризиците поврзани со ноќната работа за да преземат мерки за спречување на проблемите со здравјето.

Introduction

According to the International Labour Organization (ILO), shift work is "a method of organising working time in which workers alternate with each other in the workplace so that the undertaking can work longer than the hours of work of individual workers" at different times of the day and night[1].

The term night work covers all work performed during a period of not less than seven consecutive hours, including the interval from midnight to 5 a.m., to be determined by the competent authority after consultation with the most representative organisations of employers and workers or by collective agreements. Night worker means an employee whose work requires the performance of a significant number of hours of night work exceeding a certain limit. The limit shall be determined by the competent authority after consultation with the most representative organisations of employers and workers or by collective agreements[2]. According to Article 127 of the Law on Labor Relations (Official Gazette of the R. Macedonia No. 62/05), night work is considered to be work during the night (the period between 10 p.m. and 6 a.m. the following day), and an employer who regularly uses workers for night work is obliged to notify the State Labor Inspectorate[3].

One fifth of the global workforce is engaged in shift work, with 20% of European and American workers engaged in night shifts. Healthcare workers make up the majority of shift workers to enable the provision of 24/7 healthcare services. Shift work in the healthcare system is considered essential and necessary to ensure continuity of care in hospitals and residential facilities. Rotation and scheduling are key features of shift work and healthcare workers are largely bound to schedules that provide 24-hour care and include night shifts in their work arrangements. Night shift work is one of the most common causes of circadian rhythm disruption, causing significant changes in sleep and biological functions, which in turn can affect physical and psychological well-being and can have negative impact on work performance[4,5]. Many health problems can be directly attributed to lack of rest and sleep, such as slower reaction times, impaired learning ability, reduced cognitive ability, mood disturbances, and drowsiness. These symptoms can pose serious threats to healthcare professionals and their ability to perform their tasks accurately and correctly[6]. The challenges of shift work are associated with the intention to leave the profession, and therefore night work has been shown a risk factor for the development of disability and early retirement[7].

A comprehensive systematic review of the literature on shift work has shown that shift work combined with sleep disturbances may also be associated with lower dietary quality scores, higher body mass index, reduced physical activity and a higher prevalence of hypertension. There is an increased risk of developing type 2 diabetes, impaired glucose tolerance, and metabolic syndrome, with subsequent effects on both the cardiovascular and gastrointestinal systems8. It may also exacerbate some existing health conditions such as epilepsy, depression, anxiety, diabetes, or any other ongoing condition

that requires regular medication[9]. The occurrence of chronic adverse effects depends on several factors such as age, duration of exposure, or inappropriate behaviour. This is greatly influenced by worker's specialty, workload and ultimately the need and frequency of being involved in night shifts[10]. Night shift work in the healthcare sector is not only associated with poorer health, but also with increased frequency of absenteeism and lower levels of job satisfaction[11].

Night shift work is associated with an increased risk of heart diseases[12]. Epidemiological studies have clearly documented that cardiovascular events such as myocardial infarction, stroke, and arrhythmias have the highest incidence of morbidity and mortality in the early morning hours, as opposed to occurring at random. The exact mechanisms by which shift work causes cardiovascular diseases are not yet fully understood, but it is thought that the main contributing factors include the disrupted circadian rhythm and confounding factors such as smoking, poor dietary habits, and stressful social situations, which are common among shift workers[13]. Disrupted circadian rhythms lead to hormonal and metabolic changes, resulting in high blood pressure, atherosclerosis, diabetes, and obesity[14,15]. Shift workers have an average of 40% higher risk of ischemic heart disease compared to non-shift workers[5].

Furthermore, the combined effects of overtime and insufficient sleep can critically increase nervous system activity, potentially causing acute myocardial infarction[16].

Gastrointestinal disorders are one of the most common health problems reported in shift workers. A high prevalence of gastrointestinal problems such as gastrointestinal ulcers, gastritis, constipation, and diarrhea, as well as an increased risk of colon cancer, has been observed in shift workers. Helicobacter pylori infection is more prevalent in shift workers than in day shift workers, possibly indicating that shift work interferes with natural gastric defenses[17,18].

As early as 2007, the International Agency for Research on Cancer (IARC) classified shift work as a probable carcinogen, based on sufficient evidence in experimental models and limited evidence in humans. It has been suggested that exposure to artificial light at night and changes in sleep-wake cycles due to night-shift work schedules may be responsible for the increased risk of cancer. Due to the potential antiestrogenic effects of melatonin, it has also been suggested that night-shift workers may be more susceptible to the development of hormone-dependent neoplasms, such as breast, prostate, and endometrial cancers[19].

A higher incidence of altered menstrual cycles, premenstrual syndrome and menstrual pain, endometriosis, infertility, and reduced breastfeeding frequency have been observed in many groups of shift workers, such as medical, aviation, and industrial workers. Some studies have reported a higher incidence of spontaneous abortion and fetal growth retardation, including preterm birth and low birth weight. For these reasons, women are exempted from night work from the beginning of pregnancy, with the option of working day shifts for the first 2–3

years after the birth of the child[18,19].

Night shifts can result in significant stress and sleep disturbances, which affect the overall well-being and quality of life of healthcare workers, and night work impairs the alertness and professional performance of healthcare workers and reduces the quality of care[20,21].

The study objective was to determine the impact of night work on health and work ability of healthcare workers, as well as to prevent harmful effects on health of healthcare workers through a better understanding of the risks of night work, and to provide recommendations and guidelines for educating and advising healthcare personnel on how to deal with the risks of shift work.

Material and methods

Study design

This cross-sectional study was conducted using an anonymous questionnaire among employees of the PHI City General Hospital "8th September" - Skopje, in the period January-May 2024.

Study sample

The study included workers from the City General Hospital "8th September" in Skopje. Before the start of the survey, permission for the survey was requested and received from the management of the City General Hospital "8th September" – Skopje, while ethical approval was not requested. All subjects were previously informed about the purpose and methodology of the study and they voluntarily agreed to participate. In order to meet the set goals of the study, the study group consisted of 120 healthcare workers: 60 who also worked night shifts (first, second and third shifts), and 60 who worked only day shifts (first and/or second shift). The study included subjects of both genders aged 21 to 62 years.

According to the level of education and the work tasks they performed, they were classified into several groups: nurses/health technicians, laboratory technicians, paramedics and medical doctors and specialists. Healthcare workers from three shifts - first, second and third (night shift) from different departments were included.

Methods

The research methodology included a "Questionnaire on the impact of night work on health and work ability among healthcare workers". The questions were compiled based on the risk factors that occur during night work, lifestyle, health status, life and work satisfaction, and the subjects' perception of their work ability. All subjects who gave verbal consent to participate in the study filled out the sections of the questionnaire related to general information, information on smoking status, alcohol consumption, and information on the work process. The information provided in the questionnaire was treated as confidential and all participants in the study were anonymous.

The questionnaire used as an instrument in the study was specially designed and based on several standardized questionnaires in order to obtain the most accurate information and to ensure psychometric

properties: "Night worker's health questionnaire", "Health and Work Questionnaire", and "Validation of the Work Limitations Questionnaire in Brazilian Army Military Personnel"[22-24]. The questionnaire consists of 52 questions divided into 6 groups such as: demographic data (gender, age, ethnicity, education/qualification), data on work and workplace, data on lifestyle (cigarette smoking, alcohol consumption, physical activity), life and work satisfaction, questions on health of health workers during night work and data on the perception of personal work ability. The information obtained from the questionnaire was used to assess the degree of impact of night work on health and work ability, as well as to compare different shifts and their effect on health of the study subjects.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS), version 14.0 for Windows. Continuous variables were expressed as mean values with standard deviation (SD), and the nominal variables as numbers and percentages. Univariate statistical models were used for testing the differences in prevalence and comparison of the means. Chi-square test (or Fisher's exact test where appropriate) was used for testing difference in the prevalence, while comparison of data means was performed by independent-samples T-test. A P-value less than 0.05 was considered as statistically significant.

Results

Demographic data for the study sample is shown in Table 1.

Table 1: Demographic characteristics of study subjects

Variable		Subjects (n=120)
Gender	Males	6 (5%)
	Females	114 (95%)
Male/female ratio		0.05
Age (years)		40.9 ± 10.6
Range (years)		21 - 62
Total work experience (years)		17.1 ± 10.6
Range (years)		1 - 42
Length of service at current job position (years)		11.8 ± 8.9
Range (years)		1 - 42
Place of residence City Village		 110 (91.7%) 10 (8.3%)
Education - Secondary education - Higher education (three-year professional studies) - Higher education		 62 (51.7%) 46 (38.3%) 12 (10%)

Frequencies are presented as the number and percentage of respondents with the corresponding variable. Numeric data are expressed as mean values with standard deviations.

Job and workplace information

Among the total examined group (EG), the majority of subjects (104-86.7%) worked full-time, 8 hours per day and 40 hours per week, 5 days per week, 3 subjects (2.5%) worked 36 hours per week, 3 (2.5%) worked 37.5 hours per week, while 10 subjects (8.3%) worked more than 40 hours per week (up to a maximum of 64 hours a week). The average number of working hours was 40.9±4.2 hours per week (range 36-64 hours).

They worked in multiple job positions - medical doctors and specialists (10%), nurses and medical technicians (78.3%), laboratory technicians (8.3%) and paramedics (3.4%). The majority of subjects, i.e. 72 (60%) worked in shifts, and 48 (40%) worked only in the first shift. Thirty-four (28.3%) subjects worked overtime, and the average number of overtime hours was 3.1±6.8 hours (range 0-36 hours).

Figure 1 shows the percentage of workers in different shifts (first, second and third).

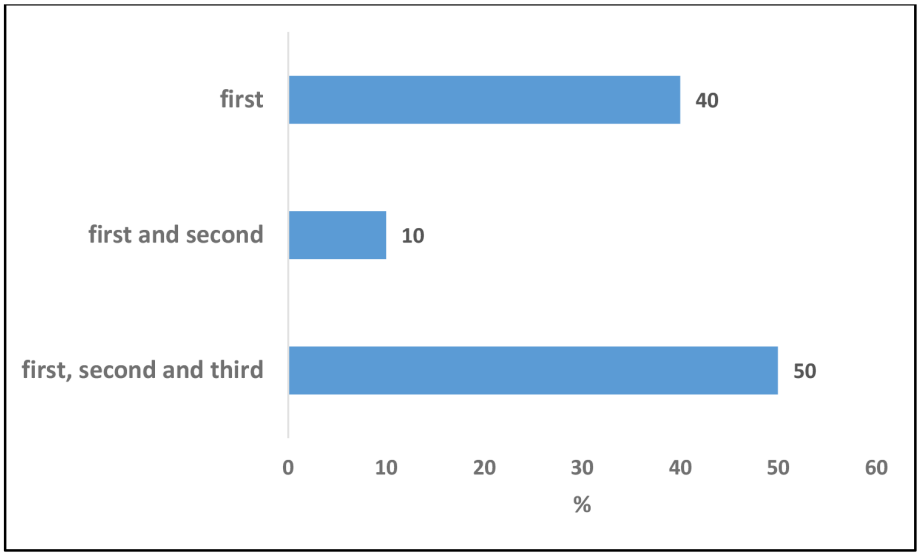

Figure 1: Number of workers in different shifts

Lifestyle of subjects

Table 2 shows the comparison between subjects who worked only the first or first and second shift with those who also worked night shifts (third shift) in terms of smoking status, alcohol consumption, and practicing some form of physical activity.

Table 2: Comparison of smoking status, alcohol consumption and physical activity levels between subjects who worked and those who did not work night shifts

Variables	Subjects with night shifts (N=60) (%)	Subjects without night shifts (N=60) (%)	*P* - value*
Active smokers	28 (46.7%)	25 (41.7%)	*P* = 0.581
Former smokers	17 (28.3%)	13 (21.7%)	*P* = 0.399
Passive smoking	45 (75%)	44 (73.3%)	*P* = 0.835
Moderate alcohol consumption	10 (16.7%)	10 (16.7%)	*P* = 1.000

Heavy alcohol consumption	15 (25%)	6 (10%)	*P* = 0.030*
Physical activity	39 (65%)	42 (70%)	*P* = 0.559
Current diseases	27 (45%)	22 (36.7%)	*P* = 0.353

Frequencies are shown as the number and percentage of subjects with the corresponding variable.

* Tested by χ^2 test or Fisher's exact test.

A significant difference existed between subjects who worked night shifts and those who did not in terms of alcohol consumption in larger quantities, which supports the fact that the night shift represents a significant risk factor for alcohol abuse.

Life and work satisfaction data

Table 3 shows the comparison between subjects who worked only the first or first and second shift with those who also worked night shifts (third shift) in terms of dissatisfaction with their job, life, friends and family, coworkers, and superiors.

Table 3: Comparison of dissatisfaction with workplace, life, friends and family, coworkers, and superiors between subjects who worked and those who did not work night shifts

Variables	Subjects with night shifts (N=60) (%)	Subjects without night shifts (N=60) (%)	*P* - value*
Job dissatisfaction	12 (20%)	4 (6.7%)	*P* = 0.031*
Life dissatisfaction	4 (6.7%)	0	*P* = 0.042*
Friends and family dissatisfaction	0	0	/
Coworkers' dissatisfaction	4 (6.7%)	3 (5%)	*P* = 0.697
Supervisors' dissatisfaction	3 (5%)	3 (5%)	*P* = 1.000

Frequencies are shown as the number and percentage of subjects with the corresponding variable.

* Tested by χ^2 test or Fisher's exact test.

A significant difference was found for job dissatisfaction and life dissatisfaction between subjects who worked and those who did not work night shifts (P=0.031 and P = 0.042, respectively).

Table 4 displays the comparison between subjects who worked only the first or first and second shift with those who also worked night shifts (third shift) in terms of conflicts, restlessness, loss of interest or boredom, difficulty concentrating, success in completing tasks, as well as feelings of exhaustion at work.

Table 4: Comparison of conflict, restlessness, loss of interest or boredom, difficulty concentrating, success in completing tasks, and feelings of exhaustion at work between subjects who worked and those who did not work night shifts

Variables	Subjects with night shifts (N=60) (%)	Subjects without night shifts (N=60) (%)	*P* - value*
Workplace conflicts	37 (61.7%)	42 (70%)	*P* = 0.336
Workplace restlessness	31 (51.7%)	36 (60%)	*P* = 0.358

Loss of interest or boredom at work	44 (73.3%)	39 (65%)	$P = 0.323$
Difficulty concentrating at work	27 (45%)	36 (60%)	$P = 0.099$
Success in completing tasks at work	59 (98.3%)	58 (96.7%)	$P = 0.559$
Feeling exhausted at work	56 (93.3%)	52 (86.7%)	$P = 0.361$

Frequencies are shown as the number and percentage of subjects with the corresponding variable.
* Tested by χ^2 test or Fisher's exact test.

No statistically significant difference was obtained for any of the examined variables between subjects who worked and those who did not work night shifts.

Health status of health care workers during night shift

The following figures provide data on the effects of night work on the work performance and health status of workers who worked at night.

Psychophysical abilities during night work among subjects who worked at night are provided in Figure 2.

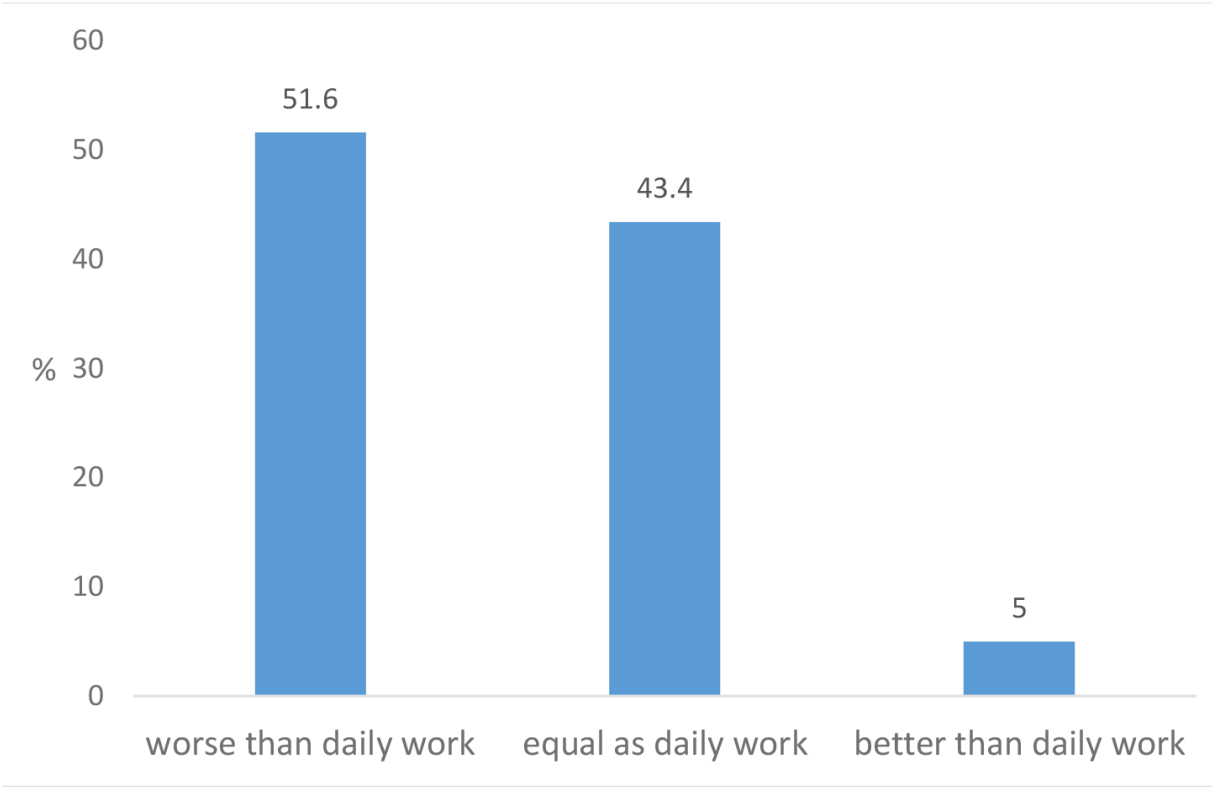

Figure 2: Psychophysical abilities during night work

The majority of subjects believed that psychophysical abilities during night work were worse than those during daily work.

Figure 3 shows the responses of subjects who worked night shifts regarding sleeping problems after working a night shift.

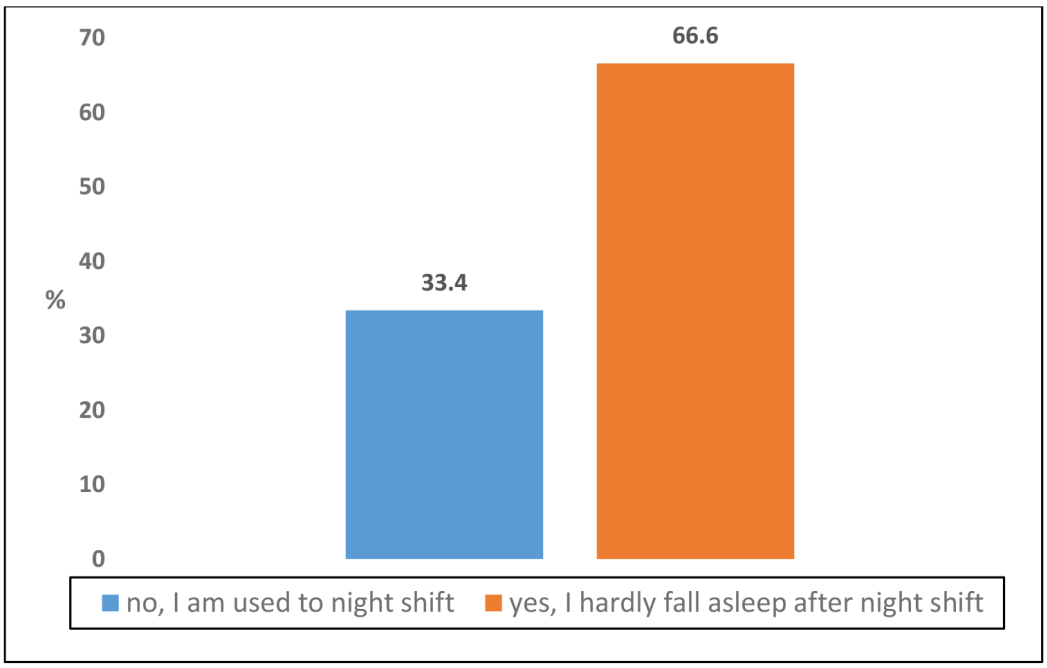

Figure 3: Sleeping problems after night shifts

The majority of subjects (66.6%) responded that they had difficulty sleeping after working a night shift.

Table 5 shows data on the occurrence of certain diseases, health disorders, and other conditions among workers who worked night shifts, as well as a comparison of the frequency of these conditions among workers who did not work night shifts.

Table 5: Frequency of certain diseases and conditions among workers who worked and those who did not work night shifts

Variables	Subjects with night shifts (N=60) (%)	Subjects without night shifts (N=60) (%)	*P* - value*
Frequency of diabetes	3 (5%)	2 (3.3%)	*P* = 0.648
Frequency of cardiovascular diseases	17 (28.3%)	8 (13.3%)	*P* = 0.043*
Frequency of gastrointestinal diseases	5 (8.3%)	3 (5%)	*P* = 0.464
Frequency of health conditions where meal timing is particularly important	8 (13.3%)	5 (8.3%)	*P* = 0.557
Frequency of conditions that affect sleep	9 (15%)	2 (3.3%)	*P* = 0.027*
Frequency of chronic diseases where symptoms are more pronounced at night	6 (10%)	2 (3.3%)	*P* = 0.272
Frequency of health conditions that require regular medication at strictly defined times	16 (26.7%)	7 (11.7%)	*P* = 0.037*

Frequencies are shown as the number and percentage of subjects with the corresponding variable.

* Tested by χ^2 test or Fisher's exact test.

The incidence of diabetes was higher among subjects who worked night shifts (5%) compared to those who did not work night shifts (3.3%), but the difference was not significant (P=0.648). The incidence of cardiovascular diseases was significantly higher among subjects who also worked night shifts (28.3%) compared to those who did not work (13.3%) (P=0.043). The frequency of gastrointestinal diseases was also higher among subjects who worked night shifts (8.3%) compared to those who did not work night shifts (5%), but the difference was not significant (P=0.464). The prevalence of health conditions where meal timing is particularly important was higher among night shift workers (13.3%) compared to non-night shift workers (8.3%), but the difference was not significant (P=0.557). The prevalence of sleep-related conditions was significantly higher among night shift workers (15%) compared to non-night shift workers (3.3%) (P=0.027). The prevalence of chronic diseases where symptoms are more pronounced at night was higher among night-shift workers (10%) compared to non-night shift workers (3.3%), but the difference was not statistically significant (P=0.272). The frequency of health conditions that require regular medication at strictly defined times was significantly higher among subjects who also worked night shifts (26.7%) than among those who did not (11.7%) (P=0.037).

According to questionnaire data, the most common symptoms that appeared during night work were stress, anxiety, flushing, weakness, insomnia, dizziness, fatigue, and irritability.

Perception of personal work ability

The comparison of the average values of current *versus* best work ability between subjects who worked night shifts compared to those who did not is shown in Table 6.

Table 6: Comparison of the average values of current *versus* best work ability between subjects who work night shifts and those who do not work night shifts

Variable	Subjects with night shifts (N=60) (%)	Subjects without night shifts (N=60) (%)	*P - value**
Current in terms of best working ability	8±1.63	7.9±1.57	*P* = 0.733

Numerical data are expressed as mean values with standard deviations.
* Tested by t-test for independent samples.

There was no significant difference in the average values of current versus best work ability between subjects who worked night shifts and those who did not work night shifts (P = 0.733).

Table 7: Comparison of the ability to perform usual daily activities over the last 3 months between night shifts workers and non-night shift workers

Variable	Subjects with night shifts (N=60) (%)	Subjects without night shifts (N=60) (%)	*P - value**
Always	32 (53.3%)	30 (50%)	*P* = 0.715
Most often	19 (31.7%)	24 (40%)	*P* = 0.080
Sometimes	8 (13.3%)	5 (8.3%)	*P* = 0.378
Rarely	1 (1.7%)	1 (1.7%)	*P* = 0.100
Never	0 (0%)	0 (0%)	/

Frequencies are shown as the number and percentage of subjects with the corresponding variable.

* Tested by χ^2test or Fisher's exact test.

No significant difference was found in the categories of ability to perform usual daily activities over the last 3 months between subjects who worked night shifts and those who did not work night shifts.

Table 8 presents the comparison of the perception of work ability among subjects who worked night shifts and those who did not work night shifts.

Table 8: Comparison of the perception of work ability among subjects who worked night shifts and those who did not work night shifts

Variable	Subjects with night shifts (N=60) (%)	Subjects without night shifts (N=60) (%)	*P - value**
Quite good	47 (78.3%)	48 (80%)	P = 0.822
Moderate	13 (21.7%)	10 (16.7%)	P = 0.487
Quite poor	0 (0%)	2 (3.3%)	P = 0.154
Very poor	0 (0%)	0 (0%)	/

Frequencies are shown as the number and percentage of subjects with the corresponding variable.

* Tested by χ^2test or Fisher's exact test.

No significant difference was found in the categories of perceived work ability between night-shift subjects and non-night shift subjects.

The comparison of the feeling of fulfillment and hope for the future among subjects who worked night shifts and those who did not work night shifts is illustrated in Table 9.

Table 8: Comparison of the perception of work ability among subjects who worked night hifts and those who did not work night shifts

Variable	Subjects with night shifts (N=60) (%)	Subjects without night shifts (N=60) (%)	*P - value**
continuously	7 (11.7%)	13 (21.7%)	*P* = 0.142
often	31 (51.6%)	30 (50%)	*P* = 0.855
sometimes	16 (26.7%)	15 (25%)	*P* = 0.835
rarely	6 (10%)	2 (3.3%)	*P* = 0.143
never	0 (0%)	0 (0%)	/

Frequencies are shown as the number and percentage of subjects with the corresponding variable.

* Tested by χ^2test or Fisher's exact test.

No significant difference was found in the categories of feeling fulfilled with hope for the future between subjects who worked night shifts and those who did not work night shifts.

Discussion

Night work has become a significant health concern in recent years and is a very serious public health problem for all workers from various sectors, including healthcare workers. The current study aimed to determine the impact of night shift work on health and work capacity among healthcare workers through analysis of personal medical history on the presence of certain diseases, conditions, symptoms and signs, lifestyle data, demographic data, data on work and workplace, length of service, life and work satisfaction, perception of personal work capacity. It also aimed to raise awareness among night shift workers about possible side effects, as well as to propose appropriate measures and recommendations for protection against the impact of negative effects of night shift work.

Shift work can also have negative health effects through its potential impact on behavior, such as poorer quality of diet or increased smoking or alcohol consumption. Bøggild and Knutsson in 1999 reported that shift workers compared to regular workers were more likely to be smokers[25]. Our results indicate that healthcare workers on night shifts had a higher rate of active smoking compared to non-night shift workers. Also, a large proportion of subjects (84.2%) were passively exposed to tobacco smoke, for less than 4 hours (44.9%) and for more than 4 hours (55.1%). The comparison between subjects who worked night shifts and subjects who did not work night shifts is as follows: active smokers (46.7% *vs.* 41.7%) (P=0.581), former smokers (28.3% *vs.* 21.7%) (P=0.399), and passive smokers (75% *vs.* 73.3%) (P=0.835).

According to the results obtained for alcohol consumption, 20 subjects (16.7%) reported occasional or daily intake of one large glass (200 ml) of beer/wine or one small glass (50 ml) of brandy or other strong drink. Comparison of subjects who worked night shifts and those who did not showed that consumption of alcohol in moderate amounts was the same in both groups - 10 (16.7%) *vs.*10 (16.7%). However, alcohol consumption in larger amounts was statistically significantly higher in night shift workers - 15 (25%) *vs.* 6 (10%) (P=0.030). The results showed that a significant difference existed between subjects who worked and those who did not work night shifts in terms of alcohol consumption in larger amounts, which supports the fact that the night shift is a significant risk factor for alcohol abuse. The comparison of physical activity between subjects who worked and those who did not work night shifts (65% *versus* 70%) showed that night workers were less physically active than those who worked day shifts, which supports the fact that the night shift is a risk factor.

Yang *et al.* investigated the association between shift work and the incidence of cardiometabolic multimorbidity (CMM) in patients with hypertension in a prospective, population-based cohort study of 36,939 participants in the United Kingdom. They used competing risk models

to examine the association between shift work and the risk of CMM, which was defined as the coexistence of hypertension and diabetes, coronary heart disease, or stroke in the study. They also investigated the association between the frequency and duration of shift work and the risks of CMM. In addition, they conducted a cross-classification analysis combining the frequency and duration of shift work, chronotype, and sleep duration as exposure metrics. During a mean follow-up of 11.6 years, a total of 5,935 participants developed CMM. They found that usually/always working night shifts was associated with a 16% higher risk of CMM compared to day workers (OR=1.16 [95% CI, RR=1.02-1.31]). They also found that a higher frequency of night shifts (>10/month) was associated with an increased risk of CMM (OR=1.19 [95% CI, RR=1.06-1.34]), which was more pronounced for >10/month in combination with a morning chronotype or <7 hours or >8 hours of sleep duration (OR=1.26 [95% CI, RR=1.02-1.56]; OR=1.43 [95% CI, RR=1.19-1.72]. They also found that night shift work was associated with a higher risk of CMM in patients with hypertension[26].

Wong *et al.* investigated the relationship between shift work and cardiovascular diseases (CVD) to identify potential gaps in the current knowledge and highlight areas for future research. Hypertension, diabetes, and a sedentary lifestyle are known risks for CVD, and the results of this study suggest that shift work should be added to that list. Elevated inflammatory markers and DNA damage in shift workers may be related to their increased progression of atherosclerosis and the positive association of shift work with coronary artery disease. There are few studies on mitigating approaches for CVD associated with shift work, such as dietary modification or exercise, highlighting the need for further focused research in this area[27].

In our study, according to the anamnestic data, cardiovascular diseases and hypertension (18.3%), musculoskeletal (6.7%) and endocrine and metabolic diseases (8.3%) predominated among the subjects, while other diseases occurred less frequently. The frequency of cardiovascular diseases in subjects who worked night shifts compared to those who did not work night shifts was significantly higher.

The study by Gao *et al.* evaluated the association between shift work and the risk of type 2 diabetes. The results of the meta-analysis showed that shift work was associated with an increased risk of type 2 diabetes (OR=1.10, 95% CI, RR=1.05-1.14). Subgroup analyses showed that shift workers had an increased risk of type 2 diabetes, while healthcare workers had the highest risk compared to clerical and manual workers, and night shift and rotating shift work were associated with an increased risk of type 2 diabetes. A dose-response meta-analysis based on three groups among female workers showed that there may be a positive association between the duration of shift work and the risk of type 2 diabetes. The authors concluded that shift work was associated with an increased risk of type 2 diabetes. Among female workers, the prolongation of years of exposure to shift work appeared to increase the risk of type 2 diabetes (P=0.043)[28].

The frequency of diabetes in our study was higher among subjects who worked night shifts (5%) compared to those who did not work night shifts (3.3%), but the difference was not significant (P=0.648).

Shift work can lead to adverse health effects, including gastrointestinal disorders. A study by Somayeh Rahimi-Moghadam *et al.* aimed to compare the prevalence of gastrointestinal disorders among day nurses, shift nurses, and office workers at the University of Medical Sciences in Kerman, Iran. This cross-sectional study was conducted in 2011, with the participation of 159 hospital nurses and 167 office workers at the same university. The results showed that anorexia (P=0.0001), dyspepsia (P=0.002), nausea (P=0.001), and hiccups (P=0.003) were more prevalent among shift workers. The results also showed that the prevalence of anorexia (P=0.02), gastric ulcer (P=0.04) and dyspepsia (P=0.02) was higher in nurses with irregular shift work than in those with regular shift work. Among demographic characteristics, gender was associated with nausea (P=0.004), and nausea was more prevalent in women (OR=4.3, 95% CI: RR=1.7-6.3). Also, older age was associated with dyspepsia (P=0.02). Gastrointestinal disorders were more common in shift workers. It was recommended that more capable and qualified nurses should be selected for shift work to cope with these adverse effects of shift work29.

Pietroiusti *et al.* investigated whether shift work was associated with an increased rate of peptic ulcer in *H. pylori*-infected workers. A total of 247 day workers and 101 night shift workers were included. The prevalence of duodenal ulcer was significantly higher in night shift workers than in day shift workers (OR = 3.92, 95% CI RR = 2.13 to 7.21). The authors concluded that shift work increased the ulcerogenic potential of *H. pylori* infection and should be considered a risk factor for duodenal ulcer in infected shift workers. Treatment of the infection in this high-risk group may improve workers' health and may reduce the economic impact of peptic ulcer[30].

In the current study, according to the anamnestic data on the presence of certain diseases and conditions in examined subjects, the frequency of digestive system diseases was 3 (%). The frequency of gastrointestinal tract diseases was higher in subjects who also worked night shifts (8.3%) compared to those who did not (5%), but the difference was not statistically significant (P=0.464).

It is clear that the acute and chronic effects of shift work can have a direct impact on health and well-being of the worker, as well as an indirect effect by the inability to work with poor health. In terms of workplace safety policy, the burden that night and shift work impose on organizations creates a need to establish a policy for the proper organization and management of shift work and especially night work. Policies and programs for the adequate scheduling and engagement of workers who work night shifts should promote the prevention, reduction and management of problems associated with night work. Health professionals should try to understand the employer's policy on the organization of work and shifts, as well as the sup-

port available to employees, in the interest of preserving and promoting health and safety at work.

The current study has some limitations. First of all, the study included a relatively small number of subjects and their distribution in individual job positions was not even, which may have affected the obtained results. Furthermore, the total sample was obtained from one hospital, which may lead to self-reporting bias and data generalizability. Also, data on the impact of night work on health and work ability among examined subjects were based mainly on the questionnaire without qualitative and quantitative assessment. Finally, the cross-sectional design of the study may be addressed as a limitation.

Conclusion

The results obtained in this study have clearly shown that night work has negative effects on health and working capacity of healthcare workers; indirectly reduces work efficiency, which, in turn, has repercussions on patients' health. In order to reduce the risks that arise during night work on health and to reduce the work capacity of healthcare workers, on one hand, and to preserve and improve the health status and working capacity, on the other hand, a cooperation between workers, employers and the union is recommended. It is also necessary to increase the motivation and engagement of workers in preserving and improving their health, as well as promoting the culture on prevention of harmful effects of night work. Continuous monitoring of health status and working ability of employees is required through timely implementation of periodic preventive health examinations, while the work process should be organized in such a way as to avoid, as far as possible, overtime work by night workers before or after the daily work period that includes night work. Full cooperation among workers, employers and trade unions is needed to improve safety, health and well-being at work, together with stronger cooperation and exchange of experiences with state institutions in planning and promoting efforts to improve health and safety of workers through dialogue with employers. Regular exercise, avoidance of unhealthy foods, smoking, and a good night's sleep in a quiet and dark room after night work are recommended. The specific restrictions for night workers should be duly taken into account by health authorities, other institutions and employers within the framework of measures to encourage training and qualification, as well as cultural, sport and recreational activities for night workers.

Competing Interests: All authors hereby have declared that no competing interests exist.

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PUBLIC HEALTH

POOR SLEEP QUALITY SIGNIFICANTLY CONTRIBUTES TO THE OCCURRENCE OF MULTIMORBIDITY IN OLDER ADULT POPULATION

Ardhya Ridha Prananda Siagian Putri[1], Erlin Listiyaningsih[1], Helda Khusun[2]

[1] *Universitas Muhammadiyah Prof. DR. Hamka, Jakarta, Indonesia*

[2] *Universitas Muhammadiyah Prof. DR. Hamka; SEAMEO Regional Center for Food and Nutrition (RECFON), Jakarta, Indonesia*

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***Correspondence:**

Erlin Listiyaningsih, Universitas Muhammadiyah Prof. DR. HAMKA, Jakarta, Indonesia.

E-mail: erlin.soedarmo@uhamka.ac.id

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Abstract

The demographic condition of the aging population in Indonesia is accompanied by an increased risk of mortality and morbidity, which is exacerbated by multimorbidity, defined as the existence of two or more chronic diseases in older adults. This has a wide impact on their health, including physical and psychological effects on the family as well as significant economic impact on the government due to the soaring health insurance expenditures. This study aimed to discover multimorbidity-related factors, such as socio-demographic characteristics, behavior, and social environment. This research is an observational analysis with a case-control study design and purposive sampling technique comprising 75 cases and 75 controls. Data were taken using a questionnaire with interview techniques and analyzed by multiple logistic regression. The multivariate analysis showed seven variables significantly related to multimorbidity: physical activity (p = 0.016), BMI (p = 0.020), age (p = 0.011), family history (p = 0.005), smoking status (p = 0.012), sleep quality (p = 0.017), and social interaction (p = 0.007). The sleep quality variable had the most significant effect on the incidence of multimorbidity in older adults, with OR= 8.445. Education for behavior change needs to focus on behavioral factors that can be altered, such as improving sleep quality accompanied by increased physical activity, quitting smoking, maintaining an ideal weight, and encouraging older adults to be active in social activities to enhance their quality of life.

ЈАВНО ЗДРАВЈЕ

ЛОШИОТ КВАЛИТЕТ НА СПИЕЊЕ ЗНАЧИТЕЛНО ПРИДОНЕСУВА ЗА ПОЈАВА НА МУЛТИМОРБИДИТЕТ КАЈ ПОСТАРАТА ПОПУЛАЦИЈА

Ардја Рида Прананда Сиагијан Путри[1], Ерлин Листијанингсих[1], Хелда Кусун[2]

[1] *Универзитет Мухамадијах Проф. ДР. Хамка, Џакарта, Индонезија*

[2] *Универзитет Мухамадијах Проф. ДР. Хамка; SEAMEO Регионален центар за храна и исхрана (RECFON), Џакарта, Индонезија*

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***Кореспонденција:**

Ерлин Листијанингсих, Универзитет Мухамадијах Проф. ДР. ХАМКА, Џакарта, Индонезија.

Е-пошта: erlin.soedarmo@uhamka.ac.id

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Извадок

Демографската состојба на старите лица во Индонезија е придружена со зголемен ризик од морталитет и морбидитет, дополнително влошена од мултиморбидитет, односно постоењето на две или повеќе хронични заболувања кај постарите возрасни лица. Тоа има големо влијание врз здравјето на постарите возрасни лица, вклучувајќи ги физичките и психолошките ефекти врз семејството, како и економското влијание врз владата поради зголемените средства за здравствено осигурување. Целта на оваа студија беше да се откријат факторите поврзани со мултиморбидитет, како што се социодемографските карактеристики, однесувањето и социјалната средина. Материјали и методи: Беше спроведена еден вид опсервациона студија која вклучуваше примерок од 75 испитаници - случаи и 75 испитаници – контролни лица. Податоците беа земени со помош на прашалник и интервју со испитаниците, а потоа анализирани со повеќекратна логистичка регресија. Мултиваријантната анализа покажа дека седум варијабли беа значајно поврзани со мултиморбидитетот: физичка активност (p = 0,016), BMI (p = 0,020), возраст (p = 0,011), семејна историја (p = 0,005), статус на пушење (p = 0,012), квалитет на спиење (p = 0,017) и социјална интеракција (p = 0,007). Квалитетот на спиењето имаше најзначаен ефект врз инциденцијата на мултиморбидитет кај постарите возрасни лица, со OR = 8,445. Интервенциите треба да се фокусираат на факторите на однесување што можат да се променат, како што се подобрување на квалитетот на спиењето придружено со зголемена физичка активност, откажување од пушење, одржување идеална тежина и охрабрување на постарите возрасни лица да бидат активни во општествените активности за да го подобрат квалитетот на својот живот.

Introduction

The increasing life expectancy is a sign of the success of development in Indonesia, and it presents new challenges in the form of a growing elderly population, which has become a global trend experienced by many countries in the world, including Indonesia. The number of the world's population aged 60 years and older is expected to increase from 1.4 billion in 2020 to 2.1 billion by 2050.[1]

The growing elderly population is directly proportional to increased health risks, considering the decline in bodily functions that accompanies older adults. Based on data from the 2023 Health Statistics Profile, older adults are most vulnerable to health problems. A total of 41.49% of older adults experienced health complaints during the 2021-2023 period, which had implications for a decline in the quality of life, reflected in the proportion of 19.72% of older adults who experienced difficulties in carrying out daily activities.[2]

This condition is exacerbated by multimorbidity, which is simultaneous appearance of various chronic or acute diseases and medical conditions in one person.[3] Literature studies indicate that the prevalence of multimorbidity in older adults ranges from 30.7% to 57%.[4] Globally, the highest prevalence of multimorbidity has been found in South America (50.1%), while the lowest prevalence was observed in Africa (28.2%).[5]

Although data related to multimorbidity studies in Indonesia is still limited, the latest study by Mathias et al. in 2021 showed that respondents aged 50 years and older in Indonesia had a multimorbidity prevalence of 22% based on data from the Indonesia Family Life Survey (IFLS) in 2014.6 In addition, a study by Nurinayah et al. in Bandung found that 166 older adults or 40.9% suffered from multimorbidity.[7]

The high prevalence of multimorbidity in the elderly has consequences in the form of a higher risk of death, greater need for health services with large costs, a decrease in productivity, and a low quality of life.[5,6]

The low quality of life after the onset of a disease will affect the level of independence in caring for oneself, the low ability to meet physiological needs and adjust to lifestyle changes as well as the low level of medication adherence.[8] This condition also burdens families and caregivers because older adults tend to depend on getting help in carrying out daily activities.

The government also feels a large impact related to the loss of Indonesia's National Health Insurance system, known as BPJS program due to the high cost of handling chronic diseases. More than 43% of Indonesia's National Health Insurance (BPJS) users who go to the hospital are identified with chronic multimorbidity.[9]

Non-communicable diseases account for around 60% of the total expenditure on health insurance programs in Indonesia.[6] The synergistic effects of multimorbidity create an urgent need for wider access to specialist services for more in-depth biomedical examinations, appropriate treatment, and comprehensive care.[10]

Based on the Indonesian National Socio-Economic Survey, according to the type of health expenditure, the largest proportion is used for

medical or curative service costs, accounting for approximately 68.15% of the total monthly health expenditure. In comparison, the cost of preventive services is around 17.54% of the total health expenditure for a month and the rest is used for drug costs of 14.32%.2 Therefore, the BPJS program is not currently able to fully finance (100%) the treatment of chronic diseases.

Factors that have been confirmed to affect the high risk of suffering from multimorbidity are female gender, old age, high socioeconomic level, overweight, family history of non-communicable disease, older adults who are married, including widows/widowers, unemployed individuals, and those who live in urban areas.[11–13] The high prevalence of multimorbidity events is also due to behavioral risk factors such as lack of fresh fruit consumption, smoking and alcohol consumption, poor sleep quality, lack of physical activity and low medication adherence.[14,15]

The health profile of the Pancoran Mas Community Health Center in 2022 showed that only about 42% of the total 9,216 elderly population had taken part in health screenings.16 This figure indicates a considerable number of older adults whose diseases have not been detected. In addition, a preliminary study found that 9 out of 15 older adults experienced multimorbidity. However, there is no accurate data on the prevalence of multimorbidity in older adults in the region, an obstacle to better health service planning.

A data gap regarding multimorbidity in older adults in Indonesia, especially in the Pancoran Mas Community Health Center area is a strong basis for researchers to conduct further studies. This study aimed to uncover the risk factors associated with multimorbidity in older adults so that it can be the foundation for developing more effective interventions.

Materials and methods

This is an observational analytical study with a case-control design. It was conducted in the working area of the Pancoran Mas Community Health Center in Depok City, which covers 2 (two) sub-districts - Depok Sub-district and Pancoran Mas Sub-district, and was conducted in June 2024. The population included were older adults aged 60 years and above who had been recorded as having received treatment in the Pancoran Mas Community Health Center working area during the research period. Meanwhile, respondents were divided into case groups, and controls were taken from elderly patients who came for treatment in the working area of the Pancoran Mas Community Health Center during the research period. The case group comprised older adults who suffered from multimorbidity based on the disease diagnosis made by a physician within the previous 6 months, while the control group included older adults who did not suffer from multimorbidity, either being disease-free or having only one type of disease.

The study samples were taken using purposive sampling. A total of 150 respondents consisted of 75 people in the case group and 75 people in the control group. The number of samples was calculated using the two-proportional difference hypothesis formula to detect differences in exposure in cases with multimor-

bidity and non-multimorbidity. Data was collected using face-to-face interviews and questionnaires for 20-25 minutes.

The dependent variable in this study was multimorbidity, while the independent variable included three aspects - sociodemographic characteristics (age, gender, family history, occupation, marital status and body mass index), behavioral factors (smoking status, sleep quality, physical activity and risky diet), and social environmental factors (family support, living arrangement and social interaction). Multimorbidity was assessed based on respondents' self-reports identifying several chronic diseases among elderly individuals diagnosed by a physician within the last 6 months, without additional examinations conducted by the researcher. Ten chronic diseases were the focus of the research: hypertension, diabetes mellitus, gastroenteritis, hypercholesterolemia, arthritis, coronary heart disease (CHD), asthma, chronic obstructive pulmonary disease (COPD), stroke and depression. Sleep quality variables were measured using a leaned questionnaire, Pittsburgh Sleep Quality Index (PSQI), and the physical activity variable was measured using a questionnaire, Physical Activity Scale for the Elderly (PASE). Next, the data were analyzed by chi-square and multiple logistic regression tests with a significance level of $p = 0.05$ and a confidence level of 95% CI. Data were presented in both tabular and narrative form. The study was approved by the Medical and Health Research Ethics Commission, University of Muhammadiyah Prof. DR. Hamka, with the number KEPKK/FK/054/04/2024.

Results

Sociodemographic characteristics are shown in Table 1. The study results showed that the majority of respondents were aged 60-69 (63.3%); there were 70.7% of females, 56.7% had no family history of illness, 62.7% were unemployed), 53.3% were married, and 52% had an abnormal BMI.

Table 1: Sociodemographic characteristics of the study population

Characteristics	n = 150	%
Age		
≥ 70 years	55	36.7
60-69 years old	95	63.3
Gender		
Woman	106	70.7
Man	44	29.3
Family History		
Yes	65	43.3
No	85	56.7
Work		
Not Working	94	62.7

Work	56	37.3
Marital Status		
Single/Divorce/Widow/Widower	70	46.7
Married	80	53.3
Body Mass Index (BMI)		
Abnormal	78	52
Normal	72	48

Source: Primary Data, 2024

The prevalence of 10 chronic NCDs is shown in Table 2. Older adults who were affected by multimorbidity had 2 to 6 types of diseases, with the most frequent co-occurrence being 4 and 5 types of diseases (16%). The top three chronic NCDs experienced by most respondents were hypertension (68.7%), diabetes mellitus (43.3%) and gastroenteritis (39.3%). The combination of hypertension and arthritis was most commonly found in older adults studied. However, about 48.7% of respondents presented with a single chronic disease, and 1.3% reported no specific chronic disease.

Table 2: Prevalence of chronic NCDs in older adults

Chronic NCDs	n	%
Hypertension	103	68.7
Diabetes Mellitus	65	43.3
Gastroenteritis	59	393
Hypercholesterolemia	58	38.7
Arthritis	56	37.3
Coronary Heart Disease (CHD)	32	21.3
Asthma	11	7.3
Chronic obstructive pulmonary disease	5	3.3
Stroke	4	2.7
Depression	3	2
Number of Chronic Diseases		
0	2	1.3
1	73	48.7
2	4	2.7
3	13	8.7
4	24	16
5	24	16

*NCD= Non-Communicable Diseases
Source: Primary Data, 2024

Table 3 shows that the majority of older adults with multimorbidity were aged ≥70 years (52%), female (80%), had a family history (61.3%), were unemployed (74.7%), had no partner (single, divorced, widow/ widower) (57.3%), had abnormal BMI (68%), smoked (58.7%), had poor sleep quality (64%), inadequate physical activity (93.3%), risky diet (89.3%), poor family support (84%), lived with family (76%) and had poor social interaction (57.3%).

Furthermore, Table 3 shows that factors related to multimorbidity included age ($p < 0.001$), gender ($p = 0.020$), family history ($p < 0.001$), occupation ($p = 0.004$), marital status ($p = 0.014$), body mass index (BMI) ($p < 0.001$), physical activity ($p < 0.001$), smoking status ($p = 0.003$), sleep quality ($p = 0.009$), risky diet ($p < 0.001$), family support ($p = 0.006$), and social interaction ($p < 0.001$). However, no significant relationship was found between living arrangements and multimorbidity in older adults.

Table 3: Relationship between multimorbidity and sociodemographic, behavioral and social environment characteristics

Variable	Multimorbidity				Total		p-value	cOR value (95%CI)
	Yes		No					
	n	%	n	%	n	%		
Age								
≥ 70 years	39	52	16	21.3	55	36.7	< 0.001	3.995 (1.955 – 8.161)
60-69 years old	36	48	59	78.7	95	63.3		
Gender								
Woman	60	80	46	61.3	106	70.7	0.020	2.522 (1.213 – 5.244)
Man	15	20	29	38.7	44	29.3		
Family History								
Yes	46	61.3	19	25.3	65	43.3	< 0.001	4.675 (2.327 – 9.393)
No	29	38.7	56	74.7	85	56.7		
Work								
Not Working	56	74.7	38	50.7	94	62.7	0.004	2.870 (1.440 – 5.720)
Work	19	25.3	37	49.3	56	37.3		
Marital Status								
Single/Divorce/Widow/ Widower	43	57.3	27	36	70	46.7	0.014	2.389 (1.238 – 4.608)
Married	32	42.7	48	64	80	53.3		
Body Mass Index (BMI)								
Abnormal	51	68	27	36	78	52	< 0.001	3.778 (1.921 – 7.431)
Normal	24	32	48	64	72	48		
Smoking Status								
Yes	44	58.7	25	33.3	69	46	0.003	2.839 (1.460 – 5.518)
No	31	41.3	50	66.7	81	54		
Sleep Quality								
Poor	48	64	31	41.3	79	52.7	0.009	2.523 (1.306 – 4.874)
Good	27	36	44	58.7	71	47.3		

Physical Activity								
Poor	70	93.3	34	45.3	104	69.3	< 0.001	16.882 (6.119 – 46.576)
Good	5	6.7	41	54.7	46	30.7		
Risky Diet								
Not Good	67	89.3	45	60	112	74.7	< 0.001	5.583 (2.347 – 13.281)
Good	8	10.7	30	40	38	25.3		
Family Support								
Not Good	63	84	47	62.7	110	73.3	0.006	3.128 (1.441 – 6.786)
Good	12	16	28	37.3	40	26.7		
Living Arrangement								
Living Alone	18	24	11	14.7	29	19.3	0.215	1.837 (0.801 – 4.216)
Living with Family	57	76	64	85.3	121	80.7		
Social Interaction								
Poor	43	57.3	13	17.3	56	37.3	< 0.001	6.409 (3.019 – 13.606)
Good	32	42.7	62	82.7	94	62.7		

*cOR = Crude Odds Ratio, Source: Primary Data, 2024

Table 4 presents logistic regression results for multimorbidity. Sociodemographic characteristics were included in modelling 1; it was found that family history was the most dominant risk factor, where the presence of family history with similar health conditions significantly increased the likelihood of a person being multimorbid 5 times (OR = 5.194; 95% CI = 2.259 - 11.94). Furthermore, individuals aged 70 years or older had a significantly higher risk of developing multimorbidity than those aged 60-69 years (OR = 3.667; 95% CI = 1.530 – 8.787). Similarly, individuals with an abnormal BMI had a significantly higher risk of developing multimorbidity than those with normal BMI (OR = 3.318; 95% CI = 1.469 - 7.494). Factors such as gender, occupation and marital status did not significantly affect model 1.

Behavioral factors in model 2 showed that, in addition to being physically inactive as the most influencing factor for multimorbidity (OR = 9.746; 95% CI = 3.346-28.385), other behavioral factors such as poor sleep quality (OR = 5.639; 95% CI = 1.951-16.300), smoking status (OR = 4.613; 95% CI = 1.588-13.400), and risky diet (OR = 4.493; 95% CI = 1.635-12.349) significantly contributed to the incidence of multimorbidity in older adults.

In model 3, social environmental factors were included in the analysis. The results showed that lack of family support and poor social interaction was significantly associated with an increased risk of multimorbidity by three times and six times, respectively, compared to older adults with good family support and social interaction (OR family support = 3.157; 95% CI = 1.348-7.397 and OR social interaction = 6.305; 95% CI = 2.875-13.828). The living arrangement factor was not significantly related.

In addition, model 4 combined sociodemographic, behavioral and social environment characteristic

factors that were analyzed simultaneously. Multivariate final modelling in model 5 showed that the variables related to multimorbidity were physical activity, BMI, age, family history, smoking status, sleep quality and social interaction. Sleep quality was the most dominant variable influencing multimorbidity (OR = 8.445; 95% CI 1.4 – 47.03).

Table 4: Multivariate regression analysis of factors associated with multimorbidity in older adults

Factors	Model 1		Model 2		Model 3		Model 4		Model 5	
	p	aOR (95% CI)	p	aOR (95% CI)	p	aOR (95% CI)	p	aOR (95% CI)	p	aOR (95% CI)
Sociodemographic Characteristics										
Older Age	0.004	3.667 (1.530 – 8.787)					0.016	4.709 (1.336 – 16.599)	0.011	4.958 (1.436- 17.117)
Gender (Woman)	0.119	1.969 (0.839 – 4.620)					0.217	2.666 (0.561 – 12.659)	0.195	2.769 (0.594 – 12.899)
Have a Family History	0.000	5.194 (2.259 – 11.94)					0.006	5.664 (1.665 – 19.271)	0.005	1.607 (0.431 – 5.991)
Not Working	0.122	1.971 (0.835 – 4.656)					0.707	1.261 (0.377 – 4.214)	/	/
Not Married	0.063	2.196 (0.958 – 5.031)					0.531	1.534 (0.402 – 5.848)	0.480	1.607 (0.431 – 5.991)
Abnormal BMI	0.004	3.318 (1.469 – 7.494)					0.019	4.161 (1.268 – 13.661)	0.020	4.057 (1.249 – 13.175)
Behavioral Factors										
Smoking			0.005	4.613 (1.588 – 13.40)			0.015	5.776 (1.413 – 23.607)	0.012	5.982 (1.477 – 24.230)
Poor Sleep Quality			0.001	5.639 (1.951 – 16.300)			0.017	8.503 (1.461 – 49.479)	0.017	8.445 (1.472 – 48.443)
Poor Physical Activity			0.000	9.746 (3.346 – 28.385)			0.019	4.906 (1.300 – 18.514)	0.016	5.085 (1.361 – 18.998)
Risky Diet			0.004	4.493 (1.635 – 12.349)			0.078	3.513 (0.871 – 14.174)	0.082	3.404 (0.855 – 13.553)
Social Environmental Factors										
No Family Support					0.008	3.157 (1.348 – 7.397)	0.356	1.906 (0.485 – 7.496)	0.324	1.979 (0.510 – 7.685)
Living Alone					0.629	1.269 (0.483 – 3.335)	0.166	3.483 (0.595 – 20.385)	0.182	3.231 (0.577 – 18.081)
Poor Social Interaction					0.000	6.305 (2.875 – 13.828)	0.007	4.972 (1.565 – 15.797)	0.007	4.788 (1.542 – 14.864)

Source : Primary Data, 2024, *aOR = Adjusted Odds Ratio, p = p-value.

Logistic Regression Equation (Y) = a+b1x1 +b2x2+.....+bnxn

Multimorbidity = -24,630 +1,626 Poor Physical Activity + 1,400 Abnormal BMI + 1,601 Older Age + 1,789 Have a Family History + 2,134 Poor Sleep Quality + 1,566 Poor Social Interaction + 0.474 Not Married + 0.683 No Family Support + 1,018 Gender +1,173 Living Alone + 1,225 Risky Diet

Discussion

Pancoran Mas Community Health Center is an urban health center located in Depok City. It is very strategically located and closest to the center of Depok City, so it has become a community treatment center and has wide coverage, especially in providing health services for older adults. This study found that

older adults in Pancoran Mas Community Health Center work area in Depok City were mostly women, predominantly in the young elderly groups (60-69 years old) and lived with their family or a partner rather than alone.

This data is supported by the 2019 national data on sociodemographic conditions of the elderly population in Indonesia in general, where the proportion of female elderly (5%) was greater than that of male elderly (4.6%) so that the life expectancy of female elderly was higher than that of men. In addition, based on age groups, older adults in Indonesia were predominantly in the young elderly groups aged 60-69 years (63.82%) compared to the elderly group aged 70 years and above. Then, based on residence status, most older adults lived with their families, partners, children, and grandchildren (40.64%) compared to a smaller proportion who lived alone (9.38%).[17]

Based on the demographic structure, Indonesia is experiencing a transition period towards an aging population structure, which has caused a shift in disease patterns, marked by a decrease in cases of infectious diseases and an increase in cases of non-communicable diseases that require attention. The incidence of NCDs in 2017 accounted for 55.3% of the disease burden in older adult group in Indonesia.[9]

Then, national data from 2019 indicated that around 51.1% of older adults experienced health complaints, and 26.2% experienced illness.[17] This situation becomes even more concerning with the existence of several chronic diseases or multimorbidity in older adults.

In this study, hypertension was the most frequently reported disease related to multimorbidity, as it was often accompanied by one other chronic condition. The combination of hypertension with cardiovascular disease, stroke, digestive diseases, hyperlipidemia, diabetes, and arthritis is a common condition in multimorbidity.[18] Similar findings were reported in previous studies illustrating that older adults suffer from top three diseases - hypertension (45.2%), diabetes mellitus (32.2%), and arthritis (29.5%).[12]

The results of the final modeling of multiple logistic regression revealed that physical activity, BMI, age, family history, smoking status, sleep quality, and social interaction were related to multimorbidity. These results are similar to previous studies.[15]

Age was significantly associated with multimorbidity. Similar findings presented in other studies found a relationship between age factors and the incidence of multimorbidity ($p < 0.05$).[13,19,20] Individuals aged 70 years or older were at a higher risk of developing multimorbidity or experiencing two or more chronic conditions simultaneously (OR= 1.46; 95% CI =1.22 - 1.74).[14]

The increasing prevalence of multimorbidity goes hand in hand with the advancing age.[21] With a tendency to live longer, it means that individuals are more likely to develop chronic diseases due to prolonged exposure to risk factors such as an unhealthy lifestyle that accumulates over time and damages organs and body systems so that disease arises.[22]

However, the study by Pereira et al. (2023) shows that younger people also

experience a high prevalence of various health conditions.[20] Therefore, multimorbidity treatment should begin from younger age rather than focusing only on older adults.

Furthermore, the family history variable was significantly associated with multimorbidity (OR= 5.730; 95% CI: 1.688 – 19.442). In line with the findings of Chen et al. in 2022, family history is considered the most significant risk factor for multimorbidity (OR: 2.22; 95% CI: 1.73-2.86).[14] Individuals with a family history of hypertension and diabetes are at higher risk of suffering from similar diseases than those without a history of these diseases.[23] Family-inherited genetic factors can increase susceptibility to developing some chronic diseases and contribute to the existence of multimorbidities.[22]

This study also showed that the BMI variable was significantly related to multimorbidity (p-value =0.020; OR= 4.057; 95% CI: 1.249 – 13.175). This study's results align with previous research, which stated a positive relationship between BMI and multimorbidity (p-value < 0.05).24–26 An unhealthy lifestyle, reflected in high BMI outcomes, results in developing chronic conditions such as cardiovascular disease, diabetes, and respiratory problems.[22] Moreover, overweight is a common phenomenon in urban areas today, where unhealthy diets and lifestyles supported by easy access to processed foods and the lack of public spaces for exercise are the main driving factors for urban residents. So, overcoming BMI through lifestyle modifications such as dietary changes and increased physical activity can help prevent and manage chronic diseases.

Furthermore, smoking status was statistically significant in relation to multimorbidity, where elderly smokers were almost 6 times more likely to experience multimorbidity than non-smokers (OR= 5.982; 95% CI: 1.477 – 24.230). This is consistent with several other studies that reported a significant association between smoking status and the incidence of multimorbidity ($p < 0.001$).[20,27,28]

Smoking status is associated with a higher risk of multimorbidity, suggesting the negative impact of smoking on health because smoking weakens the immune system and inhibits the body's ability to heal and fight infections, making it more susceptible to developing multiple chronic diseases simultaneously.[28]

The results of this study indicated that the sleep quality variable was the most dominant variable that affected the incidence of multimorbidity (p-value of 0.017). Respondents who had poor sleep quality were 8.445 times more likely to experience multimorbidity than those who had good sleep quality (OR=8.445; 95% CI 1.472 – 48.443). Similar findings were reported by Xue et al. in their 2022 study in China, which showed that sleep quality was the most dominant factor influencing multimorbidity (OR = 2.445; 95% CI: 2.043–2.927).[29]

Moreover, the study area is classified as the social status of urban communities with more crowded and busy social activities until late into the night. This may be one of the conditions that affect poor sleep quality among people in urban areas. Meanwhile, a study of regions with different population characteristics in rural areas in Tiongkok, showed that poor sleep quality significantly

affected multimorbidity (OR = 2.15; 95% CI: 1.59–2.92). Most rural residents are involved in agricultural activities daily, especially if there is busyness during the harvest season, which requires them to wake up early and stay up late, thus reducing sleep time and negatively impacting the health of older adults.[15]

Individuals with poor sleep quality had a 1.39 times higher risk of developing two chronic diseases, 1.56 times higher risk for three chronic diseases, and 2.36 times higher risk for four chronic diseases.[30] This shows that the more chronic diseases a person suffers, the higher the risk of sleep disorders. Older adults with sleep problems were 34% more likely to have a vascular-metabolic multimorbidity pattern, 62% more likely to have a cardiopulmonary pattern, 64% more likely to have a musculoskeletal multimorbidity pattern, and 88% more likely to have coexisting multimorbidity patterns.[31]

Studies on aging in Canada show that the risk of multimorbidity in both men and women of various age groups is higher in individuals who report poor sleep patterns in the form of too short or too long sleep duration, as well as dissatisfaction with sleep quality.[32] According to a study by Lin Yawen et al. in 2022, multimorbidity is more common in people with shorter (less than 7 hours) and longer (more than 9 hours) sleep duration at night while people with an ideal night's sleep duration of between 7 and 9 hours have a lower prevalence of multimorbidity.[33]

Poor sleep quality can trigger changes in autonomic activity, appetite regulation, and inflammation, all linked to chronic diseases.[30] Poor sleep quality negatively impacts happiness and quality of life because older adults who experience poor sleep quality are more susceptible to negative emotions, such as anxiety, depression, and the inability to cope with stress effectively.[13,34]

On the other hand, there is a reciprocal relationship that shows how sleep quality and a person's chronic condition can worsen each other. Multimorbidity also increases the risk of poor sleep quality; for example, individuals with multimorbidity who have to take a lot of medication, have the potential to experience negative side effects on their sleep duration.[30]

Furthermore, in diabetics, it can also cause sleep disorders such as excessive thirst and frequent urination at night, as well as hormonal system disorders that can cause difficulty sleeping. Lack of sleep can increase the risk of diabetes because it causes insulin resistance.[35] Therefore, good sleep management should be an integral part of the care of multimorbidity patients. By providing the right education and interventions, primary health care can help patients cope with sleep disorders and improve their overall quality of life.

This study also showed that physical activity was significantly associated with multimorbidity (OR= 5.085 95% CI: 1.361 – 18.998). Physical activity is effective in preventing and managing chronic diseases, as well as improving mental health and general quality of life.[36] The results of the study were in line with the explanation that there was a relationship between physical activity and the incidence of multimorbidity (p-value

< 0.05).[12,20,28] Older adults who have never been physically active are at a very high risk of multimorbidity, 3.82 times higher than those who are physically active.[12]

Multimorbidity and physical inactivity form a cycle that reinforces each other. Chronic diseases can lead to decreased physical activity; conversely, a lack of physical activity can worsen health conditions and increase the risk of developing diseases. This is evidenced by the results of studies in 46 low- and middle-income countries showing that older adults with multimorbidity have a 1.31 times higher risk of being physically inactive than healthy individuals. Conditions such as chronic pain due to arthritis can limit mobility and lead to sleep disturbances, which in turn can trigger depression and reduce motivation to exercise.[37]

The social and environmental factors associated with multimorbidity were social interactions indicated by values (p = 0.007) (OR= 4.788; 95% CI 1.542 – 14.864). Lack of participation in social activities was associated with an increased risk of developing multimorbidity (p = 0.003).[26]

Based on a study in the city of Makassar and a survey in 34 provinces in Indonesia, it was concluded that the involvement of older adults in social activities such as religious activities, social gatherings, and other social activities was still low due to declining physical conditions and a limited number of social activities in the environment where older adults lived.[38,39] Older adults who are active in socializing tend to be happier, healthier, and more independent because they can freely express their feelings and needs to others. Thus, older adults can be more independent and have a better quality of life.[40]

Limitation

The limitation of this study is using a case-control design, so recall bias is highly likely to occur. However, in this study, the recall conduct is general and does not require detailed information, so the condition of recall bias can be minimized. Furthermore, there is a limitation of data related to chronic diseases in the elderly that have not been fully registered in primary health facilities, so the prevalence of chronic diseases may be higher than in this study. This occurs because chronic disease patients are likely to visit health facilities in poor condition, thus being referred directly to secondary health services before reaching primary health facilities. Nevertheless, this study recommends that improving sleep quality must be accompanied by increasing physical activity, quitting smoking, maintaining an ideal weight, and encouraging older adults to participate in social activities. Primary health care providers must be more proactive in paying attention to sleep disorders in older adults. In addition, to maintain physical health and improve the quality of their sleep, older adults need to be motivated to be more active in doing regular exercise, especially multicomponent physical activity programs that include a combination of balance, strength, endurance, gait, and physical function training so that the quality of life of older adults can improve. Further research with broader scope and longitudinal methods is needed to better under-

stand the impact and patterns of multimorbidity in older people.

Conclusion

This study showed that the variables related to multimorbidity were physical activity, BMI, age, family history, smoking status, sleep quality, and social interaction. Sleep quality is the most dominant variable for the incidence of multimorbidity in older adults. Therefore, the target intervention needs to focus on factors that can still be changed and prevented, such as behavioral factors including sleep quality, physical activity, and smoking status. The implementation of the Chronic Disease Management Program (PROLANIS) needs to put a big emphasis on educating people about healthy behavior.

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CLINICAL SCIENCE

COMPARISON OF ESIN AND OPEN REDUCTION IN PEDIATRIC CAPITULUM RADII FRACTURES: RETROSPECTIVE STUDY

Marian Kamiloski[1], Shaban Memeti[1], Haris Sulejmani[2], Roza Sokolova[1], Monika Ardzanova[1]

[1] *University Clinic for Paediatric Surgery, Skopje, North Macedonia; Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, North Macedonia*

[2] *Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, North Macedonia*

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***Correspondence:**

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Abstract

Radial neck fractures (RNFs) in children present a clinical challenge due to variability in displacement and risk of complications. This retrospective study compared clinical outcomes between elastic stable intramedullary nailing (ESIN) and open reduction with transcondylar fixation in pediatric patients with Judet type III and IV fractures. From 2010 to 2015, 80 children aged 5.5–14.5 years with isolated RNFs were treated at the University Clinic for Pediatric Surgery in Skopje. Patients were divided into two groups: closed reposition with ESIN (n = 39) and open reposition with transcondylar fixation (n = 41). Postoperative outcomes were evaluated using the Mayo Elbow Performance Score (MEPS), radiographic alignment, and periosteal callus formation. Closed reposition with ESIN resulted in significantly higher rates of periosteal callus formation (97.44% vs. 56.10%, p = 0.000014), indicating better biological healing. Fracture alignment was comparable between groups (p = 0.13). Open reduction was more frequently required for Judet type IV fractures (63.41%). No significant differences were found in MEPS scores. The retrospective design limited structured complication reporting. ESIN is an effective, biologically favorable option for Judet type III RNFs, while open reduction remains necessary for more complex type IV fractures. Standardized long-term follow-up is essential for evaluating safety outcomes.

КЛИНИЧКИ ИСТРАЖУВАЊА

СПОРЕДБА НА ESIN И ОТВОРЕНА РЕПОЗИЦИЈА КАЈ CAPITULUM RADII ФРАКТУРИ КАЈ ДЕЦА: РЕТРОСПЕКТИВНА СТУДИЈА

Маријан Камилоски[1], Шабан Мемети[1], Харис Сулејмани[2], Роза Соколова[1], Моника Арџанова[1]

[1] *Универзитетска клиника за детска хирургија, Скопје, Северна Македонија; Медицински факултет, Универзитет „Св. Кирил и Методиј“ во Скопје, Северна Македонија*

[2] *Медицински факултет, Универзитет „Св. Кирил и Методиј“ во Скопје, Северна Македонија*

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Клучни зборови: фрактура на вратот на радиусот, еластична стабилна интрамедуларна остеосинтеза, отворена репозиција, педијатриски фрактури, класификација според Judet

***Кореспонденција:**

E-mail: risteskialeksandar@gmail.com

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Извадок

Фрактурите на вратот на радиусот (ФВР) кај децата претставуваат клинички предизвик поради варијабилноста во дислокацијата и ризикот од компликации. Целта на оваа ретроспективна студија беше да ги спореди клиничките исходи помеѓу еластичната стабилна интрамедуларна остеосинтеза (ESIN) и отворената репозиција со транскондиларна фиксација кај педијатриски пациенти со фрактури од тип III и IV според Judet. Во периодот 2010–2015 година, на Универзитетската клиника за детска хирургија во Скопје беа третирани 80 деца (возраст 5,5–14,5 години) со изолирани ФВР. Пациентите беа поделени во две групи: едната група третирана со затворена репозиција со ESIN (n = 39), а другата со отворена репозиција со транскондиларна фиксација (n = 41). Исходите беа евалуирани преку MEPS, радиографско порамнување и формирање периостален калус. Затворената репозиција со ESIN покажа значајно повисока стапка на формирање периостален калус (97,44% vs. 56,10%, p = 0,000014), што укажува на подобро биолошко заздравување. Квалитетот на репозицијата беше споредлив (p = 0,13). Отворената репозиција беше почеста кај фрактурите од тип IV (63,41%). Не беа најдени значајни разлики во MEPS скорот. Ретроспективниот дизајн ја ограничуваше евиденцијата за компликации. ESIN претставува ефикасна и биолошки поволна опција за фрактури од тип III според Judet, додека отворената репозиција останува неопходна за покомплексните тип IV фрактури. Потребно е стандардизирано долгорочно следење за оценка на безбедносните исходи.

Introduction

Proximal radius fractures are not common; they only make up 1% of all fractures and 4.5–21% of elbow fractures in children. Radial neck fractures (RNF) are the most common type. Treatment complexity arises from the possibility of spontaneous realignment and challenges with vascular supply. Although both surgical and conservative methods demonstrate favorable results, complication rates vary between 27% and 37%. Elements such as unpredictable growth-associated remodeling, excessive treatment, and a rise in surgical procedures contribute to this variability. The variability of fracture types and patient ages complicates routine examination.1 The primary injury mechanism involves a fall onto an outstretched arm, resulting in valgus tension at the elbow.[2]

The classification of radial neck injuries is determined by the angle between the radial head and neck. The Judet and O'Brien classification systems are the most often utilized. Normal x-rays can make it hard to see undisplaced fractures. The posterior fat pad, which may be present and indicate a hidden fracture, is another sign to look for.[3]

The Judet classification categorizes fractures into four patterns based on the displacement of the radial head. Type I is a non-displaced fracture, while Type II entails an angulation of less than 30°, with Type III encompassing an angulation range of 30° to 60°. Type IV fractures are characterized by an angulation of the radial head exceeding 60°.2

Radial head ossification begins around the age of four, with fusion happening at approximately 14 years in females and 17 years in males. By this age, the head and neck have reached their adult shape, with a natural lateral angulation of 12.5° in the anteroposterior (AP) plane and 3.5° anteriorly in the lateral plane. Therapy planning must take these characteristics into account.

Displaced fractures are uncommon yet difficult to treat. Complications in children encompass elbow stiffness, avascular necrosis (AVN), and radial head enlargement. The elastic stable intramedullary nailing (ESIN) method helps reduce and stabilize fractures indirectly while keeping the connections between soft tissues. This report delineates a set of pediatric instances managed using this strategy.[4]

Although more commonly used for diaphyseal forearm fractures, ESIN has also proven effective in pediatric radial neck fractures due to its minimally invasive nature and reliable stabilization.[5]

The objective of this study was to retrospectively compare the clinical outcomes of closed reduction with retrograde elastic stable intramedullary nailing (ESIN, Metaizeau technique) versus open reduction with transcondylar fixation in the treatment of pediatric radial neck fractures.

Materials and Methods

This retrospective study was conducted at the University Clinic for Pediatric Surgery in Skopje between 2010 and 2015, including 80 pediatric patients (aged 5.5–14.5 years) with isolated Judet type III or IV radial

neck fractures. Patients were divided into two treatment groups: one group treated with closed reduction with retrograde intramedullary nailing using the ESIN (Metaizeau technique, n = 39) and the other one with open reduction with transcondylar fixation (n = 41). Exclusion criteria included polytrauma, Monteggia fractures, pathological lesions, or Judet type V fractures. Surgical procedures were performed under general anesthesia. In the ESIN group, closed reposition was achieved using a titanium elastic nail (1.5–2.5 mm) introduced retrogradely under fluoroscopic guidance (Figures 1 and 2). In the open reduction group, a Kocher lateral approach was used with fixation by transcondylar screws or Kirschner wires. Clinical and radiographic data were extracted from hospital records, including patient demographics, injury mechanism, fracture classification, and treatment outcomes. Functional results were assessed using the Mayo Elbow Performance Score (MEPS). Statistical analysis was performed using SPSS software with Chi-square and Student's t-tests, and repeated-measures ANOVA where appropriate. Ethical approval was obtained from the Ethics Committee of the Faculty of Medicine in Skopje (June 2018), in accordance with the Declaration of Helsinki. Informed consent was obtained from parents or guardians of all participants.

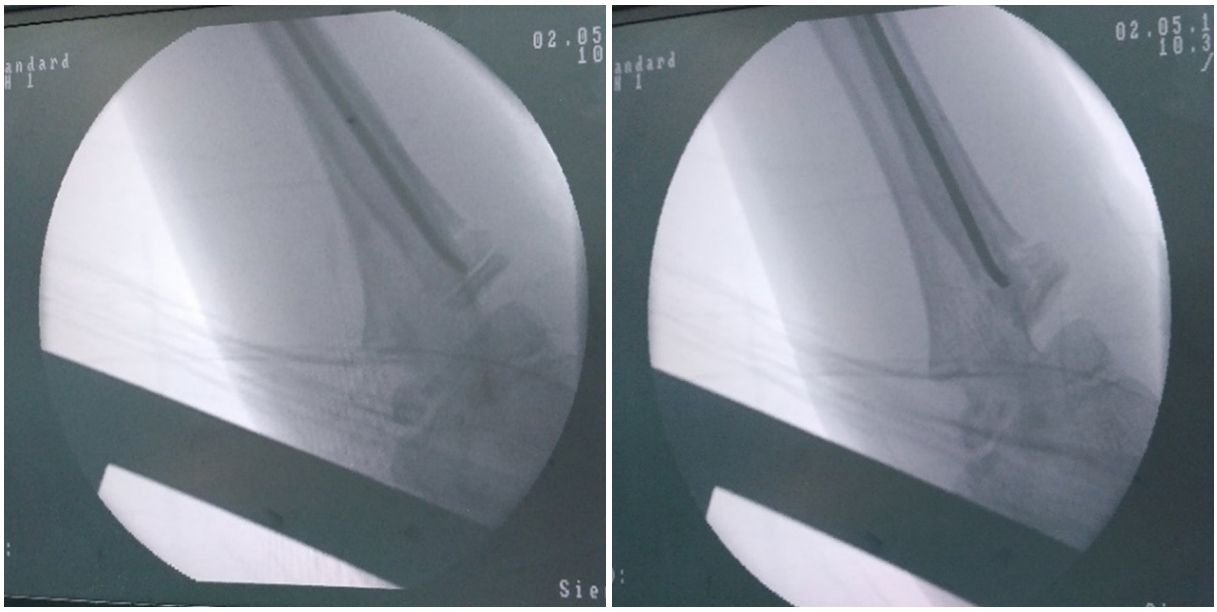

Figure 1 and 2: Repositioning of the radial head

Results

A total of 80 pediatric patients with capitulum radii fractures were included, comprising 52 males (65%) and 28 females (35%). The gender distribution was comparable between the open reposition (27 males, 14 females) and closed reposition (25 males, 14 females) groups, with no significant difference (p = 0.88) (Table 1).

Falls (53.8%), sports/play (32.1%), and traffic accidents (14.1%) were the most common injury mechanisms. Falls predominated in the open reposition group (60.98%),

Table 1. Gender distribution between treatment groups

Gender	Method			p - value
	n	Open reposition n (%) (41)	Closed reposition n (%) (39)	
Male	52	27 (65.85)	25 (64.1)	0.88
Female	28	14 (34.15)	14 (35.9)	

while sports/play was more common in the ESIN group (41.03%). No significant difference was observed between groups regarding injury mechanism (p = 0.18) (Table 2).

Table 2. Judet classification distribution between treatment groups

Mechanism of injury	Method			p - value
	n	Open reposition n (%) (41)	Closed reposition n (%) (39)	
Traffic accident	12	7 (17.07)	5 (12.82)	0.18
Fall	43	25 (60.98)	18 (46.15)	
Sports/play	25	9 (21.95)	16 (41.03)	

Judet classification revealed a significant difference in fracture type distribution (p = 0.000003). Closed reposition was predominantly used for type III fractures (87.18%), whereas open reposition was more common for type IV (63.41%) (Table 3).

Table 3. Judet classification distribution between treatment groups

Judet Classification	Method			p - value
	n	Open reposition n (%) (41)	Closed reposition n (%) (39)	
Type III	49	15 (36.59)	34 (87.18)	0.000003
Type IV	31	26 (63.41)	5 (12.82)	

All patients in the ESIN group had a good reduction (100%). In the open reposition group, 92.68% had good and 7.32% had satisfactory outcomes. No poor reductions were recorded. The difference was not statistically significant (p = 0.13). Figures 3 and 4 show representative imaging from both groups (Table 4).

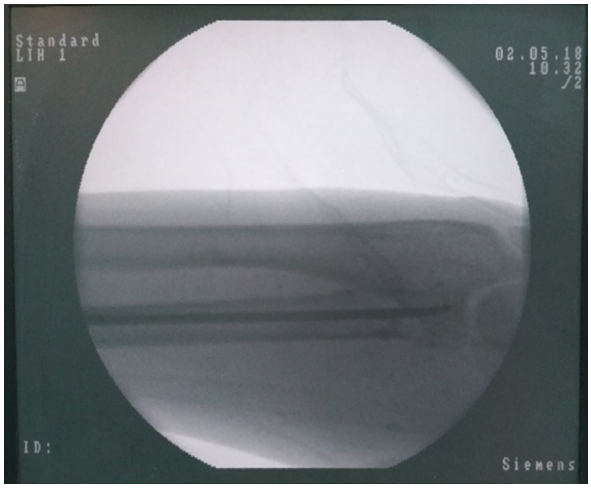

Figure 3: Postoperative fluoroscopy showing alignment after ESIN

Figure 4: Postoperative radiograph confirming anatomic reduction in open reposition group

Table4. Quality of reduction between treatment groups

Quality of reposition after primary treatment	Method			p - value
	n	Open reposition n (%) (41)	Closed reposition n (%) (39)	
Good	77	38 (92.68)	39 (100)	0.13
Satisfactory	3	3 (7.32)	0	
Poor	/	0	0	

Periosteal callus was present in 97.44% of the closed reposition group, compared to 56.10% of the open reposition group (p = 0.000014) (Table 5).

Table 5. Periosteal callus formation between treatment groups

Periosteal Callus Formation	Method			p - value
	n	Open reposition n (%) (41)	Closed reposition n (%) (39)	
Absent	19	18 (43.90)	1 (2.56)	0.000003
Present	61	23 (56.10)	38 (97.44)	

No significant complications were recorded, although the absence of structured documentation limited the reliability of complication assessment.

Discussion

Our findings align with previous studies demonstrating that fracture severity plays a central role in surgical decision-making, with Judet type IV fractures more often necessitating open reduction, while type III fractures respond well to minimally invasive treatment approaches.[6] Closed reposition with ESIN was particularly effective for Judet type III injuries, consistent with the broader trend favoring less invasive tech-

niques when anatomical alignment is achievable. [8]

ESIN demonstrated clear biological advantages in our study, reflected by significantly higher rates of periosteal callus formation compared to open reposition. This supports existing evidence that ESIN preserves periosteal integrity and facilitates bone healing.[7]

Although our analysis did not include Kirschner wire (KW) fixation, prior research positions it as a cost-effective alternative. [8] It allows for outpatient implant removal but is associated with higher rates of pin tract infections and risk of reduction loss.[9] Tian *et al.* reported no major differences between ESIN and KW fixation regarding function, hospital stay, or operative time, suggesting that the choice of technique should be tailored to individual case specifics and resource availability. [8]

While ESIN is widely accepted for pediatric fractures, complications such as nail migration, joint protrusion, and nonunion have been reported.[6] We did not observe these in our patients; however, their possibility underscores the need for consistent postoperative monitoring.

Age also influences outcomes. Studies show children ≥10 years may experience less favorable remodeling.[9] Although age-specific outcomes were not analyzed in our patients, future studies should explore age-based protocols.

Du *et al.* found that minimally invasive techniques using Kirschner wires with the Métaizeau method offered higher success and fewer complications than open reduction in Judet IV fractures.[10] Their findings support a shift toward closed techniques when feasible.

The reduction quality in our study was comparable between both methods, with no significant differences noted. This reinforces that both techniques can achieve anatomical alignment when appropriately selected.[8]

Although our results favor ESIN, especially for Judet type III fractures, KW fixation remains a relevant option where cost or implant removal logistics are a concern. However, the absence of a standardized complication registry limited our ability to draw firm conclusions about safety. Comprehensive documentation of postoperative outcomes is critical in future research to evaluate long-term safety and efficacy.

Conclusion

This study supports ESIN as a highly effective technique for managing pediatric radial neck fractures, particularly Judet type III, due to its capacity to preserve periosteal integrity and promote biological healing. Although open reduction remains necessary for more complex type IV fractures, KW fixation also presents a viable alternative, especially in resource-limited settings where outpatient implant removal is advantageous. Given the comparable functional outcomes between techniques, the choice of fixation should be individualized. Future prospective studies are warranted to evaluate long-term results, implant-related complications, and age-specific responses to treatment.

Abbreviations

ESIN – Elastic Stable Intramedullary Nailing

RNF – Radial Neck Fracture

MEPS – Mayo Elbow Performance Score

VAS – Visual Analog Scale

AVN – Avascular Necrosis

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Conflict of Interest

The authors declare no conflicts of interest in relation to this study.

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CLINICAL SCIENCE

CORROSIVE POISONINGS DURING THE COVID-19 PANDEMIC: TRENDS AND DEMOGRAPHIC SHIFTS IN THE PRE- AND EARLY VACCINATION PERIODS (2020–2021)

Zanina Pereska[1], Niko Bekjarovski[1], Lidija Petkovska[1], Andon Chibishev[1], Natasha Simonovska[1], Aleksandra Babulovska[1], Kiril Naumoski[1], Kristin Kostadinoski[1], Angjela Petrovska Simic[2], Tanja Duckinoska[3]

[1] *University Clinic for Toxicology, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje*

[2] *PHI Clinical Hospital "Dr Trifun Panovski", Bitola*

[3] *PHI Health Center "Dr. Svetozar Chochoroski", Vevchani*

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***Correspondence:**

Zanina Pereska

Email: perevska@yahoo.com

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Abstract

The COVID-19 pandemic significantly disrupted global healthcare and societal norms, leading to changes in poisoning patterns, particularly corrosive poisonings (CP). This study aimed to evaluate the impact of the pandemic on CP trends in North Macedonia by comparing observed data from 2020 and 2021 with predicted values (PV) based on a 10-year tren. A retrospective study was conducted using data from the Poisoning Registry at the Poison Information Center (PIC), University Clinic for Toxicology, Skopje. Patients with confirmed acute upper gastrointestinal corrosive injuries were included. A total of 1,668 CP cases were recorded in the period between 2010 and 2021. While an overall downward trend was observed ($y = -6.5x + 181.4$, $R^2 = 0.56$), CP cases declined by 1.5% in 2020 and by 25.5% in 2021 compared to PV. Female cases decreased by 27.5% in 2021; male cases declined by 16.6% in 2020 and 32.4% in 2021. Adolescent CP increased by 12.8% in 2020 and 80.0% in 2021; cases in those aged over 75 rose by 2.5% and 6.2%, respectively. The mean age of CP patients rose by 7.6% in 2020 and 11.0% in 2021. Suicidal poisonings increased by 9.9% in 2021. Disinfectant poisonings rose by 74.5% in 2020, while poisonings with hydrochloric acid (+6.2%), detergents (+3.4%), and degreasers (+32.0%) increased in 2021. Case fatality ratios were increased by 36.2% in 2020 and 44% in 2021. Although the overall number of cases declined, the increased severity, lethality, and demographic shifts—particularly among adolescents and the elderly—highlight the high-risk groups, mental health burden and toxicological risks associated with public health emergencies.

КЛИНИЧКИ ИСТРАЖУВАЊА

КОРОЗИВНИ ТРУЕЊА ЗА ВРЕМЕ НА ПАНДЕМИЈАТА СО COVID-19: ТРЕНДОВИ И ДЕМОГРАФСКИ ПРОМЕНИ ВО ПЕРИОДОТ ПРЕД И НА ПОЧЕТОКОТ НА ВАКЦИНАЦИЈАТА (2020–2021)

Жанина Переска[1], Нико Беќаровски[1], Лидија Петковска[1], Андон Чибишев[1], Наташа Симоновска[1], Александра Бабуловска[1], Кирил Наумоски[1], Кристин Костадиноски[1], Анѓела Петровска Симиќ[2], Тања Дучкиноска[3]

[1] *Универзитетска клиника за токсикологија, Медицински факултет, Универзитет „Св. Кирил и Методиј" – Скопје*

[2] *ЈЗУ Клиничка болница „Д-р Трифун Пановски", Битола*

[3] *ЈЗУ Здравствен дом „Д-р Светозар Чочороски", Вевчани*

Извадок

Пандемијата со COVID-19 значително го наруши глобалниот здравствен систем и општествените норми, што доведе до промени во моделите на труење, особено кај корозивните труења (КТ). Целта на оваа студија беше да се процени влијанието на пандемијата врз трендовите на КТ во Северна Македонија, споредувајќи ги податоците од 2020 и 2021 година со предвидени вредности (ПВ) базирани на 10-годишен тренд. Се спроведе ретроспективна студија користејќи податоци од Регистарот за труења при Токсиколошкиот информативниот центар (ТИЦ) на Универзитетската клиника за токсикологија во Скопје. Беа вклучени пациенти со потврдени акутни корозивни повреди на горниот гастроинтестинален тракт. Во периодот од 2010 до 2021 година беа евидентирани вкупно 1.668 случаи на КТ. И покрај општиот опаѓачки тренд ($y = -6.5x + 181.4$, $R^2 = 0.56$), бројот на случаи опадна за 1,5% во 2020 и за 25,5% во 2021 споредено со ПВ. Кај жените се забележа намалување од 27,5% во 2021, додека кај мажите опаѓање од 16,6% во 2020 и 32,4% во 2021. Кај адолесцентите се регистрира зголемување од 12,8% во 2020 и 80,0% во 2021, а кај лицата над 75 години пораст од 2,5% и 6,2%. Просечната возраст на пациентите со КТ се зголеми за 7,6% во 2020 и 11,0% во 2021. Самоубиствата со КТ се зголемија за 9,9% во 2021. Труењата со дезинфициенси се зголемија за 74,5% во 2020, додека труењата со хлороводородна киселина (+6,2%), детергенти (+3,4%) и одмастувачи (+32,0%) беа зголемени во 2021. Смртноста од КТ се зголеми за 36,2% во 2020 и 44% во 2021. Иако вкупниот број на случаи е намален, зголемената тежина, леталитетот и демографските промени – особено кај адолесцентите и постарите лица – ги истакнуваат ризичните групи, психолошкиот товар и токсиколошките закани поврзани со вонредни состојби во јавното здравство.

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Клучни зборови: корозивно труење, горен гастроинтестинален тракт, COVID-19, анализа на трендови, вонредни состојби во јавното здравство

***Кореспонденција:**

Жанина Переска

Email: perevska@yahoo.com

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Introduction

The COVID-19 pandemic has significantly influenced global public health, not only through its direct morbidity and mortality but also by altering patterns of behavior and access to healthcare services. The extensive social restrictions, psychological stress, and heightened fear of infection, especially in the period prior to the availability of effective vaccines, have had far-reaching effects on mental health and healthcare utilization[1].

These disruptions also extended to the field of clinical toxicology. Several studies have reported shifts in the epidemiology of poisonings during the pandemic, including an increase in cases involving corrosive substances[2]. In adults, corrosive poisonings (CP) are frequently associated with suicidal intent, while in children, they are more often accidental exposures[3]. The psychological burden and social isolation during the pandemic further contributed to this pattern, increasing the frequency and severity of CP in certain populations.

Corrosive poisonings remain a major toxicological concern, particularly in developing countries where access to mental health services and public education may be limited. The lack of specific antidotes for upper gastrointestinal tract injuries caused by corrosive agents leads to high morbidity and mortality. Despite global trends showing a decline in CP in high-income countries, several reports have documented an increase in such poisonings during the COVID-19 period, especially those linked to suicidal behavior and developing countries [2,4–6].

The aim of this study was to evaluate the impact of the COVID-19 pandemic on the epidemiological characteristics of corrosive poisonings in North Macedonia by comparing data from the pandemic years (2020 and 2021) to predicted values (PV) derived from a trend analysis of the previous ten-year period.

Material and method

We conducted a retrospective observational study using data from the Poisoning Registry maintained by the Poison Information Center (PIC) at the University Clinic for Toxicology, covering the period from 2010 to 2021. The study included patients with confirmed corrosive injuries of the upper gastrointestinal tract who were treated at the University Clinic for Toxicology and the University Pediatric Clinic, and whose cases were reported to the PIC.

Study Variables

Data collected included:

- Demographics: Gender, age, and age group:
  - Children (<14 years)
  - Adolescents (15–19 years)
  - Adults (20–74 years)
  - Elderly (>75 years)
- Circumstances/intent of poisoning (suicide, accidental)
- Type of corrosive substance according chemical composition (hydrochloric acid, bleach, detergents, disinfectants, alkali degreasers, sodium hydroxide)
- Clinical outcome (Patients with documented clinical outcomes - survival, postcorrosive substenosis of upper gastrointestinal tract or death within the first 72 hours following admission or intervention)
- Diagnosis and Classification
  - Acute corrosive poisoning was confirmed by esophagogastroduodenoscopy (EGD) conducted

within 48 hours of exposure. Patients with a history of corrosive injury or with chronic post-corrosive complications were excluded from the study. Endoscopic findings were classified according to the Kikendall grading system.

From all 1,668 cases, 1,081 (64.8%) were females and 587 (35.2%) were males. Over the past 12 years, the incidence of corrosive poisonings (CP) declined in both genders, reaching an almost equal distribution between males and females by 2021. The decline was more pronounced in females, with a trend line of $y = -6.65x + 132$, $R^2 = 0.7$, compared to a slight decrease in males ($y = -0.045x + 49.5$, $R^2 = 0.0003$).

However, in 2020, there was a 7.7% increase in female cases, followed by a 27.5% decrease in 2021 compared to the predicted values (PV). In males, the number of cases steadily declined, with reductions of 16.6% in 2020 and 32.4% in 2021 relative to PV (Figure 2).

Statistical Analysis

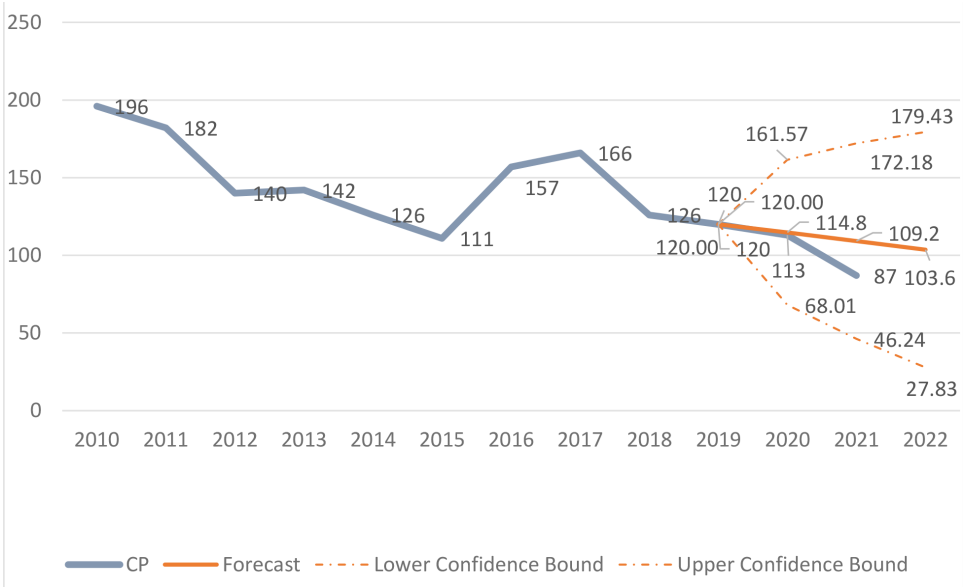
Descriptive statistics (frequencies and proportions) were used to summarize the demographic characteristics of the study population. To evaluate trends over time, linear regression analysis and linear forward trend forecasting were performed using Microsoft Excel (Microsoft Corp., Redmond, WA, USA). The mean absolute percentage error (MAPE) between actual and predicted values was calculated using the standard formula: MAPE = | (Actual − Predicted) / Actual| × 100. Case fatality ratio (CFR) was calculated with standard formula: Number of deaths due to a particular disease/ Total number of cases due to the same disease×100. A p-value of <0.05 was considered statistically significant.

Results

We registered 1668 acute CP from 2010 to the end of 2021. CP demonstrated a declining trend over the past 12 years, as indicated by the linear regression model ($y = -6.5x + 181.4$, $R^2 = 0.56$). The CP decreased by 1.5% during 2020 due to COVID-19 curfews, and by 25.5% in 2021, compared to PV (Figure 1).

From all 1,668 cases, 1,081 (64.8%)

Figure 1. CP during 2010-2021 with PV for 2020 and 2021



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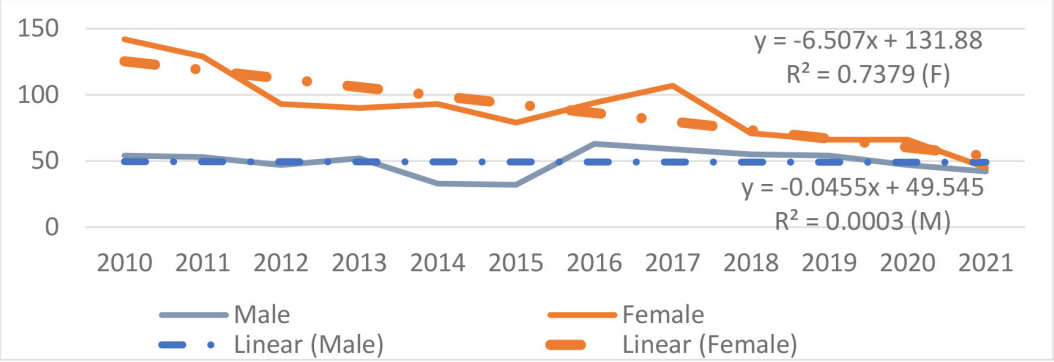
During 2020 and 2021, the incidence of corrosive poisonings (CP)

Figure 2. Gender distribution in CP



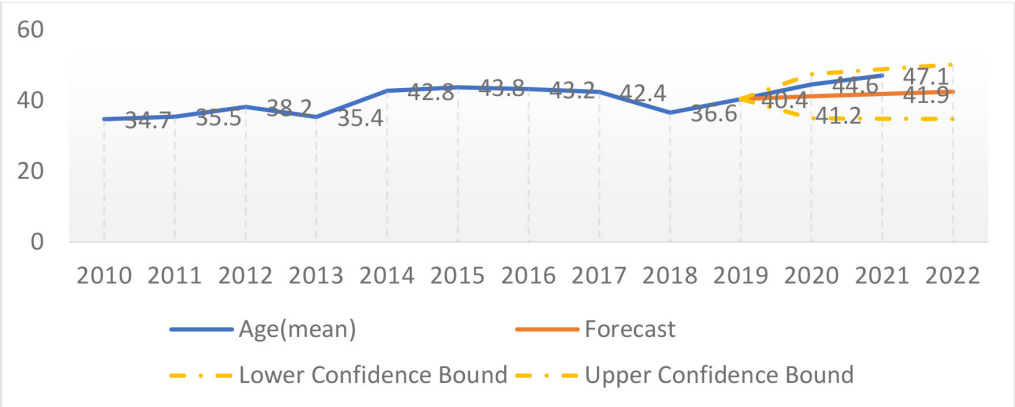
increased among adolescents, with rises of 12.8% and 80.0%, respectively, compared to predicted values (PV). A similar upward trend was observed in individuals aged over 75, with increases of 2.5% in 2020 and 6.2% in 2021.

In contrast, the adult population experienced a 2.5% increase in 2020 and 6.15% in 2021, compared to PV.

The mean age of patients with corrosive poisoning (CP) exhibited a general upward trend over the study period, with two notable declines observed in 2013 and 2018. In comparison to predicted values, the mean age increased by 7.6% in 2020 and by 11.0% in 2021 (Figure 3).

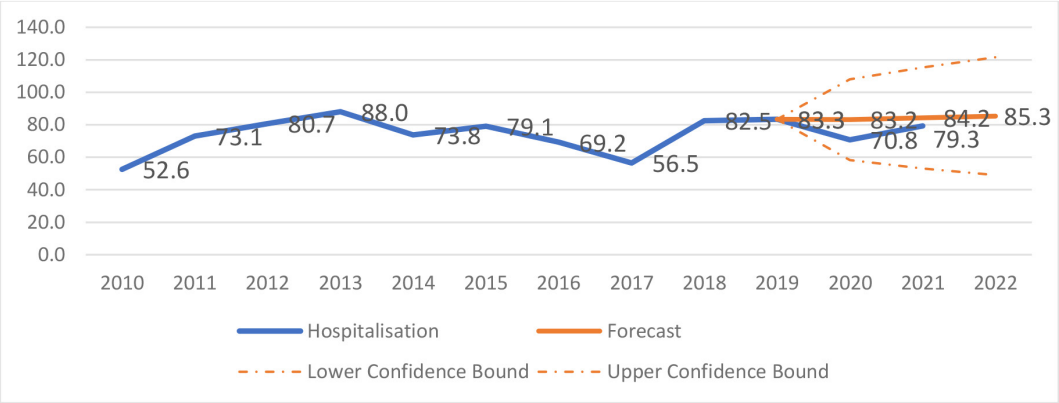
The proportion of hospitalizations followed a steady trend (y = 0.71x

Figure 3. Mean age of patients with CP and comparisons to PV for 2020 and 2021



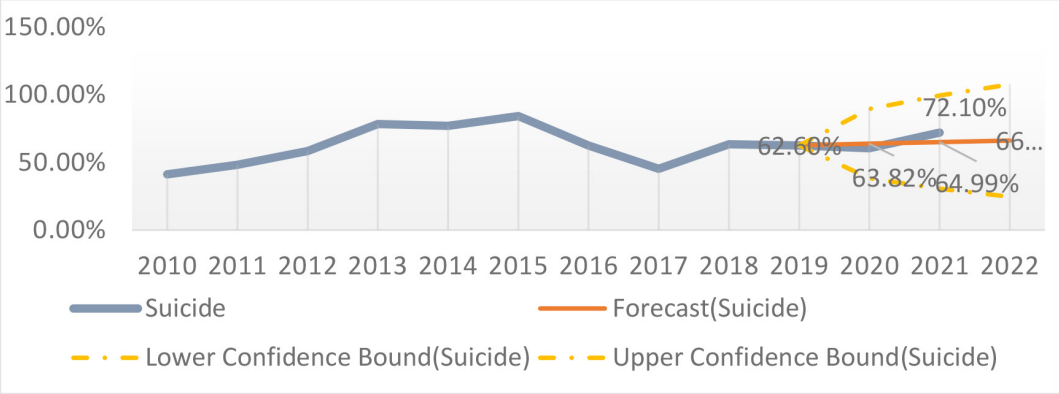
+ 69.47, R^2 = 0.058). This decrease was more pronounced in 2020, with a 17.5% reduction compared to PV, while in 2021, the decline was smaller, amounting to 6.2% (Figure 4).

Figure 4. Hospitalization (in proportion) and comparisons to PV for 2020 and 2021



The proportion of suicidal CP showed a slight upward trend over the 12-year period (y = 0.01x + 0.56, R^2 = 0.07). However, there was a 5.6% decrease in 2020, followed by a 9.9% increase in 2021, compared to predicted values (PV) (Figure 5).

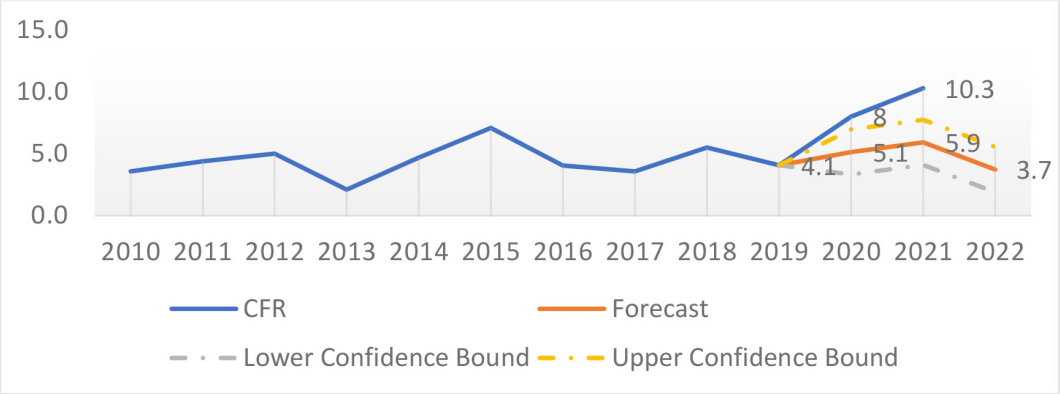
Figure 5. Suicidal CP: Observed values vs. predicted values for 2020 and 2021



Among all substances, poisonings involving bleach increased in both 2020 (by 16.0%) and 2021 (by 7.3%) compared to predicted values (PV). Additionally, disinfectant-related poisonings rose sharply by 74.5% in 2020. In 2021, there was a further increase in poisonings involving hydrochloric acid (HCl): +6.2%, detergents: +3.4%, degreasers: +32.0%, all compared to PV.

Regarding gender, mortality occurred in 22.1% of female cases and 26.4% of male cases. The case fatality ratio (CFR) for corrosive poisonings showed a substantial increase, rising by 36.2% in 2020 and 44% in 2021 compared to predicted values (Figure 6).

Figure 6. Case fatality ratio (CFR) in corrosive poisonings in 2020 and 2021, with comparisons to predicted values



Discussion

Our analysis highlights significant changes in the pattern of CP in North Macedonia during the COVID-19 pandemic, revealing distinct trends in 2020 and 2021. These shifts reflect broader societal, healthcare, and psychological impacts of the pandemic and offer context-specific insights into toxicovigilance during public health crises.

2020 – Pre-Vaccination Phase: Restricted Movement and Emergency Avoidance

In 2020, the number of CP cases decreased by 1.5% compared to predicted values, with a more prominent 17.5% reduction in hospitalizations. This decline coincided with strict lockdown measures, including prolonged curfews and restrictions on movement during national holidays. The reduced number of presentations may have stemmed from public fear of SARS-CoV-2 exposure and avoidance of emergency rooms (ERs), as previously noted in other healthcare settings[7].

Despite fewer cases, the case fatality ratio (CFR) increased by 36.2%, suggesting a higher severity among those who did seek treatment. The suicidal intent in CP was lower during this period, likely influenced by increased family presence, improved support systems, and potential links to mental health services during lockdowns[8]. However, some studies reported a higher incidence of accidental CP than suicidal poisonings in the same timeframe[5], supporting the hypothesis of more incidental exposures due to increased home disinfectant use.

Demographically, female CP cases slightly increased in 2020, in contrast to the overall downward trend in female involvement. This may reflect heightened psychosocial pressures on women during lockdown, such as increased domestic violence and economic instability[4,9]. CP incidence also rose among adolescents and the elderly, particularly those above 75 years, were highly vulnerable to pandemic-related stress. Adolescent neurodevelopmental vulnerabilities under pandemic stress have been well-documented[10] and influence on their behavior. The medical community became increasingly attentive to the mental health vulnerabilities of older adults during

the COVID-19 pandemic, recognizing their greater susceptibility to social isolation and severe illness. A survey conducted in July 2020 indicated that nearly half (46%) of individuals aged 65 and above reported that pandemic-related concerns had adversely affected their mental well-being11.

2021 – Early Vaccination Phase: Eased Restrictions, Rising Severity.

In 2021, the decline in CP cases became more pronounced, with a 25.5% decrease compared to predicted values, while hospitalizations reduced by 6.2%, a smaller reduction than the previous year. Nonetheless, the CFR rose even further by 44%, indicating sustained or worsening severity in CP cases.

Unlike 2020, suicidal CP cases increased in 2021, mirroring trends reported globally [12,13]. This rise may reflect accumulated psychological distress, prolonged isolation, and growing pandemic fatigue, all contributing to growing mental health deterioration and increased determination for self-harm[13].

The mean age of patients increased by 11.0% compared to projections, reflecting an aging CP population and more cases among those over 75 years. Adolescents also remained at elevated risk. The gender distribution continued to shift, with male prevalence remaining stable or slightly increasing, while female representation declined overall, despite the early 2020 spike.

In terms of substance use, poisonings with disinfectants increased, reflecting their widespread household availability during the pandemic[14]. Nevertheless, the most frequently used agents remained acids, followed by bleach and strong alkalis (degreasers) - a pattern consistent with other studies[5,12].

Comparison and Implications

Comparison between 2020 and 2021 revealed distinct phases in CP dynamics during the pandemic. While 2020 was marked by avoidance behavior and reduced emergency visits, 2021 saw a continuation of the case decline but a surge in suicidal intent and poisoning severity. The increasing CFR in both years (36.2% in 2020; 44% in 2021) highlights the pandemic lasting impact on the mental health and partially on quality of acute care and the timeliness of medical intervention[7,15].

Furthermore, most international reports indicated increased suicidal CP during the pandemic 2,4,5, —a trend mirrored in our findings for 2021 but not for 2020. Throughout 2020 and 2021, a stable or slightly increasing male prevalence was observed, reaching near gender parity. The evolving demographic patterns (older age, adolescent involvement, fluctuating gender distribution) call the need for targeted preventive strategies. As seen in our data, the indirect consequences of pandemics can manifest in severe, life-threatening patterns of behavior, such as CP, that require proactive healthcare planning and social support systems.

Conclusion

The COVID-19 pandemic influenced the epidemiology of corrosive poisonings in North Macedonia during 2020 and 2021. While the overall number of cases declined, the severity and lethality of CP increased, especially during the early vaccination phase.

Demographic shifts, including a rise in adolescent and elderly cases, along with gender-specific trends and substance use patterns, reflect the complex interplay between pandemic-related social changes and toxicological outcomes in CP.

Collectively, these findings underscore the importance of ensuring uninterrupted toxicological and mental health services during crises and highlight the need for integrated public health preparedness plans that include toxicovigilance, mental health support, and prevention strategies for high-risk groups.

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ORAL HEALTH

CORRELATION BETWEEN SALIVARY URIC ACID VALUES AND RISK FACTORS ASSOCIATED WITH METABOLIC SYNDROME

Martina Anastasovska[1], Bojan Poposki[2], Marija Andonovska[2], Sanela Idoska[1], Enver Idoski[3], Vlatko Kokolanski[2]

[1] *University Clinic for Surgery of the Face, Jaws and Neck – Maxillofacial Surgery, Skopje, Republic of North Macedonia*
[2] *Faculty of Dentistry – Skopje, Ss. Cyril and Methodius University in Skopje, Republic of North Macedonia*
[3] *Zan Mitrev Clinic, Skopje, Republic of North Macedonia*

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***Correspondence:**

Vlatko Kokolanski, Faculty of Dental Medicine, Skopje, Ss. Cyril and Methodius University in Skopje, North Macedonia

Email: vkokolanski@stomfak.ukim.edu.mk

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Abstract

Introduction: The fast pace of modern life contributes to an increased prevalence of metabolism-related diseases. Since these diseases can be prevented through lifestyle modification, a new approach in medicine is needed, i.e. one that focuses on the early identification of individuals at higher risk. A promising noninvasive monitoring tool is the use of salivary biomarkers. Of particular interest is salivary uric acid, as a linear association between its serum and salivary concentrations has been demonstrated. **Aim:** To determine the correlation between various risk factors associated with metabolic syndrome and the salivary concentration of uric acid. **Materials and Methods:** A cross-sectional study was conducted among 156 students (aged 20–25 years) from the Faculty of Dentistry, Faculty of Medicine, and Faculty of Pharmacy at Ss. Cyril and Methodius University in Skopje. In the Biochemical Laboratory of the Faculty of Dentistry, body weight, height, waist circumference, blood pressure, and pulse of the studied participants were measured. Unstimulated saliva samples were collected using the spitting method. Uric acid concentration was determined spectrophotometrically using the enzymatic URICASE/PEROXIDASE method. The obtained data were statistically analyzed and correlated with anthropometric parameters, blood pressure, pulse, and body mass index. **Results:** The results showed a significant correlation between salivary uric acid levels and body weight ($p<0.001$), body mass index ($p<0.001$), waist circumference ($p<0.001$), systolic blood pressure ($p<0.001$), and diastolic blood pressure ($p<0.001$). **Conclusion:** Our findings suggest that salivary uric acid may serve as a reliable noninvasive biomarker for detecting cardiometabolic risk factors.

ОРАЛНО ЗДРАВЈЕ

КОРЕЛАЦИЈА ПОМЕЃУ САЛИВАРНИТЕ ВРЕДНОСТИ НА УРИЧНА КИСЕЛИНА И РИЗИК-ФАКТОРИТЕ ПОВРЗАНИ СО МЕТАБОЛИЧКИОТ СИНДРОМ

Мартина Анастасовска[1], Бојан Попоски[2], Марија Андоновска[2], Санела Идоска[1], Енвер Идоски[3], Влатко Коколански[2]

[1] *Универзитетска клиника за хирургија на лице, вилици и врат -максилофацијална хирургија, Скопје, Република Северна Македонија*
[2] *Стоматолошки факултет - Скопје, Универзитет „Св. Кирил и Методиј“ во Скопје, Република Северна Македонија*
[3] *Клиника „Жан Митрев“, Скопје, Република Северна Македонија*

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Клучни зборови: плунка, урична киселина, метаболички синдром, оксидативен стрес, неинвазивна дијагностика

***Кореспонденција:**

Влатко Коколански, Стоматолошки факултет, Скопје, Универзитет „Св. Кирил и Методиј“, Скопје, Северна Македонија

Email: vkokolanski@stomfak.ukim.edu.mk

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Извадок

Вовед: Брзото темпо на живеење на современиот човек е една од причините за зголемување на стапката на заболувања поврзани со метаболизмот на човекот. Бидејќи овие заболувања можат да бидат превенирани преку менување на начинот на живот, се бара нов пристап во медицината кој би подразбирал идентификација на индивидуи со зголемен ризик за појава на овие заболувања. Еден од пристапите за неинвазивен мониторинг е користењето на саливарните биомаркери. Од особен интерес во истражувањата е саливарната урична киселина, бидејќи е откриена линеарна асоцијација на нејзините серумски и плунковни вредности. **Цел:** Да се утврди корелацијата помеѓу различните ризик-фактори кои се поврзуваат со метаболичкиот синдром и концентрацијата на саливарната вредност на уричната киселина. **Материјал и методи:** Беше спроведена студија на пресек (cross-sectional study), која вклучи 156 студенти (на возраст од 20–25 години) од Стоматолошкиот, Медицинскиот и Фармацевтскиот факултет во состав на Универзитетот „Св. Кирил и Методиј“ во Скопје. Во биохемиската лабораторија на Стоматолошкиот факултет беа измерени телесната тежина, висината, обемот на половината, крвниот притисок и пулсот на испитаниците. Нестимулирана плунка беше колекционирана користејќи го методот на исплукување. Концентрацијата на уричната киселина беше определена спектрофотометриски со ензимски метод (URICASE/PEROXIDASE). Добиените вредности беа статистички анализирани и корелирани со антропометриските параметри и вредностите на крвниот притисок, пулсот и индексот на телесна маса. **Резултати:** Резултатите покажаа значајна корелација помеѓу саливарните вредности на уричната киселина и телесната тежина ($p<0.001$), индексот на телесна маса ($p<0.001$), обемот на половината ($p<0.001$), систолниот крвен притисок ($p<0.001$) и дијастолниот крвен притисок ($p<0.001$). **Заклучок:** Нашите резултати укажуваат на можноста за користење на саливарната урична киселина како неинвазивен биомаркер за откривање на кардиометаболичките ризик-фактори.

Introduction

Excess body weight represents an increasingly serious public health problem in our population. This condition, together with metabolic syndrome, is considered a disease of modern society. Metabolic syndrome represents a cluster of interrelated metabolic abnormalities including abdominal obesity, elevated blood pressure, hyperglycemia, increased triglyceride levels, and decreased HDL-cholesterol values, which are factors that collectively increase the risk of developing cardiovascular diseases and type 2 diabetes mellitus[1]. Obesity most commonly arises as a result of dietary imbalance and is associated with increased morbidity and mortality from metabolic, endocrine, respiratory, cardiovascular, and other systemic diseases and health disorders[2]. The fast-paced lifestyle of modern society is one of the contributing factors to the growing incidence of metabolism-related diseases.

Various biological fluids are present in the human body, such as blood, urine, and saliva. These biological fluids play a crucial role in maintaining the homeostasis of organs and systems, as they contain proteins, metabolic degradation products, and minerals, making them valuable diagnostic media for a wide range of systemic and oral diseases. The growing prevalence of malignant, cardiovascular, and metabolic diseases has increased the demand for improved diagnostic procedures for early disease detection[3-5].

Among all biological fluids, saliva stands out as the most attractive diagnostic tool. This biofluid contains valuable information that enables early disease detection, leading to better treatment outcomes and improved prognosis[6-10]. Early detection of diseases often presents a challenge and typically requires multiple clinical and laboratory examinations, which may delay therapeutic intervention and worsen patient prognosis. Contemporary research therefore focuses on identifying noninvasive biomarkers for early disease diagnosis. An ideal biomarker should be specific to the disease, easily accessible, cause minimal discomfort during sample collection, and be cost-effective. Salivary diagnostics meet these criteria by providing an effective, noninvasive approach for early diagnosis, disease monitoring, and evaluation of therapeutic outcomes[10-13].

Whole saliva consists of secretions from the major and minor salivary glands, transudate from the oral mucosa, gingival crevicular fluid, serum-derived components, desquamated epithelial cells, microorganisms, and food residues. It is a complex biological fluid that contains hormones, enzymes, proteins, metabolites, antibodies, cytokines, and antimicrobial molecules. The analysis of these salivary constituents forms the basis for linking saliva to various systemic diseases[14].

Over the past decade, research on saliva has significantly expanded, attracting increasing interest as a diagnostic medium for detecting biomolecules associated with both health and disease. Considerable investments have been made to encourage scientists, governments, and industry to advance salivary research. An optimal diagnostic method should be functional, specific, sensitive, af-

fordable, and clinically applicable. Many of the methods developed for salivary diagnostics already meet these criteria, owing to the interdisciplinary collaboration of experts in chemistry, physics, biology, and technology[7,14].

Excess body weight profoundly affects human health and increases the incidence of diabetes and cardiovascular diseases. Since these conditions can be prevented or delayed through lifestyle modification, a new medical approach is needed, which focuses on the early identification of individuals at increased risk. One useful screening tool for identifying high-risk individuals is the detection of metabolic syndrome. The aim of this study was to determine the correlation between salivary uric acid concentrations and the various risk factors associated with metabolic syndrome.

This study was approved by the Ethics Committee of the Faculty of Dentistry - Skopje, Ss. Cyril and Methodius University in Skopje, and was conducted in accordance with the principles of the Helsinki Declaration.

Material and methods

Study Design and Participants

A cross-sectional study was conducted among 156 students from the Faculty of Dentistry, Faculty of Medicine, and Faculty of Pharmacy, all part of Ss. Cyril and Methodius University in Skopje, Republic of North Macedonia. The participants were between 20 and 25 years of age. Exclusion criteria included conditions known to affect salivation or uric acid metabolism, such as gout, renal insufficiency, Sjögren's syndrome, autoimmune diseases, acute infections, type 2 diabetes mellitus, and pregnancy. All participants completed a questionnaire to exclude any previous systemic diseases or conditions. Anthropometric measurements were performed, and unstimulated saliva samples were collected from each participant.

Anthropometric and Physiological Measurements

In the Biochemical Laboratory of the Department of Oral and Periodontal Diseases, Faculty of Dentistry – Skopje, the following parameters were measured for all subjects: body weight, height, waist circumference, blood pressure, and pulse rate. Measurements were performed in the morning, under standardized conditions.

Saliva Collection and Preparation

Unstimulated saliva was collected from all participants using the spitting method, following the recommendations of Navazesh[15]. The collection was carried out between 9:00 and 12:00 a.m., for 10 minutes. Participants were instructed to refrain from eating or drinking for at least two hours prior to sample collection. Saliva samples were centrifuged at 4000 rcf for 10 minutes at 4°C. From the supernatant, 1000 µL were transferred to Eppendorf tubes and stored at –20°C until analysis. Before biochemical determination, saliva samples were rapidly thawed by immersion in warm water.

Biochemical Analysis

The concentration of uric acid in saliva was determined spectrophotometrically using an enzymatic URICASE/PEROXIDASE method[16]. The assay was performed with a commercial reagent kit (Biosystems S.A., Barcelona, Spain). After a brief incubation at 37°C, a red-colored complex was formed. The absorbance, proportional to the uric acid concentration, was measured at 515 nm. All reagents used were of analytical grade purity.

Statistical Analysis

All data were analyzed using IBM SPSS Statistics software, version 24.0 (IBM Corp., Armonk, NY, USA). The results were expressed as mean ± standard deviation (SD). Comparisons between groups were performed using the Student's t-test, and correlations were evaluated using Spearman's rank correlation coefficient. The level of statistical significance was set at $p < 0.05$.

Results

Of all 156 students included in the study, 70 (44.9%) were male and 86 (55.1%) were female. The majority of students were from the Faculty of Dentistry (n=82, 52.6%), followed by those from the Faculty of Medicine (n=48, 30.8%) and the Faculty of Pharmacy (n=26, 16.6%), with a mean age of 22.85 ± 2.21 years in males and 22.11 ± 1.51 years in females; mean BMI 25.35 ± 4.18 kg/m² and 23.77 ± 3.52 kg/m², waist circumference 90.55 ± 15.38 cm and 74.61 ± 6.18 cm, systolic blood pressure 79.70 ± 13.16 mmHg and 78.83 ± 11.81 mmHg, diastolic blood pressure 121.60 ± 13.33 mmHg and 115.00 ± 16.09 mmHg, and pulse rate 87.30 ± 11.41 bpm and 97.94 ± 16.62 bpm, in males and females, respectively.

The mean salivary uric acid concentration in male participants was 134.65 ± 86.7 µmol/L, which was significantly higher than in females (96.06 ± 49.6 µmol/L) ($t = 3.345$, $p = 0.001$) (Table 1).

Table 1: Mean salivary uric acid concentration by gender

Parameter	Mean±SD (Male)	Mean±SD (Female)	t-value	p
Uric acid (µmol/L)	134.65±86.7	96.06±49.6	3.354	0.001

The mean salivary uric acid levels among participants with normal BMI (< 25 kg/m²) were 43.07 ± 14.2 µmol/L, whereas those with increased BMI (> 25 kg/m²) had 206 ± 71.8 µmol/L. Participants with higher BMI had significantly elevated uric acid concentrations ($t = –14.317$, $p < 0.001$) (Table 2).

Table 2: Mean salivary uric acid concentration by BMI group

Uric acid (µmol/L)	Mean±SD (BMI<25)	Mean±SD (BMI>25)	t-value	p
Male	29.71±10.05	45.24±5.44	-3.529	0.002
Female	69.96±35.2	251.25±44.1	-12.900	<0.001
Total	43.07±14.2	206±71.8	-14.317	<0.001

A positive correlation was observed between salivary uric acid levels and several risk factors associated with metabolic syndrome and cardiovascular diseases, including body weight, systolic and diastolic blood pressure, and waist circumference. No significant correlation was found between uric acid levels and pulse rate (Table 3).

Table 3: Correlation between salivary uric acid levels and risk factors associated with metabolic syndrome

Variables	r	p
Uric acid: BMI	0.906	<0.001
Uric acid: Waist circumference	0.846	<0.001
Uric acid: Systolic blood pressure	0.713	<0.001
Uric acid: Diastolic blood pressure	0.484	<0.001
Uric acid: Body weight	0.863	<0.001
Uric acid: Pulse	0.074	0.352

Discussion

Metabolic syndrome represents a combination of various metabolic disorders or risk factors, including obesity, increased waist circumference, elevated blood pressure, elevated triglycerides, decreased levels of HDL (high-density lipoproteins), and increased blood glucose levels[17,18]. Individuals who exhibit at least three of these risk factors are classified as patients with metabolic syndrome[18]. The need for screening of these factors that lead to the development of metabolic syndrome is evident. Their timely detection can help prevent serious cardiovascular complications[19.20]. However, identifying these risk factors is not always possible. There are several reasons for this: limited access to healthcare services, the high cost of certain diagnostic methods, and the reluctance toward invasive diagnostic procedures[21-23]. The use of noninvasive screening methods is a prerequisite for involving a larger number of individuals in preventive programs and for promoting healthier lifestyle changes[24].

One approach for noninvasive monitoring is the use of salivary biomarkers[25]. Several serum biomarkers such as C-reactive protein, adiponectin, and uric acid, which are associated with metabolic syndrome and cardiovascular diseases, can also be detected in saliva[26-28]. Of particular research interest is salivary uric acid, since a linear association has been identified between serum and salivary uric acid levels[29-31]. Although numerous studies have confirmed a positive correlation between salivary uric acid levels, metabolic syndrome, and cardiovascular diseases, the role of this metabolite is not yet fully understood.

Uric acid is the final degradation product of purine catabolism and has a significant antioxidative role in the extracellular environment[32]. It has been proven that uric acid is one of the main antioxidants in the human body, contributing approximately

55% of the total antioxidant capacity of plasma[33] and 70–85% of the total antioxidant capacity of saliva[29]. The enzymes responsible for uric acid formation also participate in the production of free radicals, which gives this metabolite both proinflammatory and prooxidant roles[34.35]. Whether uric acid is the cause of certain metabolic disturbances or a product formed as a result of them, it is currently being investigated as a potential biomarker for identifying individuals at risk for metabolic syndrome and cardiovascular diseases[36.37].

In our study, the amount of uric acid in saliva was significantly higher in male participants compared to females (Table 1), which is consistent with the findings of Uppin et al.[30], Riis et al.[27], and Viazzi et al.[38]. Participants with increased BMI values demonstrated significantly higher uric acid concentrations (Table 2). These results are in line with numerous studies reporting elevated serum and salivary uric acid concentrations among patients with metabolic syndrome[28,39-44].

In a study conducted on 2,380 patients, individuals with elevated uric acid levels had an odds ratio (OR) of 2.67, meaning they were 2.67 times more likely to develop metabolic syndrome[45]. Similar results were reported in a meta-analysis from 2025 (OR = 2.25)[46]. The association between uric acid and risk factors for metabolic syndrome has been confirmed in children, adolescents, and adults[40]. Soukup demonstrated a correlation between salivary uric acid levels and metabolic syndrome risk factors[28].

Our correlation analysis revealed a positive association between salivary uric acid levels and several risk factors related to metabolic syndrome and cardiovascular diseases, including body weight, systolic and diastolic blood pressure, and waist circumference (Table 3). No statistically significant correlation was found between uric acid levels and pulse rate. These results are consistent with recent studies showing that higher uric acid levels are significantly associated with components of metabolic syndrome[47,48]. Numerous studies[42,49-52] have indicated elevated uric acid concentrations in patients with metabolic syndrome. Ishizaka et al.[53] investigated the relationship between metabolic syndrome and uric acid concentration and found that the prevalence of metabolic syndrome increased proportionally with uric acid levels.

Large population-based analyses further show that individuals with hyperuricemia have greater waist circumference, higher blood pressure, and a higher prevalence of all five diagnostic criteria for metabolic syndrome[54]. These associations can be explained by several pathophysiological mechanisms. First, hyperinsulinemia associated with insulin resistance reduces renal excretion of uric acid, leading to its accumulation. Second, uric acid physiologically contributes to the worsening of metabolic disorders by inducing oxidative stress and reducing the bioavailability of nitric oxide in the endothelium, causing endothelial dysfunction and vasoconstriction - mechanisms that raise arterial pressure[54-56]. At higher concentrations, uric acid shifts from an antioxidant to a proinflammatory mediator, activating cytokines and promoting macrophage infiltration into adipose tissue, thereby exacerbating insulin resistance and encour-

aging the accumulation of abdominal fat[32,55]. This mechanism explains the strong link between uric acid and central obesity.

In other words, uric acid is not merely a marker but an active modulator of metabolic syndrome, participating in mechanisms of oxidative stress, inflammation, endothelial dysfunction, and fat accumulation[55].

Some studies have shown that hyperuricemia, through its proinflammatory effects, can enhance sympathetic tone and increase resting heart rate[57]. However, this effect is mainly observed in older individuals or in cases of pronounced autonomic dysfunction[58], which likely explains why no significant correlation was observed in our study.

Several studies have demonstrated that uric acid levels are significantly higher in individuals with metabolic syndrome and increase progressively with the number of metabolic abnormalities present. Therefore, uric acid concentration is considered an indicator of more severe cardiovascular disturbances[39,49,59]. Recent literature suggests that elevated uric acid levels may have both diagnostic and prognostic significance in the context of metabolic syndrome, proposing that hyperuricemia be included as a sixth diagnostic criterion, thereby expanding the current definition and allowing earlier identification of individuals at increased risk of developing metabolic syndrome[60].

The use of saliva as a diagnostic tool offers several advantages compared to serum or tissue samples. Its greatest advantage lies in the noninvasive method of collection. Additionally, its simple collection, storage, and handling make saliva a valuable biological fluid for disease diagnosis. New analytical technologies have enabled the detection of numerous salivary biomarkers, making salivary diagnostics an efficient tool for identifying various systemic and oral diseases.

Conclusion

Based on our results demonstrating a significant correlation between salivary uric acid concentrations and risk factors associated with metabolic syndrome, we believe that saliva can be used to determine uric acid concentration as a valid noninvasive biomarker for metabolic syndrome.

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REVIEW

EMERGING OPPORTUNISTIC YEAST INFECTIONS – LITERATURE REVIEW

Gordana Mirchevska[1]

[1] *Institute of Microbiology and Parasitology, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Republic of North Macedonia*

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***Correspondence:**

Mirchevska G, Institute of Microbiology and Parasitology, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Republic of North Macedonia

E-mail: gordmir@yahoo.com

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Abstract

The growing threat of fungal infections demands immediate attention from healthcare systems in all countries. With the advancement of modern medicine and a growing population of immunosuppressed and immunocompromised patients, as well as critically ill patients, increasingly frequent diagnoses of invasive yeast infections have become an important cause of morbidity and mortality. In the last decade, increased incidence of non-*albicans Candida species* infection compared to *C. albicans* has been registered worldwide. Several non-*albicans Candida species*, such as *C. glabrata* and *C. krusei,* may be resistant to azole antifungal therapy The emergence of multidrug-resistant *C. auris* is the latest threat in many countries, since this fungus can cause intrahospital infections. *Trichosporon* species are the second most common cause of invasive yeast infections in patients with haematological malignancies, and can be resistant to amphotericin and echinocandins. Despite diagnostic and therapeutic advances, cryptococcosis continues to be a disease with unacceptably high incidence and mortality, particularly in resource-limited settings. *Rhodotorula* species can be a significant cause of catheter-related fungaemia, sepsis, and invasive disease in severely immunosuppressed patients. Other uncommon yeasts that can cause invasive disease in severely immunosuppressed patients include *Magnusiomyces capitatus, Geotrichum candidum, Kodamaea ohmeri, Saccharomyces cerevisiae, Malassezia furfur and Sporobolomyces species*. Although rare yeasts are emerging as opportunistic human pathogens, diagnosis remains challenging and treatment suboptimal. Therefore, enhanced awareness of fungal infections is crucial among healthcare providers, and this requires great knowledge and understanding, and appropriate diagnostic testing, so every segment of the healthcare system can contribute to address the challenges posed by fungal infections.

ПРЕГЛЕД НА ЛИТЕРАТУРА

ПОНОВИ ОПОРТУНИСТИЧКИ ИНФЕКЦИИ СО КВАСНИЦИ - ПРЕГЛЕД НА ЛИТЕРАТУРАТА

Гордана Мирчевска[1]

[1] *Институт за микробиологија и паразитологија, Медицински факултет, Универзитет „Св. Кирил и Методиј“ во Скопје, Северна Македонија*

Цитирање: Мирчевска Г. Понови опортунистички инфекции со квасници - преглед на литературата Арх Ј Здравје 2025;17 (2) 99-122

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***Кореспонденција:**

Жанина Переска

Email: perevska@yahoo.com

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Извадок

Растечката закана од габични инфекции бара итна акција од здравствените системи на сите земји. Со напредокот на модерната медицина и растечката популација на имуносупримирани и имунокомпромитирани пациенти, како и критично болни пациенти, сè почестите инвазивни инфекции предизвикани од квасници стануваат важна причина за морбидитет и морталитет. Во последната деценија се регистрира зголемена инциденција на инфекции со non-*albicans Candida* видови во однос на *C. albicans*. Неколку non-*albicans* специеси, како *C. glabrata* и *C. krusei*, може да бидат отпорни на азолите. Појавата на мултирезистентната *C. auris* е најновата закана во многу земји, бидејќи оваа габичка може да предизвика интрахоспитални инфекции. *Trichosporon* species е втората најчеста причина за инвазивни габични инфекции кај пациенти со хематолошки малигни заболувања, а тие може да бидат отпорни на амфотерицин Б и ехинокандини. И покрај дијагностички и терапевтски напредок, криптококозата продолжува да биде болест со неприфатливо висока инциденција и смртност, особено во услови со ограничени ресурси. Видовите *Rhodotorula* може да бидат значајна причина за фунгемија поврзана со катетер, сепса и инвазивни болести кај сериозно имуносупримирани пациенти. Други невообичаени квасници кои можат да предизвикаат инвазивна фунгална инфекција кај сериозно имуносупримирани пациенти се: *Magnusiomyces capitatus, Geotrichum candidum, Kodamaea ohmeri, Saccharomyces cerevisiae, Malassezia furfur* и *Sporobolomyces species*. Иако ретките квасници се појавуваат како опортунистички човечки патогени, дијагнозата и понатаму е предизвик, а третманот е субоптимален. Затоа, зголемената свест за габичните инфекции е од клучно значење кај давателите на здравствени услуги, а тоа бара големо знаење и разбирање, како и соодветно дијагностичко тестирање, со цел секој сегмент од здравствениот систем да може да придонесе за справување со предизвиците што ги создаваат габичните инфекции.

Introduction

Fungi constitute an essential and diverse component of most of the Earth's ecosystems. They are eukaryotic organisms morphologically classified into yeast-like and filamentous forms. Currently, it is estimated that the number of fungal species on Earth ranges from 11.7 to 13.2 million, based on high-throughput sequencing. Nevertheless, only 150,000 fungal species have been described so far, establishing different types of relationships, such as symbiotic, commensal, opportunistic or pathogenic[1]. At least 300 fungal species are associated with human infections[2]. However, with the emergence of new pathogenic fungi, the number of fungi associated with human infections is constantly increasing. Also, sophisticated molecular investigational methods more easily identify fungi, which have led to the recognition of genetic and phenotypic diversity among different fungal pathogens. Recently, there has been a greater recognition of the importance of fungal co-infections with other microorganisms, especially respiratory pathogens, which often lead to poor patient outcome. Finally, decades of continuous use of antifungal and antibacterial agents in agriculture and medicine have changed the global microbiome, contributing to the emergence of drug-resistant fungal infections in plants, animals, and humans[3].

Fungal infections, considered rare in the past, are increasingly recognized as a major global health concern, and estimates suggest they cause over 1.6 million deaths annually[4]. Emerging evidence indicates that the incidence and geographic range of fungal infections are both expanding worldwide due to the global warming on the Earth, and the increase of international travel. Invasive fungal infections have become a major concern in modern medicine due to the increasing prevalence of immunocompromised conditions, such as HIV/AIDS, cancer, patients undergoing steroid treatment, chemotherapy resulting in severe neutropenia, hematopoietic stem cell and solid organ transplantation. Chronic lung diseases, tuberculosis and diabetes mellitus additionally increase the risk for development of invasive fungal infections. Critically ill patients in an intensive care unit (ICU), patients undergoing invasive medical procedures and receiving broad-spectrum antibiotics, are also high-risk patients. During the COVID-19 pandemic, the reported incidence of invasive fungal infections increased significantly among hospitalized patients, such as the outbreak of mucormycosis in COVID-19-infected Indian patients accounted for 71% of new mucormycosis cases globally[5]. Moreover, fungal pathogens may infect post-COVID-19 patients[6]. On October 25, 2022, the World Health Organization published the first-ever fungal priority pathogens list (WHO FPPL) of nineteen priority fungal pathogens that pose significant global threats. This was the first global effort to systematically prioritize fungal pathogens, to guide research, development, and public health actions of fungal infections. This list is divided into three groups: critical-priority, high-priority, and medium-priority. In the "critical-priority" group, *Candida albicans* and *Candida auris*, as well as *Aspergillus fumigatus* and *Cryptococcus neoformans* are included. These fungi were ranked as "critical" fungal pathogens based on

their antifungal resistance, mortality rates, lack of evidence-based diagnostic and treatment options, annual incidence, and complications and sequelae[7].

Fungal pathogens are becoming increasingly resistant to treatment with only four classes of systemically active antifungal drugs currently available, and few candidates in the clinical pipeline. Despite advancements in antifungal therapies, the mortality rates for invasive fungal infections remain unacceptably high, particularly for infections caused by multidrug-resistant fungal pathogens. Treatment is complicated by antifungal resistance to existing antifungal agents, drug toxicity, and the limited arsenal of effective antifungal agents. Also, fungal extracellular polymeric substances, which have the functions of adhesion, cell aggregation, and protection of antifungal agents contribute to treatment failure[8]. Accurate diagnosis of invasive fungal infection is still a clinical and diagnostic challenge due to nonspecific symptoms and sometimes due to lack of knowledge about the recurrence and emergence of new fungal pathogens. Limited availability of rapid and sensitive diagnostic tools also contributes to delayed or missed diagnoses of invasive fungal infections (IFI).

This review focuses on emerging yeast pathogens and is intended to raise awareness of the importance of early detection and treatment of fungal diseases in immunocompromised and critically ill patients in order to reduce the risk of mortality from IFI.

1. Candida species

Candida species is a member of the healthy microbiota, asymptomatically colonizing the gastrointestinal and reproductive tract, oral cavity, and the skin of most humans. In individuals with healthy immune system, *Candida species* is often harmless, and in balance with other members of the local microbiota. Alterations in the host microbiota (after broad spectrum antibiotic treatment), changes in the host immune response (stress, infection by microbes, or immunosuppressant therapy), or variations in the local environment (shifts in pH or nutritional content) can enable *C. albicans* to overgrow and cause infection. These infections range from superficial mucosal and dermal infections to hematogenously disseminated IFI, with mortality rates approaching 40%. *Candida* produces highly structured biofilms composed of multiple cell types. *Candida* is capable of causing infections in healthy people with implanted medical devices, and are usually the predominant fungal species isolated from medical device infections. Urinary and central venous catheters, pacemakers, mechanical heart valves, joint prostheses, contact lenses, and dentures are all very susceptible to *Candida* biofilms[9]. Once it forms on an implanted medical device, a *Candida* biofilm has the potential to seed disseminated bloodstream infections and to lead to invasive mycoses[10].

The main causative agent of candidiasis is C. albicans; however, in recent years, a tendency has been described to increase the incidence of mycoses caused by non-*albicans Candida* species in humans, such as *C. auris*, *C. glabrata*, *C. dubliniensis*, *C. tropicalis, C. blankii, C. lusitaniae, C. tropicalis, C. krusei*, and *C. parapsilosis*. However, five pathogens cause the most invasive infections: *C. albicans, C. gla-*

brata, C. tropicalis, C. parapsilosis and *C. krusei*[11].

The increasing prevalence of colonization and infection with non-albicans *Candida species* in recent years is thought to be driven largely by the increased use of prophylactic antifungals, such as fluconazole. Most of these species are inherently resistant or easily acquire resistance to commonly used antifungal drugs, usually due to the increased use and misuse of antifungal agents. Implementation of new diagnostic techniques document constant change in the epidemiology of *Candida* infections. The SENTRY Antifungal Surveillance Program, established back in 1997 in the USA, monitored the global epidemiology of invasive *Candida* infections with respect to species distribution and resistance to antifungals. This program has published its data after a 20-year surveillance period, which included over 20,000 clinical isolates collected through passive surveillance from 39 countries worldwide. According to this data, the total proportion of infections attributable to *C. albicans* has decreased from 57.4 to 46.4% over the 20-year surveillance period[12]. In 2017, the Centers for Disease Control and Prevention conducted active population-based surveillance for candidemia through the Emerging Infections Program in 45 counties in 9 states encompassing approximately 17 million persons. During this surveillance, 81 laboratories forwarded to CDC 1122 *Candida* species isolates. The most frequent *Candida* species isolated from culture was *C. albicans* (38%), followed by *C. glabrata* (30%), *C. parapsilosis* (14%), and *C. tropicalis* (7%). Six percent of all *Candida* isolates were resistant to fluconazole, with rates ranging from 0.5% in *C. albicans* to 7% in *C. glabrata* and 9% in *C. parapsilosis*. Two percent of Candida isolates were resistant to an echinocandin antifungal, of which most were *C. glabrata* (12). Recent epidemiological studies from Europe have reported an increased relative prevalence of non-*albicans Candida* species as well[13]. Prior to 1997, most data on *Candida* bloodstream infections were reported in studies carried out in the USA. Therefore, the ECMM initiated the first multicentre study aimed to present the epidemiological and mycological profile of candidemia across Western Europe[14]. The European Confederation of Medical Mycology (ECMM) conducted three pan-European multicentre studies between 1997 and 2022, to investigate epidemiology, resistance, and other aspects of invasive candidiasis[15,16,17].

There are differences in the epidemiology of *Candida* bloodstream infections among European countries, with a prevalence of *C. glabrata* and *C. parapsilosis* in Northern and Southern countries, respectively. An Italian 2-year observational survey on ICU was conducted to evaluate the species distribution and possible differences between bloodstream infections caused by *C. albicans* and non-*albicans Candida*. The results of this study confirmed 462 cases of candidemia. *C. albicans* was isolated with the highest frequency (49.4%); *C. parapsilosis* ranked on the second position (26.2%), followed by *C. glabrata* (10.4%), *C. tropicalis* (6.5%), *C. krusei* (2.8%), *C. guilliermondii* (1.5%), *C. lusitaniae* (1.3%), *C. lipolytica* (0.6%) and *C. famata, C. sake, C. utilis* (0.4%, each)[18]. Literature review of 24 articles demonstrated that *C. albicans* was the most common species in 21 countries, accounting for 51.3% to

76.3% of all *Candida* infections[19]. In four studies from southern European countries, the proportion of *C. albicans* was between 37.9% and 49%. In the remaining three studies, the proportion of *C. albicans* was extremely low. In two studies conducted in Turkey, *C. albicans* strains accounted for 18.6% and 22.9% of all *Candida* infections. In a survey from Greece, *C. albicans* and *C. parapsilosis* were almost equally distributed (33.3% and 36.4%, respectively). Regarding non-*albicans Candida* species, the three most prevalent species were *C. glabrata, C. parapsilosis* and *C. tropicalis. C. glabrata* was prevalent in studies from German-speaking countries, France, UK, and North Europe, reaching proportions of 13.2-31.2%. *C. parapsilosis* emerged as an important opportunistic fungal pathogen in the Mediterranean area: Turkey (77.1%), Italy (37%), Greece (36.4%) and Spain (28.8%). In contrast, C. parapsilosis was a less common cause of candidemia in recent surveys from France and Denmark (0% and 2.6%, respectively). *C. tropicalis* in these studies was less prevalent. It was the fourth most common species of Candida in German-speaking countries, France, Italy and Poland, and the second in Portugal and in Turkey, accounting for 21.2% and 12.7% of all *Candida* bloodstream infections, respectively. Data from a national, prospective multicentre study from Serbia, which analysed *Candida* BSI in ICUs demonstrated almost equal distributions of *C. albicans* (~56%) and non-albicans *Candida* (~44%). *C. albicans* and *C. parapsilosis* were prevalent (~90%), and the distribution of *C. parapsilosis* showed a significant variation relative to patients' age (P = .039). *C. albicans* and *C. parapsilosis* prevailed and were equally distributed in adult settings, while in paediatric/neonatal settings only *C. albicans* caused almost ¾ bloodstream infections[20].

With the emergence of the COVID-19 pandemic, these factors associated with the increased incidence of fungal infections have intensified, and non-albicans *Candida* species has been identified as emerging new infections[5].

The pathogenic potential of *Candida* species to cause invasive infections is facilitated by many virulence factors such as adherence to host tissues and medical devices, biofilm formation, and secretion of extracellular hydrolytic enzymes[8].

Candida auris and other multidrug-resistant fungi

The emergence of new fungal pathogens and the spread of multidrug-resistant strains represent a growing threat to global health due to their adaptability and ability to cause serious infections in vulnerable categories of patients.

Candida auris, a novel and major fungal pathogen in the *C. haemulonii* complex (Metchnikowiaceae), was first described in 2009 after its isolation from the external ear canal of a patient in Japan. This is an emerging pathogen that has already been isolated on five continents[21]. However, the earliest findings of multiple clades of *C. auris* were present as of 1996[22]. This fungal agent has appeared in different geographic locations simultaneously. Genomic analysis has been performed through single nucleotide polymorphism (SNP) analysis and whole genome sequencing, and results suggest that genetically distinct

clonal populations of *C. auris* emerged independently and simultaneously in different geographical areas[23]. Each clade presents unique and distinct microbiological and clinical characteristics. Clades I, III, and IV are mostly linked with IFI and nosocomial outbreaks. Warmer climates may have aided in the transmission of *C. auris*. It is hypothesized that halotolerance and thermotolerance of this fungus may have originated from a non-pathogenic strain found in high-salinity regions, and with subsequent evolutionary adaptation, this strain may have overcome the thermal barrier of mammals and become capable of causing infection.

C. auris has become a significant threat to global health. Its resistance to multiple antifungal classes, high mortality rates, ability to persist in the environment and increasing instances of outbreaks in healthcare settings constitute major concerns among healthcare practitioners across the globe. A feature that distinguishes *C. auris* from other fungal pathogens is its high capacity for skin colonization, where it persists for extended periods of time, leading to widespread outbreaks in healthcare facilities via patient-to-patient transmission. Infection and colonization have been detected mainly in critical care patients and affect both pediatric and adult populations.

Some of the most prevalent reported risk factors for *C. auris* colonization and infection include: prolonged exposure to broad-spectrum antimicrobial agents[24-26], presence of indwelling medical devices, diabetes mellitus, prolonged intensive care unit (ICU) hospitalization, haemodialysis, immunocompromised patients, admission to a hospital or long-term care (LTC) facility, and transfer from a healthcare facility with an ongoing *C. auris* outbreak[25-27].

Many studies have reported the isolation of *C. auris* from different countries, such as South Korea, India, Pakistan, Kuwait, Israel, Oman, South Africa, Colombia, Venezuela, the United States, Canada, and Europe, including the United Kingdom, Norway, Germany, and Spain[28].

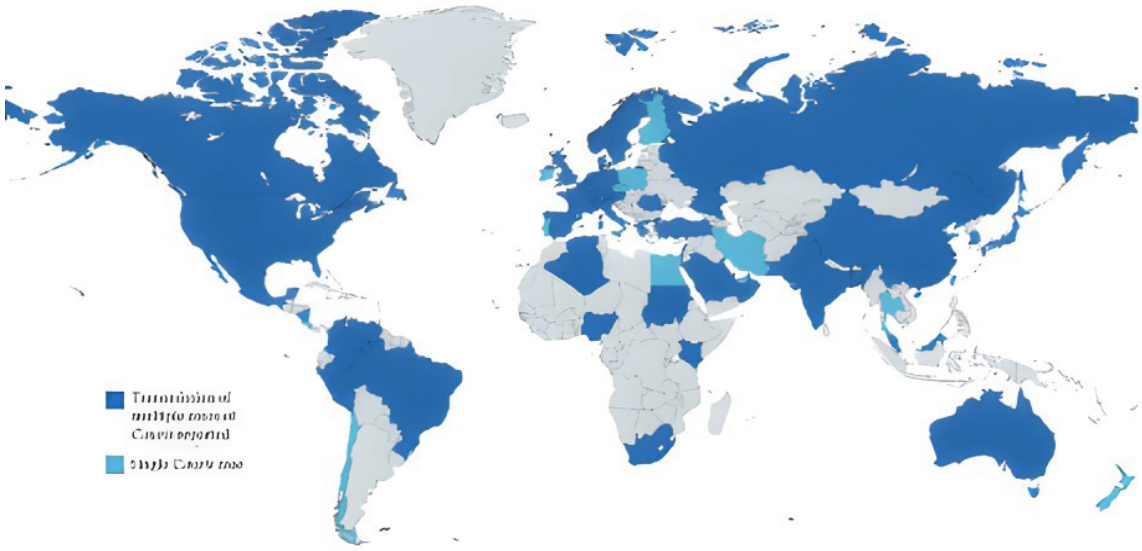

Figure 1. Global epidemiology of *Candida auris* until October 2023. The grey color represents countries with no *C. auris* cases published in the literature (Source: Silva I, Miranda IM, Costa-de-Oliveira S. Potential Environmental Reservoirs of *Candida auris*: A Systematic Review. J Fungi (Basel). 2024 May 8;10(5):336. doi: 10.3390/jof10050336. PMID: 38786691; PMCID: PMC11122228.)

Hospitalizations during the COVID-19 pandemic, frequent surgical procedures, subsequent use of catheters, misuse and overuse of antimicrobials and corticosteroids[29] and prolonged hospitalization, led to higher possibility of a fungal infection with multiresistant species[30].

There has been an increasing number of reports of *C. auris* in COVID-19 acute care units during the pandemic. Researchers suspect that these outbreaks may be related to changes in routine infection control practices due to health crisis, such as limited availability of gloves and poor cleaning and disinfection protocols[31].

2. Cryptococcus species

Cryptococcus is a budding, encapsulated, round to oval yeast found in soil, decaying wood and avian excreta. Historically, *Cryptococcus* was described as two species: *C. neoformans* (var. grubii and var. neoformans) and C. gattii. More recent phylogenetic analyses have distinguished seven clades representing species (VNI-III and VGI-IV), with varying virulence and regional distribution[32].

Members of the *C. neoformans* and *C. gattii* species complexes are the predominant causative agents of cryptococcosis, a life-threatening invasive fungal infection, that poses a significant global health challenge. *C. neoformans* is found worldwide, whereas *C. gattii* most often is found in Australia and similar subtropical regions and in the U.S. Pacific Northwest. *Cryptococcus* was included in the World Health Organization Fungal Priority Pathogens List, based on the results of systematic reviews, expert opinion, and data from the discrete choice experiments[7].

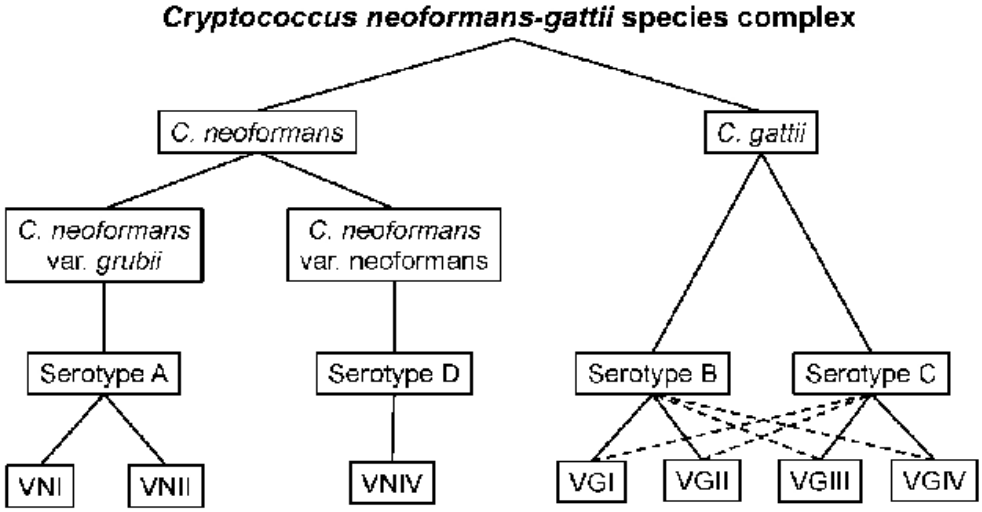

Figure 2. Schematic representation of the new taxonomic classification of the *Cryptococcus* species complexes (Source: Parums DV. Editorial: The World Health Organization (WHO) Fungal Priority Pathogens List in Response to Emerging Fungal Pathogens During the COVID-19 Pandemic. Med Sci Monit. 2022 Dec 1;28:e939088. doi: 10.12659/MSM.939088. PMID: 36453055; PMCID: PMC9724454)

C. neoformans and *C. gattii* species are acquired through the respiratory tract. *Cryptococcus* exists in the form of dehydrated spores. The ubiquitous spores are inhaled and then exposed to alveolar macrophages. This may lead to development of primary pulmonary cryptococcosis, which typically manifests as a self-limiting lower respiratory tract infection with

low-grade fevers and cough. In immunocompetent hosts, desiccated yeast cells can be cleared by the immune system or cause asymptomatic latent infection. It is estimated that up to 50% of primary infections are asymptomatic[33]. Depending on different host-related risk factors, some patients, like individuals living with HIV/AIDS, may progress rapidly to involvement of the central nervous system, causing cryptococcal meningitis, which is the most serious condition with a poor prognosis. *Although both C. neoformans and C. gattii species can cause a similarly broad range of cryptococcosis syndromes, C. neoformans has a predilection for CNS disease, and C. gattii is more often associated with pulmonary disease and large cryptococcomas.*

The most prominent features of cryptococcal pathogenesis are latency and dormancy. The pathogen may reside within phagocytes for years with incubation periods of 110 months for *C. neoformans* and 24 months for *C. gatti*. Reactivation of dormant cryptococci becomes a concern when the host's immune system becomes compromised, potentially leading to invasive disease. Most cases of invasive infection with this yeast probably arise from immunosuppression triggering conversion from latent to active infection, such as cytomegalovirus infection and tuberculosis.

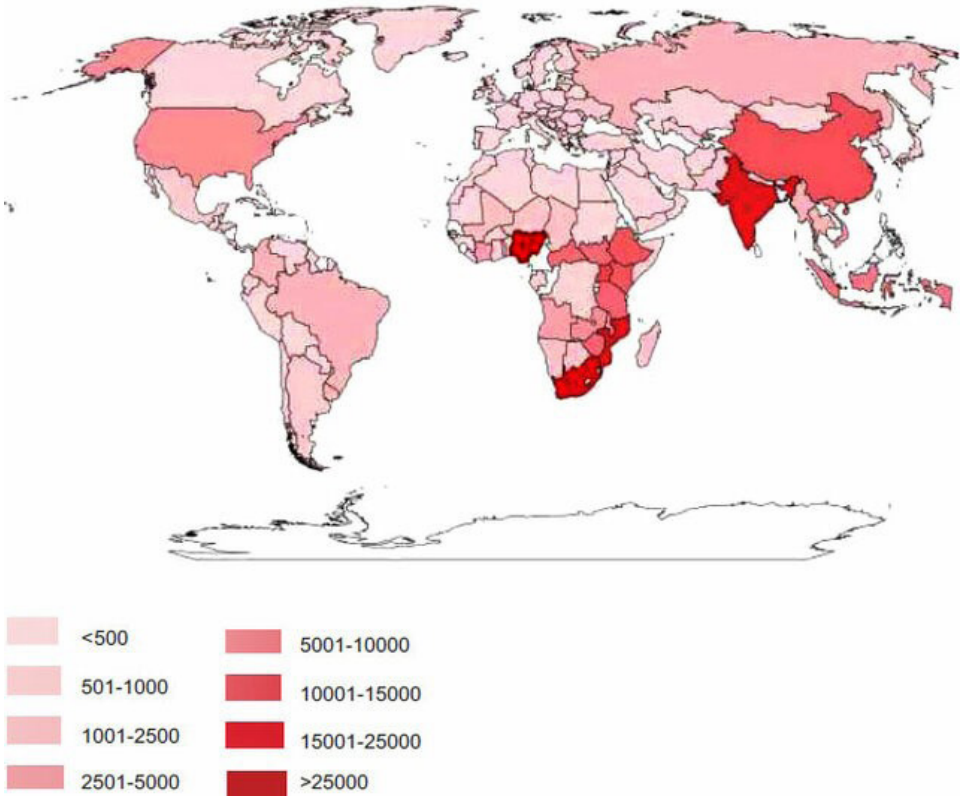

Figure 3. Global epidemiology of cryptococcal meningitis. Map depicting annual incidence of cryptococcal meningitis, per 100,000 people, as of 2023 (Source: Kebabonye K, Jongman M, Loeto D, Kasvosve I. Recent Advances in the Ecoepidemiology, Virulence and Diagnosis of Cryptococcus neoformans and Cryptococcus gattii Species Complexes, The Open Microbiology Journal, Volume 17, 2023, ISSN 1874-2858, https://doi.org/10.2174/18742858-v17-e230419-2022-28. (https://www.sciencedirect.com/science/article/pii/S1874285823000134)

Cryptococcal meningitis remains the most common cause of fungal meningitis worldwide with over 220.000 new cases and 180,000 deaths annually. The highest burden of disease is in low-income and middle-income countries, especially in sub-Saharan Africa, where HIV and AIDS are the dominant risk factor. Patients who survive cryptococcal meningitis may have long-term sequelae, such as focal neurologic deficits, blindness, deafness, cranial nerve palsies, and memory deficits[34]. Overall, the cases of cryptococcal meningitis have decreased since the advent of antiretroviral treatment for AIDS, especially in high-income countries. More recently, new, non-HIV immunocompromised risk groups, and putatively immunocompetent individuals have been increasingly reported in high-income settings and clinicians should consider this in all cases of lymphocytic meningitis. People with various types of immunodeficiency or underlying conditions and even unrecognized risk factors can also develop invasive disease. In large cohort studies of non-HIV cryptococcal meningitis, no underlying predisposing factors were found in 30% of US patients and 67% of Chinese patients[35]. Risk factors for non-HIV cryptococcal meningitis include chronic corticosteroids and treatment with biologic drugs[36], diabetes mellitus, transplantation of solid organs, malignancy and chemotherapy and liver cirrhosis. As corticosteroids potentiate fungal growth, it is important to specifically exclude cryptococcosis, if it is in the differential diagnosis before starting high-dose corticosteroid therapy. Solid organ transplant recipients account for 15%–20% of non-HIV cryptococcal meningitis cases, and this infection is the third most common fungal infection. Cryptococcal meningitis can also develop in non-transplant, non-HIV patients, in individuals with autoimmune and inflammatory conditions (systemic lupus erythematosus, rheumatoid arthritis and sarcoidosis). Despite only limited long-term follow-up data, clinical experience suggests that cryptococcal meningitis is a rare complication among patients on biologics, given their widespread use in patients with inflammatory gastrointestinal, dermatological and rheumatological conditions. Patients with cancer account for approximately 25% of non-HIV cryptococcal meningitis cohorts. Cryptococcosis manifestations vary with cancer type; pulmonary and skin involvement is more common in solid organ tumours and meningitis in haematological malignancy[37].

Treatment options for invasive cryptococcosis are limited, and development of novel anti-cryptococcal agents has been slow in recent decades. Short courses (≤7 days) of amphotericin-based therapy combined with flucytosine are currently the preferred options for induction therapy of cryptococcal meningitis. Cryptococci are intrinsically resistant to echinocandins. Optimal induction treatment is followed by a prolonged treatment with azoles[38].

3. Trichosporon species

In recent few decades, the world has also been witnessing an increasing incidence of infections caused by non-*Candida* yeast such as *Trichosporon* species. These infections are difficult to treat, due to an increased resistance to amphotericin and echinocandins, and have poor prognosis

with high mortality rates[39]. *Trichosporon* species is a ubiquitous yeast-like basidiomycete, which is found in water, soil, plants, mammals and birds. Geographical distribution of infections due to this yeast varies, but data collected from the ARTEMIS DISK Surveillance Study in the period between 1997-2005 showed that infections with *Trichosporon* were found with equal frequencies in both tropical and temperate areas, including South America, the Middle East, India, Southeast Asia, Africa, Europe, Japan, and parts of southeastern USA[40]. In humans, *Trichosporon* are occasionally found as part of gastrointestinal and oral microbiota and can also colonize the skin and mucosa of both respiratory and female genital tracts.

The pathogenic potential of *Trichosporon* has been first described by Beigel, back in 1865, explaining it as a cause of hair infection[41]. The classification of *Trichosporon* has changed over the years. Initially, all *Trichosporon* species were classified as *T. beigelii*, and it was thought that the strain mainly caused infection in superficial hair, but rarely disseminated systemic infections. However, research showed that *T. beigelii* has great morphologic, physiological and biochemical variation. In 1992, Gueho et al. revised the taxonomy of 20 species of *Trichosporon*, including six pathogens: *T. asahii, T. asteroides, T. cutaneum, T. inkin, T. mucoides and T. ovoides*[42]. Presently, 50 *Trichosporon* species are recognized, of which 16 are known to be pathogenic. *T. asahii* is the most important pathogen, with a reported mortality rate of 70% as a cause of invasive trichosporonosis. In certain conditions, they can become pathogenic causing wide spectrum of infections[39]. They are capable of causing superficial white piedra in immunocompetent children and young adults, particularly females. The main reported risk factors for transmission of superficial *Trichosporon* species are close contact, poor hygienic habits, long hair and humidity. Sexual transmission has been reported in cases of pubic white piedra. Epidemiology of invasive trichosporonosis is different. In patients with underlying history of hematological cancer, *Trichosporon species* is the second most common cause of disseminated yeast infections after *Candida*.

The mortality attributed to *Trichosporon species* in such patients, in spite of the antifungal therapy, is very high and ranges from 50-80%[43]. As per the European Organization for Research and Treatment of Cancer/Invasive Fungal Infection Cooperative Group (EORTC/IFICG) and the National Institute of Allergy and Infectious Disease Mycoses Study Group (NIAID/MSG), invasive trichosporonosis has been classified as proven or probable trichosporonosis, based on certain criteria[44]. Risk factors for invasive trichosporonosis include neutropenia, chemotherapy, diabetes, renal disease, HIV infection and immunosuppressive treatment, invasive medical devices, severe burns and cystic fibrosis[45]. Another group that has an increased risk of invasive trichosporonosis are premature neonates with low birth weight, patients on steroids or with intravascular catheters, patients undergoing heart valve surgery or liver transplant, and patients with kidney failure on dialysis[46]. *Trichosporon* species has many virulence factors that permit the establishment of the disease and its dissemination

within the human body. It has adherence abilities and capacity to form biofilms on implanted devices. It also produces and secretes enzymes for scavenging nutrients from the environment[47]. Most invasive *Trichosporon* species infections start with colonization and break in the integrity of the skin and mucous membranes, with subsequent seeding the bloodstream. This usually happens after an aggressive chemotherapy-induced epithelial damage or implantation of intravascular catheters. Antibiotics may also increase the risk of developing invasive *Trichosporon* infections. The guidelines developed by ESCMID/ECMM in 2014 recommend voriconazole for the treatment of trichosporosis[48].

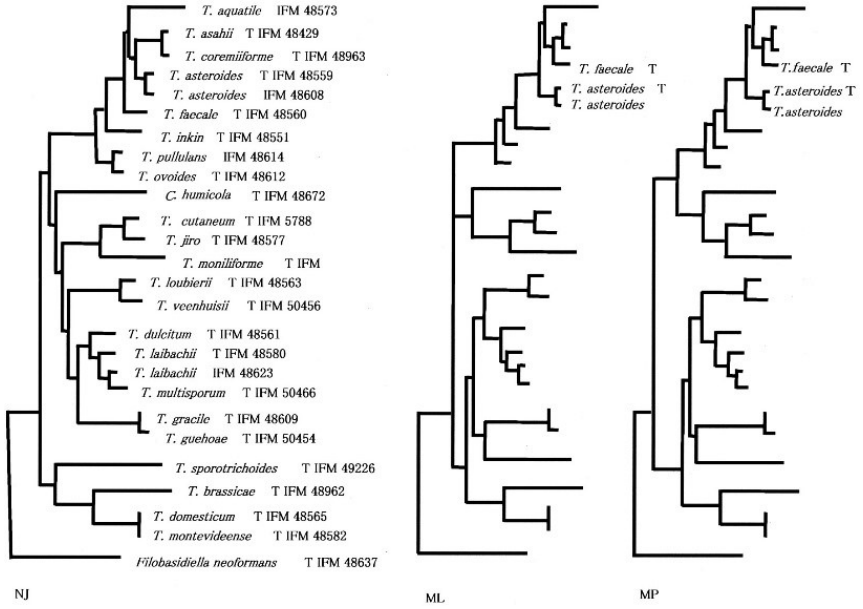

Figure 4. Phylogenetic trees based on nucleotide sequences of cyt b genes (Source: Biswas SK, Wang L, Yokoyama K, Nishimura K. Molecular phylogenetics of the genus trichosporon inferred from mitochondrial cytochrome B gene sequences. J Clin Microbiol. 2005;43(10):5171-8. doi: 10.1128/JCM.43.10.5171-5178.2005. PMID: 16207980; PMCID: PMC1248456.)

4. Magnusiomyces capitatus

Magnusiomyces capitatus (previously known as *Saprochaete capitate, Geotrichum capitatum, Trichosporon capitatum* or *Blastoschizomyces capitatus)* is an ascomycetous yeast, which is found in soil and animals. It is also found as part of the normal microbiota of human skin, respiratory and gastrointestinal tract in healthy people. *M. capitatus*, recently defined as an emerging pathogen, is mostly found in patients with hematological malignancies, particularly acute leukemia[49]. *It is* responsible for lethal fungaemia in patients with profound neutropenia in the haematology settings[50]. Systemic infections caused by *M. capitatus* have been mainly documented in the Mediterranean countries of Europe, including Italy[51], France[52], and Spain[53]. They have also been reported in other areas of Europe (Slovakia, Switzerland, and the Czech Republic)[54]. *M. capitatus* was also recently isolated from an alcoholic male patient in the United States[55]. *M. capitatus* has also been

responsible for prosthetic valve endocarditis[56]. Uncontrolled diabetes mellitus is also a high risk for invasive infection[57].

According to guidelines developed by the European Confederation for Medical Mycology and the European Society for Clinical Microbiology and Infectious Diseases, recommendations based on treatment response have been noted following amphotericin B formulation with or without flucytosine treatment and voriconazole[58]. The use of echinocandins might be associated with worse outcomes.

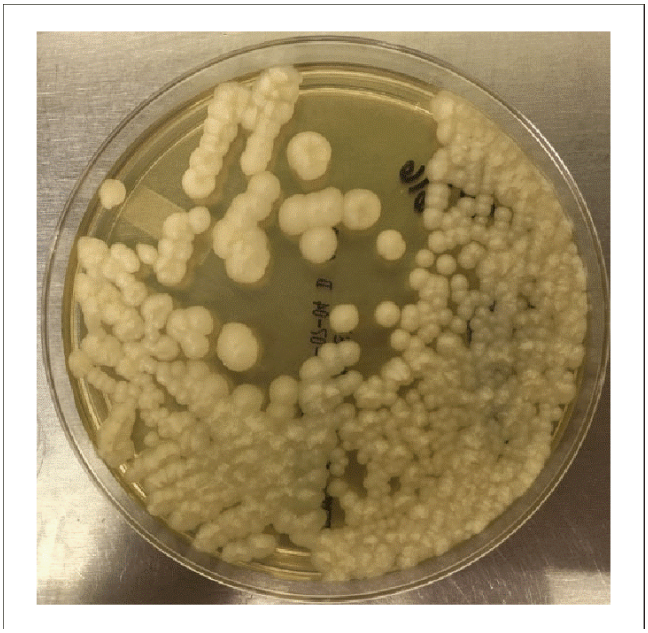

Figure 5. *Magnusiomyces capitatus*, peritoneal fluid, 5-day culture on Sabouraud Dextrose Agar (Source: D'Assumpcao C, Lee B, Heidari A. A Case of *Magnusiomyces capitatus* Peritonitis Without Underlying Malignancies. J Investig Med High Impact Case Rep. 2018;6:2324709618795268. doi: 10.1177/2324709618795268. PMID: 30151397; PMCID: PMC6104205.).

5. Geotrichum candidum

Geotrichum candidum (Galactomyces candidus) is a filamentous ascomycetous yeast that forms arthroconidia and is ubiquitous in soil, decaying organic matter and foods and is used in cheese manufacture[59].

Among 505 cases of rare invasive mycoses included in the recent FungiScope™ registry, 23 cases of invasive infections caused by these fungi have been reported from 10 countries over a 12-year period[57]. All cases of invasive infections were confirmed in adults and previous chemotherapy with subsequent neutropenia was the most common co-morbidity. Fungaemia was confirmed in 14 (61%) cases and deep organ involvement included lungs, liver, spleen, central nervous system and kidneys. The identified fungi were *S. capitata* (n=14), *S. clavata* (n=5), *G. candidum* (n=2) and *Geotrichum species* (n=2). Overall mortality in this study was 65% (n=15). Initial echinocandin treatment was associated with worse outcome at day 30 when compared to treatment with other antifungals (amphotericin B ± flucytosine, voriconazole, fluconazole and itraconazole) (P=.036). Echinocandins are not an option for these infections.

Figure 6. *Geotrichum candidum* culture (Source: Victoria, CC BY-SA 4.0, https://upload.wikimedia.org/wikipedia/commons/7/7d/Geotrichium_candidum.jpg)

6. Rhodotorula

Rhodotorula is a common environmental yeast found in air, soil, lakes, ocean water, milk, and fruit juice. *Rhodotorula* species have been isolated from skin, sputum and digestive tract samples including faeces, as part of the normal human microbiota. *Rhodotorula* produces pink to red colonies and blastoconidia that are unicellular lacking pseudohyphae and hyphae. The genus contains 46 species[60]. Three of these species have been described as rare human pathogens: *R. mucilaginosa, R. glutinis* and *R. minuta*. *R. mucilaginosa* account for the majority of infections (74–79%) followed by *R. glutinis* (7.7%)[61]. The most frequent risk factor is a CVC and underlying haematological disease[62].

Fungaemia, peritonitis, endocarditis or meningitis have also been reported in other patient groups (AIDS, extensive burns, continuous ambulatory peritoneal dialysis, cirrhosis, those who have undergone intra-abdominal surgery, intravenous drug abusers and critically ill ICU patients)[63]. *Rhodotorula* has a high affinity to adhere to plastic surfaces and can form biofilms. Hence, medical equipment can easily become colonized. *Rhodotorula* species are regarded as intrinsically resistant to azoles and echinocandins, but susceptible to amphotericin B and flucytosine[64].

Figure 7. *Rhodotorula* culture (Source: Hernández-Almanza A, Cesar Montanez J, et al. Rhodotorula glutinis as source of pigments and metabolites for food industry, Food Bioscience, Volume 5, 2014, Pages 64-72, ISSN 2212-4292, https://doi.org/10.1016/j.fbio.2013.11.007. (https://www.sciencedirect.com/science/article/pii/S2212429213000849)

7. Kodamaea ohmeri

Kodamaea (Pichia) ohmeri (previously known as *Pichia ohmeri or Yamadazyma ohmeri)* is a rarely occurring yeast that has recently been identified as a cause of fungaemia, endocarditis, cellulitis, funguria and peritonitis in neonates and children[65], and in both immunocompromised[66] and immunocompetent adult patients[67]. Most cases of invasive infections with this species have been treated with liposomal amphotericin B (or amphotericin B deoxycholate) showing good response[68].

As for treatment recommendation, amphotericin B appears to be an attractive first-line agent and echinocandins are possible promising alternatives.

Figure 8. *Kodamea (Pichia) ohmeri* culture (Al-Sweih N, Khan ZU, Ahmad S, Devarajan L, Khan S, Joseph L, Chandy R. *Kodamaea ohmeri* as an emerging pathogen: a case report and review of the literature. Med Mycol. 2011;49(7):766-70. doi: 10.3109/13693786.2011.572300. PMID: 21438792.)

8. Malassezia

Malassezia species are basidiomycetous yeasts, which are the most prevalent fungi colonizing human skin from birth and throughout life[69,70]. They are lipophilic, relying on exogenous (host) lipids for growth. It is difficult to detect them because they grow poorly in culture. *Malassezia* genus comprises 18 species with numerous functionally distinct strains based on morphology, physiological biochemistry and molecular biology[71]. Systemic infections due to lipid-dependent *M. furfur* mainly occur in premature neonates, infants on lipid-containing parenteral nutrition and children and adults with various forms of immunosuppression and underlying diseases[69]. In addition to fungemia, pneumonia, peritonitis, meningitis and disseminated infection caused by *M. furfur* have also been continuously reported worldwide in recent years[72,73].

Susceptibility testing of *Malassezia* has not been standardized because growth is not supported on the standard RPMI growth medium recommended for yeast testing by EUCAST. Most reports on treatment of these infections recommend fluconazole and amphotericin B, which are the preferred agents[74].

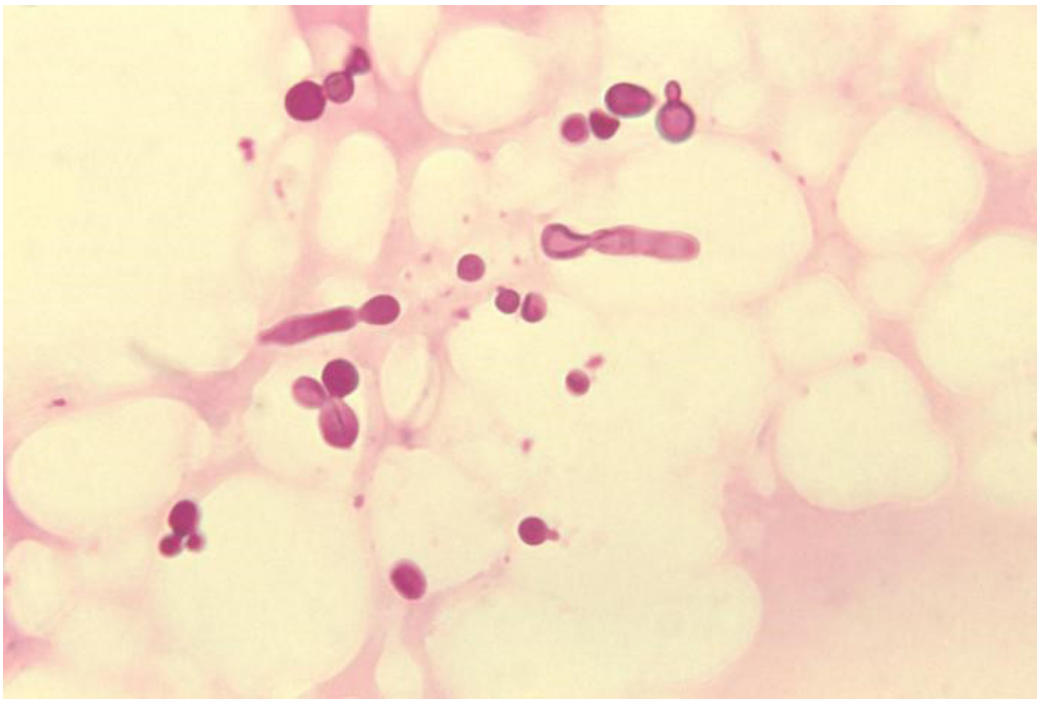

Figure 9. *Malassezia furfur* in skin scale from a patient with tinea versicolor (Source: CDS, Centers for Disease Control and Prevention, part of the United States Department of Health and Human Services. http://phil.cdc.gov/phil_images/20030610/22/PHIL_3938_lores)

9. Saccharomyces

Saccharomyces cerevisiae, also known as baker's or brewer's yeast, is a low pathogenic ascomycetous yeast. *S. cerevisiae* may be found as a harmless and transient digestive commensal and colonizer of mucosal surfaces of healthy people. Invasive infections caused by S. cerevisiae are increasingly reported in the general population, particularly in patients with risk factors and immunocompromised patients. In 1980, Mary L. Eschete and *et al*. reported the first case of fungemia caused by S. cerevisiae, showing its opportunistic characteristics[75]. Since then, cases of invasive infections have been reported all over the world, identifying *S. cerevisiae* as the 5th cause of fungemia[76]. Cases of fungaemia and disseminated infection have been described in vulnerable patients after treatment with *S. boulard*ii probiotic compound[77]. In a recent review of 92 cases of invasive *Saccharomyces* infections, *S. boulardii* accounted for half of these, was less often associated with an underlying immunocompromised condition and more often associated with a favourable outcome[78]. The use of probiotics in debilitated patients, ICU patients, neutropenic patients, preterm newborns or in patients with central lines should be carefully considered.

For the treatment of these invasive mycoses, most clinical experience exists with fluconazole and amphotericin B, for which favourable outcome was observed in 60% and 77.7% of cases, respectively[76]. Finally, amphotericin B with or without flucytosine has been used in severe or recurrent cases[79]. Also, it is strongly recommended that probiotics containing *S. boulardii* are discontinued and indwelling foreign bodies are removed, when possible, because this organism is capable of forming biofilms[76].

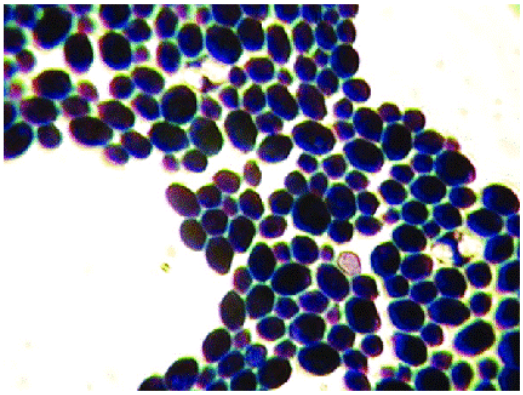

Figure 10. Morphology of *Saccharomyces cerevisiae* yeast culture („Biotechnologia Acta" v. 6, no. 2, 2013 https://doi.org/10.15407/biotech6.02.097, P. 97-106, Bibliography 13, English. Universal Decimal classification: 634.8:632.93:661.74:663.2)

10. Sporobolomyces

Sporobolomyces species are usually red-to-orange pigmented basidiomycetous yeasts, that, along to regular budding cells, also form ballistoconidia[80]. These conidia are discharged into the air. Phylogenetically, they are closely related to *Rhodotorula* species. The 53 species occur widely in nature, especially in lake water, on tree leaves and in air, and with its natural habitat in humans, mammals, birds and plants. *Sporobolomyces* have been reported as the cause of sporadic invasive bloodstream infections, particularly in AIDS patients[81].

A single case of meningitis due to *Sporobolomyces* roseus was reported in an immunocompetent cocaine abuser[82]. This fungus was also described in a case of cerebral infection, fungemia, bone marrow involvement in AIDS patients, a prosthetic cranioplasty infection, encephalitis, and lymphadenitis[83]. Amphotericin B has been efficacious in fungaemic and meningitis cases. A single case of endogenous endophthalmitis due to *Sporobolomyces salmonicolor* was reported in a patient with a history of pelvic inflammatory disease 2 years earlier. The patient recovered following intravitreal amphotericin B (5 µg) and systemic voriconazole of 200 mg twice daily[84].

Figure 10. *Sporobolomyces roseus culture* (Source: Sharma V, Shankar J, Kotamarthi V. Endogeneous endophthalmitis caused by Sporobolomyces salmonicolor. Eye (Lond). 2006;20(8):945-6. doi: 10.1038/sj.eye.6702051.

Novel environmental fungi are increasingly being recognized as potential human pathogens, driven by ecological and climate changes, as well as human activities. The continued emergence of multidrug-resistant and environmentally adaptable fungal pathogens is expected to challenge public health systems in future, necessitating enhanced surveillance, innovative antimicrobial treatments and global collaboration to mitigate their impact on public human health.

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REVIEW

PATHOGENESIS OF RETINOPATHY OF PREMATURITY: A LITERATURE REVIEW

Igor Isjanovski1, Stefan Pandilov[1], Emilija Gjoshevska-Dashtevska[1]

[1] *University Clinic for Eye Diseases, Skopje; Faculty of Medicine, Ss. Cyril and Methodius University Clinic for Eye Diseases, Skopje; Faculty of Medicine, Ss. Cyril and Methodius*

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***Correspondence:** Igor Isjanovski, University Clinic for Eye Diseases, Skopje, Republic of North Macedonia.

E-mail: dr.isjanovski@gmail.com

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Abstract

Retinopathy of prematurity (ROP) is a vasoproliferative disease of the retina that affects premature infants, especially those with low birth weight and high oxygen exposure. It is still the leading cause of blindness in children worldwide. The pathophysiological mechanism occurs in two phases: the first known as hyperoxia-induced vascular regression and the second - hypoxia-induced pathological neovascularization. An imbalance of a large number of molecules and cytokines is involved in the development of this disease. The main ones are: vascular endothelial growth factor (VEGF); insulin-like growth factor-1 (IGF-1); Hypoxia-inducible factor-1 alfa (HIF-1α); as well as a large number of proinflammatory mediators. Various factors such as: oxygen fluctuation, nutritional factors, genetic and epigenetic factors have a certain impact on the development and progression of Retinopathy of prematurity. The motive of this literature review is to present the current views and knowledge regarding the pathophysiological mechanisms as well as potential biomarkers for timely recognition of premature infants at high risk for ROP. For this purpose, we approached a data search from two large databases of biomedical literature: Medline and Embase by entering the keywords: retina, retinopathy of prematurity, hypoxia, pathogenesis, neovascularization. From the obtained data, we selected those papers that present the latest knowledge in this field of ophthalmology. Our perspective on ROP is that insights from its pathophysiological and complex cellular mechanisms should, in the future, contribute to the development and implementation of more sensitive biomarkkers for early diagnosis and tretment prognosis, ultimately aiming to improve outcomes in affected children.

ПРЕГЛЕД НА ЛИТЕРАТУРА

ПАТОГЕНЕЗА НА ПРЕМАТУРНАТА РЕТИНОПАТИЈА: ПРЕГЛЕД НА ЛИТЕРАТУРА

Игор Исјановски[1], Стефан Пандилов[1], Емилија Ѓошевска-Даштевска[1]

[1] *У1Универзитетска Клиника за очни болести; Медицински факултет, Универзитет „Св.Кирил и Методиј“ во Скопје, Република Северна Македонија*

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***Кореспонденција:** Игор Исјановски, Универзитетска клиника за очни болести, Скопје, Република Северна Македонија.

E-mail: dr.isjanovski@gmail.com

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Извадок

Прематурната ретинопатија е вазоприлиферативно заболување на ретината која ги афектира предвремено родените новороденчиња, особено тие со ниска телесна тежина и висока експозиција на кислород. Се уште претставува водечка причина за слепило кај деца во светот. Патофизиолошкиот механизам се одвива во две фази: прва позната како хипероксија индуцирана васкуларна регресија и втора-хипоксија индицирана патолошка неоваскуларизација. Дисбаланс на голем број молекули и цитокини се вклучени во настанувањето на ова заболување. Централно место заземаат: vascular endothelial growth factor (VEGF); insulin-like growth factor-1 (IGF-1); HIF-1α (Hypoxia-inducible factor-1 alfa) како и голем број на проинфламаторни медијатори. Идејата на овој литературен преглед е да ги прикаже моменталните ставови и сознанија кои се познати во врска со патофизиолошките механизми како и потенцијални биомаркери за навремено препознавање на прематурусите со зголемен ризик за РОП. За таа цел пристапивме кон пребарување на податоци од две големи датабази на биомедицинска литература: Medline и Embase со внесување на клучни зборови: ретина, прематурна ретинопатија, хипоксија, патогенеза, неоваскуларизација. Од добиените податоци ги избравме оние трудови кои ги прикажуваат најновите сознанија во ова поле од офталмологијата. Нашите согледувања за РОП се дека сознанијата од нејзините патофизиолошки и сложени клеточни механизми, во иднина, треба да придонесат за развој и имплементација на почувствителни биомаркери за рана дијагноза и прогноза на третманот, со крајна цел да се подобри исходот кај засегнатите деца.

Introduction

TRetinopathy of prematurity (ROP) is a retinal vasoproliferative disease that affects premature infants. Despite all efforts in neonatal care centers, ROP remains the leading cause of blindness in childhood[1]. However, the incidence varies from region to region due to the different levels of neonatal care and survival rates of premature infants. High-income countries have a lower rate of ROP-associated blindness compared to middle- and low-income countries. The main reason for this is thought to be better screening and management of the problem[2].

The etiology of the disease is multifactorial. Several risk factors promote its occurrence. Thus, birth weight and gestational age are considered the most influential in the pathogenesis of ROP. The lower the gestational age and birth weight, the higher the risk of developing the disease. In other words, ROP is rare in newborns born after 32 weeks of gestation and weighing more than 1500g[3]. Another important risk factor for its occurrence is oxygen. Supplementation with oxygen in combination with atmospheric oxygen disrupts the physiological hypoxia of the retina, which results in a delay in the formation of normal blood vessels, retinal ischemia and the formation of new-pathological blood vessels. The duration of oxygen therapy and the increased concentration of O2 significantly increase the risk of developing a severe form of ROP[4]. In addition to these, many other risk factors have been identified in recent decades that have a greater or lesser impact on this condition. Depending on where they originate, they are divided into: maternal factors, prenatal and perinatal factors, demographic factors, comorbidities of infant, nutritional and genetic factors[5].

The disease was first described by ophthalmologist Theodore L. Terry in 1942 as “retrolental fibroplasia” due to the formation of a fibrous membrane behind the lens in blind newborns[6]. About a decade later, it was associated with excessive oxygen supplementation in premature infants. This period is known as the “first epidemic” of ROP. About twenty years later, the so-called “second epidemic” of ROP occurred due to the increased survival rate of extremely premature infants, i.e. those born before 28 weeks of gestation and with a birth weight of less than 1000 g. Despite improved oxygen control, these newborns were at increased risk for developing ROP due to their relatively underdeveloped retinal vascular network and longer stay in intensive care. The second epidemic led to the development of screening programs and laser photocoagulation as a treatment for this condition in the 1980s. Since the 1990s, the so-called “third epidemic” occurring in low- and middle-income countries [7]. The reason for this is that in these countries, neonatal care has improved in recent decades, with better survival of premature infants, but they still lack a systematic screening program for ROP and an inability to treat the condition.

Normal development of retinal blood vessels

The fetus in utero is normally in a hypoxic state with a stable partial pressure of oxygen in the arterial

blood vessels of 22-24 mmHg[8]. This environment allows for the proper development of blood vessels starting from the level of the optic nerve up to the peripheral avascular retina. Physiological hypoxia stimulates the production of vascular endothelial growth factor (VEGF) which promotes the growth of the vascular network. This molecule is strongly regulated by oxygen. It is produced by astrocytes in the still avascular retina in response to hypoxia. In addition to VEGF, other molecules, such as insulin-like growth factor-1 (IGF-1), are also involved in this complex biochemical-embryonic process[9, 10].

The basis of blood vessels is from mesenchymal spindle cells that originate from the optic disc and progress peripherally and forward towards the outer part of the retina. Blood vessels begin to develop intrauterinely at 15 weeks of gestation. The process is called angiogenesis and occurs simultaneously in both the nasal and temporal sectors of the retina. Nasally, vascularization reaches ora serata around 34–36 weeks of gestation, and temporally it occurs between 36–40 weeks[9, 11].

Unlike hypoxia, hyperoxia inhibits the production of VEGF. Thus, premature infants exposed to high oxygen concentrations have reduced production of VEGF, which disrupts normal blood vessel development, resulting in areas of avascular retina. The lower the gestational age of the newborn, the larger these avascular zones are. This condition not only inhibits the development of the vascular network but also causes vasoconstriction and vaso-obliteration of already formed blood vessels, further aggravating the situation[12]. In this way, the retinal tissue is left without adequate oxygen support, which is the basis of the pathophysiological process in ROP.

The aim of this literature review is to present new insights into the pathophysiological mechanism of this retinal disease. That is, to understand all the molecules, cells and signaling pathways that are involved in the pathobiochemical cascade and progression of retinopathy of prematurity. As well as to present possible potential biomarkers that will find clinical application in the early recognition and appropriate management of this condition.

Materials and methods

In the preparation of this literature review, a search was conducted in two large databases of biomedical literature: Medline and Embase. The following keywords were used: retina, retinopathy of prematurity, hypoxia, pathogenesis, and neovascularization. For the analysis, papers published in English between 2003 and 2024, full-text papers, were selected, and abstracts and papers published in other languages were excluded.

Results and discussion

Pathophysiology of ROP

As previously mentioned, the development of retinal blood vessels begins in the fourth month of gestation. Since the process is completed between 34-40 weeks of gestation, premature infants have an incompletely vascularized retinal periphery. That is, the lower the gestational age of the premature infant, the

larger the avascular retinal zone. The disease is based on the processes of hyperoxia, vascular regression, followed by hypoxia and neovascularization, proliferation and traction. The course of the pathological process is continuous and is divided into two phases[12].

The first phase or initial phase is the one in which there is a decrease or cessation of vascular growth and regression of already developed retinal blood vessels. It is induced by hyperoxia in premature infants who are placed in increased O2 concentrations in intensive care units. And a second phase, or proliferation phase, in which abnormal proliferation of blood vessels occurs, a process induced by previous hypoxia in avascular areas of the retina.

Physiologically, the retina in utero develops in a hypoxic environment that stimulates the production of VEGF as an important cytokine in the formation of blood vessels. In premature infants, the process of angiogenesis is not fully completed, and atmospheric oxygen as well as oxygen supplementation in external conditions suppresses the production of VEGF. This leads to the cessation of normal growth of peripheral blood vessels and regression of those already formed. Thus, as the newborn grows, the retina matures without a sufficient number of blood vessels, which makes it hypoxic. At the same time, apoptosis of endothelial cells occurs, a mechanism that is also involved in the pathological process. Fluctuations in oxygen levels lead to the formation of reactive oxygen species (ROS), and due to the insufficiently developed antioxidant defense in premature infants, ROS damage endothelial cells and pericytes. Damaged pericytes gradually die, which disrupts the stability of blood vessels and worsens the overall situation with the vascular network. These processes lead to a systemic inflammatory response and dysregulation of VEGF and IGF-1[13].

As the newborn grows, the metabolic demand of the retina increases, emphasizing relative hypoxia, which leads to the second phase. In this phase, the secondary hypoxia causes increased expression of VEGF in the retinal tissue. On the other hand, the maturation of organs and tissues in the newborn stimulates increased production of IGF-1. It promotes and maintains high levels of VEGF, which results in neovascularization and proliferation of blood vessels at the transition between the vascularized and avascular retina. Thus, pathologically formed blood vessels begin to develop towards the vitreous. Due to the dysfunction of their development, they are susceptible to leakage, which leads to retinal edema and bleeding, together with proliferation towards the vitreous, causing scar tissue formation and retinal traction. In the final stages, traction ablates the retina, leading to irreversible vision loss - blindness[14]. In the second phase, in addition to VEGF and IGF-1, a large number of other pro-inflammatory cytokines are involved, such as: TNF-α (tumour necrosis factor-alpha), IL-1β (interleukin-1 beta), IL-6 (interleukin-6) and others, which stimulate the formation of abnormal blood vessels and progression of the disease[15].

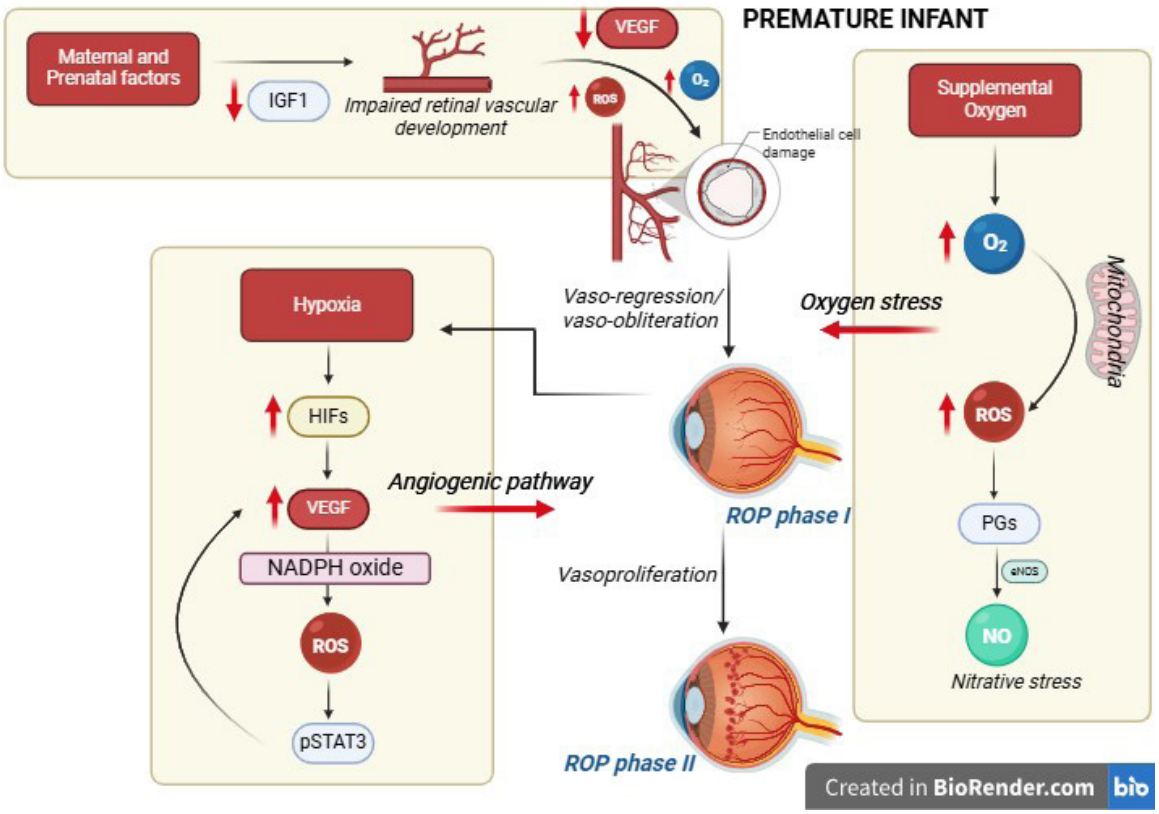

Figure 1. Pathophysiological mechanism and biochemical cascade in retinopathy of prematurity (ROP). IGF1- insulin-like growth factor-1; VEGF-vascular endothelial growth factor; ROS-reactive oxygen species; O2 – oxygen; PGs-prostaglandines; NO-nitic oxide; eNOS-endothelial NO synthase; HIFs-hypoxia-inducible factors; NADPH-dihydronicotinamide-adenine dinucleotide phosphate; pSTAT3-phophorylated signal transducer and activator of transcription 3.

Stages of ROP

The classification of ROP in terms of the severity of the clinical picture includes 5 stages and 3 zones that describe the level of retinal involvement[16].

Stages I-III have the ability to spontaneously regress at any time, while stages IV and V are most often irreversible and lead to vitreous hemorrhage, tractional retinal detachment and subsequent blindness. The first stage is characterized by the appearance of a white line that demarcates the vascular from the avascular retina. Stage II is specific in that a tissue ridge and small initial neovascular changes appear. With the development of the disease, such initial neovascular blood vessels proliferate through the ridge and towards the vitreous - stage III. Already in stage four, zones of retinal ablation are observed, extrafoveolar (IVa) and intrafoveolar (IVb). In the last, fifth stage, complete retinal detachment occurs. Additional risk factors are designated as “plus disease” and the development of the so-called aggressive ROP, AP-ROP.

Molecular and cellular mechanisms

Role of VEGF and other cytokines in the pathogenesis of ROP

VEGF plays a key role in the physiological but also in the pathological development of retinal blood vessels. As we mentioned earlier, in the first

stage of ROP, hyperoxia suppresses the production of VEGF, which leads to a delay in the development of the normal vascular network of the retina. This stimulates the activation of signaling pathways of apoptosis of endothelial cells and the loss of local pericytes, with the ultimate effect of regression of blood vessels. In the second stage of ROP, hypoxia and local acidosis promote the production of HIF-1α (Hypoxia-inducible factor-1 alfa), a major promoter of VEGF. Increased and uncontrolled production of VEGF leads to the formation and proliferation of new blood vessels. HIF-1α also acts on erythropoietin, which also contributes to angiogenesis. It should be emphasized that the angiogenesis mediated in this way is disorganized and uncontrolled. The blood vessels formed by this mechanism are fragile and susceptible to leakage, which leads to retinal edema, hemorrhages, and because they proliferate towards the vitreous, they lead to vitreoretinal traction[17].

Insulin-like growth factor-1 (IGF-1) is a key molecule that affects the function of VEGF. It is involved in the process of normal angiogenesis. In the first phase of ROP, as a result of underdeveloped organ systems in prematurity, the level of IGF-1 is low, therefore preventing the appropriate signaling and action of VEGF. In the second phase of ROP, due to the increased production of IGF-1, it additionally stimulates the production of VEGF, which leads to uncontrolled pathological neovascularization[18].

As a consequence of the processes of hyperoxia and hypoxia, a pronounced inflammatory response occurs both locally at the retinal level and systemically. The process of hypoxia promotes the activation of microglia cells and macrophages that secrete a large number of pro-inflammatory cytokines: TNF-α, IL-1β, IL-6. Such an inflammatory cascade causes further damage to blood vessels, increases hypoxia in the surrounding tissue, and stimulates neovascularization. The process of fibrosis is also a continuation of this inflammatory event in the retina[15].

Oxidative stress and endothelial damage

Oxidative stress is created in response to a disturbed equilibrium between the production of pro-oxidants and the body's capacity to detoxify them. Most often, these are: free oxygen radicals, nitric oxide (NO), superoxide anions and hydrogen peroxide. In newborns, oxidative stress is particularly pronounced because at birth the newborn passes from an environment with a low to an environment with a higher oxygen concentration. Oxidative stress in the newborn, and especially in premature infants, has a great impact because the mechanisms for antioxidant protection are not yet sufficiently developed. It has been shown through several experimental models that hyperoxia is responsible for increased generation of ROS due to insufficiently developed autoregulatory vascular systems in the retina[19]. On the other hand, hypoxia increases the concentration of oxygen donors and promotes the transfer of electrons to oxygen. It also activates enzymes that generate ROS in the electron transport system of mitochondria and cause oxygen-induced retinopathy. These two mechanisms of hyperoxia followed by hy-

poxia are considered key links in the chain of oxidative stress involved in the pathogenesis of ROP[20]. ROS participate in endothelial dysfunction, thereby interfering with the normal development of blood vessels, leading to their regression and obliteration. They damage the blood-retinal barrier by attacking the endothelium and pericytes. The selectivity of this important barrier is lost, making the tissue more susceptible to damage.

Nitro-oxidative stress is another factor considered to be involved in the pathogenesis of ROP. NO reacts with reactive oxygen radicals and generates nitrites, nitrates and peroxynitrites that cause microvascular damage [21].

Lipid peroxidation of cell membranes is also an important oxidative mechanism for endothelial damage to blood vessels and the retina. The retina is highly sensitive to lipid peroxidation because it is made up of lipids with a high percentage of polyunsaturated fatty acids. Nitric stress induces cis-trans isomerization of arachidonic acid, which causes vascular damage to the retina. All of these events lead to a proinflammatory response and the release of many inflammatory mediators, which together are involved in the pathophysiological mechanisms of ROP development[21, 22].

The organism tries to cope with oxidative stress through multiple molecules and enzyme systems. Several molecules are considered to play a key role in the antioxidant response of the organism. Ascorbic acid, reduced glutathione, Vitamin E and urate prevent oxidative damage to biological membranes and lipoproteins. They reduce and prevent retinal damage. Omega-3 fatty acids, on the other hand, although through still insufficiently known mechanisms, suppress the inflammatory response, thus having antiangiogenic and neuroprotective effects on the retina. The enzymes: catalase, superoxide dismutase, and glutathione peroxidase play a central role in the antioxidant activity of the body, and are considered an important defense factor against oxidative stress[20].

Influence of other factors in the pathogenesis of ROP

Effect of oxygen therapy and oxygen fluctuation

Oxygen fluctuation causes increased production of ROS that cause endothelial damage. Oxygen fluctuation also causes mitochondrial dysfunction that increases oxidative stress. Therefore, maintaining a target oxygen saturation between SpO2 90-95% has been shown to reduce the risk of ROP. On the other hand, hyperoxygenation SpO2 >97% should be avoided due to the above-mentioned effects. Standardized protocols for NICU (neonatal intensive care unit) aim to minimize oxygen fluctuation and reduce oxidative stress[23].

Influence of nutritional factors

DHA (docosahexaenoic acid) and EPA (eicosapentaenoic acid) are two omega-3 fatty acids that are essential for retinal and neural development. Premature infants are deficient in these two fatty acids, as they pass from the placenta to the fetus during the third trimester. The physiological role of EPA/DHA is seen in reducing proinflammatory mediators and promot-

ing physiological angiogenesis. They reduce the overexpression of VEGF, thereby preventing excessive neovascularization and have a protective effect on endothelial cells from oxidative stress and apoptosis [24].

Molecules with antioxidant activity are crucial in dealing with oxidative stress. As previously mentioned, vitamins E, C and A and the enzymes – superoxide dismutase, catalase and glutathione peroxidase play an important role in this mechanism [20].

Genetic and epigenetic predisposition

The fact that not all premature infants develop ROP indicates the presence of additional genetic and epigenetic factors. Thus, polymorphisms in certain genes are considered to be a risk factor for the occurrence of ROP. Examples include[25, 26]:

a) The VEGF-A gene influences the level of VEGF production and blood vessel growth.

b) EPAS1 (HIF-2α gene) participates in the regulation of the response to hypoxia and influences the expression of VEGF.

c) CFH gene (Complement Factor H) is associated with a tendency to inflammation and oxidative stress in patients with ROP.

Epigenetic changes such as DNA methylation, histone modification and microRNA can influence gene expression without affecting DNA. Factors that are considered to influence these epigenetic changes are: hyperoxia/hypoxia, maternal nutrition, inflammation and infections (sepsis or chorioamnionitis)[27].

Potential biomarkers for early recognition of ROP

In recent years, there has been interest in finding useful biomarkers that would timely detect oxidative stress and damage in newborns. One of the main obstacles is to determine these biomarkers in different biological fluids such as: plasma, urine, amniotic fluid and cerebrospinal fluid. Since some of the free radicals and oxidation products have a short half-life, which makes it difficult to determine them. Several molecules have the potential to be possible biomarkers in patients with ROP [20]:

Malondialdehyde - a highly toxic molecule resulting from lipid peroxidation, a sensitive marker of oxidative stress that has been shown to be elevated in patients with ROP in several studies.

8-hydroxy 2-deoxyguanosine - a sensitive marker of oxidative DNA damage. Ates et al. found elevated values of this molecule in blood and urine samples of patients with ROP [28].

GSH/GSSG Ratio (oxidized/reduced glutathione ratio) is the most commonly used biomarker for determining oxidative stress. This ratio may be a useful parameter for early recognition of ROP in premature infants [20].

Protein oxidation - certain amino acids, e.g. phenylalanine, are susceptible to oxidation by ROS. As a result of this oxidation, certain molecules are produced that can be used as markers of inflammation [29].

Lipid oxidation - the retina is quite susceptible to oxidative stress, through mechanisms of lipid peroxidation, a process that is involved in the pathogenesis of ROP. Polyun-

saturated fatty acids are particularly susceptible to oxidation caused by free radicals, forming various by-products that can be identified as potential biomarkers in patients with ROP [22,29].

Clinical application and future perspectives

Knowledge of the links in the pathophysiological mechanism will lead to appropriate ROP screening guides for appropriate recognition and management of the condition. It should be noted that patients with ROP are at increased risk of other ophthalmological diseases throughout life such as: myopia, amblyopia, strabismus and retinal detachment 30. Therefore, timely visual rehabilitation is extremely important. The development of predictive biomarkers may in the future provide guidance on which patients are at increased risk for long-term ophthalmological problems. Knowledge of the pathogenesis of the disease should enable the creation of biomarkers that will allow personalization of ROP treatment in order to achieve optimal outcomes for each patient.

Artificial intelligence has the potential in the future to enable better automated screening and staging of the disease. This will provide predictive guidance for disease progression and appropriate treatment. Telemedicine, on the other hand, has the potential to help in less developed regions for timely recognition and treatment of the condition[31].

Conclusion

To date, ROP still represents a major challenge for both neonatologists and ophthalmologists dealing with this pathology. It represents a complex multifactorial process driven by a large number of proinflammatory components, impaired angiogenic signaling, and oxygen dysregulation. Ongoing research should help in understanding the details of the pathophysiological mechanism of this disease, all in order to enable new potential therapeutic modalities and different biomarkers that will help in better management of the disease.

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REVIEW

LUNG EFFECTS OF LONG-TERM OCCUPATIONAL EXPOSURE TO SILICA DUST

Sanja Latkoska[1], Jordan Minov[2]

[1] *PHI Polyclinic Medika, Skopje, North Macedonia*

[2] *Institute for Occupational Health, Skopje, North Macedonia*

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***Correspondence:** Sanja Latkoska, PHI Polyclinic Medika, Skopje, North Macedonia.

Email: sanja.latkoska@gmail.com

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Abstract

Silicon dioxide, also known as silica, is one of the most abundant minerals in the Earth's crust, occurring in both crystalline and amorphous forms. The most common form of crystalline silicon dioxide is quartz; while the most common materials in the industry which contain quartz are sand, gravel, and rock. Occupations with the highest risk of exposure to dust containing free silicon dioxide are: metal and coal mining with underground and above-ground exploitation; construction-related activities (workers such as builders, facade installers and terrace specialists, etc.), production of building materials, road and tunnel construction, granite processing, production and processing of slate, production of cement and glass, production of ceramics and porcelain, etc. The inhalation of crystalline silicon dioxide is considered a health risk. Long-term occupational exposure to dust containing free silicon dioxide may cause irritant, toxic and/or carcinogenic effects to the lungs in exposed workers. The principal occupational diseases caused by inhalation of free silicon dioxide are silicosis, chronic obstructive pulmonary disease (COPD) and lung cancer, as well as a combination of these diseases. The primary tool in reducing morbidity, mortality and disability caused by diseases associated with exposure to free silicon dioxide is the prevention based on appropriate engineering controls, protective respiratory equipment, regular periodic medical examinations and legal regulation on the level of occupational exposure to free silicon dioxide.

ПРЕГЛЕД НА ЛИТЕРАТУРА

ЕФЕКТИ ВРЗ БЕЛИТЕ ДРОБОВИ НА ДОЛГОТРАЈНАТА ПРОФЕСИОНАЛНА ИЗЛОЖЕНОСТ НА ПРАШИНА ШТО СОДРЖИ СЛОБОДЕН СИЛИЦИУМ ДИОКСИД

Сања Латкоска[1], Јордан Минов[2]

[1] *ПЗУ Поликлиника Медика, Скопје, Северна Македонија*

[2] *Институт за медицина на трудот на Република Северна Македонија, Скопје, Северна Македонија*

Цитирање: Латкоска С, Минов Ј. Ефекти врз белите дробови на долготрајната професионална изложеност на прашина што содржи слободен силициум диоксид. Арх Ј Здравје 2025; 17 (2). 135-143.

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Клучни зборови: силикоза, хронична опструктивна белодробна болест, слободен силициум диоксид, канцер на бели дробови, превентивни мерки

***Кореспонденција:** Сања Латкоска, ПЗУ Поликлиника Медика, Скопје, Северна Македонија

Email: sanja.latkoska@gmail.com

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Извадок

Силициум диоксидот е еден од најзастапените минерали во Земјината кора, а се јавува во кристална и аморфна форма. Најчест вид на кристалниот силициум диоксид е кварцот, а најчесто користени материјали што содржат кварц се песокот, чакалот и каменот. Работни места кои се со највисок ризик на изложеност на слободен силициум диоксид се: рудниците на метали и јаглен со подземен и надземен коп, градежништвото (ѕидари, фасадери, терацери и др.) и производството на градежни материјали, изградбата на патишта и тунели, производството на цемент и стакло, производтвото на керамика и порцелан и др. Инхалацијата на прашина што содржи слободен силициум диоксид е докажан ризик за здравјето на изложените работници. Долготрајната професионална изложеност на слободен силициум диоксид може да предизвика иритативни, токсични и/или канцерогени ефекти врз белите дробови на изложените работници, а најчести професионални болести предизвикани од долготрајната изложеност на слободен силициум диоксид се: силикозата, хроничната опструктивна белодробна болест и канцерот на белите дробови, како и која било нивна комбинација. Примарна мерка во намалувањето на морбидитетот, морталитетот и онеспособенсота од болестите поврзани со професионална изложеност на прашина што содржи слободен силициум диоксид е превенцијата базирана врз мерките за инженерска контрола, примената на лични заштитни средства, редовно изведување на периодичните здравствени прегледи и одржување на концентрациите на слободен силициум диоксид на работното место во рамки на дозволените граници.

Introduction

Following oxygen, silicon (Silicium - Si) is the most abundant mineral in the Earth's crust, accounting for an estimated 27% of its composition. On the other hand, silicon dioxide, is its most common compound, occurring as free silicon dioxide, also known as silica, and bound silicon dioxide in multiple compounds, so-called silicates. In occupational pathology, occupational exposure to silica dust is of particular concern due to its harmful effects on the health of exposed workers.

Silica is encountered in crystalline and non-crystalline (amorphous) form; while the heated non-crystalline silica becomes crystalline silica. The most important natural minerals that contain crystalline silica are quartz, cristobalite, and tridymite, with quartz being the most prevalent. The principal industrial materials containing quartz are sand, gravel, and granite. Granite contains approximately 30% of pure silica, grave approximately 40%, while the sand represents almost pure crystalline silica.

Synthetic forms of crystalline silica include keatite, silica W, porosyl, etc. Dust released from naturally occurring forms of amorphous silica (diatomite, glass silicon dioxide, silicon dioxide fibers, etc.) and forms of synthetic amorphous silicon dioxide (colloidal silica, silica, etc.) has milder effects on the lungs[1, 2].

Occupational exposure to silica dust is encountered in more workplaces due to its widespread occurrence in nature, as well as its widespread application in multiple industries. It is estimated that in the United States, between 1.2 and 3 million workers were exposed to dust containing free silicon dioxide in the first decade of this century.

Occupations with the highest risk of exposure to silica dust include metal and coal mining with underground and above-ground exploitation, as well as construction-related activities (workers such as masons, facade installers, terrace specialists, etc.), production of construction materials, road and tunnel construction; granite processing, slate production and processing, cement and glass production, ceramics and porcelain production, etc.[1-3]

Confirmed by the results of clinical-epidemiological and experimental studies, the effects of silica dust on the respiratory health of exposed workers have been known for a long time. Their prevalence varies over time and geographical location depending on industries in certain countries and regions, preventive measures taken to protect exposed workers, prevalence of active smoking, etc. On the other hand, the decrease in exposure levels to silica dust in developed countries over the last century has resulted in a dramatic reduction in morbidity and mortality from silicosis and silicon tuberculosis. Nevertheless, COPD and lung cancer remain a health problem in workers exposed to silica dust.

The concentration of silica in the dust inhaled while working, as well as the characteristics of the inhaled dust and the duration of exposure, are closely related to the frequency and degree of severity of the lung damage. At the same time, individual (endogenous) characteristics of exposed workers play a major role in the lung

damage, including congenital and acquired abnormalities of mucociliary clearance in the respiratory tract, along with previous respiratory infections.

The effects of silica on the lungs can be acute, subacute, and chronic. Depending on the mechanism of lung tissue damage, they can be irritating, toxic, and carcinogenic. The most important acute and subacute effects on the lungs of exposed workers are acute or subacute silicosis. Long-term occupational exposure to free silicon dioxide in exposed workers can lead to silicosis, chronic obstructive pulmonary disease (COPD) and lung cancer, a combination of any of these diseases, or all three diseases in one worker simultaneously. Chronic lung diseases caused by occupational exposure to dust containing free silicon dioxide are among the most important diseases in occupational lung pathology. At the same time, these diseases are of particular public health importance in terms of their frequency and the large number of workers exposed to dust containing free silicon dioxide throughout their working engagement[3, 4].

The aim of the paper is to present current knowledge about harmful lung effects of silica dust, pathogenesis of chronic lung diseases caused by occupational exposure to silica dust, their diagnosis and treatment, as well as about measures and activities for their prevention.

Silicosis

Silicosis is a fibrogenic pneumoconiosis caused by inhalation of silica dust, its deposition in the lungs, and lung tissue reaction to the inhaled dust. The disease has been included in the List of Occupational Diseases of the Republic of North Macedonia since 2020, designated as *301.11. Silica* and *301.12. Silicosis combined with pulmonary tuberculosis*[5]. On the 2010 List of Occupational Diseases of the International Labour Organization (ILO), Silicosis is designated as *2.1.1. Pneumoconioses caused by fibrogenic mineral dust (silicosis, anthraco-silicosis, asbestosis)* and *2.1.2. Silicotuberculosis*[6].

In the second half of the 19th and first half of the 20th centuries, silicosis was considered as the most common occupational lung disease worldwide, resulting in a high rate of disability and mortality especially among coal and metal miners. With the implementation of adequate preventive measures and activities (legal regulation of the level of exposure to silica dust, application of personal protective equipment, regular periodic examinations of exposed workers, etc.), the prevalence of silicosis, as well as its degree of severity, has been significantly reduced, but this disease still has a significant place in occupational lung pathology[7, 8].

A silicosis nodule is a major pathohistological change in silicosis. Inhaled particles of silica penetrate deep into the alveolar ducts and sacs and are difficult to eliminate through mucus by coughing. The silicosis genesis is considered a key element in the interaction between deposited particles and alveolar macrophages. Alveolar macrophages ingest the deposited particles, thus inducing an inflammatory response by releasing cytokines (tumor necrotizing factor-α, interleukin-1, leukotriene-B4, etc). Cytokines stimulate fibroblasts to proliferate

and produce collagen around the silica dioxide particles, resulting in fibrosis and the formation of nodular lesions in the lungs[9, 10].

Silicosis may take acute, accelerated or chronic forms. The acute form occurs with exposure to very high concentrations of silica dust over a period of several months, while the accelerated form with exposure to high concentrations of free silicon dioxide over a period of several years. As a result of the implementation of the above-mentioned preventative measures, these two forms have not been reported in developed countries, including ours, for the last couple of decades.

The chronic form of silicosis is its most common form occurring with occupational exposure to moderately high and low concentrations of silica dust in a period of at least two decades. It may occur as classical or simple silicosis, or as progressive massive fibrosis (PMF), i.e. a severe form of chronic silicosis characterized by confluence of the silicosis changes and expressive pulmonary fibrosis. The simple chronic silicosis is oftentimes asymptomatic and is detected with radiologic imaging at periodic health examinations; whereas the chronic PMF silicosis is characterized by severe damaging of the lung morphology and function, which progresses to chronic respiratory insufficiency (CRI).

Silicosis is often accompanied by other diseases that significantly aggravate its course and prognosis, including anthracosis (silico-anthracosis), COPD and bronchiectasis, tuberculosis (silico-tuberculosis), lung cancer (silico-carcinoma), systemic diseases of the connective tissue, such as rheumatoid arthritis (Caplan syndrome), systemic lupus, progressive systemic sclerosis, dermatomyositis, and others[11, 12].

The diagnosis of silicosis is based on the data from the medical and work history, the radiological findings interpreted in line with the current recommendations of the ILO, the results of the functional lung tests, etc. The treatment of the disease is symptomatic, and the further work on the patient depends on the results from the working capacity assessment, i.e. on the severity of the functional damaging of the lungs and the degree of occupational exposure to silica dust. Prevention, including adequate engineering measures to control exposure, application of personal protective equipment and regular implementation of preventive medical examinations of exposed workers, are of key importance in the management of silicosis[13-15].

Chronic obstructive pulmonary disease (COPD)

Results arising from numerous studies indicate that long-term occupational exposure to silica dust can contribute to the development of chronic bronchitis, emphysema and/or diseases of the small respiratory tract in the absence of radiologically confirmed silicosis, i.e. that the occurrence of COPD can cause silica concentrations that do not lead to the occurrence of silicosis. In recent years, the academic literature uses the term COPD caused by silica dust (silica-induced COPD). Additionally, cigarette smoke emphasizes the effect of silica on the respiratory tract (the combined effect of silica and tobacco smoke is not additive, but mul-

tiplicative), as well as disability and mortality from COPD[16-18].

According to the results of existing animal model studies, the mechanism of COPD in workers exposed to silica dust does not differ from the mechanism of COPD in smokers (tobacco smoke-induced COPD): however, it is due to the disruption of the balance of proteinases and antiproteinases in the lung tissue in favor of proteinases.

Pulmonary changes are mostly emphasized in the peripheral airways (small bronchi and bronchioles), the pulmonary parenchyma (respiratory bronchioles, alveolar ducts and sacs), and in the pulmonary blood vessels. The changes are initiated by toxic and inflammatory processes in the respiratory tract and pulmonary parenchyma triggered by the release of mediators that stimulate the production of cytokines, chemokines, elastase and fibrogenic factors.

Dominant inflammatory cells involved in the thickening of the airway wall and destruction of the pulmonary parenchyma are neutrophils, macrophages, and T lymphocytes (CD8+ and CD4+). The thickening of the small airways and the narrowing of their lumen and centrilobular emphysema (identical to the type of emphysema that occurs in tobacco-induced COPD), lead to a persistent and progressive decrease in airflow through the airway. Over time, these changes can lead to a disruption of respiratory gas exchange (RGE) in the lungs, an increase in pulmonary arterial pressure (pulmonary arterial hypertension - PAH) and the development of chronic pulmonary heart.

The appearance of COPD in workers exposed to free silicon dioxide depends on the level and duration of the exposure, as well as on their individual characteristics (genetic factors, exposure to tobacco smoke, previous respiratory infections, etc.). In terms of the level of exposure, research results indicate that cumulative exposure to free silicon dioxide at average concentrations of 0.1 to 0.2 mg/m^3 can lead to the occurrence of COPD without the occurrence of accompanying silicosis, i.e. an unsafe limit with respect to the occurrence of COPD is considered occupational exposure to free silicon dioxide at concentrations higher than 0.1 mg/m^3. In terms of the duration of exposure, no specific threshold has been defined, but according to several experts in the field, COPD in workers exposed to silica dust is associated with cumulative exposure at the specified concentrations over a period exceeding 15 years [19-22].

The diagnosis of occupational COPD caused by inhalation of silica dust, as with the diagnosis of other occupational diseases, is based on evidence of a causal relationship between the disease and the workplace in a worker diagnosed with COPD. Evidence of a causal consequential relationship between the disease and the workplace is based on data from the work history (period and degree of occupational silica exposure) and on data from the risk assessment of the patient's workplace (results of measurements carried out during environmental monitoring).

Concerning the recognition of the occupational character of COPD, there is a discrepancy between the ILO List of Occupational Diseases and the List of Occupational Diseases of the Republic of North Macedo-

nia. The latter has to be corrected with the upcoming updates in our national list consistent with existing knowledge on the role of occupational agents in the development of the disease. COPD caused by occupational exposure to silica dust is included in the ILO List of Occupational Diseases alongside forms of COPD caused by other occupational agents for which etiopathogenetic mechanisms in the contingency of the disease have been confirmed *(2.1.9. Chronic obstructive pulmonary disease caused by inhalation of coal dust, dust from stone quarries, wood dust, dust from cereals and agricultural work, dust in animal stables, dust from textiles, and paper dust, arising from work activities)*, whereas the occupational nature of the disease is not linked to the smoking status of the sick worker[6]. COPD caused by occupational agents is reported only in workers in underground coal mines in the List of Occupational Diseases of the Republic of North Macedonia *(307. Chronic obstructive bronchitis or emphysema in miners working in underground coal mines)*, in which recognizing the occupational character of the disease requires that the affected worker must have never smoked in his life[5].

Treatment of COPD caused by occupational exposure to silica dust includes applying pharmacological therapy, as well as the implementation of non-pharmacological measures and activities according to the recommendations of the current guidelines. In terms of further management of the patient, the treatment depends on the results of the assessment of the working capacity, i.e. on the degree of severity of the functional impairment of the lungs and the degree of occupational exposure to silica dust. As in the case of silicosis prevention, adequate engineering measures to control exposure, the application of personal protective equipment and the regular implementation of preventive medical examinations of exposed workers are of key importance in the management of silica-induced COPD.

Lung cancer

Lung cancer is the most common malignant neoplasm in men and one of the most common malignant neoplasms in women in recent decades. The therapeutic possibilities are still limited, making the five-year survival only found in a small percentage of the diagnosed patients. Risk factors for lung cancer include exposure to tobacco smoke, radon, asbestos, polycyclic hydrocarbons, etc.

As reported by the International Agency for Research of Cancer (IARC), silica (quartz) is a proven human carcinogen for lung cancer according to the results of clinical epidemiological and experimental animal model studies, while the carcinogenic effects of natural and synthetic amorphous silicon dioxide show inconclusive evidence[23, 24, 25].

Lung cancer in workers exposed to silica dust (silicon carcinoma) can occur in workers with silicosis and/or COPD but can also occur in previously intact lungs. In its histological characteristics, clinical manifestations and therapeutic possibilities, silicon carcinoma does not differ from lung cancer of other etiologies.

The diagnosis of lung cancer caused by exposure to silica dust, i.e. the evidence of the causal relationship of the disease with the workplace, de-

rives from work history data (period and degree of occupational silica exposure) as well as from the data from the risk assessment of the patient's workplace (results of the measurements carried out during the environmental monitoring).

Once again, as in the case of other diseases resulting from chronic effects on the lungs of occupational exposure to silica dust, measures of primary prevention (control of occupational exposure) and secondary prevention (early detection of the disease by regularly conducting periodic preventive examinations in exposed workers and early intervention) are crucial in the management of silicon carcinoma[26, 27, 28].

Lung cancer caused by occupational exposure to silica dust is not yet included in the National List of Occupational Diseases, while in the ILO List of Occupational Diseases, is included under *3.1.21. Cancers caused by other agents at work not mentioned in the preceding items where a direct link is established scientifically, or determined by methods appropriate to national conditions and practice, between the exposure to these agents arising from work activities and the cancer(s) contracted by the worker*[5, 6].

Conclusion

Long-term occupational exposure to silica dust may cause irritant, toxic and/or carcinogenic effects to the lungs in exposed workers. Diseases caused by occupational exposure to silica dust, as well as other occupational diseases, are potentially preventable.

The primary tool in reducing morbidity, mortality and disability caused by diseases resulting from long-term exposure to silica dust is the prevention arising from appropriate engineering control, application of protective respiratory equipment, regular periodic medical examinations, and legal regulation of the level of occupational exposure to silica dust. Moreover, the prevention of these diseases will be significantly improved by further research and deepening knowledge of the pathogenetic mechanisms of the chronic effects of silica dust on the lungs of occupationally exposed workers.

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REVIEW

THERAPEUTIC OPTIONS IN THE TREATMENT OF CALCIFIED ROOT CANAL SYSTEMS

Ana Petroska[1], Lidija Popovska[1], Verica Toneva Stojmenova[2], Marko Mladenovski[2]

[1] *Faculty of Dental Medicine, Skopje, Ss. Cyril and Methodius University, Skopje, North Macedonia*
[2] *Faculty of Medical Sciences, Goce Delcev University, Stip, North Macedonia*

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***Correspondence:**

Ana Petroska, Faculty of Dental Medicine, Skopje, Ss. Cyril and Methodius University in Skopje, North Macedonia

Email: ana_petroska@hotmail.com

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Abstract

Calcification of root canal systems presents one of the greatest challenges even in modern endodontics. Factors such as aging, trauma, dental intervention, auto-transplantation and genetic predispositions can lead to formation of calcifications in both the pulp chamber and root canals. Diagnostic procedures, including CBCT and AI-driven tools, have significantly improved the visualization and further management of calcified canals. Despite all advanced tools, the treatment of calcified canals still remains challenging. Obstructions caused by calcifications, which may vary in size, morphology and location make management much more difficult and compromising in many cases. This paper outlines the diagnostic approaches, therapeutic strategies and future directions in managing calcified root canals. The main emphasis is placed on the role of minimally invasive procedures, improved irrigation protocols and new technologies such as guided endodontics. The guided endodontic customized approach, which uses CBCT data and 3D printed templates, offers greater precision and reduces the risk of complications. All technological innovations hold a great potential for increasing the success rate of endodontic treatment while preserving natural tooth structures.

ПРЕГЛЕД НА ЛИТЕРАТУРА

ТЕРАПЕВСТСКИ ОПЦИИ ВО ТРЕТМАНОТ НА КАЛЦИФИЦИРАНИ КОРЕНСКИ КАНАЛНИ СИСТЕМИ

Ана Петроска[1], Лидија Поповска[1], Верица Тонева Стојменова[2], Марко Младеновски[2]

[1] *Стоматолошки факултет, Скопје, Универзитет „Св. Кирил и Методиј", Скопје, Северна Македонија*
[2] *Факултет за медицински науки, Универзитет „Гоце Делчев", Штип, Северна Македонија*

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***Кореспонденција:**

Ана Петроска, Стоматолошки факултет, Скопје, Универзитет „Св. Кирил и Методиј", Скопје, Северна Македонија

Email: ana_petroska@hotmail.com

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Извадок

Калцификацијата на коренските канали претставува еден од најголемите предизвици дури и во модерната ендодонција. Факторите како стареење, траума, стоматолошки процедури, автотрансплантација и генетски предиспозиции можат да доведат до формирање на калцификати во пулпната комора и коренските канали. Дијагностичките процедури, вклучувајќи ги CBCT и алатките управувани од вештачка интелигенција, значително ја подобруваат визуелизацијата и понатамошниот третман на калцифицираните канали. И покрај сите овие напредни алатки, третманот на калцифицираните канали сè уште останува сложен. Опструкциите предизвикани од калцификати, кои можат да варираат во големината, морфологијата и локацијата, го прават справувањето многу потешко и во многу случаи компромитирачко. Овој труд ги прикажува дијагностичките пристапи, терапевтските стратегии и идните насоки во справувањето со калцифицираните коренски канали. Главниот акцент е ставен на улогата на минимално инвазивните процедури, подобрени протоколи за иригација и нови технологии како што е водена (насочена) ендодонција. Насочениот ендодонтски приспособен пристап, користејќи податоци од CBCT и 3D-печатени шаблони, нуди поголема прецизност и намалување на ризикот од компликации. Сите овие технолошки иновации имаат голем потенцијал за зголемување на стапката на успех на ендодонтскиот третман и зачувување на природните структури на забите.

Introduction

The aim of endodontic treatment is to eliminate infection, preserve the tooth and restore its function. For a successful outcome of endodontic therapy, it is essential to know the anatomy of the root canal system in detail, accompanied by a thorough understanding of the morphology of the pulp chamber and the root canal system. Attempting to treat the root canal system without a detailed anatomical description would be the equivalent of a doctor searching for an appendix without having read the Gray 's Anatomy[1].

With the advancement of technology and techniques, modern endodontic treatment is becoming much more efficient and predictable than ever before. Machine instrumentation as the basis for the processing of the canal system, supplemented by irrigation, laser sterilization of canals and the use of biological materials for obturation significantly improve the results in the final outcome of endodontic therapy. The use of modern diagnostic methods such as digital X-ray, CBCT, the inclusion of artificial intelligence (AI) and 3D models complement the precision and comfort of the patient during endodontic treatment. All of this contributes to minimizing the duration of endodontic therapy, increasing the success rate, ultimately enabling long-term preservation of natural teeth. This outcome would be ideal if there were no obstacles in the anatomy of the root canal system. Very often, root canals can be impassable, fibrotic, or obliterated by denticles, nodules, pulp stones, secondary or reactive dentin formation, diffuse calcifications, or anatomical obstructions that may prevent instrumentation[2].

There are several variations in the mineralization of pulp tissue, in structure, morphology, dimensions, or location. Within the pulp chamber, they have a nodular format, generally spherical or ovoid and sometimes they mimic the internal anatomy of the coronal aspect of the pulp chamber. In the root canal space, they have a more diffuse structure, with a tubular or cylindrical configuration, partly following the design of the root canal. The size varies from microscopic bodies to structures that occupy the entire space of the pulp chamber[3].

Pulpal canal calcification or sclerosis may be the result of physiological tooth aging, sequelae following dental trauma, autotransplants, carious lesions, excessive orthodontic treatment, iatrogenic dental treatment, or regenerative endodontic procedures[4]. Other factors, according to Beres *et al*., could be: fluoride-rich supplements, D hypervitaminosis, or a possible genetic predisposition (dentinogenesis imperfecta and dental dysplasia which can be seen even in unerupted teeth[5].

Material and methods

To achieve the aim of this paper, a literature search was conducted using the databases PubMed, Google Scholar, ScienceDirect, Wiley, Scopus, Web of Knowledge, EBSCOhost to find published scientific papers and articles related to the therapy of calcified root canals.

The search was performed using the following keywords: endodontic therapy, calcified canals, obliterated

canals, guided endodontics, artificial intelligence, 3D printed templates.

Symptoms

The symptomatology of calcified canals varies from the absence of symptoms, which is the most common finding, to minimal sensitivity. The most common complaint of patients is darkening of the teeth, which is due to reduced blood supply to the pulp tissue, which has a significantly reduced volume. Other symptoms that appear include brief pain during chewing, and the vitality test may show very low sensitivity, which may disappear over time.

McCabe *et al.* examining the impact of trauma on anterior teeth, concluded that 25% of the teeth in their cases developed calcifications, but 75% of them were asymptomatic[6]. Ogini *et al.* in their study of 168 traumatized teeth with discoloration, found that 47.6% had partial obliteration and 31.6% had complete obliteration[7].

Pulp sclerosis as a diagnosis is not a reason for endodontic treatment, but its presence may further worsen the prognosis of treatment. The presence of pathological changes in the periapical tissue is a common finding in teeth that have undergone calcific metamorphosis because of trauma and is an indication for initiating endodontic treatment. Accordingly, indications for pulp treatment are in cases of irreversible pulpitis or presence of apical periodontitis[4].

Diagnostics

Diagnosing the degree of calcification and patency of the root canals is an important aspect of endodontic treatment. Accurate diagnostics in daily routine usually include clinical examination, application of vitality test and X-ray diagnostics (Fig.1 and 2).

Clinical identification is usually based on various imaging methods, such as X-ray radiography (periapical, panoramic radiography, etc.) and cone-beam computed tomography (CBCT). Two-dimensional X-ray radiography offers advantages such as ease of use and low radiation dose. A partial disadvantage in the identification of calcifications on two-dimensional radiography is the limitation of the identification of calcifications smaller than 200 μm. Overlapping anatomical structures can also be an obstacle to the identification of calcifications in the root canals of multi-rooted teeth[3].

CBCT is a newer method used for diagnostic purposes. It provides high-resolution and three-dimensional spatial structural information (Fig. 3). It offers detailed visualization, showing the precise location, size, and extent of pulpal calcifications from axial, coronal, and sagittal perspectives[3].

Automated systems for root and root canal morphology detection have been developed, using advanced algorithms for analyzing dental images8. Artificial intelligence is used to successfully display the canal configuration, root morphology and overall tooth structure. This technology can be particularly useful in cases involving complex anatomical structures, where individual interpretation can make errors[9].

Artificial intelligence (AI) is enabling automated biomedical image analysis, decision support, and treatment

planning[10]. It should be noted that artificial intelligence-driven software has shown its help in diagnosing complex cases such as periapical lesions, fractures, and calcifications, as well as in predicting treatment outcomes. Cutting-edge technology supported by artificial intelligence will increase the precision and efficiency of endodontic procedures[9].

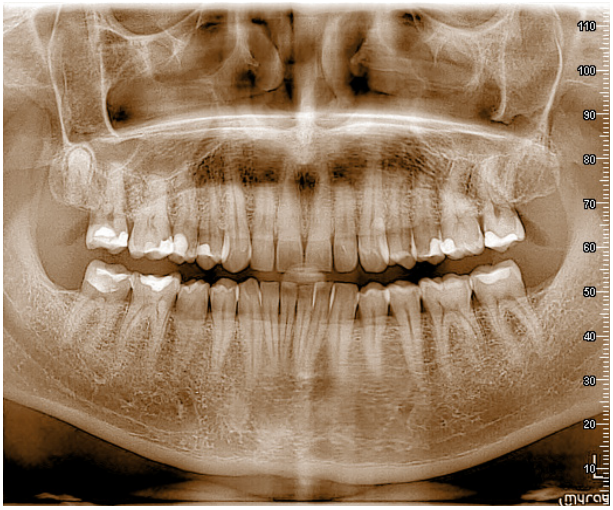

Figure1: Panoramic radiograph of a 31-year-old patient with a history of trauma to the upper anterior incisors several years ago, showing complete canal obliteration

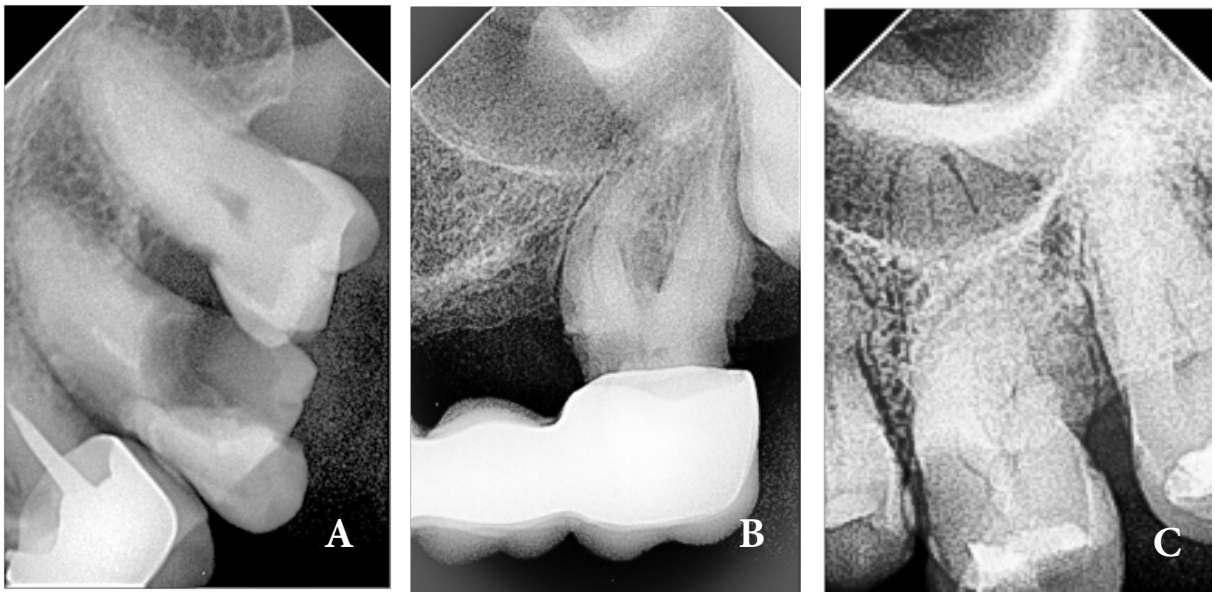

Figure2: Calcifications shown on intraoral radiographs. A) failed endodontic treatment of the upper left molar due to complete obliteration of the root canal system; B) presence of calcifications in the pulp chamber of the upper left molar, resulting from a mesial carious lesion; C) partial calcification in the pulp chamber, with a completely obliterated distal canal.

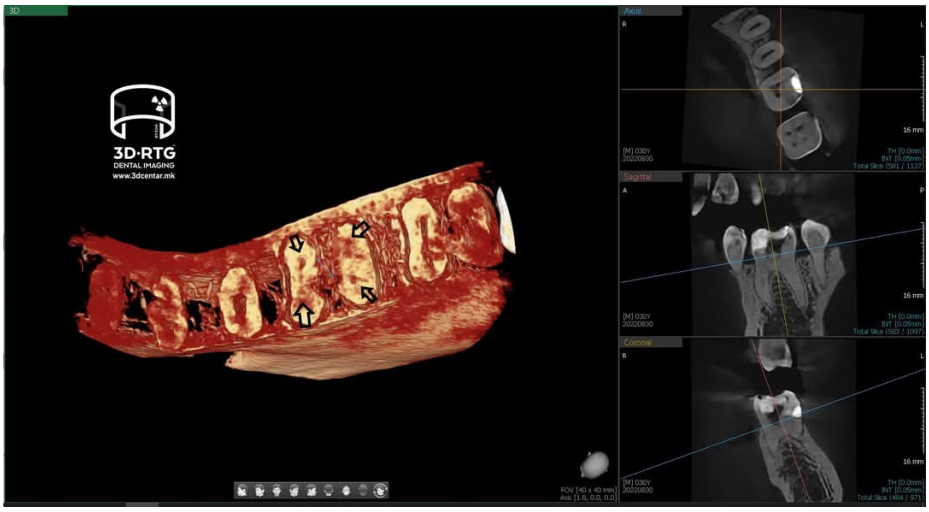

Figure3: 3D CBCT analysis of a lower left molar where horizontal cross-sections of segments show the presence of calcifications in the ventricular part, visible canal obliteration in the root canals

Management

The American Endodontic Association (AAE) classifies endodontic treatment of calcified canals as a high-risk treatment, due to the risk of complications and failure[4].

Treatment of calcified root canals requires time, patience, good skills and specialized equipment. The use of ultrasonic instruments and advanced irrigation techniques further increase the percentage of successfully completed treatments. Accurate diagnosis and careful work can prevent complications such as perforations and broken instruments.

Magnification and good illumination as an integral part of modern endodontic treatment are essential in the localization of the canals. With proper illumination and magnification, it is much easier to detect anatomical challenges and reduce the likelihood of making errors. The most commonly used devices are dental loupes and operating microscopes. Dental loupes offer magnification levels of 2.5x to 6x and are more suitable for routine procedures. Operating microscopes provide magnification levels of 6x to 30x and can be used in more complex situations, such as locating calcified root canals, better detecting broken instruments, or performing microsurgical procedures. Studies show that operating microscopes provide much improved visualization and precision in complex cases, compared to dental loupes[11,12].

Magnification combined with illumination can provide a better field of view for successful treatment of calcified canals, so that procedural errors can be minimized[13]. The operating microscope has integrated coaxial illumination and provides focused, shadow-free illumination of the surgical field. The dental loupes and microscopes use high-intensity LEDs that offer adjustable brightness levels to optimize visibility and precision[14].

Access cavity and course of endodontic treatment

Preparation of an adequate access cavity and removal of pulp tissue

are important steps at the beginning of treatment.

The design of the conventional access cavity has remained unchanged for decades, as it allows adequate visibility and facilitates identification of the root canal entrances[15]. The "systematic respect for original tissues" means that in dentistry as a profession, original tissue is valued more than its replacement[15,16,18]. This approach has led to the avoidance of the preparation of the classical access cavity and the introduction of narrower and smaller access cavities that preserve the tooth tissue.

In their study, Falcon A. *et al.*[19] highlight the so-called chamberless endodontic approach (CEA) which can mitigate the risks of treating calcified canals. The integrity of the clinical crown is preserved, creating a minimal access to the root canal. CEA modifies the endodontic approach by using the apical foramen, instead of the foramen as the determinant for the straight-line approach. With this approach, the preservation of the coronal structure of the tooth is maximized, while at the same time it provides sufficient access to perform chemomechanical removal of debris from the canal system. The advantages of this approach are not yet sufficiently documented in the literature to confirm its contribution.

Accurate detection of root canal entrances can be challenging when dealing with calcified canals, given that calcified structures may be present in the pulp chamber, covering the canal entrances. Several methods have been recommended for accurate detection of root canal entrances. One of them is the use of ultrasonic extensions to prepare the pulp floor, as the use of turbine diamond chips can easily lead to pulp floor perforations. Ultrasonic treatment removes loosely attached calcified structures, revealing lines of developmental fusion leading to the root canal entrances[20].

Another aid in canal detection is the use of dyes, such as methylene blue, which penetrate the root canal entrances and makes them visible and easier to detect. The advantage of the dye is that it can also be used to locate potential fissures.

A liquid EDTA solution can be applied to the pulp chamber (with a pipette or cotton swab) and can be useful for identifying the canal openings, as bubbles begin to emerge from the pulp tissue. According to Hülsmann *et al.*, one to five minutes is sufficient for its action. The location of narrow canal entrances is checked using the DG16 endodontic probe. With its sharp and firm tip, any calcification present can be further removed[21].

Checking the patency of the root canals and creating a glide path are the next procedures in endodontic therapy. Patency is checked by selecting an appropriate instrument with a smaller diameter (pathfinder). Pathfinder in calcified canals is a critical step, since very often calcifications prevent patency. Mannual endodontic instruments, K-files, C Files+, D-finders with the smallest diameter varying from 0.06, 0.8 and 0.10 with 2% with tapers, are commonly used as pathfinding files. These instruments are employed to pre-shape the length of the root canal space prior to transitioning to larger taper

endodontic instruments. Clockwise and counterclockwise movements are made to ensure safe navigation without damaging the canal walls. This is accompanied by irrigation with NaOCl, along with the use of EDTA gel at lower concentrations.

Regarding the efficacy of the pathfinder, Allen *et al.* cited several factors such as: design, helix density, taper, cross-sectional design, thermal tempering, type of metal, clinician skill, and clinical conditions[22].

Camps *et al.* pointed out the pathfinder cross-section as an important factor in endodontic treatment[23]. If the instrument occupies the entire endodontic volume during instrumentation, dentin scrapings are created and they cannot be removed coronally, as the space is limited by the instrument body. This leads to apical displacement of the debris, resulting in loss of working length and apical patency.

Baruwa *et al.* gave a comprehensive review of selected stainless steel dental instruments, providing valuable insights into their mechanical and physical properties. While similarities in cross-section design and metal wire composition were noted among the files, variations in the number of spirals and mechanical performance were observed. They analyzed characteristics such as the length of the active blade, which varied between 16 and 17 mm, and the number of spirals, which varied between 24 to 42 . The number of spirals in a file plays a crucial role in its performance during root canal procedures, since more spirals enhance the flexibility but decrease the cutting efficiency and rigidity. Conversely, a lower-pitch instrument, with fewer spirals, is more effective for filing but less effective for reaming[24]. Thus, all of these factors should be considered when selecting suitable files for an efficient root canal treatment.

When using these instruments in calcified canals, the choice of instrument according to hardness can be a problem. Choosing instruments with high flexibility, in addition to the fact that they are prone to deformation, may be a problem to penetrate the calcified canals. However, instruments that are too stiff with a strong bending resistance can lead to damage to the dentinal walls, i.e. create ledges and perforations, thus compromising clinical outcomes[20]. To eliminate such errors, a gradual increase in instrument size is recommended, starting from ISO size 06 to 10, using gentle clockwise and counterclockwise movements adapted to the specific clinical circumstances[24].

Instead of manual instrumentation, a patency of the root canals and glide path can be formed using NiTi rotary instruments with a small taper. But, despite the less effort, carelessness when using rotary NiTi instruments can easily lead to file fracture. Effective navigation through the complex anatomy of the canal and negotiation of tight curves relies heavily on the ability of the file to maintain centricity and prevent transport or ledging. Gambarini *et al.* present data on the use of thin stainless steel hand K-files applied to a reciprocally mounted instrument as a possible alternative for creating a glide path[25].

Once the glide path is established,

the use of rotary NiTi instruments becomes easily feasible. Almost 90% of the calcified canals can be negotiated to the apical third with the help of conventional techniques and the operating microscope. The success rate after a follow-up period of 3 years was found to be 80%[26].

An integral part of endodontic treatment is the use of irrigant, particularly in the treatment of calcified canals, where chelating agents play a significant role. Calcifications have an organic and inorganic component. The inorganic component is composed of calcium ions in the form of hydroxyapatite. For this reason, the use of chelating agents such as EDTA in gel form is necessary for their action[21].

Hulsman *et al.* emphasize that EDTA, in addition to calcium ions, also acts on the non-collagenous protein component of dentin. In combination with NaOCl, it significantly changes the calcium and phosphate content contained in the dentin of the canal. This combination improves demineralization, so that the irrigant can penetrate much more effectively[27]. The continuous chelation seems to be equally or more effective in all investigated outcomes when compared to the traditional sequential protocol. It refers to the combination of a soft chelator with NaOCl for simultaneous antimicrobial and proteolytic action with the smear layer removal. According to this protocol, NaOCl is added with the salt of a weak chelator, 1 hydroxyethylidene-1, 1-bisphosphonate or etidronate (HEBP or HEDP or etidronate), because the tetra-sodium HEDP salt is extremely compatible with NaOCl. This combination also acts on the organic component and provides an additional antibacterial effect. In particular, HEBP acts to reduce the smear layer, providing continuous chelation, minimizing dentin erosion compared to EDTA. In the tested group of chelates in the study by Zehnder *et al.* HEBP showed a three-fold lower calcium chelation capacity compared to the complexation ability of EDTA. This may limit its effectiveness in calcification, but this milder action may reduce the risk of excessive demineralization[28].

Maleic acid and peracetic acid can be used as alternatives for smear layer removal due to their stronger capabilities compared to NaOCl.

According to La Rosa *et al.*, a continuous chelation protocol maintains canal cleanliness and antimicrobial efficacy, demonstrating reduced dentin erosion. This can be achieved by using chelating agents and NaOCl simultaneously, ensuring consistent action throughout the procedure[27].

Figure 4 shows a case of a 76-year-old female patient requiring endodontic therapy and advanced pulp calcification. The patient had intraoral swelling localized to the area of the upper right lateral incisor, with old bridge construction. The examination revealed a fistula on the vestibular side. Endodontic treatment was performed without removal of the prosthetic restoration.

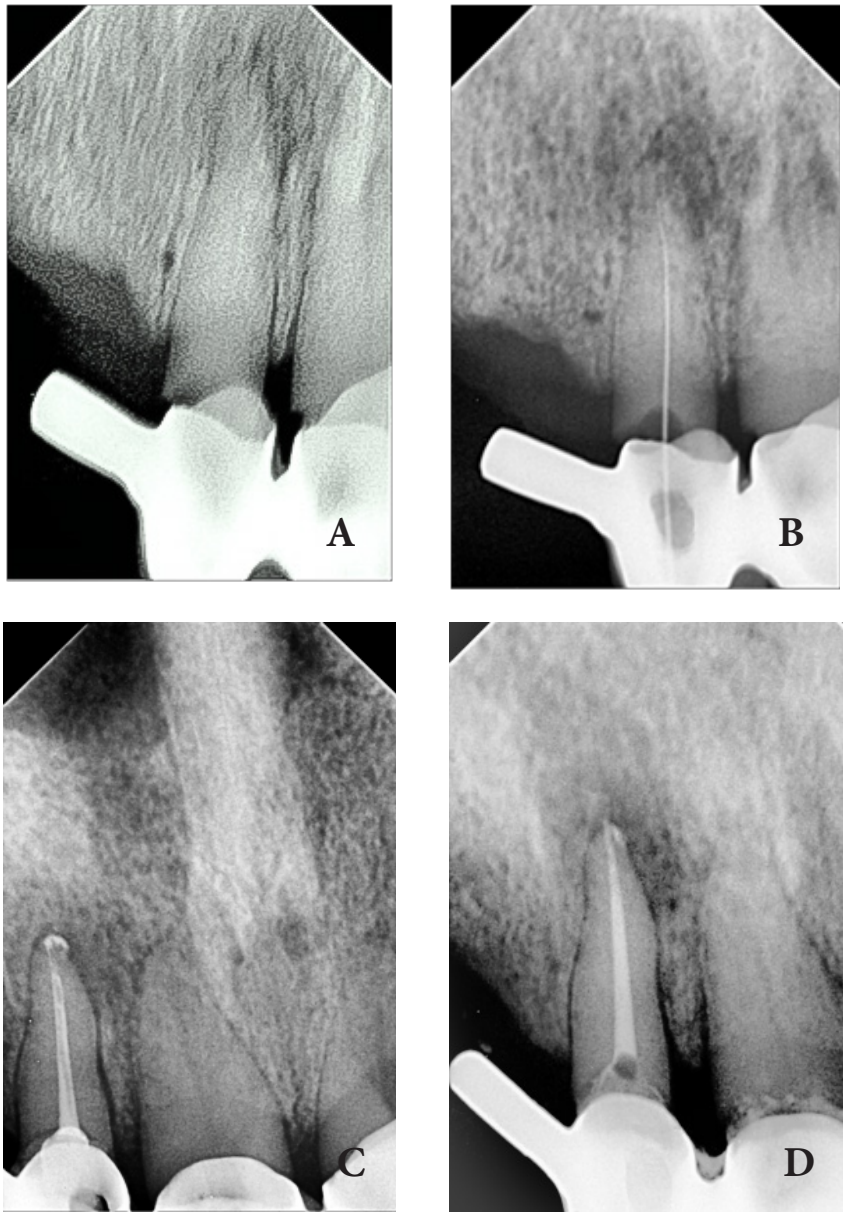

Figure4: A. Narrowing of the canal of tooth 12, accompanied by diffuse periapical change; B: Access cavity through the crown, formation of a glide path using a D-finder 0.8 hand instrument, interappointment Ca(OH) paste placed C: Control image of the filling with Ca(OH) , D: definitive obturation of the canal

Guided endodontics

The continued development of oral digital technology enables a new way to treat calcified root canals through guided endodontics. Guided endodontics is a technological approach that is not limited to finding pathways or accessing the cavity. It encompasses the entire procedure for treating calcified canals. The guided endodontic protocol involves combining oral scan data and CBCT data analysis to plan a path for opening the root canal from a three-dimensional perspective prior to the intervention, and then creating a digital guide using a 3D printing technique to guide the bur during the removal of the calcified segment of the root canal[29].

Conventional methods for treating calcified root canals rely solely on manual exploration, making treat-

ment highly unpredictable. Guided endodontic therapy improves predictability by using a digitally planned approach. CAD-based treatment planning, a custom digital guide designed with 3D printing that guides the tooth precisely to the calcified segment of the root canal, allows for a minimally invasive approach.

Several *in vitro* and *in vivo* studies and case reports have shown that treatment of calcified canals using a guided endodontic technique has higher success rates, less tooth substance loss, and avoids complications in endodontic treatment compared to conventional endodontic treatment[30].

Kulinkovich-Levcuk *et al.* in their review described different types of guided endodontics, including static guided endodontics (SGE) and dynamic guided endodontics (DGE)[31].

SGE is performed as follows: first, a CBCT image is taken of the patient's upper or lower jaw (depending on the location of the tooth to be treated). At the same time, an impression is taken that will be scanned later, or an image is taken with an intraoral scanner. The two resulting images are superimposed using software, whereby a guide is easily designed to cover the tooth to be treated (and some adjacent teeth). In this guide, a place is determined where a drill with a specific appropriate diameter and angle is placed to allow direct access to the calcified canal. Cylinders or "sleeves" are then designed to allow a drill to reach into the root canal through the drilled cavity. The inner cylinder is smaller and made of metal. Once the designs are complete, the file is exported from the planning software and used for 3D printing of the guide. To proceed with the procedure, the guide is tried on to ensure it fits the patient's teeth. The inner metal cylinder guides the drill to access and remove the calcified tissue, and once the obstruction is removed, the root canal treatment is continued in the conventional manner. However, SGE has several clinical limitations: restricted applicability in posterior teeth, anatomical constraints in curved canals and insufficient cooling (guided burs lack continuous water jet cooling)[31].

Similar to the static navigation approach, the dynamic navigation technique begins with a high-resolution preoperative CBCT scan to plan the entry point, pathway, depth, and angle of the bur. The dynamic-guided technique uses a mobile unit equipped with a stereoscopic camera for motion tracking and a computer with planning software that uses CBCT data to guide a calibrated handpiece[20]. With the help of a stereo camera connected to a dynamic navigation system, the trajectory of the drills into the pulp chamber and root canal is coordinated in real time. This way, the operator can follow everything he/she does on a monitor and can correct or adjust the angulation of the instruments as needed. The operator can visually monitor the penetration of the root canal on a laptop screen in real time, with depth indicated by changes in the color of the depth gauge[32].

Figure 5 shows the diagram of all steps in the digital workflow for the creation of an endodontic guide.

However, the high cost of acquisition and the need for operator skills are significant disadvantages of dynamic navigation.

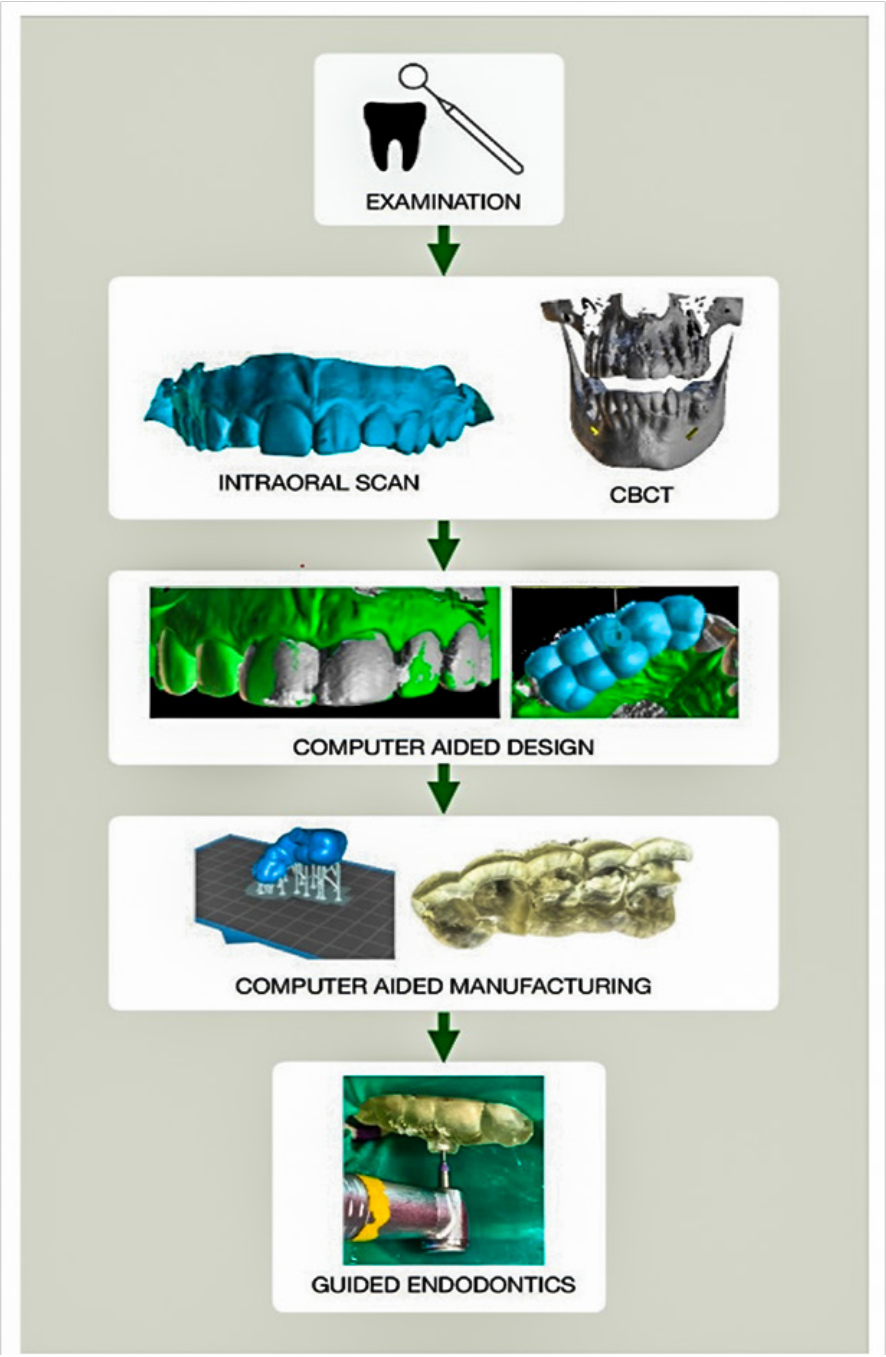

Figure4: Diagram of all steps in the digital workflow for the creation of an endodontic guide. Image reproduced from "Guided Endodontics as a Personalized Tool for Complicated Clinical Cases" by Wojciech Dabrowski, Wiesława Puhalska, Adam Zimlewski, and Ivona Ordinjec-Kwaśnica, published by MDPI under the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/). No modifications have been made to the original images.

Artificial Intelligence in Negotiating Calcified Canals

Artificial Intelligence (AI), with its technological advances, is also finding its place in the treatment of calcified root canals[33]. These technological advances improve diagnostic accuracy, treatment planning, and real-time navigation, significantly increasing efficiency in complex cases. Combining CBCT analysis, dynamic navigation, and adaptive tools, AI enables precise location and treatment of root canals, significantly reducing

the likelihood of complications. Continued advances in machine learning and AI-driven robotics are expected to further revolutionize endodontic workflows, offering improved predictability and clinical efficiency in complex cases[34].

CBCT analysis as a significant part in identifying calcified canals has been improved in its interpretation by AI-driven algorithms. By employing machine learning models, clinicians can analyze canal trajectories, facilitate more accurate preoperative planning and enable the prediction of the optimal access pathway for negotiation[35].

AI also plays significant role in reducing the risk of iatrogenic errors including perforations or excessive dentin removal by the use of AI-powered dynamic navigation systems that enable real time guidance during endodontic treatment. They allow clinicians to modify the approach based on continuous feedback[36].

AI-based systems through predictive modelling can also assist in recommending an optimal file sequence ensuring a conservative approach. Also, AI can be incorporated in instrumentation strategies enabling adaptive refinements in rotational speed and torque, preventing instrument fractures[36].

Conclusion

Calcifications in the pulp and root canals are a challenge in conventional treatment, often resulting in prolonged treatment times, increased risks during the procedure, and unpredictable outcomes.

The application of diagnostic procedures with new modern methods in the treatment of calcified root canals aims to improve the accuracy, efficiency, and success rates of endodontic treatment. The minimally invasive approach through guided endodontics, which combines CBCT data and 3D printed guides, allows a high degree of precision in accessing the canal system, significantly reducing the risk of iatrogenic errors. The use of improved irrigant and chelating agents further facilitates the process of treating calcified canals. Similarly, artificial intelligence-driven treatment planning and navigation systems allow clinicians to overcome anatomical complexities, offering new possibilities for more successful endodontic procedures.

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CASE REPORT

WHEN ROUTINE TURNS RISKY: DVT IN HEALTHY PATIENT AFTER KNEE ARTHROSCOPIC PARTIAL MENISCECTOMY- CASE REPORT

Zorica Vangelovska[1], Zoran Nestorovski[1], Ana-Marija Maneva[2], Darko Talevski[1], Nikola Gramatnikovski[3], Bozidar Blazevski[4], Berat Sejdini[1]

[1] *General Hospital "8th of September", Department of Orthopedics and Traumatology, Skopje, North Macedonia*
[2] *PHI Clinical Hospital- Shtip, Department of Orthopedics and Traumatology, Shtip, North Macedonia*
[3] *University Clinic for Thoracic and Vascular Surgery, Department of Vascular Surgery, Skopje, North Macedonia*
[4] *General Hospital "8th of September", Department of Diagnostic and Interventional Radiology, Skopje, North Macedonia*

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***Correspondence:**

Zorica Vangelovska, General Hospital "8th of September", Department of Orthopedics and Traumatology, Skopje, North Macedonia.

E-mail: vangelovskaz@gmail.com

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Abstract

Arthroscopic meniscectomy is considered a low-risk procedure with minimal incidence of venous thromboembolism (VTE). However, rare complications such as deep vein thrombosis (DVT) may still occur, even in patients without classical risk factors. We report the case of a 55-year-old male who developed acute DVT in the right lower extremity six days after undergoing an uneventful arthroscopic partial meniscectomy. The patient had no prior thrombotic events or comorbidities. Diagnosis was confirmed via duplex ultrasound, and therapeutic anticoagulation with low molecular weight heparin was initiated. Follow-up imaging after six weeks demonstrated partial recanalization. No complications from anticoagulant therapy were observed. This case highlights the importance of clinical vigilance for thromboembolic complications, even after routine orthopedic procedures in low-risk individuals.

ПРИКАЗ НА СЛУЧАЈ

КОГА РУТИНАТА СТАНУВА РИЗИК : ДВТ КАЈ ЗДРАВ ПАЦИЕНТ ПО АРТРОСКОПСКА ПАРЦИЈАЛНА МЕНИСЦЕКТОМИЈА- ПРИКАЗ НА СЛУЧАЈ

Зорица Вангеловска[1], Зоран Несторовски[1], Ана Марија-Манева[2], Дарко Талевски[1], Никола Граматниковски[3], Божидар Блажевски[4], Берат Сејдини[1]

[1] *Градска општа болница „8ми Септември", Оддел за ортопедија и трауматологија, Скопје, Северна Македонија*
[2] *ЈЗУ Клиничка болница - Штип, Оддел за ортопедија и трауматологија, Штип, Северна Македонија*
[3] *Универзитетска клиника за торакална и васкуларна хирургија, Оддел за васкуларна хирургија, Скопје, Северна Македонија*
[4] *Градска општа болница „8ми Септември", Оддел за дијагностичка и интервентна радиологија, Скопје, Северна Македонија*

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Клучни зборови: ДВТ, артроскопија, менисцектомија, нискомолекуларен хепарин, ортопедски компликации.

***Кореспонденција:**

Зорица Вангеловска, Градска општа болница „8ми Септември", Оддел за ортопедија и трауматологија, Скопје, Северна Македонија.

E-mail: vangelovskaz@gmail.com

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Извадок

Артроскопската менисцектомија се смета за процедура со низок ризик и минимална инциденција за венски тромбоемболизам (ВТЕ). Сепак, ретки компликации како што е длабока венска тромбоза (ДВТ) сè уште може да се појават и кај пациенти без класични ризик-фактори. Прикажуваме случај на 50-годишен пациент кој разви ДВТ шестиот постоперативен ден по артроскопска парцијална менисцектомија. Пациентот беше без коморбидитети и васкуларни нарушувања. Дијагнозата се потврди со доплер на долните екстремитети по што се започна со терапевтско антикоагулантно лекување со ниско молекуларен хепарин. Контролното снимање по 6 недели покажа делумна реканализација. Не се забележаа компликации од ординираната антикоагулантна терапија. Овој случај ја нагласува важноста од клиничката будност за тромбоемболиски компликации и по рутински ортопедски процедури кај лица со низок ризик.

Introduction

Arthroscopic knee surgery, particularly isolated partial meniscectomy is generally considered a low-risk procedure with minimal risk of venous thromboembolism (VTE). The implementation of early mobilization protocols and the short duration of the intervention further reduce the likelihood of deep vein thrombosis (DVT). However, recent reports suggest that (VTE) can still occur in patients without traditional risk factors. In this case report, we present a patient who developed DVT on postoperative day 6 following routine arthroscopic meniscectomy.

Case report

A 55-year-old male presented with localized pain in the medial compartment of the right knee, persisting over several months. The patient reported a history of a distortion injury to the same knee approximately five months earlier. On clinical examination, palpable tenderness was noted along the medial joint line. Active and passive range of motion were preserved and within normal limits. Both the McMurray test and the Apley compression test were positive, indicating possible meniscal involvement. Radiological evaluation included a plain radiograph (X-ray) of the right knee, which revealed early degenerative changes in the medial compartment, consistent with incipient medial compartment osteoarthritis (gonarthrosis) (Figure-1).

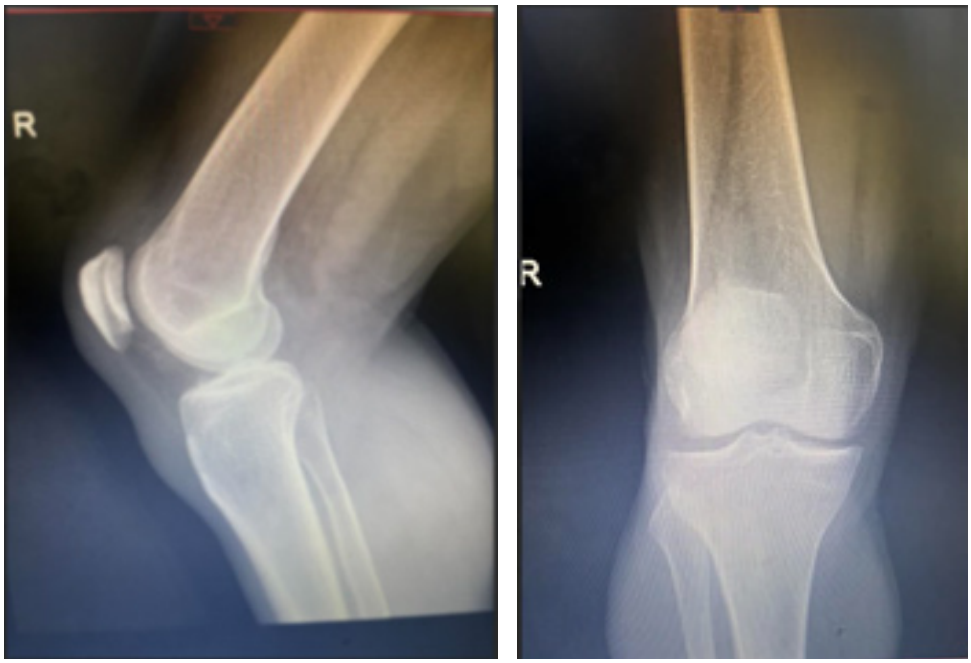

Figure 1: Radiographs of the right knee (anteroposterior and lateral views) showing early degenerative changes in the medial compartment

Further evaluation with magnetic resonance imaging (MRI) in the sagittal plane demonstrated a horizontal tear of the posterior horn of the medial meniscus in the right knee (Figure 2).

Figure 2: MRI of the right knee demonstrating a horizontal tear of the posterior horn of the medial meniscus

The patient underwent arthroscopic partial meniscectomy under spinal anesthesia. A tourniquet was applied to the proximal right thigh and inflated to 300 mmHg. The procedure was carried out through two standard arthroscopic portals (anteromedial and anterolateral). The torn segment of the posterior horn of the medial meniscus was resected. The total operative time was 30 minutes. The intraoperative and immediate postoperative course was uneventful and the patient was discharged with standard postoperative instructions and analgesia. The patient was discharged on the first postoperative day in stable condition with prescribed pharmacological thromboprophylaxis consisting of oral anticoagulant therapy Rivaroxaban (Rufixalo 10 mg once daily) in addition to standard postoperative analgesics. On postoperative day 6, the patient presented to the Emergency Department with complaints of intense pain in the right popliteal fossa and posterior lower leg, exacerbated by standing and ambulation. On physical examination, swelling and increased local temperature were noted in the right lower extremity, raising clinical suspicion for deep vein thrombosis (DVT). Physical examination revealed the following findings: pain on palpation along the posterior aspect of the right calf, localized swelling, redness, increased temperature, firmness of the affected area and positive Homan's sign (Figure 3).

Figure 3: Swelling and redness of the right lower extremity

Laboratory Findings - Coagulation profile: prothrombin time (PT): 10.3 seconds. Activated Partial Thromboplastin Time (aPTT): 9.1 seconds. International Normalized Ratio (INR): 0.8, D-dimer: 0.45 mg/L. Complete

blood count (CBC) and biochemical parameters: within normal limits. **Duplex Utrasound Report** - lower extremity venous system findings: The popliteal vein was completely filled with thrombotic material and appeared non-compressible. Evidence of a recanalization process was noted both centrally and peripherally. The anterior tibial veins were thrombosed. The small saphenous vein *(v. saphena parva)* demonstrated normal dimensions, and was partially compressible and filled with thrombotic material. Findings were consistent with deep vein thrombosis (DVT) involving the popliteal and anterior tibial veins, with early signs of recanalization in the popliteal segment. Partial involvement of the small saphenous vein was also noted. The patient was initiated on therapeutic anticoagulation with low molecular weight heparin (LMWH) – *Fraxiparine 0.6 mL (5700 IU)* administered subcutaneously twice daily (2×1 s.c.). In addition, antibiotic therapy was prescribed and local compresses with boric acid were applied to the affected area. Supportive measures included limb elevation and instructions for continued outpatient monitoring. Over the following six weeks, the patient reported gradual improvement in pain and local clinical findings. Follow-up duplex ultrasonography demonstrated partial recanalization of the affected veins. No adverse effects related to anticoagulant therapy were observed during this period. The patient remains under ambulatory follow-up with clinical vigilance for the potential development of post-thrombotic syndrome.

Discussion

Prospective[1-7] studies have reported an incidence ranging from 1.2% to 17.9% of DVT after artroscopy1-7. Arthroscopic knee procedures, particularly isolated partial meniscectomy are typically considered low-risk in terms of thromboembolic complications. Early mobilization, short operative time and the minimally invasive nature of the technique contribute to this favorable risk profile. As a result, routine pharmacological thromboprophylaxis is not universally recommended for such procedures, especially in patients without known risk factors. However, the present case challenges this paradigm by demonstrating the occurrence of deep vein thrombosis in a previously healthy, low-risk patient following a standard arthroscopic intervention. This underscores the fact that VTE can occur even in the presence of appropriate prophylactic measures, and highlights the limitations of a one-size-fits-all approach to thromboprophylaxis. This case also demonstrates the diagnostic challenge posed by normal D-dimer levels, which were within reference range despite confirmed thrombosis. Such findings stress the importance of clinical judgment and imaging (Doppler ultrasound) over reliance on laboratory screening alone, particularly in the postoperative period where D-dimer sensitivity may be reduced. This case serves as a reminder that even minor orthopedic procedures can carry thrombotic risk, and that routine administration of thromboprophylaxis does not guarantee protection. It is extensively accepted that thromboprophylaxis is necessary and perioperative thrombosis prevention treatments are rec-

ommended in many guidelines for major orthopedic surgeries, such as joint replacement and trauma-related procedures. But, no consensus has been reached about thromboprophylaxis after arthroscopic surgery[8]. Arthroscopic knee surgery (AKS) is associated with a low risk of deep vein thrombosis. Prospective studies suggest a rate of 1.2% to 17.9% DVT after AKS. The rate of symptomatic proximal thrombosis is reported much less (0.25%-0.67%). However, VTE accounts for 7% to 30% of all complications following AKS.[9] Angharad M Eynon *et al*. presented a case of fatal pulmonary embolus after knee arthroscopy. Their case was about a 71-year-old woman who underwent knee arthroscopy with a tourniquet for meniscectomy and arthroscopic lavage for osteoarthritis. Her medical history was unremarkable and the procedure was uneventful.[10] Yue Zou et al. presented meta-analysis of 22 observational studies including 998,978 patients undergoing knee endoscopic surgery. Their subgroup analysis indicated that patients with an average age over 50 years [OR= 3.18, 95%CI (1.17, 8.66), P = 0.001] and those who underwent surgery with a tourniquet for ≥ 90 min [OR = 4.79, 95%CI (1.55, 14.81), P = 0.007] were at a significantly increased risk of venous thrombosis after knee arthroscopy.[11] Piya Chavalparit *et al*. presented a case of a 55-year-old female who at 6 weeks after knee arthroscopy developed left leg swelling without pain. She was diagnosed as DVT and was initially treated with enoxaparin for three days, then warfarin for three months[12]. Zein Said et al. made a postoperative screening in Cairo University Hospital for DVT after 2 weeks from knee arthroscopy using ultrasonography technique to detect the DVT incidence after such procedure. Their study consisted of 50 patients, 44 males and 6 females, who underwent knee arthroscopy. Only one patient of the 50 developed asymptomatic silent DVT within the first 2 postoperative weeks.[13]

Our case and others in the literature confirm that even routine, short-term, low-risk arthroscopic procedures can result in DVT, even in the absence of known thrombophilic factors. Possible contributing mechanisms include: tourniquet use, local vascular compression, absence of pharmacological thromboprophylaxis and transient limb inactivity. Although clinical guidelines do not mandate routine thromboprophylaxis in these patients, this case prompts a reassessment of risk in individual patients, especially in the presence of subtle factors (age, prolonged sitting, microvascular injury).

Conclusion

Deep vein thrombosis (DVT) may occur as a rare but potentially serious complication following knee arthroscopy. It is therefore essential to maintain a high level of clinical suspicion when patients present with pain or swelling in the lower leg, even in the absence of known risk factors. Timely diagnosis and prompt initiation of treatment can significantly improve clinical outcomes.

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Correction to Arch Pub Health

Recica V, Naumovska Z. Diabetes in the Republic of North Macedonia: epidemiology and economic burden, 2018–2021 Arch Pub Health 2024; 16(1): 5-20. DOI: https://doi.org/10.3889/aph.2024.6117

In this Article, in the Results section Table 1 is deleted. The first paragraph of Results section should read "Published data by Smokovski et al., suggest that national prevalence in North Macedonia in 2015 among people aged 20 to 79 years was 11.44% or 180.180 patients with diagnosed and undiagnosed diabetes mellitus, 46.9% patients with diagnosed diabetes out of whom 43.8% on insulin therapy.30 According to the International Diabetes Federation (IDF) Diabetes Atlas, 9th edition (2019), the estimated prevalence of diabetes in North Macedonia was 11.2%, which was higher than the global average of 9.3%. This percentage corresponded to approximately 175,100 adults aged 20–79, indicating that about one in every nine adults in the country had diabetes at that time. 31 In contrast, the IDF Diabetes Atlas, 10th edition (2021) reported a national prevalence of 7.4% in North Macedonia, which was lower than the global average of 10.5%. This figure corresponded to an estimated 116,100 adults aged 20–79 living with diabetes.32 "

In the References section, one reference is listed as number 30, and this section should follow after reference 29.

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These corrections have been made to the online version as of August 25, 2025.