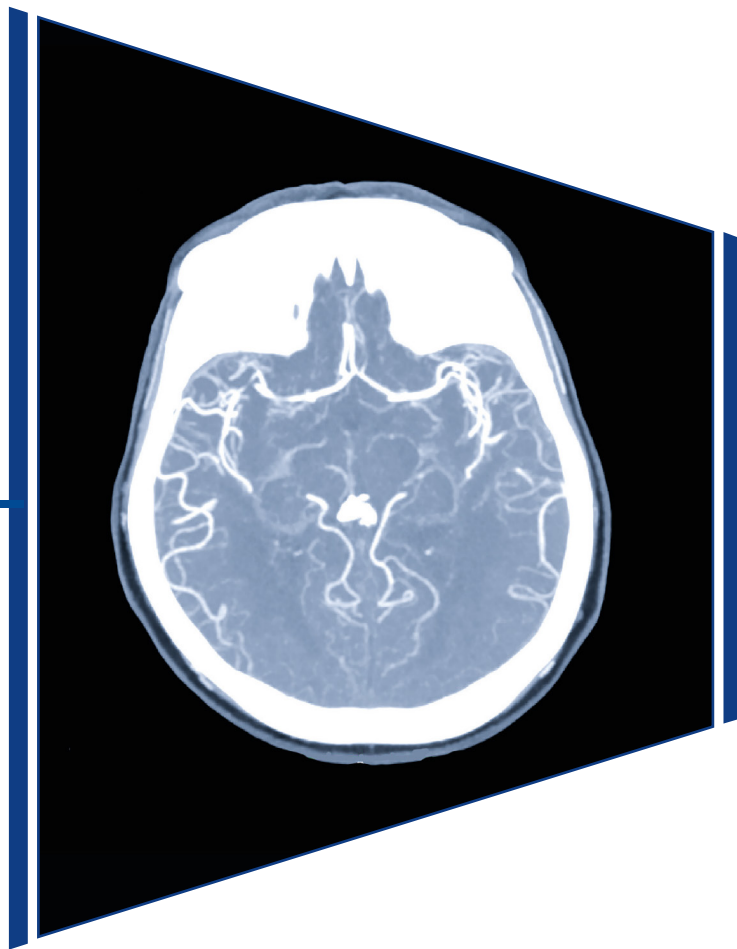




MEDICAL UNIVERSITY OF GDAŃSK

# EUROPEAN JOURNAL OF TRANSLATIONAL AND CLINICAL MEDICINE







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# In Memoriam – Prof. Stefan Raszeja MD PhD

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**Justyna Fercho** , **Izabela Szeibelis-Deskiewicz** , **Dariusz Kozłowski** 

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**Keywords:** Stefan Raszeja · Medical University of Gdańsk · ethics · editorial · in memoriam

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On March 10, 2021, professor Stefan Raszeja passed away at age of almost 100. Since 1970, he was the founder and Editor-In-Chief of *Annales Academiae Medicae Gedanensis*, the scientific journal published by the Medical University of Gdańsk. Currently, the *European Journal of Translational and Clinical Medicine* (EJTCM) continues, albeit in an updated format, the remarkable legacy of its Founder with utmost respect. From the beginning, prof. Raszeja appreciated and supported the endeavours of Medical University of Gdańsk authorities to help *Annales* enter a place on the prestigious Impact Factor Master Journal List [1]. Today, we humbly announce a partial achievement of prof. Raszeja's dream: the *EJTCM* is indexed in the Scopus database [2]! The

publishing market remains highly competitive, thus constant adjustments of the *EJTCM* are needed. Not forgetting the long-time aspirations of the Publisher, the past, current and future Editors of our journal stand in front a formidable challenge, regrettably without the support of prof. Raszeja. His experience on the Editorial Board of the *American Journal of Forensic Medicine and Pathology* helped prof. Raszeja to lay the organisational foundations for *Annales Academiae Medicae Gedanensis*, and thus ultimately and unnoticeably contributed to current shape of *EJTCM*. In our editorial work we draw from his numerous achievements, which all together are difficult to concisely summarise. All of his innovations are inspiring and somewhat transgressing the

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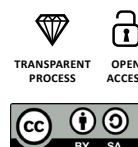
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Prof. Stefan Raszeja with his students

times he lived. His incomparable progress in work affirmed the meaning of the ancient words:

***There is nothing  
is permanent except change.***

– Heraclitus

We live and die, sometimes leaving behind more intellectual value than others, as Professor Raszeja did. Courage, self-discipline, justice and wisdom are well-known and timeless virtues of life. Looking at the heritage of professor Stefan Raszeja, we had the impression that all these virtues can be found in his work. He was born in 1922 in a family of teachers. At the start of World War II he was part of the Tajna Organizacja Wojskowa “Gryf Pomorski” (Secret Military Organization “Pomeranian Griffin”) and fought against the occupying German army Pomeranian region [3]. In the later part of the war he joined to the brave Home Army, the dominant resistance movement in Poland. We can only assume that his combat and wartime experiences imprinted the importance of those four virtues in professor’s mind. “*The path of least resistance is a terrible teacher*” seems to be the reason to take the lesson of his achievements de-

spite impediments. Numerous publications about various aspects of medicine reflect prof. Raszeja's devotion to hard work and finally the versatile proficiency in forensic medicine and ethics [4]. In the field of forensic medicine his interests focused on the pathological changes caused by mushroom poisoning, population genetics, identification of biological traces for the purposes of crime investigation, the biochemistry of dying and brain death diagnosis criteria for the purposes of organ transplantation. Professor Stefan Raszeja skilfully combined his scientific work with didactics and far-reaching organisational work which led to the growth and development of the Department of Forensic Medicine at our University. Six of his students went on to become full professors, 7 earned doctor habilitis degrees and 9 defended their doctorates. He frequently stated that every teacher, *especially professor, should be judged by his students, who should surpass their mentor* [4]. His words mirrors nothing but the ideal relationship between a mentor and student, free of competition and jealousy. In fact, splendour is attributed to our self-reliant students and passed on to next generations.

***One repays a teacher badly  
if one always remains  
nothing but a student.***

– Friedrich Nietzsche



Prof. Raszeja was not just a teacher of medical ethics but someone who put those values and rules into direct action. In 1978 prof. Raszeja formed and chaired the Ethics Committee at the MUG, the first such institution in Poland, which later served as a blueprint to form them at all medical universities in Poland [5]. Professor Stefan Raszeja's achievements were recognized with numerous national, military and scientific awards [3]. After retirement from his position as Head of the Department, prof. Raszeja remained professionally active, continued to publish research articles and to review medico-legal reports written by his fellow forensic medicine specialists. His attitude is a model worth imitating. Prof. Raszeja belongs to the generation of exceptional professors, whose knowledge, skills and values left a permanent mark on science.

In an interview published last year, asked for the recipe for longevity, he reminded that two factors are required: activity and the need to be active. His words are becoming even more prominent in the era the Internet when the access to information is so easy. By that means, prof. Raszeja left us the timeless message: have a goal and undertake the actions needed to achieve it.



Prof. Stefan Raszeja MD PhD as the MUG Rector – 1972/73 r.

***Just that you do the right thing.***

***The rest doesn't matter.***

**– Marcus Aurelius**

Professor's closest associates/co-workers remember him as a benevolent, charismatic and kind person [3]. From the EJTCM perspective, continuators of his editorial work, the unforgettable prof. Stefan Raszeja remains in our mind as an authority. He was interested in progress of the journal, always willing to help his successors. At his last years he struggled to climb the stairs to EJTCM Office and was the awaited mentor there. Let prof. Raszeja's physical struggle to achieve our common editorial goals remain an example to others.

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# Can we prevent epilepsy? Yes, we can!

**Sergiusz Józwiak** 

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## Abstract

Epilepsy appears in 1% of global population and despite a progress in medicine still around 30% of patients have drug-resistant epilepsy. In recent years increasing attention is paid to possibility of epilepsy prevention. Candidate groups for such treatment are eagerly looked for. One of them is tuberous sclerosis complex (TSC).

**Keywords:** prevention · tuberous sclerosis complex · epilepsy

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Epilepsy is one of the most common neurological illnesses, known to appear in around 1% of the global population. Six million people have epilepsy in Europe alone. It may start at any age, but most often occurs in early childhood or people over 60 years old. Peak incidence is reported in the first 12 months of life.

The etiology of epilepsy remains unknown in up to 50% of cases. Therefore, for majority of patients with epilepsy their treatment is focused on seizure prevention rather than treating the underlying cause. This strategy helps about two-thirds of the patients to enjoy a seizure-free life, whereas about 30% of them suffer from drug-resistant seizures. Epilepsy in infants and children is particularly harmful, with 50% of these patients suffering from significant comorbidities e.g. developmental delay, learning disabilities and autism spectrum disorders.

Yet fifteen years ago nobody dared to claim that epilepsy may be preventable. Since the beginning of modern neurology (second half of XIX century), neurologists were taught to start treatment after clinical seizures, usually after 2 unprovoked seizures that occurred > 24 hours apart. However, such approach proved unsuccessful and resulted in many cases of drug-resistant epilepsy. Unsatisfactory results of treatment with standard antiepileptic medication led researchers to seek new therapeutic approaches. A new practical and “operational” definition of epilepsy introduced by the International League Against Epilepsy (ILAE) allows physicians to diagnose epilepsy when the patient had at least 2 unprovoked seizures > 24 hours apart or 1 unprovoked seizure with >60% risk of having another seizure during the next 10 years [1]. However, epilepsy does not start with first clini-

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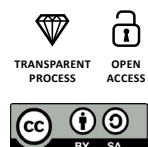
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cal seizure. It begins much earlier, during an insult to the central nervous system (CNS), e.g. stroke, inflammation or a genetic mutation. This process of changes in the brain leading to seizures is called epileptogenesis. First clinical seizures occur weeks, months or even years after the original insult. With recognition of individuals at high risk of epilepsy we may try preventing its development.

Some of the pre-clinical models of epilepsy have demonstrated that certain antiepileptic drugs may prevent or alleviate epilepsy when administered before seizures [2-3]. Clinical application of this concept in humans led to several trials assessing the effectiveness of these drugs in epilepsy prevention among patients after severe traumatic brain injury [4-6], stroke [7] or craniotomy [8-9]. Unfortunately all of these trials demonstrated that the standard antiepileptic drugs lack anti-epileptogenic effects. This could be partially explained by the inclusion of patients who had different risk of developing epilepsy, therefore highlighting the need to find reliable and clinically applicable biomarkers of epileptogenesis.

A better, human model for a study on epilepsy prevention is offered by tuberous sclerosis complex (TSC), due to its genetic homogeneity and early age of epilepsy appearance. TSC is a common autosomal dominant neurocutaneous disorder occurring in approximately 1/6000 people. Pathogenesis of the condition is caused by loss-of-function germline mutations in either of the tumor suppressor genes *TSC1* or *TSC2*. Both mutations lead to hyperactivation of the mTOR pathway, which was demonstrated to contribute to epileptogenesis after traumatic brain injury, neonatal hypoxia or to kainate-induced status epilepticus [10-11]. About 90% of patients with TSC develop epilepsy during their lifetime and in a prospective study of children followed since birth, about 71% of them developed epilepsy in the first 2 years of their life [12]. Approximately 65% of those with epilepsy have drug-resistant epilepsy. In the group of patients presenting with seizures in the first year of life, up to 82% later develop intellectual disability and ~40% are diagnosed with autistic behaviours [13].

In 2011 our group at the Children's Memorial Health Institute in Warsaw published first results of an epilepsy prevention trial among infants with TSC. Forty-five infants who were diagnosed with TSC early in life were divided in two groups: standard (31 children) and prevention (14 infants). In the standard group the antiepileptic treatment was initiated after the first seizure. Patients in the prevention group were given antiepileptic medication after paroxysmal epileptic discharges were seen in their electroencephalography (EEG, repeated out every 4 to 6 weeks), though before

the clinical onset of seizures. At 24 months of age, patients in the prevention group were more often seizure-free (93% vs 35%;  $p = 0.004$ ), had lower incidence of drug-resistant epilepsy (7% vs 42%;  $p = 0.021$ ) and fewer of them required multiple antiepileptic (21% vs 55%;  $0.039$ ) than those in the standard treatment group. Also intellectual disability was significantly more frequent and severe in the standard treatment vs prevention group (48% vs 14%;  $p = 0.031$ ; mean IQ score 68.7 vs 92.3;  $p < 0.05$ ) [12].

The results of this study influenced the current European recommendations on epilepsy management in TSC, which recommend regular EEG surveillance in infants with TSC and initiating antiepileptic treatment within the first 24 months of age when epileptiform discharges occur on EEG but before clinical seizure [14-15]. However, our results required confirmation in a large prospective randomized trial.

The EPISTOP project (NCT02098759) was a large European Union-funded study, whose aim was to examine the risk factors and biomarkers of epilepsy. Part of this project included a multicenter clinical trial assessing preventive and standard antiepileptic treatment. It included infants with a definite diagnosis of TSC, assessed from birth up to the age of 24 months with serial EEG, imaging and laboratory tests. In this study, 94 infants with TSC but without seizure history were observed with monthly video EEG and received vigabatrin either as conventional antiepileptic treatment (initiated after the first electroencephalographic or clinical seizure) or preventively when epileptiform was detected in EEG before the clinical onset of seizures. After 24 months of observation it was reported that preventive treatment reduced the risk of clinical seizures ( $p = 0.032$ ), drug-resistant epilepsy ( $p = 0.022$ ) and infantile spasms ( $OR = 0$ ,  $p < 0.001$ ) [16]. Similarly, an NIH-sponsored preventive study on epilepsy in TSC (the PREVENT trial), was launched in 2016 in the United States and the initial results are expected in 2021. In a 2019 survey of 61 epilepsy centers that provide care to patients with TSC, 70% conduct regular EEG monitoring in infants and 51,7% apply preventive treatment [17].

To answer the question stated in the title: yes, epilepsy can be prevented. Albeit, at the present moment this is possible only in very selected groups of patients with epilepsy due to a CNS insult with a known natural course of disease, as it is the case with TSC. The search of reliable biomarkers enabling early recognition of individuals with high risk of developing epilepsy is essential and still ongoing. Currently the meetings on prevention of epilepsy are a constant part of the American Epilepsy Society's annual meetings and mark a new trend in the approach to epilepsy treatment.

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# Attempt at profiling and regionalisation of COVID-19 vaccine campaigns in Poland – preliminary results

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## Abstract

**Background:** Social attitudes and context have a fundamental impact on the COVID-19 vaccine acceptance. This issue will be challenging the existing Polish public health infrastructure during the planned immunisation program. **Material and methods:** We attempt to exemplify Poland-specific social background via causal diagram and regional factor analysis based on dimensions (epidemiological potential, ability to act, magical thinking, corona scepticism, information needs etc.) by December 2020 – shortly before vaccination started. **Results:** We identified several potential target subpopulations and provide possible regional classification. We distinguish clusters of regions where communication strategies should be taken into consideration: 1) extending campaign reach, common social goods and conformism; 2) individual's profits and misinformation blocking. **Conclusions:** We are signalling the need for profiling and regionalization in campaigns and propose possible starting points for protocols for various voivodeships when safe and effective vaccines are available in Poland.

**Keywords:** vaccine coverage · vaccine uptake · information campaigns · public health interventions · COVID-19

## Citation

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## Introduction

The National Anti-Covid Immunisation Programme announced on 08.12.2020 [1] involves a widespread, voluntary and free vaccination to take place in Poland in 2021. Discovery, delivery and logistics of candidates or soon available SARS-CoV-2 vaccines seem to be one

of the biggest challenges in the history of medicine [2]. However, due to shortened clinical trials or conspiracy theories [3-4], the issue of vaccine acceptance arose in particular societies. According to the opinion polls and surveys [5-9], less than 50% of the Polish adult population are willing to undergo any kind of anti-coronavirus vaccination and the majority still remains undecided. In

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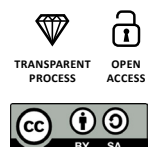
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Poland, confidence in vaccines for other diseases is a little below EU average, however Poles less confident over time [10]. The Polish government plans to carry out a large information and pro-turnout campaign [1], but empirical research on the relationship between vaccination uptake intent and acceptance in various Polish subpopulations is necessary [11-12]. The willingness [13-15] of a given person to be vaccinated is a combination of various factors: rational (*homo oeconomicus*), such as efficacy vs. safety calculation, psychological (*homo psychologicus*), such as trust or cognitive dissonance, as well as normative factors (*homo sociologicus*), like cultural or socialization issues. Achieving high acceptance of immunization in the population is required in order to achieve a high coverage level needed to reach herd immunity [11]. This will be a complex challenge [16-17] necessitating collaboration among various stakeholders, e.g. medical scientists, communication researchers and marketers, social and cognitive scientists, policy makers, public health officials, NGOs and patient group representatives and health care workers.

medical communication are extrapolating the results from foreign studies, mainly from English-speaking countries. However, it could lead to cognitive errors and misinterpretation, because the Polish sociocultural context has its own unique set of factors that significantly differ between geographical regions of Poland [18-19]. For instance, belief in conspiracy theories about COVID-19 significantly increases with eHealth literacy [20], just as vaccine safety negation increases with the education level [5, 21]. None of the conducted studies showed a univariate relationship between political views and various definitions of vaccination acceptance [5, 21-22]. On the other hand, opinions on mandatory prophylactic vaccination strongly depend on the education level, etc place of living, declared financial situation, religiosity etc [23]. In order to understand Poland-specific perspectives of COVID-19, both theoretical and pre-pandemic knowledge [11] should be accompanied with empirical research containing a rich variety of the concerns which can be captured via survey, observation, in-depth interviews or secondary data analysis [24-25]. It would then allow for identifying and profiling main target groups (Fig. 1), which in turn could increase the effectiveness of campaigns with main modifiable factors [3], such as vaccine information (information campaigns) and mitigate the harmful effects of misinformation and disinformation (information spread).

Some attempts to characterize each subpopulation have already been made (Fig. 1): for instance, it seems that young adult males are overrepresented within the “Ignorant” group, females among the “Anti-vacci-

### Material and methods

Due to the lack of empirical evidence based on the Polish population [11], some analysts and experts in

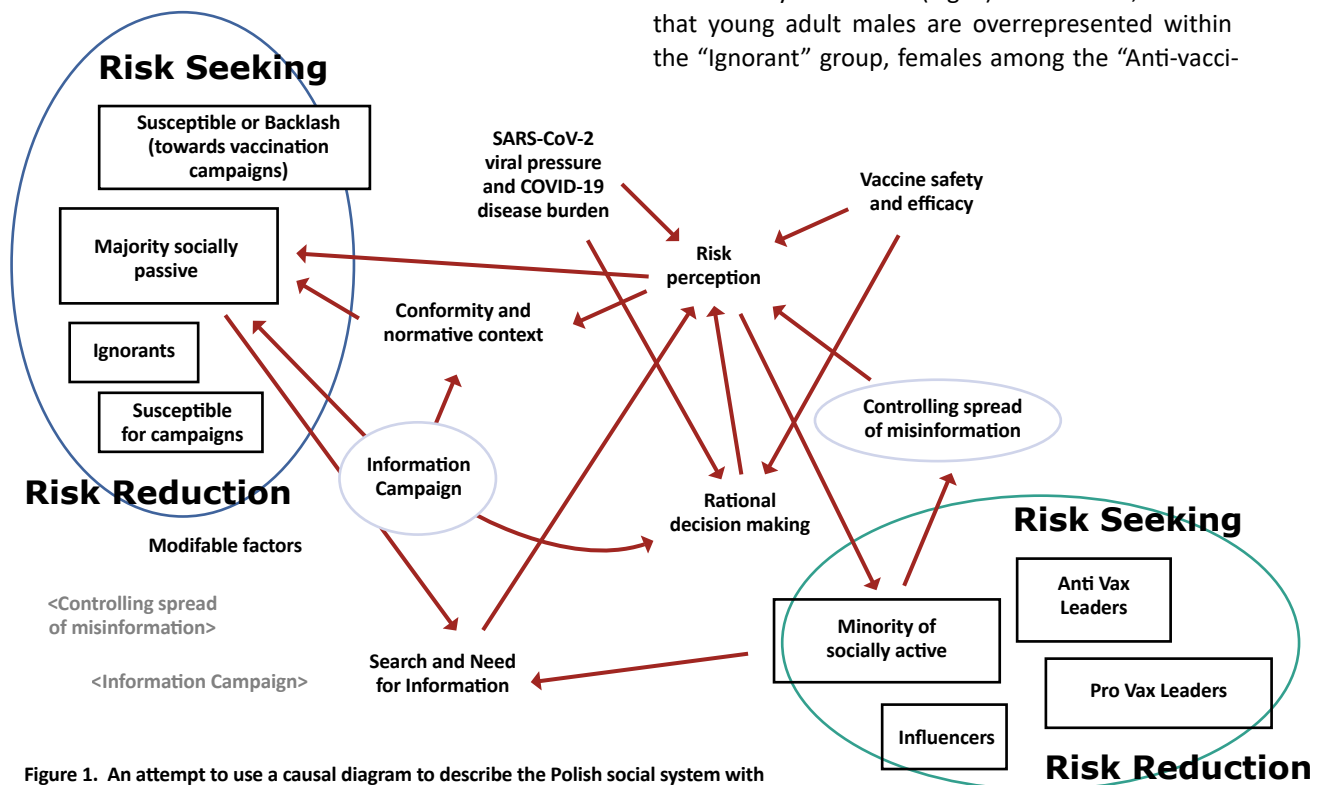


Figure 1. An attempt to use a causal diagram to describe the Polish social system with regard to vaccination amidst the pandemic. Rectangles are subpopulations (with its own composition of age, gender, place of residence, income, etc.), arrows indicate main interactions, shadow variables are modifiable factors (information campaigns and controlling the spread of (mis)-information)

nation Leaders” and the elderly among the “Susceptible to campaigns”, populists among “Susceptible to backlash” [5, 26-28]. However, some further profiling is needed. It is especially noticeable with regard to populations previously marginalized in pandemic social studies [24-25], i.e. the Polish elderly (disproportionately affected by the COVID-19), who need adequate support and information networks concerning the vaccination, as well as immigrants, who might be facing language barriers [29]. These groups are especially hardly able to properly estimate the risk-benefit ratio related to vaccination, so reaching them and providing information will be a key influencing factor. Moreover, some topics and concerns based on other vaccination programs [30-38] and COVID-19 vaccine [5, 39-41] have been preliminarily mapped.

## Results

To understand the ground for COVID-19 vaccine acceptance in Poland, let us consider the data available at the voivodeship level (NUTS-2). In the various theories of social action usually the common assumption is that one should distinguish attitudes (as well as opinions) and socio-epidemiological background (context) from the sphere of activity (actions). A given population may not be fully confident about the COVID-19 vaccine, but it could be not enough for an active refusal - for this, a fertile social environment is needed. For instance, the inhabitants of big cities declare skipping mandatory vaccination a few times more than the rest of the popula-

tion [23]. A high fraction of people who were not convinced by immunisation and did not trust doctors, science or the government, were still agreeing to vaccination [21].

In order to operationalize the concepts of interest, let us try to define the following socio-epidemiological dimensions:

1. Corona scepticism – mean Google relative search volume (RSV) [42] 25.07-25.08.2020 (30 days) for phrases: “fałszywa pandemia” (false pandemic), “plandemia” (plandemic), “epidemia+ściema” (fake epidemic). The level of corona scepticism could be a proxy for susceptibility to backlash [43] (Fig. 1).
2. General\_interest – interest of the general population in coronavirus by mean Google RSV [42] 25.07-25.08.2020 (30 days) for phrases: “koronawirus” (coronavirus), “zakażenia” (infections) and Coronavirus topic. To some extent, this measures information needs [11] with regard to the disease (Fig. 1).
3. Conspiracy\_Theorists: Conspiracy Theories Potential is defined as an interest of the general population in various paranatural or conspiracy concepts by mean Google RSV [42] 08.12.2019-07.12.2020 (12 months) for phrases: QAnon, Kabala, UFO, as well as Horoscope and New World Order topics. Magical thinking [44] is known to anticorrelate with trust in vaccines [21] in Poland.
4. Cum\_infections – Cumulative SARS-CoV-2 case notification number since the beginning of the epidemic until 8 XII 2020 per 5000 inhabitants [16].
5. Death\_trend – Trend in the number of deaths de-

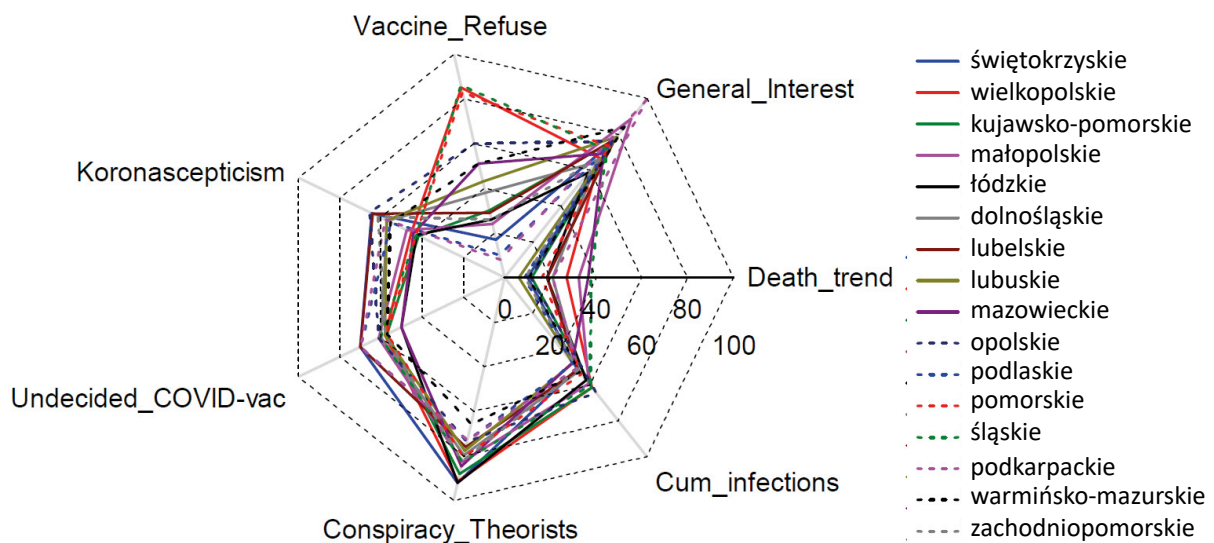


Figure 2. Radar graph of 7 chosen socio-epidemiological dimensions potentially related to willingness to COVID-19 vaccine uptake for the 16 Polish voivodeships

defined as the trend coefficient of daily death case registry due to COVID-19 1 XI – 8 XII 2020 [19]. Experienced total viral pressure (point 4) and recent disease burden (point 5) known as epidemiological potential in local neighborhoods may infer risk perception [45, 14].

6. Vaccine\_refuse – vaccination refusal rate [46] for non-medical reasons (per 10000 planned vaccination aged 0-19 in 2018). This could be a proxy of potential ability to act.
7. Undecided\_COVID-vac – percentage of respondents who in the Kantar survey [8] (mid October 2020) did not declare willingness to undergo vaccination against COVID-19 (on a macroregion NUTS-1 level only). It is a proxy of the size of subpopulation which could be susceptible to campaigns (Fig. 1).

Negative attitudes towards childhood immunisation according to surveys performed 2009 by voivodeship [47] anticorrelated with vaccine refusal rate, which suggest dissonance between attitude and action. It is worth noting that these dimensions may be defined in a different manner and many other dimensions could be added. Moreover, epidemiological potential and general interest (Fig. 1, 2) are highly temporal variables, so a longitudinal approach would be preferred as we have already seen that our observables are changing in time [48].

## Discussion

We attempt to systematize geographical diversity by factor analysis. In this simplified approach we do not assume any weights and all 7 dimensions are considered as equal predictors of attitude towards COVID-19 vaccine.

Geographical differences (Tab. 1) could be utilized in a dedicated communication practice [45, 49]:

- Factor 1 – regions with a low potential for action but with a high rate of undecided people. Recommended communication strategy should consider improving the reach of campaigns with emotionally-oriented content referring to conformism and common good [50].
- Factor 2 – regions that can significantly engage in vaccination refusal (high potential for action and high interest in conspiracy theories). Recommended communication strategy should emphasize individual profits [51] such as access to specific services and goods. Moderation of discussion in local traditional and social media could be considered for instance in Poznań, the Tricity [52] or in the górnośląskie agglomeration [53].

- Factor 3 – structurally heterogeneous vulnerable regions. Probably a separate strategy should be prepared for the Warsaw metropolitan area and the rest of mazowieckie. As usual, the opolskie Voivodeships difficult to classify due to its uniqueness [54].

It is important to mention that the proposed classification has partially revealed the socio-epide-

**Table 1. Factor loads estimated with minimum likelihood method (using Statistica 13)**

voivodeship	Factors		
	1	2	3
wielkopolskie		0.68	
kujawsko-pomorskie	-0.94		
małopolskie	-0.84		
dolnośląskie	-0.95		
łódzkie			-0.40
lubelskie	-0.90		
lubuskie	-0.96		
mazowieckie			-0.28
opolskie			0.27
podlaskie	-0.86		
pomorskie		0.65	
śląskie		0.76	
podkarpackie	-0.78		
świętokrzyskie	-0.90		
warmińsko-mazurskie			0.34
zachodnio-pomorskie	-0.93		
% Variance expl	0.73	0.15	0.04



miological structure of the regions, but a proper mix of qualitative and quantitative studies [55] should be conducted for each administrative unit to extensively explore the composition of subpopulations (Fig. 1) and the socio-epidemiological context (Fig. 2).

The issue of how to convince people to actually take the inoculum is very difficult and it requires the transfer of knowledge about audience profiling and content targeting from marketing research to public health. We showed that the simple rational and trust/information [41] deficit models alone could not easily explain vaccine hesitancy in Poland. This is just a preliminary and signalling study based on limited empirical data [56] and e.g. keywords selection in defining socio-epidemiological dimensions should be justified as the next step as well as Polish speaking Internet users are only a subset of the entire population. Vaccine discourse in core regions (factor 2), which tends to dominate due to a stronger political and economic position with a well-informed population knowing their civil rights, could be different to peripheral regions (factor 1), where counter-Enlightenment cultural and political initiative are more common [27]. However, based on this exploratory research, we can claim that the main responsibility should fall on the regional media and local governments (which on average acquire much higher trust than their national counterparts [57-58]) to prepare their own effective dissemination strategy. Especially during the first wave of COVID-19, local media (at least in dolnośląskie) broadcasted more reliable and less polarized information on coronavirus-related issues [59], in comparison with the nationwide media. Moreover, during the pandemic, central governmental agencies and the main players from the opposition parties are known to distribute fake news and manipulate the public by using sociotechnics, which is probably due to short-term political profits [59-60]. Thus, significant funds and responsibilities should be assigned to 16 voivodeships (NUTS-2) or even better to 380 poviats (NUTS-4) to prepare regional communication strategies in collaboration with local traditional and social journalists. Due to possible inequalities in organizational capital among regions, support from central institutions, think tanks and research centers could be required. Example of misclassification of mazowieckie (Table 1) suggests that even voivodeship could be too heterogeneous and deeper geographical mapping would be preferred (however it could be too difficult for logistical reasons in some less organized counties).

Nevertheless, our approach is only a local adaptation of the main information management pillars concerning COVID-19 vaccine [61-62], such as:

- accurate and timely knowledge transition on actual vaccine effectiveness (on individual and herd level) and safety, which must reach citizens and be understood by them;
- infoveillance of traditional and social media to monitor behavioral attitudes in all parts of the given society (Fig. 2);
- building (e)Health literacy, tailoring advice and messages to address various audiences (Fig. 1);
- controlling and improving knowledge propagation (e.g. fact checking), strategic partnerships should be formed across all local and central stakeholders.

## Conclusions

To conclude, only local authorities and researchers who have the knowledge of their society [63-64] and communities with special needs as elderly [65-67], could deliver information in appropriate form and content [68]. Safe and effective vaccines do not only help the inoculated people (efficacy confirmed in multiple RCT), but their primary role should be stopping the spread of SARS-CoV-2 (if proved in observational studies or clinical trials). The theoretical effect of vaccination seems to be super-linear [69], so higher vaccine coverage could mean ever more QALYs (quality-adjusted life years) saved due to infections in the local population, as long as the proper balance in delivery among essential workers and high-risk groups in the first phase is satisfied. Thus, regionalized marketing could synergize with national [1, 41, 70] and pan-European [71] evidence-based platforms on benefit-risk disseminations for vaccines and further candidates, while the first person was vaccinated against COVID-19 in Poland on 27 XII 2020.

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# Changes in the neurosurgical admissions during the COVID-19 pandemic – a comparison with 2019

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## Abstract

**Background:** The coronavirus pandemic has strongly affected health-care systems around the world, testing their patients' care capacities. Admission restrictions, patients' fear of hospitalization or other uncomprehended constraints has affected admissions to neurosurgery department. **Material and methods:** The clinical data of admissions from March 1<sup>st</sup> to July 24<sup>th</sup> 2020, as well as data of the control group in relevant periods of time in 2019 was collected from the local hospital database and compared. **Results:** The total number of procedures performed between March and July 2020 is 1545, compared to the corresponding period of the previous year it was the number of 2062, indicating a decrease by about 25%. Both head and aneurysm procedures decreased over the entire analyzed period. The number of procedures classified as "other" was higher in each of the three stages. Between March 1<sup>st</sup> and April 30<sup>th</sup> (Phase 1) mainly younger male patients were admitted. **Conclusions:** We demonstrated the impact of the COVID-19 pandemic on the work organization of our Neurosurgery Department. We report that after the introduction of appropriate solutions, it is possible to provide care to neurosurgical patients while ensuring the safety of patients and Staff during the pandemic.

**Keywords:** coronavirus · spine surgery · neurosurgery · hospital admission · COVID-19

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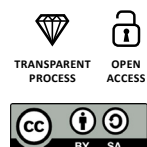
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## Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first diagnosed in December 2019 in the city of Wuhan, Hubei Province in China. The disease caused by the virus, COVID-19, can lead to severe respiratory failure. Within a few months of the first reported case, SARS-CoV-2 spread throughout the world. It was designated by the World Health Organization (WHO) a pandemic on March 11, 2020. The non-specific symptomatology, high infectivity, inexistence of a vaccine and a lack of effective treatment hampered efforts to contain and manage patients infected by SARS-CoV-2. In Poland, the first case of a SARS-CoV-2 infection confirmed by laboratory test was announced officially on March 4<sup>th</sup> 2020. Since then, health care facilities started implemented a number of procedures and solutions aimed at reducing the number of COVID-19 cases. In particular, planned admissions and hospitalizations were severely limited. This challenged the health care staff to provide patient care, while ensuring safety amidst the patients' fear of being infected with the novel virus.

In this paper, we highlight the specific conditions and efficient management methods that a neurosurgery department took in Poland. We present the pattern of neurosurgical patient admissions to a single center during 2020, depending on the phase of adaptation to the COVID-19 pandemic. We hope that this information may lead to a more calm and predictable response during any future pandemics.

## Materials and Methods

We examined the admissions to the Neurosurgery Department at the University Clinical Center (UCC) of the Medical University of Gdańsk (a tertiary care, neurotrauma centre serving a population of 1 million). The study sample consisted of data about the number and types of procedures performed from March 1<sup>st</sup> to July 24<sup>th</sup> 2020. The control group consisted of procedures performed from March 1<sup>st</sup> to July 24<sup>th</sup> 2019. Simultaneously, we collected information about the changes in restrictions associated with patient care and hospital staff safety since the SARS-CoV-2 outbreak in Poland.

### Data acquisition

The clinical data of were collected from the hospital's patient record system (CLININET, CompuGroup Medical, Lublin, Poland) using the IT tool MedStream Designer (MSD, Transition Technologies Co., Warsaw, Poland). Data related to patients undergoing COVID-19 swabs before or during hospitalization were obtained from the hospital's COVID-19 database

which has been functioning since the in-house laboratory began testing for SARS-CoV-2.

We divided the neurosurgical procedures into four groups: spinal procedures, head surgeries (brain tumors, hematomas, ventriculoperitoneal shunt insertion), aneurysm-securing procedures and other miscellaneous procedures.

### Phases of the pandemic

We divided the time from the study period into three stages based on the legal and organizational regulations implemented both at the national and hospital level. We attempted an overall quantitative and qualitative comparative analysis, considering both the type of procedures between and within the given stage of the pandemic.

Stage 1, which we will call "the Lockdown," lasted from March 1<sup>st</sup> to April 30<sup>th</sup> when our hospital was in a state of high alert. During this time all planned admissions to the Neurosurgery Department were suspended and its function was limited to emergency admissions only. Throughout the hospital, numerous restrictions and strict guidelines were introduced for patient care, as well as to ensure the safety of all hospital employees. Furthermore, family visits, bedside teaching and internships for doctors were also suspended.

Stage 2, which we will call "Unlocking," started on April 30<sup>th</sup>, when the planned procedures were gradually performed and the access to the operating room was increased. Numerous limitations and special guidelines were still in place, however they allowed somewhat flexibility and were adjusted to the patients' planned treatment options.

Stage 3, which we will call "riding out the storm," started on June 22<sup>nd</sup>, when all newly admitted patients underwent SARS-CoV-2 testing and then waited at home under self-quarantine for their results. This was the so-called, "kiss and fly" system.

**Supplementary figure 1. Pandemic milestones in Poland – timeline.** Abbreviations: UCC: University Clinical Centre. → <https://ejtcm.gumed.edu.pl/files/62>

**Supplementary table 1. General rules for admissions during a pandemic by stage.** → <https://ejtcm.gumed.edu.pl/files/65>

### Comparative analysis

The overall number of procedures performed between March 1<sup>st</sup> and July 24<sup>th</sup> 2020 (both as a whole and in the individual stages of the pandemic) were compared with procedures performed in the corresponding time period in 2019. We took into account the type of procedure, the patients' age and sex.

**Statistical methods**

Continuous variables were described by mean and standard deviation (SD) and were tested for normal distribution using the Shapiro-Wilk test. The differences between groups were identified respectively by means of a t-test, Mann-Whitney U test, chi square or two-tailed Fisher test using Statistica v. 12.0 (StatSoft, Inc., Tulsa, USA). We considered p values < 0.05 as statistically significant.

**Results**

**Total procedures: 2019 versus 2020**

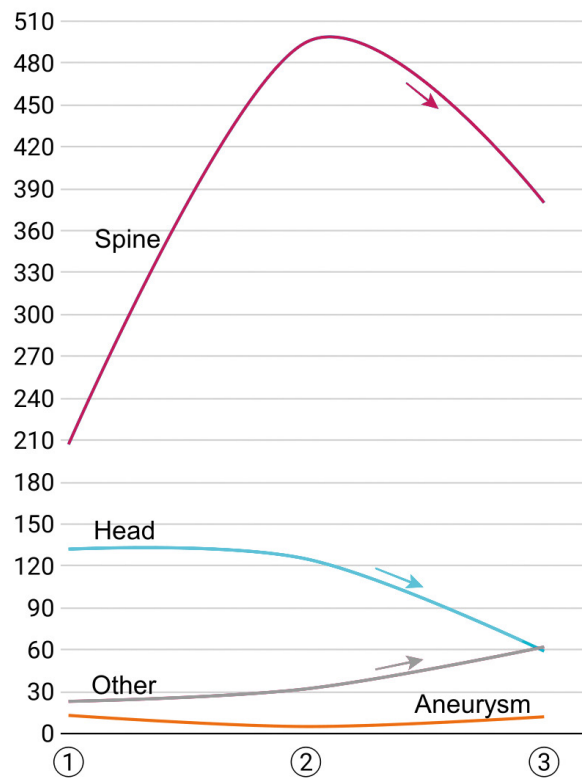
The total amount of procedures performed during the study period decreased by 25% (from 2062 to 1545) compared to the time period in 2019 (Table 1).

Both aneurysms and head procedures decreased throughout all three analyzed phases of the pandemic. Not only was there a smaller total number of aneurysms, but also they were a smaller portion of the procedures performed in 2020. We observed the highest decrease in spinal procedures during Phase 1. This was due to hospital-related restrictions, however during Phase 3 this number started to increase. Parallel to this drop, we observed that the number of “other” procedures grew steadily.

**Supplementary figure 2. Waterfall-plot depicting admission changes in pandemic phases. Explaining how the number of each type of performed procedures changed from 2019 to 2020. The gray rectangle shows the deficit between these years. → <https://ejtcm.gumed.edu.pl/files/63>**

**Age and sex of admitted patients**

More younger patients were admitted during Phase 1 (March 1<sup>st</sup> – April 30<sup>th</sup> 2020) compared to the



**Figure 1. Average distribution of neurosurgery clinic admissions**

corresponding time the year before (P = 0.05). Since April 30, 2020, there were no differences in patient age compared to the same months in 2019. Significantly more males than females were admitted in Phase 1 of the pandemic (P = 0.03). On the contrary, since the beginning of Phase 3, we observed a greater proportion of female patients (P = 0.01). Details are presented in Table 2.

**Supplementary figure 3. Age structure presentation between 2019 and 2020; The corresponding timeframes (1-4 ; 2-5; 3-6) were compared statistically. → <https://ejtcm.gumed.edu.pl/files/64>**

**Table 1. The number of performed neurosurgical procedures - a comparison between March 1<sup>st</sup> to July 24<sup>th</sup> in 2019 and 2020**

	total	spine			head			aneurysms			other					
		1st STAGE	2nd STAGE	3rd STAGE	1st STAGE	2nd STAGE	3rd STAGE	1st STAGE	2nd STAGE	3rd STAGE	1st STAGE	2nd STAGE	3rd STAGE			
<b>2019</b>	2062	850	739	473	601	545	343	192	147	95	37	24	16	20	23	19
<b>2020</b>	1545	375	657	513	207	495	380	132	125	59	13	5	12	24	32	62
					p = 0,0000	p = 4,9519	p = 5,8045	p = 0,0000	p = 6,8350	p = 0,0021	p = 4,6997	p = 0,0115	p = 3,2438	p = 0,0045	p = 0,9188	p = 0,0000



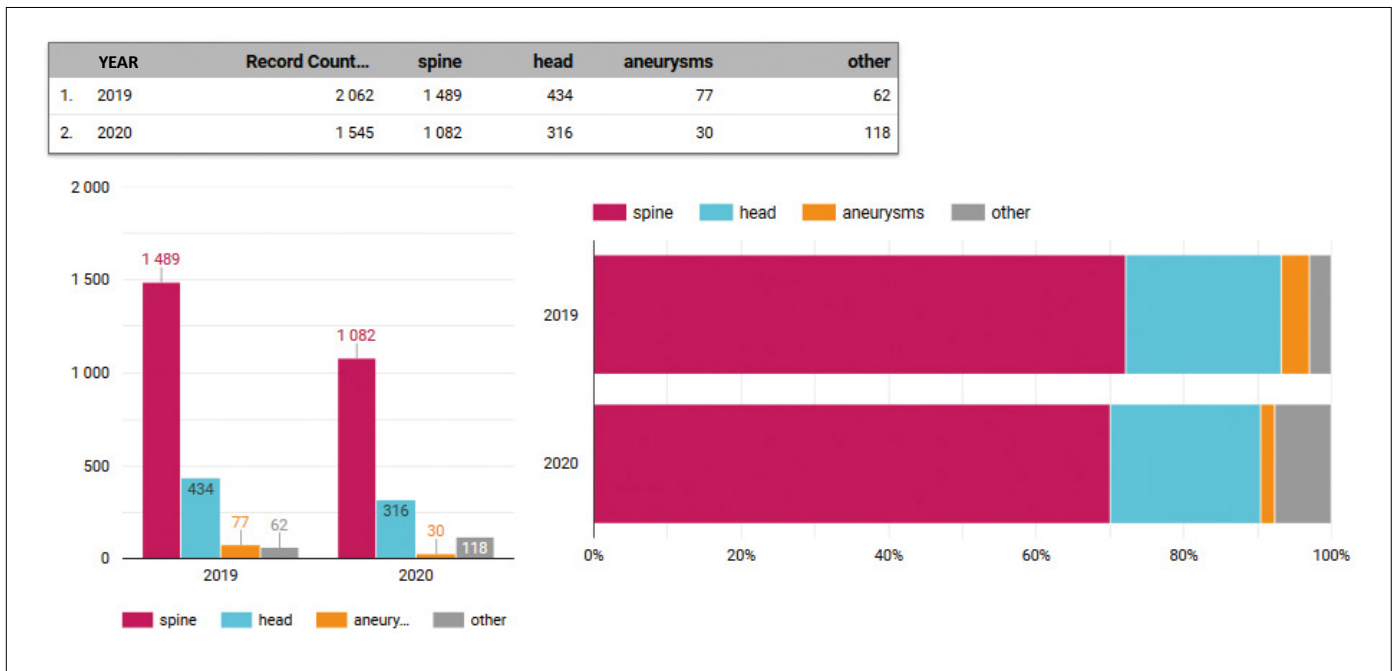


Figure 2. Qualitative distribution of performed procedures – comparison between 2019 and 2020

### Stage 1, The Lockdown

We observed a significant decrease in the number of spine, head and aneurysm procedures during Phase 1. For the other procedures, a slight increase was observed.

### Stage 2, Unlocking

During Phase 2, there was almost a complete equalization in the number of spine and head procedures. However, there was a dramatic decrease in aneurysm procedures compared to the same time period in 2019. During this phase, we observed a further increase in other procedures compared to the previous year.

### Stage 3, Riding out the Storm

We observed an increase in spine procedures during Phase 3 as compared with the same time pe-

riod in 2019. There was a decrease in the number of head and aneurysm procedures at that phase in 2020. An increase in, “other” procedures was observed.

## Discussion

Despite the several changes to clinical practice due to the COVID-19 pandemic, we found that the total amount of performed procedures decreased only by 25%. Our comparison to the same time period in 2019 aimed to demonstrate to what extent neurosurgery practice during the pandemic differed from the usual.

### Applied restrictions – a detailed historical account

#### “The Lockdown”

In March of 2020 the UCC in Gdańsk implemented a detailed action plan. First, patient visits were suspended at all departments along with internships. On March 12<sup>th</sup>, the UCC was put on high alert in connection with the SARS-CoV-2 pandemic. Most scheduled admissions were suspended, with the exception of patients with oncological, transplantation, chemotherapy, ophthalmology,

Table 2. Hospital admissions by sex a comparison between the 3 phases of the pandemic

factor	1 vs 4		2 vs 5		3 vs 6	
Sex (n, % of males)	51,53	58,13	48,85	50,08	52,85	44,83
Sex (n, % of females)	48,47	41,87	51,15	49,92	47,15	55,17
	p = 0,03269		p = 0,64737		p = 0,01183	

pregnancy and puerperium, pediatric-related needs or who were enrolled in special drug programs. SARS-CoV-2 risk was assessed via obligatory telephone epidemiological interview and body temperature measurement along with paper questionnaire upon arrival at the Scheduled Admission Center and Day Wards. Heads of Departments and other organizational units of UCK were obliged to ensure daily body temperature measurements of all employees at the start of each shift or working day. The activities of specialist clinics had to be carried out with the use of ICT systems [1]. Detailed patient management regimens were introduced at the emergency department. Stable patients had standard PCR tests for SARS-CoV-2, whereas Rapid-PCR was performed in urgent cases. If the patient's clinical condition could not afford any delays for the result of SARS-CoV-2 test, the operating procedure was performed using personal protective equipment, as if the patient had tested positive. During the complete "Lockdown" the number of performed procedures decreased dramatically, mainly due to the complete suspension of planned admissions. From March 12th, the department was limited to emergency admissions and on-call interventions. The number of spine and aneurysms procedures has decreased significantly, while the number of head interventions increased. This was probably due coding the admissions in the patient record system as emergencies and with the lack of planned spine surgeries. Moreover, there was a marked increase in "other" procedures. COVID-19 testing procedures were categorized under, "other" category. Therefore, this increase may have been related to the need for a SARS-CoV-2 swab before each admission. Notably, some of the testing-swabs were performed at the Emergency Department and therefore are not included in the presented data.

### **"The Unlocking"**

On April 30th 2020, the admission and treatment of planned patients started gradually. For the Neurosurgery department this meant about 2 to 4 planned admissions per day, depending on the expected operating time. Each elective patient underwent a SARS-CoV-2 swab and awaited the result at a "buffer ward." At that time, the physician conducted the epidemiological interview with the patient by phone. In the case of emergency admissions, the procedures were the same as during the "Lockdown" stage. This made it possible to almost equalize the number of emergency procedures performed in relation to the previous year. Both spine and head procedures constituted a fraction of treatments comparable to 2019. The number

of aneurysm procedures had decreased, while "other" procedures still accounted for a noticeably higher proportion than previous years.

### **"Riding out the storm"**

The "kiss and fly" system enabled complete unlocking of the Neurosurgery Department. The average waiting time for the SARS-CoV-2 result with a standard swab was about 3 to 5 hours depending on the laboratory workload, while the Rapid-PCR, in urgent situations, took about 1 hour. The above-mentioned solutions allowed not only to match, but also exceeded the number of procedures performed during typical clinical practice. Both spine and aneurysm procedures represented a fraction of treatments comparable to the pre-pandemic norm, while the fraction of head procedures decreased drastically. This is most likely due to a re-increase in elective procedures which, overall, reduces the percentage of urgent cases such as hematomas. As for the number of other procedures, it is still higher than typically. We assert that the obligation to test each patient for COVID-19 increases the number of this particular fraction.

### **Discussion with the main findings**

Older people have a worse prognosis and during the pandemic their hospitalization increased the threat to their health. The risk of serious comorbidities increases with age, as well as the severity of COVID-19. Older patients were not only less willingly hospitalized, but also were motivated by fear and may have decided to visit their doctor less often.

The male predominance in the admission profile could possibly result from hospital restrictions solely to emergency cases in the initial phase of the lock-up. Due to neurotrauma status of the hospital these were patients after head or back injuries.

It is worth noting that by the time this paper was written, none of the patients admitted to the neurosurgery department had a positive result for SARS-CoV-2. In the hospital's pre-hospitalization screening, it was possible to capture 5 patients with a positive result (out of the total number of 11548 performed tests). According to the worldometer.com, at this time Poland was found at the 9th place worldwide in the ranking of the most infected cases per million people. Due to this, they were transferred to an infectious disease hospital or placed under home quarantine. However, for safety reasons, each patient admitted to the hospital was regarded as an asymptomatic infected patient as per previous recommendations [2].

## Neurosurgical departments around the world

In India, the neurological and neurosurgical departments have categorized cases into three groups according to their priority: acute, sub-acute and chronic. Full personal protective equipment should be used during procedures involving a high risk of aerosol dispersion, i.e. those requiring intubation and procedures using drills or endoscopes [2].

Since most hospital visits in China are now performed remotely, there has been a significant decrease in reported physician-patient conflicts and cases of violence in hospitals, which have been of great concern so far [3].

In Lombardy (Italy), an internet platform for conference calls and radiographic image sharing was established and the patient waitlist was limited to oncological cases. Patients were categorized according to the severity of disease into 3 classes: A ++, A + and A [4]. An important educational step in response to the epidemiological situation was to increase cooperation between the centers, and thus the exchange and enrichment of surgical skills and experience [4-5].

In Bergamo (Italy), the regional neurosurgical network was concentrated at four hub hospitals. These hospitals were able to handle urgent surgical cases, so that the remaining centers focused on helping patients with COVID-19 [6].

At the University of Miami Jackson Memorial Hospital, all scheduled admissions were canceled and patients are admitted to the clinic after screening based on a survey and body temperature. Surgeons tried to use only dissolvable sutures so that they do not have to be removed later, allowing for a remote follow-up visit [7].

Elsewhere in the United States, the development of telehealth was also emphasized, proving its political, research and clinical application [8]. The authors emphasized that the provision of personal protection measures as well as broadly understood cooperation was critical during the pandemic [9].

In a survey conducted among 226 respondents around the world, all agreed that rapidly developing neurooncological conditions are non-emergency cases with the greatest risk associated with postponing treatment, however vascular events may be at high risk when delayed [10].

Any novel pandemic requires flexibility and deliberate compromises from everyone. The introduction of initial restrictions was necessary to reorganize the work of the hospital to ensure the safety of inpatients and staff [11]. However, since closures could not last

indefinitely, solutions had to be found to enable the normal functioning of the hospital. Partial defrosting was a transitional stage designed to test the safety of new solutions. However, fast adaptation has been shown to be the most important step in fighting the pandemic [12].

## Clinical Implications and Future Directions

Using the example of our center, we hope to show other health institutions that medical care delivery is possible with the introduction of appropriate system solutions. We assert that learning to adapt in the new COVID-19 pandemic is the only way to prevent paralysis and failure of the healthcare system. As we may face a new surge of COVID-19 cases, we encourage physicians to react with quick and prudent solutions to enable their clinic to function as normally as possible.

During the work on this article, the epidemiological situation in Poland changed dramatically. The sharp increase in the number of cases showed that the period between March and July 2020 was only a prelude to the first wave of the pandemic in Poland. As it turns out, this was crucial for the organization of the actions that are currently being undertaken.







## Conclusions

We demonstrated our department's preparedness for admission of trauma cases despite the restrictions in place due to the COVID-19 pandemic. Stage 1 patients were predominantly younger males. In the early phase of any future epidemic we recommend disqualifying older patients from elective neurosurgery. The number of "other" non-surgical cases significantly increased. This may possibly be due to the additional procedures such as SARS-CoV-2 screening tests required prior to admission. Patients with spinal disorders suffered the most during the early phase of the COVID-19 pandemic. The reason is that these are usually life-enhancing, not life-saving procedures. In a pandemic, the admission profile changed and only urgent and life-saving neurosurgical interventions were undertaken.

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# Morphometric study of the bilateral middle cerebral arteries in patients with a unilateral aneurysm

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## Abstract

**Background:** The middle cerebral artery (MCA) supplies a major part of the brain and is of considerable clinical importance as a common location of intracranial aneurysms. The aim of the present study was to analyze the bilateral MCAs in patients with unilateral aneurysms. **Material and methods:** Images of computed tomography angiography of 45 patients were analyzed. The morphometric parameters of MCA were measured. The measured parameters of the normal MCAs were compared with MCAs containing aneurysms located in the main trunk division. **Results:** No significant differences in the length of trunk and angles between the middle and anterior cerebral arteries were found between the non-affected and aneurysmatic MCAs. Concerning arteries with aneurysms, more branches originating from the main trunk division were found more frequently. The coexistence of the more frequent trifurcation of the MCA and an aneurysm constitutes evidence of greater anatomical variability of this arterial area in cases with a concomitant vascular malformation. **Conclusions:** This finding is consistent with literature data, showing the relationship between aneurysms and arterial variability and the fact that aneurysms are most often located at arterial divisions.

**Keywords:** computed tomography angiography · intracranial aneurysm · middle cerebral artery · morphometry

## Citation

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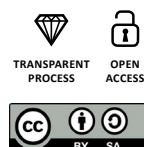
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## Abbreviations

- ACA – anterior cerebral artery
- CT – computed tomography
- CTA – computed tomography angiography
- DICOM – digital imaging and communications in medicine
- DSA – digital subtraction angiography
- ICA – internal carotid artery
- MCA - middle cerebral artery
- MRA – magnetic resonance angiography
- MRI – magnetic resonance imaging
- SAH – subarachnoid hemorrhage

## Introduction

The middle cerebral artery (MCA) is the largest terminal branch of the internal carotid artery (ICA), which delivers blood to most of the cerebral hemisphere [1-2]. Circulatory disturbances inside the MCA cause ischemic strokes with focal neurological deficits [3]. The central branches of the MCA play an essential role in brain hemorrhage because they may often rupture due to atherosclerotic lesions or arterial hypertension [2]. The MCA is also a location of saccular cerebral aneurysms [3-4]. Aneurysms of the MCA are most often located within its main trunk division where hemodynamic stress is greatest [4-5].

From an anatomical point of view, the MCA is a direct extension of the ICA, with the anterior cerebral artery (ACA) being the second major branch originating from the ICA. The MCA is separated into five segments: M1 – M5. The first segment (M1, also known as the sphenoidal segment) is positioned horizontally and passes in the lateral direction. Subsequently, at the limen insulae the M1 enters the lateral sulcus of the brain, where it splits into M2 branches [1-2]. Most frequently, such a division is bifurcated, but there exists some variability with more than two M2 branches [6-7]. Since the M2 branches extend in the posteriorly within the lateral sulcus and surround the insula, the M2 is named the insular segment [2, 6]. In the region of the operculae, the M2 branches further split into the M3 branches, also called the opercular segment. In the region of the three operculae covering the lateral sulcus, the M3 branches extend to the cerebral convexity and are distinguished as the M4 cortical segments, which eventually split into the terminal (M5) segments [2].

MCA divisions are the third most frequent location of saccular cerebral aneurysms. MCA aneurysms constitute approximately 20% of all intracranial aneurysms [8]. Saccular cerebral aneurysms occur in approximately 2% of the entire population [8-9]. Cerebral

vessels with potential vascular malformations may be visualized using three basic diagnostic methods: digital subtraction angiography (DSA), computed tomography angiography (CTA) and magnetic resonance angiography (MRA) [7, 10]. CTA used in this article is commonly considered in clinical practice. It is a rapid and accessible imaging test which can be performed at the Emergency Departments. CTA allows an immediate detection of cerebral aneurysms [10]. The aim of this study was a CTA-based comparative analysis of the bilateral MCAs in patients with unilateral saccular aneurysms localized within the M1 division.

## Material and methods

We performed a retrospective morphometric analysis of CTA images obtained from 45 patients who were treated at a single neurosurgery center in the years 2018–2019. The reason for referral was unilateral intracranial aneurysm located in the M1 division of the MCA.

CTAs in patients with unruptured aneurysms were performed in an outpatient setting. The CTA scans were acquired 0.4 mm intervals using a Discovery CT 750 HD (General Electric Healthcare, Chicago, USA) scanner and were saved in the Digital Imaging and Communications in Medicine (DICOM) format. To visualize their blood vessels, patients were administered 80 ml of intravenous contrast agent (Omnipaque by General Electric Healthcare, Chicago, USA). The exclusion criteria were: comorbidities that could affect the cerebral vessel morphology (e.g. polycystic kidney disease), co-existing cerebral aneurysm at a different location, an expansive intracerebral hematoma in the area of the MCA aneurysm, the M1 trunk not visible in CTA due to massive cerebral edema. In all patients with subarachnoid hemorrhage (SAH), a computed tomography (CT) examination was performed to diagnose SAH, and immediately afterwards a CTA examination was done. SAH visualized in these CTAs was considered acute, therefore cerebral vasospasm was not taken into account in the measurement of the MCA width.

The analysis (comparisons of MCAs with M1 division aneurysm and non-affected MCAs) was performed by two authors: a neurosurgery specialist with 15 years of professional experience in aneurysm surgery and an anatomist with 10 years of professional experience in morphometry.

The following five parameters were measured:

1. length of M1 measured bilaterally from the ICA division to the M1 bifurcation,
2. width of M1 in the proximal section of the artery,
3. width of M1 in the middle section of the artery,

4. width of M1 next to the bifurcation and
5. the angle between M1 and the ACA A1 segment – measured in the plane formed by the proximal branches of these two arteries (the angle at which the terminal branches of the ICA bifurcate).

Statistical analysis was performed using StatSoft® statistical program STATISTICA 13.1. Distribution of variables was checked using the Shapiro–Wilk (W) test, while the homogeneity of variance was checked using the Fisher's test. The results were expressed as arithmetic means with standard deviations (SD). To compare the means, Student's t-test for independent variables was used. Tukey's test was used for post-hoc analysis. If no similarity of variance occurred, the non-parametric Kruskal-Wallis test was used. The study protocol was approved by the local Bioethics Committee (document no. KB 35/2020).

## Results

The study group comprised 25 men and 20 women with the mean age of 62.34 years (men 61.24, women 64.56). In every analyzed CTA image, cerebral vessels were clearly visible and morphometric measurements were possible. Out of the 45 CTA images examined, 12 revealed unruptured MCA aneurysms, while 33 showed ruptured aneurysms and subarachnoid hemorrhage

(SAH). In 27 cases, the aneurysm was located on the right MCA, whereas in 18 cases on the left MCA. Due to the small sample size of the analyzed documentation, we decided not to compare the MCA morphometric parameters in patients with ruptured and unruptured aneurysms in this study. Since all CTAs concerned sporadic aneurysms in the population, the group was considered homogeneous.

A diagram of the measurements is shown in Figure 1. The number of M2 branches originating in the M1 division was also assessed. Mean values and standard deviations of the examined parameters of the MCA, as well as the angle between the MCA and ACA are presented in Table 1. The statistical analysis did not reveal any significant differences in terms of sex nor aneurysm laterality ( $p > 0.05$ ) referring to both the occurrence of aneurysms and the parameters measured.

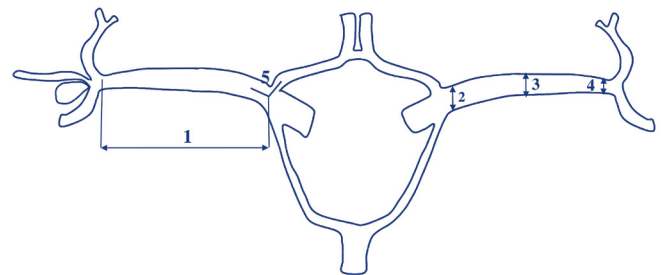


Figure 1. A diagram of the MCA measurements (1-5) and the number of M2 branches originating from the M1 division

Table 1. Values of the examined MCA parameters and ACA/MCA angle

Measurement parameters	N	normal artery		N	artery with an aneurysm		p
		Mean	SD		Mean	SD	
length of M1	45	24.1	2.43	45	23.61	2.21	0.132
width of the proximal end	45	2.19	0.19	45	2.21	0.17	0.142
width of the middle part	45	1.99	0.12	45	2.02	0.14	0.234
width of the distal end	45	1.88	0.15	45	1.92	0.13	0.145
angle of artery M1/A1	45	123.97	16.23	45	122.94	17.65	0.091
trifurcation	17	4	-	17	12	-	-

In the studied group, the mean length of segment M1 was  $24.1 \pm 2.43$  mm on the non-affected side and  $23.6 \pm 2.21$  mm on the affected side. The mean width measured in the proximal end of the MCA was  $2.19 \pm 0.19$  mm on the non-affected side and  $2.21 \pm 0.17$  mm on the affected side. The mean width of the middle part of M1 was  $1.99 \pm 0.12$  mm on the non-affected side and  $2.02 \pm 0.14$  mm on the affected side. The mean widths measured next to the division initiating the M2 segments on the non-affected and affected sides were:  $1.88 \pm 0.15$  mm and  $1.92 \pm 0.13$  mm, respectively.

The angles of division between the ACA and MCA were:  $123.97 \pm 16.23^\circ$  on the non-affected side and  $122.94 \pm 17.65^\circ$  on the affected side. The CTAs visualized the types of the M1/M2 division in terms of the number of branches. In the study group consisting of 90 arteries, a trifurcation was observed in 4 cases (8.8%) of non-affected arteries and in 12 cases (26.6%) of arteries with aneurysms. CTA with a MCA trifurcation with an aneurysm on the inferior side of the M1 division is shown in Figure 2.

## Discussion

The MCA morphometric analysis of non-affected arteries and aneurysms is a subject of interest for numerous authors. However, the literature concentrates on the microsurgical anatomy of the MCA based on cadaver specimens. Valuable reports on the topic were published by Grand et al. (1980), Gibo et

al. (1981), Umansky et al. (1984) and Yasargil (1984) [1-3, 11]. Our study focused on CTA assessment of the M1 length and the number of M2 branches in living patients, not cadavers.

The mean length of M1 in our study was  $24.1 \pm 2.43$  mm on the non-affected side and  $23.6 \pm 2.21$  mm on the affected side, which was greater than those reported by other authors. According to Umansky et al., it was 15.1 and 15.7 mm [11], respectively, and according to Yasargil, it was 14–16 mm [3]. On the basis of the microsurgical MCA anatomy in the Indian population, Pai et al. obtained the mean M1 length of 20.00 mm [6], which was relatively similar to our measurements [6]. In our study the M1 segment was bifurcated in 71 arteries (78.89%) and trifurcated in 19 arteries (21.11%). Comparable findings were published by Pai et al. [6], and earlier by Yasargil and Umansky et al. [3, 6, 11]. According to some authors, the M1 division is always a bifurcation and the presence of three or four main arterial branches results from a very early M2 division, which makes the M2 segments originate in the M1 division [6, 7, 12]. The traditional M1 division into two M2 branches (bifurcation) is observed in vascular studies in 50% of cases, even in approx. 80% according to some authors [6]. The two M2 branches are the superior and inferior ones.

According to the literature, in a bifurcation both branches may be equal in diameter or one of them may be dominant [7, 12]. A trifurcation is observed in 12–25% of cases but according to some authors it is a pseudo-trifurcation with a very early division of

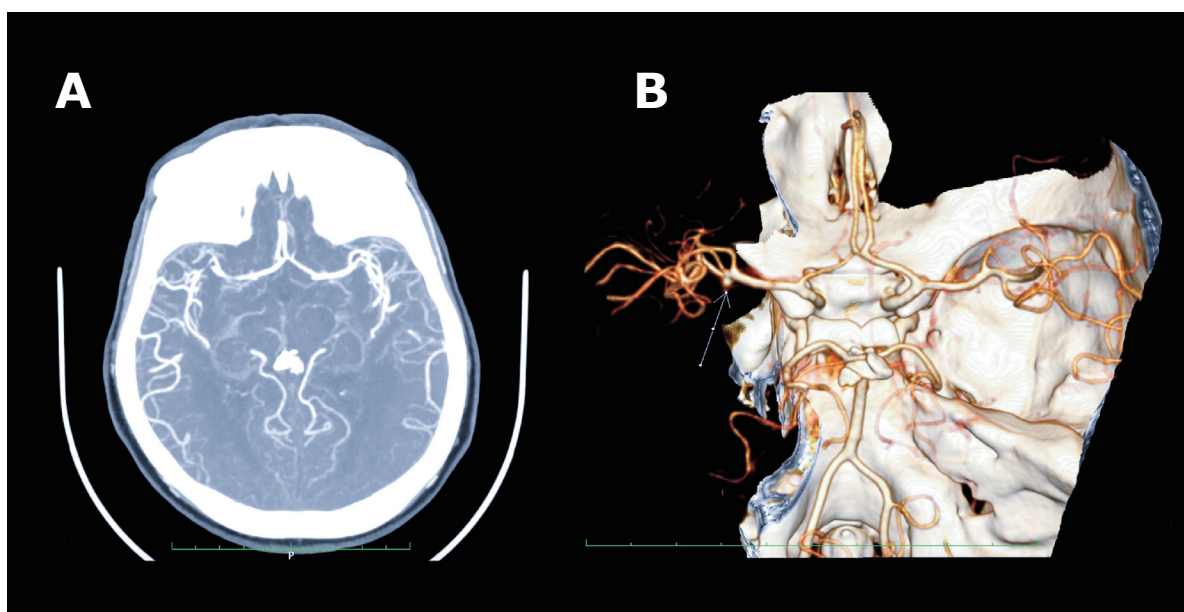


Figure 2. CTA two-dimensional axial projection with a M1 trifurcation with an aneurysm (A), CTA three-dimensional projection of the M1 division – a trifurcation of M1 with aneurysm (B)



the M2 superior branch (in 15% of cases) or the M2 inferior branch (in 10% of cases). In 5% of cases, both branches are split early which gives the appearance of a pseudo-tetrafurcation. In ~2% of cases, there is no apparent division of the M1 trunk into M2 branches, with one dominant M2 branch being the extension of M1 and the other smaller M2 branch appearing as a lateral branch [6, 12]. In our study, the number of branches originating from the M1 division was counted. Out of 19 arteries with observed a MCA trifurcation, 15 were affected by an aneurysm, and only 4 were non-affected.

Some authors have pointed out that aneurysms of the MCA division are characterized by a wide neck covering the division. Thus, the anatomy of the MCA M1 division is distorted and the visible M1 trifurcation may in fact be an early division of one of the M2 branches, not a true trifurcation [11-12]. Yasargil claims that the exact anatomy of the MCA division with the number of branches can only be determined intraoperatively [3]. Orakdogan et al. published a DSA evaluation in 128 patients with aneurysms in the area of the circle of Willis, while our study is restricted to the CTA evaluation of MCAs in 45 patients with unilateral MCA aneurysms. Orkadogen et al. reported that in patients with MCA aneurysms, anatomical differences in cerebral arteries were much less common than in aneurysms of the anterior and posterior communicating arteries (ACoA and PCoA). Anatomical differences of the MCA in patients with aneurysms are more frequent in men. The most common anatomical variation was a trifurcation of the MCA [13]. In our study, no sex differences in the morphometric parameters of the MCA were found. As in our study, Orkadogen investigated ruptured aneurysms and those detected incidentally. Patients with incidentally detected aneurysms constituted 82.8%, while those with ruptured aneurysms constituted 17.2% of the study group [13]. In our study, the proportion was similar: 73.33% and 26.67%, respectively. Both in our study and in that by Orkadogen et al., analyses of vascular examinations mostly included patients with SAH. Sadatomo et al. conducted an anatomical analysis of the MCA division in patients with aneurysms in that area and in participants with non-affected arteries.

Based on three-dimensional DSA and MRA, they evaluated the MCA division in non-affected arteries and in those with aneurysms of the M1 division, as in our study. The study group comprised 62 patients. They focused on the evaluation of the MCA division, measuring the division angles of M2 branches, their thickness and dominance of one branch [12]. We did

not perform such measurements in this study. On the other hand, Sadatomo et al. excluded cases of a MCA trifurcation from their study. They also excluded cases, in which a ruptured aneurysm caused a intracerebral hematoma, which prevented evaluation of the MCA in imaging examination [12].

## Conclusions

The morphometric parameters of the M1 segment of the MCA are not associated with the presence of an aneurysm in the M1 division. The coexistence of the more frequent trifurcation of the MCA and an aneurysm constitutes evidence of greater anatomical variability of this arterial area in cases with a concomitant vascular malformation.

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## Declarations

**Ethics approval and consent to participate:** The experiment was approved by the Bioethics Committee of the Ludwik Rydygier Collegium Medicum in Bydgoszcz (KB 35/2020). The study was a retrospective review of CTA images only without any personal data of patients used. In accordance with the approval of the Bioethics Committee, no written consent was required.

**Consent for publication:** The consent of the Bioethics Committee for the publication of this study was obtained.

**Availability of data and materials:** All relevant data is presented in the article.

**Conflict of interest:** The authors declare that they have no conflict of interest.

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# Difference in demand for analgesic and sedative medication according to the type of catheter ablation for atrial fibrillation

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## Abstract

**Background:** Our aim was to determine if there is a difference in demand for analgesic and sedative medication according to the type of catheter ablation for atrial fibrillation (AF). **Material and methods:** We collected data from protocols of 1144pts, who underwent ablation of AF. We excluded 275pts, at most due to electrocardioversion during the procedure. We divided them into 4 groups: cryoballoon ablation group (CB, n = 101), single-point radiofrequency ablation group (RFth-, n = 541), single-point radiofrequency ablation group with thermocool catheter (RFth+, n = 156) and Multielectrode Pulmonary Vein Ablation Catheter group (PVAC, n = 71). We used fentanyl and midazolam for pain control. The dose was adjusted by the operator, according to patients' request. **Results:** The median dose of fentanyl 0.04 mg (0.00-0.08) and midazolam 1.00 mg (0.00-2.00) in CB group was lower than in other groups ( $p < 0.001$ ). The median dose of fentanyl 0.12 mg (0.08-0.17) was lower in RFth- than in RFth+ group: 0.15 mg (0.1-0.2) ( $p < 0.001$ ). The demand for analgesia was higher when PVAC was used, with median dose of fentanyl 0.15 mg (0.1-0.2) ( $p < 0.0024$ ). **Conclusions:** The demand for analgesic/sedative medication was lower among patients who underwent CB. Among those who underwent RF ablation it was higher in groups with thermocool and multielectrode catheters.

**Keywords:** analgesia · atrial fibrillation · catheter ablation · conscious sedation · cryoballoon

## Citation

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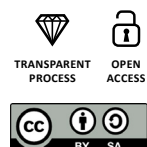
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## Abbreviations

- AF – atrial fibrillation
- PVAC – Multielectrode Pulmonary Vein Ablation Catheter
- RF – radiofrequency
- Th – thermocool
- IQR – interquartile
- SD – standard deviation

## Introduction

Atrial fibrillation (AF) is a common health care problem with a prevalence of over 30 million and increasing incidence worldwide [1]. In comparison with pharmacotherapy alone, catheter ablation of AF reduces all-cause mortality, cardiovascular hospitalizations and recurrences of atrial arrhythmia [2]. Recent meta-analysis of 14 randomized clinical trials shows reduced incidence of AF recurrence, shorter procedural time, a higher rate of phrenic nerve palsy, and a lower rate of pericardial effusion and cardiac tamponade in cryoballoon ablation (CB) in comparison with radiofrequency (RF) ablation [3]. The choice of ablation type is often based on the experience of the operator and specific circumstances. The analgesic medication most used during cardiac procedures is the short-acting fentanyl. In most cases, it is co-administered with midazolam to minimize the patient's anxiety and movements [4]. The aim of our study was to determine the difference in demand for analgesic and sedative medication according to the type of catheter ablation, as this could become a factor to consider while choosing the method of AF ablation.

## Material and methods

### Patients

We collected data from protocols of patients, who underwent catheter ablation of AF. We divided the cohort into four groups depending on the type of catheter ablation including CB, single-point radiofrequency ablation (RFth-), single-point radiofrequency ablation with active cooling of the catheter tip with the Thermocool Irrigated Tip Catheter (RFth+) and the Multielectrode Pulmonary Vein Ablation Catheter (PVAC) which delivers cycled bipolar and unipolar radiofrequency energy through multiple electrodes.

### Anaesthesia

We used midazolam and fentanyl to reduce the patients' anxiety, movements and pain during the procedure.

The doses were adjusted by the operator based on patients' request, responsiveness, and movements as well as objective parameters including heart rate, oxygen saturation and continuous arterial blood pressure.

### Ablation Procedure

We performed the first ablation of AF in our center in 2003. To reduce the learning curve bias, we excluded data from procedures performed between 2003 and 2006. We selected the type of ablation strategy based on the available staff, the anatomy of patients' heart, type of AF and the patients' co-morbidities. We performed the ablation procedure according to standard protocol, described in previous publications and the latest HRS/EHRA/ECAS recommendations [5-8]. Initially, we performed ablation, using the Lasso catheter and 4 mm tip ablation catheter, method described by Haissaguerre et al. Subsequently, we introduced the CARTO anatomical isolation with a thermocool catheter [9]. In 2008 we introduced CB ablation and in 2009 PVAC ablation.

In the single tip RF ablation, we placed the circular mapping catheter and ablation catheter with a 4 mm tip (Mariner – Medtronic) in the left atrium after transseptal puncture or via the persistent foramen ovale, if present. We set the temperature and power of the ablation catheter at 50°C and 30 W respectively. In RFth+ group, the ablation catheter was irrigated with a heparinized saline solution using a thermocool technology to lower the electrode and tissue surface temperature and to reduce the possibility of thrombus formation. The procedure was performed with 3D CARTO system (primary system, since 2010 CARTO 3). We set the temperature and power of the catheter at 48°C and 30-35 W (on the posterior wall 25-30 W). The flow rate was 20-30 ml/min for classic thermocool catheters and 8-14 for THERMOCOOL SMART-TOUCH® Surroundflow (SF) catheters. We used the 12-Fr sheath (Flex-CATH® Steerable Sheath, Abbott) to introduce the multielectrode catheter. The leading 0.0032-inch wire was positioned in all PVs to stabilize and support the circular, decapolar ablation catheter. The RF energy was delivered in a combination of 1 to 5 bipolar channels. The target temperature and maximum powers were 50-60°C and 8-10 W respectively [6]. We used different combinations of bipolar to unipolar proportions depending on the observed effect. We preferred 4:1 proportion on the posterior wall and 2:1 in other regions.

In CB ablation after a single transseptal puncture, we replaced the 8-Fr sheath with a 12-Fr sheath and introduced a 28 mm double-lumen cryoballoon (Arctic Front – Cryocath, Medtronic). We used N<sub>2</sub>O cooling temperature of -35°C to -60°C. During right pulmo-

nary vein isolation the catheter placed in the superior vena cava was used to stimulate the phrenic nerve at a rate of 30/min to prevent phrenic nerve palsy [7].

### Statistical Analysis

We presented all the categorical data as percentages. Continuous variables with non-parametric distribution were presented as median and interquartile ranges (IQR) and those with normal distribution as mean value and standard deviation (SD). We used Kruskal-Wallis equality-of-populations rank test to compare multiple non-parametric variables. We performed Wilcoxon Two-Sample Test to detect difference between two non-parametric variables. We used Spearman's Rank-Order Correlation to assess the relationship between nonparametric variables. All statistical tests were 2-tailed, and a  $p < 0.05$  was considered

significant. The analysis was performed using the SAS 9.4 software (SAS Institute Inc., Cary, 2013).

### Results

The total number of patients included in our database was 1144, from which we excluded 275 patients. 197 patients underwent electrical cardioversion during the procedure, which required general anesthesia with propofol and influenced the doses of fentanyl and midazolam. In 72 cases data were not available. Finally, in 6 cases ablation was discontinued due to tamponade and in one case due to cryoballoon failure (Figure 1).

Finally, 869 patients, were included in our study and divided in following groups based on ablation technique: CB (n = 101, 11.62%), RFth- (n = 541, 62.26%), RFth+ (n = 156, 17.95%), and PVAC (n = 71, 8.17%). The mean age in our patient population was 55 (21-79) and 594 (68%) of patients were male. There was no difference in demographic and anthropomorphic parameters between the groups (Table 1). 160 patients had persistent atrial fibrillation (18.41%). AF ablation was attempted for the first time in 518 cases.

The median dose of fentanyl 0.04 mg (0.00-0.08 mg) and midazolam 1.00 mg (0.00- 2.00 mg) was significantly lower in CB in comparison with other groups ( $p < 0.001$ ). Median dose of fentanyl and midazolam in PVAC was 0.15 mg (0.1-0.2 mg), and 2.00 mg (1-3 mg), RFth+ 0.15 mg (0.1-0.2 mg), and 2 mg (1.5-3 mg), RFth- 0.13 mg (0.08-0.17 mg), and 2.00 mg (1-3 mg) for fentanyl and midazolam respectively (Figures 2 and 3). Midazolam was not required in 37 (37%), fentanyl in 29 (29%), and neither of the drugs in 22 (22%) in group; 5 (7%), 1 (1%), and 1 (1%) in PVAC group; 9 (6%), 2 (1%), and 2 (1%) in RFth+ group, and 54 (10%), 24 (4%), and 22 (4%) in RFth- group respectively.

The median dose of fentanyl 0.12 mg (0.08-0.17 mg) was significantly lower in the RFth- in comparison with the RFth+ group 0.15 mg (0.1-0.2 mg) with  $p < 0.001$ . Patients in PVAC group 0.15 mg (0.1-0.2 mg) required more fentanyl than patients in RFth- group 0.12 mg (0.08-0.17 mg) with  $p < 0.0024$ .

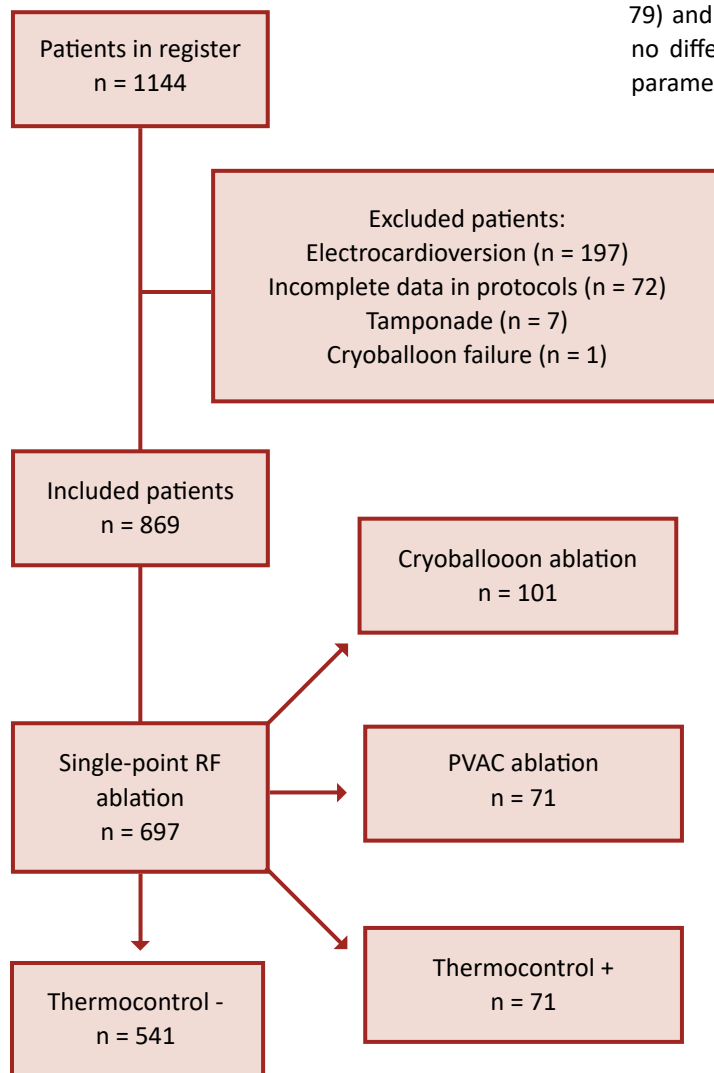
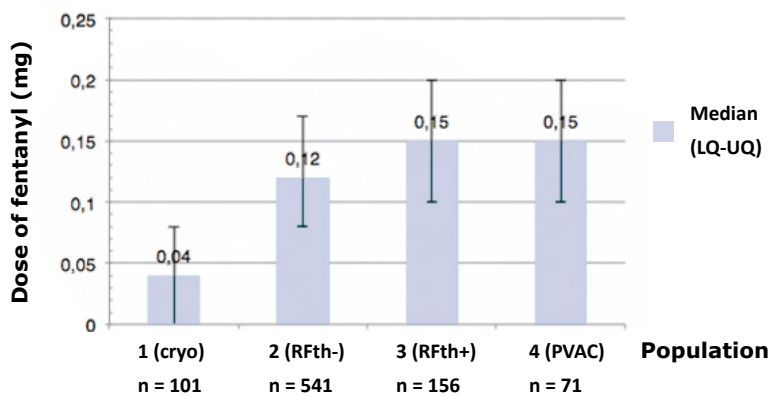


Figure 1. Patient flowchart

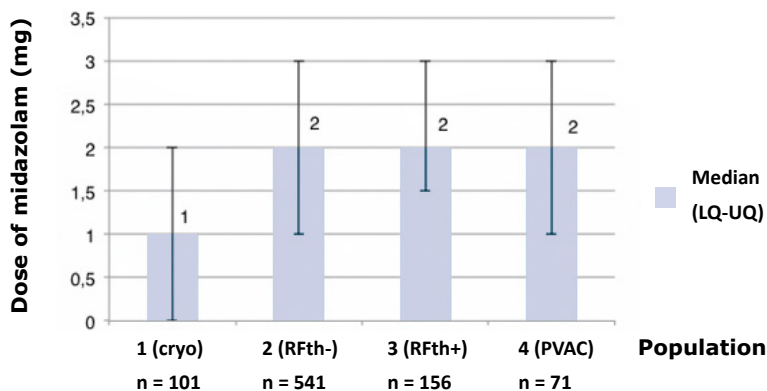
Table 1. Comparison of population basic characteristics

Variable	Cryoballoon (n=101)	RFth- (n=541)	RFth+ (n=156)	PVAC (n=71)	P value
Age	56.6 (26-72)	54.7 (21-79)	56.1(23-74)	55.4 (24-70)	0.1704
Male (%)	72%	68%	67%	66%	0.8206
Weight (kg/m <sup>2</sup> )	92.5 (80-98)	88 (81-95)	89 (73-98)	92.5 (88-102)	0.4259
Height (cm)	175.5 (169-181)	175 (167.5-180)	174 (164-178)	177 (175-182)	0.1730
BMI (m <sup>2</sup> )	29.4 (26.2-31.8)	28.4 (26.8-31.4)	28.5 (26.4-31.8)	29.9 (27.5-33.3)	0.7818



P 1#2 < 0.0001; 1#3 < 0.0001; 1#4 < 0.0001; 2#3 < 0.0001; 2#4 0.0024; 3#4 < 0.75  
 1 – cryoballoon ablation group; 2 – radiofrequency group without thermocool;  
 3 – radiofrequency group with thermocool; 4 – PVAC Group  
 LQ – lower quartile; UQ – upper quartile, SD – standard deviation

Figure 2. Total doses of fentanyl (mg) used during particular ablation procedures



P 1#2 < 0.0001; 1#3 < 0.0001; 1#4 < 0.0002; 2#3 < 0.0084; 2#4 0.4753; 3#4 < 0.31  
 1 – cryoballoon ablation group; 2 – radiofrequency group without thermocool;  
 3 – radiofrequency group with thermocool; 4 – PVAC Group  
 LQ – lower quartile; UQ – upper quartile, SD – standard deviation

Figure 3. Total doses of midazolam (mg) used during particular ablation procedures

Mean (range) for age, percent for sex and median (interquartile range, IQR) for other data.

- 1 – cryoballoon ablation;
- 2 – radiofrequency without thermocool;
- 3 – radiofrequency with thermocool;
- 4 – PVAC – Multielectrode Pulmonary Vein Ablation Catheter

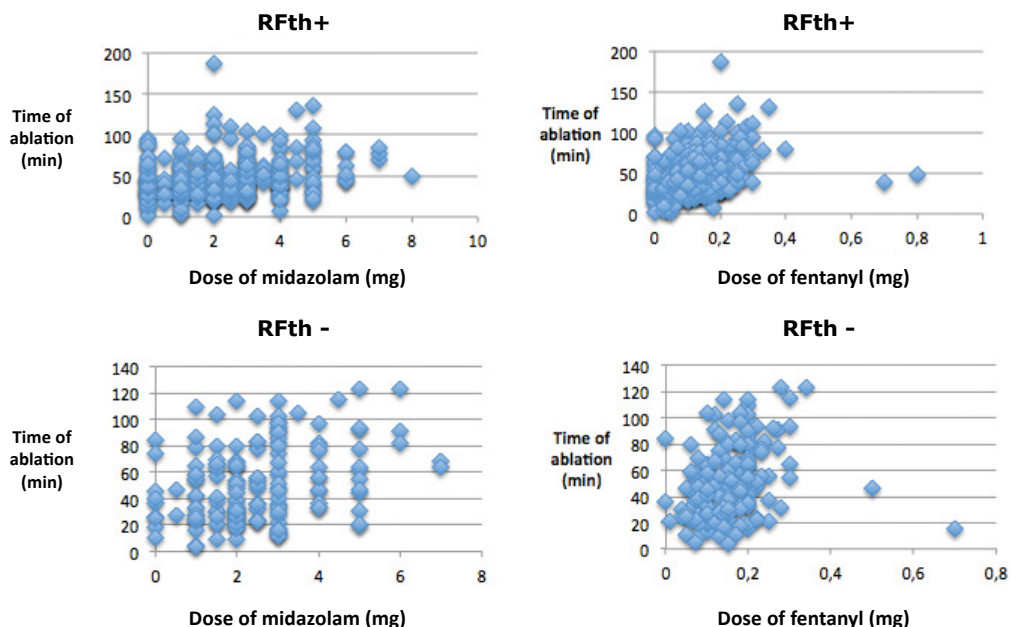
There was no difference in demand for sedation and analgesia in groups with first and those with subsequent ablation procedures with p = 0.37 for both of administered drugs. Time of application correlated with the dose of fentanyl (r = 0.38, p < 0.0001) and midazolam (r = 0.30, p > 0.0002) in RFth+ group and in RFth- group (r = 0.3, p < 0.0001, r = 0.25, p < 0.0001) (Figure 4). There was a trend in correlation for midazolam (p = 0.08) and fentanyl (p < 0.13) in PVAC group. The dose of fentanyl (p < 0.96) and midazolam (p < 0.68) did not correlate with time of application in CB group. The median total application time was longer in cryoballoon ablation 62.00 (49.50-78.00) in comparison to other groups: PVAC 40.70 (32.62-51.97, p < 0.0001), RFth+ 45.59 (26.92-68.84, p < 0.0001), RFth- 41.05

(31.13- 52.83,  $p < 0.0001$ ). There was no statistically significant difference in the application time between RFth+ and RFth- ( $p < 0.2221$ ), RFth+, and PVAC ( $p < 0.3655$ ), RFth- and PVAC ( $p < 0.9823$ ) (Table 2). The median total procedure time was longer in cryoballoon ablation 160.20 min (130.20-187.80) in comparison to PVAC 124.20 min (109.80-154.80) and RFth- 130.20 min (105-160.20) ( $p < 0.0001$ ) and there was no significant difference in comparison with RFth+ group 160.20 min (130.20-195,  $p < 0.3941$ ). The procedure was longer in RFth+ group than in PVAC and in RFth- ( $p < 0.0001$ ). There was no statistically significant difference between RFth- and PVAC ( $p < 0.7342$ ) (Table 2). The median fluoroscopy time was longer in cryoballoon ablation group 19.13 min (14.67-30.29) than in other groups: RFth- 16.00 min (10.20-23.87), RFth+ 12.39 min (8.59-16.88,  $p < 0.0001$ ), and close to statistical significance for PVAC group 17.88 (14.62-21.40,  $p < 0.065$ ) (Table 2).

## Discussion

Administration of benzodiazepines and opioids during cardiac electrophysiological procedures is considered safe mostly due to the broad therapeutic

range and reversal agents [4]. According to Kezershvili et al. administration of intravenous sedation in 9.558 cardiac procedures, was associated with only 9 complications, with 6 of them related to electrophysiological procedures [10]. We found that patients, who underwent CB ablation, required lower doses of fentanyl and midazolam in comparison with RF ablation. In a similar study, Defaye et al. show a lower dose of morphine administered to patients in CB group ( $3 \pm 1.53 \text{ mg/m}^2$ ) in comparison with RF group ( $2.09 \pm 1.02 \text{ mg/m}^2$ ,  $p < 0.01$ ) with no difference in the administered dose of midazolam ( $p < 0.135$ ) [11]. Patients in this study had similar demographic and anthropometric parameters and the lack of significant difference in midazolam dose was likely related to smaller n-size ( $n = 60$ ). In a small randomized trial including 32 patients, Collins et al. found no difference in the dosing of fentanyl and midazolam. However, based on a numeric scale, he described much lower procedural discomfort among patients, who underwent cryoballoon ablation in comparison to RF ablation [12]. Lowe et al. reported increased patient satisfaction with CB ablation in comparison with RF ablation in patients who underwent ablation for supraventricular arrhythmias ( $1.3 \pm 2.2$  vs  $6.1 \pm 3.5$ ,  $p < 0.01$ ) [13]. In a recent analysis of 71 patients, Miśkowiec D et al. show that CB ablation for AF



RFth+ fentanyl  $r = 0.38$ ,  $P < 0.0001$ ; RFth+ midazolam  $r = 0,30$ ,  $P < 0.0002$

RFth- fentanyl  $r = 0.3$ ,  $P < 0.0001$ ; RFth- midazolam  $r = 0,25$ ,  $P < 0.0001$

RFth+ radiofrequency group with thermocool; RFth- radiofrequency without thermocool

Figure 4. Correlation of ablation time with the doses of midazolam and fentanyl used in particular ablation techniques

Table 2. Procedural data

Parameters	CB	RFth-	RFth+	PVAC
Duration of procedure [min]	160.20 (130.20-187.80)	130.20 (105-160.20)	160.20 (130.20-195)	124.20 (109.80-154.80)
Duration of X-ray [min]	19.13 (14.67-30.29)	16.00 (10.20-23.87)	12.39 (8.59-16.88)	17.88 (14.62-21.40)
Ablation time [min]	62.00 (49.50-78.00)	41.05 (31.13-52.83)	45.59 (26.92-68.84)	40.70 (32.62-51.97)

Median (interquartile ranges, IQR), CB – cryoballoon ablation; RFth- – radiofrequency ablation without thermocool; RFth+ – radiofrequency ablation with thermocool; PVAC – Multielectrode Pulmonary Vein Ablation Catheter

is safe and efficacious with only one case of transient phrenic palsy, 4.2% of patients developing a hematoma and an acute procedural success rate of 95.8% [14]. Attanasio et al. examined painful ablation sites in patients sedated with midazolam and propofol and found that 92% of patients, who underwent RF ablation had a  $\geq 1$  pain reaction in comparison with only 13% in CB group [15]. Furthermore, patients in the RF group had more pain reactions ( $3.6 \pm 4.7$ ) than in CB group ( $1.3 \pm 0.6$ ,  $p = 0.005$ ) [15].

The reason for the reduced demand for analgesia and sedation in cryoballoon ablations might be due to different character of lesion in this ablation type. Hypothermia generated in the tissue causes a three-phase response including: freeze/thaw phase, the hemorrhagic-inflammatory phase, and the replacement fibrosis phase [16]. Consequently smaller and partially reversibility lesions caused by the cooling process as well as more stable energy delivery might indicate better preservation of tissue integrity [13, 16].

Recent studies support the use of propofol, administered by either cardiologist or anesthesiologist for unconscious sedation during ablation of AF. Wutzler et al. reported reduced motion of patients during ablation and no complications related to sedation [17]. In a study of 152 patients, Yamaguchi et al show feasibility of total intravenous anesthesia by a cardiologist with support from an anesthesiologist with no major anesthesia-associated complications, 4% of ablation-associated complications and a success rate of 85% at 12 months [18]. Some of the theoretical risks of this approach include the use of muscle relaxants during the general anesthesia, which might prevent muscle

contraction in response to pacing of the phrenic nerve and increase the rate of phrenic nerve palsy. General anesthesia may also delay the recognition of cerebrovascular events as well as decrease alertness of physicians for patients' pain. In a study of 120 cases, Tang et al. reported more hypotension and hypoxia (21.7% vs 6.7%) in the propofol group in comparison with the midazolam and fentanyl group [19]. In a randomized trial Di Biase et al. reported a better success rate of AF ablation under general anesthesia with a higher rate of esophageal injuries [20]. The use of propofol for elective electric cardioversion is a standard of care and because it impacts doses of fentanyl and midazolam administered during ablation we have excluded all of the patients who underwent this procedure from our study.

We noticed longer application time and fluoroscopy time in cryoballoon ablation, which is consistent with the results of Schmidt et al [21]. We found no difference in procedure time, in contrast to Ciconte et al., who found shorter procedure time and radiation exposure with second-generation cryoballoon technique in comparison with RF ablation [22]. We found a positive correlation between application time and doses of midazolam and fentanyl in RFth+ and RFth- groups and no correlation in CB group. We did not adjust our analysis for application time since it would only emphasize our results. Increased dose of fentanyl in RFth+ group could be related to deeper lesion formation of irrigated tip ablation catheter in comparison with standard single-point RF catheter due to higher power, which is reached by lowering the temperature [23-24]. The higher demand for analgesia in PVAC ablation group could be related to higher cumulative energy of electrodes.



## Limitations

Our study has several limitations. We used a standard protocol for the administration of analgesic and sedative medications based on the subjective perception of pain and objective data including patients' motion and vital signs observed by the operator. Yet, some confounding factors including individual variance in perception of pain and biases of the operator could be contributing to the patient's demand for analgesics. At the time our study, there was no literature suggesting any type of ablation to be more painful, which limits the operator bias. Taking into consideration the complex and subjective character of pain, even a prospective study would face limitations e.g. the standardization bias.

Patients receive sedation during ablation, which limits their ability to manage patient controlled analgesia or respond to a VAS scale questionnaire.

## Conclusions

The dose of fentanyl and midazolam was lower among patients who underwent CB in comparison with RF. This suggests that CB is a less painful technique and should be considered in patients at high risk for general anesthesia. Patients in the RFth+ group required higher dose of fentanyl in comparison with RFth-, which likely reflects increased destruction of the tissue during single application.

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# Inflammatory response to a marathon run in amateur athletes

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## Abstract

**Background:** While moderate physical exercise has positive effects on the cardiovascular system, the data regarding intensive endurance sports is biased with studies suggesting that the inflammatory response to strenuous exercise may act proarrhythmogenic. In amateurs, the effects of intensive endurance exercise on the cardiovascular system have not been studied. Analysis of the effects of a marathon on the kinetics of inflammatory biomarkers may bring new insights into this issue. **Material and methods:** We studied the effect of a marathon on the kinetics of inflammatory biomarkers: Endothelin-1 (ET-1), Pentraxin-3 (PTX-3), Neopterin and Interleukin-6 (IL-6) in the population of 35 amateur male marathoners. The study was divided into 3 stages: two weeks prior to the marathon (S1), at the finish line (S2) and two weeks after (S3). Blood analyses for biomarkers were performed at each stage. **Results:** The concentrations of ET-1 ( $3.20 \pm 0.90$  vs.  $1.30 \pm 0.34$  pg/ml,  $p < 0,001$ ), PTX-3 ( $441.09 \pm 295.64$  vs.  $279.99 \pm 125.68$  pg/ml,  $p < 0,001$ ), Neopterin ( $9.97 \pm 2.17$  vs.  $8.36 \pm 2.68$  nmol/l,  $p < 0,05$ ) and IL-6 ( $32.5 \pm 13.90$  vs.  $0.97 \pm 0.77$  pg/ml,  $p < 0,001$ ) were significantly higher at S2 compared to S1. **Conclusions:** Running a marathon causes an acute rise in concentrations of inflammatory biomarkers. Further research is needed on the long-term effects of intensive endurance exercise on the cardiovascular system.

**Keywords:** neopterin · endothelin-1 · pentraxin-3 · marathon · amateur runners

## Citation

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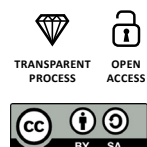
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## Introduction

Statistics reveal a trend of increasing participation in mass endurance sports events, with the runners older and slower than ever before [1], which means that the number of amateur runners has increased. Amateur runners constitute a heterogeneous group in terms of fitness level, training regimen, medical history and cardiovascular risk factors. Moreover, the definition of an “amateur athlete” is not precise. The American Heart Association distinguishes elite, competitive and recreational athletes. The first and the second groups train with high intensity in organized teams with an emphasis on competition and performance, whereas the latter engage in sports activity for pleasure and in their spare time.

Regular exercise reduces the cardiovascular risk and all-cause mortality, with a 20-30% reduction in cardiovascular adverse events compared with patients who have sedentary lifestyle. The current European Society of Cardiology guidelines recommend a minimum of 150 min of exercise of moderate-intensity over 5 days or 75min of vigorous exercise over 3 days per week for a healthy adult [2].

Although the benefits of regular moderate intensity exercise remain indisputable, there is a concern that the long duration high-intensity endurance sports may elicit negative effects on the heart by triggering the structural, functional and electrical remodeling, hence increasing the risk of arrhythmias. One of the postulated mechanisms is the inflammatory response following an intensive endurance exercise [3]. Sorokin et al. in their review showed that endurance-trained athletes are at increased risk of developing atrial fibrillation with the possible mechanisms being increased parasympathetic tone, increased atrial size and increased inflammatory reaction [4]. There are also reports that high-intensity leisure-time physical activity by stimulating the inflammatory reaction may contribute to the development of atherosclerosis in the long run [5].

For over 50 years, the utility of various biomarkers in the diagnosis of cardiovascular diseases was analyzed [6], yet their implications still remain not fully understood. Many novel biomarkers were recently discovered including inflammatory biomarkers such as pentraxin-3 (PTX-3) and neopterin. However, there is a lack of data about amateur athletes as to whether such sport activities are associated with the activation of an inflammatory reaction. The aim of this study was to investigate the effect of running a marathon on the inflammatory response in the group of male amateur runners.

## Material and Methods

The study was carried out on a group of 40 male amateur marathoners, who competed in and finished the 2nd PZU Marathon in Gdańsk, Poland. The participation in the study was voluntary. Enrolment into the study was completed via invitations sent to sports clubs. Each participant signed a written consent form prior to enrolment. The study protocol was approved by Independent Bioethics Committee for Scientific Research at Medical University of Gdańsk (No. NKBBN 104/2016). Information about health and training conditions was gathered via structured interviews. Exclusion criteria were: history of past or chronic illness/es. After the finishing the marathon run, we asked the participants to suspend high-intensity training as well as participation in any upcoming competitions. The characteristics of a study group were described previously [7].

We divided the study into three stages. Blood samples from the cubital vein were collected at each stage. Stage 1 was carried out 2 weeks before the run, Stage 2 directly after finishing the run on the finish line and Stage 3 took place 2 weeks after the marathon. Fasting blood samples at Stage 1 and Stage 3 were collected at the cardiology department. Serum was prepared immediately after collection by centrifugation at 2000 rpm at room temperature for 12 minutes and then stored in  $-80^{\circ}\text{C}$  for the further analysis [7].

Samples from each stage were analyzed in terms of the amount of leukocytes, neutrocytes, lymphocytes, monocytes, eosinophils, basophils, immature granulocytes and the concentration of fibrinogen and creatine kinase. Biochemical parameters were analyzed using Architect c8000 (Abbott). Endothelin-1 (ET-1) concentration was measured using a solid phase sandwich Quantikine ELISA (R&D Systems) with sensitivity of 0.207 pg/ml and detection range from 0.39 to 25 pg/ml. PTX-3 concentration was measured using a solid phase sandwich ELISA Human Pentraxin 3/TSG-14 DuoSet (R&D Systems) with detection range from 218 to 14000 pg/ml. Neopterin concentration was measured using a solid phase competition ELISA (Demeditec Diagnostics) with sensitivity of 0.7 nmol/l and detection range from 1.35 to 111 nmol/l. Interleukin 6 (IL-6) concentration was measured using a solid phase sandwich Quantikine ELISA (R&D Systems) with a sensitivity of 0.7 pg/ml and detection range from 3.1 to 300 pg/ml.

Continuous variables were expressed as means  $\pm$  standard deviation (SD). Before the statistical analyses, Shapiro-Wilk test was used to test the normal distribution of variables. Analysis of variance (ANOVA) for repeated measures was used to test statistical differences between groups of variables. Post-hoc analysis

was performed with a Tukey's test. For the variables analyzed at two stages only, the t-test for dependent variables was used. The data was analyzed using Statistica 12 software (StatSoft). A p value < 0.05 was considered statistically significant [7].

## Results

### Study group

The characteristics of the studied group are presented in Table 1 [7].

### Biochemical analysis

The results of the analysis of white blood cells counts fibrinogen and creatine kinase concentrations are presented in Table 2.

Mean leukocyte count at Stage 1 was 5.8 G/l. At Stage 2 it was 16.5 G/l and it differed significantly from the results at Stage 1 and Stage 3. There was no significant difference between leukocyte count at

**Table 1. Characteristics of the studied group**

Demographics	Amateur runners (N = 35)
Age [years]	39 ± 8
Gender	35 males (100%)
BMI [kg/m <sup>2</sup> ]	25 ± 2
Ethnicity	35 Caucasian (100%)
Smokers/non-smokers	35 non-smokers (100%)
Training intensity	
hours of running/week	6.2 ± 2.3
kilometers run/week	54.5 ± 18.6
Marathon finish time [min]	234 ± 25

**Table 2. Biochemical analysis of blood samples collected 2 weeks before the marathon (S1), at the finish line (S2) and 2 weeks after the marathon (S3)**

Parameter	Laboratory norms	S1	S2	S3	ANOVA	Post-hoc P value		
		Mean ± SD			P value	S1 vs. S2	S2 vs. S3	S1 vs. S3
Leukocytes [G/l]	4.0-10.0	5.8 ± 1.2	16.5 ± 3.5	6.0 ± 1.8	< 0.001	< 0.001	< 0.001	1.0
Neutrocytes [G/l]	2.0-7.0	3.2 ± 0.8	13.9 ± 3.1	3.4 ± 1.5	< 0.001	< 0.001	< 0.001	0.95
Lymphocytes [G/l]	1.0-3.0	1.9 ± 0.5	1.4 ± 0.6	2.1 ± 1.1	< 0.001	0.007	< 0.001	0.67
Monocytes [G/l]	0.2-1.0	0.5 ± 0.2	1.1 ± 0.4	0.6 ± 0.2	< 0.001	< 0.001	< 0.001	1.0
Eosinophils [G/l]	0.02-0.5	0.2 ± 0.1	0.0 ± 0.0	0.2 ± 0.1	< 0.001	< 0.001	< 0.001	0.98
Basophils [G/l]	0.0-0.1	0.0 ± 0.0	0.1 ± 0.0	0.0 ± 0.0	< 0.001	< 0.001	< 0.001	0.92
Immature granulocytes [G/l]	0.00-0.03	0.0 ± 0.0	0.1 ± 0.0	0.0 ± 0.0	< 0.001	< 0.001	< 0.001	0.99
Fibrinogen [g/l]	1.8-3.5	2.7 ± 0.4	3.0 ± 0.5	2.5 ± 0.4	< 0.001	0.014	< 0.001	0.08
Creatine kinase [U/L]	30-200	148 ± 76.3	411 ± 170	208 ± 135	< 0.001	< 0.001	< 0.001	0.09

Stage 1 and Stage 3. The same trend was observed for neutrocytes, lymphocytes, monocytes, eosinophils, basophils and immature granulocytes, as well as for fibrinogen and creatine kinase concentrations. The concentration of creatine kinase at Stage 2 was significantly higher compared to Stage 1 and Stage 3.

### Biomarkers

Table 3 shows the concentrations of the analyzed biomarkers.

The mean concentration of ET-1 was the highest at Stage 2 ( $3.2 \pm 0.9$  pg/ml) and it differed significantly from both Stage 1 and Stage 3. Neopterin showed the same trend. PTX-3 concentrations differed significantly between all the stages, with the highest concentration at Stage 2 and the lowest at Stage 3. The concentration of IL-6 was significantly higher at Stage 2 compared to Stage 1 and exceeded the norm many times (Norm: lower or equal to 1.8 pg/ml). At S3 the mean concentrations of IL-6 were undetectable.

### Discussion

In our study, we found that running a marathon increased the inflammatory response in amateur runners. This was probably due to skeletal muscle damage, as inflammatory biomarkers were normalizing 2 weeks after the run. To our knowledge, this is the first study to demonstrate the impact of a bout of intense exercise on the inflammatory response in male amateur marathoners, assessed on the basis of changes in PTX-3 and neopterin concentrations.

In our study group, increased concentrations of creatine kinase at Stage 2 suggest exercise-induced muscle damage. This was accompanied by a significant increase in concentrations of all the studied biomarkers, compared with Stage 1 and Stage 3. At Stage 2 significant leukocytosis with an increase in all leukocyte-fractions was also observed. Kosowski et al. investigated cardiovascular stress biomarkers in middle-aged non-athlete marathon runners. Blood samples were collected (before, just after and 7 days after the marathon) and analyzed for endothelin-1, troponin I and N-terminal pro B-type natriuretic peptide concentrations. The authors concluded that the marathon was associated with a significant increase in cardiovascular stress biomarkers but the profile of these changes did not suggest irreversible myocardial damage [8].

It has been suggested that completing a marathon has similar physiological sequelae to the acute-phase response: neutrophil leucocytosis, increased creatine kinase activity, a rise in C-reactive protein and fibrinogen levels and an increase in plasma cortisol concentration [9]. On the other hand, significant increases of the creatine kinase concentration and elevation of inflammatory markers have been observed after prolonged cardiopulmonary resuscitation [10] or direct current cardioversion [11].

Endothelin-1, which is released by leukocytes, macrophages and fibroblasts [12], is not only a potent vasoconstrictor of the smooth muscle cells but it also has a pro-inflammatory effect [13, 14]. Its expression is increased in response to cytokines, reactive oxygen species, angiotensin II and thrombin [15]. ET-1 has been shown to stimulate monocytes to produce interleukin-8 (IL-8) and monocyte chemoattractant

**Table 3. Concentrations of cardiac injury and overload biomarkers: 2 weeks before the marathon (S1), at the finish line (S2) and 2 weeks after the marathon (S3)**

Parameter	S1	S2	S3	ANOVA	Post-hoc P value		
	Mean $\pm$ SD			P value	S1 vs. S2	S2 vs. S3	S1 vs. S3
Endothelin-1 [pg/ml]	1.30 $\pm$ 0.34	3.20 $\pm$ 0.90	1.20 $\pm$ 0.26	< 0.001	< 0.001	< 0.001	1.0
Pentraxin-3 [pg/ml]	279.99 $\pm$ 125.68	441.09 $\pm$ 295.64	165.34 $\pm$ 70.79	< 0.001	< 0.001	< 0.001	0.95
Neopterin [nmol/l]	8.36 $\pm$ 2.68	9.97 $\pm$ 2.17	7.82 $\pm$ 1.94	< 0.001	0.007	< 0.001	0.67
IL-6 [pg/ml]	0.97 $\pm$ 0.77	32.5 $\pm$ 13.90	ND	< 0.001	< 0.001	< 0.001	1.0

Interleukin 6 (IL-6), not detectable (ND)

protein-1 (MCP-1)[16], and also acts as a mast cell activator resulting in the release of inflammatory cytokines such as tumor necrosis factor alpha (TNF-alpha) and IL-6 [17]. A study of mice showed that intensive endurance exercise increases the occurrence of atrial fibrillation in a mechanism of inflammation and atrial fibrosis with the involvement of a soluble TNF-alpha signaling pathway [18]. More than a 33-fold increase in the mean concentration of IL-6 at S2 compared to the baseline value is consistent with the observations of Pinho et al. [19] (a group of Ironman race participants) and Schobersberger et al. [15] (participants of an ultramarathon). Intensive physical exercise causes an increase in oxygen consumption and induces oxidative stress due to free radical production, which in turn stimulates cytokine production from various cell types and upregulates the inflammatory cascade [20-21].

Neopterin is a biomarker of the cellular immune response released by activated macrophages and dendritic cells upon activation with gamma-interferon and acts as a modulator and mediator in inflammatory and infectious processes [22]. A significant increase in the post-run concentration of neopterin is consistent with the observations published by Schobersberger et al. [23] and Sprenger et al. [24] who examined well-trained runners after running 20 km in 2 hours. The pentraxins superfamily comprises of short and long pentraxins. PTX-3 is a member of long pentraxin group and is believed to play a regulatory role in innate immunity, sterile and non-sterile inflammation, tissue repair, and cancer [25]. PTX-3 is an acute phase protein, produced locally by monocytes, endothelial cells and fibroblasts in response to pro-inflammatory signals like interleukin 1 beta or TNF alpha. The major source of PTX-3 are vascular endothelial cells [26]. Increased plasma levels of PTX-3 were found in patients with acute myocardial infarction, heart failure, atherosclerosis and after cardiac arrest. Salio et al. indicated that PTX-3 plays a protective role against myocardial ischemia in their study on a mouse model of myocardial infarction. PTX3-deficient mice showed exacerbated cardiac damage with greater no-reflow area, increased neutrophil aggregation, decreased number of capillaries and increased number of apoptotic cardiomyocytes [27].

The influence of intense endurance exercise on plasma concentrations of PTX-3 in humans has not yet been extensively studied. Miyaki et al. measured plasma PTX-3 concentrations in young male endurance runners and sedentary controls and found higher concentrations in the first group as a result of a postulated training-induced cardioprotection [28]. In contrast, Suzuki et al. showed a hypertrophic response and left ventricular systolic dysfunction as a consequence of increased afterload in a mouse model of transverse

aortic constriction. Transverse aortic constriction (TAC) is one of the most common surgical models of pressure overload-induced cardiac hypertrophy and heart failure. In the TAC model, a permanent constriction is placed around the transverse aorta, limiting left ventricular outflow and thereby creating pressure overload in the left ventricle. Echocardiography indicated that PTX-3 overexpression promoted tissue remodeling, left ventricular systolic dysfunction and myocardial fibrosis, while these responses were suppressed in PTX3-deficient mice [29].

Two weeks after the marathon, white blood cell counts, creatine kinase and fibrinogen levels, as well as ET-1 and neopterin concentrations returned to baseline, and PTX-3 level fell below the Stage 1 value. The concentration of IL-6 at S3 was undetectable. We explain this by the lack of intensive training or participation in any sporting events between S2 and S3 compared to the pre-marathon preparation period according to the study protocol. This trend suggests that a marathon run does not cause a prolonged inflammatory response.

On the other hand, numerous studies have reported that health benefits from extreme forms of physical activity such as ultra-endurance sports, are attenuated in an inverted J-curve dose-response model, with increased risk of adverse ventricular remodeling, fibrosis and arrhythmias. La Gerche emphasizes the phenomenon of cardiac overtraining in the potential mechanism of arrhythmogenesis in endurance athletes, in which a chronic adverse cardiac remodeling depicts an imbalance between the exercise-induced injury and an insufficient period of regeneration [30-31].

Kwaśniewska et al. observed the population of physically active men for over 25 years and reported that the most favourable effect against atherosclerosis was associated with energy expenditure between 2050 and 3840 kcal/week. Regular and very high physical activity was accompanied by the deterioration of the examined indicators of atherosclerosis (increased calcification of the coronary arteries and intima-media thickness). The authors postulated that intense physical activity in free time may be associated with the intensification of low-grade inflammation and thus has a pro-atherosclerotic effect [5].

Currently, there is little data available regarding the long-term effects of intense endurance activity on the inflammatory response. However, a prospective, long-term study of at least 130 marathon runners is currently underway by Schoenfeld et al. [32] and may provide important information on this topic. The aim of this study is to assess the physiological response of the cardiovascular system and potential abnormalities after 10 years of long-term vigorous endurance exercise.

The main limitation of our study is the lack of a long-time observation. The biomarker kinetics were not monitored in the time interval between S2 and S3. Secondly, the study was conducted on a relatively small group of male participants only. Finally, we did not include echocardiographic imaging, however this was not the purpose of this part of the study.

## Conclusions

Our study appears to be the first to investigate the changes in PTX-3 and neopterin concentrations in amateur athletes. We demonstrated that male amateur marathon runners follow similar trends in

inflammation biomarker kinetics as in Ironmen, ultramarathoners and elite athletes. Intensive endurance exercise causes an acute transient rise in the concentrations of inflammatory biomarkers in amateur marathon runners together with leukocytosis and increased creatine kinase. In the short-term follow-up, the concentrations of all studied parameters normalized, suggesting that the inflammatory cascade is mainly induced by exercise-induced muscular damage. Further research is needed to investigate the long-term effects of recurrent exercise-induced inflammation on the cardiovascular system.

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# Rhinological factors predisposing to headaches: our experience

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## Abstract

**Background:** This study aimed to present the correlation between headaches and anatomical changes within the nasal cavity and paranasal sinuses. **Material and methods:** This study includes a literature search and our observations of 24 patients regarding the correlation of headaches with the nasal cavity and paranasal sinus anatomy. **Results:** According to the literature, about 12% of the population suffer from chronic/recurrent headaches. In about 60% of patients, the headache was accompanied by different types of the anatomical structure of the nasal cavity and paranasal sinuses, which may predispose to frequent recurrence or poor control of pain. We observed 2 groups of patients. Group I consisted of 18 patients, who in according to the according to ICHD-3 classification were diagnosed with a headache or facial pain attributed to disorder of the head or neck. Group II included 6 patients with a non-diagnosed recurrent headache, who after septoplasty reported either complete headache resolution or a significantly reduced frequency of headache attacks and duration. Statistically significant differences in the surgical treatment outcomes between patients before and after therapy were observed ( $p = 0,00001$ ). **Conclusion:** Several anatomical changes can predispose or cause recurrent headaches. In most cases, they require surgical intervention.

**Keywords:** nasal septum deviation · Haller cells · concha bullosa · nasal turbinate hypertrophy · headaches · nasal sinus · treatment.

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## Introduction

Recurrent headache often causes the patient to consult an otolaryngologist. In addition to headache, these patients have various types and degrees of discomfort

in the nose and the paranasal sinuses (e.g. feeling of blockage/pressure in the nasal cavity, impaired nasal patency, chronic runny nose) [1-3]. Patients describe the headache as a pain in the paranasal sinuses region (frontal, maxillary) or the face, pain in the maxilla or jaw,

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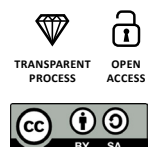
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pain in the temporal area or auricle. However, when these symptoms are accompanied by gastrointestinal complaints or sensory hypersensitivity (to light or noise), patients may suffer from primary headaches such as migraine and trigeminal neuralgia. According to the International Classification of Headache Disorders 3rd edition (ICHD-3), this type of headache is classified as headache or facial pain attributed to disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cervical structure (part 11) [4].

In this review, we would like to discuss the otolaryngologist's role in identifying the causes and the treatment of recurrent headaches. We also reviewed the latest evidence-based diagnostic criteria and treatment methods, both new and traditional, concerning otolaryngological practice.

## Material and methods

The first part of our work was to find current literature about chronic/recurrent headaches. Changes in the anatomy of the nasal cavity and paranasal sinuses may be the mechanism that induces them. We used the MEDLINE, PubMed and Scopus databases to search for English-language literature published in the years 2000-2020. The search keywords were "migraine," "headache," "nasal septum deviation," "concha bullosa," "septal bullosa," "Haller cell" and synonyms of these words.

The second part of the study presents our observations in the period 2014-2020. We studied the correlation between headache occurrence and anatomical changes in the nasal cavity and paranasal sinuses. We analyzed the medical data of 18 patients with chronic headaches (Group I). A neurologist diagnosed these headaches as a headache or facial pain attributed to a disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cervical structure (ICHD-3, part 11). The second group (Group II) consisted of patients (n = 6) with impaired nasal patency who qualified for nasal septum plastic surgery. In the postoperative period, these patients reported a noticeable reduction in the frequency of headaches. However, in the pre-operative period during the nasal septum surgery qualification, they did not mention these complaints.

To assess the headache severity level, we used the generally accepted visual analogue scale (VAS) [5]. In patients from group II, pre-surgery pain assessment was performed retrospectively based on the patient's information after surgery. According to VAS before and after treatment, numerical characteristics and percentage rates were determined to evaluate patients' headache severity level, both in groups I and II (Table 1). The significance of differences between the treatment outcomes was determined using the Mann-Whitney U test.

**Table 1. Symptoms of migraine headaches caused by anatomical variations of the nasal cavity and paranasal sinuses**

Group (n)	Sex (n)	VAS pre-op mean (SD)	VAS 1 month post-op mean (SD)	VAS 6 months post-op mean (SD)
I	F	7	6	5
I	F	8	7	5
I	F	8	7	5
I	F	7	7	4
I	F	8	7	6
I	F	8	7	6
I	F	8	7	5
I	F	7	7	4
I	F	7	4	0
I	F	8	7	5
I	F	8	7	5
I	F	8	8	5
I	F	8	7	5
I	F	8	7	6
I	F	7	6	4
I	M	7	6	0
I	M	8	6	4
I	M	8	7	3
II	F	4	3	2
II	F	4	3	2
II	F	4	3	2
II	F	4	3	2
II	M	4	3	0
II	M	5	4	2

F – female, M – male, VAS – visual analogue scale

## Results

### Review of literature

Seventy-five full-text articles were found and analyzed. According to the literature, about 12% of the population, including 18% women and 6% men, suffer from chronic headaches [6-8]. In a large proportion of them (about 60%), a headache was accompanied by different types of the anatomical structure of the nasal cavity and the paranasal sinuses, which may predispose to frequent recurrences or poor pain control [2, 9-10]. Understanding this relationship and using various therapeutic methods to remove these anomalies is very rewarding for both the patient and the surgeon. It is crucial to obtain detailed history about headaches, to ask the patients the right questions before the planned surgery on the nose and paranasal sinuses. Many patients did not report this because they do not see the relationship between the nasal sinus problem and headaches.

The correct diagnosis of chronic/recurrent headaches is essential. The differential diagnosis of headache should include meningitis, and cerebral meningitis, vascular disorders of the central nervous system, proliferative disorders (primary and secondary) and inflammatory diseases of the head and neck. The consequences of an incorrect diagnosis can be catastrophic. On the other hand, some patients may experience headaches associated with using (often misusing) medications (rebound headaches). In this group of patients, surgical treatment of concomitant rhinological changes did not resolve or reduce the level of complaints [3, 11-12]. The ad-hoc pharmacological control of chronic headaches usually is sufficient. The lack of complementary/adjunctive rhinological therapy may lead to frequent recurrences of the headache after discontinuing the medication [13-14]. Guyuron et al showed that the operation gave permanent results with limited or often discontinuation therapy [2].

### Symptoms

In patients with chronic headaches and predisposing factors in the nasal cavity and sinuses, the pain is often induced by a change in weather and usually begins behind the eyes [11, 15]. The patient often reports waking at night up or in the morning with a headache. These symptoms may be accompanied by a runny nose or stuffy nose, usually one-sided. The recurrent headache can also be associated with menstruation because the nasal turbinates' volume depends on estrogen concentration [11]. Pain is usually described as "exploding" and may begin with deeper head structures, later radiating to the periphery (Table 2) [9-11].

Table 2. Patient demographic characteristics and results of surgical treatment

• The pain starts behind the eye.
• Weather changes may cause migraine headaches.
• The patient wakes up in the middle of the night or in the morning because of a headache.
• Rhinitis/nasal obstruction on the affected side.
• The pain is described as exploding.

The otolaryngological examination of the nasal cavity most often reveals a "C" shaped nasal septum deviation. This particular anatomy means that the nasal septum is in direct contact with the lateral wall of the nasal cavity or nasal turbinate, thus causing mucosal edema (or hypertrophy) and chronic headaches. These patients often have a reduction in headaches after using nasal decongestants (e.g. xylometazoline, oxymetazoline, phenylephrine, pseudoephedrine) [3, 8, 16]. Other anatomical factors predisposing to migraine headaches can be detected only in imaging.

### Imaging

The best imaging technique for identifying anatomical changes is a non-contrast computer tomography (CT) scan (Fig. 1). Particular attention should be paid to the nasal septum, particularly its bony segment (often invisible on rhinoscopic examination). Usually, these images show a significant deflection of the septum (or spur) penetrating the lower and/or middle nasal turbinate (Fig. 2B) and even reaching the nasal cavity's lateral wall. CT scans may also reveal concha bullosa (Fig. 2A), paradoxical curling of the middle nasal turbinate (Fig. 3A), septa bullosa (Fig. 3B), or Haller cell (Fig. 3C) [3, 10, 17].

### Treatment

Patients with nasal and nasal sinus anomalies who were examined by a neurologist are good candidates for nasal and sinus surgery. A neurological examination revealed at least two headaches per month, which are so severe that they require prescription drugs and significantly change the patient's quality of life [9, 17-18]. According to the literature, using functional sinus endoscopic surgery (FESS) in the treatment

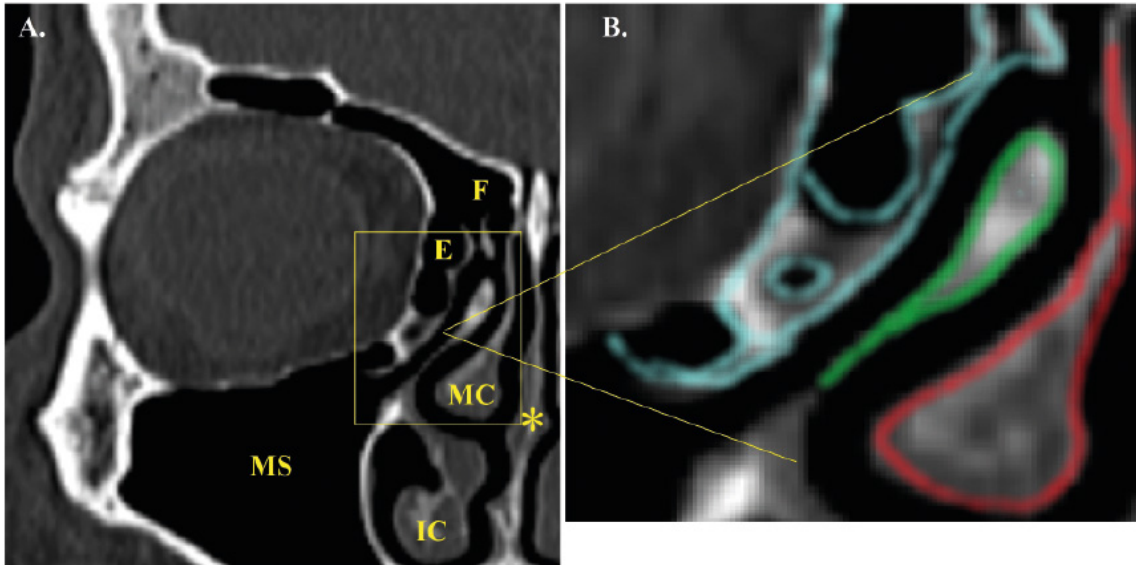


Figure 1. Computed tomography. (A) Image of normal anatomical structures of the nose and paranasal sinuses. The nasal septum is straight. The ostiomeatal complex and the paranasal sinuses are patent. Normal pneumatization of the paranasal sinuses. Nasal turbinates are not enlarged. (B) Image of a normal right ostiomeatal complex (blue – ethmoid sinus cells; green – uncinate process of ethmoid bone; red – middle nasal turbinate). MS – maxillary sinus; E – ethmoid sinus; F – frontal sinus; MC – middle concha; IC – inferior concha; \* – nasal septum.

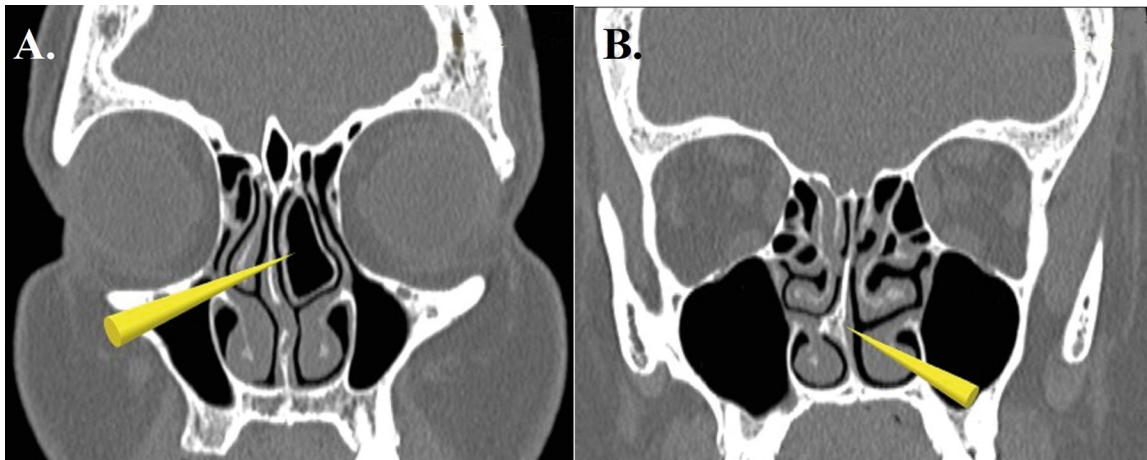


Figure 2. Computed tomography. (A) Concha bullosa – the air cell forms the shaft of the nasal turbinate. (B) The nasal septum spike touches the medial surface of the lower right nasal turbinate.

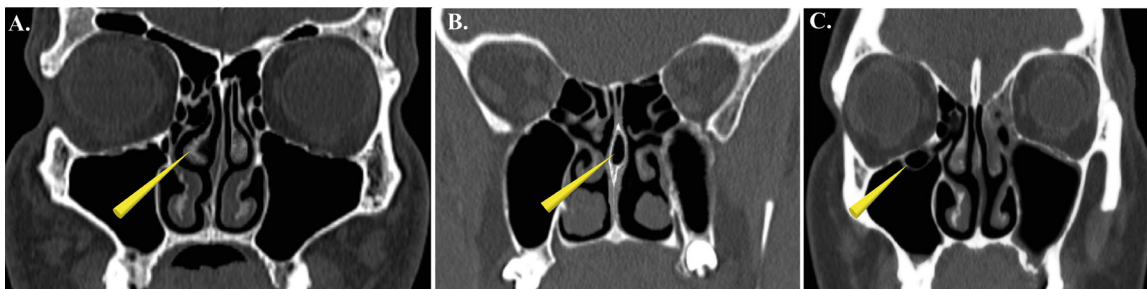


Figure 3. Computed tomography. (A) The hook-shaped middle nasal turbinate on the right side and (B) the septa bullosa. The nasal septum contains an air cell in the posterior 1/3 of its length. (C) The right maxillary sinus contains a Haller cell located near the lower-medial orbital wall.

of patients initially qualified for conchoplasty and/or septoplasty to eliminate migraine-related factors can make surgery results more satisfactory. Under these conditions, compliance with the criterion of the minimum frequency of headaches is not critical [2, 17].

Patients can still use the medication if they still have headache recurrence (botulinum toxin A injection into masseter muscle) [19]. The presence of these symptoms in the early postoperative period, in which we often observe edematous changes in the nose, should not worry either the patient or the surgeon. Headache regression or reduction may take up to 3-6 months. However, many patients experience positive effects soon after the surgery and consider this surgery very beneficial [2, 12, 14, 18, 20].

### Our experience

In 2014-2020, we observed 18 patients with a chronic headache diagnosed by a neurologist (Group I) (Table 3). Before surgery in this group, the headache attack duration was 4-48 hours (mean 14 hours). Whereas after septoplasty, these patients reported either complete resolution of headaches or a significant reduction of the frequency and/or duration of the headache attacks.

In group I before nasal septum surgery, 4 patients (22%) suffered from recurrent headache experienced  $\geq 4$  strong attacks per month, 8 (44%) had 1-4 strong attacks/month, and 6 (34%) had a  $\leq 1$  severe attack in a month. In the postoperative period, the frequency of attacks decreased: 2 patients (11%) suffering from the recurrent headache had  $\geq 4$  strong attacks per month, 5 (27%) had 1-4 strong attacks/month, and 9 (51%) had a  $\leq 1$  strong attack per month. In 2 patients (11%), recurrence of headaches resolved entirely (Table 4).

We also observed a group of patients ( $n = 6$ ) with impaired nasal patency (Group II) who reported a noticeable reduction in the frequency of the headache attack in the postoperative period. Although in the pre-operative period (during the qualification for surgery) they did not report a recurrent headache because they thought it had no cause-and-effect relationship (Table 2).

The probability value (p-value) analysis was made only for the group of women in Group I ( $p < 0,00001$ ) because it is the only group in our patient sample that was large enough to statistically analyze their results (Table 2).

## Discussion

The available literature contains information that confirms the correlation between anatomical changes

Table 3. The incidence of migraine headaches in patients in Group I applied before and after surgery

Group (n)	Sex (n)	Age Min-Max (mean; SD)	Partial improvement	Complete resolution	VAS pre-op mean (SD)	VAS 1 month post-op mean (SD)	VAS 6 months post-op mean (SD)	P < 0,05
I (18)	F (15)	24-52 (37,3; 8,8)	14	1	7,7 (0,85)	6,75 (0,86)	4,7 (1,4)	$p < 0,00001$
	M (3)	27-39 (33; 8,5)	2	1	7,6 (0,78)	6,5 (0,7)	2,3 (2,1)	undefined
II (6)	F (4)	31-45 (37,3; 6,1)	4	0	4,0 (0,8)	3,0 (0,8)	2,0 (0,8)	undefined
	M (2)	29-34 (31,5; 3,5)	1	1	4,5 (0,7)	3,5 (0,7)	1,0 (1,4)	undefined

F – female, M – male, VAS – visual analogue scale

**Table 4.** The incidence of migraine headaches in patients in Group I applied before and after surgery

Group (n)	≥ 4 severe pain attacks in a month	1-4 severe pain attacks in a month	≤ 1 severe pain attacks in a month	No complaints
<b>Pre-operative period</b>	22% (n = 4)	44% (n = 8)	34% (n = 6)	0
<b>Post-operative period</b>	11% (n = 2)	27% (n = 5)	51% (n = 9)	11% (n = 2)

in the nasal cavity and the frequency of headache attacks [1, 11, 18]. The groups of patients in whom surgery of the nasal septum, concha bullosa, septa bullosa, or Haller's cells led to decreased headaches, and the frequency of its attacks were described. Diagnosis and differentiation of headaches are an indispensable part of treating a patient with chronic headaches. Physicians of different specialties should participate in this process because a multi-disciplinary treatment approach can lead to the positive outcomes. CT of the nose and paranasal sinuses is very helpful and is the gold standard in detecting anatomical factors predisposing to a headache's intensification.

Our study provided similar results and indicated improvement in patients' quality of life after nasal surgery. According to our observation, headaches may appear/worse in patients with impaired nasal patency. Often, patients do not report these complaints during the qualification for surgery of the nose and paranasal sinuses because they are not aware their headache and a nasal or nasal sinus problem are related. Therefore, before surgery it seems crucial to ask these patients questions about headaches. Analyzing the treatment results of our patients in groups I and II, we observed that the female patients with nasal septal deformation reported a significant improvement there headache condition after septoplasty. Our study is limited because it covered a small group of patients with a chronic headache associated with the nasal septum deformation. Furthermore, our study did not include patients with the concha bullosa, the septa bullosa, and Haller cells.

## Conclusions

Approximately 60% of the recurrent headaches were accompanied by different types of the anatomical structure of the nasal cavity and paranasal sinuses, which may predispose to frequent recurrence or poor control of pain. The most common pathology diagno-

sed in the nasal cavity predisposing to a recurrence of a headache is a nasal septum deformation and the concha bullosa. The nasal septum most often has contact with the nasal turbinate (middle, lower) or even the nasal cavity's lateral wall. A chronic headache that originates in the nasal cavity and sinuses (usually located behind the eyes) is sensitive to hormonal changes in the body and fluctuations in atmospheric pressure. It occurs more often in the morning and/or can wake up the patient at night. It is often associated with a running nose and has an exploding nature. CT images allow us to visualize the nasal septum's point of contact with the nasal cavity's lateral wall, recognize the concha bullosa, the septa bullosa, and Haller cells in the maxillary sinus. CT scan allows visualizing various stages of the inflammation and the cancerous lesions within the paranasal sinuses. Surgical treatment includes septoplasty, conchoplasty, decompression of the concha bullosa, the septa bullosa, or Haller cells.

## Declarations

**Conflicts of interest:** The authors certify no conflict of interest with any financial organization regarding the material discussed in this manuscript.

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**Ethical approval:** Ethical approval was not necessary for the preparation of this article.

## Authors' contributions:

**Dmitry Tretiakov:** literature search, study design, data analysis, data interpretation, writing, critically revised manuscript, gave final approval.

**Andrzej Skorek:** contributed to the study concept, design and data acquisition, critically revised manuscript, gave final approval.

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# The effectiveness of screening for major cardiovascular risk factors in the population of small towns in Poland

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## Abstract

**Background:** Screening represents an important tool to improve detection of cardiovascular risk factors. Uniform standards for screening programs and for evaluation of their effectiveness are still lacking. **Material and methods:** The results of the Polish 400 Cities Project (P400CP) were analyzed by age and gender, and with regard to the prevalence and awareness of cardiovascular risk factors. The P400CP population were volunteers reporting for screening tests in small towns, and a representative sample was used as control. **Results:** Mean age in the screening group was 10 years more than in the representative sample. Two thirds of participants were women. First-time diagnosis rates for elevated arterial blood pressure, hyperglycemia and hypercholesterolemia in the screening were 28%, 15% and 51%, respectively. Almost 40% of participants reported previously diagnosed hypertension (vs. 25% of the control sample), 7% vs 4% reported diabetes and 16% vs 9% - hypercholesterolemia. Smokers represented 16.5% of participants (36% of the control sample). **Conclusions:** "Open" screening programs fail in targeting young adults, especially males, and people reporting for screening are often already diagnosed with arterial hypertension and/or diabetes. Despite these limitations, "open" screening is effective in detecting undiagnosed cases of hypercholesterolemia. Non-smokers report for screening tests more often.

**Keywords:** cardiovascular diseases · risk factors · screening

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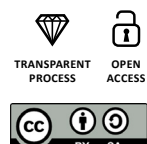
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## Introduction

Over the past dozen years or so, a decrease in cardiovascular mortality was recorded in Poland. However, cardiovascular diseases still remain the main cause of mortality, including premature mortality, especially among males [1-4]. The results of epidemiology studies indicate several concurrent reasons for this situation: wide prevalence and low detection rates of cardiovascular risk factors and also a disparity between highly-urbanized regions and small-town or rural communities in Poland [5-6]. Therefore, regional and/or national prevention programs have been launched, with screening for cardiovascular risk factors as their main component [7-10]. Polish recommendations (based to a large extent on European guidelines) define criteria such as scope, frequency and target group, but they do not determine all the aspects of screening programs [11-13]. In 2003-2008, under the National POLKARD Program, the Polish 400 Cities Project (P400CP) was carried out, including a screening study [9, 14].

The objective of this article is to provide an assessment to what extent screening programs targeting adult residents of small towns in Poland may be effective in improving the detection of cardiovascular risk factors. To attain this objective, the results of the P400CP were analyzed, including the age and gender structure as well as the prevalence and awareness of selected cardiovascular risk factors. These analyses were carried out both for the population of volunteers reporting for screening tests and for the control sample (a sample representative for the population of small towns).

## Methods

### Design and execution of the screening study

The P400CP activities were carried out in 319 towns with population below 8000 residents. The project was preceded by an extensive information campaign. Because of the project design (including extensive educational activities and a promotional campaign), and because Poland is lacking an established standard concerning the manner in which people are recruited for screening, a decision was made to take an "open" approach, whereby any adult visiting a medical center could volunteer to participate in screening. The information campaign was based on articles published in the press and online (town council websites), broadcasts on local radio and television, posters and leaflets [9, 14]. Moreover, every household received informa-

tion in the mail [9, 14]. The materials promoting the program emphasized that screening was targeted to those who had not been diagnosed with the disorders before, and the campaign carried a message about men being the group specifically at risk of prematurely developing cardiovascular conditions. Consequently, men should take particular care to have any risk factors detected early.

The screening took place at established medical centers/local outpatient clinics and was carried out by trained nurses. Over five consecutive days the following tests were performed: a questionnaire interview, anthropometric measurements, two arterial blood pressure readings and strip tests for blood glucose and blood cholesterol. In the afternoons, additional blood pressure readings were taken from those with newly detected elevated values.

### The representative survey

The sample in the representative survey included 1278 men and women, aged 19-75, who lived in 85 towns randomly selected out of the pool of 319 towns included in the P400CP screening project. In order to ensure a representative group of subjects, both male and female, within the age range of 19-75 years, a two-tiered sample selection process was applied. Stratified and proportional sampling procedure was used. Territorial layers in all the 16 provinces (województwa) were created, where two classes of towns were specified: towns below 4000 residents and towns with 4000-8000 residents. Each territorial layer was then divided into demographic strata – four age categories for women and men aged 19-30, 31-45, 46-60, and 61-75 years. The number of interviews carried out in each demographic stratum was proportional to the size of the population represented by that stratum in its territorial layer. Individual respondents were drawn by the Ministry of Internal Affairs and Administration. The sampling frame was the central PESEL database (National Electronic System of Population Records).

The representative survey was carried out before the start of the information campaign for the project. Blood pressure readings were taken in a manner identical to that used later in the screening. Blood pressure was measured during two separate visits. The results were analyzed using the outcomes of two readings taken during the first visit, the same as in the screening. In the questionnaire interview, responses to a specific group of questions provided the data for analysis regarding risk factor awareness. No cholesterol or blood glucose readings were taken in the representative survey (according to the original study design assumptions for the Polish 400 Cities Project).

Statistical analyses were produced using the SAS System for Windows Release 8.02. Simple associations were assessed with frequency tables and Pearson's chi-squared tests for two independent proportions. Means and medians were calculated to summarize continuous effects and were compared by t-tests.

## Results

### Age and gender structure

In total, 92385 people reported for the screening tests (61318 female and 31067 male subjects). Of those screened, 7.3% were people older than 75. This means a group of 6,754 people (4748 women and 2006 men) who, according to the study desi-

gn, were not included in further analyses since they exceeded the upper age limit of the representative survey. The representative survey included in total 1278 subjects (710 women and 568 men). Mean age of subjects in the screening study was 55.3 (SD 12.1), vs. 44.4 (SD 15.7), in the representative survey ( $p < 0,01$ ). Women accounted for 66.1% of screening study participants, vs. 55.3% in the representative sample. Tables 1 and 2 show the age and gender structure for the representative sample and for the group of screening test participants.

The largest group among the volunteers in the P400CP screening were women aged 46-60 (26.7% of all participants), followed by women aged 61-75 (23.1%). The smallest volunteer group were men aged 19-30 (1.1%). Men aged 31-45 accounted for 5.6% of volunteers. Percentages of the screening

**Table 1. Age and gender structure of the sample in the representative survey, number of subjects; (figures in brackets indicate percentages of men and women in each age group)**

Age group (years)	women	men	total women and men
<b>19-30</b>	157 (52.1)	144 (47.9)	<b>301</b>
<b>31-45</b>	209 (55.4)	168 (44.6)	<b>377</b>
<b>46-60</b>	203 (55.9)	160 (44.1)	<b>363</b>
<b>61-75</b>	141 (59.4)	96 (40.6)	<b>237</b>

**Table 2. Age and gender structure of volunteers in the screening study, number of subjects; (figures in brackets indicate percentages of men and women in each age group)**

Age group (years)	women	men	total women and men
<b>19-30</b>	1,928 (65.0)	1,038 (35.0)	<b>2,966</b>
<b>31-45</b>	8,908 (62.9)	5,254 (37.1)	<b>14,162</b>
<b>46-60</b>	24,394 (65.8)	12,680 (34.2)	<b>37,074</b>
<b>61-75</b>	21,340 (67.9)	10,089 (32.1)	<b>31,429</b>

study participants in all the groups defined by age and gender differed significantly from those obtained in the representative sample (Table 3).

### Awareness of arterial hypertension, diabetes and hypercholesterolemia

Of the participants in the screening study 39.6% declared previously diagnosed hypertension, vs. 24.8% of respondents in the representative survey ( $p < 0.001$ ). Over 7% of screening study participants declared previously diagnosed diabetes, compared to ~4% in the representative survey, ( $p < 0.001$ ). Whereas 16.3% of screening test participants had been already diagnosed with hypercholesterolemia (19% in the representative survey, not statistically significant). Table 4 shows the data split by gender.

The analysis of the awareness of existing risk factors by age groups (19-30, 31-45, 46-60 and 61-75) did not reveal any statistically significant differences between the population of volunteers in the screening and the control sample. This suggests that higher awareness of existing (already diagnosed) hypertension, diabetes and hypercholesterolemia may be linked to the fact that the age distribution in the group of volunteers was generally skewed towards the older age groups.

Prevalence of newly detected conditions of elevated blood pressure, hyperglycemia and hypercholesterolemia.

In the screening study elevated blood pressure at the first visit ( $\geq 140/90$  mmHg) was detected in over 28% of the volunteers who did not declare an earlier diagnosis of hypertension. Whereas in the representative sample previously undiagnosed elevated blood

pressure was reported in 25.3%. Two-thirds of the volunteers in the screening study who were diagnosed with raised blood pressure for the first time in their life reported for the second visit (control visit) in order to confirm the hypertension diagnosis. Hyperglycemia ( $\geq 100$ mg%) was detected in over 15% of screening study participants who had not been earlier diagnosed with diabetes.

**Table 3. Structure of participants, split by age and gender (in percentages)**

Age group	Screening study		Representative sample	
	women	men	women	men
<b>19-30</b>	2.1	1.1	12.1*	11.2*
<b>31-45</b>	9.6	5.6	16.3*	13.1*
<b>46-60</b>	26.7	13.7	15.7*	12.4*
<b>61-75</b>	23.1	10.8	10.9*	7.5*

\* $p < 0.05$  vs. volunteers in the screening study

**Table 4. Awareness of existing (already diagnosed) risk factors in the surveyed groups (data in percentages)**

age		women		men	
		volunteers (screening)	representative sample	volunteers (screening)	representative sample
<b>19-75</b>	<b>Already diagnosed with arterial hypertension</b>	42.3	26.7*	34.5	23.0*
	<b>Already diagnosed with diabetes</b>	7.1	4.6*	7.4	3.1*
	<b>Already diagnosed with hypercholesterolemia</b>	18.1	22.7*	12.9	14.7

\* $p < 0.05$  vs. volunteers in the screening study

Table 5 shows the prevalence of newly-diagnosed carbohydrate metabolism disorders in the group of screening study participants. An increased level of cholesterol ( $\geq 190$  mg/dl) was detected in over 51% of screening study participants unaware of the condition. Data on the prevalence of newly detected risk factors, split by gender, are shown in Table 5.

### Prevalence of cigarette smoking

36% of respondents in the representative sample were smokers, compared to 16.5% in the screening study population ( $p < 0.05$ ). The statistically significant difference exists for men and women alike, and it is also valid across all age groups (Table 6).

## Discussion

Many prevention programs targeting cardiovascular diseases were carried out in Poland over a period of the past decade, but their principal component (and quite often the only one) tended to be a screening study. Data collected for the Council of the POLKARD Program reveal that in the years 2004-2005 alone there were 704 screening study programs carried out in Poland, with a total of over 740 thousand participants [15]. The same data indicate that there are no uniform standards concerning this type of activities. The screening programs differed with regard to the scope of tests, their target groups, or methods used to invite people to participate.

Table 5. Prevalence of newly detected risk factors in the surveyed groups (data in percentages)

age		women		men	
		volunteers (screening)	representative sample	volunteers (screening)	representative sample
<b>19-75</b>	<b>Newly-detected hypertension</b>	25.1	17.9*	34.4	34.2
	<b>Newly-detected hyperglycemia</b>	13.0	-	20.0	-
	<b>Newly-detected hypercholesterolemia</b>	51.7	-	50.6	-

\*  $p < 0.05$  vs. volunteers

Table 6. Prevalence of tobacco smoking in the surveyed groups. (Data shown in percentages)

Age group	women		men	
	volunteers	representative sample	volunteers	representative sample
<b>19-75</b>	13.2	27.0*	22.9	47.2*
<b>19-30</b>	14.5	25.6*	23.4	47.5*
<b>31-45</b>	20.0	29.8*	29.3	51.1*
<b>46-60</b>	17.8	38.3*	26.6	49.3*
<b>61-75</b>	4.1	9.2*	14.8	37.5*

\*  $p < 0.05$  vs. volunteers

In the P400CP study the screening tests were preceded by a public awareness campaign in the media [16-19]. The campaign provided information about the objective of the study and explained who should participate in the tests (emphasis was placed on those who had not been diagnosed before and on men of working age). On the other hand, it should be emphasized that the screening study had an “open” design. Consequently, any person who received information about the tests and wished to participate was eligible. Due to this recruitment method, men accounted for only one third of participants, and in the group of young males (< 45 years of age) for only 7%; whereas the data obtained from the representative sample indicate that this could have not been caused by the actual demographic structure of the small town population. It seems that in order to redress the gender imbalance in screening programs addressed to both men and women, these programs would need an extensive support of psychology and sociology experts.

The mean age of participants in the screening study was 10 years above the mean age in the control (representative) sample. This might, to a certain extent, result from the fact that the test hours for taking blood pressure, fasting glycemia and cholesterolemia readings were scheduled for mornings (for obvious reasons). This schedule could have been inconvenient for those participants who were employed, despite the fact that screening points in many towns were open on a Saturday as well. When planning and organizing future screening programs, this issue must be taken into account.

An analysis of hypertension-related data indicates that as much as 40% of screening test participants declared a condition which had been diagnosed before. Including these subjects in screening tests is somewhat contradictory to the core concept of screening, even though their participation allows drawing conclusions about hypertension control in the population. After all, collecting hypertension control data should not be the objective of screening tests. On the other hand, the results of the control survey indicated that as much as a quarter of the representative small-town population were unaware of their hypertensive condition, which gives a well-founded rationale for widely designed screening in the target population. In the screening study the proportion of subjects diagnosed with elevated blood pressure for the first time in their lives reached almost 30% of participants. These people were invited for a second visit, to confirm the diagnosis [20-21]. However, only two thirds of this group took the opportunity of a second visit. This is an indicator of the need to develop tools that would effectively motivate patients to complete

the full diagnostic process. When carbohydrate metabolism disorders are analyzed, conclusions similar to those valid for arterial hypertension may be drawn.

The age difference between the screening study population and the representative sample resulted in a much higher awareness of existing hypertension or diabetes in the former group. This does not apply to hypercholesterolemia, for which no statistically significant differences were detected between the groups. If we analyze the female population only, the awareness of hypercholesterolemia was more often declared in the representative sample. This seems to be a result of a generally very low awareness of hypercholesterolemia, despite the fact that this condition is the risk factor with the highest prevalence [5]. While only 16% of participants in the screening study declared previously diagnosed hypercholesterolemia, the condition was diagnosed for the first time in over half of the screened group. This, in turn, indicates that an “open” design of the screening study provides the most effective format when screening for hypercholesterolemia in the small-town population.

Interesting results were obtained with regard to the prevalence of cigarette smoking. In the representative survey the proportion of male smokers in small towns exceeds 47%, whereas in the screening study smoking was much less prevalent, among both men and women and across all age groups. We may hypothesize that non-smoking and taking part in screening tests are both an expression of a health-conscious attitude, and this the reason why non smokers are over-represented in the screening. Therefore, anti-nicotine activities in small towns should be primarily based on measures extending beyond screening, such as social campaigns and education.

To conclude, it should be emphasized that, despite their limitations, screening programs are effective in improving the detection of risk factors. In the group of over 90 thousand participating volunteers, the screening study revealed many previously undiagnosed cases of raised blood pressure, carbohydrate metabolism disorders and, specifically, hypercholesterolemia. On the other hand, the “open” design of screening does not fully accomplish the assumed objective of reaching the hard-to-include group, i.e men under 45. This should be taken into consideration when planning future cardiovascular prevention programs.

## Conclusions

“Open” screening programs do not ensure adequate access to the sub-population of young adults,

especially males aged up to 45, despite social campaigns addressed specifically to this group, whereas those who willingly participate in “open” screening tests are older people, often already diagnosed with arterial hypertension and diabetes. However, regardless of these limitations, “open” screening tests are a useful tool, as they help to identify many newly detected cases of hypercholesterolemia – a widespread condition of which awareness is low. A similar situation, even though to a lesser extent, occurs also in the case of hypertension. People reporting for screening tests are more often non-smokers, whereas prevalence of smoking in the control population is much higher, especially among men. This, in turn, points out that there is a specific need to develop methods of effective anti-tobacco intervention in small towns in Poland.

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# Survey design method – the key component of building the Polish Biobanking Network

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## Abstract

The Polish Biobanking Network was created to connect Polish biobanks and gain information about their collections, thus facilitating their cooperation both in the national and international area. Based on MIABIS (Minimum Information About Biobank data Sharing) and considering the specificity of the Polish scientific community, two surveys were created. The aim of the first survey was to collect general information about Polish biobanks, e.g. their localization and type of collected material. The second survey was more detailed and concerned the biobank's structure, information about collected material, willingness to share the collected material, implementation of an informatics system. Significant information about Polish biobanks could be obtained through appropriate recognition of the biobank's scope of practice and correctly asked questions. The analysis of collected results could give a full picture of Polish biobanks.

**Keywords:** biobank · biobanking · data · survey · survey design

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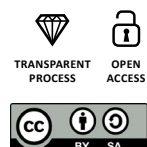
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## Introduction

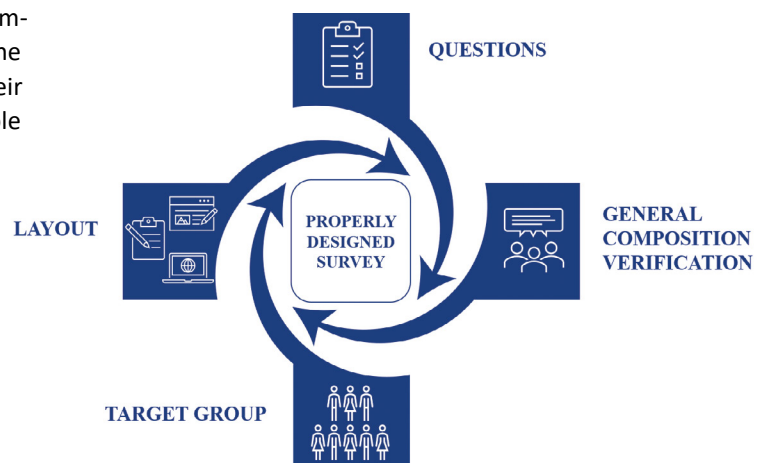
Biobanks are research units that collect biological material of various origin and data connected with it [1-3]. There are different types of biobanks: population, specialized, clinical and mixed. Population biobanks gather material of the chosen population and the conditions that exist in it. Specialized biobanks focus on collecting material related to particular conditions, e.g. oncological, genetic or rare diseases [3-4]. Clinical biobanks collect material obtained after diagnostics procedures and are often *de facto* part of pharmaceutical/diagnostic companies conducting clinical trials using novel drugs, research on biomarker detection and validation of various types of tests introduced for *in vitro* diagnostics. Mixed biobanks are characterized by combining the mission of population-type biobanks with specialized or clinical ones and/or both [5]. The material collected in biobanks is an excellent basis for further research because of its diversity and uniqueness [4, 6-7]. Biobanks are often created at medical universities and research centers. Thanks to this it is possible to increase the collections of these biobanks and thus support the development in science [8].

The process of obtaining biological material is inextricably linked with collecting data related to it [9-10]. An appropriate method for gathering the information connected with collected material is crucial because it can support the research carried out on biobanked material. Data describing biological material usually come from questionnaires that are completed by the donors, doctors and researchers. The method of gathering the collected data affects their usefulness. It is not necessary to store all possible data. Therefore, selection of data that is relevant and possible to collect with the sample, is also crucial. In order to select the proper data collection algorithms, it is important to create a special system that will enable this. The basis of such a system is designing a suitable survey whose aim is to gather the most important data that will complement the uniqueness of the collection stored in the biobanks. It is also critical to ensure adequate security of data storage, e.g. by implementing a properly designed informatics system. There are some guidelines, such as Minimum Information About Biobank data Sharing (MIABIS), which aim is to assist with the development of such questionnaires [2, 11]. The MIABIS describes, among other

things, the most important data which should be obtained about biobanks by surveys.

Poland is in the initial stage of building its biobank infrastructure and network [12]. Since 2016 Poland, has been a full member of the European Biobanking and BioMolecular resources Research Infrastructure-European Research Infrastructure Consortium (BBMRI-ERIC) which links biobanks from all over Europe [12-14]. Thanks to the activity of the Biobanking and BioMolecular resources Research Infrastructure Consortium in Poland (BBMRI.pl), the process of creating the Polish Biobanking Network (PBN) has begun. One of the main tasks of the PBN is to facilitate cooperation between biobanks and other research institutions located throughout Poland. Activity of the PBN will make biobanks more visible not only in the country but also abroad. It could spread the cooperation between biobanks and other units – research and/or commercial companies. That could also lead to the acceleration of personalized medicine development [6, 9-10]. To achieve this goal, it is important to obtain information about biobanks and biorepositories existing in Poland, first. Then, collected information should be placed in a special database where it would be available to all interested bodies.

The aim of this work is to show how to design surveys that enable obtaining relevant information about biobanks. Figure 1 summarizes the most important factors which should be taken into account during survey designing.



**Figure 1. Factors which should be taken into account during survey design.**

The target group – should be clearly defined at first. The layout – cannot be distracting to the respondents. Its main task is to guide the respondent from the first question to the last in a clear and transparent manner. Surveys authors have to decide if it will be in paper or electronic form. The questions – they should be easy to understand, regardless of type (single-choice, multiple-choice, closed, and open-ended). The general format – independent reviewers should verify if the survey is understandable to potential recipients.

## Material and methods

Before starting the process of survey design, it is important to decide what type of information should be obtained from it. The questionnaire should include questions that are closely related to its main purpose. The subject of the questions should be clearly defined [15]. It is important to prioritize the desired responses - authors have to decide which answers are required and which are optional [16].

### Who is the target group?

The survey's aim is to obtain specific information from specific recipients, so it should be designed to suit that target group [17].

### Does the layout matter?

It is necessary to define the layout of the survey, whether it will include only text or will images (or other sources of information) also be included. The purpose of the layout is to clearly and transparently guide the respondent from the first question to the last [18-19]. Therefore, the layout of the survey cannot be distracting to the respondents. In order to provide responses that are valuable to the survey designers, the respondent must see the purpose of completing the survey.

### Paper or electronic format?

Another important aspect that should be considered when designing a survey is its form. Depending on the target group to which the survey is addressed to and regarding its general structure, it is necessary to decide whether the survey should have paper, electronic or both formats. Computer-based surveys are increasingly common. This format is useful when the survey consists of many related questions. The respondents receive only questions tailored to the scope of their biobank work (e.g. after marking that the particular biobank collects samples of human tissues only, then questions about animal tissue samples will not appear in the survey). Thus, the survey becomes clearer and less overwhelming. Online surveys are cheaper, more environmentally friendly and can reach a larger target group in a shorter time.

However, it should be remembered that in some cases classic paper format can also be a good solution. Paper questionnaires are not vulnerable to hackers and reduce the probability of modifying the data selected in them. Some target groups prefer to fill in the paper questionnaire. For example,

while waiting for an appointment with their doctor, patients can use that time to complete paper questionnaires.

When deciding on the form of the survey, it is worth considering the analysis of the data obtained from it. Computer-based questionnaires are often connected with software that performs automatic analysis of the collected data. Whereas when choosing the paper format, it should be remembered that the data cannot be analyzed until a human finishes entering it into the chosen database.

The choice of survey format also determines the method of archiving. In case of computer-based surveys, this can be a secured server or a cloud service. Considering the paper questionnaires, it should be a place with restricted access, e.g. a dedicated cabinet locked with a key or code. Data collected using surveys can be sensitive, thus every effort should be made to properly secure them regardless of format.

### What should the questions look like?

The questions in the survey should be easy to understand. To achieve this, it is recommended to use short sentences and avoid multiple complex sentences. If the question includes terminology or abbreviations that may be unfamiliar to the respondent, they have to be clearly defined in the text. It is good when questions in questionnaires are related to each other. Thanks to this, respondents who are filling in the questionnaires can be guided by an appropriate path, tailored to their needs.

The survey may include single-choice, multiple-choice, closed and open-ended questions. Single-choice closed questions simplify data analysis and allow assigning respondents to a given group. However, the character of those type of questions limits the responses. The survey authors should strictly select the possible answers, which helps with obtaining precise results. Whereas the multiple-choice closed questions give the respondents the freedom to respond fully. To facilitate this, authors should include an answer choice "other" and in a text field the respondent should be able to enter an answer that has not been suggested by the authors of the survey. Therefore, the open-ended questions reveal the so-called respondent's frame of reference. This type of question is often overlooked by the respondents. It is important to make respondents aware of the purpose of participating in the survey [18, 20]. Another advantage of the computer-based surveys is that questions regarding information that is particularly valuable to the survey designers can be marked as obligatory and the respondent cannot complete the survey without an-

swering them. Only the appropriate combination of all these types of questions makes it possible to collect complete and useful answers which fully describe the particular biobank.

### **Who should verify the format and content of the survey questions?**

The survey should be verified by a person who was not involved in developing it. This person should be familiar with the topics addressed by the survey, however does not have to be a specialist in the given field. Such verification serves to check the legibility of the format and the respondents' understanding of the content.

## **Results**

To create a database of information describing Polish biobanks, two surveys were designed: Informational and Detailed. The purpose of these surveys was to collect particular information about research units involved in the biobanking of biological material. Both surveys were developed based on the authors' prior experience, other questionnaires and guidelines such as MIABIS. The target group were research centers, universities, clinical centers, private companies and other biobanking-related units located in Poland. Each of the questionnaires contained related single-choice, multiple-choice and open-ended questions.

Both surveys are available in electronic form on a dedicated platform [<https://ankietypsb.wum.edu.pl/>]. Before completing the questionnaires, participants went through a verification process. The data collected from both surveys were stored in a computer system with limited access, thus protecting the survey respondents and authors from unwanted email (spam).

The Informational Survey consists of 39 questions. Its main task was to obtain general information about Polish biobanks. This survey made it possible to start the process of identifying biobanks existing in Poland and describing their collections. The survey consists of questions about biobank localization, its type, its parent entity (if applicable), information describing the biobank's collections (the species the material comes from, the general type of gathered material, the size of collections and storage methods), the quality management and informatic systems. The Informational Survey also included the question of whether a given entity is interested in possible participation/accession to the PBN. Only those units that expressed their willingness to cooperate and consequently joined the PBN were invited to complete the Detailed Survey.

The Detailed Survey consists of 57 questions and is divided into five parts: biobank and its structure, collected material (including information about the samples and their donors, the type of research conducted, ethical issues), sharing biological material (including willing to cooperate with national or international research or commercial companies), informatic system and final questions (general questions asking for i.a. determining respondent's attitude towards biobanking, trainings and PBN). This questionnaire is a continuation of the Informational Survey and aims to determine the status of identified biobanks and the characteristics of their activities in the context of compliance with BBMRI standards. Although the Detailed Survey is a continuation of the Informational Survey and its questions concern similar topics, it collected more comprehensive information about Polish biobanks and broadened the knowledge about them.

## **Discussion**

Surveys are one of the most common tools for data collection [19]. Through proper recognition of the biobanking topic and the correct questions' design, it is possible to obtain relevant and reliable information about biobanks and biorepositories. Thanks to the Information and Detailed Surveys it is possible to obtain information not only about the general characteristics of Polish biobanks but also about problems affecting its development and their need for new solutions. Information obtained thanks surveys confirm the need for establishing international networks and organizations, which could share their experience with emerging entities what was presented also by other researchers [2].

The knowledge about biobanks makes it possible to improve research [4]. That in turn can lead to the development of novel personalized therapies [9, 21]. This is important not only in Poland, where the biobanking society is in an early stage of development, but also in other countries and scientific societies.

It is important because like in Poland, PBN connects entities from the whole country and makes all best to implement within their structure the proper standards. It is needed for maintaining high quality of specimens collected in biobanks. The implementation of at least minimum standards strategies developed by networks make it possible to obtain proper samples access, and reached large-scale, efficient use of human biological samples [11, 22-23]. Such standards can be designed more precisely only if their authors know the recipients' demands, which are defined in surveys.

Conducting surveys designed on the basis of special guidelines, general experience and knowledge

of properly qualified biobank's employees, allows for obtaining the necessary information which is crucial not only in the process of Polish Biobanking Network creating but also for other scientific environments which start building a biobanking network. Collection information about biobanks using properly-designed surveys has taken place not only in Poland but also in other countries in Europe. Networks like the BBMRI-ERIC provide such activities to gain information about biobanks located throughout Europe [24-26]. That improves the development of not only singular entities but also all biobanking field.

## Conclusions

Through appropriate recognition of the biobank's topic and correctly asked questions, significant and descriptive information about Polish entities could be obtained. Based on the obtained results and their analysis, a full picture of Polish biobanks can be formed. Such activities will contribute to the harmonization of issues related to biobanking.

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# Translational medical research in Nigeria: challenges, prospects and recommendations for the future

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## Abstract

In this review we discussed the challenges and prospects for translational medical research in Nigeria, a developing African country. We also provided some relevant recommendations on how to improve the future of translational medical research in the Nigeria.

**Keywords:** translational medical research · challenges · prospects · recommendations · Nigeria

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## Introduction

Translational medical research is the process of applying knowledge from basic biology and clinical trials to techniques and tools that address critical medical needs [1]. The concept of translational medical research is hinged on ethical, systematic and purposeful enquiries into nature [2]. This inherent complexity leads researchers in this field of translational medicine

to face various challenges. These challenges are noteworthy, ubiquitous and capable of affecting the quality of a translational medical research project. Some of these challenges include poor funding to lack of functional equipment to poor political will, inadequate international exposures/collaborations or unfavorable bureaucracies, just to mention a few [3]. It is noteworthy that many of the above-mentioned challenges are more evident in developing nations when compared

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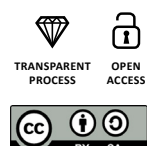
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to the developed world [3-4]. In this narrative review, we aimed briefly discuss the notable and historical achievements of translational medical research in Nigeria and beyond and also to examine the prospects and challenges of conducting translational medical research in Nigeria – a typical developing African country.

## Materials and methods

This study was a narrative review of relevant medical literature about the history, prospects, challenges and conducts of translational medical research in Nigeria. We searched the following research databases: Google Scholar, PubMed, ResearchGate, SCOPUS, CINAHL, PsycINFO and AJOL.

### Notable achievements in the field of translational medical research in Nigeria and beyond

Over the years, many problems had been solved worldwide through translational medical research [5-10]. For example, the discovery of insulin by Frederick Banting in 1922 radically changed the medical management of the then-notoriously deadly diabetes mellitus [6]. Paul Ehrlich's discovery of the first chemotherapeutic drug revolutionized the field and clinical practice of oncology [7]. The discovery of penicillin by Sir Alexander Fleming increased the effectiveness of bacterial infection treatment [8]. The ground-breaking research on human blood circulation by William Harvey was the foundation for countless innovation in physiology and cardiology [9]. Karl Landsteiner's discovery of human blood groups revolutionized the concept of blood transfusion [10]. These and many more are notable humanitarian achievements made by translational medical researchers.

In Nigeria, the practice of medical research commenced in 1920 with the arrival of the Rockefeller Foundation and the Yellow Fever Commission [11]. Over the years, academic and/or research institutions like the University of Ibadan (1948), the University College Hospital as well as other universities and tertiary health care facilities were established. These institutions continue to “produce” local and international researchers in all fields of study including medical sciences. For example, Professor Temidayo O. Ogundiran is best known for his translational medical research on breast cancer among African women [12], Professor Adesola Ogunniyi pioneered translational research on dementia in the sub-Saharan Africa [13], and Professor Lanre Wasiu Adeyemo is nationally known for his translational research contribution in the area of

genetics of orofacial clefts [14]. The research output of these researchers have significantly contributed to the field of translational medicine in Nigeria and beyond [12-14]. At the moment, many notable translational medical research projects are on-going in Nigeria; hence, translational medical research has come to stay in Nigeria.

### Challenges facing translational medical research in Nigeria

As mentioned earlier, translational medical research has globally revolutionized the practice of medicine. However, the conduct of translational medical research is more challenging in the developing countries due to some peculiar problems such as lack of funding and functional equipment, unfavorable policies and practices, inadequate international exposures as well as lack of political will [3, 15-20]. However this is not the case in developed countries (e.g. the United States of America, United Kingdom etc.) where there is relative ease in conducting research [21-22] – this ease is partly due to the availability of support system through funding, mentoring and collaborations.

Despite the huge contributions of translational medical research toward the prevention, diagnosis, investigation and management of different medical conditions in Nigeria [12-14], conducting such research endeavor in Nigeria is quite difficult due to enormous challenges [13]. The causes of this situation can be grouped into human, environmental and other non-human resource factors [15-16], all of which are discussed below.

#### A. Environmental and non-human resource factors

Environmental and non-human resource factors [15] in conducting translational medical research in Nigeria center on the environment where researchers work as well as the non-human resources needed for such endeavor. Below are common factors of such in Nigeria:

##### I. Inadequate funding

Funding is a very important aspect of translational medical research. Unfortunately, Nigeria spends a very low percentage (0.2 – 0.4%) of its gross domestic product (GDP) on research and development projects [23]. Most medical researchers in Nigeria fund their projects out of pocket due to massive lack of financial support from the Nigerian government and private institutions [24-25]. The reagents, equipment, consumables and other materials needed for translational medical research, often times are capital-intensive.



Therefore, it is usually (if not always) distressing for medical researchers to find support for novel research projects. Self-funding sometimes impedes the progress of their research project or causes them to outright abandon it.

## II. Embezzlement and other corrupt practices

Embezzlement and other corrupt practices (such as bribery) are common practices in many African countries. Particularly in Nigeria these practices are also found in the medical research institutes and tertiary healthcare institutions [26]. It is therefore worthy of note that funds meant for research are being embezzled or short-sized along the chain of disbursement. Research funding is more often than not embezzled by government officials or institute managers for bribery and other personal benefits. These unethical practices certainly leave the researchers with far less funds to support their projects and certainly deters advances in translational medical research [17, 20].

## III. High cost of modern medical equipment and maintenance

Due to the perpetual inflation of Nigeria's currency (naira) [27], the cost of modern medical equipment is rising annually. The persistently high cost of modern medical equipment (as well as all reagents) and maintenance makes much of the equipment unaffordable. If they are eventually acquired, the spare parts or skilled personnel needed for their maintenance or repair are not easily accessible, once again due to high costs.

This problem frequently limits the progress or completely halts a translational medical research or adversely affects its quality or outcomes. For example, the use of immunohistochemistry techniques in the diagnosis of cancerous cells and in the expression of proteins in biological samples is a rare practice in Nigeria due to heavy financial implications associated with such medical procedures. This specific problem has affected many immunology researchers in Nigeria and the laboratory diagnosis of cancer cells is limited to the use of the hematoxylin and eosin stains. Furthermore, the use of modern diagnostic equipment such as computer tomography or magnetic resonance imaging is unavailable in most of the tertiary healthcare facilities in Nigeria. Where they are available, their level of maintenance is very poor, leading to their abandonment. This situation can be very frustrating both to clinicians performing patient care and to translational medical researchers who need to use this equipment for a collaborative research project.

## IV. Unavailability of advanced computer technology/information technology

The unavailability of advanced computer technology and quality information technology in many Nigerian research institutions create additional limitations for translational medical researchers in Nigeria [28]. For example, the availability of reliable institution-provided internet services is grossly limited. Therefore, many people in Nigeria, including researchers, rely on mobile data services for access to the internet. Unfortunately, the mobile data services in Nigeria are very unreliable and irregular. As a result, Nigerian translational medical researchers have a barrier to keeping up with scientific developments due to limited access to online journals, books, electronic data bases and forum discussions [28-29].

## V. Unfavorable institutional policies and practices

The policies and practices within the institutions in Nigeria also impede translational medical research [24, 30-31]. Some institutional policies limit the access to research laboratories unless with the approval of heads of department, deans of faculties, etc. This may limit early career researchers from carrying out independent medical research projects [30-31]. However, in some situations junior medical researchers involved their senior coworkers in their translational medical research projects only to have the project hijacked. This practice is obviously unethical and must be abolished in the Nigerian medical research settings.

## VI. Government priorities

The priorities of the Nigerian government and its institutions have shifted away from funding research (including translational) and healthcare and now are focused on food availability, improving security and abolishing corruption [25, 27]. It has therefore become an uphill task for Nigerian scientists to access funding for translational research projects. The low level of priority given to research by the Nigeria government is quite worrisome because we observed that this shift in priorities is not a universal practice among African countries. In fact, non- or less-oil rich nations like Mozambique, Tanzania, Malawi and Uganda spend  $\geq 0.4\%$  of their GDP on research and development (compared to Nigeria with 0.2 – 0.4% of its GDP) [23].

## B. Human Factors

The commitment of the individual carrying out a medical research project plays a very crucial role in the outcome of such project. The human factors affecting medical research are mentioned below.

### **I. Lack of interest/motivation**

Some medical researchers in Nigeria often engage in research only for the purpose of promotion and many of them stop publishing once they reach the zenith of the promotion ladder. In order to advance their careers, some of these researchers engage in unethical practices e.g. plagiarism, falsification or outright fabrication of data [30-32]. Many are only interested in climbing the promotion ladder for financial benefits. Furthermore, some senior medical researchers sometimes edit and publish the research works of their undergraduate students without giving proper authorship credit after publication. This is another common unethical practice and it further underscores their lack of interest in contributing to knowledge through original efforts.

### **II. Inadequate mentoring**

Mentoring and counseling of medical science students/trainees at both undergraduate and postgraduate levels has been neglected or even abused at many Nigerian tertiary institutions [24, 33]. Specifically, the relationship between the students and their lecturers is more of a master-servant, instead of the required mentor-mentee. In fact, some lecturers who supervise final year projects and research of students frustrate the students involved either by being unnecessarily unavailable or not showing enough leadership in encouraging their students. In view of this, many undergraduates conclude that research is not intended for them and therefore fail to learn this art early in their career. Therefore, undergraduates complete their final year research project for the purpose of scoring marks and not to prepare themselves for engaging in research and contributing to medical knowledge. In sum, a proper mentor-mentee relationship can go a long way in encouraging the young generation to get involved in translational research [24, 33].

### **III. Lack of local and international exposure and collaboration**

Collaboration and exposure also play a role in the quest for translational medical research [24]. A lack of either of these factors limits the robustness of translational medical research projects. Many at times, translational medical research involves collaborations and wide horizon of exposure; these two factors are vital when it comes to harnessing one's strength in translational medical research for obtaining holistic results. Unfortunately, many Nigerian medical researchers lack these two factors/opportunities [24].

### **IV. Deficient English language proficiency**

English language proficiency (especially writing) is an important skill for the translational medical research

cher [34]. Unfortunately, quite many Nigerian researchers are not proficient in the English language which is a barrier between them and the reviewers of their manuscript as well as their target audience. The numerous grammatical errors seen in the research papers of many Nigerian medical researchers are capable of distorting the reviewers' and readers' understanding of the methodology and outcomes of the described projects.

## **Prospects for translational medical research in Nigeria**

As massive and discomfoting the above-described challenges may appear, there are still many prospects. A look at the history of translational medical research in Nigeria underscores the fact that despite all the challenges, this field of research can and should be continuously explored in order to promote health care and wellness. There are several topics of medical science that still require exploration, regardless of these above-mentioned challenges, some of which are mentioned below.

### **A. Highly infectious diseases**

The emergence of highly infectious diseases (e.g. the current SARS-CoV-2 infections, Lassa fever, Ebola viral disease, HIV/AIDS etc.), require more research in order to control spread, manage and treat the condition, to educate the population and to implement effective prevention strategies. The COVID-19 pandemic is a revelation of how much we need to intensify our efforts in conducting in-depth translational research projects on epidemic-prone infectious diseases [35]. The need for a comprehensive understanding of the mode of spread, rapid diagnosis via dedicated kits, vaccines and curative treatment will require a lot of translational medical research efforts and this is a significant opportunity for live-saving medical research in Nigeria.

### **B. Increasing incidence and prevalence of neoplasms**

The etiology, pathogenesis, diagnosis and management of neoplasms (particularly of the head and neck, cervical cancer and breast cancer) are also key topics to explore in the Nigerian population through translational medical research. The reason is rather evident: the persistently rising rates of neoplasm-associated morbidities and mortalities in Nigeria [36-38].

### **C. Increasing incidence of mental disorders**

Mental disorders such as depression, substance abuse or anxiety disorders have an estimated inciden-

ce of about 20-30% of the Nigerian population [39-41]. This rate is alarming and should stimulate more translational medical research in order to hopefully answer many current questions about the causes and effective treatment/prevention of these disorders. It seems that through rigorous translational medical research that informs policy and medical practice, the burden of the psychological disorders in Nigeria can be significantly reduced.

#### **D. Increasing incidence of hypertension, diabetes and other non-communicable diseases**

Non-communicable diseases such as hypertension or diabetes are also an area of significant prospects for translational medical researchers in Nigeria. The persistently rising trend of unhealthy behaviors (unsafe sexual practices, use of tobacco, alcohol and other psychoactive substances) among young Nigerians is worthy of note. It is up to the researchers to explore the influence of the above-mentioned behaviors on the persistent rise in the incidence rates of hypertension, diabetes and other diseases in Nigeria [42].

### **Recommendations for the future**

Having mentioned several challenges and prospects of translational medical research in Nigeria we attempted to make several recommendations for the future of translational medical research in Nigeria.

#### **A. Improvement of Funding for Translational Medical Research**

An improvement in funding will go a long way in reducing several of the above-mentioned barriers to conducting translational medical research in Nigeria. These funds could be provided as grants, donations or interventions. The availability of funding will also serve as motivation for Nigerian medical researchers.

Also, as a way of reducing costs of translational research projects, Nigerian scientists should consider the following options (list not exhaustive):

- I. publishing research articles in reputable journals that do not charge the authors any fees (article processing charges),**
- II. recruitment of enthusiastic and qualified persons who are willing to work as laboratory or research assistants on a volunteer basis,**
- III. engagement in group collaboration such that the financial burden of the research project can be shared among the participating researchers,**
- IV. applying for research funding from foreign sources.**

#### **B. Dedicated research institutions**

Encouragement and improving the environment to practice translational medical research in Nigeria can be achieved by provision of special research institutions e.g. the national dental institute, infectious disease research laboratories or cardiovascular research institution to promote research and train researchers. This can be achieved through the contribution of interested non-governmental organizations or governmental institutions or agencies. Certainly there must be significant commitment to the sustainability of such facility in order for this strategy to succeed.

#### **C. Mentorship**

The re-vitalization of mentorship programs in the tertiary institutions is highly desired. Students who are enthusiastic about translational research should be encouraged (and given an opportunity to do so) via proper mentor-mentee relationship. They should be motivated by getting the authorship credit for research articles, chapters, books, reviews they contributed to.

#### **D. International exposure**

The need for international exposure among medical researchers in Nigeria is also essential. The curriculum of the undergraduate and postgraduate medical training should be expanded to accommodate international exposure through outside postings and exchange programs. This will make collaboration with colleagues abroad easy and is likely to improve the Nigerian researchers' output.

#### **E. Implementing favorable policies and practices**

The era of junior medical researchers being restricted by policy to their supervisors' permission should be thrown into the bin of history. Many young medical researchers were forced to bury their dreams of conducting potentially ground-breaking translational research due to lack of approval from their superiors. We suggest that once a junior researcher's research proposal obtains approval from the local ethical committee/board, there should be no other reason (such as objection from the supervisor) for not conducting that study. The policies that currently dominate Nigerian research institutions should be completely abolished and be substituted with favorable ones.

#### **F. Regular training and re-training of personnel**

Sometimes, the procurement of scientific equipment is easier than assuring its proper maintenance. Researchers using the equipment as well as the technicians who repair it should not engage in trial

& error attempts and thereby underutilize or disrupt their function. In order to remove this barrier to translational research, we recommend that sufficient funds are expertise are reserved for training and re-training of all research staff.

### G. English language proficiency among researchers

As earlier mentioned, poor English communication skills among medical researchers in Nigeria is a serious problem. In order to mitigate it, medical researchers should have take dedicated English language lessons and tests. This will make medical research outcomes well-understood by reviewers and the readers. We also recommend that the Nigerian government should fund opportunities for professional training and mentorship on scientific writing for researchers.

## Conclusion

In order for Nigeria to achieve significant and sustained improvement in healthcare, it needs to allocate a greater percentage of its GDP for research. Currently there is a significant and urgent need for well-planned investment in translational medical research in Nigeria.

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# Limitation of patients' rights during the COVID-19 pandemic in Poland

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## Abstract

**Background:** The COVID-19 pandemic has had an impact on the observance and limitation of patients' rights all over the world, including Poland. **Material and methods:** We analysed in detail the Polish legal acts relevant to healthcare in terms of their impact on the patients' rights. Our analysis is based on the Bill of Patients' Rights that was in force in Poland before the announcement of the state of epidemic (March 20th 2020). The legal acts were analysed by use of the exegesis of legal texts and comparative legal literature rules. **Results:** The patients' right to family life and presence of relatives during the performance of healthcare services and to additional nursing care has been directly limited. Rights that have been limited indirectly include the right to healthcare services (limited by the use of telemedicine) and the right to dignified death and pastoral care (patients often die alone). The limitations also have an indirect impact on the right to confidentiality and respect for privacy and dignity. **Conclusions:** Our analysis identified limited patients' rights in Poland without entitlement to pursue claims thereunder.

**Keywords:** legislation · patients' rights · COVID-19 · compassionate use

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## Introduction

The COVID-19 pandemic has contributed to significant changes in social and economic life all over the world. However, the direct impact of the pandemic

refers to human life and the functioning of the healthcare system, hospitals, outpatient clinics. The Patients' Rights and the Patients Ombudsman Act of 6 November 2008 [1] introduces the term of fundamental rights of patients and guarantees the observance of

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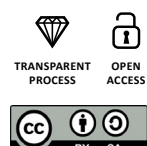
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those rights. In accordance with applicable regulations, patients have, among others, the right to obtain healthcare services immediately, to obtain full and sufficient information about their health, to give their definite and well-informed consent to medical treatment, to preserve their privacy and dignity (including their family life) and to access their medical documentation. The regulations interpret the patient as a subject and order to treat the patient, like each human being, with due respect. Nevertheless, the legislator stipulated possible limitations to the observance of the patients' rights due to a threat of epidemic, as referred to in Art. 5 of the Act. That regulation was already incorporated in the original text of the Act, however it has never been as up-to-date as nowadays. The *ratio legis* of the regulation was to protect the functioning of a healthcare institution if there is a risk of a state of epidemic within the institution's operating area.

At present, we observe an unprecedented scale of limitations to the freedom of human beings. On March 11<sup>th</sup> 2020 the World Health Organisation announced the worldwide pandemic and on March 20<sup>th</sup> 2020 the state of epidemic was announced in Poland. In the light of the spreading epidemic of the SARS-Cov-2 virus, which we still know very little about, it is obvious that restrictions aimed at limiting the infection are introduced. These actions are taken to protect human life and health on a nation-wide basis and to warrant the capacity of the healthcare system in order to prevent the dramatic events which took place in Italy or Spain. Therefore, it is very important to balance interests of the entire society with respect for rights of a human being. In the case of the SARS-Cov-2 virus pandemic, public authorities have to face the problem of uncertainty and insufficient medical knowledge, as a result of which legal regulations are also developed based on incomplete and fast-changing data, as well. The safety of medical personnel in comparison with the safety of patients is also an important aspect. These are difficult issues both in terms of organisation and ethics. That is why the literature describes this dilemma as "pandethics" [2-3]. There are many doubts regarding how to avoid infecting other people, social distance, the distribution of personal protection equipment, the obligation to treat or the right to waive treatment [2]. The moment the state of epidemic threat was enforced in Poland, the statutory right to limit patients' rights at all healthcare centres all around Poland came in force. Those limitations have very wide implications and influence everyday life of patients in the healthcare system. In this article we analyse legal acts and infection control authorities' guidelines which apply in Poland in terms of the enforcement of limitations to the bill of

patients' rights, which was in force before the announcement of the epidemic in Poland.

## Material and methods

This work was prepared through the exegesis of a legal text in order to analyse the present status of regulations on patients' rights in Poland. We conducted a systematic review of the Bill of Patients' Rights guaranteed in various legal acts in terms of limitations thereto connected with the state of epidemic announced in Poland on March 20<sup>th</sup> 2020. At the same time we took into consideration the lawfulness of such limitations. The source of the analysis was the Patients' Rights Act, which was compared to official guidelines published by the state infection control inspectorate and the Supreme Medical Council, as well as legal acts amending the scope of the bill of patients' rights in Poland. This allowed us to compare using legal comparative literature rules. The rights that have been limited or even blocked are identified and discussed. We identified the rights to: healthcare services, respect for family life, dignified death, respect for dignity and privacy, additional nursing care, secrecy, and pastoral care. Those specific seven rights were analysed in detail.

## Results

The patients' rights in wide terms are inseparably connected with human rights and constitutional rights stemming from the Constitution of the Republic of Poland. That is why Article 5 of the Patients' Rights Act is interpreted restrictively, which means that the doctrine does not allow for the limitation of all, but solely a part of, the patients' rights, e.g. the right to respect for family life, including personal contact. Based on Article 5 of the Act, the limitation of the patients' rights to services and consent is considered unacceptable. It is necessary to note that the Act only allows for the limitation, and not complete elimination, of the patients' rights. Nevertheless, given the pandemic and the limitations connected with restricting or preventing personal contacts, there are no doubts that widely understood patients' rights and the exercise of such rights have been indirectly, but effectively, blocked in practice [4].

During the epidemic state, the Polish legislature introduced new competences to the state infection control inspectorate whose recommendations have become new sources of law, which is unprecedented. This act is not foreseen by the Polish Constitution. Such recommendations may concern entities providing he-



althcare services and each person residing in Poland must obey. Such recommendations were made, inter alia, in the area of primary healthcare, including: telemedicine, rules of carrying out COVID-19 tests, rules for practicing family medicine [5].

Our comparative analysis indicates that the right to healthcare services has been formally limited. In particular, rehabilitation services have been limited temporarily by suspending the operation of rehabilitation centres and closing treatment facilities at health resorts. That is based on new provisions of the Act on Preventing and Counteracting Human Communicable Diseases, as well as regulations of the Minister of Health and the Government. The permission to limit the patients' rights to healthcare services also results from the existing standards and guidelines published by the state infection control inspectorate and the Supreme Medical Council, which point out that in-person appointments with specialist doctors must be limited and replaced with telephone consultation.

Based on the Resolution No. 89/20/P-VIII of the Presidium of the Supreme Medical Council on the adoption of guidelines for the provision of telephone medical services, "telephone consultations" are recommended during the COVID-19 pandemic and specific guidelines for doctors and dentists to be applied during such consultations have been passed. The standards explicitly underline that the doctor must respect the patients' rights without change. Given the patients' right to information, the doctor should inform the patient in detail about worrying symptoms, in the case of which diagnostic tests and further examination might be necessary. In addition, the doctor must also inform the patient that they have the right to an in-person appointment/service if the telephone consultation does not meet their expectations or their problem cannot be solved by phone. The resolution also clearly stipulates that: "The telephone consultation must not be overused if it does not allow for the reliable examination of symptoms and health of the patients and the patient's health problems cannot be solved in such a way". The resolution also points out that the principles of doctors' civil and professional liability for healthcare services do not change [6]. According to data obtained by the Patient Ombudsman, there were 22144 telephone calls received from patients regarding limitations of their right to primary healthcare services in the period of January – September 2020 [7]. Comparing with data from previous years, we can observe a significant growth. In 2019, there were 9743 such telephone calls regarding this particular area, while in 2018, there were 7306. During the SARS-CoV-2 pandemic patients mostly reported the refusal to provide healthcare services on the given day or the

refusal to be registered as an emergency. There were also reports concerning the refusal to provide personal visits or objections regarding the quality of telephone consultations provided during this pandemic [7].

Moreover, patients who used to be treated with chemotherapy or drug programmes in specialist hospitals are no longer able to receive such treatment. This issue arises from the increased number of hospital beds for patients with COVID-19 or even from the transformation of hospitals or hospital departments to provide care solely for patients with COVID-19. When patients suffering from chronic diseases are not able to receive treatment due to the lack of ability of hospitals to provide such care, the situation translates into a limitation of the patients' right to healthcare services in the area of outpatient specialist care [7]. However, according to new recommendations of National Health Fund, it is recommended to suspend or postpone most of planned surgeries to avoid potential spread of Sars-CoV-2 virus. The recommendation specifically excludes only cancer treatment and diagnosis [8].

The patients' right to healthcare services also applies to treatment consistent with the existing medical knowledge. The case of COVID-19 pandemic shows that the latest pharmacotherapy and the use of new procedures can be considered a medical experiment. Some of the therapies are recommended officially. In accordance with the information published by the President of the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products on April 3<sup>rd</sup> 2020, Remdesivir may be used in the COVID-19 therapy on a compassionate use basis. The Committee for Medicinal Products for Human Use at the European Medicine Agency issued a recommendation concerning the use of an active substance of Remdesivir in the treatment of COVID-19 under the compassionate use programmes in the European Union [9]. The Regulation (EC) No 726/2004, specifically Article 83, provides the legal basis for the management of a compassionate use programme at the European level [10]. The purpose of these programmes is to provide an access to therapies and medicines for which a marketing authorisation has not been obtained yet, but which are to help patients suffering from long-lasting diseases which pose a threat to life, cause serious disabilities or for which there are no treatment options. The results of laboratory tests indicate that Remdesivir counteracts SARS-CoV-2 and other coronavirus types. Nevertheless, the data concerning its use for patients with COVID-19 are limited [11].

The limitation of the patients' rights to respect for family life stems directly from Article 5 of the Patients' Rights Act and comes into force as a result of the occurrence of a premise for an epidemic threat. The de-

cision is made on a case-by-case basis by the head of a healthcare institution. Given the existing situation, such a decision is also authorised by guidelines published by the state infection control inspectorate and the Supreme Medical Council.

There is not, however, any basis for the limitation of the patients' right to respect for privacy and dignity. This right is strictly connected with the inherent dignity of each human being, therefore it cannot be undermined. This right includes the right to dignified death, which, as a result of the recommendations and guidelines issued by the state sanitary supervision office and the Supreme Medical Council, has been actually limited. The presence of family members and clergymen in the rooms of COVID-19 patients has been forbidden. Dying persons have been also deprived of additional nursing care.

The patients' right to secrecy and confidentiality, which are correlated in the context of COVID-19, are

limited because it is necessary to identify a source of infection and persons the patients had contact with. When information about people having contact with the infected person is provided by the infected person and then when the sanitary office contacts those people, the relationship and source of infection are disclosed, which violates the patient's right to secrecy with regard to the disease. This limitation stems from the guidelines of the state infection control inspectorate.

The patients' right to pastoral care was effectively limited. This right is subject to limitation on the basis of Art. 5 of the Patients' Rights Act, because it is connected with the right to contact stemming from the right to respect for family life. In addition, in accordance with the guidelines of the state sanitary supervision office and the Supreme Medical Council, as well as an order to limit interpersonal contacts and visits, pastoral visits at hospital wards are limited in order to minimise the risk of COVID-19 infection.

**Table 1. List of patients' rights that have been limited in Poland**

Patients' right to	Source of regulation	The source of regulation permits limitation of this right	Source of limitation	Standards and guidelines published by the state infection control inspectorate permit limitation of this right
Access healthcare services	Act	No	Regulation	Yes
Respect for family life	Act	Yes	Act	Yes
Dignified death	Act	No	None	Yes
Respect for dignity and privacy	Act	No	None	Yes
Secrecy	Act	No	Regulation	Yes
Additional nursing care	Act	No	Regulation	Yes
Pastoral care	Act	Yes	Act	Yes

## Discussion

Given the interpretation in the doctrine, the patients' right to healthcare services is strictly connected with the provision of such services in accordance with medical standards and existing medical knowledge. This underlines the quality of services that the patient is entitled to. Therefore, doctors must study, improve and expand their medical knowledge and knowledge connected with new techniques and technologies all the time. In the light of the low level of knowledge about the SARS-COV-2 virus, it is not possible to provide the patient with healthcare services in the same manner that the patient is used to. The personal contact with a doctor was replaced with a telephone consultation.

The World Health Organisation defines "telemedicine" as the delivery of healthcare services, where distance is a critical factor, by all healthcare professionals using information and communication technologies for the exchange of valid information for diagnosis, treatment and prevention of disease and injuries, research and evaluation, and for the continuing education of healthcare providers [12]. A detailed history taken by an experienced doctor via telephone may solve a medical problem, particularly if it is possible to send photographs which can help make the correct diagnosis. However, the problem of the limitation of the patients' right to healthcare services will also exist if the telephone consultation is insufficient or if the patient is a small child or an elderly person. Elderly patients often do not have an access modern technologies or are not proficient in their use (e.g. are not able to send a photo to their doctor), which means that they are not provided with a healthcare service they are entitled to by law. The situation is also difficult in the case of small children if a parent is not able to define the problem because he or she is not able to identify the source of pain due to the lack of a relevant level of communication with the child. Moreover, according to a recent Ministry of Health Regulation, it is now forbidden to consult via telephone a patient who is < 2 years old [13].

It is necessary to point out that the decision to replace in-person appointments with telephone consultations was not a personal decision of a doctor, but the supervisor of the healthcare facility. The purpose of such a decision is not only to protect the medical staff but also the patients. When appointments at the outpatient clinics are reduced, people will not gather in the small waiting rooms and can avoid potential infection. Although reliable telephone consultations can be obtained and the permanent implementation of such a solution in the healthcare system can form a remedy for medical treatment acceleration, they

must not constitute the only method for healthcare service provision. A physician is obliged firstly to provide a telephone consultation, according to the decision of the head of the entity providing healthcare services. However, when it is not possible to solve a medical problem via telephone, the doctor is obligated to examine the patient in-person. In addition, it is the physician's personal obligation as a medical professional to remember that telephone consultations must not be overused. Due to data obtained by the Patient Ombudsman, there are reports from patients regarding limitations of personal appointments regardless of the medical requirements. Another problem concerns home visits, such as those provided by midwives following labour, which should take place 48 hours after discharge from hospital. The Patient Ombudsman explicitly indicates that an outpatient clinic should ensure that its schedule considers time required for telephone consultations, personal visits, home visits and healthcare for healthy children, such as vaccinations or routine health checks. There is also a recommendation for the careful use of telephone consultations, especially in situations with patients who have their first appointment or have a worsening condition [7].

The right to healthcare services and the limitation of that right in the times of COVID-19 give rise to ethical dilemmas. Should an access to such services be prioritised by age or health condition? Should the provision of such services to medical staff, who is very prone to infections, form a priority? Who provides such services and rescues the life of other patients at the same time [14]?

Certainly, the patients' right to dignity and privacy has been restricted as relatives are not able to be present during the provision of healthcare services. The same applies to the right to additional nursing care. It is strictly connected with the limitation of the patients' right to respect for private and family life, as set out in Art. 33 of the Patients' Rights Act, which was restricted directly on the basis of Art. 5 of the Act. At present, patients cannot be visited during hospitalisation and relatives cannot be present during the provision of healthcare services. The exception is family births, which were suspended during the first period of the pandemic and which depend on the decisions of the healthcare institution supervisor.

It is necessary to perform a more detailed analysis of the degree to which the patients' right to dignified and peaceful death in the times of COVID-19 is respected, which results from the specific situation we are amidst. Those rights are limited, however not directly on the basis of a specific regulation, but as a result of the enforcement of the infection control regulations and the equipment of healthcare institutions. Digni-

fied death is understood very broadly, starting from relevant nursing care, psychological support, through access to analgesia, to the presence of relatives. During the pandemic, the presence of relatives at the patient's bed is not possible for sure. However, in the case of the COVID-19 patient, the problem may also include a relevant nursing care, given the increased sanitary regime and HR shortages. There is also an ethical dilemma which orders to consider the right to dignified death and the obligation to prevent the epidemic through the application of dignified, but safe, procedures during the burial of people infected with COVID-19 or suspected of such an infection [15-16].

The relevant observation of the patients' right to secrecy and confidentiality is also a problem. On the one hand, to prevent the virus spread, people having contact with the infected person must be isolated. That is why infection control services perform a thorough interview and the infected person discloses information concerning people they have had contact with. Then, the infection control office contacts those people and informs them about the identity of the infected person: here the patient's right to secrecy is violated. What is more, as the society, we obtain information about the number of the infected people in the country, voivodships, towns and municipalities everyday. The information is given, however, in the most anonymised way possible in order to balance the interest of the public with the interest of an individual [17-18]. However, as a result of such a situation members of the society may be stigmatised or even subject to social ostracism or hostility towards the ill people or those in quarantine.

The limitation of the patients' right to pastoral care means the restriction of the presence of clergymen at hospital wards. This is a difficult issue, in particular to elder, chronically ill or continually hospitalised patients. To meet their needs, mobile communication devices (e.g. tablets and telephones) are used. Such solutions must be considered innovative and very necessary because they enable pastoral care for patients [19].

## Conclusions

The limitation of the patients' rights during the COVID-19 pandemic is the fact. The legal basis for such a situation partially stems from Article 5 of the Patients' Rights Act, which allows for the limitation of the patients' rights during the epidemic threat, as well as partially from regulations of the Minister of Health and the Government and guidelines of the state infection control inspectorate. Some of the patients' rights have been limited, but not eliminated. The patients' right to family life and presence of relatives during the performance of healthcare and to additional nursing care has been limited directly. Rights that have been limited indirectly include the right to healthcare services which is limited by the use of telemedicine and the provision of remote medical aid. Similarly, as a result of the above, the patients' rights to dignified death and pastoral care were limited when the patient must die alone without family, loved ones or a member of the clergy. The rights to confidentiality, privacy and dignity were limited indirectly. The limitations are set out by law or in official guidelines, which means that any claims against such limitations are doubtful.

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