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Uranium associations with kidney disease of South Kazakhstan uranium region population

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ABSTRACT

Uranium mining activities in South Kazakhstan may result in environmental pollution that may affect the health of people living in the uranium industry operating area due to the dangerous toxic and radioactive properties of uranium. In preliminary studies it was shown that the inhabitants of the uranium ore province of Syrdarya are dominated by the pathology of the urinary system. We conducted a retrospective cohort study to assess the prevalence of kidney disease and urinary uranium concentrations in adults living in close proximity to a uranium mine. The study included the entire population, men and women over the age of 18 diagnosed with kidney disease. The uranium concentration in daily urine samples was determined on a mass spectrometer with inductively coupled plasma. The prevalence of kidney pathology in the population of the main group was 239.5 per 1000 people, statistically significantly exceeding this indicator in the control groups by 1.3-1.5 times. At the same time, we determined the relationship between kidney diseases and gender, employment status and length of stay in the Uranium Ore Province territory. The uranium content in the urine of the residents of the village of Bidaykol was higher than in the control groups. This study provides fundamental and useful information to address public health and environmental concerns in the uranium mining areas of Kazakhstan.

Keywords: Environmental, Uranium mining, Urinary, Kidney pathology.
Article type: Research Article.

INTRODUCTION

The Republic of Kazakhstan has significant reserves of natural uranium and ranks first in the world in the extraction of uranium ore (Boitsov, 2021; Ibrayeva *et al*. 2020; Hosseini *et al*. 2023). The main uranium deposits on the territory of Kazakhstan are grouped into six uranium ore provinces. One of the largest is the Syrdarya Uranium Province in southern Kazakhstan. It was discovered in the 70s -80s and has 3 groups of deposits: north (Karamurun, Kharasan, Irkol), south (Asarchik, Zhautkan, Zarechnoye) and east (Lunnoye, Kyzylkol, Chayan; Taraborin & Demina 2012). In the countries of the former Soviet Union, uranium industries and radioactive waste storage sites were often located beside human settlements and directly in the canals of major rivers that flow into densely populated areas of the region (Uranium Tailings in Central Asia 2009). The Syrdarya River is the main water artery for large agricultural and industrial regions of Turkestan and Kyzylorda regions of Kazakhstan. There are many settlements and more than 90 industrial enterprises on the banks of the river. The uranium mining enterprise of NAC Kazatomprom JSC is located in the Shieli district of the Kyzylorda region at the site of the mining department No. 6, which was established back in 1983. Next to it are a number of settlements: Bidaykol, Akmay, Shieli, Zhakaev and others (Zhanbekov 2010). Currently, 100% of uranium production at the enterprises of Kazakhstan is carried out by the underground borehole leaching method. However, this technology can be ecotoxic and have serious impacts on the environment and human health. When leaching from underground wells, transuranic radionuclides can enter surface and groundwater, and through water and vegetation - into food for animals and further - through the food chain to a person (Farjana *et al*. 2020). This means that there is a risk of internal exposure to the population living beside the mine, as well as in adjacent areas and towns (Meirbekov *et al*. 2017). Although all uranium isotopes are radioactive, uranium's chemical toxicity in food and drinking water is of more concern than its radiotoxicity. After ingestion, most of the uranium passes through the intestines. Uranium is absorbed in the gastrointestinal tract (1-6%) and enters the bloodstream and then accumulates mainly in the kidneys, liver and bones (Brugge *et al*. 2011). Soluble uranium compounds accumulate in the kidneys and can damage them if ingested for a long time (Ma *et al*. 2020). The burden on the overall excretory function of the kidneys and urinary tract can increase by constant environmental pollution, which in turn contributes to the more frequent development of environmentally-related kidney diseases. In this regard, the violation of the functional state of the urinary system can be considered an important indicator of pollution of the residential area. Risk factors for kidney disease, in addition to the state of the environment, include age, some non-communicable diseases, alcohol and smoking, climate, types and traditions of diet, genetic characteristics of the population of this population, etc. (Inogamova 2016). The health of the population of the uranium province of Syrdarya is characterized by risk factors such as an arid, strongly continental climate and the salinity of the areas located in the Aral Sea Basin. The population is thus exposed to the harmful effects of polluted air, soil and water of all kinds (Ibraeva & Seksenova 2017). Investigating the influence of the region's existing ecosystem on the health of the population requires a great deal of effort, in particular to find out which risk factors make the greatest contribution to eco-dependent kidney pathology. It is possible that uranium and its progeny have synergistic nephrotoxic effects for the development of kidney disease among the population living near uranium plants. It is known that incorporated uranium is excreted from various tissues in the urine and this occurs at different rates: within a few days, months or years. The amount of uranium absorbed in food and water can be roughly estimated from the amount of uranium in the urine (Taylor & Taylor 1997). In this regard, the purpose of our study was to establish a causal relationship between the prevalence and structure of renal pathology and the content of uranium in the urine in the population living in the area affected by uranium industry enterprises.

MATERIALS AND METHODS

The work used materials obtained during the project "Development of methods for levelling negative technogenic risk factors for the environment and public health of the Syrdarya Uranium Ore Province" (No. 158/36-21-23 of 04/27/2021, IRN AP 09261243).

Study population

The epidemiological study included residents of Bidaykol Village in Shieli District, located 4 km from the uranium mining company, as the main group and residents as control groups in Sunakata Village in Zhanakorgan District, Kyzylorda Region, located 15 km from the nearest uranium mining company. As the second control group, the settlement of Shardara in Shardara district of Turkestan region, which is more than 400 km away from the uranium industry enterprise, also along the Syrdarya River, was chosen. The location of the settlements is shown in Fig. 1. The residents of these settlements were divided into main and control groups not only according to the distance to the uranium industry, but also according to the radiation situation in the village. Radiation studies on the territory of the settlement of Bidaykol revealed a 9-fold excess of gamma radiation compared to the background values on the outskirts of the adjacent uranium mining enterprise, as well as an excess of the specific activity of radionuclides 226 Ra and 232 Th in samples of soil, water and bottom sediments of reservoirs in comparison to the average Republican values. On the territory of the control settlements of Sunakata and Shardara, the radiation situation was stable and the specific activity of radionuclides of the uranium and thorium series in water and soil samples corresponded to the national average (Kazymbet *et al*. 2020). The cohort was tracked from 2010 to 2022. At the first stage of the study, the coverage of the residents of the villages of Bidaykol and Sunakata and Shardara was complete: 10305 people. Collection of medical records of outpatients and inpatients in polyclinics and district hospitals was carried out. Furthermore, the medical data of the population of the main and control groups were entered into the sectoral radiation and epidemiological register of the Institute of Radiobiology and Radiation Protection of NJSC "Astana Medical University" in order to dynamically monitor the population living beside the uranium mining enterprises. From the general population of the uranium ore province of Syrdarya, according to medical records, individuals of both sexes over the age of 18 with a confirmed diagnosis of diseases of the urinary system were selected. 758 people were examined in Bidaykol village, 297 in Sunakata and 649 in Shardara.

Fig. 1. Syrdarya Uranium Ore Province, Northern Karamurun deposit.

The main selection criterion for the study groups was a longer stay in these areas of more than 10-15 years. The fact of long-term stay was recorded by ambulance cards: the date of registration in the regional polyclinic and the place from which the person came. All the studied main groups, in which kidney pathology was detected, permanently resided in the territory close to the uranium industry enterprise. The exclusion criterion was professional contact with sources of ionizing radiation: the fact of working at uranium mining enterprises. For each subject, an examination card was created in the electronic database, containing: personal data of a person, place of residence, length of stay in a certain place, place of work and occupation, medical data from preventive examinations, a list of existing diseases, information on registering with a Pharmacy. In addition, data from the medical history and additional methods of studying the nephrological profile: a general urinalysis (CLA) and an ultrasound scan of the kidneys, if available. Design research is shown in Fig. 2.

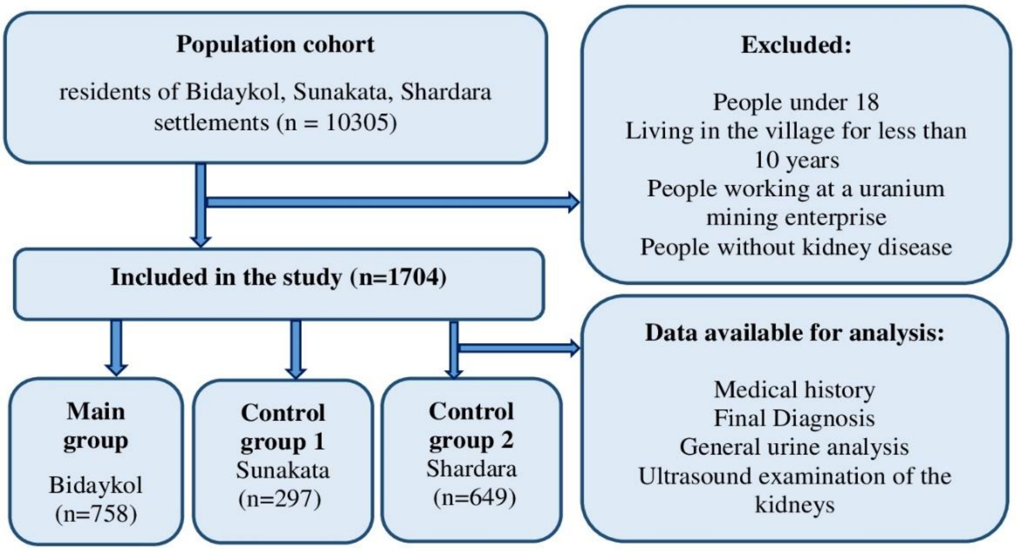

Fig. 2. A flow diagram showing the study design.

Biological sample collection, sample preparation and analysis

Residents of the settlements of Bidaykol, Sunakata and Shardara, who lived for a long time, were examined for the content of uranium in their urine. A total of 118 urine samples were collected daily for analysis: 66 samples from residents of Bidaykol village, 22 from Sunakata and 30 from Shardara. Samples were placed in a sterile 30 mL- plastic container and acidified with concentrated nitric acid HNO_3 (0.2 mL per 10 mL sample) to minimize degradation and uptake of uranium by the walls of the container. The ASTM C1844-16 method was used to prepare urine for analysis by microwave digestion of biological material using adsorption or emission spectrometry at concentration levels corresponding to the minimum required detection limit. The following reagents were used: standard samples "7500 Series PA Tuning 1" 1000 mg L^{-1} (23 elements) from Agilent Technologies (USA); concentrated nitric acid for spectral analysis; Ultrapure water (Mirae ST, Korea) and Multiwave microwave reactor Pro 5000 (Anton Paar, Austria). For the quantitative determination of uranium in the prepared samples, we used an Agilent 7800 ICP-MS quadrupole mass spectrometer with inductively coupled plasma (Agilent Technologies, Japan). For bioassay measurements on ICP-MS, the following standards and blanks were used: high purity nitric acid HNO_3, uranium standard 1000 µg mL^{-1} U in 5% HNO3, and thorium standard 1000 µg mL^{-1} Th in 5% HNO_3 (Agilent Technologies, USA).

Statistical analysis

Quantitative indicators were evaluated for compliance with the normal distribution using the Kolmogorov-Smirnov test. In the absence of a normal distribution, quantitative data were described using the median (Me) and the lower and upper quartiles (Q1 – Q3). Categorical data were described with absolute values and percentages. Comparison of two groups in terms of a quantitative indicator, the distribution of which differed from the normal one, was performed using the Mann-Whitney U-test and the Kruskal-Wallis test. Comparison of percentages in the analysis of four-field contingency tables was performed using Pearson's chi-square test. A two-sided p-value < 0.05 was considered significant for all statistical tests.

RESULTS AND DISCUSSION

Analyses of the data showed that the main diseases characteristic of the region under study are diseases of the genitourinary system (Saifulina *et al*. 2023). In addition, their prevalence among the adult population was 239.5 per 1000 people in the village of Bidaykol and exceeded this indicator in the village of Sunakata by almost 1.3 times (185.5 per 1000 people, $\chi^2 = 20.93$, p = 0.00) and 1.5 times in Shardara (160.6 per 1000 people $\chi^2 = 82.33$, p=0.00) Among them, 758 cases of kidney disease were detected - 201.9 per 1000 people, which was also 1.3 - 1.5 times higher than in the population of the control groups. The basic characteristics of the residents of the villages involved in the stage of studying the factors are presented in Table 1.

Table 1. Characteristics of patients at the stage of studying risk factors for kidney disease.

Options	Bidaykol	Sunakata	Shardara
Quantity	758	297	649
Average age	41 ±14	44 ±15	43 ±16
Men	241 (31.8%)	119 (40.1%)	197 (30.4%)
Women	517 (68.2%)	178 (59.9%)	452 (69.6%)
Main nephrological diagnosis, %			
Chronic pyelonephritis	647 (85.4%)	242 (81.5%)	520 (80.1%)
Tubulointerstitial nephritis	84 (11.1%)	53 (17.9%)	118 (18.2%)
Urolithiasis disease	20 (2.6%)	1 (0.3%)	4 (0.6%)
Kidney cyst	6 (0.8%)	1 (0.3%)	5 (0.8%)
Glomerulonephritis	1 (0.1%)	0 (0.0%)	2 (0.3%)

Among the residents of villages with kidney diseases selected for the study, a possible association with risk factors was analyzed: age, gender, employment status, length of residence in the area near the uranium deposit. When comparing the frequency of occurrence of kidney disease among the residents of the villages studied by age, no distinct patterns could be identified. The mean age of the nephrological patients in the main group was 41 years, while in the control groups it was slightly higher than 43-44 years. Kidney diseases in all villages prevailed in women with a noticeable statistically significant preponderance (p = 0.01): 2.1 in the village of Bidaykol, 1.4 times in the village of Sunakata, 2.2 times in Shardara. The high incidence of kidney disease among women is well known, so, according to statistics, pyelonephritis occurs 5-7 times more often in young women than in men (Wang *et al*. 2020). Statistically significant correlations were identified in terms of the “employment status” parameter in residents with kidney disease: for instance, in the main group, 53% of cases of kidney pathology occurred in the employed population, while in the control groups opposite to kidney pathology, it was more common in the non-employed population: higher than 60% ($p < 0.001$). An analysis was made of the incidence of kidney diseases in people, depending on the length of stay in the territory in the zone of influence of a uranium mining enterprise. To do this, the population was divided into groups: living in the area for 10-20 years, 20-30 years and more than 30 years. No significant differences were found between the groups. The possible association with risk factors was then analyzed separately in men with kidney disease. The fact is that due to the anatomical and physiological characteristics of the urinary system, women are more likely to suffer from pyelonephritis may be due to hormonal alterations during pregnancy that put additional strain on the kidneys, using hormonal contraceptives, etc. (Haroun *et al*. 2003). Many concomitant risk factors for renal disease in women make it difficult to establish a causal relationship between nephrological disease and radiochemical environmental factors in a uranium province. In this case, significant relationships were found in men with nephrological pathology with the length of stay in the villages between the population of the village of Bidaykol and Sunakata (Table 2).

Table 2. Population with kidney disease, depending on the length of residence in the village.

Index	Categories	Locality		p
		Bidaykol village	Sunakata village	
Length of stay in the area	Over 30 years	13.4%	23.9%	0.028*
	20-30 years old	85.8%	76.1%	
	10-20 years	0.8%	0.0%	

* differences in indicators are statistically significant ($p < 0.05$).

As shown in Table 2, kidney diseases are recorded in men of the main group during previous stays in the area in the sphere of influence of the uranium mining company. As shown in Table 1, most subjects in the final diagnosis revealed chronic pyelonephritis and chronic tubulointerstitial nephritis. With regard to the final diagnostic parameter ($p = 0.312$), we could not determine any statistically significant differences between the main and the control group. Next, we analyzed the disease history as well as the available results from laboratory and instrumental studies. Among the complaints of patients, pain in the lumbar region, frequent urination, and weakness were more often reported. Some patients reported mostly nocturnal urination. In the case of renal diseases, it is recommended to carry out a standard examination algorithm, including: general urinalysis, bacteriological analysis of urine, complete blood count and biochemical blood test. With pyelonephritis in a laboratory study of urine, leukocyturia and bacteriuria are usually detected. Minor proteinuria, microhematuria, hypostenuria and alkaline urine reaction are possible (Dasaeva *et al*. 2012). In tubulointerstitial nephritis, inflammatory damage to the structures of the renal tubulointerstitium occurs due to the influence of various factors, including toxic ones. This pathology is characterized by a clinical violation of the concentration and often the filtration function of the kidneys. In the KLA, a decrease in the relative density of urine, its alkaline reaction, erythrocyturia, sterile (no bacteriuria), leukocyturia, proteinuria, which does not reach 3 g/day or is absent at all, are usually noted (Sigitova & Arkhipov 2010). In the population of the main group with kidney pathology, data from a general urine test in outpatient cards was 392 people (51.7%), in Sunakat 98 (57%), and in Shardara, 346 (53.3%). Deviations from the norm in the analysis are presented in Table 3.

Table 3. Characteristics of urinalysis in a population with kidney disease (%).

Index	Bidaykol	Sunakata	Shardara
Proteinuria	17.8	11	12.6
Enlargement of squamous epithelium	40.8	39.7	42.8
Leukocyturia	58.6	78.1	75.6
Hematuria	0.5	-	0.8
Salts in the urine	23.0	24.7	20.8
Bacteriuria	1.5	-	2

As shown in Table 3, the main qualitative abnormalities in the urinalysis at each site were leukocyturia, an increase in squamous epithelium and urinary salt, with uric acid and proteinuria being predominant. The significantly less frequent leukocyturia in the main group compared to the control group and the more frequent proteinuria were

pointed out. In general, the pathological changes revealed in urinalysis are characteristic of both pyelonephritis and tubulointerstitial nephritis, but the absence of bacteriuria in patients makes differential diagnosis difficult.
In the case of renal diseases, it is recommended to perform ultrasound of the urinary system organs from instrumental research methods, which allows diagnosing parenchymal oedema during exacerbation, as well as a decrease in the size of the kidney, its deformation, and increased echogenicity of the parenchyma (signs of nephrosclerosis) in long-term pyelonephritis (Ciccarese *et al*. 2021). Instrumental studies conducted with these residents also did not clarify the situation: in the main group, only 52 people had ultrasound data, half had no pathology, the rest had almost the same conclusions: expansion of the pyelocaliceal system of the kidneys and signs of chronic pyelonephritis. A similar situation was observed in the control groups. All chronic tubulointerstitial diseases eventually lead to chronic renal failure, regardless of the primary lesion (glomerular, vascular, or directly tubulointerstitial; Meola *et al*. 2016). Among residents of the village of Bidaykol with kidney diseases, only 5 people suffered from chronic pyelonephritis complicated by chronic renal failure, while in Sunakat and Shardara there were 2 people. Currently, it is generally accepted that comorbidities largely determine the clinical severity and long-term survival prognosis of a patient with renal disease (Vedernikova *et al*. 2010). Data on the comorbidity of nephrological patients was collected in the analysis of outpatient records. The most common comorbidities in the main group were arterial hypertension (22%), osteochondrosis (10.4%), chronic cholecystitis (8.7%), anaemia (5.0%), etc. In the control groups, arterial hypertension was also recorded as a comorbidity, but the differences in the odds for the presence of arterial hypertension in renal diseases between the main and control groups were not statistically significant (95% CI: 0.739 - 2.322). Anaemia in the population of Bidaykol village with kidney pathology was detected in 219 people (28.9%), while in the control groups as a concomitant pathology, anaemia occurred in 29 (9.8%) and 54 (8.3%), respectively ($p< 0 .001$). In addition, there were significant differences in the chances in the main group, where among the concomitant pathology in men, prostatitis occurred 10 times more often than in the population of the control group (95% CI: 1.708 - 19.076, $p = 0.002$). At the stage of the epidemiological study, we encountered a number of difficulties and limitations. Firstly, it was a small number of qualified specialists working in the polyclinic compound in the villages of the Kyzylorda region, which made it difficult to assess the real prevalence and structure of kidney diseases at all stages of their development. The high prevalence of kidney diseases in the population living in the sphere of influence of the uranium industrial enterprises underlines the importance of their timely, i.e. early detection and adequate prevention and therapy, which today is not possible without the involvement of a nephrologist. There were no such specialists in the villages. In the next step of our study, the uranium concentration in the urine of the residents of the examined settlements was examined. The concentration of natural uranium in the urine of people all over the world whose occupation does not involve occupational contact with uranium is 0.040-0.40 g L^{-1} (Snyder & Cook, 1975; Tolmachev *et al*. 2006). Notably, the upper limit of this range (0.40 g L^{-1}) was found in the area with a high concentration of natural uranium in the water (Roth *et al*. 2001). The results of the study of the concentration of uranium in the urine of the population showed the following results (Table 4): 117 urine samples exhibited normal values of uranium content, only one resident (1.5%) of the village of Bidaykol displayed an excess of the conditional limit (0.47 µg L^{-1}).

Table 4. The content of uranium in urine (µg L^{-1})

	Bidaykol	**Sunakata**	**Shardara**
Number of samples	66	22	30
Range	$0,9 \cdot 10^{-4}$-0,467	$0,74 \cdot 10^{-4}$-0,188	0, $54 \cdot 10^{-4}$ -0,188
Average value	$0,92 \cdot 10^{-1}$ *	$0,57 \cdot 10^{-1}$	$0,38 \cdot 10^{-1}$*

* $p < 0.001$ (according to the Kruskal-Wallis test).

Nevertheless, the average uranium concentration in the urine of residents of Bidaykol village was 1.6 times higher than in Sunakata village and statistically significantly 2.4 times higher than in Shardara. Some studies in this direction have shown a connection between the concentration of uranium in urine and microalbuminuria, but no connection with the clinical manifestations of kidney disease has been established (Arzuaga *et al*. 2010; Okaneku *et al*. 2015). In our study, we could not establish direct correlations, but indirectly, the uranium concentration in urine and the prevalence of kidney diseases were changed in the same direction: in Bidaykol village, the prevalence of nephrological diseases was changed, so that, the uranium concentration in urine was the highest, since it was changed from of the uranium industry in the village. These numbers were lower in Sunakata and even lower in Shardara village. As part of this study, methodological recommendations with the main organizational approaches to reducing radiation risks and somatic morbidity in the population living in the sphere of influence of technogenic radiation factors by uranium industrial enterprises were formulated and published. This can only be done with the joint participation of local medical organizations, employers and the residents of these settlements themselves.

In particular, recommendations were made:

1) Conducting systematic studies of the radiation situation in the territory of settlements located in the vicinity of uranium mining enterprises;

2) Carrying out annual dynamic monitoring of the state of health in the population within the framework of preventive examinations and medical examinations living in the sphere of influence of uranium mining companies, taking into account the prevalence of kidney diseases and with special attention to the inclusion of a nephrologist in the medical commission;

3) Screening for kidney pathology should be carried out and be performed on all subjects exposed to technogenic risk factors as well as on subjects with complaints suggesting the presence of renal pathology: polyuria or oliguria, nocturia, arterial hypertension unexplained for other reasons;

4) When performing a survey on the population of the uranium provinces, depending on the indications, it is recommended to conduct biochemical blood tests with the determination of the level of creatinine, potassium, calcium, chlorine, as well as the determination of the concentration of uranium in the urine as biological markers of the risk of developing eco-dependent kidney pathology.

CONCLUSION

In this study, we collected and analyzed data on the urinary uranium concentration of the population living close to a uranium mining company and on the prevalence of kidney diseases that could potentially be associated with uranium exposure in the body. The results of the studies showed a high prevalence of kidney disease among residents living in the sphere of influence of the uranium industrial company: 239.5 per 1000 residents compared to two control groups. Kidney pathology was prevalent in the population over 40 years of age, was more common in women, and in men depended on the length of stay in the area in the sphere of influence of the uranium industrial enterprise. The structure of the kidney diseases was represented by tubulointerstitial kidney diseases. The concentration of uranium in urine in the Bidaykol settlement was above the conditional normal limit in 1.5% of the samples, the average values of the uranium concentration were higher in the main group and decreased by elevating distance from the uranium industrial enterprise. The prevalence of kidney disease and the urinary uranium content in the study groups was changed in the same direction. In conclusion, based on the data of our studies, the health risk associated with uranium exposure for the adult population is still probable. The facts considered provide sufficient reason to consider the high prevalence of pathologies of the urinary system as one of the important indicators of environmental diseases to consider.

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Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the local bioethical committee of NJSC "Astana Medical University" (protocol No. 9 dated September 15, 2020).

Informed Consent Statement

Informed consent was not required.

Conflict of Interest

The authors declare no conflict of interest.

Author Statement

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