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Original Article

Trends in SARS-CoV-2 seroprevalence in Albania during the 2021–2022 pandemic year

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ABSTRACT

Background: Monitoring SARS-CoV-2 seroprevalence dynamics during the COVID-19 pandemic is crucial for understanding population immunity and providing insights into public health policies. Limited data exist on this from Albania and other Eastern European countries. This study aimed to investigate SARS-CoV-2 seroprevalence in Albania, comparing August 2021 and August 2022 data from two representative samples of the general population. The objective was to understand the temporal dynamics of SARS-CoV-2 antibodies across age groups and assess the impacts of natural infection and vaccination on population immunity.

Methods: This longitudinal study was conducted in two consecutive cross-sectional assessments 12 months apart in Albania's urban all-ages population. IgG anti-Spike-1 and anti-Nucleoprotein SARS-CoV-2 antibodies were measured using ELISA, focusing on seropositivity rates and antibody levels.

Methods: The study encompassed 2143 and 2183 individuals in August 2021 and 2022, respectively, with the anti-S1-IgG seropositivity rate escalating from 70.9 % to 92.1 %. In 2021, seroprevalence ranged from 49.6 % (0–15 years) to 82 % (>60 years). By August 2022, it surpassed 90 % in most age groups, except 0–15 years (73.8 %). "Hybrid" immunity (COVID-19+ and Vaccine+) reached 56.6 % in 2022, or 2.8 times higher than in 2021, exhibiting the highest antibody levels compared to the only vaccinated or previously COVID-19-infected individuals.

Conclusion: This study highlights an overall 94 % seroprevalence in the Albanian population in August 2022 and robust "hybrid" immunity, suggesting substantial protective immunity against SARS-CoV-2. The lower immunity in the 0–15 age group underscores the necessity for youth-targeted vaccine campaigns. These findings provide valuable insights for shaping healthcare measures and vaccination policies.

1. Introduction

Evaluating trends in SARS-CoV-2 seroprevalence has been essential for determining the population's immune status to the virus during the Covid-19 pandemic [1]. Although seropositivity does not necessarily indicate immune protection, information about SARS-CoV-2 seroprevalence helps evaluate the anti-SARS-CoV-2 immune response in specific population sectors, including different age groups [2,3]. Seroprevalence data can provide valuable information for guiding preventive measures and determining the most appropriate target and outreach strategies during vaccination campaigns [4,5]. Knowing the seropositivity rates, the levels of specific antibodies, and the extent of the influence of natural infection and vaccination in promoting an immune response against SARS-CoV-2 also provides information about the protective role of these

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antibodies in the population [6,7].

The seroprevalence of SARS-CoV-2 antibodies in different populations and age groups depends on various geographic, social, and economic factors, the vaccination rate, and other preventive measures within the population [8,9]. Because there has been little research on SARS-CoV-2 in Albania previously, we studied the seroprevalence of anti-SARS-CoV-2 antibodies in representative samples of the Albanian population to understand the temporal dynamic changes in the seroprevalence of these antibodies in different sectors of the population. Another goal of the study was to assess the effect of natural infection and vaccination on the population's level of immunity.

2. Materials and methods

2.1. Sampling methodology

Two consecutive cross-sectional assessments in the general population using two independent samples and covering all age groups were conducted 12 months apart, during July–August 2021 and July–August 2022, to represent the Albanian general population as much as possible. For this purpose, the population samples were randomly selected from electronic population registries of four urban primary health centers (HCs) in Tirana and one in Berat city, representing 281,000 inhabitants.

The physicians and head nurses in each of the five HCs were instructed to randomly select approximately 100 non-family related individuals from each of the five age groups studied (0–15 years, 16–30 years, 31–45 years, 45–60 years, and over 60 years) in intervals of every 20, from randomly sorted records of the electronic family doctor registries containing a list of all residents in their catchment area. Health professionals, other family members of participants, and individuals with acute health problems were considered non-eligible and were substituted by next in the list during sampling. The selected individuals were invited to participate in the study by phone calls and were asked to come to the HC to provide a blood sample and participate in an interview after approval for the study and laboratory testing.

A standardized questionnaire collected information about the participants' demographics and health status, including symptoms of previous COVID-19 infection and vaccination data. For children under 18 years old, their parents provided the information. The blood samples were transported to the laboratory within three3 hours for serological testing.

The response rate varied among different age groups, with 25 % for those aged 0–15, 65 % for those aged 16 to 30, and 90 % for those over 30. In the age groups over 30, non-responders were replaced from the next in the electronic population list until at least 100 patients for each age group over 30 were recruited. This was not possible for those aged 0 to 30 due to the combination of low response rate and a small number of patients of this age seen at the HCs during the study period. To reach the minimum number of 100 individuals in younger age groups, children aged 0–15 years old visiting hospital ambulatory facilities for non-infectious health problems were enrolled, while in the 16 to 30-year-old group, high school and university students were also included.

2.2. Serological testing of IgG class anti-Spike (S1) and anti-Nucleoprotein (N) SARS-CoV-2 antibodies

Serological testing of all blood samples was conducted using an ELISA method with two commercially available diagnostic kits that detect the IgG class of anti-Spike 1 (S1) and anti-Nucleoprotein (N) SARS-CoV-2 virus antibodies (IgG Anti-S1-SARS-CoV-2 and IgG Anti-NCP-SARS-CoV-2 ELISA, Euroimmun, Luebeck, Germany). According to the manufacturer, the kits have a sensitivity and specificity of 94.4 % and 99.6 % for IgG anti-S1-SARS-CoV-2 and 94.6 % and 99.8 % for IgG anti-N-SARS-CoV-2, respectively. The results of both diagnostic kits were evaluated quantitatively by computing the sample's optical density ratio to that of the calibrator (Index Ratio or IR), following the manufacturer's protocol. For both antibody types, values above 1.1 were considered positive.

The primary outcomes were the seropositivity rate (using the 1.1 Index Ratio threshold) and the IR levels of IgG anti-S1-SARS-CoV-2 antibodies in the serum. Demographic factors (age groups) and immunity-related factors (previous infection and vaccination status) were used to define categories of interest. The differences in proportion rates and comparisons of median antibody levels for each category were compared using the chi-square test for categorical variables and Student's t-test for continuous variables or the Mann-Whitney *U* test in case of the non-normal distribution of variable series. Data analysis was performed using MedCalc®Statistical Software version 20.210 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2022).

The study protocol was approved by the ethical committee of the Albanian Academy of Sciences (Project number 33-07-05-2020), and informed written consent was obtained from all participants enrolled in the study.

3. Results

3.1. Seropositivity and antibody levels, previous COVID-19 infection, and vaccination rate among all individuals studied

In July–August 2021, 2143 individuals (age range 1–97, median 48 years) were included in the study, and one year later, in July–August 2022, 2183 other individuals (age range 0.2–87, median 48 years) were studied. Both samples had a similar distribution of sex and average age. The seropositivity rate of IgG anti-S1-SARS-CoV-2 antibodies in 2022 was 92.1 %, a 29.9 % increase from 2021 when the rate was 70.9 % ($p < 0.0001$) (Table 1).

In August 2022, participants reported 12.8 % more previous COVID-19 infections compared to 2021 (Table 1, $p < 0.0001$), while the percentage of vaccinated individuals was 29.1 % higher ($p < 0.0001$). Additionally, the rate of those with hybrid immunity (individuals who had both previous COVID-19 and had been vaccinated) [10] was 2.8 times higher in 2022 compared to 2021 ($p < 0.0001$) (Table 1).

Also, the proportion of asymptomatic seropositive individuals (those with positive anti-S1-SARS-CoV-2 seropositivity, unvaccinated, and with no previous COVID-19 disease) in 2022 was 11.4 % higher compared to 2021 ($p = 0.0001$) (Table 3).

Among all individuals studied, 3.1 % in 2021 and 1.8 % in 2022 were found to have the serological profile S1-IgG (−) and N-IgG (+). Considering these persons as seropositive and adding them to the S1-IgG (+) category, the overall SARS-CoV-2 seroprevalence was estimated to be 73.5 % in 2021 and 93.9 % in 2022.

The median level of anti-S1-SARS-CoV-2 antibodies in all individuals in 2022 was 2.4 times higher compared to 2021 (Table 1). Fig. 1 presents the index ratio (IR) levels of anti-S1-SARS-CoV-2 IgG antibodies among the subgroups of individuals with different previous COVID-19 infection and vaccination statuses. The figure clearly shows that in August 2022, all the values were significantly higher than in August 2021, except for individuals with hybrid immunity (Covid+ and Vaccine+), which show the same high antibody levels. In both years, the highest anti-S1-SARS-CoV-2 antibody values were found among the individuals with hybrid immunity (Covid + Vaccine+), followed by those only vaccinated (Covid-Vaccine+) and those with only previous COVID-19 infection (Covid + Vaccine-) (Fig. 1).

Regarding IgG antibodies against N-SARS-CoV-2, the seropositivity rate was generally lower than that of anti-S1-SARS-CoV-2 IgG antibodies. Among the unvaccinated individuals with previous COVID-19 infections (Covid + Vaccine-), the seropositivity of IgG antibodies against S1-SARS-CoV-2 was 76.3 % in 2021 and 83.3 % in 2022, while the seropositivity of anti-N-SARS-CoV-2 IgG antibodies was 62.6 % in 2021 and 66.7 % in 2022.

Table 1
Anti-SARS-CoV-2 IgG seropositivity and antibody levels, previous COVID-19 infection, vaccination rate, and demographic characteristics in August 2021 and 2022.

Year	Main characteristics and anti-SARS-CoV-2 seropositivities of the two general population samples studied							
	Nr. of individuals studied	Sex (% females; 95 % CI)	Age (years; median; 95 % CI)	IgG anti-S1 Seropositivity (%; 95 % CI)	IgG anti-S1 IR (median; 95 % CI)	IgG anti-N Seropositivity (%; 95 % CI)	Covid (+) Individuals (%; 95 % CI)	Vaccine (+) Individuals (%; 95 % CI)	Covid (+) and Vaccine (+) Individuals (%; 95 % CI)
August 2021	2143	59.4 % (57.2–61.4)	48 (47–49)	70.9 % (68.9–72.8)	2.78 (2.63–2.98)	38.9 % (36.7–41.2)	48.8 % (46.6–51.1)	43.4 % (41.0–45.7)	19.9 % (18.1–21.9)
August 2022	2183	59.9 % (57.8–61.9)	48 (47–50)	92.1 % (90.9–93.2)	6.75 (6.67–6.88)	60.4 % (58.3–62.5)	61.6 % (59.3–63.7)	72.5 % (70.6–74.4)	56.0 % (53.9–58.2)
Statistical significance		$p = 0.7375$	$p = 1.00$	$P < 0.0001$	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$

3.2. Differences by age categories

In August 2021, the lowest seroprevalence rate of anti-S1-IgG antibodies was 49.6 % among ages 0 to 15. Other age groups showed a progressive increase in seroprevalence, ranging from 57.3 % for 16 to 30-year-olds to 82.0 % for those over 60 (Table 2).

One year later, in August 2022, compared to 2021, the seroprevalence of anti-S1-IgG was 24.2 % higher in the 0 to 15 age group ($p = 0.0002$) and 34.9 % higher in the 16 to 30 age group ($p < 0.0001$). The other age groups showed an increase of 27.8 % ($p < 0.0001$), 16.7 % ($p < 0.0001$), and 11.8 % ($p < 0.0001$), in the 31 to 45, 46 to 60, and over 60 age groups, respectively. In August 2022, in all age groups, the anti-S1-IgG seroprevalence was over 90 %, except for the 0 to 15 age group, which remained at 73.8 % (Table 2).

In 2022, the level of anti-S1-IgG showed the most significant increase in the 16–30 age group (4.4 times, $p < 0.0001$). In the other age groups, we observed a more moderate but still highly significant rise ($p < 0.0001$) in antibody levels (2.9, 2.9, 1.8, and 1.66, in the age group 0–15 years, 31–45 years, 46–60 years, and >60 years, respectively) (Table 2).

In August 2021, the lowest percentage of previous COVID-19 infection was found in children under 15, with 18.2 %, while at the other age groups, these rates were similar, ranging from 58.6 % in the 16–30 age group to 45.4 % in those over 60. In August 2022, all age groups reported similar levels of previous COVID-19 infection (61.1 %–66.0 %), while the 0 to 15 age group remained at 26.5 % (Table 2).

The rate of those reporting to have been vaccinated with at least one dose of vaccine in 2022 was zero in the age group 0–15 years, consistent with Albania's not introducing the children vaccination at that time. In the other age groups, the reported vaccination rates ranged from 69.9 % in the 16–30 age group to 73.8 %, 78.5 %, and 79.7 % in the age groups 31–45, 46–60, and over 60 years, respectively ($p = 0.0004$) (Table 2).

In 2021 and 2022, asymptomatic seropositive individuals were more frequently found among 0 to 15-year-old children (71.7 % and 68.3 %, respectively) (Table 3). This proportion gradually decreased with age in 2021 (from 38.6 % among 16 to 30-year-olds to 27.6 % among those over sixty), although without statistical significance ($p = 0.09$). In August 2022, there was a statistically nonsignificant increase in the proportions of asymptomatic seropositive individuals across the age groups (from 35.5 % in the 16 to 30 age group to 43.5 % in those over 60 ($p = 0.250$) (Table 3).

4. Discussion

In this report, we present the results of our study on trends in anti-SARS-CoV-2 IgG seroprevalence rates and antibody levels among the Albanian population of all ages, comparing data from August 2021 (just before the start of the Delta variant wave) to data from August 2022 (when the Delta and Omicron variants had already spread through the population).

At the very beginning of the pandemic, it was predicted that the immunization of about 70 % of the population would be sufficient to reach the herd immunity threshold [11]. Still, the emergence of the Delta and Omicron variants with higher transmission rates and better ability to evade immunity changed the rules, leading to the continued spread of the virus despite the higher immunization rates [12].

Despite an anti-S1-IgG seroprevalence of 73.5 % in August 2021, the SARS-CoV-2 infection continued spreading in Albania during the Delta and Omicron variant waves. However, in August 2022, at the end of the second Omicron wave, the overall seroprevalence of anti-SARS-CoV-2 IgG antibodies reached 93.9 %. In the following months and until November 2023, despite the arrival of the cold season and new Omicron subvariants, infection rates remained stable, and no new epidemic waves were observed in Albania [13]. This finding suggests that the 93.9 % seroprevalence figure obtained in the general Albanian population in August 2022 probably represents a dynamic level of protective immunity against SARS-CoV-2, preventing further epidemic waves of

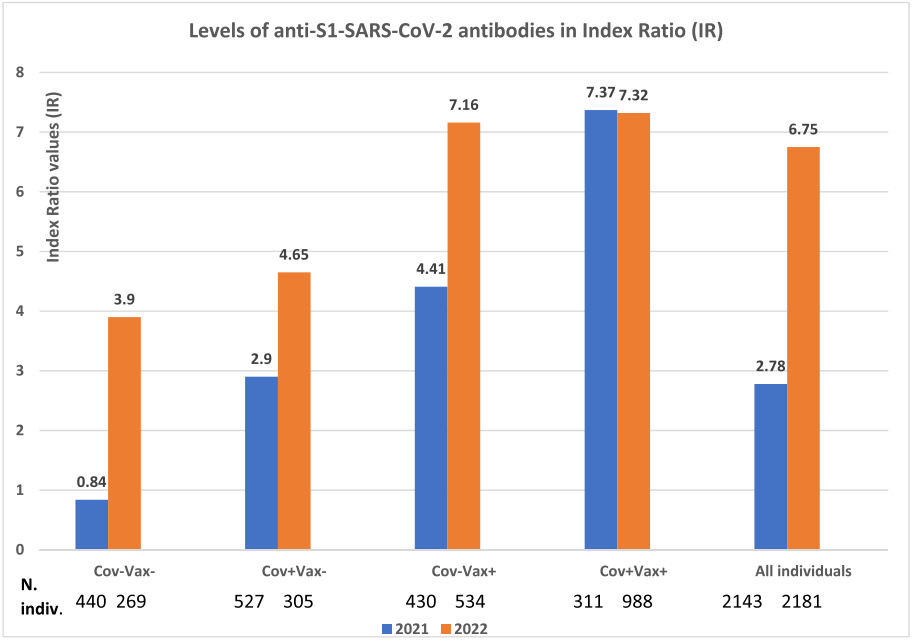

Fig. 1. Anti-S1-SARS-CoV-2 IgG antibody levels (in Index Ratio: IR) among the individuals studied in 2021 and 2022 classified into subgroups according to their past-COVID-19 infection and vaccination status.

Table 2
Main characteristics and seropositivity rates and levels of anti-S1-SARS-CoV-2 IgG antibodies by age groups in August 2021 and 2022.

Parameters studied	Age groups					
	Age in years	0–15	16–30	31–45	46–60	>60
Nr. of individuals	**2021**	121	379	490	651	500
	2022	107	374	462	592	648
Females (%, 95 % CI)	**2021**	39.7 (31.0–52.0)	57.8 (52.5–62.8)	58.8 (54.3–63.2)	63.6 (59.8–67.3)	54.8 (50.3–59.2)
	2022	42.1 (32.6–49.0)	65.2 (60.2–70.1)	56.9 (52.3–61.5)	64.7 (60.7–68.6)	57.4 (53.5–61.3)
Median age in years; (95 % CI)	**2021**	6 (4–8)	21 (20–22)	38 (38–39)	53 (53–54)	66 (65–67)
	2022	4 (3–6)	21 (21–22)	39 (38–39)	54 (53–54)	67 (66–68)
S1-IgG seropositivity (%, 95 % CI)	**2021**	49.6 (40.4–58.8)	57.3 (52.1–62.3)	63.3 (58.8–67.5)	77.4 (74.4–80.6)	82.0 (78.0–85.3)
	2022	73.8 (64.5–81.8)	92.2 (89.1–94.7)	91.1 (88.2–93.6)	94.1 (91.9–95.5)	93.8 (91.7–95.5)
Median S1-IgG IR (95 % CI)	**2021**	0.96 (0.38–1.79)	1.5 (1.29–1.8)	2.17 (1.59–2.72)	4.0 (3.35–4.41)	4.41 (3.98–4.88)
	2022	2.77 (1.9–3.77)	6.6 (6.3–6.7)	6.2 (5.9–6.5)	7.27 (7.0–7.42)	7.3 (7.1–7.5)
Individuals with previous COVID-19 (%, 95 % CI)	**2021**	18.2 (11.8–26.2)	58.6 (53.2–63.9)	49.9 (45.0–54.8)	51.7 (47.7–55.7)	45.4 (41.0–49.9)
	2022	26.5 (18.2–36.1)	62.1 (56.9–67.1)	64.0 (59.4–68.4)	66.0 (62.0–69.9)	61.2 (57.3–65.1)
Vaccinated individuals (%, 95 % CI)	**2021**	0.0	15.7 (10.7–21.9)	33.5 (29.0–38.3)	41.6 (37.7–45.6)	64.0 (59.6–68.2)
	2022	0.0	69.9 (65.0–74.5)	73.8 (69.5–77.8)	78.5 (75.0–81.8)	79.7 (76.3–82.7)

Table 3
Percentage of asymptomatic individuals by different age groups studied in August 2021 and 2022.

		Group-ages in years					
		0–15	16–30	31–45	46–60	>60	All ages
[a]Percentage of asymptomatic individuals (95 % CI)	2021	71.7 (58.6.-82.5)	38.6 (28.1–49.0)	33.1 (25.2–41.4)	30.5. (24.7–36.7)	27.6 (20.0–36.2)	31.8 (28.1–35.7)
	2022	68.3 (56.9–78.4)	35.5 (25.8–46.1.)	36.2 (26.5–46.7)	37.3 (27.9–47.4)	43.5 (34.0–53.4)	43.2 (38.7–47.7)
Statistical significance		p=0.5766	p=0.3788	p=0.3076	p=0.0114	$P < 0.0001$	$P < 0.0001$

[a] Asymptomatic individuals are calculated as the ratio of S1-IgG (+) Covid (−) Vaccine (−) individuals to all S1-IgG (+) Vaccine (−) (%; 95 % CI) individuals.

COVID-19 cases.

Global SARS-CoV-2 seroprevalence in the world increased sharply during 2021 due to high levels of infection in some regions, such as Africa (from 26.6 % to 86.7 %), and mass vaccinations in other high-income countries, such as in Europe (from 9.6 % to 95.9 %) [14]. In the USA, between August 2021 and May 2022, 91.5 % of adults had SARS-CoV-2 anti-S antibodies, and 41.6 % had anti-N antibodies [15].

In the age group 0–15 years, we observed a seroprevalence of only 73.8 % in July–August 2022. This finding is mainly due to widespread reluctance among the population to vaccinate young children [16]. This low level of immunization in this age group leaves them highly susceptible to natural infection with SARS-CoV-2. However, clinical infections among children are milder and with fewer complications than in older age groups [17]. This pattern is supported by the high rate of asymptomatic infection in the 0 to 15 age group, estimated to be around 70 % in our study over the two observed years. In comparison, the

asymptomatic infection rate fluctuated from 30 to 45 % among older age groups, as has also been reported by other authors [18,19].

In Romania, an Eastern European country, the overall seroprevalence of SARS-CoV-2 antibodies in children was 46.7 % in June 2021, similar to the findings in our study [20]. In contrast, during the same time interval, a German study found a seroprevalence of only 14.6 % in children aged 0 to 17 [21]. As of February 2022, approximately 75 % of children and adolescents in the US had evidence of previous infection with SARS-CoV-2, with one-third becoming newly seropositive since December 2021 [22]. In Navarra, Spain, the seroprevalence among 5 to 17-year-olds was estimated at 85.1 % in April–June 2022 [23].

In our study, the level of anti-S1-SARS-CoV-2 IgG antibodies, which contribute to the population's immune protection, was 2.4 times higher in July–August 2022 than in the same period of 2021. High levels of anti-Spike-SARS-CoV-2 IgG antibodies have been shown to correlate with neutralizing antibodies, which are a well-known indicator of protective immunity against the virus [24].

We detected anti-N-SARS-CoV-2 IgG antibodies in only about 80 % of unvaccinated individuals who tested positive for anti-S1-SARS-CoV-2 IgG antibodies. This finding confirms other studies that have reported a faster decline of these antibodies after infection and have concluded that anti-N-SARS-CoV-2 antibodies have no value in assessing the long-term immune response after infection with SARS-CoV-2 [25].

The anti-S1-SARS-CoV-2 seroprevalence increase in August 2022 results from the vaccination campaign for individuals over 15 years old and the circulation of the virus in the community. In our study, over 60 % of the interviewed individuals, excluding the 0-15-year-old age group, reported having experienced previous COVID-19 infection. This result reflects a high level of hybrid immunity in the Albanian population, found in 56 % of our general sample population. Hybrid immunity indicates a high level of protection [26]. A population study in the Dominican Republic found hybrid immunity in 37 % of individuals from June to October 2021 [27].

Our study has limitations, such as the limited number of individuals in the 0-15-year-old age group producing a relatively wide 95 % CI of the seroprevalence at this age. The humoral immunity was studied only through anti-S1 and anti-N SARS-CoV-2 and not SARS-CoV-2 neutralizing antibodies. The data on previous clinical COVID-19 infection and vaccination were obtained from self-reported data and not through medical records. Also, more women (60 %) than men were studied because more women were enrolled at Albanian HCs during the study period.

To the best of our knowledge, there are no previously published data on the changes in COVID-19 seroprevalence rates in Eastern European countries in the August 2021–August 2022 time interval, which included the period just before and immediately after the Delta and Omicron epidemic vawes. In a previous publication, we reported a rise in the seroprevalence rate among the Albanian population over 18 years of age, from 48.2 % in December 2020 to 73.3 % in August 2021 [28].

In conclusion, our data suggest that the overall SARS-CoV-2 seroprevalence rate of approximately 94 % in the Albanian population in August 2022, along with a high level of hybrid immunity, provide strong evidence that this population may have reached the herd immunity threshold level at that time point. The 0-15-year-old age group presents a lower level of immunization and is at risk for spreading the virus, warranting a vaccine awareness campaign. Additionally, elderly individuals and those with weakened immune systems should receive booster vaccinations to prevent infection or re-infection from new SARS-CoV-2 variants.

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Ethical consideration

The study was approved by decision Nr. 33, dated May 7, 2020, of the Ethics Committee of the Academy of Sciences of Albania. All study participants provided written informed consent.

Author contributions

Sulcebe, Ylli, Cenko, Prifti, Shyti, Dashi-Pasholli had full access to all the study data, and they take responsibility for their integrity and accuracy.

Concept and design: Sulcebe, Ylli, Cenko, Perry.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Sulcebe, Perry, Ylli, Cenko.

Critical revision of the manuscript for important intellectual content: Perry, Sulcebe, Ylli, Cenko.

Statistical analysis: Sulcebe, Cenko, Ylli, Prifti, Shyti, Dashi-Pasholli.

Manuscript revision: All authors.

Obtained funding: Sulcebe, Ylli.

Administrative, technical, or material support: Sulcebe, Ylli,

Supervision: Sulcebe, Ylli.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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