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The evaluation of complete blood count ratios in children with 2019 novel coronavirus (2019-ncov) infection

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Abstract

We investigated hematological parameters included WBC, neutrophil, lymphocyte, monocyte, eosinophil, basophil and platelet count. Moreover, we evaluated hematological ratios such as NLR, MLR, ELR, BLR, PLR and MPV/PC. Two groups were classified as positive RT-PCR with bilateral patchy shadows or ground-glass opacity in their lungs and negative RT-PCR for 2019-nCoV. A total of 204 children were enrolled 2019-nCoV positive and negative. Seven 2019-nCoV positive patients were asymptomatic. Fever was mostly seen symptom in 2019-nCoV positive and negative patients at admission. White blood cell, neutrophil, monocyte, eosinophil, basophil and platelet count were significantly lower in 2019-nCoV positive patients than that of negative patients ($p<0.05$). While NLR, MLR, PLR and MPV/PC had no statistically difference, ELR and BLR ratios showed distinct significance between two groups ($p<0.05$). Hematologic indices haven't been analyzed before in children with 2019-nCoV. WBC, ELR and BLR might be valuable ratios for the situation of inflammation in coronavirus infection.

Keywords: Children, hematology, infection, lymphocyte, novel coronavirus

Introduction

The novel coronavirus disease-2019 (2019-nCoV) is clearly shown as a pulmonary infection, emerging data indicate that it should be regarded as a systemic disease involving many organs including cardiovascular, respiratory, gastrointestinal, neurological, hematopoietic and immune system [1-3]. In the incubation period and the early phase of the disease, white blood cell count (WBC) and lymphocyte counts are normal or a little diminished. The patient admitted firstly might have lymphocytopenia; some of them had thrombocytopenia, and leukopenia. There is distinctive relation with increased neutrophils and decreased lymphocytes for pulmonary disease [4].

Neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), eosinophil-to-lymphocyte ratio (ELR), basophil-to-lymphocyte ratio (BLR), platelet-to-lymphocyte ratio (PLR), and mean platelet volume-to-platelet count (MPV/PC) ratio have been investigated as potential biomarkers from routine complete blood count (CBC) in the clinical setting. Previous investigations pointed that NLR and MLR were not limit in normal and were related to inflammation [5]. PC correlated with MPV may indicate autoimmune disease activity, response to anti-inflammatory therapies, and presence of various comorbidities [6]. CRP (C-reactive protein) is used mostly as a diagnostic marker in acute inflammation [7]. CRP was elevated in 60.7% of patients, high lactate dehydrogenase (LDH) was seen in 41% of patients. Considerable sick patients showed more increased LDH levels than that of non-severe ones [8,9].

The hematological results data in children with 2019-nCoV infection is limited. The aim of our study is to investigate hematological parameters included WBC, neutrophil, lymphocyte,

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monocyte, eosinophil, basophil and platelet count. Moreover, we also wanted to study hematological indices such as NLR, MLR, ELR, BLR, PLR and MPV/PC levels whether they have conventionally significant value in children with 2019-nCoV infection.

Materials and Methods

Study design and patients

The study was retrospectively conducted with hospital electronic medical information system between March and May 2020 in a university hospital (Kartal Dr. Lutfi Kirdar City Hospital, Istanbul, Turkey) and the approval of study was obtained from the Ministry of Health. Two groups were classified as positive real time reverse transcriptase-polymerase chain reaction (RT-PCR) with bilateral patchy shadows or ground-glass opacity in their lungs and negative RT-PCR for 2019-nCoV infection. Children with 2019-nCoV positive and negative, aged ≤18 years old were included. Age, gender, symptoms such as cough, fever, myalgia, dyspnea and sore throat were recorded in both group. Patients had no symptom and only with suspicion of contagiousness were classified as asymptomatic. The ethical approval was obtained from "The Local Scientific Research Permission Commission" (document no: 2020/514/177/4) and performed in suitability with the Helsinki Declaration ethical rules. Parental written informed consent was received for all the children.

A nasopharyngeal swab was collected from single nostril from all children presented with fever, muscle ache, sore throat and respiratory symptoms such as cough and shortness of breath according to our Health Ministry guideline [10]. Polymerase chain reaction (PCR) was used for detecting viral RNA (ROCHE Light Cycler RT-PCR). All children hospitalized after RT-PCR methods generated positive results and chest computed tomographic scans showed bilateral patchy shadows or ground-glass opacity in the lungs.

Blood specimens were obtained for full blood count into BD Vacutainer K2 EDTA tubes within 2 hours from venipuncture. Differentials including lymphocytes, neutrophil, monocyte, eosinophil, basophil, platelet and MPV were recorded at enrollment. The analysis was performed by impedance method (Beckman Coulter LH 780). Turbid metric method (Roche Cobas C 501) was used for serum CRP levels. The normal reference values for the parameters were as follows: White blood cell 4–10×109/L; neutrophil 1.9–8×109/L; lymphocyte 1.5–4.5×109/L; monocyte 0-1×109/L; eosinophil 0.15–0.2×109/L; basophil 0.1×109/L; platelet 150–450 ×109/L, MPV 7.4-10.4 fL, C-reactive protein (CRP) 0-5 mg/dL and Lactate Dehydrogenase (LDH) 110-245 U/L.

NLR, MLR, ELR, BLR and PLR were determined by dividing absolute neutrophil, monocyte, eosinophil, basophil and platelet counts by absolute lymphocyte counts, respectively for each case. In addition, mean platelet volume (MPV) and platelet count (PC) were measured at the time of admission. MPV/PC ratio was calculated as [MPV value/(PC/103)]×100 for each patient [11].

Statistical Analysis

Data were evaluated by using SPSS (version 20, SPSS, Chicago, IL). Descriptive statistics are reported as the mean and standard deviation. The evaluation of linear correlation was done with Pearson correlation coefficient in two continuous variables. The results were visualized with using heatmap analysis. Normal distribution was estimated by Kolmogorov-Smirnov or Lilliefors test. Student t-test and Mann–Whitney U Test were used for normal and non-normal distributed data, respectively. Receiver operation characteristic (ROC) curve analysis were performed to determine cutoff values, sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV). $p<0.05$ was considered statistically significant.

Results

A total of 204 children including 103 boys (50.50%) and 101 girls (49.50%) mean aged 107.7±69.6 months (age range, 1 month to 18 years) were recorded in the study. Of these 98 and 106 patients were enrolled 2019-nCoV positive and negative, respectively.

The demographic and clinical features of patients are shown in Table 1. Children aged more than 96 months-year old were mostly recorded in both groups. Seven (7/98;7.14%) 2019-nCoV positive children were asymptomatic. Fever (81/204;39.70%) was the most common symptom in 2019-nCoV positive and negative patients at admission. Cough (30/98;30.62%), shortness of breath (5/98;5.10%) and sore throat (7/98;7.14%) were recorded in cases with 2019-nCoV positive. Among clinical features, muscle ache (9/98; 9.18%) was slightly considerable in children with 2019-nCoV infection. Although CRP levels were almost closely approximate in both groups, cases (12/106;11.32%) with 2019-nCoV negative had >50 mg/dl CRP level. Similarly LDH was more than 245 U/L in 2019-nCoV negative children than that of positive patients.

Mean CRP and LDH levels were mainly increased as 41.9±45.97 mg/dl and 249.3±73.1U/L, respectively in 2019-nCoV negative patients. The significant differences were not seen in age or gender between two groups. White blood cell, lymphocyte, neutrophil, monocyte, eosinophil, basophil and platelet count were lower in 2019-nCoV positive patients than that of negative patients. Among these parameters, statistical analysis of all patients revealed that WBC ($p<0.001$), neutrophil ($p<0.001$), monocyte ($p=0.011$), eosinophil ($p=0.003$), basophil ($p<0.001$), and platelet count ($p=0.001$) were strong significant in 2019-nCoV positive cases compared with negative ones. While NLR, MLR, PLR and MPV/PC had no statistically difference, ELR ($p=0.005$) and BLR ($p<0.001$) ratios showed distinct significance between two groups. Although MPV/PC ratio was not significant statistically, it was higher in 2019-nCoV positive patients than that of negative patients. In addition, there were statistically significant differences between 2019-nCoV positive and negative patients according to CRP ($p=0.001$) and LDH ($p=0.026$) values. Complete blood count results, NLR, MLR, ELR, BLR, PLR and MPV/PC of all patients are shown in Table 2. The comparing of all hematological parameters was depicted in scatter plot (Figure 1).

Receiver Operation Curve Values sensitivity, specificity, PPV and

NPV are given in Table 3. Sensitivity and specificity of 0.714 and 0.358 values respectively were recorded in the cutoff value of 2 for NLR. ELR distinguished 2019-nCoV positive cases from negative patients with the high sensitivity and specificity of 0.786 and 0.396 with a cutoff value of 0.058. For BLR, sensitivity 0.888 and 0.340 were highest if 0.010 was used as the cutoff value. Hematological parameters included WBC and basophil had larger AUC compared with 2019-nCoV positive and negative patients. Among ratios, BLR presented high AUC value. Corresponding heat maps of laboratory results were shown in Figure 2.

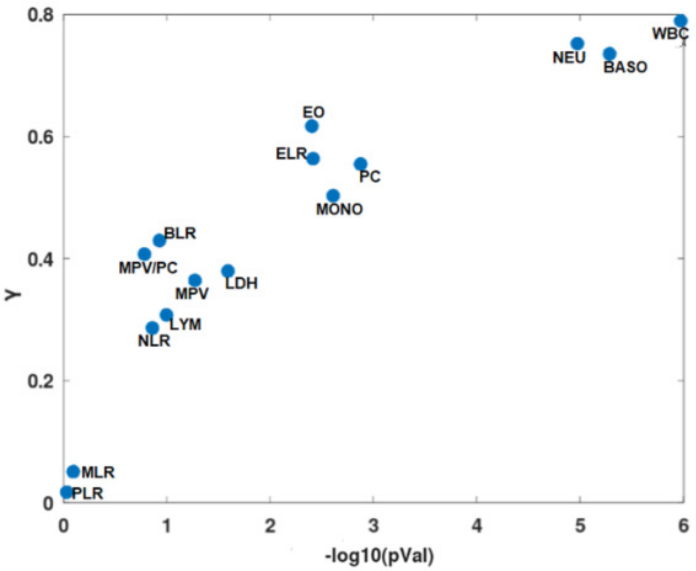

Figure 1. To assess whether a selected parameter can correctly identify the case or control groups, the gamma parameter has been defined as the ratio of distance between centroids of case and control groups and maximum of the total distance within each group. WBC was the dominant parameter.

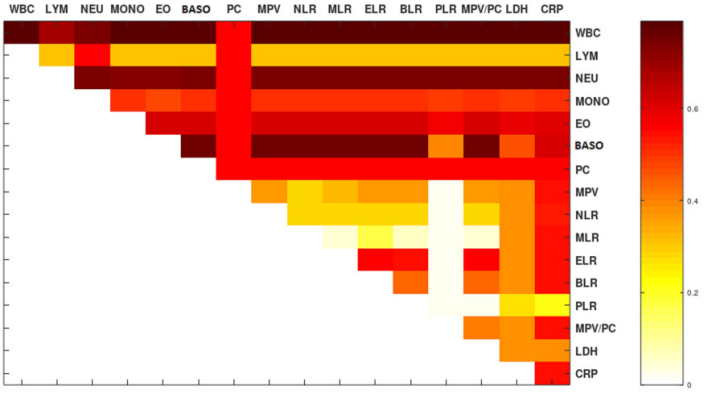

Figure 2. Correlation coefficient and significance levels based on laboratory results were shown with heatmap . WBC and BLR results showed a good-high correlation

Discussion

2019-nCoV infection is an acute and highly contagious respiratory disease. Children with 2019-nCoV positive were mostly presented slight symptoms due to their healthier pulmonary system and fewer underlying disease. Fever and cough that also seen in adults are the most common symptoms [12]. In Turkey, by the beginning of March 2020, even if the possibility of exposing to infectious people and environment is less, all families were in a flap and children with respiratory complaints were transferred to emergency services by their families. In our single center data, while fever was the most common symptom, asymptomatic cases whose history of close contact with 2019-nCoV infection diagnosed family members were barely seen. Almost all of patients were followed up without severe respiratory problem. It could be explained that 2019-nCoV positive children had no underlying organ dysfunction.

The data of hematological findings in children with 2019-nCoV infection are few in literatures. Previous studies showed that WBC count results were normal in most of the cases [13-15]. Wang et al. presented that WBC and lymphocyte counts decreased and PC increased [16]. An adult study noted that decreased WBC and lymphocyte counts related to severity of infection [17]. Another data noted that adult cases had significant lymphopenia, but not that of in children [15]. In our investigation, WBC, lymphocyte and neutrophil were decreased in 2019-nCoV positive patients compared to negative cases. Monocytes have an immune role for protecting the body from viral infection. Eosinophils and basophils are potent proinflammatory cells. Decreased eosinophils and basophils due to glucocorticoid secretion and increased monocytes may be found in viral infection [18]. In an adult report, the comparison between influenza and 2019-nCoV infection presented decreased monocyte and increased basophil in 2019-nCoV infection [19]. Once again, the comparing of our two groups demonstrated that monocyte, eosinophil and basophil counts were decreased in the present study. In an interesting manner, Zhang et al pointed that more than half the adult patients transferred with 2019-nCoV had eosinopenia on the day of hospital admission [20]. Similarly, Du et al. noted that most of the cases had absolute eosinophil counts below the normal range [15]. Eosinopenia, however, may serve as a prognostic indicator for more severe 2019-nCoV infection [21]. Evidently, resolution of eosinopenia may be a determiner of improving clinical status. Decreasing basophils in 2019-nCoV patients may remark disruption of adaptive immunity from infection, since the adaptive immunity of infection was checked by basophils [22].

Qin et al. presented higher leukocyte and neutrophil counts, lower lymphocytes, monocytes, eosinophils and basophils counts in severe adult cases with 2019-nCoV infection [23]. Little is known about eosinophil and basophil counts in 2019-nCoV infected children. Another study revealed that infected children had higher absolute lymphocyte and monocyte counts [24]. Even if monocyte, basophil and eosinophil values were normal, these results were decreased in 2019-nCoV positive patients compared to negative ones in the present data. The different attributes of differentials including lymphocytes, neutrophil, monocyte, eosinophil and basophil counts in children with 2019-nCoV infection should be analyzed in large series. Nowadays, PC and MPV are studied for diagnostic criteria in children with 2019-nCoV infection, but there they have no descriptive value. Qu et al pointed that cases with 2019-nCoV, whose increased thrombocyte count along with disease had poor prognosis [25]. Our findings demonstrated that platelet count was a little lower in 2019-nCoV positive patients than that of negative cases and mean platelet volume had no discriminative function in 2019-nCoV positive patients at admission. It was the limitation of our study that we could not follow up 2019-nCoV positive patients. Therefore further prospective studies should be brought to existence for PC and MPV parameters to conduce both diagnosis and prognosis in children with 2019-nCoV.

Table 1. The demographic and clinical findings of patients

Characteristics	All patients	2019-nCoV positive	2019-nCoV negative
Number of patients (%)	204 (100%)	98 (48.04%)	106 (51.96%)
Gender (Boy/Girl)	103 (50.50%)/101(49.50%)	45 (45.91%)/53(54.09%)	58 (54.72%)/48(45.28%)
Age (mean±SD)	107.7 ± 69.6	105.0 ± 67.3	110.5 ± 72.2
Age (month)			
0-1	2 (1.00%)	2 (2.04%)	0 (0.00%)
1-12	22 (10.78%)	14 (14.28%)	8 (7.55%)
12-36	22 (10.78%)	7 (7.14%)	15 (14.16%)
36-60	24 (11.76%)	10 (10.21%)	14 (13.20%)
60-96	20 (9.80%)	9 (9.18%)	11(10.37%)
>96	114 (55.88%)	56 (57.15%)	58 (54.72%)
Symptom			
Asymptomatic	17 (8.34%)	7 (7.14%)	10 (9.44%)
Fever	81 (39.70%)	40 (40.82%)	41 (36.67%)
Cough	65 (31.87%)	30 (30.62%)	35 (33.01%)
Muscle ache	11(5.39%)	9 (9.18%)	2 (1.88%)
Shortness of breath	15 (7.35%)	5 (5.10%)	10 (9.44%)
Sore throat	15 (7.35%)	7 (7.14%)	8 (7.55%)
CRP (mg/dl)			
<0.3	88 (43.13%)	43 (43.88%)	45 (42.46%)
0.3-1.0	41 (20.09%)	24 (24.48%)	17 (16.04%)
1.0-10.0	26 (12.75%)	13 (13.27%)	13 (12.26%)
10-50	36 (17.65%)	17 (17.35%)	19 (17.92%)
>50	13 (6.38%)	1 (1.02%)	12 (11.32%)
LDH (U/L)			
<245	128 (62.75%)	71 (72.45%)	57 (53.77%)
>245	76 (37.25%)	27 (27.55%)	49 (46.23%)

CRP: C-reactive protein; LDH: Lactate Dehydrogenase

Table 2. Comparision between 2019-nCoV positive and negative patients acording to hematological parameters, CRP and LDH levels

Characteristics	All patients	2019-nCoV positive	2019-nCoV negative	P value
WBC (109/L)	8607.2±4136.99	7174.7±3220.84	9931.6±4451.85	<0.001
Lymphocyte (109/L)	3245.6±2405.15	2958.3±2211.95	3511.3 2552.55	0.099
Neutrophil (109/L)	4415.5±2951.82	3457.4±2260.45	5301.2±3236.75	<0.001
Monocyte (109/L)	737.8±471.75	634.6±376.39	833.2±529.39	0.011
Eosinophil (109/L)	180.0±329.26	111.3±125.82	243.4±431.87	0.003
Basophil (109/L)	27.4±45.32	13.2±21.71	40.6±56.31	<0.001
PC (109/L)	281034.3±102021.94	257418.4±91741.79	302867.9±106517.52	0.001
MPV (fL)	8.07±0.854	8.18±0.880	7.97±0.821	0.082
NLR	2.20±2.449	1.93±1.970	2.44±2.808	0.133
MLR	0.321±0.278	0.316±0.268	0.326±0.288	0.805
ELR	0.058±0.089	0.039±0.044	0.075±0.114	0.005
BLR	0.010±0.023	0.008±0.027	0.013±0.018	<0.001
PLR	116.2±70.77	115.8±67.76	116.6±73.77	0.931
MPV/PC	3.38±2.39	3.63±2.76	3.16±1.90	0.159
CRP (mg/dL)	31.4±38.56	15.5±11.87	41.9±45.97	0.001
LDH (U/L)	238.3±73.40	226.4±72.21	249.3±73.11	0.026

Abbreviations: WBC, white blood cell count; PC, platelet count; MPV, mean platelet volume; NLR, neutrophil-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; ELR, eosinophil-to-lymphocyte ratio; BLR, basophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MPV/PC, mean platelet volume -to-platelet count ratio; CRP: C-reactive protein; LDH: Lactate Dehydrogenase.
p<0.05: Statistically significant.

Table 3. According to hematological parameters and their Receiver Operation Curve Values

Parameter	Cut-off	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
WBC (109/L)	8600	0.703	0.755	0.528	0.593	0.691
Lymphocyte (109/L)	3246.0	0.592	0.714	0.387	0.515	0.586
Neutrophil (109/L)	4415	0.6945	0.755	0.500	0.579	0.679
Monocyte (109/L)	738	0.602	0.704	0.443	0.535	0.610
Eosinophil (109/L)	180	0.619	0.796	0.330	0.520	0.625
Basophil (109/L)	27	0.707	0.878	0.434	0.586	0.780
PC (109/L)	281034	0.634	0.684	0.472	0.541	0.610
MPV (fL)	8	0.570	0.500	0.443	0.449	0.485
NLR	2	0.568	0.714	0.358	0.483	0.525
MLR	0.321	0.501	0.663	0.311	0.471	0.500
ELR	0.058	0.613	0.786	0.396	0.543	0.656
BLR	0.010	0.693	0.888	0.340	0.554	0.766
PLR	763.159	0.500	0.592	0.377	0.468	0.500
MPV/PC	3.385	0.625	0.531	0.311	0.416	0.418
CRP (mg/dL)	31.4	0.675	0.255	0.736	0.472	0.517
LDH (U/L)	238.279	0.601	0.673	0.481	0.545	0.614

Abbreviations: AUC (95% CI), area under the receiver operating characteristic curve (95% Confidence Interval)
PPV positive predictive value, NPV negative predictive value

Recently, some readily available parameters, originated NLR, MLR, PLR and MPV/ PC ratio have been investigated as potential biomarkers from routine complete blood count (CBC) in the clinical setting [26]. The NLR was a widely used marker for the assessment of the severity of bacterial infections and the prognosis of patients with pneumonia and tumors. NLR had the highest area under receiver operating characteristic curve (AUC) (0.849, 95% CI 0.707–0.991), and had higher sensitivity and specificity [27]. Xia et al. noted that NLR was an independent risk factor for severe 2019-nCoV infection [28]. We found AUC of 0.568 (95% CI), a sensitivity of 0.714, and a specificity of 0.358. Monocyte-lymphocyte ratio has potency for inflammation. Nevertheless, barely research examined the MLR and 2019-nCoV infection association. Our study indicated that MLR was not significant similar to NLR. The clinical usefulness of NLR and MLR should be defined with various pediatric studies in 2019-nCoV infection.

Among all hematological ratios, ELR and BLR showed the distinct value for differentiating positive 2019-nCoV cases from that of negative patients in the present study. Although the detailed mechanisms remained to be investigated, our findings suggested that eosinophil and basophil could have a role in inflammatory process in children with 2019-nCoV infection. As far as we know, no study related to ELR and BLR in 2019-nCoV infected children was noted. The ratios of eosinophil and basophil to lymphocytes defined in peripheral blood could be notable in 2019 novel coronavirus infection. They were investigated in the clinical practice with good predictive value regarding outcome. The platelet to lymphocyte ratio at the time of platelet peak emerged as an independent prognostic factor for prolonged hospitalization. It was suggested that a high platelet to lymphocyte ratio might indicate a more pronounced cytokine storm due to enhanced platelet activation [25]. In other study revealed that the ratio of MPV/PC was a better indicator of platelet function compared to MPV or PC alone. MPV/PC ratio had a predictive value of on outcomes [29]. Unfortunately, there was no data about MPV/PC ratio related to 2019-nCoV infection in children. Although the present PLR and MPV/PC ratios had no significant features, the capacity of these parameters should be revealed in 2019-nCoV infected children.

Among other laboratory tests, while we found increased CRP level in both 2019-nCoV positive and negative patients, LDH level was normal in 2019-nCoV positive ones. Mild clinical symptoms and different laboratory results may be due to lower inflammatory response in most of children with 2019-nCoV infection [30]. Du et al. depicted that LDH level increased in children whose underlying disease such as cardiopulmonary disorder [15]. In one study presented by Wang et al., elevated LDH showed poor clinical outcome [31]. Regarding high CRP value was related to increased risk of ARDS [20]. CRP was normal in the majority of infected children but LDH levels were high [13]. These laboratory findings were needed to be examined in the envisaging of clinical progression and deterioration of illness. The present investigation had a few restrictions. Firstly, it was only one hospital research and count of cases was little. Secondly, even if all patients with 2019 novel coronavirus infection had a good prognosis, they could not be followed up for a long time.

Conclusion

The hematological parameters and ratios have not been analyzed before in children with 2019 novel coronavirus infection. Our study highlighted that WBC, ELR and BLR might be convenient

parameters to express inflammatory situation of coronavirus infection. Presented parameters can be very readily estimated with total leucocyte count and other ratios for every patient. In addition, there is no necessity of another expense and technique. Hematological parameters and ratios could be necessarily taken into consideration in terms of diagnosis and predictable prognosis for children with 2019 novel coronavirus infection in clinical practice. More clinical and basic research is necessary to understand 2019 novel coronavirus infection in children.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval
The ethical approval was obtained from "The Local Scientific Research Permission Commission" (document no: 2020/514/177/4) and conducted in accordance with the ethical principles of the Helsinki Declaration.

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