ARTICLE

Association of the *IL-6R* gene polymorphic variant rs2228145 (C>A) with *IL-6* gene polymorphisms in a healthy cohort of Turkish population

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The main aim of this study was to investigate the relationship of the carriership of rs2228145 allelic variations of *IL-6R* with two other allelic variations in *IL-6* gene at rs1800795 and rs1800796 loci and with the laboratory data of a healthy cohort of the Turkish population. The data of 121 healthy Turkish subjects (aged 12–84 years) including the past diseases, comorbidities were collected. The laboratory parameters were compared by the frequency of alleles of rs2228145 (C>A). The possible association of polymorphism at rs2228145 locus with the age, gender, and body mass index (BMI) and the frequencies of alleles of rs1800795 and rs1800796 polymorphisms were evaluated. The majority of the subjects had allele A at rs2228145 locus and allele G at rs1800796 locus. The number of white blood cells, platelets, neutrophils and monocytes were significantly higher in the subjects with allele C than those with allele A at rs2228145 locus ($P < 0.05$). The concentrations of total and direct bilirubin, iron, Sex Hormone Binding Globulin (SHBG) and folic acid of the subjects with allele C were significantly lower than those with allele A ($P < 0.05$). The uric acid and fasting insulin levels were higher in the subjects with allele C compared with those allele A ($P = 0.04$). The diversities of the hematological parameters, laboratory findings of liver function tests and renal panel and hormone levels may be explained by the variants of rs2228145 locus at *IL-6R* gene among healthy Turkish individuals.

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INTRODUCTION

Interleukin-6 (IL-6) is a well-known cytokine produced by a number of cells. Today, several molecular features of IL-6 have been identified to be used as a target in the clinical practice for various infective, cancerous, autoimmune and viral diseases, including novel coronavirus disease 2019 (COVID-19) [1–4]. IL-6 functions by binding to IL-6 receptor (IL-6R) composed of two transmembrane glycoproteins represented as the IL-6Rα and gp130/IL-6ß (gp130) subunits [5, 6]. The IL-6 interacts to IL-6R forming a complex which associates with gp130 on the extracellular surface of T cells, B cells, vascular endothelial cells, monocytes and hepatocytes, which is referred to as classic signaling. The IL-6 + IL-6R complex interactions trigger downstream intracellular signaling pathways mainly involved in the immunoinflammatory response. A soluble form of IL-6R (sIL-6R) comprising the extracellular portion of the receptor can bind IL-6 with a similar affinity as the membrane-bound IL-6R. The complex of IL-6 and sIL-6R can bind to gp130 on cells, which do not express the IL-6R, and which are unresponsive to IL-6. This process has been called trans-signaling [7–9]. It has been clearly shown that IL-6 trans-signaling via the soluble IL-6R has significant functions in metabolism and obesity [10, 11].

IL-6 is also implicated in interfering with cellular immunity by manifesting pro-inflammatory and anti-inflammatory functions [12, 13]. The pro-inflammatory activities of IL-6 were dependent on trans-signaling. Besides, IL-6 has regenerative activities, which, when absent, aggravated the development of the inflammatory process. Since intestinal epithelial cells express the membrane-bound IL-6R, it can be concluded that these anti-inflammatory activities of IL-6 most likely depended on classic signaling via the membrane-bound IL-6R [12].

The human IL-6 gene has been exactly localized on p15.3 region of the chromosome 7 [14, 15]. Two polymorphic loci, rs1800795 and rs1800796, have been identified in the *IL-6* promoter region [2]. Recognizing genetic mutations in this genomic sequence has helped the researchers correlate IL-6 function with the several diseases including chronic, cancerous or infectious diseases in diverse populations [4]. However, no study has reported the frequencies of the single nucleotide polymorphisms (SNPs) in rs1800795 and rs1800796 loci in a healthy Turkish population.

One of the most frequently observed missense variants in the *IL-6R* gene is at rs2228145 locus which was predicted to alter the exonic splicing enhancer sites and/or create new silencer sites, and was also predicted to affect the protein function due to the amino acid substitution in the extracellular domain of the receptor, which is essential for IL-6R interaction with extracellular ligands. Thus, the variant may alter the domain conformation, potentially interfering with IL-6 recognition. In fact, rs2228145 is correlated with increased levels of soluble IL-6R in blood, serum. [16, 17]. However, the effect

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Table 1. Demographic characteristics of the individuals selected from a Turkish population.

Gene polymorphism	Allele	*N*	Frequency	Genotype	*N*	Frequency	Age $\overline{X} \pm SD$	Gender (M/F)	BMI (kg/m^2) $\overline{X} \pm SD$
rs1800795	C	62	0.512	CG	55	0.455	49.75 ± 14.62	35/27	26.98 ± 6.42
	G	59	0.488	CC	7	0.058	46.45 ± 15.81	33/26	28.43 ± 6.58
				GG	59	0.488	$P = 0.24$	$P = 0.95$	$P = 0.41$
rs1800796	G	120	0.992	GG	98	0.810	48.11 ± 15.3	67/53	27.59 ± 6.5
	C	1	0.008	GC	22	0.182	52	1/0	31.6
				CC	1	0.008	–	$P = 0.37$	–
rs2228145	A	78	0.856	AA	35	0.385	49.47 ± 16.91	42/36	27.06 ± 5.85
	C	13	0.144	AC	43	0.472	41.00 ± 10.63	9/4	31.25 ± 9.01
				CC	13	0.143	$P = 0.10$	$P = 0.28$	$P = 0.09$

M/F Male/Female, $\overline{X} \pm SD$ Mean ± Standard deviation.

Table 2. Comparison of the distribution of blood group types according to the gene polymorphisms.

Gene polymorphism	Alleles	Blood group *N* (%)				*P* value
		0	A	AB	B	
rs1800795	C	6 (22.2)	13 (48.1)	2 (7.4)	6 (22.2)	0.99
	G	7 (25.9)	12 (44.4)	2 (7.4)	6 (22.2)	
rs1800796	G	13 (24.5)	24 (45.3)	4 (7.5)	12 (22.6)	0.81
	C	0 (0)	1 (100)	0 (0)	0 (0)	
rs2228145	A	9 (19.6)	22 (47.8)	4 (8.7)	11 (23.9)	0.4
	C	4 (50)	3 (37.5)	0 (0)	1 (12.5)	

of variations in this gene polymorphism was not reported for a healthy Turkish population.

The main purpose of this study was to investigate the relationship of the carriership of rs2228145 (C>A) allelic variations with the two other allelic variations in *IL-6* gene at rs1800795 and rs1800796 loci and with the laboratory data of a healthy cohort of Turkish population.

MATERIALS AND METHODS

In the present study, 170 individuals were recruited from a healthy Turkish population who applied to the Gentest Institute of Public Health Genomics and Personalized Medicine for a whole body check-up. 121 subjects (aged 12–84 years) were chosen according to the criteria of being natives of Turkish localities for at least two generations, being completely healthy, not having a serious disease or disorder, and giving a written consent that their data can be used in scientific studies before the analysis was performed. The exclusion criteria were being non-healthy which involves any severe disease or disorder including cancer, autoimmune diseases, chronic diseases (renal, heart, lung, kidney diseases), diabetes, neurological disorders, obesity, sickle cell disease or thalassemia, cerebrovascular diseases, and pregnancy, being non-native of Turkish origin and not giving written consent that their data can be used in scientific studies before the analysis.

The research protocol was approved by the local Non-interventional Research Ethical Committee of Biruni University (Date: 30th Dec 2020, Number: 46) and was performed in compliance with the 2013 Declaration of Helsinki. All subjects were aged 18 years or over who gave detailed information about the study and their informed consent. All of the parents of children were younger than 18 years and they gave the informed consent on the behalf of their children.

Genotyping of *IL-6R* gene polymorphic variant rs2228145 (C>A) is performed with the Infinium Global Screening Array v3 DNA-microarray and the iScan scanner by Illumina. All DNA tests started with the collecting a biological sample (i.e., saliva or buccal epithelium) into a stabilizer fluid of the Oragene DNA OG-500 collection kit (DNA Genotek) and stored for genotyping. Up to 110 µg of DNA was extracted from a 2 mL sample which was sufficient for DNA-microarray genotyping. Information on genetic variants was taken from the ClinVar public database [18]. Carrier, homozygous and heterozygous status were reported for the known associations between a given genomic variant and phenotype by using OMIM and Genetics Home Reference [19].

All data from each participant, including the past diseases, disorders, family histories, comorbidities were collected during an interview in an open-ended manner. The laboratory parameters were compared by the frequency of alleles of *IL-6R* gene polymorphic variant rs2228145 (C>A). The possible association of SNPs at rs2228145 locus of *IL-6R* with the age, gender, and body mass index (BMI) and the frequencies of alleles of two interleukin polymorphisms (rs1800795 and rs1800796) were evaluated as well.

Statistical analysis

All data were analyzed by the SPSS (statistical package for social sciences) for Windows 22 program. In order to decide which tests (parametric/nonparametric tests) to apply initially in the analysis of the data, the assumptions that must be met were tested. So as to decide the normality of the distribution, Kolmogorov–Smirnov, the other assumptions of the normal distribution, kurtosis and skewness values and histogram graph were used. When comparing two independent groups, *t* test (Independent sample *t* test) and Man–Whitney *U* test were used. Chi-square and Fisher's Exact tests were used for comparing the relationship between the categorical variables. $P < 0.05$ was accepted as the level of significance.

RESULTS

The general characteristics of the studied sample and the allele and genotype frequencies of the analyzed genes are reported in Table 1. 121 subjects including 68 males and 53 females were recruited to investigate the *IL-6* gene polymorphisms at rs1800795 and rs18000796 loci, and 91 subjects including 51 males and 40 females were recruited to investigate the *IL-6R* gene polymorphisms at rs2228145 locus. The frequencies of alleles C and G at rs1800795 locus were 0.512 and 0.488, respectively. Only one individual had allele C while the rest had allele G at rs1800796 locus with a frequency of 0.992. The frequencies of alleles A and C at rs2228145 locus were 0.856 and 0.144, respectively. The mean ages, the distribution of genders and the mean BMI of the individuals in each gene polymorphism group did not differ significantly among the allele groups ($P > 0.05$) (Table 1). The distribution of the blood

group did not differ significantly among the allele groups either ($P > 0.05$) (Table 2).

Comparison of the frequencies of the alleles at rs2228145 locus according to the polymorphisms in *IL-6* genes indicated that most of the subjects in this Turkish cohort had allele A at rs2228145 locus and allele G at rs1800796 locus. In contrast, only one patient had allele C at both rs2228145 and rs1800796 loci. However, the frequencies of the alleles at rs2228145 locus did not alter significantly in terms of the frequencies of both polymorphisms in *IL-6* genes ($P > 0.05$) (Table 3).

Considering the hematological parameters, the mean WBC, mean platelets count, the median neutrophil count and monocyte count was significantly higher in the subjects with allele C than those in the subjects with allele A of *IL-6R* gene polymorphism ($P < 0.05$) (Table 4). The laboratory findings of glucose and lipid metabolism were comparable among the individuals when compared with the variations in alleles ($P > 0.05$) (Table 5). However, the medians of total and direct bilirubin concentrations of the subjects with allele C were significantly lower than those of the subjects with allele A ($P < 0.05$) (Table 6). In addition, the mean iron concentration of the subjects with allele C was significantly lower than those of the subjects with allele A ($P < 0.05$) (Table 6). The laboratory findings in the renal panel were comparable among the allele groups except the median uric acid concentration which was higher in the subjects with allele C compared with those in the subjects with allele A ($P = 0.04$) (Table 7). Comparison of the hormone and vitamin levels according to the alleles of *IL-6R* gene polymorphism indicated that the median of fasting insulin level was higher while the median concentration of Sex Hormone Binding Globulin (SHBG) and folic acid of the subjects with allele C were lower than those in the subjects with allele A ($P < 0.05$) (Table 8).

Table 3. Comparison of the frequencies of the alleles at rs2228145 locus according to the polymorphisms in IL-6 genes.

IL-6 gene polymorphisms	Alleles	rs2228145 alleles *N* (%)		*P* value
		A	C	
rs1800795	C	41 (83.7)	8 (16.3)	0.54
	G	37 (88.01)	5 (11.9)	
rs1800796	G	77 (86.5)	12 (13.5)	0.14
	C	1 (50)	1 (50)	

Table 4. Comparison of the hematological parameters according to the alleles of IL-6R gene polymorphism.

	Allele A	Allele C	*P* value
RBC × 10^6/μL	4 ± 0.6	4.9 ± 0.6	0.88
WBC × 10^5/μL	6 ± 1.9	7.7 ± 2.0	**0.04**
Hemoglobin (g/dL)	14 ± 1.6	13.3 ± 2.6	0.26
Hematocrit (%)	42 ± 4.0	41.2 ± 6.3	0.39
Platelets (×10^3/μL)	224 ± 55.8	268.8 ± 54.8	**0.02**
Neutrophil (×10^3/μL)	3.2 (2.3–4.3)	4.4 (3.5–6.9)	**0.02**
Lymphocyte (×10^3/μL)	2.0 (1.7–2.7)	2.3 (1.9–3.2)	0.20
Monocyte (×10^3/μL)	0.5 (0.4–0.6)	0.8 (0.7–1.0)	**0.01**
Eosinophil (×10^3/μL)	0.2 (0.1–0.3)	0.2 (0.1–0.3)	0.78
Basophil (×10^3/μL)	0.03 (0.02–0.03)	0.02 (0.02–0.04)	0.95

All data are presented as $\overline{X} \pm$ SD or Median (Q1–Q3).
RBC Red blood cells, *WBC* White blood cells.
Bold values indicates statistically significant p values less than 0.05

DISCUSSION

The role of genetic variation in *IL6R* in the etiology of human diseases has been emphasized in genetic reports suggesting the correlation of allelic variants with the severity or risk of several diseases including acute and chronic diseases [20, 21], inflammatory diseases [22], and viral diseases [23]. A common non-synonymous variant Asp358Ala in *IL6R* has been implied to be the causative variant at rs2228145 locus (A>C) in European and Asian HapMap populations, due to its strong correlation with circulating concentrations of sIL-6R [24]. The minor allele of rs2228145 was demonstrated to regulate IL-6R surface expression at the protein level in specific immune cell subsets, resulting in altered IL-6 signaling and the onset and progression risk in some diseases [25, 26]. Cell-based experiments have suggested that the rs2228145 variant in IL6R might impair classic IL6R signaling [24] and dampen inflammation by reducing membrane-bound IL6R levels. Moreover, large-scale human genetic and biomarker evidence on this variant indicated a causal association between IL6R-related pathways and coronary heart disease [27, 28]. Although rs2228145 has been described as a major determinant of circulating soluble IL-6R levels, its frequency in a Turkish population remains unclear. In the present study, we investigated the frequencies of *IL-6R* gene polymorphic variant at rs2228145 (C>A) locus and the frequencies of *IL-6* gene polymorphic variants at rs1800795 and rs1800796 loci in a healthy cohort of the Turkish population. We found no correlation between the frequencies of alleles at rs2228145 locus with the frequencies of both SNPs in the *IL-6* gene and with the demographics of individuals. However, there were significant differences in some hematological parameters, in the laboratory findings of liver function tests and renal panel and the hormone levels according to two alleles of rs2228145 locus at *IL-6R* gene.

A number of studies reported the biochemical implications of the variations in rs2228145 locus at human *IL-6R* gene have been studied in great detail [16, 26, 29, 30]. This SNP is associated with a 2-fold increase in soluble IL-6R serum levels, resulting in reduced IL-6-induced C-reactive protein (CRP) production. It was suggested that the increased soluble IL-6R level leads to decreased IL-6 classic or increased IL-6 trans-signaling. Increased proteolytic ectodomain shedding mediated by the A Disintegrin and metalloproteinase domain (ADAM) proteases ADAM10 and ADAM17 increased sIL-6R serum level in vitro as well as in healthy volunteers homozygous for the Asp358Ala allele [29]. There are also reports indicating that the variant allele of rs2228145 may modulate the balance with membrane-bound and soluble IL-6R, affect the responsiveness of immune cells to IL6 stimulation [16, 26, 30]. In contrast, another study reported a significant change in serum levels of IL-6R and, to a lesser extent, of IL6 levels, but could not find any association with gp130 levels or pro/anti-inflammatory markers tests [31]. This is probably the reason of why we also did not find any correlation between the frequencies of the variant allele A and C of the rs2228145 with the frequencies of the variant allele A and C of the variants of rs1800795 and rs1800796 loci. Nevertheless, the functional role of SNPs at rs2228145 locus in *IL-6R* gene in the healthy status and its possible effects within tissue-specific perspectives are as-yet-unknown and require advance research. Still, our findings open a new window into the metabolic and functional effects of variants in *IL-6R* gene in the physiological processes even in healthy status and point out the possible association of this genetic variant with human diseases.

In a more recent study, we investigated the correlation between interleukin gene polymorphisms and the prevalence and mortality rates due to COVID-2019 in 23 countries, and the analysis between the frequencies of rs1800796/rs1800795 polymorphism in *IL-6* gene and rs2228145 polymorphism in *IL-6R* gene, and the prevalence of COVID-19 and mortality rates per country demonstrated that there was no significant correlation between the

Table 5. Comparison of the laboratory findings of glucose and lipid metabolism according to the alleles of IL-6R gene polymorphism.

	Allele A	Allele C	*P* value
Glucose (fasting) (mg/dL)	93.0 (82.0–101.0)	93.5 (88.0–100.0)	0.71
Total cholesterol (mg/dL)	204 ± 55.3	211.2 ± 40.0	0.70
HDL cholesterol (mg/dL)	53.5 (39.0–64.5)	45.0 (38.0–57.0)	0.29
LDL cholesterol (mg/dL)	145 ± 46.1	151.7 ± 37.2	0.67
Triglyceride (mg/dL)	122.0 (76.0–168.0)	151.5 (89.0–193.0)	0.40
Amylase (U/L)	66.5 (51.0–88.0)	51.0 (43.0–68.0)	0.11
Lipase (U/L)	40.0 (26.0–58.0)	37.0 (26.0–54.0)	0.90

All data are presented as $\overline{X} \pm$ SD or Median (Q1–Q3).
HDL High Density Lipoprotein, *LDL* Low Density Lipoprotein.

Table 6. Comparison of the laboratory findings of liver function tests according to the alleles of IL-6R gene polymorphism.

	Allele A	Allele C	*P* value
AST (U/L)	19.0 (16.0–23.0)	20.0 (17.0–22.0)	0.77
ALT (U/L)	20.0 (14.0–28.0)	19.0 (14.0–32.0)	0.90
GGT (U/L)	16.0 (10.0–29.0)	21.5 (11.0–29.0)	0.56
Total bilirubin (mg/dL)	0.5 (0.5–0.7)	0.4 (0.3–0.5)	**0.04**
Direct bilirubin (mg/dL)	0.2 (0.1–0.2)	0.1 (0.1–0.2)	**0.02**
Total protein (g/L)	70.1 (67.1–72.9)	71.4 (66.9–74.8)	0.73
Albumin (g/L)	44.7 (43.0–46.2)	43.3 (40.5–48.3)	0.47
Iron (µg/dL)	100 ± 27.9	72.7 ± 33.9	**0.01**
TIBC (µg/dL)	312.0 (276.0–363.5)	329.5 (293.5–380.0)	0.41
Ferritin (µg/dL)	91.0 (48.6–143.5)	167.9 (52.0–204.0)	0.24

All data are presented as $\overline{X} \pm$ SD or Median (Q1–Q3).
ALT Alanine transaminase, *AST* Aspartate transaminase, *GGT* Gamma-glutamyl transferase, *TIBC* Total Iron Binding Capacity.
Bold values indicates statistically significant p values less than 0.05

Table 7. Comparison of the laboratory findings of renal panel according to the alleles of IL-6R gene polymorphism.

	Allele A	Allele C	*P* value
BUN (mg/dL)	14.0 (11.0–16.0)	13.0 (10.0–16.0)	0.46
Creatinine (mg/dL)	0.8 (0.7–1.0)	0.8 (0.8–1.0)	0.44
Uric Acid (mg/dL)	5.0 (3.8–5.7)	6.0 (4.5–7.4)	**0.04**
Calcium (mg/dL)	9 ± 0.4	9.4 ± 0.5	0.93
Sodium (mmol/L)	139.0 (138.0–142.0)	139.5 (138.0–141.0)	0.90
Magnesium (mg/dL)	2.1 (2.0–2.2)	2.2 (1.9–2.2)	0.41
Zinc (µg/dL)	107 ± 20.4	116.9 ± 26.2	0.25
Selenium (µg/dL)	83.0 (76.0–95.0)	90.0 (80.5–111.0)	0.22

All data are presented as $\overline{X} \pm$ SD or Median (Q1–Q3).
BUN Blood Urea Nitrogen.
Bold values indicates statistically significant p values less than 0.05

Table 8. Comparison of the hormone and vitamin levels according to the alleles of IL-6R gene polymorphism.

	Allele A	Allele C	*P* value
Insulin (fasting) (mU/L)	7.9 (5.6–13.5)	13.6 (10.4–16.0)	**0.03**
FSH (U/L)	6.7 (3.2–30.1)	6.8 (3.4–9.9)	0.59
LH (U/L)	7.1 (4.4–16.7)	5.0 (4.2–7.8)	0.37
DHEA-S (µg/dL)	155.6 (108.9–267.6)	180.6 (141.6–263.0)	0.60
Total testosterone (µg/L)	3.2 (0.2–5.2)	1.5 (0.2–3.8)	0.43
SHGB (nmol/L)	44.2 (33.1–61.8)	26.6 (21.4–48.1)	**0.03**
Total IgE (IU/mL)	74.4 (25.1–161.6)	48.7 (25.2–86.6)	0.41
Free T3 (ng/L)	3 ± 0.4	2.9 ± 0.5	0.11
Free T4 (ng/dL)	1 ± 0.2	1.3 ± 0.1	0.85
TSH (mU/L)	2 ± 1.8	2.0 ± 0.7	0.42
Free PSA	0.3 (0.2–0.5)	0.2 (0.1–0.4)	0.41
Total PSA	1.0 (0.6–1.6)	0.7 (0.2–1.2)	0.25
Vitamin B12 (ng/L)	480.0 (372.0–623.0)	466.0 (311.0–572.0)	0.63
Folic acid (folate) (µg/L)	8.9 (6.9–11.7)	5.6 (3.9–8.0)	**0.02**
25-Hydroxyvitamin D (µg/L)	37.0 (30.0–47.0)	28.5 (26.0–54.0)	0.39
Homocysteine (µmol/L)	10.4 (8.9–12.7)	12.7 (10.2–12.8)	0.14
hsCRP (mg/L)	1.5 (0.7–3.8)	2.4 (2.0–4.1)	0.07
IGF-1 (µg/L)	134.0 (108.0–150.0)	120.0 (103.0–130.0)	0.34
Growth hormone (µg/L)	0.2 (0.1–1.0)	0.1 (0.1–0.5)	0.44

All data are presented as $\overline{X} \pm$ SD or Median (Q1–Q3).
FSH Follicle-stimulating hormone, *LH* Luteinizing Hormone, *DHEA-S* Dehydroepiandrosterone Sulfate, *SHBG* Sex Hormone Binding Globulin, *IgE* Immunoglobulin E, *TSH* Thyroid Stimulating Hormone, *PSA* Prostate Specific Antigen, *hs-CRP* high-sensitivity C-reactive protein, *IGF-1* Insulin-like growth factor 1.
Bold values indicates statistically significant p values less than 0.05

prevalence and mortality rates, and the frequencies of polymorphisms found in these genes [32]. However, the metabolic effects of these variants in healthy individuals remains unclear. To the best our knowledge, this is the first study reporting the frequencies of alleles of rs2228145 polymorphism in *IL-6R* gene in a Turkish population and correlate the findings with the gender,

age, BMI, blood groups, hematological parameters, the laboratory findings related to the glucose and lipid metabolism, liver function tests, renal panel and the hormone and vitamin levels. Yet, more work is required to expand the horizon of the functional genetic variation in *IL-6* and *IL-6R* genes for identifying the pharmacogenetic biomarkers or applying personalized medicine approaches in people with different genetic profiles.

DATA AVAILABILITY

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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AUTHOR CONTRIBUTIONS

All authors have contributed significantly to the study.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APPROVAL

The research protocol was approved by the local Non-interventional Research Ethical Committee of Biruni University (Date: 30th Dec 2020, Number: 46) and was performed in compliance with the 2013 Declaration of Helsinki.

ADDITIONAL INFORMATION

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