IL36G Genetic Variant is Independently Associated with Susceptibility, Severity and Joint Involvement in Psoriasis

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Abstract

Psoriasis (PsO) is a chronic, immune-mediated, inflammatory and polygenic dermatosis and may be associated with psoriatic arthritis (PsA). Interleukin 36 (IL-36) has important role in to make the interaction between the innate and adaptive immune response. Variants in genes encoding cytokines can modulate the susceptibility as well as the severity of diseases. This study aims to assess the frequency of *IL36G* intron C > T (rs13392494) and *IL36G* 3'untranstaled region (UTR) A > G (rs7584409) single nucleotide variants and their association with susceptibility, joint involvement and severity of PsO in Brazilian patients. The study included 154 patients with PsO and 154 healthy individuals. The *IL36G* rs13392494 and *IL36G* rs7584409 were genotyped by the allelic discrimination assay using the real-time polymerase chain reaction (qPCR). The severity of PsO was assessed using the Psoriasis Area and Severity Index (PASI). The rs7584409 variant showed a protective effect in PsO whereas the rs13392494 variant was not associated with susceptibility to PsO. We demonstrated that the G allele of *IL36G* rs7584409 (dominant model) was associated with 2.3 more chance to PASI > 10, as well as the patients carrying the *IL36G* rs7584409 GG genotype showed about 5.0 times more chance of PsA than those carrying the AA genotype. The presence of the G allele of the *IL36G* rs7584409 variant was associated with protection to PsO, higher PASI and the presence of PsA than the A allele, suggesting that this variant may be used as a potential genetic biomarker to predict severity and joint involvement of the PsO.

Introduction

Psoriasis (PsO) is a chronic, immune-mediated, inflammatory and polygenic dermatosis that is associated with both physical and psychological burden [1] and can be triggered by injury, trauma, infections and medications [2]. Although the etiology of PsO is not fully elucidated, genetic, epigenetic and environmental factors are involved [3]. It is not a rare skin disease affecting approximately 2.0% of the population; males and females being equally affected [1]. Because to systemic and chronic inflammatory response, organs other than the skin can be affected, mainly joints, nails and cardiovascular system [4]. In addition, almost 30.0% of PsO patients can develop psoriatic arthritis (PsA) characterized by the presence of spondylitis enthesitis or peripheral arthritis [5].

PsO shows traces of autoimmune and autoinflammatory disease, with both innate and adaptive immune response overlapping and even potentiating each other [6]. Previous studies have demonstrated that the activation of interferon gamma (IFN-γ), interleukin (IL)-36, and IL-23/IL-17 axis are pivotal events in the pathophysiology of PsO [1, 7]. In addition, our group showed that there is an imbalance between inflammatory and anti-inflammatory cytokine profiles, with predominantly from the first one [8]. IL-36 has gained considerable importance in PsO pathophysiology because its emergent role in the interaction between the innate and adaptive immune response. It composes the IL-1 family of cytokines that includes IL-36α, IL-36β, IL-36γ and IL-36 receptor antagonist (IL36Ra), which are transcribed by the *IL36A, IL36B, IL36G* and *IL36RN* genes, respectively [9]. IL-36 family members play important roles in inflammatory responses in barrier tissues and their deregulation has a pivotal role in PsO [10]. Furthermore, previous studies have reported upregulation of IL-36 family members in PsO and PsA [10, 11].

Genetic variants associated to PsO can be involved in different biological processes, including those in genes encoding cytokines and its susceptibility. Single nucleotide variants (SNV) in genes encoding important components of the inflammatory pathway, such as IL-23 receptor and in untranslated region (UTR) of IL-12B, were previously reported [12, 13]. However, until now, only one previous study has evaluated *IL36G* genetic variants in PsO [14]. Thus, this study aims to assess the frequency of the rs13392494 intron C > T and rs7584409 3'UTR A > G variants of *IL36G* gene and their association with the susceptibility, severity of PsO and the presence of PsA in Brazilian patients.

Subjects And Methods

The study included 308 individuals; of them, 154 patients with PsO consecutively recruited from Dermatology Outpatient of the State University of Londrina, Londrina, Paraná, South Brazil, and 154 healthy individuals selected among blood donors of the Regional Blood Bank of Londrina. The individuals were unrelated, both sexes and aged between 18 and 70 years old and from the same geographic region. The diagnosis of PsO was established clinically by a dermatologist and histopathological analysis. The disease severity was measured using Psoriasis Activity Severity Index (PASI) [15]. None of the participants in the study presented other autoimmune diseases, acute or chronic infectious diseases, heart, kidney, hepatic or oncologic diseases. The ethnicity was self-reported as Caucasian and non-Caucasian [16, 17]. PsA was classified according to the Classification Criteria for Psoriatic Arthritis (CASPAR) [18].

Demographic, epidemiological and anthropometric data of the participants, as well as clinical history, symptoms, and the treatment of PsO were obtained using a standard questionnaire. Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared.

Blood collection and Inflammatory Parameters

After fasting for 12 h, venous blood samples were obtained with anticoagulant ethylenediaminetetraacetic acid (EDTA), centrifuged at 3000 rpm for 15 min; further, serum, plasma, and buffy-coats were separated, aliquoted, and stored at -80°C until analysis.

IL36G genetic variants genotyping

Two SNV of the *IL36G* gene located on chromosome 2q14.1 were genotyped: intron C > T (rs13392494) at position 112982098 and 3'UTR A > G (rs7584409) at position 112985157 according to the international single nucleotide polymorphism (SNP) database (https://www.ncbi.nlm.nih.gov/snp/). Genomic DNA was extracted from peripheral blood cells using a resin column procedure (PureLink Genomic DNA, Invitrogen by Life Technologies, Carlsbad, CA, USA), following the manufacturer's recommendations. DNA concentration was quantified at 260 nm and DNA purity was assessed by measuring the 260/280 nm ratio using a NanoDrop 2000c™ spectrophotometer (ThermoScientific, Waltman, MA, USA). The *IL36G* rs13392494 and rs7584409 SNV were genotyped by TaqMan™ allelic discrimination assay on real-time polymerase chain reaction (qPCR) system (StepOne, Applied Biosystems by Life Techonologies, Carlsbad, CA, USA) and performed using 0.5 µL TaqMan™ SNP Genotyping Assay (C__32060205_10 and C__2146458_10, Applied Biosystems, Foster City, CA, USA) containing two sequence-specific primes and two allele-specific TaqMan™ MGB probes with a reporter dye

at its 5’ end (VIC™ or FAM™), 5 µL TaqMan Universal Genotyping Master Mix (Applied Biosystems, Foster City, CA, USA), and 5 ng of genomic DNA.

Statistical Analysis

The sample size for the study was calculated in the R software [19] as described in Gail and Haneuse [20], using the package sample size logistic case control. Assuming power = 0.9 and 95% of confidence, the sample size necessary for the study was 154 subjects in each group. Categorical variables were expressed as absolute number (n) and percentage (%) and continuous variables were expressed as median and interquartile range 25.0%-75.0% (IQR). Analysis of contingency tables ($\chi 2$ or Fisher’s exact test) were employed to check the associations between categorical variables and diagnostic groups. We assessed the differences in continuous variables between groups using the Mann-Whitney test. The association between the *IL36G* genetic variants and the study variables was analyzed in allelic, dominant, codominant, overdominant and recessive models. Inference of recombination sites between *IL36* alleles were determined using the PHASE software version 2.1.1 by assigning each haplotype with maximum probability [21, 22]. Hardy-Weinberg equilibrium (HWE) and the estimation of pairwise linkage disequilibrium (LD) were performed in Haploview software version 4.2. LD between the specified SNV was provided by describing D and r-squared value (r^2). Binary or multinomial logistic regression analysis was performed to assess the effect of the genetic variants in the study group and related odds ratio (OR) and 95% confidence interval (CI) were determined. For all statistical tests $p < 0.05$ was considered for significance level. Statistical analyses were performed using IBM SPSS windows version 24 (SPSS, Inc., Chicago, IL, USA).

Results

Table 1 shows the sociodemographic and clinical data of the patients with PsO and controls. The patients were older ($p < 0.001$) and had higher BMI ($p < 0.001$) than controls. As expected, there were no significant differences in sex ($p = 0.013$) and ethnicity ($p < 0.781$) between both study groups; 95.8% of the patients had plaque PsO and 16.1% had PsA; 43 patients (27.9%) had PASI > 10 with median of 5.1 (11.1–29.3). In relation to treatment, 55.8% were under systemic treatment while 40.3% were using topical therapy.

Table 1
Sociodemographic and clinical data of patients with psoriasis and controls

	Controls (n = 154)	**Psoriasis (n = 154)**	**p-value***
Age (Years)	36 (29–44)	54 (44–63)	**< 0.001**
Sex (Female/Male)	87 (56.5)/ 67 (43.5)	74 (48.1)/ 80 (51.9)	0.138
Ethnicity (Caucasian/Non-Caucasian)	120 (77.9)/ 34 (22.1)	122 (79.2)/ 32 (20.8)	0.781
Body mass index (kg/cm^2)	25.17 (22.27–28.58)	29.88 (26.22–33.02)	**< 0.001**
Plaque psoriasis	-	137 (95.8)	-
Psoriatic arthritis	-	23 (16.1)	-
PASI Score	-	5.1 (11.1–29.3)	-
PASI ≥ 10	-	43 (27.9)	-
Systemic treatment	-	86 (55.8)	-
Topic treatment	-	62 (40.3)	-

Bold values represent statistically significant values; χ^2 test. Data were expressed by absolute number (%). Mann-Whitney test. Data were expressed as median and percentile (25–75%). PASI: Psoriasis Area and Severity Index

Table 2 shows the two SNV of *IL36G* (rs13392494 and rs7584409) divided into four genetic models (dominant, codominant, overdominant, and recessive) to assess their association with PsO susceptibility. The HWE of rs13392494 and rs7584409 were observed among the PsO patients and controls and were consistent with the expected ($p > 0.05$). Regarding the *IL36G* rs1339294 variant, no significant association was found between the allele frequencies (OR 0.938, 95% CI 0.625–1.404, $p = 0.758$) and the PsO. In addition, the frequency of the CC, CT, and TT genotypes (codominant, dominant, recessive, and overdominant genetic models) also did not differ between PsO patients and controls ($p > 0.05$). Regarding the *IL36G* rs7584409 variant, no significant association was found between the allele frequencies (OR 0.887, 95% CI 0.617–1.271, $p = 0.517$) and the PsO. However, the frequency of AA, AG, and GG genotypes differed between PsO patients and controls in the dominant genetic model. The AG + GG genotypes were associated with lower odds for PsO diagnosis than the AA genotype (OR 0.525, 95% CI 0.283–0.975, $p = 0.041$). When the overdominant and recessive genetics models were evaluated, no significant association were observed ($p > 0.05$). All data showed in the Table 2 were adjusted by age, sex, ethnicity, and BMI.

Table 2
Distribution of genotypes and allele frequencies of *IL36G* single nucleotide variants in Brazilian patients with psoriasis and healthy controls

Model		Controls (n = 154)	Psoriasis (n = 154)	OR (95% CI)	p-value
IL36G **rs13392494 (C > T)**					
Allelic	C	248 (80.52)	251 (81.49)	Reference	-
	T	60 (19.48)	57 (18.51)	0.938 (0.625–1.404)	0.758
Codominant	CC	98 (63.6)	103 (66.9)	Reference	-
	CT	52 (33.8)	45 (29.2)	0.938 (0.501–1.755)	0.841
	TT	4 (2.6)	6 (3.9)	1.413 (0.273–7.315)	0.680
Dominant	CC	98 (63.6)	103 (66.9)	Reference	-
	CT + TT	56 (36.4)	51 (33.1)	0.973 (0.529–1.788)	0.929
Recessive	CC + CT	150 (97.4)	148 (96.1)	Reference	-
	TT	4 (2.6)	6 (3.9)	1.447 (0.284–7.369)	0.657
Overdominant	CC + TT	102 (66.2)	109 (70.8)	Reference	-
	CT	52 (33.8)	45 (29.2)	0.921 (0.495–1.712)	0.794
IL36G **rs7584409 (A > G)**					
Allelic	A	226 (73.38)	233 (75.65)	Reference	-
	G	82 (26.62)	75 (24.35)	0.887 (0.617–1.271)	0.517
Codominant	AA	86 (55.8)	91 (59.1)	Reference	-
	AG	54 (35.1)	51 (33.1)	0.575 (0.296–1.116)	0.102
	GG	14 (9.1)	12 (7.8)	0.375 (0.123–1.140)	0.084
Dominant	AA	86 (55.8)	91 (59.1)	Reference	-
	AG + GG	68 (44.2)	63 (40.9)	0.525 (0.283–0.975)	**0.041**
Recessive	AA + AG	140 (90.9)	142 (92.2)	Reference	-
	GG	14 (9.1)	12 (7.8)	0.458 (0.157–1.342)	0.155
Overdominant	AA + GG	100 (64.9)	103 (66.9)	Reference	-
	AG	54 (35.1)	51 (33.1)	0.654 (0.344–1.244)	0.195

Bold values represent statistically significant values; χ^2: results of analyses of contingency tables. Data were expressed as absolute number (n) and percentage (%). OR: odds ratio; CI: confidence interval. Results of logistic regression analysis adjusted by age, sex, ethnicity, and body mass index.

Four possible haplotype combinations with *IL36G* rs1339294 (C > T) and *IL36G* rs7584409 (A > G) variants were investigated in our study: C/A, C/G, T/A, and T/G. The predominant haplotype was C/A (79.2%, dominant model) while no individual with T/G haplotype was found. In the association study of the *IL36G* haplotypes, the following genetic models were analyzed: C/A dominant (C/A carriers *versus* C/G and T/A carriers), C/A recessive (CACA *versus* C/G and T/A carriers), C/G dominant (C/G carriers *versus* C/A and T/A carriers), C/G recessive (CGCG carriers *versus* C/A and T/A carriers), T/A dominant (T/A carriers *versus* C/A and C/G carriers), and T/A recessive (TATA carriers *versus* C/A and C/G carriers). Table 3 shows the distribution of *IL36G* rs13392494 and *IL36G* rs7584409 haplotypes among PsO patients and controls. We found an association between the CACA haplotype (recessive model) with PsO (OR 1.995, 95% CI 1.050–3.788, p = 0.035) adjusted by age, sex, ethnicity, and BMI. On the other hand, we found a protective effect of the C/G haplotype (dominant genetic model) with PsO (OR 0.525, 95% CI 0.283–0.975, p = 0.041) adjusted by age, sex, ethnicity, and BMI.

Table 3
Distribution of the *IL36G* rs13392494 (C > T) and *IL36G* rs7584409 (A > G) haplotypes among Brazilian patients with psoriasis and healthy controls

Haplotypes*	Controls n (%)	Psoriasis n (%)	OR (95% CI)	p-value
C/A dominant	122 (79.2)	122 (79.2)	1.417 (0.683–2.942)	0.349
C/A recessive	44 (28.6)	54 (35.1)	**1.995 (1.050–3.788)**	**0.035**
C/G dominant	68 (44.2)	63 (40.9)	**0.525 (0.283–0.975)**	**0.041**
C/G recessive	14 (9.1)	12 (7.8)	0.458 (0.157–1.342)	0.155
T/A dominant	56 (36.4)	51 (33.1)	0.973 (0.529–1.788)	0.929
T/A recessive	4 (2.6)	6 (3.9)	1.447 (0.284–7.369)	0.657

Bold values represent statistically significant values; OR (odds ratio) and CI (confidence interval) 95% estimated by binary logistic regression controlling by age, sex, ethnicity, and body mass index.

* C/A dominant: C/A carriers *versus* C/G and T/A carriers; C/A recessive: CACA *versus* C/G and T/A carriers; C/G dominant: C/G carriers *versus* C/A and T/A carriers; C/G recessive: CGCG carriers *versus* C/A and T/A carriers; T/A dominant: T/A carriers *versus* C/A and C/G carriers; T/A recessive: TATA carriers *versus* C/A and C/G carriers; the T/G haplotype was not found in the cohort of the study.

We used different regression analyses models to delineate whether these *IL36G* variants were independently associated with PASI score and the presence of PsA. Table 4 shows the results of binary logistic regression analysis with moderate to severe disease (PASI > 10) as dependent variable and those in remission or mild severity (PASI ≤ 10) as reference group. The presence of G allele of *IL36G* rs7584409, in heterozygosis and homozygosis (AG + GG group), was positively associated with PASI > 10 (OR 2.311, 95% CI 1.079–4.951, p = 0.031), independently of sex, ethnicity, and age (regression #1). On the other hand, CACA haplotype was negatively associated with PASI score (OR 0.418, 95% CI 0.182–0.962, p = 0.040), independently of sex, ethnicity, and age (regression #2).

Table 4
Result of binary logistic regression analysis with an increased PASI score (> 10) as dependent variable and those with lower PASI score (≤ 10) as reference group

Regression	Explanatory Variables	Wald	df	p value	OR	95% CI
#1	Age	3.292	1	0.070	0.975	0.948–1.002
	Sex	0.044	1	0.833	1.083	0.515–2.280
	Ethnicity	0.002	1	0.963	1.022	0.402–2.599
	IL36G rs7584409 A > G	4.646	1	**0.031**	**2.311**	**1.079–4.951**
#2	Age	2.888	1	0.089	0.977	0.951–1.004
	Sex	0.140	1	0.709	1.152	0.549–2.418
	Ethnicity	0.164	1	0.685	0.825	0.326–2.087
	CACA haplotype	4.208	1	**0.040**	**0.418**	**0.182–0.962**
PASI: Psoriasis Area and Severity Index; df: degree of freedom; OR: odds ratio; CI: confidence interval						
IL36G rs7584409 A > G: AA vs AG + GG (dominant model).						
CACA haplotype: CACA *versus* C/G and T/A carriers						

Table 5 shows the results of binary logistic regression analysis with PsA as dependent variable and genotypes, haplotypes, sex, ethnicity and age as covariates. Regression #1 shows that *IL36G* rs7584409 GG genotype was independently associated with the presence of PsA (OR 5.187, 95% CI 1.403–19.182, p = 0.014), while C/A dominant haplotype has a protective effect on PsA diagnosis (OR 0.324, 95% CI 0.123–0.857, p = 0.023).

Table 5
Result of binary logistic regression analysis and psoriatic arthritis as dependent variable

Regression	Explanatory Variables	Wald	df	p value	OR	95% CI
#1	Age	0.132	1	0.716	1.006	0.972–1.042
	Sex	0085	1	0.770	0.870	0.341–2.217
	Ethnicity	0.030	1	0.863	0.899	0.267–3.028
	IL36G rs7584409 A > G	6.086	1	**0.014**	**5.187**	**1.403–19.182**
#2	Age	0.279	1	0.597	1.009	0.975–1.045
	Sex	0.133	1	0.715	0.841	0.332–2.132
	Ethnicity	0.151	1	0.697	0.788	0.237–2.619
	C/A dominant haplotype	5.158	1	**0.023**	**0.324**	**0.123–0.857**
Df: degree of freedom; OR: odds ratio; CI: confidence interval;						
IL36G rs7584409 A > G: AA + AG vs GG (recessive model).						
C/A dominant haplotype: C/A carriers *versus* C/G and T/A carriers						

Discussion

The main findings of the present study are that the *IL36G* 3'UTR A > G (rs7584409) variant shows a protective effect in PsO. Patients carrying the G allele (AG + GG) showed about 48.0% of protection to PsO whereas *IL36G* intron C > T (rs13392494) variant was not associated with susceptibility to PsO. Regarding the haplotype distribution of the intron C > T and 3'UTR A > G variants, the C/G haplotype (dominant genetic model) also shows a protective effect, corroborated with the finding that patients with CACA haplotype (recessive genetic model) have 2 times more chance to have the PsO diagnosis. On the other hand, the G allele (AG + GG) of the *IL36G* rs7584409 3'UTR A > G variant was associated with moderate to severe disease and PsA.

Is well established in previous study that the IL-36 family of cytokines has an important role in the inflammatory response in barrier tissues and its deregulation may be fundamental in PsO [7]. Keratinocytes express primarily IL-36 and can be induced by other proinflammatory cytokines, such as IL-17, tumor necrosis factor (TNF)-α, and IL-36 itself [23]. IL-36 cytokines act synergistically with IL-23/Th-17 axis [24]. in a feed-forward amplification in PsO, promoting continuous increased inflammatory activity and influx of other immune cells on injured skin [25, 26]. D'Erme et al. [27] showed that IL-36γ is a valuable biomarker to diagnosis and measurement of disease activity during the clinical course of PsO.

In last decades, different genes and proteins have been highlighted as potential biomarkers for PsO. Thus, then, due to the evidence of the involvement of IL-36 in the pathophysiology of PsO and PsA, we target genetic variants that could interfere in the regulation of the synthesis of this cytokine. In the present study, we demonstrated that *IL36G* rs7584409 *IL36G* variant, but not *IL36G* rs13392494 variant, was associated with PsO susceptibility. The presence of the G allele (dominant model) of the *IL36G* rs7584409 variant was associated with approximately 48.0% of protection for PsO. Until now, there is only one study that investigated these SNV

in PsO and found no association between both studied variants [14]. We hypothesized two possibilities for this disagreement. First, genetic differences between the studied populations. Traks et al. [14]. evaluated the population of Estonia that is more homogeneous than the Brazilian population, which is highly miscegenate. Second, *IL36G* could be in linkage disequilibrium with another gene associated with high association to PsO development. Since the several genes associated with inflammation are closely to the same region of chromosome 2 (IL-1 family), we can have the presence of the *IL36G* variant indirectly associated with PsO. In fact, the gene that would be next to the *IL36G* gene is that it would lead to high or low chance of having the disease or more disease activity.

Regarding the haplotypic distribution of the *IL36G* rs13392494/rs7584409 variants, the presence of the C/A haplotype (dominant model) was associated with about 2 times more chance of presenting PsO while the presence of the C/G haplotype was associated with approximately 48.0% of protection. These data suggest that possibly protection and risk are linked to *IL36G* rs7584409, as the combination with the other variant (*IL36G* rs13392494) did not increase the percentage of protection already obtained by itself.

In the present study, we demonstrated that the G allele of the *IL36G* rs7584409 (dominant model) was associated with 2.3 more chance to PASI > 10. Our data are in disagreement with a previous study that did not find any association between this variant and PASI [14]. The *IL36G* rs7584409 A > G variant occurs in a untranslated region of the *IL36G* (3'UTR), and this change could affect the regulation of gene expression of molecules or transcription factors involved in the inflammatory response of PsO [28] and could explain high severity in patients with the *IL36G* rs7584409 variant.

The frequency of PsA was observed in 16.1% of the PsO patients, which is in agreement with previous data [7]. Therefore, we also demonstrated that patients with the GG genotype of the *IL36G* rs7584409 *IL36G* variant had about 5 times more chance of PsA than those with the AA genotype. Inflammatory joint diseases, such as rheumatoid arthritis and PsA also show high expression of cytokines of the IL-36 family, with increased expression of IL-36α in synovial tissue of patients with PsA as well as expression of IL-36 receptor (IL36R) in fibroblasts [11]. Although the individual role of IL-36 isoforms has not yet been fully elucidated, IL-36α and IL-36γ have greater similarity in their sequence than IL-36β, suggesting that the first two cytokines have more functions to be shared [10].

Some limitations of this study should be considered. This is a case-control design, which does not allow inferences on causal relationship, as well as the limited number of participants with PsA, and the lack of serum quantification of IL-36γ. However, this study has some strengths, such as the adjusting for some confounding variables including age, ethnicity, and BMI in the statistical analysis. To our knowledge, this is the first study that investigated the role of two *IL36G* variants, individually and in haplotypes, in the severity and the presence of PsA in Brazilian psoriatic patients.

Conclusions

Taken together, our results demonstrated that the presence of the G allele of *IL36G* rs7584409 variant was associated with protection to PsO, high PASI and the presence of PsA. Thus, our data suggested that this variant can be used as a possible genetic biomarker to predict severity and joint involvement of PsO. Further studies are needed to elucidate the genetic and epigenetic mechanisms involved in these associations.

Declarations

Ethics approval and consent to participate

This study was conducted after approval by the Institutional Research Ethics Committees of University of Londrina, Paraná, Brazil (CAAE: 37420820.0.0000.5231). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Consent for publication

The studied participants were informed about the present research, and a written consent form was taken from all of them before their enrollment. Moreover, all the authors and co-authors participated and contributed sufficiently in the research, and all of them concur with the submission. The manuscript has been approved by the responsible authorities where the work was carried out. The authors also concur that, if accepted, the manuscript shall not be published elsewhere in the same form in either the same or any other language, without the consent of the Editor-in Chief of Clinical and Experimental Medicine (CLEM)._

Human rights

All procedures performed in this study involving human participants were in accordance with the ethical standards of the Institution and/or National Research Committee and with the World Medical Association 1964 Helsinki Declaration.

Standards for reporting

The manuscript was prepared taken into account the recommendations of the guidelines hosted by the Strengthening the Reporting of Observational studies in Epidemiology (STROBE). STROBE is used for observational studies (cohort, case-control, or cross-sectional designs) according to the STROBE statement (www.strobe-statement.org)

Availability of data and materials

The dataset generated during and/or analyzed during the current study will be available from ANCS upon reasonable request and once the dataset has been fully exploited by the authors.

Competing interests

The authors declare that they have no competing interest. None of the authors are involved in the publication process or have a financial or other beneficial interest in the products or concepts mentioned in the submitted manuscript.

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Authors' contributions

1) conception and design of the study: CRM, CCA, TF, ANCS; 2) acquisition of data: CRM; CCA, LMMM; 3) laboratory analysis: TF, MABL; 4) statistical analysis: TF, ANCS; 5) analysis and interpretation of data: CRM, ANCS, TF, EMVR, drafting of the manuscript, tables and figures: CRM, TF, EMVR, ANCS; 6) manuscript review: CRM, EMVR, ANCS. All authors read and approved the final manuscript.

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