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ORIGINAL ARTICLE

IS THERE A RELATIONSHIP BETWEEN INTERLEUKIN-6 (RS1800795) POLYMORPHISM AND HUMAN PAPILLOMAVIRUS?

Malene Lima Gomes Pereira[1], Alice de Sá Ferreira[2], Pablo de Matos Monteiro [3]
Ilka Kassandra Pereira Belfort[4], Ana Paula Almeida Cunha[5]
Francisco Pedro Belfort Mendes[6], Gerusinete Rodrigues Bastos dos Santos[7]
Flávia Castello Branco Vidal[8], Maria do Desterro Soares Brandão[9],
Sally Cristina Moutinho Monteiro[10]

Highlights:
(1) The prevalence of HPV in the study was 34.88%, which can be considered high.
(2) This is the first study in the state of Maranhão to address the relationship between IL6 polymorphism and the presence of HPV.
(3) The data obtained in that study did not demonstrate an association between the presence of HPV-DNA and the IL6 -174G>C polymorphism (rs1800795) in sexually active women from Ludovica.

ABSTRACT

Objective: To assess the relationship between interleukin-6 (IL-6) polymorphism and the human papillomavirus (HPV) infection among women in a capital city in Northeastern Brazil. *Methods:* This cross-sectional study included sexually active women who received care through the public health system in São Luís, Maranhão State, Brazil. Information was collected on sociodemographic characteristics, sexual health, and number of pregnancies. Cytopathological analysis was performed using the Papanicolaou stain. HPV was detected using a nested polymerase chain reaction (PCR), and IL-6 −174G>C (rs1800795) polymorphism was detected by real-time PCR. For analysis of relationships with epidemiological and clinical data, patients were divided into two groups according to HPV status (HPV DNA-positive and -negative), and differences were deemed significant at $p < 0.05$. *Results:* The sample comprised 195 participants, 68 (34.88%) of whom were positive for HPV DNA. The prevalence of IL-6 −174G>C polymorphism was 28.72%, with 26.67% of patients exhibiting heterozygosity (GC) and 2.05% homozygosity (CC), indicating Hardy–Weinberg equilibrium. *Conclusion:* There was no association between IL6 −174G>C polymorphism and HPV status in the analyzed population. The findings of this study do not support the association between HPV DNA positivity and IL-6 −174G>C polymorphism among sexually active women in São Luís, Brazil.

Keywords: Inflammation. Interleukin-6. Human papillomavirus. Polymorphism.

[1] Federal University of Maranhão – Ufma. São Luís, Maranhão, Brazil. https://orcid.org/0000-0001-7699-4695
[2] Federal University of Delta of Parnaíba – UFDPar. Parnaíba, Piauí Brazil. https://orcid.org/0000-0001-5401-0843
[3] Federal University of Maranhão – Ufma. São Luís, Maranhão, Brazil. https://orcid.org/0000-0002-3879-5326
[4] Federal University of Maranhão – Ufma. São Luís, Maranhão, Brazil. https://orcid.org/0000-0002-0734-0353
[5] Federal University of Maranhão – Ufma. São Luís, Maranhão, Brazil. https://orcid.org/0000-0003-2594-0296
[6] Federal University of Maranhão – Ufma. São Luís, Maranhão, Brazil. https://orcid.org/0000-0003-4969-2776
[7] Federal University of Maranhão – Ufma. São Luís, Maranhão, Brazil. https://orcid.org/0000-0002-1602-4563
[8] Federal University of Maranhão – Ufma. São Luís, Maranhão, Brazil. https://orcid.org/0000-0002-4721-6824
[9] Federal University of Maranhão – Ufma. São Luís, Maranhão, Brazil. https://orcid.org/0000-0003-2783-362X
[10] Federal University of Maranhão – Ufma. São Luís, Maranhão, Brazil. https://orcid.org/0000-0002-4425-1552

INTRODUCTION

Human papillomaviruses (HPV) are a large family of sexually transmitted DNA viruses known to play a major role in the development of cervical cancer. Persistent infection with high-risk types, such as HPV-16 and HPV-18, is the primary cause of cervical cancer and its precursor lesions[1]. In 2020, an estimated 604,127 women were newly diagnosed with cervical cancer worldwide, and 341,831 died from the disease[2].

HPV infection remains a global public health concern, particularly among women. Worldwide, its prevalence is estimated to range from 10% to 20% among sexually active adults[1]. In Brazil, data from an epidemiological study assessing HPV prevalence rates (POP-Brasil) indicated a prevalence of 53.6%[3]. Prevalence rates were even higher in some regions, reaching 60.2% in São Luís, the capital of Maranhão State[3].

Cervical cancer is a multifactorial disease, with HPV acting in conjunction with other risk factors, including family history, age, socioeconomic status, sexual and reproductive behavior, smoking, co-infections, immunosuppression, inflammatory response, and cytokine polymorphisms, among others[2,4]. Inflammation, angiogenesis, and thrombosis are known to participate in cancer development by generating a protumoral microenvironment. The relationship between inflammation and cancer is well-established, particularly chronic inflammation[5]. Different cytokines can inhibit or promote cancer progression, depending on their action on different stages of the disease (e.g., initiation, malignant conversion, invasion, promotion, and metastasis)[6]. A growing body of evidence demonstrates that polymorphisms in cytokine and interleukin genes play a critical role in the development and prognosis of cervical cancer[5-7].

Interleukin-6 (IL-6) is one of the most well-characterized cytokines implicated in cervical carcinogenesis. This pleiotropic cytokine participates not only in the regulation of the immune response but also in cell proliferation and differentiation. Additionally, it induces the expression of vascular endothelial growth factor genes and promotes tumor growth[5,8]. Elevated levels of IL-6 were detected in tumor tissues[6,9] as well as in individuals with HPV infection[10]. Notably, a single nucleotide polymorphism (SNP) in the *IL6* gene (rs1800795) was found to be associated with an increased risk of cervical cancer[5,7,11-12] and HPV positivity[7,13]. However, findings remain controversial and vary across different populations[14-15], possibly due to confounding factors, such as ethnic group, age, and geographic distribution. In view of these considerations, this study aimed to investigate the potential relationship between IL-6 polymorphism (rs1800795) and HPV infection among women in a capital city in Northeastern Brazil.

METHODS

Study design

This is a cross-sectional study comprising 195 sexually active adult women who received care at primary healthcare units of the Unified Health System (SUS).

Study site

Study participants were women who sought care through spontaneous demand at public primary healthcare units in São Luís, Maranhão State, Brazil. A semi-structured questionnaire was administered face-to-face for the collection of sociodemographic (age, ethnic group, and civil status), behavioral (smoking status), and reproductive (menarche, sexarche, number of pregnancies, and oral contraceptive use) data.

Inclusion criteria were sexually active women aged 20 years or older. Exclusion criteria included pregnant women, women in the early puerperium period (up to 45 days postpartum), lactating women, hysterectomized women, women who had undergone surgery within the three months prior to sample collection, and women who were menstruating on the day of sample collection.

Sample collection for cytopathological examination

Cytological specimens were collected using an Ayre spatula and endocervical brush (ectocervical and endocervical sample), smeared on a glass slide, and fixed with ethanol. Subsequently, slides were stained by the Papanicolaou method. Cell segmentation and classification were performed according to the Brazilian Guidelines for Cervical Cancer Screening[16]. The results were provided to the participants, who also received case-specific guidance and medical referrals when necessary.

Sample collection for DNA extraction

For extraction of genetic material (DNA), cervical specimens were collected using the cervical brush included in the HC2 DNA Collection kit (Qiagen, Valencia, CA, United States). Samples were placed in Tris-EDTA buffer, pH 7.4, and stored in a freezer at −20°C until use.

Genomic DNA extraction was performed using a QIAamp DNA Mini and Blood Mini kit (Qiagen, Valencia, CA, United States), according to the manufacturer's instructions. Total DNA was eluted in Tris-EDTA buffer and stored at −20°C. DNA purity and concentration were determined at 260 and 280 nm using a NanoDrop spectrophotometer (Thermo Fisher Scientific, CA, United States).

HPV detection and genotyping

HPV DNA was detected by a nested polymerase chain reaction (PCR). Two sets of primers were used: PGMY09 and -11, which amplify 450 bp fragments of the L1 region of viral DNA, and GP+5 and GP+6, which amplify 190 bp fragments of the L1 region[17]. Reactions were performed on a Veriti Dx 96-Well thermal cycler (Applied Biosystems, Thermo Fisher Scientific, CA, United States). Previously confirmed HPV-positive samples were used as positive control, whereas ultrapure water was used as negative control. Nested PCR amplification products were separated by agarose gel electrophoresis (1.5%), stained with 0.1% GelRed, and visualized using an ultraviolet light transilluminator (Bio-Rad Laboratories, United States).

HPV DNA-positive samples were purified using the GenElute PCR Clean-Up kit, as per the manufacturer's protocol (Sigma–Aldrich, United States). Genotyping was performed by the Sanger method at ACTGene Análises Moleculares Ltda. (Center for Biotechnology, Federal University of Rio Grande do Sul, Porto Alegre, Rio Grande do Sul, Brazil), using an AB 3500 Genetic Analyzer equipped with 50 cm capillaries and POP-7 polymer (Applied Biosystems, Thermo Fisher Scientific, California, United States). DNA templates were purified with ExoSAP-IT™ PCR Product Cleanup reagent (Applied Biosystems, Thermo Fisher Scientific, California, USA) and quantified on a NanoDrop 2000c spectrophotometer (Thermo Fisher Scientific, California, United States). HPV genotypes were identified using BLASTn (Basic Local Alignment Search Tool, http://blast.ncbi.nlm.nih.gov/).

IL-6 polymorphism detection

IL-6 −174G>C polymorphism was analyzed by real-time PCR using a StepOne system (Life Technologies, United States) and TaqMan probes (Applied Biosystems, Thermo Fisher Scientific, California, United States) specific for the rs1800795 SNP. The reaction mixture consisted of 10 µL of TaqMan™ GTXpress™ Master Mix (Applied Biosystems, Thermo Fisher Scientific, California, United States), 20 ng of DNA, and 0.5 µL of TaqMan probe. Reaction conditions were as follows (40 cycles):

60°C for 30 s, 95°C for 20 s, 95°C for 3 s, 60°C for 20 s, and 60°C for 30 s. Primer Express® software version 3.0 (Life Technologies, United States) was used to visualize and analyze amplified products. All samples were genotyped in duplicate.

Ethical aspects

The participants were informed about the study's objective and procedure. Those who agreed to participate signed an informed consent form, according to resolution 466/12 of the Brazilian National Health Council (CNS)[17]. The research complied with ethical guidelines for health research involving human subjects, according to CNS resolution No. 466/2012 and was approved by the Research Ethics Committee at the Presidente Dutra University Hospital of the Federal University of Maranhão (Process nº 6,562,945 and CAAE nº 75975223.2.0000.5086).

Statistical Analysis

The relationship between epidemiological and clinical data and HPV prevalence was assessed using the chi-squared test and Fisher's exact test. A significance level of $p < 0.05$ was adopted. The Hardy – Weinberg equilibrium was evaluated using the chi-squared test. Pairwise comparisons of alleles and genotypes in contingency tables were conducted using chi-squared or Fisher's exact tests, as appropriate. Statistical analyses were performed by stratifying the sample according to HPV DNA positivity or IL-6 −174G>C (rs1800795) polymorphism. Thus, the sample was divided into HPV DNA-positive or HPV DNA-negative. For analysis of cytopathological results, the sample was also categorized according to IL-6 −174G>C (rs1800795) polymorphism. All statistical analyses were performed at a significance level of $p < 0.05$ using IBM SPSS version 24.

RESULTS

This study comprised 195 adult women, of whom 68 (34.88%) were positive for HPV DNA. Demographic, behavioral, and reproductive characteristics (age, ethnic group, civil status, menarche, sexarche, menopause, number of pregnancies, smoking status, and oral contraceptive use) were stratified according to HPV DNA positivity. Ethnic group and smoking status differed significantly ($p < 0.05$) between groups (Table 1).

Table 1 – Demographic, behavioral, and reproductive characteristics of sexually active women who sought care at primary healthcare units in São Luís, Maranhão, Brazil, 2022, stratified by human papillomavirus (HPV) DNA positivity

Characteristic	HPV DNA-negative (*N* = 127), *n* (%)	HPV DNA-positive (*N* = 68), *n* (%)	*p*-value
Age			
22 to 34 years	49 (38.6)	24 (35.3)	
35 to 64 years	61 (48.0)	30 (44.1)	0.423
≥ 65 years	17 (13.4)	14 (20.6)	
Ethnic group			
White	12 (9.4)	0 (0)	
Pardo	81 (63.8)	42 (61.8)	0.028
Black	29 (22.8)	24 (35.3)	
Indigenous	5 (3.9)	2 (2.9)	
Civil status			

With partner	60 (47.2)	38 (55.9)	0.250
Without partner	67 (52.8)	30 (44.1)	
Menarche			
<13 years	52 (40.9)	31 (45.6)	0.532
≥13 years	75 (59.1)	37 (54.4)	
Sexarche			
<15 years	50 (39.4)	27 (39.7)	0.964
≥15 years	77 (60.6)	41 (60.3)	
Nº of pregnancies			
None	19 (15.0)	9 (13.2)	0.751
1 to 3	72 (56.7)	39 (57.4)	
4 to 6	31 (24.4)	15 (22.1)	
≥7	5 (3.9)	5 (7.4)	
Smoker			
No	6 (4.7)	9 (13.2)	0.040
Yes	101 (79.5)	44 (64.7)	
Ex-smoker	20 (15.7)	15 (22.1)	
Oral contraceptive use			
No	110 (13.4)	11 (16.2)	0.596
Yes	17 (86.6)	57 (83.8)	

Relative frequency data were assessed by the chi-squared test at $p < 0.05$.

HPV genotyping identified that, among the 68 HPV DNA-positive women, 35.29% had low-risk HPV (types 6, 11, 66, 54, 71, 72, and 81). High-risk HPV was detected in 64.70% of cases (types 16, 18, 33, 35, 39, 45, 52, 58, and 67). Among high-risk HPVs, types 16 and 18 were the most frequent, accounting for 28.89% and 17.78% of occurrences, respectively (Figure 1). It was also observed that 38.24% of women were infected with multiple types of HPV.

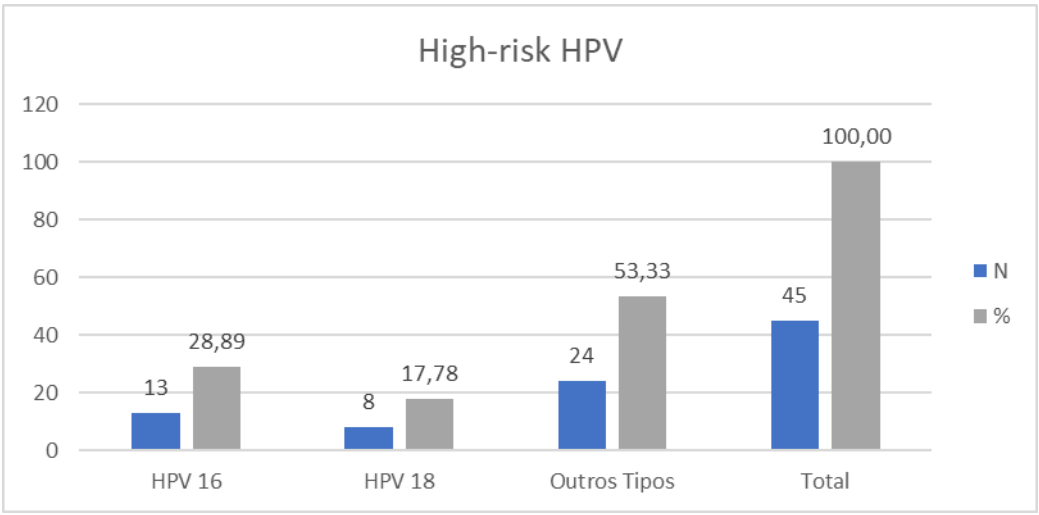

Figure 1 – Distribution of high-risk human papillomavirus (HPV) types 16 and 18, as well as other types, among sexually active women who sought care at primary healthcare units in São Luís, Maranhão, Brazil, 2022.

The results of cytopathological examination revealed that 91.8% of samples did not have cellular alterations. Additionally, *Trichomonas vaginalis* was detected in 27.17% of samples. The data are shown in Table 2.

Table 2 – Cytopathological results of sexually active women who sought care at primary healthcare units in São Luís, Maranhão, Brazil, stratified by human papillomavirus (HPV) positivity

Item	HPV DNA-negative (*N* = 127), *n* (%)	HPV DNA-positive (*N* = 68), *n* (%)	*p*-value
Cytopathological finding			
No alteration	118 (92.9)	61 (89.7)	
Low-grade squamous intraepithelial lesion	2 (1.6)	1 (1.5)	
High-grade squamous intraepithelial lesion	0 (0.0)	0 (0.0)	0.174
Atypical squamous cells	3 (2.4)	0 (0.0)	
Atypical squamous cells of undetermined significance	4 (3.1)	6 (8.8)	
Trichomonas vaginalis			
No	101 (79.5)	41 (60.3)	0.004
Yes	26 (20.5)	27 (39.7)	

Relative frequency data were assessed by the chi-squared test at $p < 0.05$.

Regarding IL-6 polymorphism, the distribution of the C allele of IL-6 −174G>C (rs1800795) was 28.72%, with 26.67% of patients exhibiting heterozygosity (GC) and 2.05% homozygosity (CC), confirming Hardy–Weinberg equilibrium (Table 3).

Table 3 – Genotypic and allelic frequencies of IL-6 −174G>C (rs1800795) polymorphism in sexually active women who sought care at primary healthcare units in São Luís, Maranhão, Brazil, 2022

IL-6 −174G>C	*N*	Frequency (%)
GG	139[a]	71.28[a]
GC	52[a]	26.67[a]
CC	4[a]	2.05[a]
G	191	97.95
C	56	2.05

[a] Hardy–Weinberg equilibrium ($p = 0.838$) was evaluated by the chi-squared test by comparing observed values (GG, 139; GC, 52; CC, 4) with expected values (GG, 139; GC, 50; CC, 3). GG, wild homozygous; GC, heterozygous; CC, polymorphic homozygous.

HPV groups did not differ significantly in IL-6 −174G>C (rs1800795) polymorphism (Table 4). The relationship of IL-6 polymorphism with high-risk HPV and presence of more than one type of HPV was also investigated, but differences were not significant (Table 5).

Table 4 – Relationship between IL-6 −174G>C polymorphism (rs1800795) and human papillomavirus (HPV) status in sexually active women who sought care at primary healthcare units in São Luís, Maranhão, Brazil, 2022

Polymorphism	HPV DNA-negative (*N* = 127), *n* (%)	HPV DNA-positive (*N* = 68), *n* (%)	*p*-value
IL-6 (rs1800795)			
GG	87 (68.5)	52(76.5)	
GC	36 (31.5)	16 (23.5)	0.232
CC	0 (0)	0 (0)	
Presence of polymorphic allele			
No	16 (23.5)	16 (23.5)	0.241
Yes	52 (76.5)	52 (76.5)	

GG, wild homozygous; GC, heterozygous; CC, polymorphic homozygous.

Table 5 – Relationship between IL-6 −174G>C (rs1800795) polymorphism and prevalence of high-risk human papillomavirus (HPV) or multiple types of HPV in sexually active women who sought care at primary healthcare units in São Luís, Maranhão, Brazil, 2022

IL-6 −174G>C (rs1800795)	HPV type			Number of HPV types		
	High-risk	Other	*p*-value	1 type	>1 type	*p*-value
Allele, *n* (%)						
G	44 (81.48)	24 (80)	0.868	42 (79.25)	26 (83.87)	0.602
C	10 (18.52)	6 (20)		11 (20.75)	5 (16.13)	
Genotype, *n* (%)						
GG	34 (77.3)	6 (25)		31 (73.8)	21 (80.8)	
GC	10 (22.7)	18 (75)	0.833	11 (26.2)	5 (19.2)	0.511
CC	0 (0)	0 (0)		0 (0)	0 (0)	

Relative frequency data were assessed by the chi-squared test at $p < 0.05$.

DISCUSSION

This study recorded a high prevalence of HPV (34.88%) among sexually active women in São Luís. Nevertheless, the rate was lower than previous reports for Maranhão State. Cunha et al.[19] observed a prevalence of 59.7% among women attending primary healthcare units in São Luís, and Ross et al.[20] recorded a prevalence of 41.37% among quilombola women in Caxias. Together, these findings demonstrate a high prevalence of HPV in the population of Maranhão State, in agreement with the POP-Brasil study[3].

IL-6 −174G>C (rs1800795) polymorphism is known to play an important role in the development of cervical cancer, owing to its contribution to HPV pathogenesis and persistence in cervical tissues. IL-6 polymorphism is related to variations in serum and local levels of IL-6. For instance, the presence of polymorphic allele C correlates with low pro-inflammatory cytokine production, creating an environment conducive to HPV infection and persistence[21]. The presence of HPV may induce chronic inflammation, which stimulates the development and growth of cancer cells[5-7].

Here, the frequency of allele C was 24.4%; however, there was no association between IL-6 −174G>C (rs1800795) polymorphism and HPV status. Albosale and Mashina[22], Fernandes et al.[23], Marangon et al.[24], and Lima Júnior et al.[25] also found no association between IL-6 −174G>C (rs1800795) polymorphism and HPV status. The last three studies were conducted in Brazil.

Although this study did not identify a significant relationship between IL-6 −174G>C (rs1800795) polymorphism and HPV status, global scientific literature has shown that IL-6 is widely associated with cervical cancer[5,7,11-12] and HPV positivity[7,13]. IL-6 regulation and alteration are related to the mechanism of control and management of HPV infection. Therefore, the polymorphism of proteins involved in immune system regulation, such as IL-6 −174G>C (rs1800795), may alter the levels of interleukin production, leading to changes in signaling pathways such as Janus kinase (JAK). These modifications may trigger local proliferation of epithelial cells, metastasis, and progression of cervical injury to cancer[22].

Prema et al.[14] and Porto et al.[15] underscored that ethnic group, age, and geographical distribution may influence the association between IL-6 −174G>C (rs1800795) polymorphism and HPV infection or cervical cancer. Such effects might have occurred in the present study, although the small sample cannot be considered representative of the general population. Nevertheless, this is the first study of its kind in Maranhão State, and few similar studies have been conducted in Brazil[23-25].

Intergenic interactions may influence HPV infection, in that the type, presence, or persistence of HPV may be affected by one or more genes[22]. Given that HPV is a major factor influencing the development of cervical cancer, it is essential to raise public awareness about its underlying causal mechanisms. Moreover, further research is needed to investigate the causal role of IL-6 in HPV persistence and its contribution to the carcinogenic process.

CONCLUSION AND FINAL CONSIDERATIONS

No association was found between HPV status and IL-6 −174G>C (rs1800795) polymorphism among sexually active women residing in São Luís, Brazil. However, the study revealed a high overall prevalence of HPV, particularly high-risk types. These findings underscore the critical need for ongoing public health initiatives focused on education, vaccination, prevention, and regular screening for cervical cancer.

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Author contributions	
Malene Lima Gomes Pereira:	Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing.
Alice de Sá Ferreira:	Methodology, Resources, Validation, Visualization, Writing – original draft, Writing – review & editing.
Pablo de Matos Monteiro:	Formal analysis, Investigation, Methodology, Validation, Visualization.
Ilka Kassandra Pereira Belfort:	Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources
Ana Paula Almeida Cunha:	Formal analysis, Investigation, Methodology, Validation, Visualization.
Francisco Pedro Belfort Mendes:	Formal analysis, Investigation, Methodology, Validation, Visualization.
Gerusinete Rodrigues Bastos dos Santos:	Investigation, Methodology, Validation
Flávia Castello Branco Vidal:	Conceptualization, Methodology, Project administration, Resources, Supervision, Validation, Visualization.
Maria do Desterro Soares Brandão:	Conceptualization, Data curation, Project administration, Resources, Supervision, Validation, Visualization.
Sally Cristina Moutinho Monteiro:	Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.
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Corresponding author:	Alice de Sá Ferreira Federal University of Delta of Parnaíba – UFDPar Av. São Sebastião, 2819 – Nossa Sra. de Fátima, Parnaíba/PI, Brazil ZIP CODE 64202-020 ferreiraalicedesa@gmail.com
Editor:	Matias Nunes Frizzo Ph.D
Editor-in-chief:	Adriane Cristina Bernat Kolankiewicz Ph.D