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The Differential Role of Cyclooxygenases and Inflammatory Biomarkers in the Pain of Sickle Cell Vaso-Occlusive Crises in Brazzaville

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Abstract

Introduction: Sickle cell disease is a recessive hereditary disorder manifested by vaso-occlusive crises (VOCs), associated with intense pain and inflammation. Although biomarkers such as IL-6, CRP, COX-1/2 and VCAM-1 are involved in these processes. Their relationship with pain intensity remains poorly elucidated. This study aims to assess this correlation in homozygous sickle cell patients in Brazzaville. **Methodology:** A prospective observational study was carried out on 85 patients (2 - 62 years). Biomarkers (CRP, IL-6, COX-1/2, VCAM-1) were measured by turbidimetry and ELISA. Pain intensity was assessed using a validated scale, and data were statistically analyzed. **Results:** 45.88% of patients were in CVO, while intense pain was reported in 84.62% of patients in crisis. CRP, COX-2 and VCAM-1 showed significantly higher concentrations during CVO ($p < 0.05$, for CRP; $p < 0.0001$, for COX-2 $p = 0.0035$ and $p = 0.0165$ for VCAM-1), in contrast to IL-6 and COX-1, which showed no statistically significant difference ($p = 0.06$ for IL-6 and $p = 0.02$ for COX-1). A significant positive correlation was observed between COX-2 and pain intensity ($r = 0.65$; $p < 0.0001$), while the other biomarkers showed no significant relationship. **Conclusion:** These results suggest that COX-2 may be considered a promising biomarker for assessing inflammatory pain during CVO and its potential usefulness in therapeutic pain monitoring in

sickle cell crisis patients, although further studies are needed to confirm its clinical role.

Keywords

Sickle Cell Disease, Vaso-Occlusive Crisis, Inflammation

1. Introduction

Sickle cell disease (SCD) is a genetic disorder which has spread beyond its geographical origins (mainly sub-Saharan Africa and India), in France and throughout the world, and has become a major public health problem with around 5 million people affected, It is an autosomal recessive hereditary disease linked to a mutation in the HBB gene, resulting in the production of abnormal hemoglobin (HbS) responsible for painful vaso-occlusive crises (CVO) and chronic hemolysis [1]-[3]. In Brazzaville, where the prevalence of sickle cell trait exceeds 25% and homozygous forms (SS) 2% [4], patient management relies essentially on symptomatic measures: analgesics (paracetamol, morphine), hydration and emergency transfusions [5]. However, these approaches remain limited by the absence of predictive markers for seizures, subjective pain assessment and insufficient resources for personalized follow-up [6].

CVOs, the most frequent and disabling manifestations, generate acute pain whose intensity does not systematically correlate with conventional biological parameters (hemoglobin, reticulocytes) [4] [7]. This discordance complicates therapeutic stratification, leading either to under-treatment (increasing the risk of complications), or to excessive use of opioids, with their adverse effects [7]. Furthermore, chronic pain significantly alters patients' quality of life, increasing hospitalizations, medical costs and interruptions to school or work [7] [8].

Faced with these challenges, the identification of objective biomarkers of inflammation and endothelial dysfunction could improve management. Several mediators have been implicated in the pathophysiology of sickle cell pain, including interleukin-6 (IL-6) and C-reactive protein (CRP), whose levels rise during CVO, reflecting macrophagic activation and systemic inflammation [9] [10]. A Nigerian study has shown that IL-6 correlates with the frequency of hospital admissions for pain [11]. In addition, cyclooxygenases (COX-1/COX-2), key enzymes in prostaglandin synthesis, amplify both inflammation and nociception [12]. COX-2 inhibitors are being tested to reduce sickle cell pain [13]. Finally, VCAM-1, a vascular adhesion molecule, is a marker of endothelial damage and adhesion phenomena in sickle cell red blood cells [14]. Its overexpression has been associated with CVO severity in US cohorts [15].

However, no study in Brazzaville has simultaneously assessed these biomarkers in relation to pain intensity, even though local factors (high prevalence of malaria, nutritional deficiency, genetic diversity) could modify their expression. This study

therefore aims to establish correlations between pain scores (visual analog scales) and levels of IL-6, CRP, COX-1, COX-2 and VCAM-1 in SS patients in crisis. It also aims to propose prognostic tools adapted to the Congolese context for more targeted management.

By filling this local data gap, this work could guide the rational use of anti-inflammatory drugs or endothelial-protective therapies, thereby reducing CVO-related morbidity.

2. Methodology

- Study setting and design

This prospective observational study was conducted over a 12-month period from January to December 2024 at the Centre National de Référence de la Drépanocytose (CNRDr) in Brazzaville for patient recruitment, and at the TRIOS Laboratory, the research laboratory of the Faculty of Health Sciences (FSSA) and the Centre National de Transfusion Sanguine (CNTS) for biological analyses.

- Study population

- Participant selection

An exhaustive and consecutive recruitment was carried out among 85 patients with homozygous sickle cell disease (SS genotype), aged 2 to 62 years, in a hospital setting in Brazzaville.

- Inclusion criteria

CVO patients were recruited on admission, before any administration of analgesics, as confirmed by their medical records and a standardized interview. Patients included in this study presented with a vaso-occlusive crisis (VOC), with emergency or day hospitalization, prior to any administration of analgesics, a stable intercritical state, no history of blood transfusion in the previous 3 months or hospitalization in the previous 72 hours and a signed agreement of informed consent, by participants over the age of majority or by parents/legal guardians for minors, in accordance with the ethical principles of the Declaration of Helsinki (WMA, 2013) [16].

- Exclusion criteria

The following criteria led to the exclusion of participants: biological samples that were not usable (hemolyzed, coagulated or insufficient in volume), anti-inflammatory or immunosuppressive treatment within 7 days prior to sampling and a lack of confirmation of the diagnosis of homozygous sickle cell disease by hemoglobin electrophoresis, in line with WHO recommendations.

- Non-inclusion criteria

Patients with any of the following characteristics were excluded from the study; non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids taken within 7 days prior to sampling, hydroxyurea treatment at an unstable dose, blood transfusion within the previous 3 months, acute infection (or active inflammatory pathology), recent hospitalization (<72 hours) for a cause unrelated to CVO, pregnancy and refusal of participation or consent not obtained (for minors: absence

of parental/guardian consent).

- Data collection

- Epidemiological approach

A standardized questionnaire was administered to collect demographic data, medical history and frequency of CVO episodes.

- Clinical approach

The diagnosis of CVO was established based on validated clinical criteria (presence of typical acute pain with no alternative etiology identified), with confirmation by a physician from the National Centre de Reference of Sickle Cell (CNRDr) [3].

Pain intensity was assessed using the adult Visual Analogue Scale (VAS) (0 to 10) [17].

- Biological approach

Blood samples were taken in 5 ml EDTA tubes for biomarker assays and dry tubes for C-reactive protein (CRP) determination.

CRP determination was performed turbidimetrically on a Cobas c501 (Roche Diagnostics), using CRP Latex reagent (ref. 05168787), cytokines and signalling molecules, notably IL-6, were assayed by ELISA using the human interleukin-6 (IL-6) ELISA kit from Pars Biochem, COX-1/2 was assayed using the human serum ELISA kits from Pars Biochem, and VCAM-1 was assayed using the Human VCAM-1/CD106 ELISA kit (Thermo Fisher, ref. BMS232).

Ethical considerations

The study was approved by the Research Ethics Committee in Health Sciences of Brazzaville, under number 056-40/MESRSIT/DGRST/CERSSA/-23, in accordance with international standards for research involving human subjects [18].

- Statistical analysis

Data was entered in Microsoft Excel 2021 and analyzed using GraphPad Prism version 5. Statistical tests included comparison of means by Student's t-test for normally distributed data; Mann-Whitney test for non-parametric distributions. Analysis of proportions using the Chi^2 test or Fisher's exact test for categorical variables, and correlation using Spearman's coefficient. The significance threshold was set at $p < 0.05$.

3. Results

Table 1. Distribution of patients by age and sex.

Age groups (years)	Sex		Total n (%)	p-value
	Male n (%)	Female n (%)		
2 - 11	8 (57.14)	6 (42.86)	14 (100)	p = 0.490
12 - 17	16 (57.14)	12 (42.86)	28 (100)	
18+	19 (44.19)	24 (55.81)	43 (100)	
Total	43 (50.59)	42 (49.41)	85 (100)	

a. Epidemiological characteristics of homozygous sickle cell patients (Tables

1-3)

- The age distribution shows a predominance of patients aged 18 and older (50.59%), with no significant difference between sexes (p = 0.490), reflecting a young adult population often affected by complications of sickle cell disease (Table 1).

b. Clinical characteristics of homozygous sickle-cell patients

- Our results showed that 39 homozygous sickle-cell patients (45.88%) were in CVO and 46 (54.12%) in inter-critical phase. These results show no significant difference between men and women (p = 0.906), suggesting that gender does not influence the occurrence of CVO.

Table 2. Distribution of CVO occurrence by gender.

Sex	CVO		Total n (%)	p-value
	Yes n (%)	No n (%)		
Male	20 (46.51)	23 (53.49)	43 (100)	
Female	19 (45.24)	23 (54.76)	42 (100)	P = 0.906
Total	39 (45.88)	46 (54.12)	85 (100)	

- The distribution of CVOs by age showed a higher percentage in children aged 2 to 11. Children aged 2 to 11 had the highest proportion of CVOs (57.14%), possibly due to immune immaturity or poorer compliance. However, the age difference showed no statistically significant difference (P = 0.362) (Table 2).

Table 3. Distribution of CVO occurrence according to age.

Age groups (years)	CVO		Total n (%)	p-value
	Yes n (%)	No n (%)		
[2]-[11]	8 (57.14)	6 (42.86)	14 (100)	
[12]-[17]	10 (35.71)	18 (64.29)	28 (100)	P = 0.362
[18+]	21 (48.84)	22 (51.16)	43 (100)	
Total	39 (45.88)	46 (54.12)	85 (100)	

c. Clinical characteristics of pain in sickle-cell crisis patients

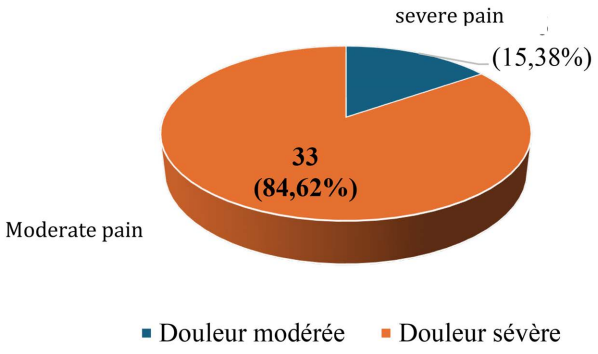

Figure 1. Clinical characteristics of pain during CVOs.

- Figure 1 shows that pain intensity during CVO is very high in 84.62% of patients in crisis.

d. Measurement of biomarkers of inflammation in homozygous sickle cell patients

- Our data showed a statistically significant difference in C-Reactive Protein concentration between groups of homozygous sickle cell patients in the inter-critical and crisis phases ($p < 0.0001$). This difference reflects the intensity of the systemic inflammatory response associated with CVO (Figure 2).

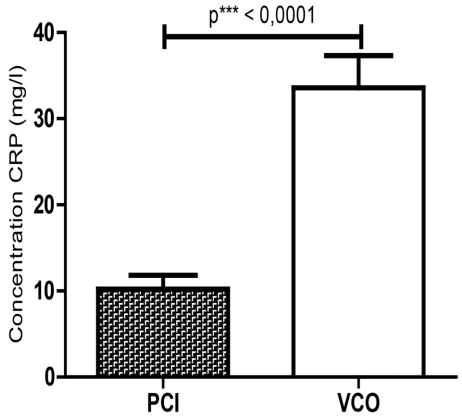

Figure 2. CRP concentration in homozygous sickle cell patients.

- Our results showed no statistically significant difference in IL6 concentration in homozygous sickle cell patients ($p = 0.06$) (Figure 3).

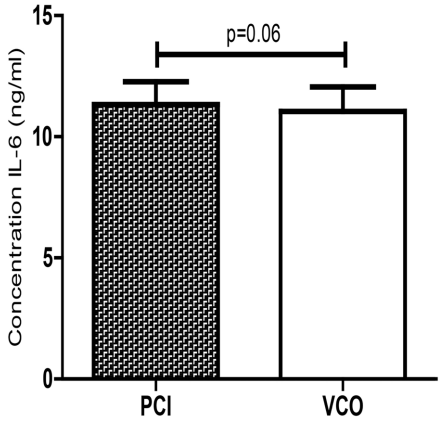

Figure 3. IL-6 concentration in homozygous sickle cell subjects.

- The results obtained show no statistically significant difference in COX-1 concentration in homozygous sickle cell patients in the inter-critical and critical phases ($p = 0.02$) (Figure 4).
- The results obtained show a statistically significant difference in COX-2 concentrations in homozygous sickle cell patients in the inter-critical and critical phases ($p = 0.0035$) (Figure 5).

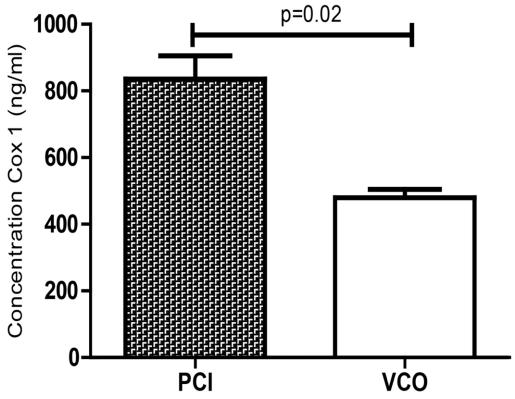

Figure 4. COX-1 concentration in homozygous sickle cell subjects.

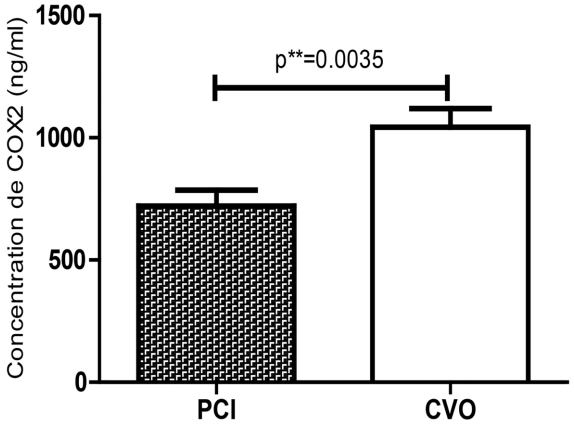

Figure 5. COX-2 concentration in homozygous sickle cell subjects.

e. Measurement of VCAM-1 plasma concentration

- Our results show higher VCAM-1 values in CVO with a statistically significant difference (p = 0.0165) in VCAM-1 concentration in homozygous sickle cell patients in the inter-critical and critical phases (Figure 6).

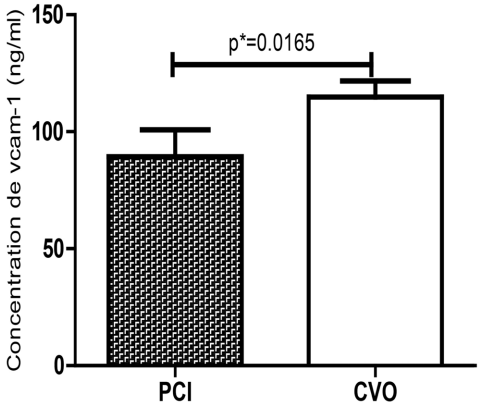

Figure 6. VCAM-1 concentration in homozygous sickle cell subjects.

- **Correlation between pain intensity and inflammatory markers.**

Our results show a weak, non-significant correlation IL-6 and pain in homozygous sickle cell patients in crisis and not in crisis (r = −0.11, p = 0.24) (Figure 7).

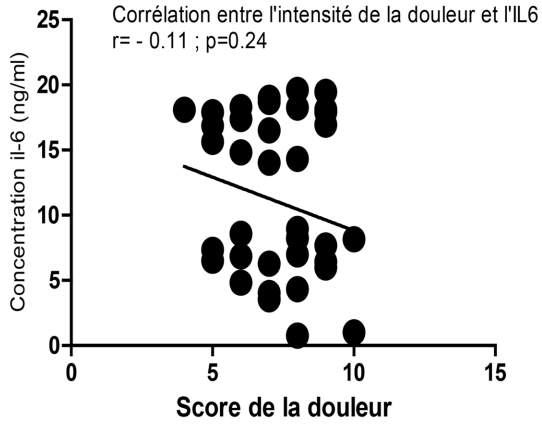

Figure 7. Correlation between IL-6 and pain score in sickle cell subjects' homozygotes.

- Our results show a non-significant correlation between pain intensity and CRP in homozygous sickle cell patients in crisis and not in crisis (r = 0.053; p = 0.37) (Figure 8).

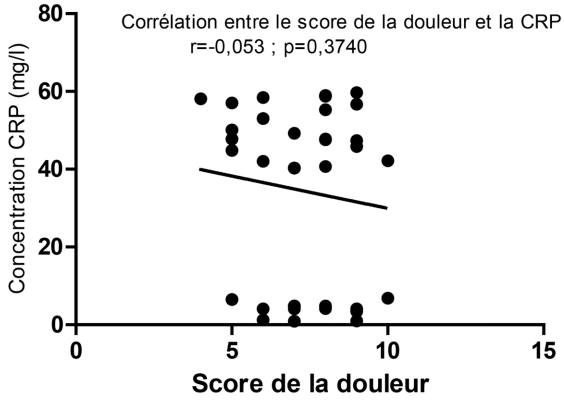

Figure 8. Correlation between CRP and pain score in homozygous sickle cell subjects.

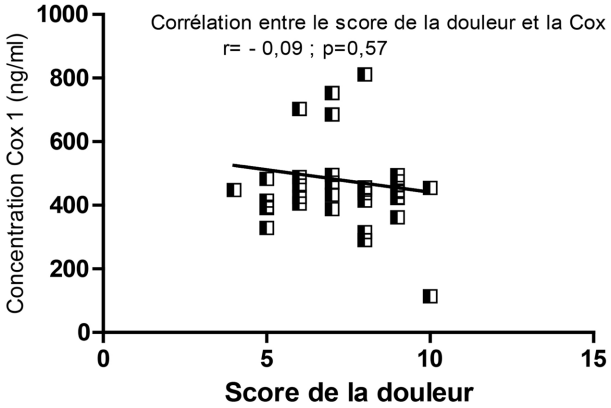

Figure 9. Correlation between COX-1 and pain score in homozygous sickle cell subjects.

- Our results show a non-significant correlation between pain intensity and COX-1 in homozygous sickle cell patients in crisis and not in crisis (r = −0.09; p = 0.57) (Figure 9).
- Our results indicate that when pain increases, COX-2 expression or concentration also increases significantly in homozygous sickle cell patients (r = 0.65, p < 0.0001) (Figure 10).

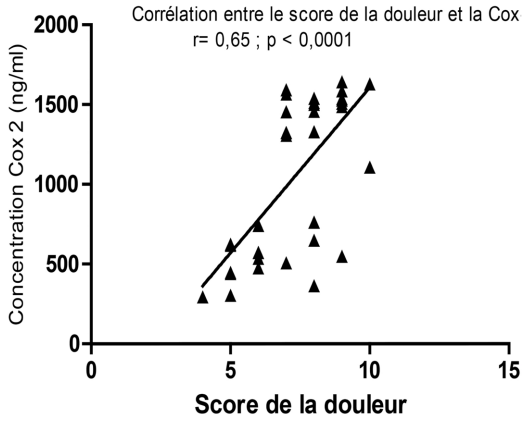

Figure 10. Correlation between COX-2 and pain score in homozygous sickle cell subjects.

- **Correlation between pain intensity and endothelial marker (VCAM1)**

Our data show a very weak and non-significant correlation between VCAM-1 concentration and pain in homozygous sickle cell patients (r = 0.08 and P = 0.59) (Figure 11).

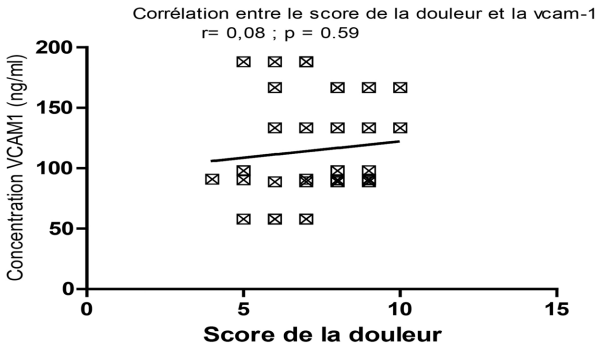

Figure 11. Correlation between VCAM-1 and pain score in homozygous sickle cell subjects.

4. Discussion

The objective of this work was to analyze the correlation between pain scores and levels of IL-6, CRP, COX-1, COX-2, and VCAM-1 in sickle cell subjects followed in Brazzaville. Our results showed the involvement of cyclooxygenase 2 (COX-2) and CRP as biomarkers of pain and inflammation in homozygous sickle cell patients presenting vaso-occlusive episodes (VOE). The analysis of sociodemographic factors showed that the age group of 18 years and older, accounting for

50.59%, was the most represented. The average age was 18.70 ± 9.30 years, with extremes ranging from 2 to 62 years and no statistically significant difference by sex (p = 0.490). These results are like those obtained by Shah *et al.* in 2019 in the United States, where the average age was 17.94 ± 15.17 years and the age group of 18 - 30 years was the most represented. This observation corroborates those of S. Diop *et al.* in 2003, where the average age was 27 years (from 20 to 51 years), the 20 - 29 age group represented 67.5%, the 30 - 39 age group represented 26.9%, and the over 40 age group 5.6% with a sex ratio of 1.25. This is explained by the fact that young homozygous sickle cell subjects with CVO often do not reach adulthood due to pain and repeated crises.

The distribution of patients by sex showed a slight male predominance (43 men) or 50.59%, while the female frequency with 42 cases was 49.41% or a sex ratio (M/F) of 1.02 which is consistent with the studies carried out in Dakar by Diagne *et al.*, in 2000 [10] [19] [20], those of S. Diop *et al.* in 2003 [20] in whom on the results, at the level of sex, there was a slight male predominance with a sex ratio of 1.25. These results corroborate those of the study carried out in Congo, at the National Reference Center for Sickle Cell Disease in Niger by Mounkaila and *al.* in 2015 [21] where they found a slight male predominance with respectively sex ratios (M/F) of 1.02 and 1.2. The difference in gender distribution between series could be explained by the fact that sickle cell disease is a hereditary condition whose transmission is not linked to sex.

Of the 85 patients included in our study, 39 (45.88%) homozygous sickle cell patients were in CVO and 46 (54.12%) in the inter-critical phase. Many patients in the CVO phase presented severe bone pain (84.62%). This result corroborates that found by Mekone Nkwele I. *et al.* in 2022 in Cameroon [22] whose study showed that the most frequent vaso-occlusive crises involved osteoarticular pain (34.6%), followed by hand-foot syndrome (26.4%) and abdominal pain (20.3%). The high proportion of patients suffering from CVO in this series could be explained by a failure to comply with hygiene and dietary measures which would result from a feeling of social exclusion described in carriers of chronic diseases. Therapeutic constraints and lifestyle restrictions would lead to an alteration in treatment compliance in the latter, hence the resurgence of CVO.

We observed a statistically significant increase in CRP concentration in homozygous sickle cell patients in the CVO phase compared to homozygous sickle cell patients in the inter-critical phase (p = 0.000). These results were like those found by E. P. L. Nanitelamio *et al.* in 2021 in Brazzaville [4] who stated in their study that the increase in CRP confirms the fact that homozygous sickle cell patients are prone to numerous crises. These results could be explained by the fact that sickle cell disease is an inflammatory disease, one of the markers of which is leukocytosis. IL-6 Essay in our study population did not reveal any statistically significant difference between homozygous sickle cell patients in CVO and homozygous sickle cell patients in the inter-ictal phase (p = 0.06). However, IL-6 levels were elevated in both cases. This justifies its sensitivity at a very early stage of inflammation. These results are like those of A C Makis *et al.* in 2000 [23] who, in their

study, observed an increase in IL-6 levels in sickle cell disease at steady state.

The lack of a significant link between IL-6/CRP and pain could reflect their more general role in systemic inflammation, rather than in the specific modulation of nociception. Factors such as sampling timing or inter-individual variations could also explain this discrepancy.

Nos Our results showed no statistically significant difference in COX1 in homozygous sickle cell patients, either in crisis or in the inter-critical phase, however, the concentrations in both groups were elevated. We found no studies that link COX-1 and sickle cell disease; however, several studies show that COX-1 is linked to inflammation and pain as stated by Smith CJ *et al.* in 1998 [24]. However, COX2 results were found to be elevated during crisis in homozygous sickle cell patients with a correlation to pain score. These results corroborate those of Chun KS *et al.* in 2024 [25] who when measuring COX2 in cancer patients, the pro-inflammatory functions of COX-2, showed that COX2 also catalyzes the production of pro-resolving and anti-inflammatory metabolites from polyunsaturated fatty acids with high values. The strong correlation between COX-2 and pain ($r = 0.65$) is explained by its role in the synthesis of prostaglandins, which sensitize nociceptive neurons. This result is consistent with studies on other inflammatory pathologies, supporting the potential use of COX-2 inhibitors for the management of sickle cell pain.

Although VCAM-1 concentrations are elevated in homozygous sickle cell patients, results that corroborate those of María Emilia Solano *et al.*, in 2011 [26] who demonstrated the involvement of VCAM-1 in the inflammatory process and in the aggravation of PCOS symptoms by promoting the recruitment of leukocytes in the ovaries and perpetuating local inflammation. Our results show no difference between the interictal phase and the critical phase of sickle cell disease.

Finally, although we documented pain intensity, the exact duration of VOCs and comorbidities (such as malaria or nutritional deficiencies) was not systematically recorded. These factors could influence biomarker levels and deserve further study.

5. Conclusion

Although homozygous sickle cell disease is an inflammatory disease, the manifestation of inflammatory and painful vaso-occlusive crises and the results of this study highlight some realities of inflammatory biomarkers and pain scoring. Our study highlighted the involvement of inflammatory and pain biomarkers in pain and inflammation in homozygous sickle disease patients in the inter-ictal and critical phases. Our results concluded that cyclooxygenase-2 (COX-2) and CRP are biomarkers involved in pain and inflammation in sickle cell disease in homozygous patients during vaso-occlusive crises (VOCs).

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Conflicts of Interest

The authors declare there are no conflicts of interest regarding the publication of this article.

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