Original Article

DOI: 10.7860/JCDR/2023/68121.18826

Biochemistry Section

Plasma Interleukin-6 Levels in Relation to the Severity of Pain in Cancer Patients: A Case-control Study from a Tertiary Care Centre in North East India

FIRDUSHI BEGUM[1], SUMI DEKA[2], ARUN DEKA[3], ARCHITA BOIRAGI[4]

ABSTRACT

Introduction: With increased levels of ferritin, C-Reactive Protein (CRP), and the proinflammatory cytokine Intrleukin-6 (IL-6) frequently seen in cancer patients, inflammation is acknowledged as a critical component in the context of cancer. For medical professionals, managing pain in cancer patients, whether from the illness or its treatment, remains a constant struggle.

Aim: To compare the markers of inflammation between controls and cancer patients with pain and to correlate the degree of pain and IL-6 levels in this group of patients.

Materials and Methods: The present case-control study was conducted from January 2022 to December 2022 on 45 age-matched controls and 40 cancer patients with varied levels of pain who were included in the Palliative Care Unit of a State Cancer Hospital, Guwahati, Assam, India. The intensity of pain was measured using a Numerical Rating Scale (NRS). Blood samples were taken to assess the levels of IL-6, ferritin, and CRP. The data were analysed statistically using one-way Analysis of Variance (ANOVA) and linear regression, and were presented as mean±Standard Deviation (SD).

Results: Compared to controls, cancer patients had significantly higher levels of IL-6, CRP, and ferritin (p-value <0.001). Spearman's correlation analysis revealed a positive link between pain intensity and IL-6 (p-value <0.001, r-value=0.516) and between pain and CRP (p-value=0.002, r-value=0.474) was found using Spearman's correlation analysis.

Conclusion: The study results suggest a possible role for IL-6 in cancer-related pain by indicating a clear correlation between elevated IL-6 levels and the severity of pain experienced by cancer patients. This lays the foundation for investigating IL-6 antagonists as potential painkillers for cancer patients.

Keywords: C-Reactive protein, Ferritin, Inflammation

INTRODUCTION

With a substantial influence on their quality of life, pain continues to be one of the most upsetting symptoms that cancer patients face. Approximately 30.6% of cancer patients report moderate to severe degrees of discomfort, accounting for over half of all cancer patients, or 44.5%, according to a recent meta-analysis [1]. Pain associated with cancer is still a major worldwide health concern, even with advances in pain management [2,3]. Approximately 19-85% of cancer patients suffer from Chemotherapy-Induced Peripheral Neuropathy (CIPN), one of the most common neuropathies brought on by antineoplastic drugs [4,5]. A major detriment to the well-being of people afflicted, this illness frequently results in persistent neuropathic pain with irreparable nerve damage [6].

It is difficult to define cancer pain because it may result directly from the cancer or indirectly from different forms of treatment. Based on its pathophysiology, which may have nociceptive or neuropathic components, cancer pain is classified as inflammatory, neuropathic, and cancer-specific pain. The mechanisms interact intricately in cancer pain, which is regarded as a mixed-mechanism pain condition [7].

Cytokines have a significant impact on the inflammatory response and are important modulators of numerous biological processes [8,9]. They have been linked to the aetiology of neuropathic pain [10]. Research indicates that specific proinflammatory cytokines, like interferon-gamma, are essential in triggering and maintaining pain hypersensitivity linked to inflammation or nerve damage [11]. After nerve degeneration, it has been demonstrated that Tumor Necrosis Factor α (TNFα), IL-6, and Interleukin-1 (IL-1) indirectly activate pain receptors [12]. TNFα and IL-1 inhibitors or blockers have been effective in lowering pain hypersensitivity in animal models of chronic pain [13].

IL-6, a multifunctional cytokine implicated in immunological control, hematopoiesis, and inflammatory responses, makes an essential connection between inflammation and carcinogenesis [14-17]. Clinical studies have demonstrated the correlation between inflammatory cytokines, specifically IL-6, and the burden of symptoms, such as pain and fatigue, that are brought on by radiation therapy for lung cancer patients [18] and by chemotherapy and radiation therapy for patients with colorectal or oesophageal cancer [19].

The aim of the present study was to investigate the importance of inflammation for the development of cancer, the speed at which cancer spreads, and how cancer reacts to radiation and chemotherapy. It was predicted that proinflammatory cytokines, especially IL-6, would rise in cancer patients, and that there would be a positive association between the levels of these cytokines the intensity of their pain. The strong correlation between inflammation and pain served as the foundation for this theory. The following goals were pursued to investigate this hypothesis:

a) Blood levels of important inflammatory indicators, such as ferritin, CRP, and IL-6, were measured in a cohort of cancer patients and healthy controls. The results were compared between the two groups.

b) Examination of any possible relationship between the levels of IL-6 in cancer patients and the severity of their pain.

Comprehending the complex relationship between inflammation and pain in the context of cancer may enhance the understanding of the underlying mechanisms and open the door to more focused

and efficient therapies aimed at reducing the misery that cancer patients endure.

MATERIALS AND METHODS

The current case-control study was carried out on patients who visited the State Cancer Hospital's Palliative Care Unit (PCU), an adjunct of Gauhati Medical College and Hospital, between January 2022 and December 2022. After receiving the required institutional Ethics Committee (IEC) permission and the participants' signed agreement, the study was carried out. The study was approved by the institutional ethical committee with IEC number: MC/190/2007/Pt-II/Dec-2021/7.

Inclusion criteria:

- Patients aged 15 years or older.
- Recently registered PCU patients with cancer.
- Patients not displaying any signs of cognitive decline.
- Patients who gave consent.

Exclusion criteria:

- Individuals taking steroids or Non-steroidal Anti-Inflammatory Drugs (NSAIDs).
- Individuals with a past medical history of autoimmune or chronic inflammatory conditions such as diabetes mellitus, renal failure, rheumatoid arthritis, or chronic liver disease.
- Healthy volunteers who were at least 15 years old and willing to take part in the study were enrolled as conrols. The same exclusion criteria applied to controls as to cases.

Sample size: Strict inclusion and exclusion criteria were followed in the enrollment of 40 cancer patients and 45 controls in this study.

Procedure

A thorough interview was conducted to acquire vital information, such as personal history, medical history, socio-economic status, and a comprehensive pain history, after the participants gave their informed consent. A proforma created especially for the study contained all these details, which were thoroughly recorded. Haematological investigations were then performed; CRP and ferritin measurements were made using a clot vial, whereas the assessment of IL-6 was done using EDTA vials. The blood samples were promptly transferred, taking all necessary precautions along the way, to the Central Clinical Laboratory's (CCL) Biochemistry department to preserve sample integrity. After the samples arrived, they were centrifuged for 10 minutes at 3000 rpm to extract serum and plasma. These were then kept at -20°C until the IL-6, ferritin, and CRP assays were performed.

IL-6 assay: The Human IL-6 ELISA Kit (Biodetect, Human IL-6 ELISA Kit, CA, USA) was used to measure IL-6 levels, employing the double antibody sandwich technological principle of ELISA. The levels of ferritin and CRP were estimated using the Vitros 5600 system and specific reagents. The ferritin assay employed an immunometric technique, whereas the CRP assay depended on an enzymatic heterogeneous sandwich immunoassay.

Pain analysis: Cancer patients used a 10-point Numeric Rating Scale (NRS), which ranging from 0 (indicating no pain) to 10 (marking the greatest imaginable pain), to express the intensity of their discomfort. Based on their NRS ratings, the patients were then divided into three groups: mild pain (1-4), moderate pain (5-6), and severe pain (7-10) [20].

STATISTICAL ANALYSIS

The mean±Standard Deviation (SD) of the results was calculated. One-way ANOVA was used to compare the mean values. Linear regression analysis was conducted to determine if the levels of ferritin, CRP, and IL-6 were associated with pain intensity, linear regression analysis was carried out. IBM's Statistical Package for Social Sciences (SPSS), version 20.0, was utilised for the statistical analysis, and Microsoft Excel was used for graph creation. A p-value <0.05 was considered significant.

RESULTS

The main clinical and demographic details of the cancer patients with different levels of pain are shown in the [Table/Fig-1]. The cancer patients had higher levels of IL-6, CRP, and ferritin, and these differences were statistically significant (p-value <0.0001) for all three markers. The increased levels of these inflammatory markers in cancer patients, specifically, ferritin (368.86±56.9 ng/mL), CRP (56.3±26.86 mg/L), and IL-6 (215.4±108.4 pg/mL), suggest a possible link between increased inflammation and pain perception in cancer patients [Table/Fig-2].

Variables	Control	Cancer patients	Mild pain	Moderate pain	Severe pain
Age (years)†					
Range	23-57	31-68	34-56	31-67	39-68
Mean±SD	38.09±10.1	47.8±11.2	42.6±8.7	46.8±14.7	47.8±11.2
Gender‡					
Male N (%)	30 (66.7)	19 (47.5)	3	7	9
Female N (%)	15 (33.3)	21 (52.5)	5	4	12
Primary cancer site‡					
Lung	-	7 (17.5)	1	2	4
Oesophagus	-	3 (7.5)	1	1	1
Buccal cavity	-	4 (10)	1	1	2
Breast	-	10 (25)	4	1	5
Gallbladder	-	8 (20)	1	3	4
Stomach	-	5 (12.5)	0	3	2
Rectum	-	3 (7.5)	0	0	3
Cancer metastasis					
Bone	-	7 (17.5)	0	2	5
Liver	-	15 (37.5)	2	4	9
Brain	-	3 (7.5)	1	0	2
Lung	-	8 (20)	2	2	4
Previous treatment					
Surgery	-	23 (57.5)	6	6	11
Chemotherapy	-	31 (77.5)	4	9	18
Radiation	-	9 (22.5)	1	3	5

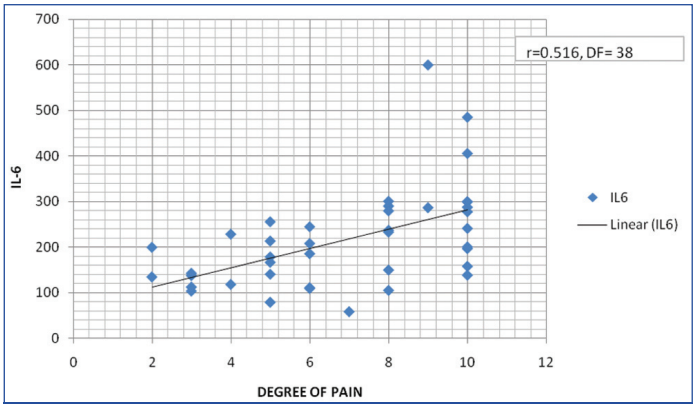
[Table/Fig-1]: Demographic and clinical characteristics of cancer patients with mild, moderate and severe pain.

Parameters	Normal range	Controls Mean±SD	Cancer patients Mean±SD	p-value
IL-6 (pg/mL)	≤15	28.89±25.9	215.4±108.4	<0.0001
C-Reactive protein (mg/L)	0-10	6.11±2.03	56.3±26.86	<0.0001
Ferritin (ng/mL)	11-306.8	52.43±31.3	368.86±56.9	<0.0001

[Table/Fig-2]: Comparison of inflammatory markers between controls and cancer patients with pain.

Additionally, the sick group's mean CRP and ferritin levels in the sick group were significantly higher than those in the control group. In the group of cancer patients under study, Spearman's correlation analysis analysis indicated a positive relationship between IL-6 levels and the degree of discomfort in the group of cancer patients under study.

The relationship between cancer patients' pain scores and plasma IL-6 levels is shown in [Table/Fig-3]. The results demonstrate a strong positive correlation between IL-6 levels and pain ratings, suggesting that reported pain intensity tends to increase with higher IL-6 concentrations [r=0.516, DF=38]. This observed association highlights the potential involvement of IL-6 in exacerbating pain perception in individuals with cancer.



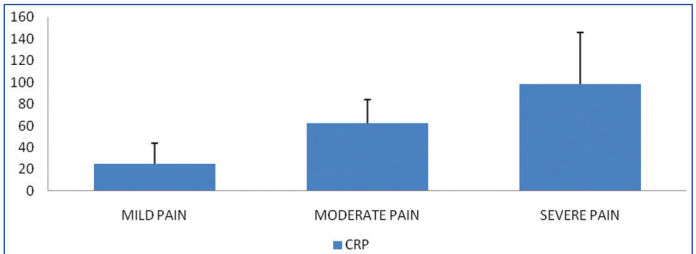
[Table/Fig-3]: Correlation between plasma IL-6 concentration and pain score in cancer patients.

The associations between cancer patients' pain threshold and the inflammatory markers ferritin, CRP, and IL-6 are presented in [Table/Fig-4]. Pain and CRP (0.474) and IL-6 (0.516) showed somewhat favorable associations, according to the Pearson correlation coefficients. However, the relationship between ferritin and pain seems to be less strong (0.218). The statistical significance of these correlations is supported by the corresponding T-statistics for IL-6 (3.716) and CRP (3.314), indicating a strong relationship between pain and these inflammatory markers. The p-values for CRP (0.002) and IL-6 (0.0006) further support the significance of these associations. Overall, these findings support the hypothesis that inflammatory processes play a crucial role in cancer-related pain by emphasising the potential influence of IL-6 and CRP in contributing to the pain experience of cancer patients. However, the correlation between pain and ferritin appears to be less pronounced, as indicated by a lower correlation coefficient (0.218) and a higher p-value (0.177).

Pain	IL-6	CRP	Ferritin
Pearson's correlation	0.516	0.474	0.218
T Statistics	3.716	3.314	1.376
P-Value	0.0006	0.002	0.177

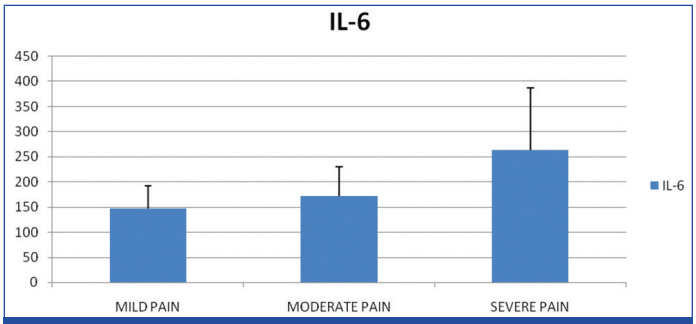
[Table/Fig-4]: Relationship between pain, IL-6, CRP and Ferritin in cancer patients.
IL-6: Interleukin 6
**CRP: C-Reactive protein

[Table/Fig-5] presents the CRP levels in cancer patients divided into three groups based on the intensity of their pain: mild, moderate, and severe. The data show a significant statistical difference (p-value <0.001) in the mean CRP levels between patients with mild pain and those with moderate to severe pain. This suggests that the intensity pain in cancer patients' pain may correlate with an increase in CRP levels. These results highlight the potential utility of CRP as a marker for monitoring pain levels in cancer patients and suggest its potential role as a predictor of pain severity in this context.



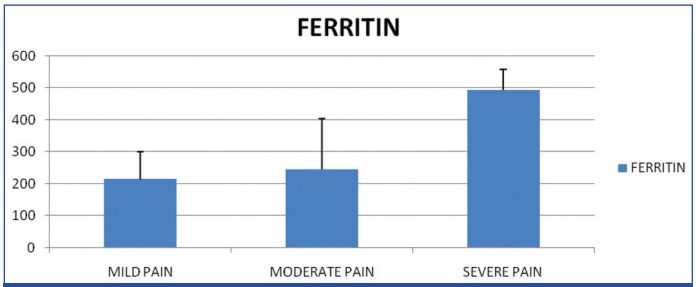
[Table/Fig-5]: CRP levels in cancer patients with mild, moderate and severe pain. Mean CRP level in cases with mild pain vs cases with moderate and severe pain gave p-value <0.001.

The IL-6 levels in cancer patients are shown in [Table/Fig-6] according to three categories: mild, moderate, and severe pain. According to the research, there is no discernible difference (p-value >0.05) in the mean IL-6 levels between cases with mild pain and those with moderate pain. However, there is a statistically significant difference in mean IL-6 levels between patients with mild pain and those with severe pain (p-value <0.001). This suggests that while IL-6 levels may not vary much between mild and moderate cases, they do increase significantly when cancer patients experience severe pain. These results highlight the possible correlation between elevated IL-6 levels and pain severity, especially in cases of excruciating pain in cancer patients.



[Table/Fig-6]: IL-6 levels in cancer patients with mild, moderate and severe pain. Mean IL-6 level in cases with mild vs moderate pain, p-value >0.05, cases with mild pain vs severe pain, p-value <0.001.

[Table/Fig-7] shows the average ferritin levels in cancer patients divided into three groups based on the amount of pain they were experienced: mild, moderate, and severe. Based on the study, it appears that there was no significant statistical difference (p-value >0.05) in the mean ferritin levels between patients with mild pain and those with moderate pain. However, there was a significant difference (p-value <0.001) in the mean ferritin levels between patients with mild pain and those with severe pain. These findings suggest that while there may not be a significant difference in ferritin levels between cases of mild and moderate pain, there was a noticeable increase in ferritin levels with the intensity of pain experienced by cancer patients suffer. These results highlight the potential correlation between elevated ferritin levels and pain severity, particularly in cases of excruciating pain in cancer patients.



[Table/Fig-7]: Mean ferritin levels in cancer patients with mild, moderate and severe pain. Mean ferritin level in cases with mild pain vs moderate pain, p-value >0.05. Mean ferritin level in cases with mild pain vs severe pain, p-value <0.001.

DISCUSSION

Pain is a challenging issue faced by many cancer patients, and treatments such as chemotherapy and radiation can exacerbate it. Inflammatory processes play a significant role in cancer pain, acting as triggers or potential targets for therapeutic interventions. Since its discovery in 1986, IL-6 has gained attention as a crucial cytokine involved in the initiation and maintenance of cancer-related pain [21,22]. Notably, IL-6 is a proinflammatory cytokine essential to the chronic inflammatory cascade associated with cancer, which contributes to the emergence of excruciating pain in these patients [22].

The primary objective of the research was to investigate the hypothesis that IL-6 functions as a vital mediator of the inflammatory processes in cancer patients, thereby worsening the pain experienced by this patient population. Establishing clear connection between IL-6 and cancer-related pain would be highly beneficial for doctors in helping patients manage this often challenging aspect of cancer

treatment. Interestingly, drugs that target the IL-6 pathway have shown effectiveness in reducing the symptoms of several autoimmune diseases like rheumatoid arthritis. In this context, the study also examined CRP and ferritin, which are well-established indicators of inflammation as acute phase proteins. Given the focus on exploring inflammation as the underlying mechanism of pain in cancer patients, assessing CRP and ferritin levels was considered essential.

Increased ferritin, IL-6, and CRP levels have been observed in cancer patients compared to healthy controls in several studies conducted by Chaturvedi AK et al., Muller DC et al., Ito H et al., Khanna V et al., Kwon KA et al., and Lukaszewicz-Zajac M et al., [23-28]. These findings suggest the possible involvement of these inflammatory markers in the development of cancer. Only a few studies, conducted by Oliveira KG et al., and Amano K et al., have specifically examined the relationship between CRP levels and pain severity [29,30], while a single study by Al-Mazidi S et al., focused on the relationship between IL-6 levels and pain score in prostate cancer patients [31]. This study is notable as one of the first attempts to explore the connection between IL-6 levels and the level of pain experienced by cancer patients.

The results showed that IL-6 levels were significantly higher in cancer patients compared to the control group (215.4±108.4 pg/mL versus 28.89±25.9 pg/mL, p-value <0.0001). These findings align with previous studies conducted by Kwon KA et al., and Lukaszewicz-Zajac M et al., which also found elevated IL-6 levels in cancer patients [27,28]. Further research is needed to determine whether the increased IL-6 levels in cancer are caused by the systemic immune response or by the enhanced cytokine synthesis by tumour cells. However, elevated IL-6 levels have been associated with a negative impact on patients' clinical condition and a decrease in cancer cells' susceptibility to traditional anticancer treatments [32]. It is interesting to note that the IL-6 levels found in this study were higher than those reported in several other studies, both in the group of cancer patients experiencing varied degrees of pain and the healthy control group. For example, a meta-analysis involving 72 trials found a median IL-6 level of cancer patients was found to be 6.95 pg/mL (range: 0.23-78.5 pg/mL) in cancer patients, while a study by Lippitz BE and Harris RA reported a median level of 1.31 pg/mL (range: 0-37 pg/mL) in controls [33]. The study found that the median IL-6 level in cancer patients was significantly higher than the median in the control group, measuring 21.2 pg/mL (IQR: 10.6-39.91) compared to 154.25 pg/mL (IQR: 94.41-252.87). Differences in research populations and assay techniques may contribute to these discrepancies.

Furthermore, the findings revealed a positive association (r=0.516, DF=38) between IL-6 levels and pain intensity. The three groups with mild, moderate, and severe pain also showed a significant difference in IL-6 levels, with mean IL-6 levels increasing as pain intensity (p-value <0.001 between mild and moderate pain and p-value <0.001 between mild and severe pain).

One notable aspect of the study was the inclusion of cancer patients regardless of their previous treatment experience. Previous studies examining cytokine levels in individuals with prostate cancer following chemotherapy have shown a strong and positive relationship between IL-6 levels and the level of discomfort experienced during treatment, as was observed by Lippitz BE and Harris RA [33]. Similarly, other research has demonstrated a significant increase in inflammatory cytokine levels, including IL-6, after chemotherapy and radiation therapy, along with a favourable correlation between these cytokines and the patients' discomfort levels after treatment. The observed increase in IL-6 levels in patients undergoing chemotherapy or radiation therapy may exacerbate the inflammatory condition typically seen in this patient population, characterised by fever, fatigue, and discomfort [18,19].

It has been determined that inflammation is the eighth characteristic of cancer [34]. The assessment of ferritin and CRP levels is of significant importance in this context. Numerous studies have shown increased CRP levels in cancer patients at different organ sites. It is worth noting that IL-6, secreted by tumour cells, regulates the synthesis of CRP in the liver [24,35]. An imbalance between proinflammatory and anti-inflammatory cytokines may play a role in how pain perception. The research also found a significant difference in ferritin and CRP levels between pain cancer patients experiencing pain and healthy controls. Many cancer studies have used CRP levels as a prognostic predictor. Additionally, CRP levels showed a positive correlation (Pearson correlation coefficient (r) of 0.474 and matching p-value of 0.002) with pain intensity. This finding is consistent with a related study done by Oliveira KG et al., which investigated the association between inflammatory markers and pain in cancer patients and found that CRP levels were significantly higher in cancer patients experiencing pain compared to healthy controls or those without pain [29].

Limitation(s)

One limitation of the study was the small sample size. The results may not be widely applicable due to the lack of diversity, as the study was conducted in a single tertiary medical center in Northeast India. Including cancer patients regardless of their treatment history may introduce confounding variables concerning regarding the effects of different treatments on IL-6 levels and pain perception. The tudy was also limited by the lack of control over potential confounding factors such as specific cancer types, stages, co-morbidities, and pain medications, which could have influenced the outcomes. The cross-sectional design hampers the establishment of a causal relationship, and biases may arise from the use of laboratory data and self-reported pain scores. The generalisability of the findings to different healthcare settings may be limited by geographic constraints. Additionally, the study focused exclusively on IL-6 levels without considering psychological variables or other inflammatory markers, which may restrict our understanding of cancer-related pain. Future studies that address these limitations may enhance our knowledge of the role of IL-6 and lead to improved treatments for cancer-associated pain.

CONCLUSION(S)

The present study demonstrates a strong correlation between pain levels in cancer patients and elevated IL-6 levels, highlighting the critical role of IL-6 in mediating cancer-related pain. The simultaneous increase in ferritin and CRP levels with higher pain intensity underscores the underlying inflammatory processes contributing to these patients' discomfort. Due to IL-6's proinflammatory properties, IL-6 inhibitors such as tocilizumab, currently used for treating rheumatoid arthritis, may hold potential for the treatment of cancer-associated pain.

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PARTICULARS OF CONTRIBUTORS:
1. Associate Professor, Department of Biochemistry, Gauhati Medical College, Guwahati, Assam, India.
2. Assistant Professor, Department of Biochemistry, Nalbari Medical College, Nalbari, Assam, India.
3. Professor, Department of Oncoanaesthesia and Critical Care, State Cancer Institute, Gauhati Medical College, Guwahati, Assam, India.
4. Postgraduate Trainee, Department of Biochemistry, Gauhati Medical College, Guwahati, Assam, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Firdushi Begum,
Associate Professor, Department of Biochemistry, Gauhati Medical College,
Guwahati-781032, Assam, India.
E-mail: firdushi72@gmail.com

PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Oct 18, 2023
- Manual Googling: Nov 18, 2023
- iThenticate Software: Nov 20, 2023 (5%)

ETYMOLOGY: Author Origin

EMENDATIONS: 5

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. NA

Date of Submission: **Oct 17, 2023**
Date of Peer Review: **Nov 17, 2023**
Date of Acceptance: **Nov 22, 2023**
Date of Publishing: **Dec 01, 2023**