

## Original Research Article

# Association between pre-operative high sensitive C-reactive protein and immediate post-operative radicular pain following prolapsed lumbar intervertebral disc surgery

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## ABSTRACT

**Background:** Nerve root compression is often inadequately understanding radicular pain due to prolapsed lumbar intervertebral disc, a common neurosurgical presentation. Inflammation is proved as an important etio-pathological component of radiculopathy, even after surgery.

**Methods:** This cross-sectional intervention study conducted from March 2022 to September 2023. Data collected from 45 patients with prolapsed lumbar intervertebral Disc, who underwent surgical intervention in Department of Neurosurgery, BSMMU.

**Results:** The mean±SD age of the patients was 38.4±11.6 years, most of them 37 (82.2%) aged within 29 to 60 years. Majority 30 (66.7%) of them were male. Patients presented with pain, numbness and weakness was 45 (100%), 33 (73.3%) and 8 (17.8%) respectively. Among the participants most 36 (80%) had right sided and 9 (20%) had left sided radiation. The mean±SD level of pre-operative high sensitive C-reactive protein was 2.1±1.7. Pre-operative high sensitive C-reactive protein was significantly associated pre-operative, post-operative and mean change in visual analogue score ( $p<0.001$ ,  $p<0.001$ ,  $p=0.006$  respectively). Correlation of high sensitive C-reactive protein and VAS score (both pre and post-operative) were also statistically significant with  $p=0.017$  and  $p<0.001$  respectively.

**Conclusions:** In our study, there is an association between pre-operative serum high sensitive C- reactive protein and post-operative radicular pain following surgical intervention in patients with prolapsed lumbar intervertebral disc.

**Keywords:** Biomarker, C-reactive protein, Low back pain, Lumbar intervertebral disc, VAS score

## INTRODUCTION

LBP affects up to 80% of all individuals at some point in the course of their lives.<sup>1</sup> Over the past few decades, LBP has been the predominant musculoskeletal problem

affecting people's quality of life. It is the leading cause that contributing to the overall 'Years Lived with Disability' (YLD) worldwide, which is around 10.7% of all YLDs.<sup>2</sup> In Bangladesh, the age-standardized prevalence of LBP is estimated that around 19.4% and

the prevalence is on the rise.<sup>3</sup> Intervertebral disc degeneration and prolapse are the most typical specific causes of LBP. More than 90% of LBP related symptoms are attributed to prolapse of lumbar disc. Disc herniation is associated with Prolapsed Intervertebral Disc (PID).<sup>4</sup> Majority of the spinal disc herniation occurs at the site of lumbar region (95%).<sup>5</sup> Lumbar disc herniation (LDH) due to PID in the lumbar region (PLID) is undoubtedly is a serious medical and societal issue, with remarkable economic consequences at both individual and community level as well as significant human suffering.<sup>1</sup> A common problem that leads people to seek medical attention in the field of neurosurgery is LBP associated with radiculopathy. Studies in both clinical and experimental settings suggest that the inflammation brought on by a herniated disc near a nerve root may be a significant contributor to the pain response.<sup>6</sup> The disc herniation in PLID causes nerve root compression. Radicular pain may be the result of subsequent inflammation following the compression of nerve root. As the inflammatory response is brought on by leakage of inflammatory mediators following LDH, these mediators produce discomfort and pain throughout the nerve root's distribution.<sup>7-9</sup> Numerous studies have identified pro-inflammatory cytokines (e.g., IL-1alpha, IL-1beta, IL-6, and tumor necrosis factor alpha (TNF-alpha), leukotrienes, prostaglandin E2, immunoglobulins, phospholipase A2, nitric oxide (NO)) and autoimmune reactions (e.g. - macrophages expressing IL-1beta, intercellular adhesion molecules) at the site of disk herniation as inflammatory mediators.<sup>10,11</sup> A convincing theory is, the release of these compounds may activate the nociceptors, result in a direct neural damage, produce nerve inflammation, or raise sensitivity to other pain-inducing substances (such as bradykinin), which would afterwards cause pain in the nerve roots and its distribution.<sup>9</sup> Plans for treating PLID must take into account the patient's age upon presentation, severity of the disease, comorbidities, compression of neural elements, and spinal column stability.<sup>12</sup> The management algorithm is complex, and complicating factors affect how effectively symptoms handled.<sup>13</sup> The general incremental invasiveness ladder of management in the treatment of such disorders is pain reduction through conservative management, restorative, reconstructive and ultimately surgical intervention.<sup>14</sup> The types of surgical interventions includes: decompression and/or replacement and/or rigid fusion surgery.<sup>4</sup> However, it is typical in clinical practice to observe people with pain and radiculopathy, even after surgical intervention, such as having a discectomy operation. Given that the surgeon did his job by entirely removing mechanical compression, it is most likely because of the inflammation around the nerve roots, which, sadly, is the cause of postoperative discomfort.<sup>10</sup>

This study aimed to evaluate the association between pre-operative hs-CRP level and immediate post-operative radicular pain following PLID surgery. Also, to measure the mean difference between pre-operative and post-

operative VAS score and to determine the association between pre-operative hs-CRP level and pre-operative VAS score.

## METHODS

This is a cross-sectional intervention study carried out in the Department of Neurosurgery, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh from March 2022 to September 2023. The study population was the patients diagnosed as case of prolapsed lumbar intervertebral disc (PLID) who underwent relevant surgical intervention in the study place with fulfilling the selection criteria. This cross sectional intervention study was carried out among 45 patients suffering from prolapsed lumbar intervertebral disc (PLID) for which they underwent surgery in Department of Neurosurgery of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka within the eighteen months of March 2022 to September 2023.

### Inclusion criteria

Patients clinically and radiologically diagnosed as case of prolapsed lumbar intervertebral disc (PLID), age range of 18 to 60 years, and underwent PLID surgery (Fenestration and Microdiscectomy) during the study period in Department of Neurosurgery, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka were included.

### Exclusion criteria

Patients with any systemic inflammatory diseases including colitis, rheumatoid arthritis, and/or connective tissue disorder, individuals with previous history of spinal surgery, fracture, spinal canal stenosis, tumor, instability problems such as spondylolisthesis, patients, who developed any surgical site infection, i.e.: discitis, wound infection etc and recurrent/Residual cases of lumbar disc herniation were excluded.

### Operational definitions

#### High sensitive C-Reactive protein (hs-CRP)

For this study pre-operative hs-CRP for each patient measured in the laboratory facility of Bangabandhu Sheikh Mujib Medical University (BSMMU). The lab uses latex method (Nephelometric system) to determine hs-CRP (instrument: BN ProSpec, SIEMENS, USA). In this study the level of hs-CRP classified as below:

#### Classification of hs-CRP level<sup>11</sup>

**Low risk:** This category includes hs-CRP values below 1.0 mg/l.

**Average risk:** hs-CRP values ranging from 1.0 to 3.0 mg/l fall into this category.

**High risk:** This category encompasses hs-CRP values exceeding 3.0 mg/l.

#### Visual analogue scale

The visual analogue scale (VAS) gauges the degree of pain. The VAS is a 10 cm line with 2 ends, that stand for 0 (meaning “no pain”) and 10 (meaning, “pain as awful as it can be”/ “unbearable”/ “worst pain”). Investigator has to ask the patient to rate their present level of discomfort/ pain by putting a mark on the line. Measuring the distance in centimeters between the “no pain marker” (also known as zero) and the current pain mark put on by the patient using a ruler, gives a score for pain intensity out of 10. VAS is a fairly valid and reliable tool for musculoskeletal pain, and could be used effectively as well for neurogenic pain.<sup>12,13</sup> In this study, VAS score obtained from the patients classified in three groups.

#### Postoperative period

Immediate post-operative period: Starts from 0 to 30 days in case of spine surgery.<sup>14</sup>

#### Classification pain according to VAS scores

**Mild pain:** Pain with a VAS score ranging from 1 to 3.

**Moderate pain:** Pain classified as moderate falls within the VAS score range of 4 to 6.

**Severe pain:** Pain categorized as severe corresponds to VAS scores ranging from 7 to 10.

#### Data collection process

Before data collection, ethical approval obtained from Department of Neurosurgery and Institutional Review Board (IRB), Bangabandhu Sheikh Mujib Medical University (BSMMU). All the patients with PLID with radiculopathy, who were scheduled to undergo PLID operation in Department of Neurosurgery, BSMMU and met the selection criteria, were approached for inclusion. Patients who agreed to provide a written and informed consent (the purpose of the study completely explained to them by the investigator) was included for the study. The investigator completed the semi-structured data collection sheet. A short interview of each patients taken to collect the relevant demographic data.

#### Data analysis

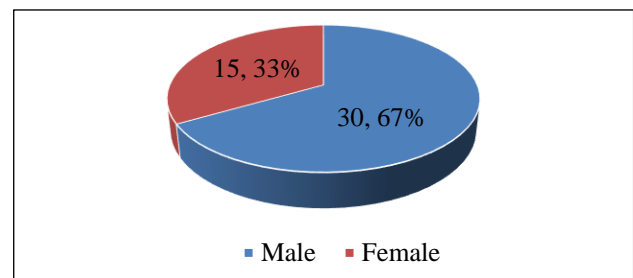
Microsoft Excel 2019 and ‘Statistical Package for the Social Sciences’ software (SPSS version 26) was used for data analysis. The results continuous data expressed in mean with standard deviation ( $\pm$ SD) and median with inter quartile range (IQR), discrete data presented and utilized as percentages or proportions. Continuous variables analyzed with Paired sample t test. For determining the association and co-relation between the

finale assessment variables (Pre and post-operative VAS score and hs-CRP levels) one-way ANOVA and Pearson correlation test used respectively. Analyzed data presented as frequency distributions through suitable tables and graphs. Tests of significance performed according to the objectives as needed at the 95% confidence level, the p value at 0.05.

Ethical clearance obtained from Department of Neurosurgery and Institutional Review Board (IRB), Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh. Patients and their relatives were informed in details about the study, its merits and demerits explained to them in easy and understandable language and then informed consent taken.

## RESULTS

Figure 1 shows the distribution of sex, majority of the participants 30 (66.7%) were male and 15 (33.3%) were female.



**Figure 1: Gender distribution of our study patients (n=45).**

Largest number, 20 (44.4%) of the patients were aged between 29 to 39 years followed by those 17 (37.8%) who were aged between 40 to 60 years and 8 (17.8%) were aged between 18 to 28 years. Mean age of the patients was  $38.4 \pm 11.6$  years (Table 1).

**Table 1: Distribution of the patients according to age group (n=45).**

Age group (years)	Frequency (N)	Percentage (%)
18 to 28	8	17.8
29 to 39	20	44.4
40 to 60	17	37.8
Mean $\pm$ SD	38.4 $\pm$ 11.6	

Concerning the presentation of radiculopathy, all patients 45 (100%) had pain and/or 33 (73.3%) had numbness. Weakness was found among 8 (17.8%) patients (Table 2).

Regarding the high sensitive C-reactive protein (hs-CRP) level, mean hs-CRP was  $2.1 \pm 1.7$  mg/l. Among the patients, 18 (40%) had low level of hs-CRP, 17 (37.8%)

had average and 10 (22.2%) had high blood hs-CRP (Table 3).

**Table 2: Distribution of the patients according to clinical symptoms (n=45).**

Clinical symptoms	Frequency (N)	Percentage (%)
Pain	45	100
Numbness	33	73.3
Weakness	8	17.8

**Table 3: Distribution of the patients according to hs-CRP level (n=45).**

hs-CRP (mg/l)	Frequency (N)	Percentage (%)
Low	18	40
Average	17	37.8
High	10	22.2
Mean±SD (Median, IQR)	2.1±1.7 (1.5, 0.87-2.8)	

Regarding the visual analogue scale score, pre-operatively and post-operatively mean VAS score of pain were 7.3±1.1 and 1.2±1.3 respectively. Post-operative mean VAS score of pain was significantly ( $p<0.001$ ) higher than pre-operative VAS score. Pre-operative and post-operative and mean change in VAS score of pain was significantly ( $p<0.001$ ,  $p<0.001$ ,  $p=0.006$  respectively) associated with high pre-operative hs-CRP (Table 4).

**Table 4: Distribution of VAS score of pain among the patients (n=45).**

VAS score of pain	Pre-operative	Post-operative	P value*
Mean±SD	7.3±1.1	1.2±1.3	<0.001

\*p-value determined by Paired sample t test

$\alpha$  denotes significant difference between normal vs high group regarding preoperative hs-CRP. B denotes significant difference between average vs high group regarding preoperative hs-CRP.  $\Gamma$  denotes significant difference between normal vs average and high group regarding pre-operative hs-CRP.  $\S$  denotes significant difference between average vs high group regarding pre-operative hs-CRP.  $\mu$  denotes significant difference between normal vs high group of pre-operative hs-CRP regarding mean change (Table 5).

Regarding the correlation between hs-CRP and VAS score of pain, pre-operative hs-CRP was positively correlated with both pre-operative VAS score ( $r=0.318$ ) and post-operative VAS score ( $r=0.824$ ) of pain. This correlation of pre-operative hs-CRP was statistically significant in both cases ( $p=0.017$  and  $p<0.001$ , respectively for pre and post-operative VAS score) (Table 6).

**Table 5: Association of hs-CRP with VAS score of pain among the patients (n=45).**

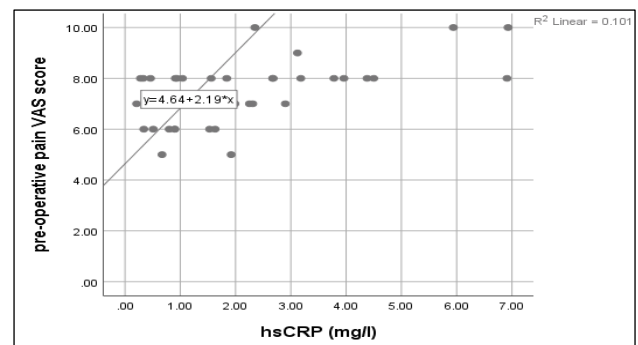
VAS score of pain	Low <1.0	Average 1.0-3.0	High >3.0	P value*
	Mean±SD	Mean±SD	Mean±SD	
Pre-operative	6.9±0.9	7.2±1.1	8.5±0.8 $\alpha\beta$	<0.001
Post-operative	0.22±0.4	1.2±0.7 $\gamma$	3.3±0.6 $\gamma\delta$	<0.001
Mean change	6.7±1	6±1.3	5.2±0.9 $\mu$	0.006

\*p-value determined by Post-hoc analysis of Bonferroni test by One-Way ANOVA test

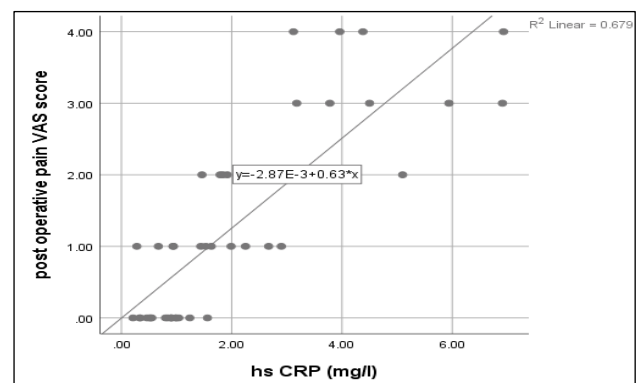
**Table 6: Correlation of hs-CRP and VAS score of pain (n=45).**

	Correlation coefficient (r)	P value*
Pre-operative hs-CRP vs pre-operative VAS score	0.318	0.017
Pre-operative hs-CRP vs post-operative VAS score	0.824	<0.001

\*p-value determined by Pearson correlation test



**Figure 2: Correlation between pre-operative hs-CRP and pre-operative VAS score of pain.**



**Figure 3: Correlation between pre-operative hs-CRP and post-operative VAS score of pain.**



Figure 2 scattered plot is showing a positive correlation ( $r=0.318$ ) between pre-operative hs-CRP and pre-operative VAS score of pain.

Figure 3 scattered plot showing positive correlation ( $r=0.824$ ) between pre-operative hs-CRP and post-operative VAS score of pain. This is to be noted again that this correlation was found statistically significant.

## DISCUSSION

The age of the study sample was between 29 to 60 years old, mostly 37 (82.2%) aged. From a recent large prevalence study the reported mean age of patients with low back pain (LBP) in Bangladesh was 45.3 years.<sup>3</sup> This study finding is also similar to the findings of Fjeld et al, who reported the mean age of patients who underwent surgical procedure in that study was 45 years and from the third through the fifth decade of life, Lumbar disc herniation (LDH) is most widespread among Norwegian population.<sup>15</sup> Another study that worked with patients with lumbar discectomy of Sudanese origin found that 90.1% of their patients aged between 31 to 65 years.<sup>16</sup> This difference in age distribution may be due to combined effects of hormonal and biomechanical differences, physical activity level and other variable factors.

In this study, majority of the patients were male then female. The ratio of man and woman stands at 2:1. This is similar to the report of Qaraghli and Jesus 2023. This finding also resembles the consensus of male predominance of PLID in various scientific work.<sup>2,15-17</sup> However, more than one study reported the ratio of male: female nearly at 1.5:1, which is slightly lower than the findings of this study for the male population.<sup>15-17</sup> However, our statistical finding does not resemble the finding of the work of Majumder et al. who reported female predominance (63% of total patients) in the cases of LBP in Bangladesh.<sup>3</sup> This may be due consideration of whole spectrum of LBP instead of a single diagnosis of PLID.

All of the patients of this study presented with radicular lower pain with numbness and/or weakness. Similar to this study, Dydyk, Khan and Singh reported paresthesia and/or radicular pain affects around 98% or more of lumbar radiculopathy patients.<sup>18</sup> However, they reported numbness endorsed by 27% of patients and up to 37% of people with muscle weakness.<sup>18</sup> Another similar study concerning about LDH surgery outcome had 97.4% and 57.6% of their sample presenting with radicular pain and numbness respectively, which reflects the findings of the current study.<sup>19</sup>

Inflammation plays a role in the etiology of cardiovascular events, and monitoring indicators like high sensitivity C-reactive protein (hs-CRP), can assist predict the risk of cardiovascular events.<sup>20,21</sup> This study relied on the consideration that not only nerve root

compression, but also inflammation plays a role in the pre-operative and post-operative radiculopathy related to LDH, similar to CVD.<sup>7,9,10</sup> Hence, in this study the level of hs-CRP classified in same three level as of CVD risk. Noticeably, most of the patients had average or high blood hs-CRP in current study. Therefore, this study finding can be linked with the theory that inflammation is a causative factor for radiculopathy. Current study finding can be considered more noteworthy considering the mean $\pm$ SD hs-CRP level of this study was  $2.1\pm1.7$  mg/l, which is greater than  $1.8\pm0.8$ , the range described by Rathod et al.<sup>10</sup>

Inflammatory procedure depends on several immune response and it differ patients to patients and also hs-CRP assays have been standardized across several commercial platforms, may produce difference, the level of hs-CRP in my study.

This study used the visual analogue scale to score radiculopathy of the patients, both pre-operatively and post-operatively. The pre-operative mean $\pm$ SD of VAS was  $7.3\pm1.1$  and post-operatively the mean $\pm$ SD was the  $1.2\pm1.3$ . The pre and post-operative change in the VAS score was analyzed with paired sample t-test and the change was found significant ( $p<0.001$ ). This significant reduction of VAS score following surgery reflects the satisfactory outcome among patients after surgery regarding radicular pain in the Department of Neurosurgery, BSMMU. This change of VAS score before and after surgery shows similarity with the pre and post-operative VAS score (pre-operative mean $\pm$ SD  $7.29\pm0.90$  and post-operative mean $\pm$ SD  $1.84\pm0.89$ ) measured in another retrospective cohort study that had post discectomy patients as participants.<sup>22</sup> Another study evaluated surgical outcome for LDH patients, reported pre and post-operative VAS score for radicular pain in patients who underwent laminectomy. They also reported mostly similar finding like the current study. Pre-operatively their mean score was  $9.22\pm1.86934$  and mean VAS after surgery was  $1.39\pm2.07277$ . They also reported this change in VAS score to be significant.<sup>19</sup> Pain has psychological, social, and physical dimensions and is greatly influenced by cultural factors and subjective in nature, this may be the cause of difference in pain assessment.

In this study, the association of different class (low, average and high) of pre-operative hs-CRP examined with the VAS score at three different domains (pre-operative, post-operative and mean change). High level of hs-CRP was very significantly more associated with greater pre-operative VAS score ( $p<0.001$ ), than that of low and average level of hs-CRP. This finding denotes that patients with high hs-CRP will present with greater extent of radicular pain. However, the association of pre-operative VAS was not significant between low and average hs-CRP level. Therefore, the strong association of pre-operative greater VAS score compartmented only for high hs-CRP level. Similarly, the mean $\pm$ SD change in

VAS score was  $6.7 \pm 1$ ,  $6 \pm 1.3$ , and  $5.2 \pm 0.9$  for low, average and high pre-operative hs-CRP level group, respectively. This mean change is significantly associated with high hs-CRP group only ( $p=0.006$ ). However, for post-operative VAS score, both average and high level of hs-CRP had very significant association with greater post-operative VAS ( $p<0.001$ ). It is statistically evident that, both average and high level of pre-operative hs-CRP is significantly associated with post-operative radicular pain measured as VAS score. Therefore, the pre-operative hs-CRP at average and/or high level effectively could have predicted high post-operative VAS score for this study's subjects.

Regarding the correlation between hs-CRP and VAS score of pain, hs-CRP was positively correlated with both pre-operative VAS score ( $r=0.318$ ) and post-operative VAS score ( $r=0.824$ ) of pain. This correlation of hs-CRP was statistically significant in both cases ( $p=0.017$  and  $p<0.001$ , respectively for pre and post-operative VAS score). As the hs-CRP level measured before surgery had statistically significant association with both the pre-operative and post-operative VAS score, in this study we also calculated the level of correlation the hs-CRP level had with the two different set of VAS score. Both sets of VAS score showed statistically significant positive correlation with hs-CRP level. However, the correlation of pre-operative hs-CRP and post-operative VAS score showed a very strong positive linear connection with a correlation coefficient ( $r$ ) of 0.824 ( $p<0.001$ ), while a weak positive correlation indicated by  $r=0.318$  among hs-CRP level and pre-operative VAS score ( $p=0.017$ ). It is also noteworthy that, similar to this study findings, a previous study that also calculated the correlation between pre-operative hs-CRP level and pre and post-operative VAS score, found post-operative VAS significantly ( $p<0.001$ ) correlates with hs-CRP level. However, their correlation coefficient value ( $r=0.677$ ) was less than that of this study. Yet they concluded that in patients with LDH, hs-CRP would be a useful prognostic marker for surgical decision-making.<sup>10</sup>

Therefore, it is a statistical certainty that, pre-operative average and/or high level of hs-CRP is strongly predictive for higher post-operative VAS score considering both the association and co-relation outcome between the both variables.

This study has few limitations. A relatively small sample size from a single center was included for this study. This limitation is due to the finite number of patients of the specific medical condition in the given period of the study. Purposive sampling technique used in the current study to include the patients; therefore, generalization of the findings must be with caution. The classification of hs-CRP level is based on the classification established for cardio-vascular event. This is due to scarcity of previous scientific work with potential and/or specific classification or cut-off point of hs-CRP for patients with PLID or LDH.

## CONCLUSION

We can conclude that this study established preoperative hs-CRP as prognostic biomarker for postoperative radicular low back pain, in PLID patients.

## Recommendations

Preoperative serological test of high sensitive-CRP should be considered in LDH patients for assessing preoperative and postoperative radicular low back pain. Predicting perineural inflammation, neurosurgeon should counsel patients preoperatively regarding preoperative and postoperative radicular pain with treatment plan by using preoperative serum hs-CRP. Multicenter study should be done with a larger sample size for a longer duration.

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