

# High sensitive C-reactive protein-Effective tool in determining postoperative recovery in lumbar disc disease

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## ABSTRACT

**Background:** It is common in medical practice to see patients having persistent pain and radiculopathy even after undergoing discectomy surgery. Inflammatory cytokines, such as interleukins are produced at the site of disc herniation and are now considered responsible for the pain perceived by the patient. This study has used high sensitive C-reactive protein (HSCRP) assay for predicting inflammation around the nerve roots on very same principle, which has used HSCRP for predicting coronary artery diseases in current clinical practice. Thus, purpose of this study is to test whether HSCRP can stand as an objective tool to predict postoperative recovery in patients undergoing lumbar discectomy. That is, to study association between preoperative HSCRP blood level and postoperative recovery with the help of modified Oswestry Back Disability Score.

**Materials and Methods:** A study group consisting of 50 cases of established lumbar disc disease and control group of 50 normal subjects, matched with the study group. Both the study and control groups were subjected to detailed evaluation with the help of modified Oswestry Low Back Pain Scale both pre and postoperatively at 3 months, 6 months and 1-year. The preoperative blood samples were analyzed to assess the HSCRP concentration. All the cases underwent surgery over a period of 1-year by the same surgeon.

**Results:** The level of HSCRP in the study group was between 0.050– and 0.710 mg/dL and in the control group, 0.005-0.020 mg/dL. There was highly significant positive correlation between preoperative HSCRP level and postoperative score at  $P < 0.005$ . Cases with HSCRP level in the range of  $0.1820 \pm 0.079$  mg/dL, showed better recovery (score improved  $> 10$  points), while those with HSCRP level in the range of  $0.470 \pm 0.163$  mg/dL, showed poor recovery (score improved  $< 10$  points).

**Conclusion:** HSCRP will serve as a good supplementary prognostic marker for operative decision making in borderline and troublesome cases of lumbar disc disease.

**Key words:** Lumbar disc disease, sciatica, discectomy, high sensitive C-reactive protein

**MeSH terms:** Lumbar, disc, herniated, sciatica, blood proteins

## INTRODUCTION

It is common in medical practice to see patients having persistent pain and radiculopathy even after undergoing discectomy surgery.<sup>1,2</sup> This has remained a significant

source of dissatisfaction on the part of both patient as well as the surgeon. Hence, it has always been a surgical dilemma for a surgeon to do a proper case selection for disc surgery.<sup>3-5</sup>

Sciatic pain has been thought to be caused by the mechanical compression of nerve roots by the herniated nucleus pulposus.<sup>6</sup> Now, it has increasingly become evident that intervertebral disc disease (IDD) also involves an underlying inflammatory component. Inflammatory cytokines, such as interleukin-1 (IL-1), IL-6 and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) are produced at the site of disc herniation and are now considered responsible for the pain perceived by patient.<sup>7-12</sup> Hence, it is not only the mechanical compression of nerve root, but also the inflammation around the nerve roots, which unfortunately is responsible for postoperative pain, perceived by the patient in spite of surgeon doing his job of removing mechanical compression completely. We, in this study, have specifically tried to address this problem of predicting postoperative recovery in patients undergoing discectomy by using high sensitive C-reactive

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protein (HSCRCP) levels as a prognostic marker. Underlying inflammation around disc herniation causes an increase in CRP level by the miniscule amount.<sup>13</sup> Similar marginal increase in CRP has also been noted in atherosclerosis by various studies aimed at predicting risk of coronary and cerebrovascular disease in apparently healthy populations much before its occurrence.<sup>14-17</sup> CRP usually is measured in clinical laboratories by either immunonephelometric or immunoturbidimetric assays.<sup>18</sup> The current methods are generally reproducible, fully automated, and capable of measuring CRP with a detection limit of 3-5 mg/L.<sup>18</sup> Although this detection limit is adequate for the traditional clinical utility of CRP in monitoring infection, it renders most of the current assays useless in assessing and measuring the amount of inflammation around disc or atherosclerosis in apparently otherwise healthy populations. Hence, this study has used HSCRCP assay for predicting inflammation around the nerve roots on very same principle, which has used HSCRCP for predicting coronary artery diseases. This ultrasensitive assay is capable of measuring HSCRCP at a concentration of 0.00095 mg/dL using ultrasensitive latex-enhanced immunoassay (latex) on the BN II nephelometer.<sup>18</sup> In this study, we evaluated the clinical utility of this immunoassay and compared its usefulness in predicting postoperative recovery in patients undergoing lumbar discectomy. We aimed to study association between preoperative HSCRCP blood level and postoperative recovery with the help of modified Oswestry Back Disability Score.

## MATERIALS AND METHODS

We selected a study group consisting of 50 cases of established lumbar disc disease that underwent disc surgery by the same surgeon over a period of 1-year. All patients were reevaluated at 3 months, 6 months and 1-year with modified Oswestry Back Disability Score [Table 1]. The control group consisted of 50 normal subjects matched with the study group for age, sex and body mass index. Study group had 17 cases of L4-L5 herniation, 22 cases of L5-S1 and 11 cases of combined L4-L5 with L5-S1 herniation [Figure 1]. Our inclusion criteria in the study group consisted of age between 20 and 60 years, clinical evidence of herniation in the form of disc related radicular pain of >3 months duration, not responding to conservative treatment and interfering with daily activities, radiological evidence of herniation: Magnetic resonance imaging (MRI) obtained during symptomatic period with 1.5 T using T2-weighted (TR/TE of 4000/90 ms) and T1W (TR/TE of 600/10 ms) sequences showing evidence of disc degeneration that is, dark nucleus pulposus after comparing its signal intensity with adjacent CSF that is, Grade 2 and above of Schneiderman's classification<sup>19</sup> and disc protrusion in the spinal canal.

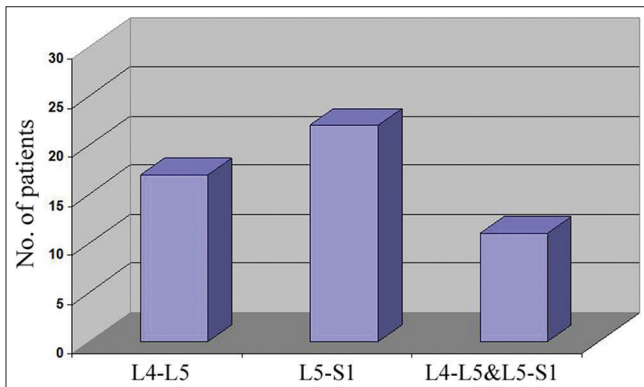
**Table 1: Modified Oswestry back disability score**

Questionnaire	Score
<b>Pain intensity</b>	
I can tolerate the pain I have without having to use pain medication	0
The pain is bad, but I can manage without having to take pain medication	1
Pain medication provides me with complete relief from pain	2
Pain medication provides me with moderate relief from pain	3
Pain medication provides me with little relief from pain	4
Pain medication has no effect on my pain	5
<b>Lifting</b>	
I can lift heavy weights without increased pain	0
I can lift heavy weights, but it causes increased pain	1
Pain prevents me from lifting heavy weights off the floor, but I can manage if the weights are conveniently positioned (e.g., on a table)	2
Pain prevents me from lifting heavy weights, but I can manage light to medium weights if conveniently positioned	3
I can lift only very light weights	4
I cannot lift or carry anything at all	5
<b>Sitting</b>	
I can sit in any chair as long as I like	0
I can only sit in my favorite chair as long as I like	1
Pain prevents me from sitting for >1 h	2
Pain prevents me from sitting for >½ h	3
Pain prevents me from sitting for >10 min	4
Pain prevents me from sitting at all	5
<b>Sleeping</b>	
Pain does not prevent me from sleeping well	0
I can sleep well only by using pain medication	1
Even when I take medication, I sleep <6 h	2
Even when I take medication, I sleep <4 h	3
Even when I take medication, I sleep <2 h	4
Pain prevents me from sleeping at all	5
<b>Traveling</b>	
I can travel anywhere without increased pain	0
I can travel anywhere, but it increases my pain	1
My pain restricts my travel over 2 h	2
My pain restricts my travel over 1 h	3
My pain restricts my travel to short necessary journeys under ½ h	4
My pain prevents all travel except for visits to the physician/therapist or hospital	5
<b>Personal care</b>	
I can take care of myself normally without causing increased pain	0
I can take care of myself normally, but it increases my pain	1
It is painful to take care of myself, and I am slow and careful	2
I need help, but I am able to manage most of my personal care	3
I need help every day in most aspects of my care	4
I do not get dressed, I wash with difficulty, and I stay in bed	5
<b>Walking</b>	
Pain does not prevent me from walking any distance	0
Pain prevents me from walking >1 mile	1
Pain prevents me from walking >½ mile	2

*Contd...*

**Table 1: Contd...**

Questionnaire	Score
Pain prevents me from walking >¼ mile	3
I can walk only with crutches or a cane	4
I am in bed most of the time and have to crawl to the toilet	5
<b>Standing</b>	
I can stand as long as I want without increased pain	0
I can stand as long as I want, but it increases my pain	1
Pain prevents me from standing for >1 h	2
Pain prevents me from standing for >½ h	3
Pain prevents me from standing for >10 min	4
Pain prevents me from standing at all	5
<b>Social life</b>	
My social life is normal and does not increase my pain	0
My social life is normal, but it increases my level of pain	1
Pain prevents me from participating in more energetic activities (e.g., sports, dancing)	2
Pain prevents me from going out very often	3
Pain has restricted my social life to my home	4
I have hardly any social life because of my pain	5
<b>Employment/homemaking</b>	
My normal homemaking/job activities do not cause pain	0
My normal homemaking/job activities increase my pain, but I can still perform all that is required of me	1
I can perform most of my homemaking/job duties, but pain prevents me from performing more physically stressful activities (e.g., lifting, vacuuming)	2
Pain prevents me from doing anything but light duties	3
Pain prevents me from doing even light duties	4
Pain prevents me from performing any job or homemaking chores	5

**Figure 1:** Bar diagram showing level of lesion

Exclusion criteria consisted of patients who have chronic inflammatory diseases or malignancy, medically unfit for surgical intervention, patients having any local and systemic source of infection, chronic smokers, patients with ischemic heart disease and stroke (high baseline CRP levels). All cases were subjected to detailed evaluation with the help of modified Oswestry Low Back Pain Scale. It consisted of low back pain disability index questionnaire about pain intensity, personal care, lifting, standing, walking, sitting, sleeping, social life, travelling and employment/homemaking. Thus, total 10 points; each had score range

of 0-5. Hence, total score had range of 0-50. Severe the disc disease, more is the disability score. Preoperative 2cc blood sample was collected under all aseptic precautions in plain bulb for estimation of HSCRCP level from all cases and controls.

We have used radiological classification for disc degeneration severity that is, Schneiderman's classification for MRI which is Grade 1 (normal), normal height and signal intensity; Grade 2 (intermediate), speckled pattern or heterogeneous, decreased, signal intensity; Grade 3 (marked), diffuse loss of signal; Grade 4 (absent), signal void [Figure 2].

Written informed consent was obtained from all cases and controls participating in the study after explaining the nature of the test and study design. Institutional Ethics Committee clearance regarding study and collection of blood samples for CRP tests after informed consent of individuals was obtained.

The preoperative blood samples were analyzed to assess the HSCRCP concentration, as measured by an ultrasensitive latex-enhanced immunoassay (N-latex CRPII).

## RESULTS

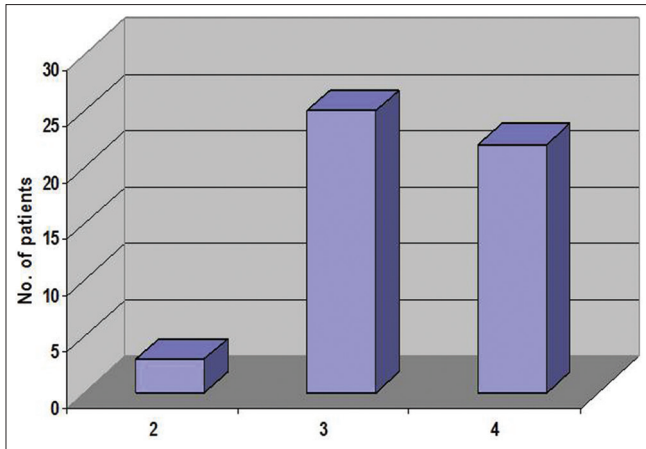
The mean age in the study group was 44.20 years with 31 males and 19 females in the study group. Both study and control group are comparable with respect to age and sex at  $P < 0.05$  [Figures 3 and 4]. The level of HSCRCP in the study group was between 0.050 and 0.710 mg/dL and in the control group, 0.005-0.020 mg/dL [Figure 5].

### Statistical analysis

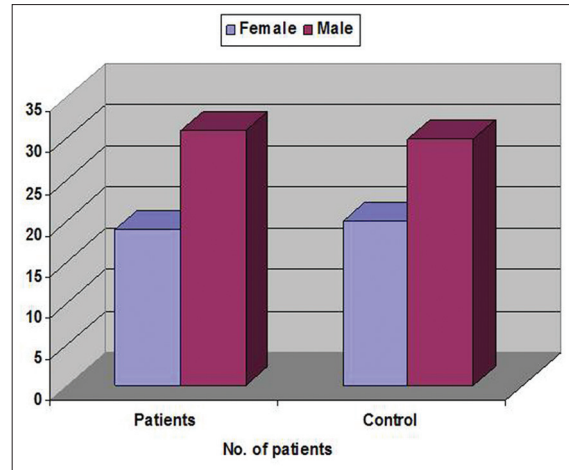
Data were entered using MS-Excel-2007 and analyzed using SPSS-16 software. Following statistical tests of significance are used. Un-paired *t*-test –for comparison between two group comparison (for comparison of mean between study and control groups). One-way ANOVA test with Bonferroni's *posthoc* test –for comparison between three groups (for comparison of mean between three groups –numerical data). Pearson's correlation –for Correlation between two numerical variables (e.g. HSCRCP, pre and postscores etc.) Chi-square test (for comparison of proportions between two groups –categorical data).

The  $P < 0.05$  was taken as statistically significant.

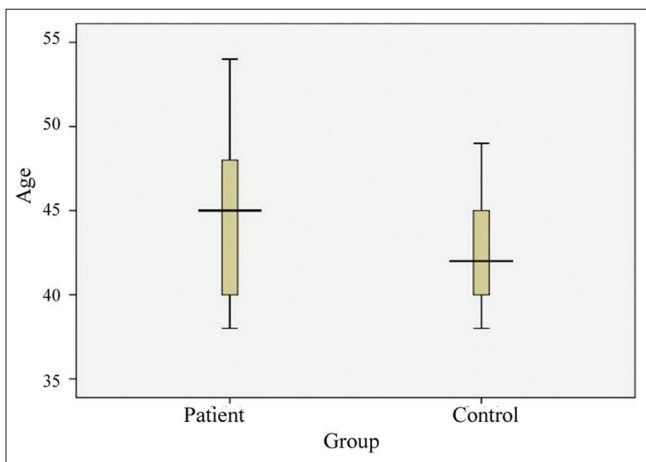
Mean HSCRCP level in the study group was 0.321 mg/dL  $\pm$  standard deviation (SD) 0.192 mg/dL, as compared to 0.011 mg/dL  $\pm$  SD 0.007 mg/dL in the control group, which is Statistical significant at  $P < 0.01$  [Table 2]. Mean



**Figure 2:** Bar diagram showing radiographic grading



**Figure 4:** Bar diagram showing comparison of sex distribution between two groups



**Figure 3:** Graph showing comparison of age distribution between two groups

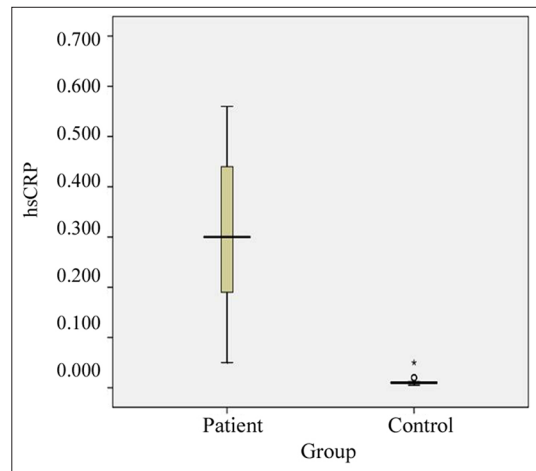
postoperative score was 15.78 as compared with the mean preoperative score of 33.08.

In the study group, there was no other correlation between preoperative score and level of disc herniation or radiological severity with the HSCRCP level at  $P < 0.001$ .

However, there is highly significant positive correlation between preoperative HSCRCP level and postoperative score at  $P < 0.005$  (Pearson correlation) [Table 3]. Cases with HSCRCP level in the range of  $0.1820 \pm 0.079$  mg/dL, showed better recovery (score improved  $>10$  points), while those with HSCRCP level in the range of  $0.470 \pm 0.163$  mg/dL, showed poor recovery (score improved  $<10$  points) [Table 4 and Figure 6].

## DISCUSSION

C-reactive protein is an acute-phase reactant, the levels of which rise dramatically during infection/inflammatory processes occurring in the body. This increment in CRP is due to a rise in the plasma concentration of IL-6, which



**Figure 5:** Graph showing comparison of high sensitive C-reactive protein levels between two groups

**Table 2: Comparison of HSCRCP levels between two groups**

Group	n	Mean	Standard deviation	Range	P value	Significance
Study	50	0.321	0.192	0.100-0.710	<0.001	Significant
Control	50	0.011	0.007	0.005-0.020		

(Unpaired t test) ( $P < 0.05$ - Significant), HSCRCP=High sensitive C-reactive protein

**Table 3: Correlation between HSCRCP level and pre/postoperative score**

Preoperative score	
Pearson correlation	0.028
P value	0.849
Significance	Not significant
n	50
Postoperative score	
Pearson correlation	0.677
P value	<0.001
Significance	Significant
n	50

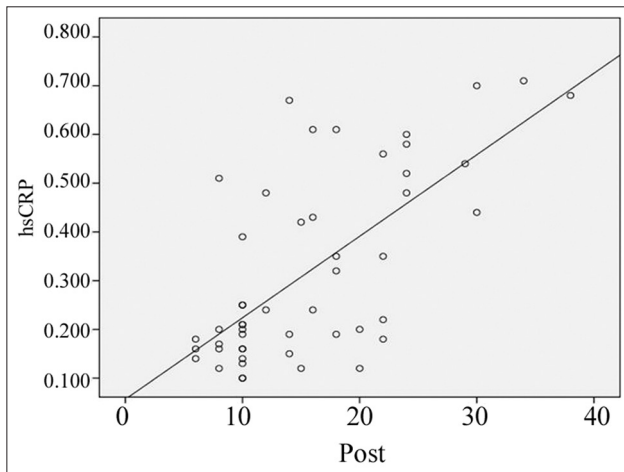
Pearson's correlation. HSCRCP=High sensitive C-reactive protein

is produced predominantly by macrophages around the disc tissue.<sup>20</sup> Hence, CRP is commonly used parameter for

**Table 4: Correlation between HSCRCP level and postoperative recovery**

Group with score difference	n	Mean	Standard deviation	P value	Significance
<10	24	0.470	0.163	<0.001	Significant
>10	26	0.182	0.079		

(Unpaired t test) (P<0.05- Significant), HSCRCP=High sensitive C-reactive protein



**Figure 6:** Graph showing comparison between high sensitive C-reactive protein levels and post operative score

monitoring infection/inflammation hours after tissue injury/infection.<sup>16</sup> This study shows that, those with higher HSCRCP level preoperatively (in the range of  $0.470 \pm 0.163$  mg/dL) showed poor recovery after surgery in the form of pain relief, which was assessed with modified Oswestry Back Disability Score. This may suggest that pre op inflammatory neuritis as suggested by high HSCRCP level may determine the outcome of disc surgery. Contrary to expected, we did not find any relation between preoperative score or radiological grading severity with preoperative HSCRCP level, which was similar to findings in related studies.<sup>21</sup>

Until now, only two studies by Sugimori *et al.*<sup>21</sup> and Le Gars *et al.*<sup>22</sup> have studied the correlation of preoperative HSCRCP level with postoperative scores. Both have found positive correlation between two as found out in our study. We have used modified Oswestry Back Disability Score as compared with Japanese Orthopedic Association score in these studies. In both these studies, there was no correlation found between the level of disc herniation and HSCRCP level. Sugimori *et al.*<sup>21</sup> used highly sensitive assay similar to one, which has been used in this study that is, ultrasensitive latex-enhanced immunoassay (N-latex CRPII), while Le Gars *et al.*<sup>22</sup> used an enzyme-linked immunosorbent assay with limit detection of 0.0005 mg/dL. In both these methods, a systemic inflammatory response to local inflammation around the nerve roots was found using highly sensitive analysis of CRP. This inflammatory response is due to the inflammatory cytokines, which are

produced by macrophages and monocytes, in response to nerve root inflammation. Many studies have shown and confirmed the inflammatory responses occurring in the herniated disc region. Hence, further research is necessary to explore the possibility of the use of agents, such as TNF- $\alpha$  blocker like Infliximab.<sup>23</sup>

A positive correlation between the preoperative concentration of HSCRCP and the Back Disability Score postoperatively, indicate that patients with a higher preoperative level of HSCRCP showed poor postoperative recovery due to persistent postoperative inflammatory neuritis in them. Thus, HSCRCP will serve as a good supplementary prognostic marker for operative decision making in borderline and troublesome cases of sciatica. Thus, this risk stratification using HSCRCP level is important because information about likely poor results after surgery may help the surgeon to reconsider treatment strategy and discuss same with patient while doing case selection for surgery.

To conclude, high sensitive C-reactive protein will serve as a good supplementary prognostic marker for operative decision-making in borderline and troublesome cases of Lumbar Disc Disease.

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