Predictive value of lymphocyte ratio and CRP level for early detection of surgical site infection following lumbar spinal surgery

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Abstract

Objective To investigate the predictive value of laboratory predictors, such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood cell (WBC) count, and WBC differential count, for the early diagnosis of surgical site infection (SSI) after lumbar spinal surgery. We also sought to determine the diagnostic thresholds for these markers.

Methods A total of 112 patients participated in the study: 11 patients who developed SSI after lumbar spinal surgery (SSI group) and 91 non-SSI patients as controls (non-SSI group). White blood cell (WBC) count, WBC differential count, CRP level, and ESR were determined 1 day before surgery and on postoperative day (POD) 1, POD3, and POD7. The diagnostic thresholds for these markers were determined with the receiver operating characteristic curve.

Results CRP, ESR, and WBC were significantly higher in the SSI group than in the non-SSI group on POD3 and POD7 (P < 0.05). The lymphocyte ratio was significantly lower in the SSI group, compared with the non-SSI group, on POD3 (P < 0.05). Analysis of the receiver operating characteristic curve revealed that lymphocyte ratio < 11.5% on POD3 (sensitivity 90.9%, specificity 75.4%, area under the curve [AUC] 0.919), and C-reactive protein level > 26 mg/dL on POD7 (sensitivity 90.9%, specificity 87.7%, area under the curve [AUC] 0.954) were significant laboratory predictors for the early detection of SSI.

Conclusion Lymphocyte ratio < 11.5% on POD3 and CRP levels > 26.5 mg/dL on POD7 are reliable predictors for SSI after lumbar spinal surgery.

Background

With the increasing prevalence of lumbar spinal surgery, surgical site infection (SSI), which was first described as a clinical entity by Turnbull in 1953\(^1\), remains a common and costly complication of lumbar spinal surgery. SSI infection rates of 0.7–16% after...
instrumented spinal fusion have been reported\textsuperscript{2,3}. The complications associated with SSI after lumbar spinal surgery include pseudoarthrosis, the deterioration of neurological function, sepsis, and even death.

When SSI occurs, early diagnosis and treatment greatly improve outcomes and shorten post-operative recovery. The diagnosis of SSI should be based on indicators such as systemic infection, laboratory data, imaging techniques \textsuperscript{4−7}, and local findings such as tenderness, swelling, redness, and purulent discharge\textsuperscript{8}. Due to their objectivity, low cost, convenience and non-invasiveness, several laboratory markers, such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood cell (WBC) count, and WBC differential count \textsuperscript{8−10} are garnering increased attention as tools with which to screen for SSI. However, clinicians often struggle to interpret these indicators correctly.

Our study was designed to investigate the predictive value of total WBC count, WBC differential count, CRP level, and ESR in the diagnosis of SSI after lumbar spinal surgery. We sought to identify the most significant laboratory predictors for the early detection of SSI and to determine the appropriate cut-off values for these predictors using the receiver operating characteristic (ROC) curve.

**Methods**

During the period from January 2015 to June 2018, there are 851 patients who underwent lumbar spinal surgery at the Department of Orthopedic Surgery, Shaanxi Provincial People’s Hospital. We retrospectively reviewed the medical records of 112 patients. SSI was determined according to criteria provided by the U.S Centers for Disease Control and Prevention \textsuperscript{11}. The study included 11 patients who developed SSI after lumbar spinal surgery (SSI group) and 91 patients who did not develop SSI after lumbar spinal surgery (non-SSI group). Patients were included in the SSI group if the attending surgeon had
performed debridement, obtained positive blood cultures, or drained surgical wounds. Patients were excluded if they had a trauma, tumor, or infection at the time of surgery, previous surgery on the lumbar spine, or were under 20 years of age. Second-generation cephalosporins were administered prophylactically 30 minutes pre-operatively and 48 hours postoperatively. Complete records for blood testing on POD1, POD3, and POD7 were obtained for all patients.

The study protocol was approved by the institutional review board of Shaanxi Provincial People’s Hospital [Clinical Ethics Committee of Shaanxi People’s Hospital (2014), No. 027]. Age, gender, operating time, and intraoperative blood loss were evaluated and recorded. CRP, ESR, WBC count, and neutrophil and lymphocyte ratio before surgery and on postoperative day (POD) 1, POD3, and POD7 were collected and analyzed. CRP and ESR were measured by latex agglutination, and WBC count was measured with an automatic cell counter. Neutrophil and lymphocyte ratios were determined by analyzing the WBC count.

Statistical analysis was performed with SPSS 24.0 for Windows (SPSS, Inc., IBM) and Graphpad Prism 7 (GraphPad Software, La Jolla, CA, USA). Data are expressed as mean ± standard deviation (SD). Continuous variables are presented as means and standard deviations. Categorical variables are summarized as the number and percentage of the total study population. Normally distributed continuous variables were compared using the two-sided independent t-test. Categorical variables were analyzed with the Chi-square test. We determined appropriate diagnostic cutoffs for the markers selected with the ROC curve. Statistical significance was defined as P < 0.05.

Results

Demographics and patient information
The final sample consisted of 112 patients: 11 patients who developed deep SSI (SSI group) and 91 who did not (non-SSI group). The SSI group included 7 male and 4 female patients; the non-SSI group included 37 female and 54 male patients. The mean age of patients in the SSI group was 55.82 ± 20.89 years; the mean age of patients in the non-SSI group was 55.55 ± 14.43 years. Operating time was 223.64 ± 90.36 minutes in the SSI group (range, 120-420), and 189.74 ± 80.70 minutes (range, 60-450) in the non-SSI group. Intraoperative blood loss was 600.00 ± 303.32 mL (range, 200-1000) in the SSI group and 442.11 ± 251.21 mL (range, 100-1000) in the non-SSI group. There were no significant difference between the groups in age, sex, operating time, or intraoperative blood loss (P > 0.05) (Table 1). The patients who had degenerative disease had undergone PLIF or discectomy surgery. There was no difference between groups in terms of surgical technique, anesthetic procedure, etc.

Table 1
Demographic data for all study participants

|                      | Non-SSI group (n = 91) | SSI group (n = 11) | P   |
|----------------------|------------------------|-------------------|-----|
| Age (years)          | 55.55 ± 14.43          | 55.82 ± 20.89     | 0.958|
| Sex                  | Male 54                | 7                 | 0.296|
|                      | Female 37              | 4                 |     |
| Operating time (min) | 189.74 ± 80.70         | 223.64 ± 90.36    | 0.215|
| blood loss(ml)       | 442.11 ± 251.21        | 600.00 ± 303.32   | 0.069|

Outcomes in the SSI group

An SSI was confirmed only when the surgeon diagnosed SSI, conducted debridement, and obtained a positive microbiological culture. Among 11 patients diagnosed with SSI, 10 patients underwent debridement, and instrumentation was removed in 8 cases. The other 1 patient received antibiotic treatment without surgery. Among the 10 patients who underwent re-operation, the bacterial species detected at the surgical site was identified as Staphylococcus aureus in 4 cases, Klebsiella pneumonia in 3 cases, Pseudomonas aeruginosa in 2 cases, and unknown in 1 case. Among the patients treated with antibiotics, the bacterial species identified by blood culture was S. aureus. The timeline
for the onset of infection after surgery is shown in Table 2. All patients recovered after undergoing surgery or receiving treatment with antibiotics (Table 2).

Table 2
Demographic data for SSI patients included in the study

| Patient No. | Age (yr) | Sex   | Method of Diagnosis | Culture                      | Method of Treatment                  | Timeline of onset of infection |
|-------------|----------|-------|---------------------|------------------------------|-------------------------------------|-------------------------------|
| 1           | 40-50    | Male  | Debridement         | staphylococcus aureus        | Debridement, implant removal        | 7                             |
| 2           | 60-70    | Male  | Debridement         | Unknown                      | Debridement                         | 11                            |
| 3           | 60-70    | Male  | Wound drainage      | klebsiella pneumonia         | Debridement, implant removal        | 6                             |
| 4           | 60-70    | Male  | Debridement         | staphylococcus aureus        | Debridement, implant removal        | 10                            |
| 5           | 20-30    | Male  | Debridement         | staphylococcus aureus        | Antibiotic medication               | 5                             |
| 6           | 60-70    | Male  | Debridement         | klebsiella pneumonia         | Debridement, implant removal        | 8                             |
| 7           | 20-30    | Male  | Wound drainage      | pseudomonas aeruginosa       | Debridement                         | 10                            |
| 8           | 60-70    | Female| Debridement         | staphylococcus aureus        | Debridement, implant removal        | 15                            |
| 9           | 80-90    | Female| Wound drainage      | pseudomonas aeruginosa       | Debridement, implant removal        | 6                             |
| 10          | 70-80    | Female| Debridement         | klebsiella pneumonia         | Debridement, implant removal        | 10                            |
| 11          | 40-50    | Female| Debridement         | staphylococcus aureus        | Debridement, implant removal        | 11                            |

Biochemical markers

There were no significant differences between groups in the level of any chemical marker measured before surgery. On POD 1, the WBC count in the SSI group (15.65 ± 6.05) was significantly higher than that in the non-SSI group (12.07 ± 3.95; t = -2.51; p = 0.01), but there was no significant difference between groups in CRP, ESR, neutrophil ratio, or lymphocyte ratio (Fig. 1).

On POD 3, there was no significant difference in WBC count between the SSI group (12.55 ± 3.78) and the non-SSI group (10.29 ± 3.65; t = -1.69; p = 0.096) (Fig. 2). The neutrophil ratio in the SSI group (0.84 ± 0.07) was significantly higher than that in the non-SSI group (0.75 ± 0.10; t = -2.77, p = 0.007). Lymphocyte ratio was significantly lower in the SSI
group (0.06 ± 0.03), compared with the non-SSI group (0.16 ± 0.06; t = 4.94; p < 0.001).
CRP levels were significantly higher in the SSI group (116.27 ± 72.84), compared with the non-SSI group (26.93 ± 23.16; t = -7.64; p < 0.001). ESR was significantly higher in the SSI group (64.27 ± 26.67), compared with the non-SSI group (37.96 ± 24.28; t = -3.24; p = 0.002).
On POD 7, there was no significant differences in WBC count between groups (Fig. 3). Neutrophil ratio was significantly higher in the SSI group (0.79 ± 0.10), compared to the non-SSI group (0.72 ± 0.10; t = -2.391; p = 0.020). Lymphocyte ratio was significantly lower in the SSI group (0.12 ± 0.07), compared with the non-SSI group (0.18 ± 0.09; t = 2.267, p = 0.027). CRP was significantly higher in the SSI group (118.27 ± 63.68), compared to the non-SSI group (17.68 ± 24.65; t = -5.165; p < 0.001). ESR was significantly higher in the SSI group (63.91 ± 33.06), compared with the non-SSI group (36.46 ± 27.23; t = -2.957; p = 0.004).
The ROC curve was used to determine the appropriate diagnostic cut-off values for important laboratory predictors. ROC curve analysis showed that lymphocyte ratio on POD 3 and CRP level on POD 7 could effectively distinguish SSI patients from non-SSI patients. The results were as follows: lymphocyte ratio POD3, cutoff < 11.50% [sensitivity 90.9%, specificity 75.4%, area under the curve (AUC) 0.919; Fig. 4A]; CRP POD7, cutoff = 26 mg/dL (sensitivity 90.9%, specificity 87.7%, AUC 0.954; Fig. 4B).
Discussion
Although large-scale efforts have been initiated to help mitigate postoperative SSIs after lumbar spinal surgery, associated morbidity remains high. The incidence of spinal SSI ranges from 0.7–16%, depending on the type of surgery and the area involved. A postoperative course complicated by SSI may require long and repeated hospitalizations
and multiple surgical interventions, including irrigation and debridement, hardware removal, and complex wound closure. Early diagnosis and treatment greatly improve patient outcomes and shorten the time to recovery.

SSI is typically diagnosed by a surgeon or based on the assessment of images [e.g. computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET)]. Other indicators, such as clinical laboratory markers, are also of great value in predicting and monitoring SSI because of their objectivity, low cost, and convenience.

The biochemical markers used most widely for the early diagnosis of SSI are CRP, ESR, total WBC count, and differential WBC count. Several studies have reported the usefulness of these biomarkers and found that the combined use of normal CRP, ESR, and WBC levels reliably predicts the absence of infection after lumbar spinal surgery. Changes in ESR and CRP after surgery may be used to distinguish between infected and non-infected patients. Larsson et al. were the first to report changes in CRP level after lumbar posterior surgery; the authors observed that CRP level returned to baseline (< 10 mg/L) within 21 days after surgery. However, Takahashi et al. reported that postoperative CRP level peaked on day 2, and Aono et al. reported that CRP level peaked on day 4.

Postoperative CRP levels peaked between POD2 and POD4. Iwata et al. reported that a CRP level > 10 mg/dL at 4 days postoperatively was useful for the definitive diagnosis of SSI. Kyu et al. reported that the observation of abnormal CRP levels three days postoperatively should cause the clinician to be highly suspicious of infection.

It is believed that CRP levels remain elevated or increase further at POD4, suggesting that SSI is more likely to occur. The results showed that the level of CRP had increased
significantly on POD 3 in the SSI group and remained high on POD7. In the non-SSI group, CRP levels had increased significantly on POD3, then decreased slightly by POD7 (Fig. 1D). In both the SSI and the non-SSI group, ESR levels had increased significantly at POD3, but were then observed to have decreased slightly on POD7 (Fig. 1E). ESR increased to peak levels at POD5, followed by a slow and irregular decreasing trend\(^\text{17}\). Therefore, CRP appears to be more suitable than ESR for evaluating infection.

Our results showed that CRP levels had increased in all patients on POD1. In non-SSI patients, decreases in CRP levels were observed on POD3 and POD7. However, in the SSI group, CRP levels were higher on POD3 and decreased on POD7. We determined the diagnostic cutoff for CRP by using the ROC curve. If CRP levels are > 26 mg/dL on POD7, infection should be highly suspected, and the antibiotic regimen should be changed or increased in dose.

Several factors have been reported to affect postoperative CRP levels. These factors include blood loss, preoperative CRP levels, and the segment on which spinal surgery was performed. For example, surgery in the lumbar region is associated with higher postoperative CRP levels than surgery in other areas.\(^\text{21}\). Given the uncertainty of the use of CRP as a diagnostic tool for SSI, additional laboratory predictors are needed to distinguish between infected and non-infected patients at the postoperative stage.

WBC counts and lymphocyte counts were first reported to be helpful for the early diagnosis of surgical wound infections after lumbar surgery by Takahashi et al.\(^\text{22}\).

Takahashi et al. found that lymphocyte ratio ≤ 10% or count < 1,000/\(\mu\)L at POD4 were associated with increased risk for surgical wound infection. The authors suggest that lymphocytopenia represents an immunosuppressive state. This increase in the body's susceptibility to infection may lead to the development of postoperative infection.
Subsequent studies supported these claims. Iwata et al. showed that a lymphocyte count < 1,000/µL at POD4 was the only significant independent laboratory marker for the early detection of SSI \(^{16}\). Furthermore, Chao-Jun Shen et al. reported \(^{23}\) that neutrophil/lymphocyte count ratio (NLR) at POD4 and POD7 was a valuable marker for SSI in patients who had recently undergone posterior lumbar spinal surgery. When ROC results were analyzed for NLR > 5.19 at POD4, the sensitivity and specificity of the NLR were 61.5% and 77.6%; the AUC was 0.708. For NLR > 3.85 at POD7, sensitivity and specificity were 69.2% and 62.7%; the AUC was 0.663. The cutoff for the percentage of lymphocytes at POD4 was < 15%; sensitivity of this marker was 61.5%, and specificity was 73.3% (AUC = 0.682).

Our results showed that, in all patients, neutrophil count increased and lymphocyte count decreased on POD1. In non-SSI patients, neutrophil count began to decrease on POD3, which is also when lymphocyte count began to increase. However, in infected patients, a further increase in neutrophil count and decrease in lymphocyte count were detected on POD3 (Fig. 1B,C). We therefore chose to determine the diagnostic cutoff for lymphocyte ratio using the ROC curve. If lymphocyte ratio was less than 11.5% at POD3, infection was highly suspected, as in studies performed previously. We believe that POD4 lymphocyte count is more useful than POD7 lymphocyte count because the data can be obtained earlier during the course of postoperative recovery. POD4 lymphocyte count appears to be an important indicator of SSI after posterior lumbar surgery.

In this study, we analyzed the sensitivity and specificity of five laboratory markers for the early detection of SSI. Two laboratory markers were found to have acceptable levels of sensitivity and specificity. The first indicator was CRP level > 26 mg/dL on day 7 after surgery. For this marker, sensitivity and specificity were 90.9% and 87.7%, respectively, and the AUC was 0.954. The other indicator was lymphocyte ratio < 11.50% on the third
day after surgery. For this marker, sensitivity and specificity were 90.9% and 75.4%, respectively, and the AUC was 0.919. If the lymphocyte ratio was $< 11.50\%$ on POD 3, or the CRP level is $> 26 \text{ mg/dL}$ on POD 7, clinicians should check the surgical wound more carefully. If necessary, imaging diagnostic tools such as CT and MRI may be used.

Our research has several limitations. First, this was a retrospective study. Therefore, there may be inherent bias associated with patient selection and missing patient information. Second, chronic SSI patients may have been included in the non-SSI group. Patients were assigned to groups based on the results of the hospitalization exam. The actual number of SSI cases may therefore have been underestimated. In future studies, we will expand the study population as well as the duration of follow-up.

Conclusion

In conclusion, a lymphocyte ratio $< 11.50\%$ at 3 days postoperatively and CRP levels $> 26 \text{ mg/dL}$ at 7 days postoperatively may be valuable markers for the early diagnosis and control of SSI following lumbar surgery. These predictors appear to have high sensitivity and can be measured early during the course of postoperative recovery.

Abbreviations

AUC
area under the curve
CRP
C-reactive protein
ESR
erythrocyte sedimentation rate
ROC
receiver operating characteristic
SSI
surgical site infection
WBC
white blood cell

Declarations

Consent for publication

N/A

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Availability of data and materials

All data generated or analyzed during this study are included in this article. We confirm that the availability of data and materials refers to the raw data generated and used for this study. The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Authors’ contributions

WBB supervised the project and contributed to all stages of the present study. DPD and LQG participated in the design of the study, revised the manuscript, and approved the final version. WBB and SJD contributed to interpreting the data and writing the final manuscript. LW and JW contributed to writing and editing the manuscript. All authors read and approved the final manuscript.

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Ethics approval and consent to participate

The study protocol was approved by the Institutional Review Board of Shaanxi Provincial People’s Hospital (No. 027, 2014), and written informed consent was obtained from all study participants.

Competing interests
The authors declare that they have no competing interests.

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Figures
Figure 1

A. WBC-time profile (*P < 0.05). B. Neutrophil %–time profile (*P < 0.05). C. Lymphocyte %–time profile (*P < 0.05) D. CRP–time profile (*P < 0.05). E. ESR–time profile (*P < 0.05).
Figure 2

Laboratory measurements obtained on POD3 for patients with SSI (n = 11) and non-SSI (n = 91) patients. (A) WBC count; (B) neutrophil ratio; (C) lymphocyte ratio; (D) CRP; (E) ESR. The blue line represents median values. All comparisons were performed with the Mann-Whitney U-test.
Laboratory measurements obtained on POD7 for patients with SSI (n = 11) and non-SSI (n = 91) patients. (A) WBC count; (B) neutrophil ratio; (C) lymphocyte ratio; (D) CRP; (E) ESR. The blue line represents median values. All comparisons were performed with the Mann-Whitney U-test.
Figure 4

ROC analysis for lymphocyte ratio at POD3 (A) and for CRP at POD7 (B).