Predictive Value of Lymphocyte Percentage and CRP Level for Early Detection of Deep Surgical Site Infection Following Posterior Lumbar Spinal Surgery

Wenbo Wei

Shaanxi Provincial People's Hospital

Shajie Dang

Shaanxi provincial cancer hospital

Dapeng Duan

Shaanxi Provincial people's Hospital

Liqun Gong

Shhaanxi Provincial People's Hospital

Ling Wei (✉ sxweiling@126.com)

YangLing demonstration zone hospital

Jue Wang

Xi'an Jiaotong University

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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 deep surgical site infection (SSI) after posterior lumbar spinal surgery. We also sought to determine the diagnostic thresholds for these markers.

Methods: A total of 243 patients participated in the study: 11 patients who developed deep SSI after lumbar spinal surgery (SSI group) and 232 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 percentage 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 percentage $< 11.5\%$ on POD3 (sensitivity 90.9%, specificity 75.4%, area under the curve [AUC] 0.919), and C-reactive protein level > 26 mg/L 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 percentage $< 11.5\%$ on POD3 and CRP levels > 26.5 mg/L on POD7 are reliable predictors for SSI after posterior 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 1953¹, remains a common and costly complication of lumbar spinal surgery. SSI infection rates of 0.7–16% after instrumented spinal fusion have been reported^{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^{4–7}, and local findings such as tenderness, swelling, redness, and purulent discharge⁸. 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^{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 deep SSI after posterior lumbar spinal surgery. We sought to

identify the most significant laboratory predictors for the early detection of deep SSI and to determine the appropriate cut-off values for these predictors using the receiver operating characteristic (ROC) curve.

Methods

We retrospectively reviewed the medical records of 243 patients who underwent posterior lumbar spinal surgery with instrumentation at the Department of Orthopedic Surgery, Shaanxi Provincial People's Hospital, during the period from January 2015 to June 2018. Deep SSI was determined according to criteria provided by the U.S Centers for Disease Control and Prevention ¹¹. The study included 11 patients who developed deep SSI after posterior lumbar spinal surgery (SSI group) and 232 patients who did not develop SSI after posterior lumbar spinal surgery (non-SSI group). Patients were included in the deep 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, without complete laboratory data or were under 20 years of age. Surgeons checked for SSIs every day during the hospital stay and at every outpatient clinic follow-up visit (for at least 3 months post-surgery).

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 percentage were determined by analyzing the WBC count. The reference intervals for blood cell analysis and the cut-off for CRP were determined based on the National Standard of the People's Republic of China WS/T 404.9–2018.

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 $\pm$ 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

Among 451 patients who underwent posterior lumbar spinal surgery, the final sample consisted of 243 patients: 11 patients who developed deep SSI (SSI group) and 232 who did not (non-SSI group). The SSI

group included 7 male and 4 female patients; the non-SSI group included 85 female and 116 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).

Table 1
Demographic data for all study participants

		Non-SSI group (n = 91)	SSI group (n = 11)	P
Age (years)		55.65 ± 14.43	55.82 ± 20.89	0.918
Sex	Male	116	7	0.314
	Female	85	4	
Operating time (min)		191.35 ± 80.70	223.64 ± 90.36	0.226
blood loss(ml)		442.11 ± 251.21	600.00 ± 303.32	0.069

Notes: Values are expressed as mean $\pm$ SD or number of patients (%).

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	13
4	60–70	Male	Debridement	staphylococcus aureus	Debridement, implant removal	10
5	30–40	Male	Debridement	staphylococcus aureus	Antibiotic medication	21
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	8
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) $\times 10^9$ /L was significantly higher than that in the non-SSI group (12.07 ± 3.95) $\times 10^9$ /L ($t = -2.51$; $p = 0.01$), but there was no significant difference between groups in CRP, ESR, neutrophil percentage, or lymphocyte percentage (Fig. 1).

On POD 3, there was no significant difference in WBC count between the SSI group (12.55 ± 3.78) $\times 10^9$ /L and the non-SSI group (10.29 ± 3.65) $\times 10^9$ /L ($t = -1.69$; $p = 0.096$) (Fig. 2). The neutrophil percentage 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 percentage 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) mg/L, compared with the non-SSI group (26.93 ± 23.16) mg/L ($t = -7.64$; $p < 0.001$). ESR

was significantly higher in the SSI group (64.27 ± 26.67) mm/h, compared with the non-SSI group (37.96 ± 24.28) mm/h ($t = -3.24$; $p = 0.002$).

On POD 7, there was no significant differences in WBC count between groups (Fig. 3) Neutrophil percentage 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 percentage 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) mg/L, compared to the non-SSI group (17.68 ± 24.65) mg/L ($t = -5.165$; $p < 0.001$). ESR was significantly higher in the SSI group (63.91 ± 33.06) mm/h, compared with the non-SSI group (36.46 ± 27.23) mm/h ($t = -2.957$; $p = 0.004$).

The ROC curve was used to determine the appropriate diagnostic cut-off values for important laboratory predictors. ROC curve analysis showed that lymphocyte percentage on POD 3 and CRP level on POD 7 could effectively distinguish SSI patients from non-SSI patients. The results were as follows: lymphocyte percentage POD3, cutoff $< 11.50\%$ [sensitivity 90.9%, specificity 75.4%, area under the curve (AUC) 0.919; Fig. 4A]; CRP POD7, cutoff = 26 mg/L (sensitivity 90.9%, specificity 87.7%, AUC 0.954; Fig. 4B).

Discussion

Although large-scale efforts have been initiated to help mitigate postoperative deep SSIs after posterior 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^{2,3}. 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^{13–15} because of their objectivity, low cost, and convenience^{12,16}.

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^[14,15]. Changes in ESR and CRP after surgery may be used to distinguish between infected and non-infected patients. Larsson et al.¹⁷ 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.¹⁸ reported that postoperative CRP level peaked on day 2, and Aono et al.¹⁹ reported that CRP level peaked on day 4. Postoperative CRP levels peaked between POD2 and POD4. Iwata et al.¹⁶ reported that a CRP level > 10 mg/L at 4 days postoperatively was useful

for the definitive diagnosis of SSI. Kyu et al.²⁰ 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.^{16,18,22} 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 trend¹⁷. 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/L 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, surgical approaches 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.^{21, 11}. 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.²³ Takahashi et al. found that lymphocyte percentage $\leq 10\%$ or count $< 1,000/\mu\text{L}$ 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 $< 1,000/\mu\text{L}$ at POD4 was the only significant independent laboratory marker for the early detection of SSI¹⁶. Furthermore, Chao-Jun Shen et al. reported²⁴ 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 $\text{NLR} > 5.19$ at POD4, the sensitivity and specificity of the NLR were 61.5% and 77.6%; the AUC was 0.708. For $\text{NLR} > 3.85$ 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 percentage using the ROC curve. If lymphocyte percentage 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/L 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 percentage < 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 percentage was < 11.50% on POD 3, or the CRP level is > 26 mg/L 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. Third, the number of SSI patients included in our samples was small; there may be a selective bias. Fourth, in this study, we investigated the predictive value of biochemical markers in patients who underwent posterior lumbar spinal surgery only. Therefore, in future studies, we will expand the study population as well as the duration of follow-up.

Conclusion

In conclusion, a lymphocyte percentage < 11.50% at 3 days postoperatively and CRP levels > 26 mg/L 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

WBW 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. WBW 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.

Figure 3

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).