

Temporal Evolution of White Blood Cell Count and Differential: Reliable and Early Detection Markers for Surgical Site Infection Following Spinal Posterior Decompression Surgery

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Abstract:

Introduction: For early detection of surgical site infection (SSI) following spinal decompression surgery, we compared temporal changes in the values of laboratory markers that are not affected by operative parameters.

Methods: The study included 302 patients, which were divided into an SSI group (patients who developed deep SSI) and a non-SSI group for analysis. We reviewed data on C-reactive protein level, total white blood cell (WBC) count, and WBC differential percentage and count before spinal decompression, on postoperative day 1, and on postoperative day 4. We identified laboratory markers that are not affected by operative parameters (operating time, intraoperative blood loss, and number of operative segments). Laboratory markers with a significant difference observed between the peak or nadir value and the value in the subsequent survey day were considered as an indicator of SSI. We examined the utility of each indicator by calculating sensitivity and specificity. Furthermore, we investigated the utility of the combination of all five indicators (wherein the recognition of one marker was considered positive).

Results: Temporal changes in five laboratory markers were considered indicators of SSI. The changes from postoperative day 1 to postoperative day 4 were as follows: (1) increased WBC count (42% sensitivity, 88% specificity), (2) increased neutrophil percentage (25% sensitivity, 96% specificity), (3) increased neutrophil count (25% sensitivity, 94% specificity), (4) decreased lymphocyte percentage (25% sensitivity, 95% specificity), and (5) decreased lymphocyte count (25% sensitivity, 85% specificity). The combination of these five markers showed a 50% sensitivity, 81% specificity, and 0.65 AUC.

Conclusions: Five markers were found to be reliable indicators of SSI following spinal decompression surgery because they were not affected by operative parameters. The combination of all five indicators had moderate sensitivity and high specificity. Therefore, this may be reliable and useful for the early detection of SSI.

Keywords:

surgical site infection, laboratory marker, lymphocyte, neutrophil, diagnosis

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Introduction

Surgical site infection (SSI) after spinal surgery occurs in around 0.7-12% of patients, varying according to the operation type and patient characteristics¹⁻³⁾. SSIs are potentially fatal and significantly increase hospital stay, healthcare costs, and morbidities^{4,5)}. Preventing SSIs should be prioritized for every operation; if infection occurs, early diagnosis

and treatment are paramount to prevent exacerbation⁶⁻⁹⁾.

SSI can be initially diagnosed through an evaluation of the wound, investigation of clinical signs (i.e., presence of fever), and assessment of laboratory markers. More definitive diagnostics include imaging methods, such as contrast-enhanced computed tomography (CT), contrast-enhanced magnetic resonance imaging (MRI), and positron emission tomography-computed tomography (PET-CT)^{6,7,9-12)}. Though

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more accurate, these imaging modalities are expensive and may be inaccessible for some patients. Thus, if a clinician suspects SSI on initial diagnosis, more definitive imaging modalities may be requested to confirm the diagnosis. Further, spinal surgeons should be aware of the caveat that postoperative fever can also occur without wound infection¹³.

Moist wound healing has recently become a widely used approach in managing wounds and is performed by covering wounds with a dressing material¹⁴. This makes it difficult to monitor the wound directly, potentially increasing the risk of delayed SSI diagnosis. Postoperative laboratory markers are frequently used to assess SSI owing to their objectivity and convenience^{6,9,15-19}. For instance, acute-phase C-reactive protein (CRP) levels, white blood cell (WBC) count, and WBC differential count can be used to detect and monitor postoperative wound infections⁹. However, clinicians often have difficulty interpreting these markers because they might be affected by operative parameters, such as operating time, intraoperative blood loss, and the number of operative segments.

Our previous report found that lymphocyte count (at postoperative days 4 and 7) and CRP level (at postoperative day 7) were the most reliable laboratory markers for SSI following instrumented spinal fusion because they were not affected by operative parameters¹⁸. We also reported that the temporal evolution of neutrophil and lymphocyte counts (at postoperative days 1 and 4) was reliable for early detection of SSI following instrumented spinal fusion because these were not affected by operative parameters as well²⁰. However, previous reports showed that operative instrumentation affected laboratory markers^{21,22}. Hence, we considered that reliable laboratory markers are needed for the early detection of SSI after spinal decompression surgery (without instrumentation). We found that lymphocyte percentage and count (at postoperative day 4) are reliable markers for SSI after spinal decompression surgery because these were not affected by operative parameters¹⁹. Similar to instrumented spinal fusion, we hypothesized that temporal evolution of laboratory markers may be another reliable indicator for SSIs in spinal decompression surgery. In this study, we aimed to compare temporal changes in laboratory markers following spinal decompression surgery. This comparison will allow us to identify markers that are independent of operative parameters and to examine the utility of the markers for SSI detection.

Materials and Methods

This study was approved by the institutional review boards of the participating institutions. We retrospectively reviewed the medical records of 520 patients who underwent posterior spinal decompression surgery (lumbar decompression and cervical laminoplasty) for degenerative spine disease at two hospitals between January 2009 and December 2014. The occurrence of SSIs and laboratory data of the pa-

tients were retrieved. SSI was defined according to the criteria of the Centers for Disease Control and Prevention²³. Patients were identified as having deep SSI if after diagnosis, the attending surgeon conducted debridement, performed a blood culture that was positive for infectious agents, or drained the surgical wound within 4 weeks. Patients were excluded if they had trauma, tumor, or infection at the time of surgery or if they were under 20 years of age. Patients who did not undergo laboratory tests before surgery and days 1 and 4 postoperatively were also excluded. These tests were performed routinely for patients who underwent spinal surgery and not only in cases of suspected infection. The final sample population comprised 302 patients, which were grouped into patients who developed deep SSI (n=12) and those who did not (n=290).

CRP level, WBC count, neutrophil percentages, and lymphocyte percentages were obtained before surgery and days 1 and 4 postoperatively. CRP level was measured using the latex agglutination method, and the WBC count was determined using an automatic cell counter. Neutrophil and lymphocyte counts were calculated from the WBC count and differential percentages. Operating time, intraoperative blood loss, and number of operative segments were also recorded. All the patients remained hospitalized for 7 days postoperatively.

We initially calculated the median of three operative parameters (operating time, intraoperative blood loss, and number of operative segments) and classified the non-SSI group into two categories based on the median of each operative factor (L group \leq median; H group $>$ median). A total six groups were formed (L and H groups in operating time, intraoperative blood loss, and number of operative segments).

We investigated the normal evolution of the biochemical markers in all six groups before surgery and days 1 and 4 postoperatively. If the markers reached their peak or nadir values on the same day in all six groups, we considered them unaffected by operative parameters. If there was a significant difference between the peak or nadir value and the values in the subsequent survey day, we considered the comparison between these markers as an indicator of SSI. We also examined the possible utility of these indicators by calculating their sensitivity and specificity in predicting SSI. Furthermore, we examined the combination of all indicators (wherein the recognition of one marker was considered positive) by calculating their sensitivity and specificity in predicting SSI.

Statistical analyses

Primary analysis was carried out using repeated measures analysis of variance to examine the differences among values before surgery and days 1 and 4 postoperatively in each laboratory marker. Subsequently, a post hoc paired t-test with Bonferroni correction was performed to determine the difference between the peak or nadir value and the values in the subsequent survey day. Differences in quantitative char-

Table 1. Patient Data.

	SSI group (n=12)	Non-SSI group (n=290)	P
Age, years (median [range])	79 [40–86]	71 [20–88]	0.023*
Sex	Male 6, female 6	Male 170, female 120	0.767
Type of surgery	LD 8 CL 4	LD 174 CL 116	0.769
Operating time, min (median [range])	169 [124–260]	142 [57–299]	0.043*
Blood loss volume, mL (median [range])	100 [0–1250]	100 [0–988]	0.829
Number of operative segments (median [range])	3 [1–7]	3 [2–5]	0.836

*Statistically significant ($P < 0.05$) using the Mann–Whitney U test

SSI, surgical site infection; LD, lumbar decompression; CL, cervical laminoplasty

Table 2. Patient Data in the SSI Group.

Patient No.	Age (y)	Sex	Type of surgery	Method of diagnosis	Time from surgery to diagnosis (days)	Culture	Method of treatment
1	76	F	LD	Wound drainage	4	MRSA	Antibiotic medication
2	68	M	LD	Wound drainage	6	MRSA	Antibiotic medication
3	86	F	LD	Debridement	4	Unknown	Debridement, antibiotic medication
4	73	F	LD	Debridement	11	Unknown	Debridement, antibiotic medication
5	76	M	LD	Debridement	13	Unknown	Debridement, antibiotic medication
6	86	F	LD	Debridement	9	CNS	Debridement, antibiotic medication
7	84	F	LD	Wound drainage	7	<i>Escherichia coli</i>	Antibiotic medication
8	84	M	LD	Wound drainage	9	MRSA	Antibiotic medication
9	40	M	CL	Debridement	11	MRSA	Debridement, antibiotic medication
10	82	M	CL	Wound drainage	8	Unknown	Antibiotic medication
11	85	M	CL	Debridement	6	MRSA	Debridement, antibiotic medication
12	59	F	CL	Wound drainage	8	CNS	Antibiotic medication

SSI, surgical site infection; F, female; M, male; LD, lumbar decompression; CL, cervical laminoplasty; CNS, coagulase-negative *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*

acteristics, such as age, operating time, intraoperative blood loss, and number of operative segments, between the SSI and non-SSI groups, were analyzed using the Mann–Whitney U-test. The ability of each laboratory marker to distinguish SSI cases from non-SSI cases and the differences in qualitative characteristics, such as sex, between SSI and non-SSI cases, was assessed using Fisher’s exact probability test. All statistical analyses were carried out using SPSS version 24.0 for Windows (IBM, Armonk, NY, USA). A P value of < 0.05 was considered statistically significant.

Results

Demographics and operative parameters

The median age at surgery was 79 years in the SSI group and 71 years in the non-SSI group. The SSI group comprised 6 men and 6 women, while the non-SSI group included 170 men and 120 women. The operative parameters

were as follows: median operating time (SSI: 169 min, range: 124–260) (non-SSI: 142 min, range: 57–299); median intraoperative blood loss (SSI: 100 mL, range: 0–1250) (non-SSI: 100 mL, range: 0–988); and median number of operative segments (SSI: 3, range: 1–7) (non-SSI: 3, range: 2–5). There were significant differences in age and operating time and no significant differences in sex, type of surgery, intraoperative blood loss, and number of operative segments between the two groups (Table 1).

Outcomes in the SSI group

Among the 12 patients in the SSI group, we conducted debridement in 6. The other six patients were treated with only antibiotics. All patients recovered (Table 2).

Evolution of the biochemical marker values in six groups

We classified the non-SSI group into two categories based on the median of each operative factor and formed a total of six groups. The WBC count and the neutrophil percentage

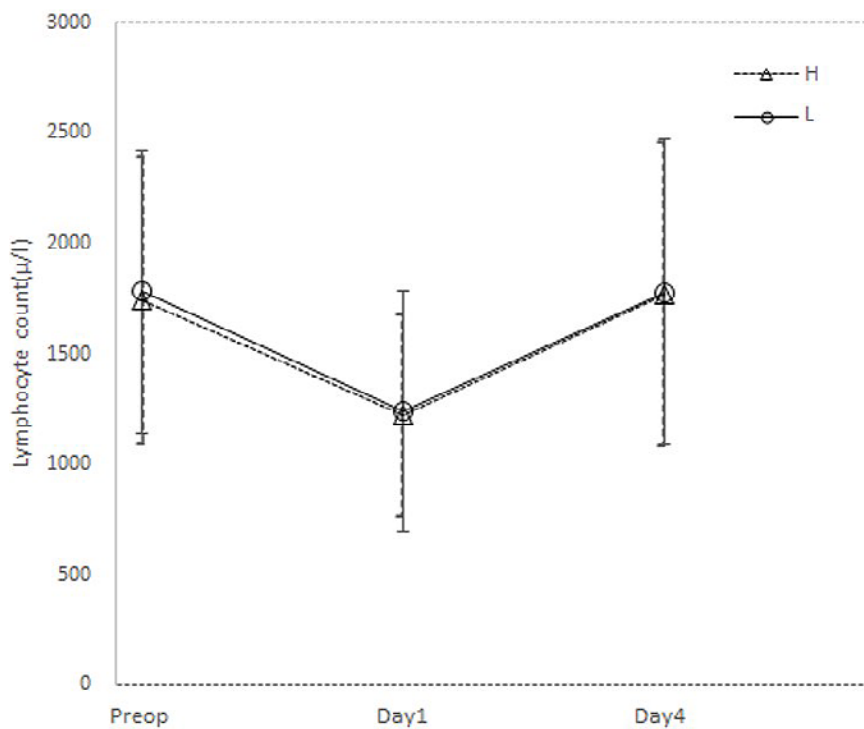


Figure 1. Changes in postoperative lymphocyte count in the L and H groups of operating time. Each group reached the nadir value on the same day, i.e., postoperative day 1. Values are mean and standard deviation.

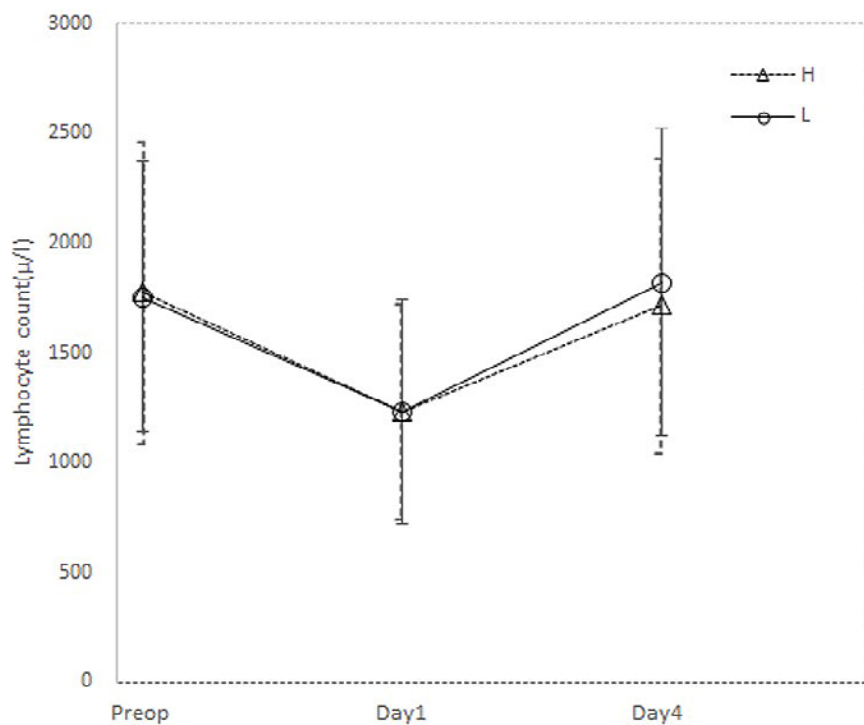


Figure 2. Changes in postoperative lymphocyte count in the L and H groups of intraoperative blood loss. Each group reached the nadir value on the same day, i.e., postoperative day 1. Values are mean and standard deviation.

and count of all six groups peaked on the same day, i.e., postoperative day 1. The lymphocyte percentage and count of all six groups reached the nadir value on the same day, i.e., postoperative day 1 (Fig. 1-3). The CRP levels of all six

groups peaked on the same day, i.e., postoperative day 4 (Table 3).

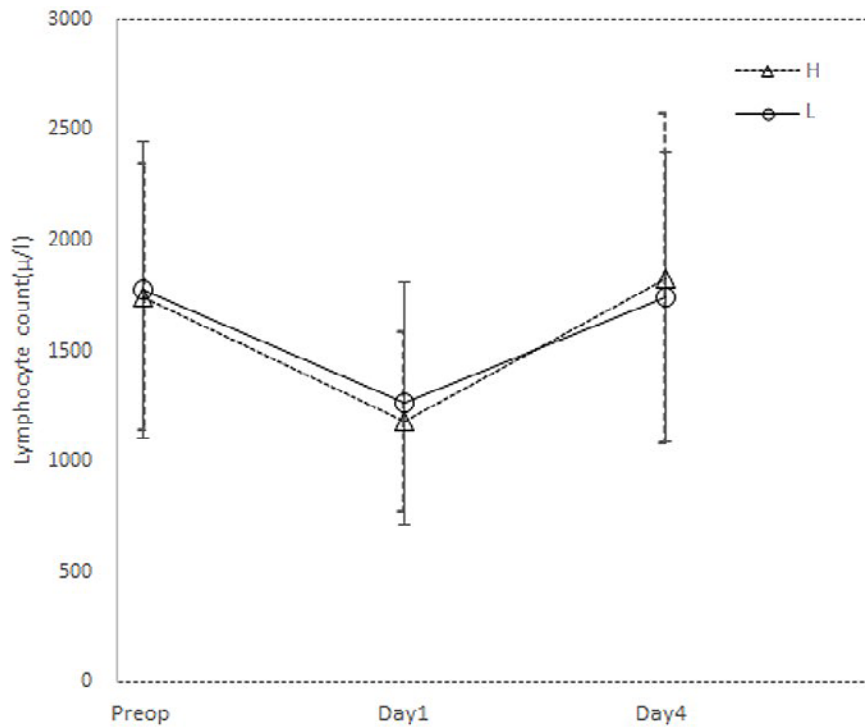


Figure 3. Changes in postoperative lymphocyte count in the L and H groups of number of fusion segments. Each group reached the nadir value on the same day, i.e., postoperative day 1. Values are mean and standard deviation.

Table 3. Peak or Nadir Value Day in the Six Groups.

	WBC count	Neutrophil percentage	Neutrophil count	Lymphocyte percentage	Lymphocyte count	CRP level
Operating time						
<i>L group</i> (n=146)	1 day	1 day	1 day	1 day	1 day	4 days
<i>H group</i> (n=144)	1 day	1 day	1 day	1 day	1 day	4 days
Intraoperative blood loss						
<i>L group</i> (n=166)	1 day	1 day	1 day	1 day	1 day	4 days
<i>H group</i> (n=124)	1 day	1 day	1 day	1 day	1 day	4 days
Number of operative segments						
<i>L group</i> (n=182)	1 day	1 day	1 day	1 day	1 day	4 days
<i>H group</i> (n=108)	1 day	1 day	1 day	1 day	1 day	4 days

Peak or nadir values and values in the subsequent survey day

We excluded the assessment of the CRP level because it exhibited the peak value 4 days postoperatively, which is the final investigation day. For each group, there was a significant difference between the peak or nadir values and the values in the subsequent survey day (Table 4).

SSI indicators not affected by operative parameters

We identified five indicators of SSI, obtained at postoperative day 4 and day 1, as follows: (1) increased WBC count, (2) increased neutrophil percentage, (3) increased neutrophil count, (4) decreased lymphocyte percentage, and (5) decreased lymphocyte count.

Sensitivity and specificity of each indicator of SSI

The sensitivity and specificity of each indicator of SSI, obtained at postoperative day 4 and day 1, were as follows: (1) increased WBC count was 42% sensitive and 88% specific, (2) increased neutrophil percentage was 25% sensitive and 96% specific, (3) increased neutrophil count was 25% sensitive and 94% specific, (4) decreased lymphocyte percentage was 25% sensitive and 95% specific, and (5) decreased lymphocyte count was 25% sensitive and 85% specific. Significant statistical difference was observed for all indicators. Furthermore, the combination of all these indicators (wherein the recognition of one marker was considered positive) showed a 50% sensitivity, 81% specificity, and 0.655 AUC (Table 5).

Table 4. P Value of the Peak or Nadir Values and Values in the Subsequent Survey Day in the Six Groups.

	WBC count	Neutrophil percentage	Neutrophil count	Lymphocyte percentage	Lymphocyte count
Operating time					
<i>L group</i> (n=146)	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*
<i>H group</i> (n=144)	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*
Intraoperative blood loss					
<i>L group</i> (n=166)	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*
<i>H group</i> (n=124)	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*
Number of operative segments					
<i>L group</i> (n=182)	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*
<i>H group</i> (n=108)	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*

*Statistically significant ($P<0.05$) using repeated measures analysis of variance and paired t-test with the Bonferroni correction.

Table 5. Sensitivity and Specificity of Each Indicator of SSI.

	Sensitivity	Specificity	AUC	P
[a] WBC count at postoperative day 4 more than day 1	42%	88%	0.650	<0.001*
[b] Neutrophil percentage at postoperative day 4 more than day 1	25%	96%	0.604	<0.001*
[c] Neutrophil count at postoperative day 4 more than day 1	25%	94%	0.597	<0.001*
[d] Lymphocyte percentage at postoperative day 4 less than day 1	25%	95%	0.597	<0.001*
[e] Lymphocyte count at postoperative day 4 less than day 1	25%	85%	0.547	<0.001*
Combination ([a], [b], [c], [d], or [e]) [†]	50%	81%	0.655	0.018*

*Statistically significant ($P<0.05$). SSI, surgical site infection

[†]Even if each marker ([a], [b], [c], [d], or [e]) was recognized, it is considered positive.

Discussion

In this study, we compared the temporal changes in laboratory markers for SSI prediction after spinal decompression surgery and identified whether these markers are affected by operative parameters. Increased WBC count, neutrophil percentage, and neutrophil count and decreased lymphocyte percentage and count on postoperative day 4 (compared to postoperative day 1) were the most reliable laboratory markers for SSI. These markers were not affected by operative parameters and had a high specificity. To address their low sensitivity, we investigated the utility of the combination of all these markers and discovered high specificity and moderate sensitivity. These laboratory markers enable the early diagnosis of SSIs at postoperative day 4.

Postoperative laboratory markers are frequently used to assess SSIs due to their objectivity and convenience^{6,9,15-19}. WBC count and differential, CRP level, erythrocyte sedimentation rate (ESR), serum amyloid A level, procalcitonin level, and CD64 level were reported as SSI markers^{9,15,16,21,24-28}. The most widely used laboratory markers for SSI are CRP levels, ESR, and WBC count and differential, which are accessible in most medical institutions.

In previous reports, ESR is not useful in the diagnosis of acute infection because it tends to return to normal much slowly after the prosthetic surgery. On the contrary, CRP levels return to the baseline levels more quickly^{22,26}. CRP is produced by the liver in response to inflammation, infection, malignancy, and tissue damage, and CRP levels are charac-

terized by a high sensitivity and immediate response^{22,26}. However, factors other than infection, such as operative circumstances, have been reported to influence CRP levels. Clayton et al. reported that the varying peaks depend on the amount of tissue injury during surgery²⁵. Larsson et al. compared different types of orthopedic surgical procedures and found varying correlations between the extent of surgery and peak CRP levels postoperatively. They postulated that the increase in CRP depends not only on the amount of tissue injured but also on the type of tissue damaged²⁶. Thus, peak postoperative CRP levels vary by tissue type and type of surgery.

Takahashi et al. reported that WBC count and differential, another frequently used marker, are useful for early detection of SSI following spinal surgery^{9,21}. Furthermore, temporal changes in the WBC count, especially the neutrophil count, serve as useful markers for postoperative progress²¹. The renewed elevation of the neutrophil count at days 4-7 postoperatively may be a critical sign of infection; the same was found to be true for a neutrophil percentage >75% after postoperative day 4^{9,21}. On the other hand, lymphocytes, which are involved in nonspecific biophylaxis, often decrease postoperatively regardless of infection. In patients who developed infections, the percentage and number of lymphocytes were found to be significantly decreased on postoperative day 4. This signifies immunodepression which made the patients susceptible to infection, which may have been associated with a high concentration of anti-inflammatory cytokines and attendant compensatory anti-

inflammatory response syndrome^{22,24}). Thus, we consider postoperative lymphopenia (no more than 10% or 1000/ μ L) after 4 days to be indicative of possible surgical wound infection^{9,21}).

Inose, et al.¹⁶) reported that the neutrophil-lymphocyte ratio (NLR) could be a useful predictor of SSI after spinal instrumentation surgery. The NLR is calculated using the neutrophil and lymphocyte counts; therefore, this is another SSI marker that can be measured conveniently.

Clinicians often have difficulty interpreting these markers because these markers might be affected by operative parameters. Thus, it is important that laboratory markers for SSI are not affected by operative parameters. Our previous report identified laboratory markers for SSI not affected by operative parameters following spinal decompression surgery¹⁹). Lymphocyte percentage and count at 4 days postoperatively were a reliable marker for screening because it has a high sensitivity and can be measured early. These markers were absolute value representation. In this study, we report the utility of WBC, neutrophil, and lymphocyte percentage and counts at postoperative days 1 and 4 as reliable and early detection markers for SSI following spinal decompression surgery.

Our study has several limitations. First, each indicator of SSI and combination had low AUC. Second, this was a retrospective study. As a result, there may have been an inherent bias associated with patient selection and missing patient information. Patients who did not fit the criteria for deep SSI were placed in the non-SSI group, which may underestimate the actual number of SSI cases. Another limitation is the possibility of a type 2 error due to the comparatively small number of SSI cases. A prospective study in a large cohort may eliminate these problems.

In patients undergoing spinal posterior decompression surgery, increased WBC count, neutrophil percentage, and neutrophil count and decreased lymphocyte percentage and count at postoperative day 4 (compared to postoperative day 1) should prompt clinicians to assess the surgical wound more carefully. More accurate diagnostic tools, such as contrast-enhanced CT, contrast-enhanced MRI, and PET-CT, could be used subsequently to confirm the diagnosis. After a definite diagnosis, debridement or antibiotics administration should be performed. The combination of the five laboratory markers for diagnosis of SSI in the present study has moderate sensitivity and high specificity. In conjunction with our previous report¹⁹), these findings suggest reliable and useful markers for the early detection of SSI, enabling accurate diagnosis of patients. A prospective study is necessary to further confirm the obtained findings.

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pared the manuscript. All authors participated in the study design and have read, reviewed, and approved the article.

Ethical Approval: Approval code: the institutional review boards of Nara Medical University (1078) and Otemae Hospital (2015-010).

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