

Comparison of neutrophil and lymphocyte at 1 and 4 days postoperatively: reliable and early detection markers for surgical site infection following instrumented spinal fusion

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Abstract:

Introduction: To identify the temporal comparison of biochemical markers for early detection of surgical site infection (SSI) following instrumented spinal fusion that are not affected by operative factors.

Methods: We reviewed data on C-reactive protein level and total white blood cell count and differential count before instrumented spinal fusion and at 1, 4, and 7 days postoperatively. The 141 patients in our sample were divided into an SSI group (patients who developed deep SSI) and a non-SSI group. We investigated the peak or nadir value day and identified those not affected by operative circumstances (operating time, intraoperative blood loss, and number of fusion segments) in the non-SSI group. If there was a significant difference between the peak or nadir value day and the next survey day, we considered the temporal comparison between these unaffected markers as an indicator of SSI and examined the usefulness of these indicators by calculating sensitivity and specificity. Furthermore, we investigated the usefulness of the combination of these markers (if even each one marker was recognized, we considered it positive).

Results: Four biochemical markers of SSI were selected: neutrophil percentage at postoperative day 4 more than day 1 (sensitivity 36%, specificity 95%), neutrophil count at postoperative day 4 more than day 1 (sensitivity 46%, specificity 93%), lymphocyte percentage at postoperative day 4 less than day 1 (sensitivity 36%, specificity 90%), and lymphocyte count at postoperative day 4 less than day 1 (sensitivity 36%, specificity 90%). The combination of these markers showed sensitivity 100%, specificity 80%, respectively.

Conclusions: Four markers are reliable indicators for early detection of SSI following spinal instrumented fusion because they are not affected by operative factor. The combination of each indicator had both high sensitivity and specificity. Therefore, it is reliable and much useful for early detection of SSI.

Keywords:

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

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Introduction

Instrumented spinal fusion has been increasingly performed in recent years because it can achieve strong fixation and correct deformities. However, this procedure is associated with more complications than surgeries without instrumentation, and surgical site infection (SSI) is one of the most serious complications^{1,2)}. Insertion of instrumentation

may lead to infection if a relatively small number of bacteria adhere to the surface of the implanted device and form a glycoprotein biofilm. This process is generally attributable to intractable infections that are resistant to antibiotics and result in increased infection rates³⁾. Infection rates of 2.2% to 8.5% after spinal instrumentation surgery have been reported^{4,6)}. SSI is potentially devastating with significant increase in hospital stay, health care costs, and morbidities^{7,8)}.

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Preventing SSI should be prioritized, and when an infection does occur, early diagnosis and treatment are important to prevent aggravation^{6,9-11}. An SSI diagnosis should be made based on a combination of systemic indicators of infection, such as fever and biochemical markers, and localized symptoms, such as tenderness, swelling, redness, and pus discharge⁶.

Most tests for SSI rely on postoperative biochemical markers because of their objectivity and convenience^{9,12,13}. For instance, acute-phase-related C-reactive protein (CRP) and white blood cell (WBC) count and differential can be used to detect and monitor postoperative wound infections¹¹. However, clinicians often struggle with interpreting these markers because they might be affected by operative factors, such as operating time, intraoperative blood loss volume, and number of fusion segments. Our previous report found that lymphocyte count obtained at postoperative days 4 and 7 and CRP level at postoperative day 7 were the most reliable biochemical markers for SSI following instrumented spinal fusion because they were not affected by operative factors¹⁴.

Are there other reliable biochemical markers not affected by operative factors? We hypothesized that temporal comparison of biochemical markers may be another reliable marker. The present study aims to perform temporal comparison of biochemical markers. This comparison will allow us to identify markers that are not affected by operative factors and to examine the usefulness of the markers for SSI detection following instrumented spinal fusion. Furthermore, we examined the usefulness of the combination of these indicators and our previous reported marker.

Materials and Methods

This study was approved by the institutional review boards of the participating institutions. We retrospectively reviewed the medical records of 221 patients who underwent posterior spinal instrumented fusion for degenerative spine disease at two hospitals between January 2009 and December 2014, and searched for evidence of deep SSI and laboratory data. SSI was defined according to the criteria of the Centers for Disease Control and Prevention¹⁵. Patients were identified as having deep SSI if the attending surgeon diagnosed deep SSI and conducted debridement, performed a blood culture that was positive for infectious agents, or drained the surgical wound within four weeks. Patients were excluded if they had trauma, tumor, or infection at the time of surgery or were under 20 years of age. Patients who did not undergo laboratory tests before surgery and 1, 4, and 7 days postoperatively were also excluded. These tests were performed routinely and not only in cases of suspected infection. The final sample comprised 141 patients, which were divided into 11 patients who developed deep SSI and 130 who did not.

Data on CRP, WBC count, and neutrophil and lymphocyte percentages were collected before surgery and 1, 4, and

7 days postoperatively. CRP was measured using the latex agglutination method, and an automatic cell counter was used to determine the WBC count. Neutrophil and lymphocyte counts were calculated from the WBC count and differential percentages. Operating time, intraoperative blood loss, and number of fusion segments were also recorded. All the patients remained hospitalized 7 days postoperatively.

We initially calculated the median of three operative factors (operating time, intraoperative blood loss, and number of fusion 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). Finally, six groups were formed (L and H groups in operating time, intraoperative blood loss, and number of fusion segments).

We investigated the normal kinetics of the biochemical markers in all six groups before surgery and 1, 4, and 7 days postoperatively. If these markers indicated the same peak or nadir value day in all six groups, we considered them unaffected by operative factors. If there was a significant difference between the peak or nadir value day and the next survey day, we considered the comparison between these unaffected markers as an indicator of SSI. We also examined the usefulness of these indicators by calculating sensitivity and specificity as SSI.

Furthermore, we examined the usefulness of the combination of these indicators (if even each one marker was recognized, we considered it positive) by calculating sensitivity and specificity as SSI.

Statistical analyzes

Primary analysis was carried out using repeated measures ANOVA to examine significant difference before surgery and 1, 4, and 7 days postoperatively in each biochemical marker. Subsequently, a post hoc test (using paired t-test with Bonferroni correction) was performed to determine the significant difference between the peak or nadir value day and the next survey day. Differences in quantitative characteristics, such as age, operating time, intraoperative blood loss, and number of fusion segments, were analyzed with Mann-Whitney *U*-test. We performed Fisher's exact probability test to investigate the possible association of each biochemical indicator of SSI and to distinguish SSI cases from non-SSI cases and differences in qualitative characteristics such as sex. All statistical analyzes were carried out using SPSS version 23.0 for Windows (IBM, Armonk, NY, USA). A *P* value <0.05 was considered statistically significant.

Results

Demographics and operative factors

The SSI group comprised 3 men and 8 women and the non-SSI group included 51 men and 79 women. The median age at surgery was 73 years in the SSI group and 84 years in the non-SSI group. The operative factors were as follows:

Table 1. Patient Data.

	SSI group (n=11)	Non-SSI group (n=130)	P
Age, years (median [range])	73 [47-84]	68 [22-87]	0.444
Sex	male 3, female 8	male 51, female 79	0.330
Operating time, min (median [range])	315 [143-552]	234 [80-849]	0.317
Blood loss volume, mL (median [range])	349 [100-600]	273.5 [0-2440]	0.563
Number of fusion segments (median [range])	2 [1-7]	1 [1-11]	0.475

SSI, surgical site infection

Table 2. Patient Data in the SSI Group.

Patient No.	Age (y)	Sex	Method of diagnosis	Time from surgery to diagnosis (days)	Culture	Method of treatment
1	71	F	Debridement	11	<i>Escherichia coli</i>	Debridement, implant removal
2	73	F	Debridement	4	Unknown	Debridement
3	73	F	Debridement	15	Unknown	Debridement
4	77	M	Wound drainage	7	MSSA	Antibiotic medication
5	57	M	Debridement	7	MRSA	Debridement, implant removal
6	78	F	Debridement	16	CNS	Debridement
7	84	F	Debridement	18	MRSA	Debridement, implant removal
8	47	F	Wound drainage	14	MRSA	Antibiotic medication
9	74	M	Wound drainage	9	MRSA	Implant removal
10	51	F	Blood culture	7	CNS	Antibiotic medication
11	70	F	Debridement	10	<i>Pseudomonas aeruginosa</i>	Debridement

SSI, surgical site infection; F, female; M, male; CNS, coagulase-negative *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*

median operating time, 315 min (range 143-552) for the SSI group, 234 min (range 80-849) for the non-SSI group; median intraoperative blood loss, 349 mL (range 100-600) for the SSI group, 273.5 mL (range 0-2440) for the non-SSI group; and median number of fusion segments, 2 (range 1-7) for the SSI group, 1 (range 1-11) for the non-SSI group. No significant differences existed in the age, sex, operating time, intraoperative blood loss, or number of fusion segments between the groups (Table 1). We classified the non-SSI group into two categories based on the median of each operative factor and finally formed six groups.

Outcomes in the SSI group

Of the 11 patients who developed deep SSI (3 men and 8 women), we conducted debridement in 7, 4 of whom had to have their instrumentation removed. The other 4 patients were treated with antibiotics. All patients recovered (Table 2).

Kinetics of the biochemical markers in Six Groups

The WBC count of all six groups indicated the same day of the peak value, i.e., 1 day postoperatively. The neutrophil percentage and count of all six groups showed the same day of the peak value, i.e., 1 day postoperatively. The lymphocyte percentage and count of all six groups indicated the same day of the nadir value, i.e., 1 day postoperatively (Fig. 1, 2, 3). The CRP level of all six groups exhibited the same

day of the peak value, i.e., 4 days postoperatively (Table 3).

Peak or nadir value day and the next survey day

There was a significant difference between the peak or nadir value day and the next survey day in each group (Table 4).

Indicator of SSI not affected by operative factors

There were six indicators of SSI: [a] WBC count at postoperative day 4 more than day 1; [b] neutrophil count at postoperative day 4 more than day 1; [c] neutrophil percentage at postoperative day 4 more than day 1; [d] lymphocyte count at postoperative day 4 less than day 1; [e] lymphocyte percentage at postoperative day 4 less than day 1; and [f] CRP level at postoperative day 7 more than day 4.

Sensitivity and specificity of each indicator of SSI

The sensitivity and specificity of each indicator of SSI were as follows: [a] WBC count at postoperative day 4 more than day 1 was 36% and 86%; [b] neutrophil percentage at postoperative day 4 more than day 1 was 36% and 95%; [c] neutrophil count at postoperative day 4 more than day 1 was 46% and 93%; [d] lymphocyte percentage at postoperative day 4 less than day 1 was 36% and 90%; [e] lymphocyte count at postoperative day 4 less than day 1 was 55% and 81%; and [f] CRP level at postoperative day 7 more than day 4 was 9% and 97%. Significant statistical difference

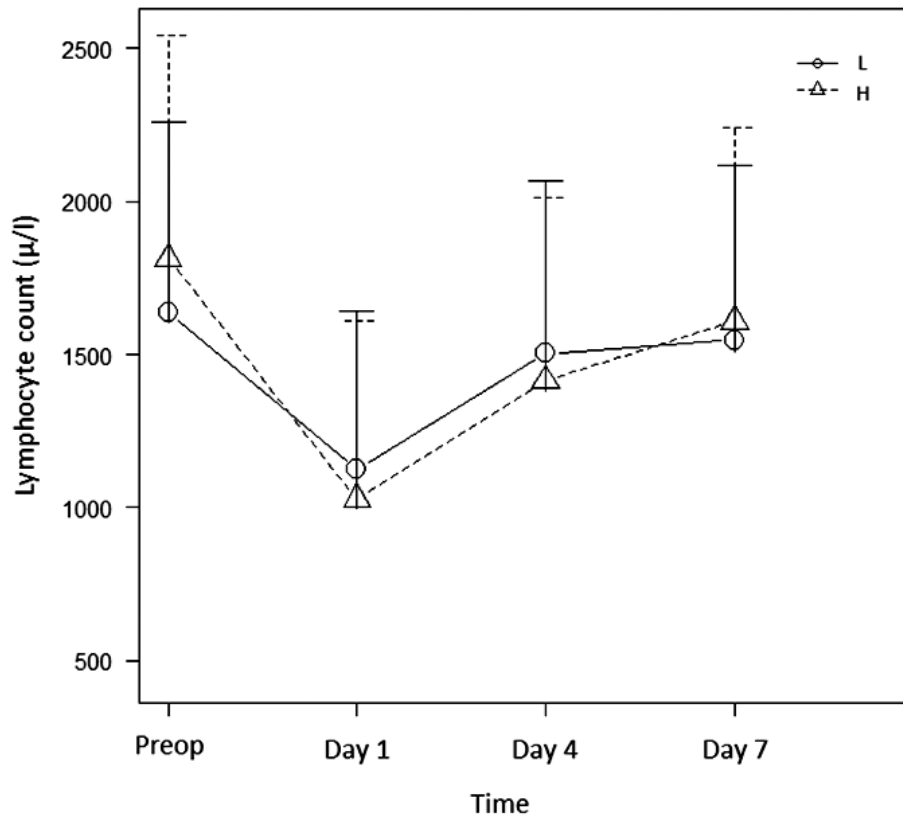


Figure 1. Kinetics of postoperative lymphocyte count in the L and H groups of operating time. Each group indicated the same day of the nadir value, i.e., 1 day postoperatively. Values are mean and standard deviation.

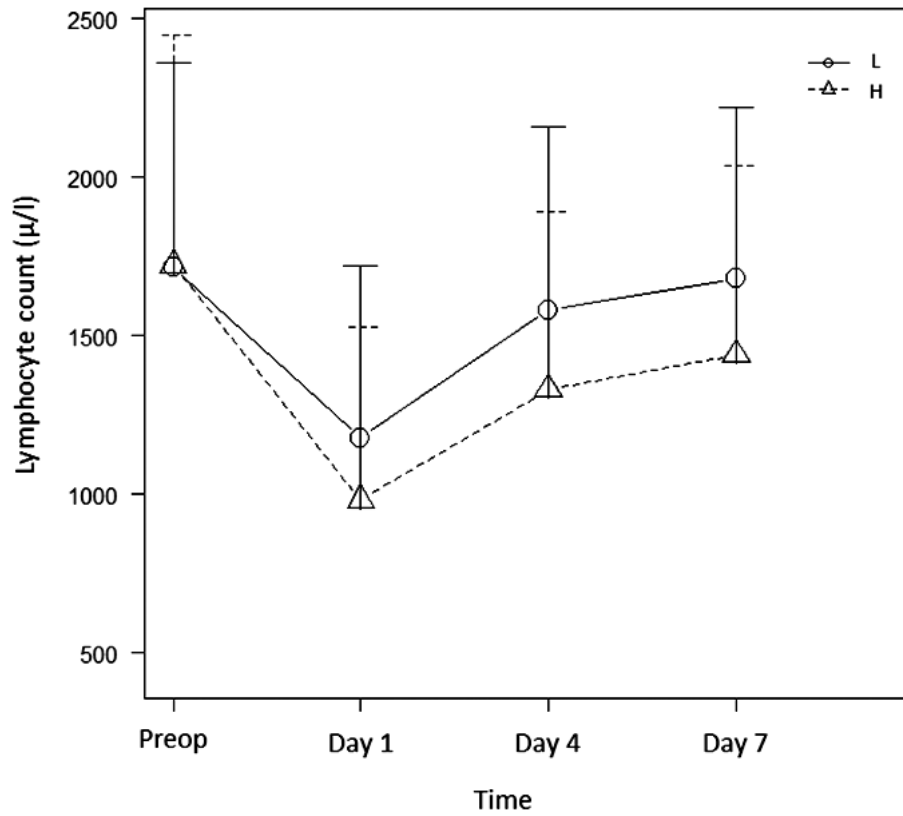


Figure 2. Kinetics of postoperative lymphocyte count in the L and H groups of intraoperative blood loss. Each group indicated the same day of the nadir value, i.e., 1 day postoperatively. Values are mean and standard deviation.

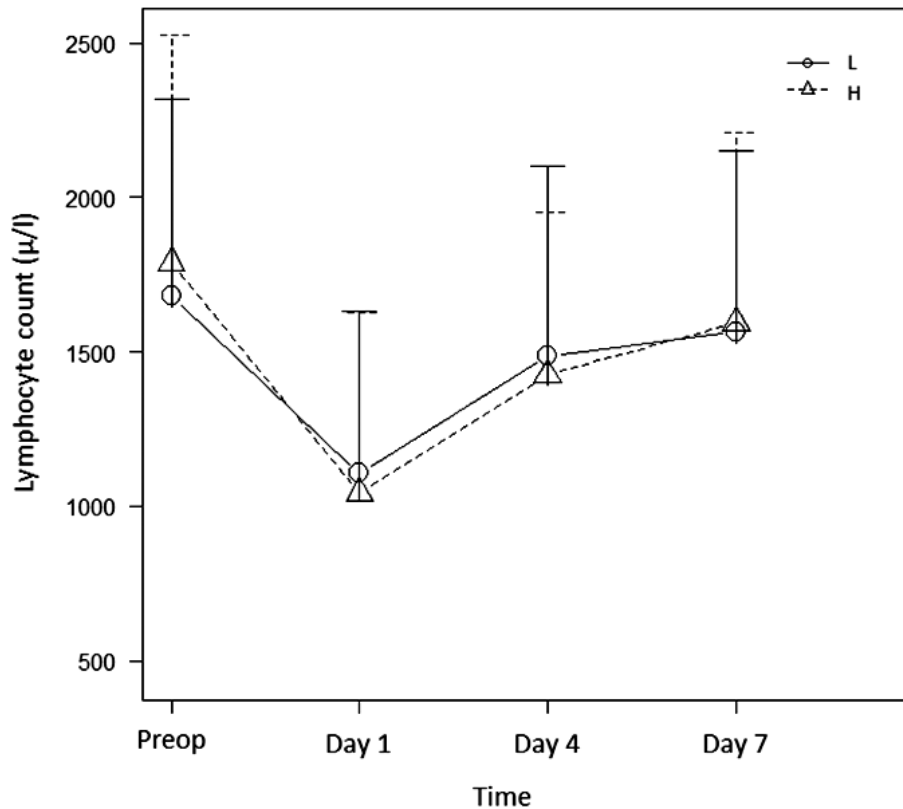


Figure 3. Kinetics of postoperative lymphocyte count in the L and H groups of number of fusion segments. Each group indicated the same day of the nadir value, i.e., 1 day postoperatively. Values are mean and standard deviation.

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=64)	1 day	1 day	1 day	1 day	1 day	4 days
<i>H group</i> (n=66)	1 day	1 day	1 day	1 day	1 day	4 days
Intraoperative blood loss						
<i>L group</i> (n=66)	1 day	1 day	1 day	1 day	1 day	4 days
<i>H group</i> (n=64)	1 day	1 day	1 day	1 day	1 day	4 days
Number of fusion segments						
<i>L group</i> (n=55)	1 day	1 day	1 day	1 day	1 day	4 days
<i>H group</i> (n=75)	1 day	1 day	1 day	1 day	1 day	4 days

was observed for indicators [b], [c], [d], and [e].

Furthermore, the combination of these indicators (if even each one marker was recognized, we considered it positive) was 100% and 80% (Table 5).

Discussion

The aim of SSI treatment after spinal instrumentation surgery is not only to resolve infection but also to maintain spinal stability, i.e., avoid implant removal. Ishii et al. reported that patients who developed SSI are more likely to be able to retain their implants if diagnosed early¹⁶. SSI can be initially diagnosed through evaluation of wound, presence fe-

ver, and comparison of biochemical markers. The more accurate diagnosis includes imaging methods, such as enhanced computed tomography (CT), enhanced magnetic resonance imaging (MRI), and positron emission tomography-computed tomography (PET-CT)^{9-11,13,17,18}. Such more accurate methods are expensive, and they are impossible to carry out in all cases. Thus, if initial diagnosis is positive, it is followed by more accurate diagnosis.

In recent years, moist wound healing has become a widely used approach in managing wounds. This is promoted by covering a wound with a dressing material, which makes it more difficult to monitor the wound directly, potentially increasing the risk of delayed SSI diagnosis.

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

	WBC count	Neutrophil percentage	Neutrophil count	Lymphocyte percentage	Lymphocyte count	CRP level
Operating time						
<i>L group</i> (n=64)	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*
<i>H group</i> (n=66)	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*
Intraoperative blood loss						
<i>L group</i> (n=66)	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*
<i>H group</i> (n=64)	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*
Number of fusion segments						
<i>L group</i> (n=55)	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*
<i>H group</i> (n=75)	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*

*Statistically significant ($P<0.05$) using repeated measures ANOVA and paired t-test with Bonferroni correction

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

	Sensitivity	Specificity	P
[a] WBC count at postoperative day 4 more than day 1	36%	86%	0.070
[b] Neutrophil percentage at postoperative day 4 more than day 1	36%	95%	0.005*
[c] Neutrophil count at postoperative day 4 more than day 1	46%	93%	0.002*
[d] Lymphocyte percentage at postoperative day 4 less than day 1	36%	90%	0.029*
[e] Lymphocyte count at postoperative day 4 less than day 1	55%	81%	0.015*
[f] CRP level at postoperative day 7 more than day 4	9%	97%	0.338
Combination ([b], [c], [d], or [e]) [†]	100%	80%	<0.001*

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

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

Aono et al. reported that body temperature varies widely at different times of the day and among individuals⁹. Therefore, biochemical markers are useful as initial diagnosis indicators of SSI. WBC count and differential, CRP, erythrocyte sedimentation rate (ESR), serum amyloid A, procalcitonin, and CD64, among others, were reported as SSI markers^{11,12,19-24}. The most widely used biochemical markers of SSI are CRP levels, ESR, and WBC count and differential, which can be measured easily in most medical institutions.

CRP is significantly superior to ESR as a marker of SSI; in previous reports, CRP shows more reliable peaks and more stable values^{22,25}. Hence, ESR was not used as an SSI marker in the present study. CRP is produced by the liver in response to inflammation, infection, malignancy, and tissue damage, and CRP levels are characterized by a relatively high sensitivity and quick response^{22,25}. However, factors other than infection, such as operative circumstances, have been reported to influence CRP level. Clayton et al. reported that the varying peak response depends on the amount of iatrogenic tissue injury at surgery²¹. Larsson et al. compared different types of orthopedic surgical procedures and could not always find a correlation 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 being damaged²². As a result, the maximum postoperative CRP level varies by region and type of surgery.

Another frequently used marker is WBC count and differ-

ential. Takahashi et al. reported that WBC count and differential are useful for early detection of surgical wound infection following instrumented lumbar spinal fusion^{11,12}. Furthermore, changes in the WBC count, especially the neutrophil count, over time serve as useful markers of postoperative progress¹². According to Takahashi et al., the renewed elevation of the WBC count, particularly the neutrophil count, after 4 to 7 postoperative days may be a critical sign of infection; the same may apply to a neutrophil percentage >75% after postoperative day 4^{11,12}. On the other hand, lymphocytes, which are involved in nonspecific biophylaxis, often decrease after invasion, regardless of infection. In patients who developed infections, the percentage and number of lymphocytes significantly decrease on day 4. This signifies immune depression, making the patients more susceptible to infection, which may have been associated with a high concentration of anti-inflammatory cytokines and attendant compensatory anti-inflammatory response syndrome^{19,25}. Thus, the authors consider postoperative lymphopenia (no more than 10% or 1000 / μ L) after 4 days to be indicative of possible surgical wound infection^{11,12}.

On the other hand, clinicians often struggle to interpret these markers because they might be affected by operative factors. Clarification of biochemical markers for SSI not affected by operative factors is important. Our previous report identified biochemical markers for SSI not affected by operative factors following instrumented spinal fusion¹⁴. These markers were absolute value representation. In the present

study, we performed temporal comparison of biochemical markers and identified markers not affected by operative factors. Neutrophil percentage and count at postoperative day 4 more than day 1 and lymphocyte percentage and count at postoperative day 4 less than day 1 were the most reliable biochemical markers for SSI. These markers were not affected by operative factors and high specificity. However, these were low sensitivity, so, we investigated the usefulness of the combination of these markers and was cleared both high sensitivity and specificity. In addition, early diagnosis at postoperative day 4 was possible.

Our study has several limitations. First, it 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 significantly underestimate the actual number of SSI cases. Another limitation is the possibility that a type 2 error might have occurred because of the comparatively small number of SSI cases. A prospective study in a large cohort may eliminate these problems.

In cases of neutrophil percentage and count at postoperative day 4 more than day 1 and lymphocyte percentage and count at postoperative day 4 less than day 1 in patients undergoing spinal instrumented fusion, clinicians should assess the surgical wound more carefully. More accurate diagnostic tools, such as enhanced CT, enhanced MRI, and PET-CT, could then be used as soon as possible. After a definite diagnosis, clinicians should perform debridement or administer antibiotics. The combination of four biochemical markers for diagnosis of SSI in the present study has both high sensitivity and specificity. Therefore, it is reliable and much useful for early detection of SSI. By additional referring to our previous report¹⁴, we could diagnose more accurately. A prospective study is necessary to prove the obtained findings.

Conflicts of Interest: The authors declare no conflicts of interest.

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