Review Article

The neutrophil-to-lymphocyte ratio (NLR) levels predicting the surgical site infection in spinal surgery: a systematic review

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Background: Surgical site infection (SSI) is a prevalent complication in spinal surgery, associated with significant morbidity, prolonged hospital stays, and increased healthcare costs. The early detection of SSI can lead to timely intervention. Among available diagnostic methods, the neutrophil-to-lymphocyte ratio (NLR) has emerged as a simple, accessible marker with potential predictive value for SSIs. This systematic review aims to evaluate the diagnostic role of NLR, in the early detection of SSIs following spinal surgery.

Methods: Following PRISMA guidelines, we conducted a comprehensive literature search in MEDLINE, Web of Science, Embase, and Scopus databases for studies examining the utility of NLR in predicting SSIs in all types of spinal surgery patients. Ultimately, 7 studies met the inclusion criteria; all retrospective in design, with sample sizes ranging from 77 to 384. Studies focused on NLR values measured at different postoperative days, solely or along with some integrating additional markers, including C-reactive protein (CRP) and body mass index (BMI), into predictive models.

Results: Our study confirmed that NLR serves as a significant predictor of SSIs post-spinal surgery. Analyses of included studies revealed variable optimal NLR cutoff values, ranging from 3.21 to 4.91, dependent on postoperative day and surgery type. The highest predictive accuracy was observed when NLR was combined with CRP and lymphocyte percentage, enhancing early SSI detection. However, the variability in cutoff values and measurement timing across studies suggests limitations due to heterogeneity in study designs and patient populations, indicating the need for further research to establish standardized protocols.

Conclusions: NLR could be of value for early SSI detection in spinal surgery, with its diagnostic accuracy potentially improved by combining it with other markers. However, variability in cutoff values and timing across studies suggests the need for further research to standardize these parameters. Establishing consistent protocols could improve SSI detection, enabling faster interventions and potentially enhancing patient outcomes in spinal surgery.

Keywords: Neutrophil-to-lymphocyte ratio (NLR); surgical site infection (SSI); spinal surgery

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Introduction

Techniques for spine surgery have recently seen significant advancements. However, postoperative complications from spinal procedures continue to exist due to factors including extended operating periods, the requirement for instrumental installation, and expanded surgical techniques in lumbar diseases (1). Surgical site infection (SSI) is a postoperative spinal surgery complication that ranks third among the most common complications following lumbar surgeries, after pneumonia and urinary tract infections (2). The occurrence of SSI in patients with spine surgery is reported to range from 0.2% to 16.1% (3). The SSI incidence after laminectomy and spinal fusion surgeries was estimated by the National Nosocomial Infections Surveillance System in 2001 as 1.2% and 2.4%, respectively (4,5). SSI is counted as a major post-operative complication which is classified into three types including superficial, deep, and organ space SSI, based on the infection site (2,6). Superficial SSI affects only skin and subcutaneous tissue around the lesion; deep SSI involves the fascia and muscle layer; while the organ space SSI extends beyond the skin, fascia, and muscle layer (2,7). Various risk factors are proposed for spinal SSI comprising diabetes, hypertension, obesity, smoking, alcohol abuse, steroid use, longer operation times, history of previous SSI, type of surgical approach, larger blood loss volume, and instrumentational injury (2,3,8). Despite numerous efforts to prevent SSI, it has been indicated that infection of the surgical site is associated with serious consequences including worse clinical outcomes, requiring further surgeries, prolonged hospital stay, and having poor prognosis after surgery (9-11).

Given the mentioned complications following SSI that could be coupled with medical, economic, or psychological burdens for both patients and health organizations, it is of great importance to detect SSI at early stages following lumbar surgery to initiate prompt treatment and shorten the course of infection (9,10,12). Although a direct diagnosis of SSI could be made by clinical examination and radiologic imaging, some laboratory markers are identified to correlate with the presence of SSI after spinal operations (13,14). Among the postoperative clinical laboratory tests, acute phase-related C-reactive protein (CRP) quantitative titer and peripheral white blood cell (WBC) counts and differential percentages and changes are frequently employed as inflammatory markers (15). Previous studies demonstrated that the postoperative measurement of lymphocyte counts at days 4th and 7th, and CRP level at day 7th after spinal surgery could be a reliable indicator of developing SSI (15). The following is the typical healing trajectory after surgery without SSI linked to postoperative inflammation: on postoperative days 1 and 2, the lymphocyte count quickly drops to about 1,000/mL, rises steadily to 1,000/mL by day 4, and then in two to three weeks returns to preoperative values. In a similar vein, the neutrophil count rises quickly, peaks on postoperative days 1 and 2, progressively declines on day 4, and returns to normal in 2–3 weeks (12,15,16). Early stages of developing a postoperative infection are associated with an increase in neutrophil count and a reduction in lymphocyte number, which leads to an increased neutrophil-to-lymphocyte ratio (NLR) (12,15). The NLR is a simple, inexpensive, and available inflammatory marker calculated by dividing the number of neutrophils (count/mL) by the lymphocyte counts (count/mL) in which its usefulness has been indicated in stratification of mortality in major cardiac disease, determining the prognosis of various cancer types, and detecting inflammatory and infectious processes (e.g.,

Highlight box

Key findings

- The neutrophil-to-lymphocyte ratio (NLR) is a significant predictor of surgical site infection (SSI) in patients undergoing spinal surgery. Optimal NLR cutoff values vary by postoperative day and surgery type, typically 3–7 days after surgery.
- Combining NLR with other inflammatory markers, such as C-reactive protein (CRP) and body mass index (BMI), enhances predictive accuracy.

What is known and what is new?

- SSI is a common and severe complication in spinal surgery, often leading to prolonged hospital stays and poorer outcomes. Traditional inflammatory markers, including white blood cell (WBC) count and CRP, are used in SSI detection but can vary in reliability.
- This review establishes NLR as a reliable and cost-effective marker for early SSI detection in spinal surgery. Additionally, it highlights combined predictive models (e.g., NLR with CRP and lymphocyte ratio) as potentially more effective than NLR alone.

What is the implication, and what should change now?

- NLR measurement can be integrated into routine postoperative care for spinal surgery patients to aid early SSI detection.
- Further research is necessary to standardize NLR cutoff values by surgery type and postoperative timing, which would improve its clinical utility.
- Adoption of combined marker models, validated through future studies, may improve the accuracy and timeliness of SSI diagnosis, leading to faster interventions and better patient outcomes.

pediatric appendicitis) (17-21).

The NLR could be a robust delegate to WBC counts and CRP level in discovering SSI, owing to its high predictive value and steady nature during numerous physiological conditions, such as physical exercise and dehydration (20). The preoperative importance of lymphocyte percentage/count, platelet-lymphocyte ratio (PLR), and NLR as prognostic predictors have been widely proposed in cardiovascular surgery, cerebrovascular accidents (CVA), and cancers (22). Some studies on postoperative spinal surgery outcomes reported the usefulness of the aforementioned parameters in detecting the development of SSI following surgery. Iwata *et al.* showed that a lymphocyte count of <1,000/μL at postoperative day 4 is significantly related to SSI occurrence in patients undergoing posterior lumbar instrumentation surgery (23). In this systematic review, we aimed to evaluate the effects of preoperative and postoperative laboratory markers including NLR and PLR in the early detection of SSI in patients who go through spine surgery. We present this article in accordance with the PRISMA reporting checklist (available at https://jss.amegroups.com/article/view/10.21037/jss-24-106/rc).

Material and methods

Search strategy and study selection

The study design adhered to the PRISMA reporting guidelines (24), and the study plan, including inclusion criteria, was registered in PROSPERO (CRD42023439591). A comprehensive literature search was conducted across MEDLINE, Web of Science, Embase and Scopus databases to identify relevant publications from the database inception to July 1st 2024. The search strategy involved the use of specific keywords neutrophil OR lymphocyte OR neutrophil to lymphocyte ratio OR white blood cell differential AND spine OR lumbar spine OR spine injury OR vertebra OR surgery AND SSI. The search was limited to English-language papers. Furthermore, the reference lists of identified articles and the "related articles" feature on PubMed were employed to locate additional relevant studies. Initially, two authors independently screened the titles and abstracts of the retrieved articles. Subsequently, the full texts of potentially eligible studies were reviewed by the same two authors. Any discrepancies arising during both stages were resolved by a third independent author.

Criteria for inclusion and exclusion

We identified eligible literature based on the PICOS (population, intervention, control, outcomes, and study design) (25) principle to ensure a systematic search. The inclusion criteria were as follows:

Population

The study population was defined as individuals undergoing spinal surgery. This included patients undergoing various types of spinal surgeries such as lumbar spine surgery, vertebra surgery, and other spinal procedures.

Intervention

Studies obtaining NLR data from individuals undergoing spinal surgery.

Control

Studies comparing NLR data from individuals undergoing spinal surgery with those who did not develop SSIs versus those who did. Only studies comparing these two groups were included.

Outcomes

The primary outcome was the diagnostic role of NLR in predicting SSIs following spinal surgery.

Studies

Cohort, cross-sectional, and case-control studies were included for analysis.

The criteria for exclusion were as follows: (I) studies with duplicate data; (II) animal studies, letters to editors, reviews, case series, and case reports.

The quality of all literature was evaluated by two researchers using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) (26), which is composed of patient selection, index test, reference standard, and flow and timing.

Data synthesis

Microsoft Excel (Microsoft Corp., USA) was used to extract data. Simple descriptive synthesis was undertaken. Meta-analysis was planned to be undertaken to assess the overall predictability of NLR as detailed in our PROSPERO-registered protocol. However, we couldn't proceed because

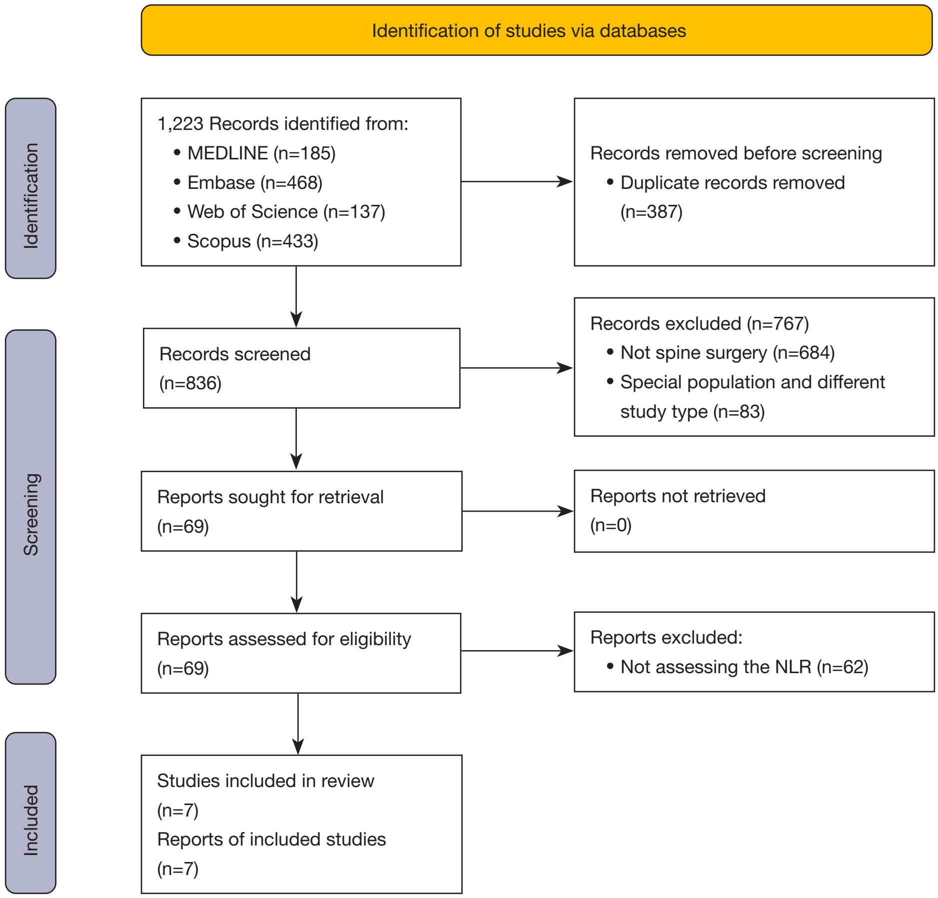

Figure 1 Flow diagram for new systematic reviews which includes searches of databases, registers, and other sources (24).

we didn't have consistent data outcomes to create the necessary subgroups for the meta-analysis.

Results

The flow-diagram (*Figure 1*) shows study identification, inclusion, and exclusion process. Our search process in 4 databases resulted in 1,223 articles, of which 836 were included in the title and abstract screening after removing duplicates. After that, full-text screening was done on a total of 69 articles, which resulted in 7 articles that were eligible for the final systematic review (22,27-32); 5 studies were identified from citation searching which was overlooked due to duplication (27-31). All studies were retrospective in design, with sample sizes ranging from 77 (22) to 1,467 (32) patients. The studies were published between 2019 and 2024.

SSI incidence rates varied across studies, ranging from 2.7% (27) to 13% (22). The details of each study have been summarized in *Table 1*. Most studies used a combination of clinical signs, laboratory tests, and microbiological cultures for SSI diagnosis (*Table 2*). Treatment methods generally included debridement, antibiotic therapy, and in some cases, replacement of instrumentation.

All studies found NLR to be a significant predictor of SSI, but the optimal cut-off values and timing of measurement varied. Our included studies demonstrated significant differences in postoperative NLR between SSI and non-SSI groups in patients undergoing spinal surgery. Shen *et al.* (29) found that the medians of NLR were markedly increased in the SSI group compared to the non-SSI group at 4 and 7 days post-operation. By assessing the area under the curve (AUC) their study showed that NLR at 4 days (cut-off >5.19; sensitivity: 61.5%; specificity: 77.6%; AUC =0.708) and 7 days (cut-off >3.85; sensitivity: 69.2%; specificity: 62.7%; AUC =0.663) post-operation could significantly discriminate between the SSI and non-SSI groups. Both included studies by Inose *et al.* (30,31)

Table 1 Study characteristics

Author (year)	Study objective	Design	Country	Surgical setting	Number of patients	Patients developing SSI [female]	Sampling times and timespan	Prevalence (%)	Exclusion criteria
Shen *et al.* 2019 (29)	Predictive value of postoperative NLR for SSI in posterior lumbar spinal surgery	Retrospective	China	Posterior lumbar spinal surgery	293	13 [5]	1 week before operation, 4 and 7 days post-operation	4.40	Existing infection, trauma, chronic inflammatory disease, and previous lumbar spine surgery
Kobayashi *et al.* 2020 (28)	BMI and mGPS as predictors of SSI after spinal instrumentation surgery	Retrospective observational	Japan	Spinal instrumentation surgery	384	14 [8]	3 m preoperative and 12 m postoperatively	3.60	Infection at time of operation and renal failure
Imabayashi *et al.* 2022 (27)	Establish a combination of serological markers to diagnose SSI following spine surgery	Retrospective	Japan	Spine surgery (excluding infectious spondylitis)	329	9 [3]	Preoperative, 2 and 7 days post-operation	2.70	Unplanned antimicrobial use and missing serological data
Osunronbi *et al.* 2022 (22)	Preoperative lymphocyte percentage and NLR as predictors of 30-day postoperative complications	Retrospective	United Kingdom	Lumbar fusion (one- or two-level)	77	3 [NR]	Preoperative	13	Previous lumbar spine surgery, three or more level fusion, hematological disorders, and emergency cases
Inose *et al.* (instrumentation study) 2019 (31)	Procalcitonin and NLR after spinal instrumentation surgery	Retrospective observational	Japan	Spinal instrumentation surgery	242	10 [6]	6 to 7 days postoperatively	4.10	Spinal infectious diseases, other sources of infection, decreased renal function, and preoperative CRP >2
Inose *et al.* (decompression study) 2020 (30)	Postoperative lymphocyte percentage and NLR as early predictors of SSI in spinal decompression surgery	Retrospective observational	Japan	Spinal decompression surgery	254	7 [0]	1, 3–4, and 6–7 days postoperatively	2.80	Spinal infectious diseases and other sources of infection
Ge *et al.* 2024 (32)	diagnostic model for predicting early SSI based on postoperative inflammatory markers	Retrospective cohort	China	Posterior spinal fusion surgery	Reviewed: 1,467; included: 344	Reviewed: 145; included: 91	10 consecutive days postoperative	9.8	Postoperative pneumonia, other sources of infection and inflammatory disease

SSI, surgical site infection; NLR, neutrophil-lymphocyte ratio; BMI, body mass index; mGPS, modified Glasgow Prognostic Score; CRP, C-reactive protein; NR, not reported.

Table 2 Summary of the studies evaluating NLR as predictor factor for SSI

Author (year)	SSI diagnosis method	Age (years)†	Sex (female %)	Majority of culture results	Method of treatment	Method of statistical analysis of risk	Reported mean or ROC for NLR
Shen *et al.*, 2019 (29)	According to U.S. Centers for Disease Control and Prevention criteria; confirmed when surgeon diagnosed deep SSI, conducted debridement, and had positive microbiological culture	SSI: 62 [44–72]; non-SSI: 61 [34–98]	SSI: 38.46%; non-SSI: 48.57%	*Staphylococcus epidermidis* (n=4)	Debridement	ROC curve analysis, logistic regression	AUC for 4 days postoperative NLR: 0.708; AUC for 7 days postoperative NLR: 0.663
Kobayashi *et al.*, 2020 (28)	According to medical records: debridement (n=11), MRI (n=2), blood culture (n=1)	SSI: 72.9; non-SSI group: 66.9	SSI: 57.1%; non-SSI: 58.9%	*Staphylococcus aureus* (n=5)	Debridement in 10 patients, replacement of instrumentation in 4 cases	Univariate analysis, multivariate logistic regression	No ROC reported for NLR, mean (SD) SSI: 4.1 (2.6) non-SSI: 2.6 (1.8)
Imabayashi *et al.*, 2022 (27)	According to the Centers for Disease Control and Prevention criteria; need for debridement, blood cultures positive for infectious agents, or drainage of the surgical wound	SSI: 77; non-SSI: 68	SSI: 33.3%; non-SSI: 47.8%	Not reported	Not reported	ROC curve analysis	AUC for NLR on postoperative day 7: 0.768, but included in best combination‡ with AUC 0.946
Osunronbi *et al.*, 2022 (22)	Not reported	SSI: 48.2±19.1; non-SSI: 55.5±13.6	SSI: 50%; non-SSI: 58.2%	Not reported	Not reported	ROC curve analysis	AUC for postoperative 30-day NLR: 0.720, mean±SD: 2.76±2.57
Inose *et al.*, 2019 (31)	According to the Centers for Disease Control definition; confirmed by reoperation or by histopathological or radiological investigation	SSI: 75.3; non-SSI: 68	SSI: 60%; non-SSI: 68.1%	*Staphylococcus aureus* (n=3)	Debridement in 7 patients, replacement of instrumentation in 3 cases	Univariate analysis, ROC analysis	AUC for NLR at 6–7 days postoperatively: 0.688
Inose *et al.*, 2020 (30)	According to U.S. Centers for Disease Control and Prevention criteria; confirmed when surgeon diagnosed deep SSI, conducted debridement, and had positive microbiological culture	SSI: 66.7; non-SSI: 65.8	SSI: 0%; non-SSI: 35.6%	MSSA (n=2)	Debridement and antibiotics (n=5), only antibiotics in (n=2)	Univariate analysis, ROC analysis	AUC for NLR at 3–4 days postoperatively: 0.748; AUC for NLR at 6–7 days postoperatively: 0.800
Ge *et al.*, 2024 (32)	Combination of clinical signs, laboratory tests, and microbiological cultures	SSI: 56 [45–66]; non-SSI: 54 [42–62]	SSI: 64%; non-SSI: 55.7%	Not reported	Not reported	Stepwise logistic regression, ROC analysis	AUC for NLR on 7 days postoperatively: 0.909

†, data are presented as median (range), mean ± SD or median. ‡, AUC of 0.946 comprising the least number of markers (4 markers) included neutrophil count, NLRRp7, LR27, and CR27. NLR, neutrophil-to-lymphocyte ratio; SSI, surgical site infection; ROC, receiver operating characteristic; AUC, area under the curve; MRI, magnetic resonance imaging; SD, standard deviation; MSSA, methicillin-sensitive Staphylococcus aureus; NLRRp7, NLR from preoperative day to postoperative day 7; LR27, lymphocyte count ratio from postoperative days 2 and 7; CR27, C-reactive protein ratio from postoperative days 2 and 7.

reported that NLR at 6 to 7 days postoperatively had different cut-off value (3.87 for decompression surgery and 3.21 for spinal instrumentation surgery). Instrumentation surgery also showed predictive NLR for 3–4 days post operation with cut-off of 4.91. Kobayashi *et al.* (28) focused on preoperative factors and found that while NLR was a significant factor in univariate analysis, it was not an independent risk factor in their multivariate analysis. Osunronbi *et al.* (22) investigated preoperative NLR and found that a value ≥2.32 significantly discriminated between the "complication" and "no-complication" groups. They noted that a unit increase in preoperative NLR was associated with a 23% increase in the odds of a complication occurring within 30 days after lumbar fusion. Imabayashi *et al.* (27) developed a more comprehensive SSI scoring system that combined four markers; neutrophil count, NLR, lymphocyte count ratio, and CRP. This combination showed high accuracy with an AUC of 0.95, suggesting that NLR in combination with other markers may provide better predictive power than NLR alone. Ge *et al.* (32) created a prediction model that included neutrophil counts on the seventh day after surgery, along with other factors such as body temperature, CRP, and erythrocyte sedimentation rate (ESR). Their model achieved high predictive accuracy. They reviewed data of 1,467 patients with the prevalence of 9.9% (145 patients) but after applying inclusion and exclusion criteria they included 344 patients with 91 SSI patients. Shen *et al.* (29) reported significant differences in NLR at 4 and 7 days post-operation between SSI and non-SSI groups with cut-off values of >5.19 and >3.85.

Several studies identified additional predictors of SSI, including CRP levels, lymphocyte percentage, and body mass index (BMI) (*Table 1*). Kobayashi *et al.* (28) found that modified Glasgow Prognostic Score (mGPS) and BMI were independent risk factors for SSI. Imabayashi *et al.* (27) found that CRP ratio from postoperative days 2–7 improved SSI prediction when combined with other markers. Ge *et al.* (32) included WBC count in their predictive model for SSI. Shen *et al.* (29) found significantly higher ESR in the SSI group at 4 days post-operation. Inose *et al.* (31) found prolactin was not a reliable predictor for early SSI diagnosis after spinal instrumentation surgery.

More than half of the studies (4 out of 7, 57%) (*Figure 2*) lacked sufficient details to confirm using an appropriate patient selection method. The risk of bias due to patient selection was low in 43% of the studies (3 out of 7) (22,30,32). Concerns about patient selection applicability were rated as low in all studies (7 out of 7). The index test details were unclear in the majority of studies (5 out of 7, 71%). Thus, the risk of bias related to the index test was low in only 29% of the studies (2 out of 7) [Kobayashi *et al.* (28), Imabayashi *et al.* (27)]. However, all included studies (7 out of 7) were judged to have low concerns regarding the applicability of the index test. In all studies, researchers assessed the reference standard appropriately. Consequently, the risk of bias due to the reference standard was low in 100% of the studies. All studies had low concerns regarding the applicability of the reference standard. The flow and timing were appropriate in 86% of the studies (6 out of 7). Accordingly, 86% of the studies had low bias risk in the flow and timing domain (22,27-31). Reviewers' judgments about each domain's risk of bias and applicability concerns for each included study are presented in *Figure 2*. The assessment determined whether each included study has low, high, or unclear risks concerning patient selection, index test, reference standard, flow, and timing. Additionally, an analysis of applicability concerns was incorporated, showing low concerns across all domains for all studies.

Discussion

Our study denoted that the postoperative NLR showed a significant increase in the SSI group in comparison to patients who did not develop SSI, in subjects going through spinal surgery, indicating that NLR could serve as an early infection predictor in the spine operation setting.

Included studies consistently demonstrate an association between elevated NLR and increased risk of SSI. Shen *et al.* (29) and Imabayashi *et al.* (27) found significant NLR differences between SSI and non-SSI groups at 7 days post-operation, with cut-off values of 3.85 and 4.5, respectively. Osunronbi *et al.* (22) identified a preoperative NLR cut-off of ≥2.32 as predictive of complications. Inose *et al.*'s studies (30,31) reported NLR cut-offs of ≥3.87 and 3.21 at 6–7 days postoperatively, and 4.91 at 3–4 days. Ge *et al.* (32) included NLR in a prediction model for SSI, showing high accuracy (AUC 0.909) on the seventh postoperative day. The variability in cut-off values for NLR across studies likely stems from differences in study design, patient populations, timing of NLR measurements, and clinical criteria for diagnosing SSI.

Immediately following the surgical invasion, the production of pro-inflammatory cytokines is triggered through a physiological stress response, leading to an increase in neutrophil counts (33-35). In addition, the release of anti-inflammatory cytokines including interleukin-10

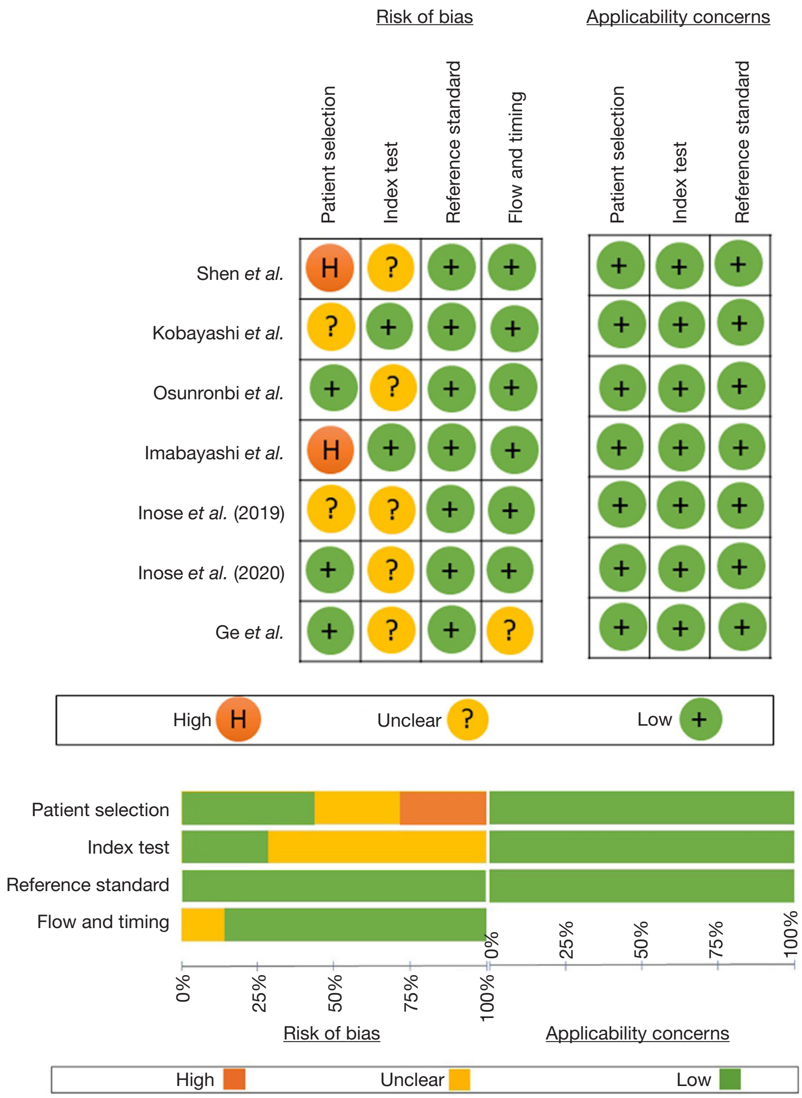

Figure 2 The QUADAS-2 score assesses the risk of bias (22,27-32).

and cytokine antagonists is also induced during the stress condition, providing an immunodeficient state, which leads to lymphocyte number reduction due to accelerated cellular apoptosis (34,35). Takahashi *et al.* discovered that in patients with desirable postoperative conditions, the neutrophil counts start to decline, and the lymphocyte counts rise on postoperative day 4, reaching the pre-operative levels after three weeks (12).

Immune response in infection consists of two major reactions including innate and adaptive response (36-40). Innate response as the first phase of the immune response recruits neutrophils as the main effector cells in systemic inflammatory response (SIRS) to produce pro-inflammatory and immunomodulatory cytokines and chemokines, igniting the following cascade (41,42). In a stable state, the half-life of neutrophils is short and determined by apoptosis (43,44). During inflammatory states, the apoptosis of neutrophils is inhibited, leading to a heightened neutrophil lifespan which is associated with an increase in neutrophil migration to the injured areas (43,45). Conversely, septic conditions accelerate the apoptosis of lymphocytes and instill lymphocytic migration into the liver, spleen, and lymphatic system by modifying their distribution (36,43,46). Thus, infectious states after surgical treatment involve an increase in neutrophils and a decrease in lymphocyte counts owing to immunomodulation, which is determined by higher neutrophil activation and lymphocyte redistribution (41,47-49), leading to a higher post-surgical neutrophil to lymphocyte ratio in patients who develop postoperative infection. Regarding this, the previous studies suggested that a re-elevation of neutrophils and reduced lymphocyte numbers after postoperative day 4 could be a potential sign of post-surgical infection (16). Takahashi *et al.* highlighted that a spontaneous recent increase in WBC counts including the neutrophils, as well as the neutrophil percentage >75% following the postoperative days 4 to 7, could indicate the beginning of an infectious process (12,16). However, Takahashi *et al.* found a significantly decreased lymphocyte number after postoperative day 4, suggesting that postoperative lymphopenia (not more than 10% or 1,000/μL) can be an indicator of SSI (34).

It has been proposed that regarding the concomitant changes of neutrophils and lymphocytes during sepsis, using NLR as an identifier that combined these two parameters, has a higher predictive value in SSI diagnosis than neutrophil counts or lymphocytes alone (50). Goodman and colleagues reported NLR as a more sensitive indicator than the total WBC counts in predicting appendicitis (51). The neutrophil-to-lymphocyte ratio is an approved predictor for infection development, disease severity, and mortality (52). However, the normal range of the index is still debated (52). Liang *et al.* reported the reference value for NLR, spanning between 0.88 to 4.0, disregarding age and sex (53). Domagalska *et al.* considered the NLR values above 3.0 as pathologic, associated with conditions like infection, inflammation, stress, and cancer (52).

Zahorec *et al.* in a prospective observational study displayed a marked neutrophilia and lymphocytopenia in critically ill patients with severe sepsis and septic shock admitted to the intensive care unit (ICU). They also stated a significant association between NLR values and the severity of the disease in the mentioned population (54).

De Jager and colleagues observed a significantly higher NLR and lower postoperative lymphocyte counts in emergency-admitted patients with positive blood cultures compared to the negative blood culture group (55), which was in the same direction as our finding in this quantitative analysis.

Zhao *et al.* performed a retrospective analysis on patients undergoing total joint arthroplasty to evaluate the difference in NLR, PLR, and lymphocyte-to-monocyte ratio in those who develop primary periprosthetic joint infection (PJI) compared to non-PJI group. The study revealed significantly increased NLR and PLR values in the PJI group than in non-PJIs, which was consistent with our analysis results. The authors also discern that NLR had the highest predictive probability among other parameters, with a cut-off value of 2.7 (56).

While our analysis focused primarily on NLR, it's important to consider how this marker compares to other predictors. Kobayashi *et al.* (28) found that the mGPS, with a cut-off value of 1, had an AUC of 0.74 for predicting SSI, making it a valuable marker. Additionally, the BMI cut-off of 20.39 yielded an AUC of 0.76, further supporting the relevance of nutritional status in infection risk. However the study lacks further justification to this matter and points out that further investigation must be made to make definite decisions. The context around BMI has also been inconsistent but the overall meta-analysis has shown BMI-defined obesity to be a risk factor associated with postoperative spine surgery SSI (57,58).

Lymphocyte percentage has also emerged as a significant predictor. Inose *et al.* (30) reported an AUC of 0.847 for lymphocyte percentage at 6–7 days post-op, which was higher than the AUC for NLR (0.800) in the same study. Osunronbi *et al.* (22) found that patients with a preoperative lymphocyte percentage ≤29.5% had 13.9 times greater odds of postoperative complications, including SSI. Also, Shen *et al.* (29) demonstrated that neutrophil percentage at 4 days post-op had an AUC of 0.713, comparable to that of NLR. Imabayashi *et al.* (27) found that CRP at 7 days post-op had the highest AUC of 0.83, outperforming NLR in their study.

When comparing the performance of other factors to NLR in predicting SSI, we see that NLR generally performs well but is not always the best predictor. CRP, neutrophil percentage, and lymphocyte percentage often showed similar or sometimes better predictive ability. For instance, in the Imabayashi study, CRP had the highest AUC (0.83) at 7 days post-op (27). However, NLR consistently appeared as a significant predictor across studies and was often included in final predictive models, suggesting its reliability as a marker for SSI prediction. The combination of NLR with other markers, particularly CRP and neutrophil/lymphocyte percentages, seems to provide the most robust predictive power for SSI after spinal surgery. CRP being one of the first inflammatory predictors has been shown to predict the chances of infection but CRP could be affected by other factors like surgical circumstances and is dependent on the surgery type (15,23,59).

To the best of our knowledge, our study was the first systematic review that investigated the association between WBC differential counts and developing SSI following spinal surgery. Even though, our study has several limitations that are important to address. Firstly, the number of included studies was small, which could affect the strength of our quantitative analysis. Further studies would warrant the reliability of our estimated results. Secondly, the heterogeneity of the included studies was high regarding the type of spinal surgery. However, the subgroup analysis based on surgery type was unable to be conducted owing to the restricted number of relevant studies. Additionally, the lack of a meta-analysis limits our ability to provide a quantitative synthesis of the data, which could have offered more robust conclusions. Furthermore, the variability in NLR cut-off values and measurement timings across studies makes it challenging to establish a standardized threshold for clinical application.

Conclusions

This systematic review highlights the predictive value of the NLR for early detection of SSI in patients undergoing various types of spinal surgery. While NLR shows promise as a simple, accessible, and cost-effective inflammatory marker, variations in optimal cutoff values and timing post-surgery underline the need for standardized protocols. Combining NLR with additional markers, such as CRP, lymphocyte counts, and BMI, may enhance diagnostic accuracy and early identification of SSI. However, the variability across studies regarding cutoff thresholds and measurement timing suggests that further research is necessary to refine these parameters. Standardizing NLR monitoring as part of routine postoperative assessments, potentially alongside other predictive models, could lead to earlier intervention, reduce SSI-associated morbidity, and improve long-term patient outcomes following spinal surgery. This approach could minimize the healthcare burden associated with SSIs, supporting both improved patient care and cost efficiency within healthcare systems.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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