International Platform of Registered Systematic Review and Meta-analysis Protocols

INPLASY

Preoperative neutrophil-to-lymphocyte ratio and postoperative delirium after orthopaedic surgery: a systematic review with an exact randomization test

INPLASY2026110103
doi: 10.37766/inplasy2026.11.0103
Received: 25 November 2026
Published: 25 November 2026

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ADMINISTRATIVE INFORMATION

Support - No support.

Review stage at the time of initial registration - Completed but not published.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY2026110103

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 25 November 2026 and was last updated on 25 November 2026.

INTRODUCTION

Review question / Objective To evaluate the association between preoperative neutrophil-to-lymphocyte ratio (NLR) and postoperative delirium (POD) in patients undergoing orthopedic surgery by comparing preoperative NLR between patients who develop POD and those who do not. The review also aims to examine the consistency of this association across orthopedic surgical populations and consider potential confounding factors.

Rationale Delirium following orthopedic procedures is an important postoperative complication associated with poorer clinical outcomes. Inflammatory processes have been proposed as contributors to its development, raising interest in blood-based markers such as NLR. Although previous evidence has examined the relationship between NLR and POD across different surgical specialties, orthopedic patients have received relatively limited attention. A focused evaluation of this population is therefore needed to characterize the available evidence, examine differences across studies, and identify methodological limitations that may influence the reported associations.

Condition being studied The condition of interest is postoperative delirium following orthopedic surgery. Delirium is an acute disturbance of attention, awareness, and cognitive function that typically fluctuates over time. It can occur after various orthopedic procedures, including operations involving the hip, knee, and spine. Its occurrence has been linked to longer hospital stays, increased postoperative morbidity, and poorer patient outcomes.

METHODS

Search strategy "Neutrophil to lymphocyte ratio" OR NLR (All Fields) and "delirium" (All Fields) and "spine" OR "Hip" OR "Knee" OR "Fracture" OR "Arthroplasty" OR "orthopaedic" (All Fields).

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Participant or population Individuals undergoing orthopedic operations, including procedures involving the hip, knee, spine, or other musculoskeletal structures, with available information on preoperative NLR and the occurrence or absence of postoperative delirium.

Intervention The exposure of interest is preoperative NLR, a blood-derived inflammatory index calculated from neutrophil and lymphocyte counts. As this is a review of observational evidence, no therapeutic intervention is being evaluated.

Comparator The comparison involves orthopedic surgical patients who did not develop POD. Their preoperative NLR measurements are compared with those of patients who subsequently experienced POD.

Study designs to be included Observational studies.

Eligibility criteria Eligible publications were observational studies involving orthopedic surgical patients that provided preoperative NLR data separately for groups with and without POD. Studies were excluded if they were duplicate records, conference abstracts, or letters. Investigations that failed to exclude individuals with delirium before surgery were also considered ineligible. No limits were imposed on publication year or language.

Information sources Evidence was obtained through electronic searches of PubMed, Embase, Scopus, and Web of Science. Additional potentially relevant publications were identified by examining the bibliographies of retrieved articles.

Main outcome(s) The primary outcome was the association between preoperative NLR and subsequent POD among orthopedic surgery patients.

Additional outcome(s) An additional objective was to identify potential clinical and demographic covariates that may influence the association between preoperative NLR and postoperative delirium. By examining factors reported in the included studies, we aimed to highlight potential sources of confounding and identify variables that should be considered in future prospective studies to better clarify the independent association between NLR and POD.

Data management Two investigators independently evaluated retrieved records for eligibility and extracted relevant information from the included publications. Differences in their assessments were discussed with a third investigator until agreement was achieved. Extracted variables covered study design, demographic characteristics, surgical procedures, delirium assessment, and NLR measurements. Statistical computations were performed in Stata version 19.

Quality assessment / Risk of bias analysis Methodological quality was evaluated with the Newcastle–Ottawa Scale (NOS).

Strategy of data synthesis Preoperative NLR was compared between POD and non-POD groups in each study using ratios of arithmetic means. Missing means and standard deviations were estimated using the Luo and Wan methods. Study-specific estimates and 99% confidence intervals were calculated using generalized pivotal quantities and 999,999 Monte Carlo simulations, with $P < 0.01$ considered significant. An exact sign-flipping randomization test was used to assess the overall evidence of association. No pooled estimate was calculated due to potential confounding and inconsistent covariate adjustment across studies.

Subgroup analysis No subgroup analyses were undertaken.

Sensitivity analysis No separate sensitivity analyses were performed.

Language restriction Studies were considered regardless of the language in which they were published.

Country(ies) involved United States, Iran.

Other relevant information The review was reported in accordance with PRISMA guidance.

Keywords Neutrophil-to-lymphocyte ratio; NLR; Postoperative delirium; Orthopaedic, anaesthesia, randomisation.

Dissemination plans The results are intended for dissemination through publication in a peer-reviewed medical journal, making the findings accessible to clinicians, researchers, and others interested in perioperative care.

Contributions of each author

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