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General Versus Regional Anesthesia in Orthopedic Surgery: Effects on Neutrophil-Lymphocyte Ratio, Platelet-Lymphocyte Ratio, and Systemic Immune-Inflammation Index: A Systematic Review with Narrative Synthesis

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ABSTRACT:

Background: Neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and the newer systemic immune-inflammation index (SII = neutrophil × platelet / lymphocyte count) and systemic inflammation response index (SIRI = neutrophil × monocyte / lymphocyte count) are inexpensive, complete-blood-count-derived indices increasingly used to characterize the perioperative inflammatory response and to predict complications such as delirium, infection, and mortality in orthopedic patients. Anesthetic technique general anesthesia (GA) versus regional anesthesia (spinal, neuraxial, or peripheral nerve block, PNB) is a modifiable perioperative exposure that may independently shape these indices, separately from surgical trauma itself, and has already been studied extensively for its effect on hard clinical outcomes in orthopedic surgery.

Methods: MEDLINE/PubMed and general academic web search (search-engine mediated; institutional access to Embase, Scopus, Web of Science, and Cochrane CENTRAL was not available for this review) were searched for studies in adult patients undergoing orthopedic surgery that directly compared GA against a regional anesthesia technique and reported at least one of NLR, PLR, or SII/SIRI as a perioperative outcome. Risk of bias was assessed with Cochrane RoB 2 for the included randomized trial and the Newcastle-Ottawa Scale for the included retrospective/cohort studies. Given cross-study heterogeneity, biomarker findings were synthesized narratively rather than by pooled meta-analysis.

Results: Four studies met inclusion criteria for the biomarker synthesis, spanning upper-limb fracture/forearm surgery and total knee arthroplasty (TKA). Regional anesthesia was associated with a smaller postoperative rise in NLR in 2 of 3 studies reporting it, and with lower PLR in 1 of 3 studies reporting it. One large retrospective TKA cohort found anesthesia type to be an independent predictor of the change in SII, favoring spinal anesthesia. Risk-of-bias assessment found the included RCT at some concern (chiefly

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unclear allocation concealment) and the three retrospective cohorts at moderate-to-good quality on the Newcastle-Ottawa Scale, with confounding by indication (anesthesia type was not randomized in three of four studies) as the principal shared limitation. Mechanistic evidence from total hip arthroplasty, shoulder surgery, and older cytokine-based TKA studies is broadly consistent with an anti-inflammatory effect of regional anesthesia, though generally modest and often not statistically significant. This biomarker-level signal contrasts somewhat with the larger randomized and registry literature on anesthetic technique in orthopedic surgery, which has found little or no difference in hard outcomes such as postoperative delirium or 60-day mortality between spinal and general anesthesia in hip fracture surgery.

Conclusions: Active and recent evidence base suggests regional anesthesia may attenuate the postoperative rise in NLR and, in large cohort, SII, relative to general anesthesia in orthopedic surgery, without any study reporting the reverse. This biomarker-level signal is a laboratory finding, an established clinical benefit larger trials addressing hard outcomes have reached more conclusions.

1. INTRODUCTION

Orthopedic surgery whether elective joint arthroplasty or acute fracture fixation triggers a systemic inflammatory response driven by tissue injury, the neuroendocrine stress axis, and activation of circulating innate immune cells [1]. Complete-blood-count-derived ratios, particularly the neutrophil-lymphocyte ratio (NLR) and platelet-lymphocyte ratio (PLR), and more recently the systemic immune-inflammation index (SII, calculated as neutrophil × platelet / lymphocyte count) and systemic inflammation response index (SIRI, neutrophil × monocyte / lymphocyte count), have gained wide attention as inexpensive, routinely available surrogates for this response. SII was first introduced in 2014 by Hu et al. as a prognostic marker in resected hepatocellular carcinoma [2], and SIRI followed in 2016, introduced by Qi et al. in metastatic pancreatic cancer [3]; both have since been adopted well beyond oncology, including in orthopedic and perioperative research. Reference ranges for NLR in a healthy, non-geriatric adult population (approximately 0.78–3.53) have been established by Forget et al. [4], providing a baseline against which the perioperative rise reported throughout this literature can be interpreted.

In orthopedic trauma populations specifically, elevated NLR has been associated with postoperative delirium after hip fracture surgery [5], and NLR, PLR, and SII have each been linked to postoperative pneumonia, mortality risk scores, and overall surgical-trauma severity in hip fracture cohorts [6-9], which is what makes the magnitude of the perioperative NLR/PLR/SII rise clinically relevant rather than merely a laboratory curiosity.

Before narrowing to these specific biomarkers, it is worth situating anesthetic-technique choice within the broader clinical-outcome literature in orthopedic surgery, since that literature is what originally motivated interest in a biomarker-level mechanism. Regional anesthesia's comparative effectiveness for hip fracture surgery has been studied extensively at the registry level [10], and large randomized trials have since tested it directly: a pragmatic, multicenter trial by Neuman et al. found spinal and general anesthesia produced similar rates of death or inability to walk independently at 60 days in patients undergoing hip fracture surgery [11], a result the accompanying editorial framed as reassuring for the safety of either technique rather than as evidence against any role for anesthetic technique in more specific outcome domains [12]. The RAGA trial similarly found no significant reduction in postoperative delirium with regional versus general anesthesia in a Chinese hip fracture population, despite earlier observational signal suggesting a benefit [13]. A subsequent long-term-outcomes randomized trial [14] and a 2023 meta-analysis of randomized trials in elderly hip fracture patients [15] have continued to probe this question without settling it definitively. In elective total knee and hip arthroplasty, large national-registry studies have found spinal anesthesia associated with modestly lower complication and 90-day readmission rates than GA [16-18]. This registry-and-trial literature on hard clinical outcomes is distinct from, but provides essential context for, the narrower biomarker-level question this review addresses: even where large trials have not found anesthetic technique to change outcomes like delirium or mortality, it remains biologically plausible, and separately testable, that it shifts inexpensive laboratory surrogates of the inflammatory response — and that narrower question is this review's focus.

Mechanistically, general anesthesia (GA) exposes the patient to systemic hypnotic and opioid agents and to airway instrumentation, whereas regional techniques spinal/neuraxial anesthesia or peripheral nerve blocks (PNB) blunt afferent nociceptive transmission and avoid systemic hypnotic exposure. Several anesthetic and local-anesthetic agents have documented anti-inflammatory pharmacology independent of their sedative or analgesic effects [19], and regional techniques specifically have been proposed as a modifiable target for attenuating the perioperative inflammatory response through sympathetic blockade and reduced nociceptive afferent traffic [20], consistent with the broader literature on perioperative inflammation and its modulation by anesthetic choice [21]. Whether this translates into a measurably smaller rise in NLR, PLR, or SII the same inexpensive indices already used prognostically in orthopedic patients is a distinct and increasingly studied question from the depth-of-anesthesia-monitoring literature, which addresses titration within general anesthesia rather than the choice between general and regional technique. Beyond the GA-versus-regional distinction itself, the specific pharmacological composition of the GA arm propofol-based total intravenous anesthesia versus volatile-agent maintenance is increasingly recognized as its own modulator of postoperative NLR and related indices in other surgical contexts, a factor this review returns to in Section 4.2.

This review frames anesthetic technique (GA vs. regional anesthesia) in adult orthopedic surgery as the exposure of interest and NLR, PLR, and SII/SIRI as the outcomes, synthesizing the currently available comparative literature, formally assessing its risk of bias, and situating it against the broader trial and registry evidence on anesthetic technique in orthopedic surgery. It does not address depth-of-anesthesia monitoring within general anesthesia, which has been addressed elsewhere; it is scoped specifically to the anesthesia-modality question and to these blood-count-derived indices, consistent with their growing use as low-cost prognostic tools in orthopedic patients.

2. MATERIALS AND METHODS

2.1. Protocol

This review follows the general reporting structure of PRISMA 2020, including a flow diagram (Figure 1) and a formal risk-of-bias assessment (Section 2.4). It should be read as a single-reviewer, search-engine-mediated review rather than a full multi-database, dual-reviewer systematic review; Section 2.3 states this scope explicitly, and its implications are carried through the Results and Limitations.

2.2. Eligibility Criteria

Eligibility was defined using a PECO (Population, Exposure, Comparator, Outcome) framework, summarized in Table 1.

Table 1. PECO framework defining eligibility for the primary biomarker synthesis.

Element	Definition used in this review
Population	Adults (≥18 years) undergoing orthopedic surgery: elective joint arthroplasty or fracture/trauma fixation of any anatomic site
Exposure	General anesthesia (GA)
Comparator	Regional anesthesia — spinal/neuraxial anesthesia or peripheral nerve block (PNB)
Outcome	At least one of: neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), systemic inflammation response index (SIRI), measured perioperatively
Study designs eligible	Randomized controlled trials; prospective or retrospective comparative cohort studies
Exclusions	Pediatric populations; non-orthopedic surgical populations; case reports; animal studies; studies comparing two regional techniques without a GA arm; studies reporting only cytokine/CRP/DAMP outcomes with no NLR/PLR/SII/SIRI; retracted publications

Studies meeting the population and exposure/comparator criteria but reporting only cytokine, CRP, or DAMP outcomes (no NLR/PLR/SII/SIRI) were excluded from the primary synthesis but retained for mechanistic discussion where explicitly marked as such (Section 3.4). Separately, large randomized trials, meta-analyses, and national-registry studies addressing anesthetic technique and hard clinical outcomes (delirium, mortality, complications, readmission) in orthopedic surgery were reviewed narratively to provide background and discussion context; these were not required to meet the PECO criteria in Table 1 and are clearly distinguished from the primary synthesis throughout.

2.3. Search Strategy and Its Limits

Searches were run iteratively against PubMed/MEDLINE and general academic web search using combinations of terms for anesthesia technique ("general anesthesia," "spinal anesthesia," "regional anesthesia," "peripheral nerve block," "brachial plexus block," "interscalene block") and blood-count-derived inflammatory indices ("neutrophil-lymphocyte ratio," "NLR," "platelet-lymphocyte ratio," "PLR," "systemic immune-inflammation index," "SII," "SIRI"), combined with orthopedic/perioperative terms ("total knee arthroplasty," "total hip arthroplasty," "fracture surgery," "orthopedic trauma," "shoulder surgery"). A separate set of searches using terms for clinical outcomes ("delirium," "mortality," "complication," "readmission") combined with anesthesia-technique terms was used to identify the broader trial and registry literature discussed in Sections 1 and 4. Reference lists of included and closely related studies were hand-searched (citation chaining). This review did not have institutional access to Embase, Scopus, Web of Science, or Cochrane CENTRAL, and screening, eligibility assessment, and risk-of-bias judgments were performed by a single reviewer without a second independent assessor for consensus. This is disclosed here, rather than only in the Limitations, because it materially affects how confidently the completeness of the evidence base and the precision of the risk-of-bias judgments in Section 3 should be read.

2.4. Risk-of-Bias Assessment

The single included randomized controlled trial [28] was assessed with the Cochrane Risk of Bias 2 (RoB 2) tool across its five domains: the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result, each rated as low risk, some concerns, or high risk, with an overall judgment derived from the highest level of concern across domains. The three included retrospective/cohort studies [27,29,30] were assessed with the Newcastle-Ottawa Scale (NOS), which scores selection (up to 4 stars), comparability (up to 2 stars), and outcome (up to 3 stars) for a maximum of 9 stars, with higher scores indicating lower risk of bias. Both tools were applied by a single reviewer based on published methods sections and abstracts; full-text re-verification and a second independent assessor would be needed to finalize these judgments to publication standard, as noted in the Limitations.

2.5. Data Synthesis

Given heterogeneity across surgical sites (upper-limb fracture vs. lower-limb arthroplasty), regional technique (PNB vs. spinal), and biomarker sampling timepoints, and because not every source publication reported extractable effect sizes for every index, biomarker findings were synthesized narratively by direction and statistical significance of effect per biomarker rather than by pooled meta-analysis. This is a deliberate, disclosed choice.

3. RESULTS

3.1. Search Results and Study Characteristics

Four studies directly comparing general anesthesia against a regional anesthesia technique and reporting NLR, PLR, and/or SII/SIRI met inclusion criteria for the primary synthesis: two in upper-limb fracture/forearm surgery comparing GA against peripheral nerve block, and two in total knee arthroplasty (TKA) comparing GA against spinal anesthesia. One additional total hip arthroplasty (THA) study directly compared GA against spinal anesthesia but reported ex vivo cytokine production and plasma danger-associated molecular patterns (DAMPs) rather than NLR/PLR/SII, and is retained for mechanistic context only (Section 3.4). Figure 1 summarizes the approximate identification and screening flow.

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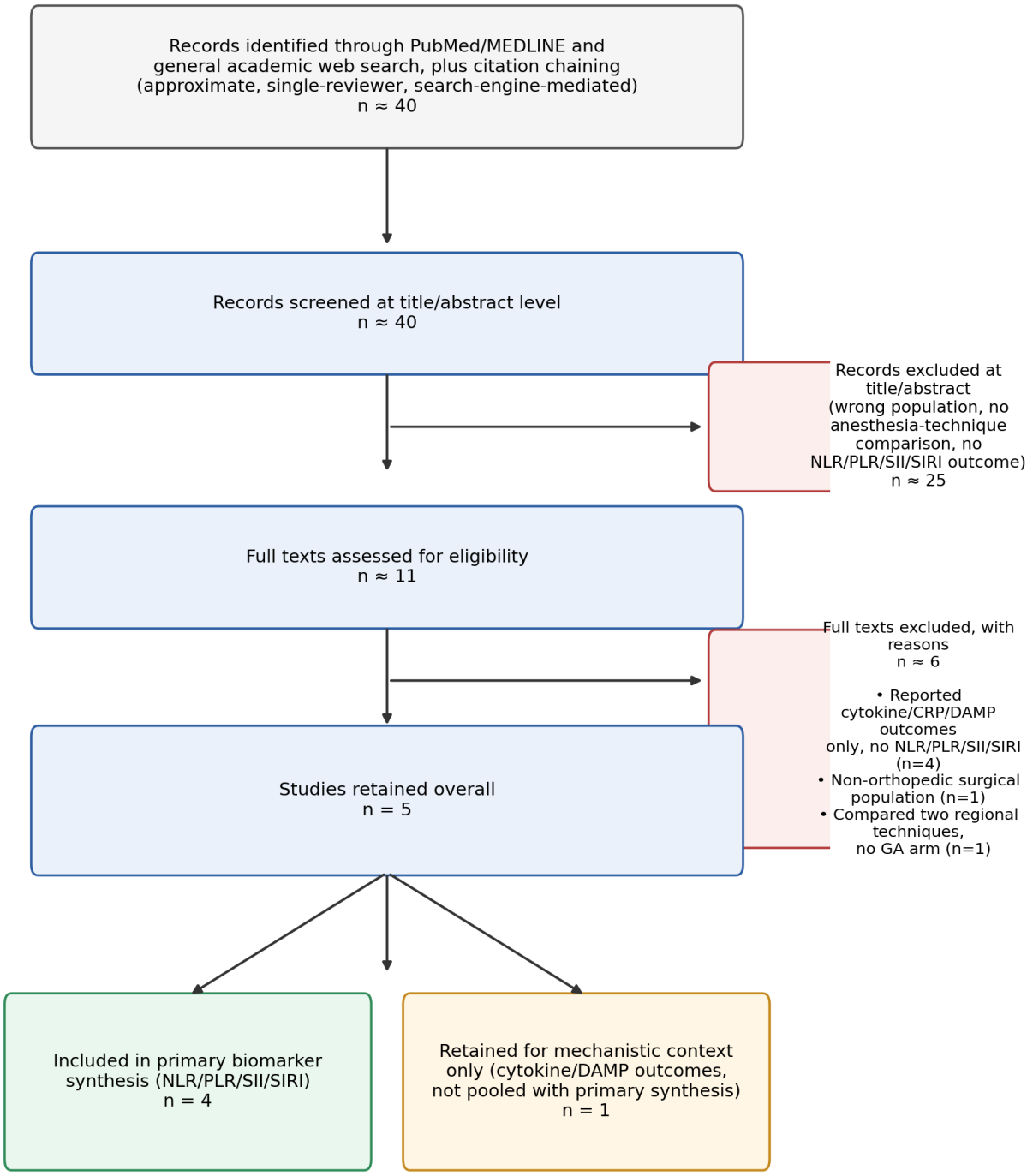

Figure 1. PRISMA 2020-style flow diagram of the approximate, single-reviewer, search-engine-mediated identification and screening process (see Section 2.3).

Table 2. Characteristics and key findings of the four studies included in the primary biomarker synthesis.

Study	Design	Population/Surgery	Comparison	Indices Reported	Key Finding
Köksal et al., Medicine (Baltimore), 2024 [27]	Retrospective (n=157)	Adult, forearm (trauma) surgery	General anesthesia vs. infraclavicular peripheral nerve block	NLR, PLR, TLC, MPV	PNB associated with significantly lower postoperative NLR, TLC, and PLR than GA
Shukla et al., Cureus, 2025 [28]	RCT (n=50)	Adult, upper-limb fracture surgery	General anesthesia vs. brachial plexus block	Neutrophil count, NLR, PLR	GA associated with significantly higher neutrophil count and NLR than BPB; PLR numerically lower in GA but not statistically significant
Kim et al., Medicina, 2021 [29]	Retrospective, propensity-matched (n=1311)	Elderly, total knee arthroplasty	General anesthesia vs. spinal anesthesia	CRP, NLR, PLR	Spinal anesthesia associated with significantly lower maximal CRP and CRP change than GA; no significant difference in NLR or PLR between groups
Genç et al., BMC Anesthesiol, 2025 [30]	Retrospective (n=849)	Adult, total knee arthroplasty	General anesthesia vs. spinal anesthesia	NLR, PLR, SII, SIRI	Both groups showed significant pre-to-postoperative rises in all four indices; anesthesia type was an independent predictor of the magnitude of SII change, with GA showing a significantly greater ΔSII than spinal anesthesia

3.2. Risk-of-Bias Findings

Randomized trial (RoB 2). Shukla et al. [28] was judged overall "some concerns." The randomization process was rated some concerns: the trial was registered prospectively (CTRI/2024/03/064439) with a pre-calculated sample size based on NLR as the primary outcome, but the method of allocation concealment was not confirmed from the available text. Deviations from intended interventions were rated low risk: the trial was open label (anesthesia type cannot practically be blinded), but the outcome is an objective laboratory value unlikely to be influenced by lack of blinding of participants or clinicians. Missing outcome data was rated some concerns, as completeness of follow-up across all four sampling timepoints could not be confirmed from the available text. Measurement of the outcome was rated low risk, being an objective, assay-based laboratory measurement. Selection of the reported result was rated low risk, as NLR was the prospectively registered primary outcome and neutrophil count and PLR were reported as prespecified secondary outcomes.

Table 3. Cochrane RoB 2 domain-level judgments for the one included randomized controlled trial [28].

Domain	Judgment	Basis
Randomization process	Some concerns	Prospectively registered, sample size pre-calculated; allocation concealment method not confirmed

Domain	Judgment	Basis
Deviations from intended interventions	Low risk	Open label by necessity (anesthesia type); outcome is objective and unlikely to be affected
Missing outcome data	Some concerns	Completeness of follow-up across all timepoints not confirmed from available text
Measurement of the outcome	Low risk	Objective, assay-based complete blood count parameters
Selection of the reported result	Low risk	NLR was the prespecified primary outcome; PLR/neutrophil count prespecified secondary outcomes
Overall	Some concerns	Driven by unconfirmed allocation concealment and missing-data reporting

Retrospective/cohort studies (Newcastle-Ottawa Scale). Kim et al. [29] scored highest (8/9) of the three retrospective cohorts, reflecting its use of propensity score matching to control for baseline confounding between anesthesia groups the strongest comparability control among the included cohort studies. Genç et al. [30] scored 7/9: exposure and outcome ascertainment were secure and objective, but comparability relied on multivariate adjustment for selected confounders (including ischemic heart disease) rather than matching, and patients with incomplete laboratory data were excluded, a possible source of selection bias. Köksal et al. [27] scored lowest (6/9): selection and outcome domains were adequately met, but no adjustment or matching for baseline confounders (age, comorbidity, surgery duration) was reported, and loss to follow-up in this retrospective chart-review design was not clearly quantified.

Table 4. Newcastle-Ottawa Scale scores for the three included retrospective/cohort studies.

Study	Selection (/4)	Comparability (/2)	Outcome (/3)	Total (/9)	Principal limitation
Köksal et al., 2024 [27]	4	0	2	6	No adjustment/matching for confounders; unclear follow-up completeness
Kim et al., 2021 [29]	4	2	2	8	Unclear completeness of follow-up in bilateral/staged cases
Genç et al., 2025 [30]	4	1	2	7	Adjustment rather than matching; exclusion of incomplete-data patients

Across all four included studies, the principal shared risk-of-bias concern is confounding by indication: anesthesia type was not randomized in three of the four studies, and patient or anesthesiologist/surgeon preference plausibly correlated with baseline frailty, comorbidity, or inflammatory status in ways that could bias the observed NLR/PLR/SII differences in either direction. The one randomized trial [28] is the least susceptible to this specific bias but carries its own uncertainty around allocation concealment and missing-data reporting. No included study was rated high risk of bias overall, but none was rated low risk of bias overall either; the evidence base should be read as moderate-to-good quality with meaningful, disclosed uncertainty rather than as definitive.

3.3. Synthesis by Biomarker

Neutrophil-lymphocyte ratio (NLR). Three of the four included studies reported NLR. Two — the forearm-surgery cohort [27] and the upper-limb fracture RCT [28] — found a significantly smaller postoperative rise in NLR with regional anesthesia (peripheral nerve block) than with GA. The third, the propensity-matched TKA cohort [29], found no significant difference in maximal NLR or its perioperative change between spinal and general anesthesia. No included study found NLR to rise more under regional anesthesia than under GA.

Platelet-lymphocyte ratio (PLR). All four studies reported PLR. The forearm-surgery cohort [27] found significantly lower PLR with PNB than GA. The upper-limb fracture RCT [28] found PLR numerically lower in the GA group at most timepoints, but the between-group difference was not statistically significant the sole point in this literature where the numerical direction (though not significance) ran counter to the pattern seen elsewhere. The TKA cohort by Kim et al. [29] found no significant PLR difference between spinal and general anesthesia. Genç et al. [30] reported PLR alongside NLR, SII, and SIRI in their 849-patient cohort, with group-level comparisons shown graphically; the only index for which their multivariate analysis specifically identified anesthesia type as an independent predictor was SII (below).

Systemic immune-inflammation index (SII) and systemic inflammation response index (SIRI). Only Genç et al. [30] reported these newer indices. Both SII and SIRI rose significantly from preoperative to postoperative values in both anesthesia groups, reflecting the expected inflammatory response to TKA itself. In multivariate linear regression, anesthesia type emerged as a statistically significant independent predictor of the absolute change in SII (ΔSII), with general anesthesia associated with a significantly greater increase than spinal anesthesia. This is, to date, the only included study to test and report a formally adjusted association between anesthetic technique and one of these newer composite indices in orthopedic surgery.

C-reactive protein (CRP), reported as a secondary/comparator marker. Although outside the core NLR/PLR/SII scope, CRP was reported alongside the ratio-based indices in the TKA cohort by Kim et al. [29], where spinal anesthesia was associated with significantly lower maximal CRP and CRP change than GA. a finding not mirrored in that same study's NLR/PLR results, illustrating that these indices do not always move together within a single cohort.

3.4. Mechanistic Context

Several additional lines of evidence, using cytokine, DAMP, or acute-phase measurements rather than NLR/PLR/SII, reinforce the plausibility of an anesthesia-technique effect without directly extending the biomarker synthesis above. In a matched cohort derived from two randomized-controlled trials in total hip arthroplasty, Jacobs et al. [26] found that GA transiently suppressed ex vivo interleukin-1β production capacity shortly after induction and at the end of surgery relative to spinal anesthesia, and was associated with higher plasma TNF and IL-10 at some timepoints; however, no differences in innate immune markers remained by postoperative day 1, and plasma DAMP concentrations did not differ between groups at all — the authors concluded the clinical significance of this transient effect was likely limited. In arthroscopic shoulder surgery, a randomized trial by Mejía-Terrazas et al. [22] found that an ultrasound-guided interscalene block was associated with a significantly smaller rise in erythrocyte sedimentation rate and CRP at 24 hours than balanced general anesthesia, alongside reduced opioid consumption and shorter hospital stay, extending the anatomic scope of this mechanistic evidence beyond the lower limb and TKA literature. Zura et al. [23], studying orthopedic arthroplasty patients, reported that postoperative release of the pro-inflammatory cytokine IL-6 was greater after general anesthesia than after spinal anesthesia. Earlier, smaller studies in TKA using classic cytokine panels (IL-6, IL-8, IL-1β, TNF-α, CRP) have shown a more mixed picture: Eroğlu et al. [24] found both GA and spinal anesthesia produced significant CRP and IL-6 rises by 24 hours, while Wang et al. [25], studying a smaller tumor-type TKA population, found no significant difference in CRP, TNF-α, or IL-8 between GA and spinal anesthesia at any timepoint. Taken together, the cytokine- and acute-phase-level literature is directionally consistent with, but statistically less uniform than, the more recent NLR/PLR/SII literature summarized in Section 3.3, which may reflect smaller sample sizes in the older studies, differing assay sensitivity, or a genuine difference in what these marker families capture.

4. DISCUSSION

4.1. Synthesis Across the Included Studies

This review positions anesthetic technique general versus regional as a modifiable exposure that may shape the same inexpensive, complete-blood-count-derived indices already used prognostically in orthopedic trauma and arthroplasty patients

[5-9]. Across the four studies meeting inclusion criteria, no study found regional anesthesia associated with a larger rise in NLR, PLR, or SII than general anesthesia; where a statistically significant difference was found, it consistently favored regional anesthesia (lower NLR and PLR with peripheral nerve block in upper-limb surgery [27,28]; lower ΔSII with spinal anesthesia in TKA [30]). At the same time, two of the four studies found no significant difference for at least one of these indices [28,29], the risk-of-bias assessment in Section 3.2 identified confounding by indication as a shared concern across the three non-randomized studies, and the evidence spans only two anatomic contexts upper-limb fracture surgery under peripheral nerve block, and TKA under spinal anesthesia leaving lower-limb fracture surgery, hip arthroplasty, and spine surgery entirely unstudied for this specific exposure-outcome pairing at the time of this search, despite each being well studied for NLR/PLR/SII as prognostic (rather than anesthesia-comparative) markers [5-9].

4.2. Mechanistic Account and the Role of the Specific Anesthetic Agent

A plausible mechanistic account, distinct from but complementary to the ratio-based findings, comes from the THA cohort of Jacobs et al. [26], the shoulder-surgery trial of Mejía-Terrazas et al. [22], and the orthopedic cytokine studies of Zura et al. [23], Eroğlu et al. [24], and Wang et al. [25]: general anesthesia was associated with a transient suppression or greater rise in various cytokine and acute-phase markers relative to regional anesthesia across several of these studies, though not all, and the THA cohort specifically found this did not persist to postoperative day 1 and was not accompanied by any measurable difference in circulating DAMPs. This is a useful caution against over-interpreting the NLR/PLR/SII differences reported in Section 3.3 as evidence of a large, clinically consequential immunomodulatory effect of anesthetic technique; it is equally consistent with a genuine but modest and largely self-limited perioperative effect that is nonetheless detectable in the specific ratio-based indices this review addresses, precisely because those indices are sensitive to the same neutrophil-mobilization and lymphocyte-redistribution changes that accompany sympathoadrenal activation under GA [1,20,21], and because local anesthetics and several general anesthetic agents themselves carry direct anti-inflammatory pharmacology [19].

A further layer of heterogeneity, orthogonal to the GA-versus-regional distinction this review is scoped to, is that "general anesthesia" is not pharmacologically uniform. Outside the orthopedic literature specifically, several recent studies have found that propofol-based total intravenous anesthesia (TIVA) is associated with a smaller postoperative rise in NLR than volatile-agent-based general anesthesia: in colorectal cancer surgery, propofol anesthesia produced significantly lower NLR than sevoflurane anesthesia at postoperative days 2 and 5 [32], and in radical prostatectomy, propofol-based TIVA was associated with a significantly lower absolute neutrophil count, NLR, and CRP, and faster lymphocyte recovery, than volatile anesthesia after propensity-score adjustment [31]. Mechanistically, this is consistent with in vitro evidence that propofol and sevoflurane act on different arms of the innate immune response — propofol inhibiting NF-κB-mediated pro-inflammatory signaling in monocytes and neutrophils, while sevoflurane's effects on neutrophil migration and monocyte phagocytic capacity are more context-dependent and, in some experimental sepsis models, run in the opposite direction [33]. None of the four core studies in this review's primary synthesis reported or controlled for which specific GA agent (propofol-based TIVA versus volatile maintenance) predominated; where this detail is available, Kim et al.'s GA arm used inhalational maintenance with propofol induction only [29]. If the propofol-versus-volatile distinction demonstrated in other surgical contexts also operates in orthopedic surgery, then the "GA" arm compared against regional anesthesia in each of the four included studies is itself a heterogeneous exposure, and the true magnitude of the NLR/PLR/SII difference attributable to regional anesthesia specifically could be under- or over-estimated depending on which general-anesthetic agent predominated at each site. This is a concrete, testable gap for future orthopedic-specific trials ideally randomizing GA agent as well as GA-versus-regional technique to close, rather than a reason to discount the direction of effect already observed in Section 3.3.

4.3. Clinical Relevance of the Biomarkers

The clinical rationale for caring about this pairing is that NLR, PLR, and SII are not academic curiosities in orthopedic patients: elevated NLR has been linked to postoperative delirium and mortality after hip fracture surgery [5,8], and SII specifically has been linked to postoperative pneumonia and surgical-trauma severity in hip fracture cohorts [6,9]. If anesthetic technique and, per Section 4.2, the specific anesthetic agent within the GA arm measurably shifts the same indices used to risk-stratify these patients, that has plausible downstream relevance to risk prediction and, speculatively, to outcome.

4.4. Alignment with the Broader Clinical-Outcome Literature

Large randomized trials and registry studies have found little or no difference in hard outcomes such as postoperative delirium [13] or 60-day mortality and functional recovery [11] between spinal and general anesthesia in hip fracture surgery, even as a 2023 meta-analysis of randomized trials [15] and a subsequent long-term-outcomes trial [14] have continued to probe this question without a clearly settled answer, while registry-level data in elective TKA and THA have found modestly lower complication and 90-day readmission rates with spinal anesthesia [16-18]. One reading of this pattern is that anesthetic technique produces a real but modest shift in inflammatory biomarkers that is too small, or too inconsistently coupled to clinically meaningful thresholds, to reliably move hard outcomes like delirium in adequately powered trials; another is that the specific patient populations, fracture types, and outcome definitions used in the large RCTs and registries differ enough from the smaller NLR/PLR/SII cohorts synthesized in Section 3.3 that direct comparison is premature no study in this review tested a downstream clinical outcome (delirium, infection, length of stay) as a function of anesthesia-technique-driven NLR/PLR/SII change specifically. Either way, this review's biomarker-level findings should not be read as implying an established clinical benefit of regional anesthesia beyond what the larger trial and registry literature has already found; they describe a laboratory-level signal whose clinical significance remains to be established, and this review's contribution is to characterize that signal, and its risk of bias, on its own terms, not to adjudicate the broader anesthetic-technique-and-outcomes debate.

4.5. Sources of Heterogeneity

Heterogeneity across surgical site (upper-limb trauma vs. lower-limb arthroplasty), regional technique (PNB vs. spinal), sampling timepoint (immediate, 4-hour, 24-hour, and longer postoperative windows were all used across the four core studies), the specific GA agent within each GA arm (Section 4.2), and which subset of NLR/PLR/SII/SIRI each study chose to report currently precludes a single pooled effect estimate. This should be read as a call for future trials to report a standardized panel of these indices at standardized timepoints, with a standardized and reported GA regimen, in orthopedic populations, not as evidence against the underlying relationship: the direction of effect, where significant, was consistent across four independent research groups working in different countries and surgical subspecialties, and is broadly corroborated by the mechanistic literature in Section 3.4 spanning upper-limb, knee, hip, and shoulder surgery.

5. LIMITATIONS

A quantitative meta-analysis was not performed because source publications reported different subsets of indices at different timepoints without a consistent, extractable effect-size format across studies; narrative synthesis by direction and significance (Section 3.3) was used instead as a transparent, conservative alternative. Publication bias could not be formally assessed given the small number of included studies, and the evidence base is concentrated in two surgical contexts (upper-limb fracture and TKA), limiting generalizability to other orthopedic procedures. None of the four included studies reported or controlled for the specific GA agent (propofol-based TIVA versus volatile maintenance) used within their GA arm; as Section 4.2 discusses, agent choice is independently associated with NLR magnitude in other surgical contexts, so the biomarker differences attributed here to regional-versus-general technique may be partly confounded by unreported variation in GA agent across sites and studies.

6. CONCLUSIONS

Within the bounds of a search-engine-mediated, single-reviewer literature search, regional anesthesia (peripheral nerve block or spinal anesthesia) shows a directionally consistent association with an attenuated postoperative rise in NLR and, in one large cohort, SII, relative to general anesthesia in orthopedic surgery, with no included study reporting the reverse direction for any index, and this signal is broadly corroborated by mechanistic cytokine- and acute-phase-level evidence spanning upper-limb, knee, hip, and shoulder surgery. Formal risk-of-bias assessment found moderate-to-good quality across the included studies, with confounding by indication as the principal shared concern in the three non-randomized studies. The evidence is nonetheless limited to upper-limb fracture surgery and total knee arthroplasty for the core biomarker comparison, and it sits alongside a larger, more rigorously tested trial and registry literature on hard clinical outcomes that has reached more mixed conclusions about anesthetic technique in orthopedic surgery. A fully resourced systematic review multi-database search, dual independent screening, dual independent risk-of-bias assessment, and meta-analysis where data allow is needed before these biomarker-level findings can inform anesthetic technique selection in orthopedic practice.

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