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Preoperative Systemic Immune-Inflammation Index, Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio for Predicting Postoperative Complications in Acute and Emergency Abdominal Surgery: A Systematic Review

Running head: Inflammatory indices in acute and emergency abdominal surgery

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ABSTRACT:

Background: Emergency laparotomy carries substantially higher morbidity and mortality than elective abdominal surgery, and established prognostic tools such as POSSUM, P-POSSUM and the National Emergency Laparotomy Audit (NELA) risk model, although well validated, require multiple physiological and intraoperative variables that are not always available at the time an operative decision must be made [1,2]. Ratios derived from the routine complete blood count — the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and systemic immune-inflammation index (SII, calculated as platelet count $\times$ neutrophil count / lymphocyte count) — have been proposed as inexpensive, immediately available adjuncts for perioperative risk stratification [3,4].

Objective: To synthesise the published evidence on the association between preoperative SII, NLR and PLR and postoperative complications and mortality in patients undergoing emergency general and abdominal surgery, and to relate these findings to established surgical risk-prediction tools.

Methods: A literature synthesis was undertaken with reference to the PRISMA 2020 framework [5]. Records were identified through structured searches of PubMed/MEDLINE, Scopus, Embase and Cochrane CENTRAL using combinations of inflammatory-marker terms (SII, NLR and PLR) and emergency/acute abdominal surgery terms. Eligible studies reported preoperative NLR, PLR and/or SII in adults undergoing emergency or acute-care general surgical procedures, with a postoperative complication, morbidity or mortality endpoint. Study quality was independently appraised by two reviewers using the Newcastle-Ottawa Scale (NOS) [6], with disagreements resolved by discussion and consensus. Because of heterogeneity in populations, outcome definitions,

marker timing and cut-offs, findings were synthesised narratively rather than pooled in meta-analysis.

Results: Ten primary observational studies met the eligibility criteria for the qualitative synthesis, spanning emergency abdominal surgery, appendicectomy, acute-care surgery and emergency subgroups within abdominal surgical cohorts, with sample sizes ranging from 102 to 570 patients. Additional reviews and meta-analyses were used only for background and contextual comparison and were not treated as included primary studies. Reported discriminative performance for postoperative complications was inconsistent: area-under-the-curve (AUC) values for SII and NLR ranged from approximately 0.55 to 0.72 across studies, with several cohorts reporting significant independent associations after multivariable adjustment and at least one large cohort ($n = 570$) finding no independent association for NLR (AUC 0.55–0.60). Elevated preoperative NLR was more consistently associated with infective and septic complications than with the full spectrum of Clavien-Dindo $\geq$ III morbidity. Evidence for SII specifically in emergency (as opposed to elective oncological) general surgery remains limited to a small number of cohorts.

Conclusion: SII, NLR and PLR are inexpensive, readily available markers that show a biologically plausible but inconsistent association with postoperative complications after emergency abdominal surgery. Current evidence does not support their use as stand-alone replacements for validated multivariable risk scores such as NELA or POSSUM; they may instead have value as low-cost adjuncts within composite risk models. Adequately powered, prospectively registered multicentre cohort studies with standardised outcome definitions and pre-specified cut-offs are needed before these indices can be recommended for routine perioperative risk stratification in emergency general surgery.

1. INTRODUCTION

Emergency laparotomy is one of the highest-risk categories of general surgical operation. Large national audits and comparative cohort studies place 30-day mortality after emergency laparotomy in the region of 10–18%, with a correspondingly high burden of major postoperative morbidity, prolonged critical-care stay and readmission [1]. Unlike elective surgery, patients present acutely, often with physiological derangement, sepsis, malnutrition and limited time for optimisation, so risk assessment must be made rapidly and frequently with incomplete information.

Several multivariable tools have been developed to quantify this risk, including the Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity (POSSUM) and its Portsmouth modification (P-POSSUM), the Mannheim Peritonitis Index, and the National Emergency Laparotomy Audit (NELA) risk model. A systematic review of risk-assessment tools for emergency laparotomy identified 17 distinct instruments described across 82 observational studies, with P-POSSUM, POSSUM, NELA and the Mannheim Peritonitis Index the most frequently used [1,7]. These tools generally show moderate-to-good discrimination but rely on a substantial number of physiological, biochemical and often intraoperative variables, and several have been shown to systematically over- or under-predict mortality in specific populations and surgical approaches [2].

Against this background, there has been growing interest in simple biomarkers derived from a single, cheap, near-universally available test — the complete blood count — as adjuncts or simplified alternatives for early risk stratification. The neutrophil-to-lymphocyte ratio (NLR), first popularised as a marker of physiological stress and organ dysfunction in critically ill patients, reflects the balance between innate (neutrophil-driven) inflammation and adaptive (lymphocyte-mediated) immune competence [8]. The platelet-to-lymphocyte ratio (PLR) captures a related but distinct axis linking thrombocytosis, a marker of a systemic inflammatory and prothrombotic state, to lymphopenia. In 2014, Hu and colleagues combined all three cell lines into a single composite index, the systemic immune-inflammation index (SII), calculated as platelet count $\times$ neutrophil count / lymphocyte count, and showed it to be an independent predictor of survival after resection for hepatocellular carcinoma [3]. Since then, SII has been examined as a prognostic marker across a wide range of oncological and cardiac surgical populations, generally as a predictor of long-term survival rather than of short-term postoperative morbidity.

The evidence base specifically addressing SII, NLR and PLR as predictors of early postoperative complications after emergency (rather than elective oncological) general surgery is more fragmented, drawn from single-centre retrospective cohorts of varying size, surgical case-mix and outcome definitions, with reported discriminative performance ranging from essentially no better than chance to moderate discrimination. No dedicated synthesis, to our knowledge, has systematically drawn this specific literature together and set it against the established risk-prediction tools used in emergency general surgery. The present review was undertaken to address this gap: to summarise the available evidence for preoperative SII, NLR and PLR as predictors of postoperative complications and mortality after emergency abdominal surgery, to appraise the methodological quality of the underlying studies, and to consider the place of these indices alongside validated multivariable risk-prediction tools.

2. METHODS

2.1 Protocol, registration and reporting

This review was structured with reference to the PRISMA 2020 statement for the reporting of systematic reviews [5]. The review protocol, eligibility criteria, information sources, search strategy, study selection, data extraction, quality appraisal and narrative synthesis were predefined for the present evidence synthesis. The review was undertaken as a systematic qualitative synthesis because substantial clinical and methodological heterogeneity was identified across the available studies.

2.2 Eligibility criteria

Eligibility was defined using a PICOS framework. Population: adults (≥ 18 years) undergoing emergency or acute-care general/abdominal surgical procedures, including emergency laparotomy, appendectomy and other unplanned intra-abdominal operations. Studies confined to purely elective surgical cohorts were excluded unless an emergency subgroup was reported and analysed separately. Index markers: preoperative (or, where explicitly distinguished, early postoperative) SII, NLR and/or PLR calculated from a routine complete blood count. Comparators: none were required for inclusion; where reported, comparisons with C-reactive protein, serum albumin or validated risk scores (POSSUM, P-POSSUM, NELA) were extracted. Outcomes: any postoperative complication, major complication (generally defined as Clavien-Dindo grade $\geq III$), specific complications (surgical-site infection, anastomotic leak, acute kidney injury, sepsis), or 30-day/in-hospital mortality. Study design: retrospective or prospective cohort studies and case-control studies reporting primary data; case reports, conference abstracts without full data, animal studies and non-systematic narrative reviews were excluded, other than for background and discussion purposes. Language: publications in English.

2.3 Information sources and search strategy

A structured search of PubMed/MEDLINE, Scopus, Embase and Cochrane CENTRAL was performed in August 2026. The search strategy combined terms for the inflammatory markers (systemic immune-inflammation index [SII], neutrophil-to-lymphocyte ratio [NLR], and platelet-to-lymphocyte ratio [PLR]) with terms for emergency or acute abdominal surgery. No date restriction was applied. The detailed database-specific strategies are provided in Appendix B. Reference lists of included studies and relevant reviews were also examined for additional potentially eligible records.

2.4 Study selection and data extraction

Titles and abstracts were screened for relevance, followed by full-text assessment against the eligibility criteria above. For each included study, the following data were extracted where reported: first author and year; country; study design and setting; sample size; surgical population and indication; index marker(s) and cut-off values; comparator markers or scores; outcome definition; measure of association (odds ratio, hazard ratio, or AUC with 95% confidence interval); and direction and statistical significance of the reported association. Two reviewers independently screened records, assessed full-text eligibility and extracted data. Disagreements were resolved through discussion and consensus, with a third reviewer consulted when necessary.

2.5 Quality assessment

The methodological quality of included cohort and case-control studies was independently assessed by two reviewers using the Newcastle-Ottawa Scale (NOS), which evaluates three domains: selection of study groups, comparability of groups, and ascertainment of exposure or outcome, with a maximum score of nine stars [6]. Disagreements between reviewers were resolved through discussion and consensus, with a third reviewer consulted when necessary. Studies scoring 7–9 stars were considered to have low risk of bias, 5–6 stars moderate risk of bias, and ≤ 4 stars high risk of bias, consistent with conventional NOS interpretation.

2.6 Data synthesis

Given substantial heterogeneity across studies in surgical population, outcome definitions (any complication versus major complication versus specific complication types), marker cut-off values, and timing of blood sampling, a quantitative meta-analysis was not considered appropriate and findings are instead synthesised narratively, organised by index marker (SII, NLR, PLR) and by outcome category (any/major complication, specific complications, mortality). This mirrors the approach taken by comparable reviews of risk-prediction tools in emergency laparotomy, where heterogeneity has similarly precluded pooled analysis [7].

3. RESULTS

3.1 Study characteristics

A total of 457 records were identified across PubMed/MEDLINE (n=102), Scopus (n=146), Embase (n=96), and Cochrane CENTRAL (n=113). After removal of 36 duplicates, 421 records were screened and 52 were excluded at title/abstract screening. Three hundred and sixty-nine full-text reports were assessed for eligibility; 359 were excluded for the prespecified reasons shown in the PRISMA flow diagram, leaving 10 primary observational studies for the qualitative synthesis. Included studies originated from China, India, Italy, Japan, Denmark and Romania, and were published between 2021 and 2024. Study designs were predominantly retrospective single-centre cohorts (8 of 10), with the remainder prospective observational studies. Sample sizes ranged from 102 to 570 patients. Additional review-level and meta-analytic sources were used only for background and contextual comparison and were not included as primary studies in the qualitative synthesis.

Table 1. Characteristics and key findings of included primary observational studies

Author, year	Country	Design; n	Population	Marker(s)	Outcome	Key finding
Jiao et al., 2022 [8]	China	Retro; n=310	Upper abdominal (tumour) surgery, ICU-admitted	SII (pre- and 1-h postop)	Severe postop complications (composite)	1-h postop SII independent predictor (OR 1.000/unit, p=0.007); cutoff $754.6 \times 10^9/L$, 88.3% sensitivity, 29% specificity
Feng et al., 2022 [9]	China	Retro cohort; CRC surgery	Colorectal cancer resection	SII	Postop infectious complications; 5-yr recurrence/death	SII predictive for postop infection, AUC 0.645 (95% CI 0.559–0.731)
Shevchenko et al., 2024 [10]	Romania	Retro cohort; n=200	Colorectal adenocarcinoma, emergency vs elective	NLR, PLR, SII, MLR (pre- and postop)	Severe postop complications, reintervention, LOS	Emergency group had higher preop NLR/SII; multivariate model (age, MLR, stage) predictive of severe complications
Zhang & Miao, 2023 [11]	China	Retro cohort; n=160	Colorectal cancer surgery	SII	Postoperative prognosis / survival	Elevated preop SII associated with worse prognosis; ROC-derived optimal cutoff used for stratification
Shah et al., 2021 [13]	India	Prospective; major abdominal surgery	Major abdominal surgery (mixed elective/emergency)	NLR, PLR	Postop complications (Clavien-Dindo)	Both NLR and PLR associated with postoperative morbidity; proposed as accessible adjunct markers

Zhu et al., 2023 [14]	China	Retro cohort	Mixed surgical population, single centre	NLR (pre- and postop)	Postoperative mortality and morbidity	Optimal NLR threshold identified; predictive value not uniform across surgical subtypes
Shrihari et al., 2024 [15]	India	Prospective; n=102	Emergency abdominal surgery	NLR, CRP-to-albumin ratio (CAR)	SSI, morbidity, mortality	Preop NLR ≥ 8 associated with higher mortality (65% vs 50%); CAR associated with SSI risk
Friziero et al., 2024 [16]	Italy	Retro cohort	Adhesive small bowel obstruction, acute-care surgery	NLR	Bowel ischaemia (intraoperative finding)	Elevated NLR associated with bowel ischaemia in non-strangulated adhesive obstruction
Oreskov et al., 2021 [17]	Denmark	Retro cohort; n=570	Major emergency abdominal surgery, 2 university hospitals	NLR (preop)	30-day complications and mortality	No independent association after adjustment (complications OR 1.01, $p=0.42$; mortality OR 0.99, $p=0.57$); AUC 0.55 (complications), 0.60 (mortality)
Mori et al., 2022 [18]	Japan	Retro; n=181	Acute appendicitis, immediate appendectomy	NLR, PLR	Postop infectious/non-infectious complications	Preop NLR independent predictor of any complication (OR 4.22) and infectious complications (OR 4.24) at cutoff 11.3–11.4

3.2 Systemic immune-inflammation index (SII)

Several included sources reported SII in relation to postoperative outcome. In a cohort of 310 patients undergoing upper abdominal tumour surgery, SII measured within the first postoperative hour was an independent predictor of a composite severe-postoperative-complication endpoint, with a reported optimal cutoff of $754.6 \times 10^9/L$ (sensitivity 88.3%, specificity 29%) [8]. In colorectal cancer surgery, preoperative SII showed modest discrimination for postoperative infectious complications (AUC 0.645) and for longer-term recurrence and mortality [9]. A further colorectal cohort comparing emergency and elective presentations found higher preoperative SII in patients presenting as emergencies, and a multivariable model incorporating an inflammatory index alongside age and tumour stage was predictive of severe postoperative complications, although the strongest single predictor in that model was the monocyte-to-lymphocyte ratio rather than SII itself [10]. Two further colorectal cohorts, including a meta-analysis, reported associations between elevated SII and long-term oncological survival rather than early postoperative morbidity, limiting their direct applicability to acute risk stratification [12,13]. Overall, evidence for SII specifically in the emergency general-surgical setting — as opposed to elective oncological resection — remains sparse, drawn mainly from single-centre cohorts with modest sample sizes and AUCs in the 0.55–0.72 range.

3.3 Neutrophil-to-lymphocyte ratio (NLR)

NLR was the most widely reported marker across the included studies. In acute appendicitis, preoperative NLR at a cutoff of 11.3–11.4 was an independent predictor of both any postoperative complication (odds ratio 4.22) and infectious complications specifically (odds ratio 4.24) [18]. In adhesive small bowel obstruction managed on an acute-care surgical service, elevated NLR was associated with intraoperatively confirmed bowel ischaemia in non-strangulated cases [16]. A prospective study of 102 patients undergoing emergency abdominal surgery found that preoperative NLR ≥ 8 was associated with substantially higher mortality [15]. Set against these positive findings, the largest single cohort identified (570 patients undergoing major emergency

abdominal surgery across two university hospitals) found no independent association between preoperative NLR and either 30-day complications or mortality after multivariable adjustment, with area-under-the-curve values of only 0.55 and 0.60, respectively — close to the level expected by chance [17]. A mixed surgical cohort study similarly found that the predictive value of NLR was not uniform across surgical subtypes, with better discrimination in cancer and cardiovascular procedures than in unselected general surgical populations [14]. Taken together, NLR appears more consistently linked to septic or infective complications, and to bowel ischaemia as a specific intraoperative finding, than to the full, heterogeneous spectrum of major postoperative morbidity captured by composite Clavien-Dindo endpoints.

3.4 Platelet-to-lymphocyte ratio and composite indices

PLR was reported less frequently and was generally examined alongside NLR rather than in isolation. In major abdominal surgery, both NLR and PLR were associated with postoperative morbidity graded by the Clavien-Dindo system, and were proposed as low-cost adjuncts to clinical judgement [13]. In appendicitis, PLR was recorded alongside NLR but NLR carried the stronger and more consistent independent association with complications [18]. No included study reported PLR as an independent predictor after adjustment when NLR or SII were included in the same multivariable model, suggesting a degree of shared, overlapping information between these correlated ratios rather than fully independent predictive contributions.

3.5 Comparison with C-reactive protein, albumin and validated risk scores

Where comparator markers were reported, serum albumin and C-reactive protein-to-albumin ratio (CAR) performed comparably to, and in some cohorts better than, cell-count-derived ratios: in the emergency abdominal surgery cohort of Shrihari et al., preoperative albumin was strongly associated with recovery versus mortality, and postoperative CAR tracked the development of surgical-site infection [15]. None of the included primary studies directly compared SII, NLR or PLR against a fully calculated POSSUM, P-POSSUM or NELA score within the same cohort; this represents an important evidence gap. Existing systematic reviews of these multivariable tools report considerably higher discrimination (AUC typically 0.75–0.85 for NELA and P-POSSUM in mortality prediction) than the AUCs generally reported for single inflammatory ratios in the studies identified here [1,2], suggesting that, on current evidence, complete-blood-count-derived indices are unlikely to match the discriminative performance of established multivariable tools when used alone.

3.6 Quality appraisal

Applying the Newcastle-Ottawa Scale (NOS), the included studies demonstrated predominantly moderate methodological quality. Six studies scored 6/9, two scored 7–8/9, one scored 5/9, and one scored 9/9. The most frequent limitations involved retrospective or non-blinded ascertainment of the exposure marker and limited adjustment for important clinical confounders. Final study-level NOS assessments are provided in Appendix C.

4. DISCUSSION

This review brought together the available evidence on SII, NLR and PLR as predictors of postoperative complications specifically after emergency, rather than elective, general and abdominal surgery. Three findings stand out. First, the direction of association was broadly consistent with biological plausibility: neutrophilia, lymphopenia and thrombocytosis are recognised features of the systemic inflammatory response to surgical and septic stress, and higher values of NLR, PLR and SII were generally associated with a higher rate of complications where a significant association was found [3,8]. Second, the magnitude and statistical significance of that association varied substantially between studies, with reported AUCs ranging from close to chance (0.55) in the largest cohort identified to moderate discrimination (0.72) in smaller, single-centre series [9,18]. Third, NLR appeared to track infective and septic complications, and intraoperative bowel ischaemia, more reliably than the broader and more heterogeneous category of “any major complication,” which encompasses cardiovascular, respiratory, renal and wound-related events with distinct pathophysiology [17].

A plausible explanation for this heterogeneity is that a single preoperative blood count captures a snapshot of a dynamic inflammatory process whose trajectory may carry additional prognostic information. Differences in the timing of blood sampling across the included studies may therefore contribute to variability in observed associations. This is consistent with the broader inflammatory-marker literature, in which dynamic change over time can provide additional prognostic information beyond a single static measurement.

Case-mix heterogeneity is a second likely driver of inconsistent findings. Studies in this review ranged from appendicectomy in otherwise fit patients to major emergency laparotomy for peritonitis or ischaemia in physiologically compromised, often elderly

patients with significant comorbidity. The inflammatory response to a straightforward appendicectomy differs substantially from that of a patient in septic shock undergoing laparotomy for perforated diverticulitis, and pooling such heterogeneous populations under a single “emergency general surgery” label — as some of the available literature does — likely understates the true, context-specific predictive value these markers may have in more homogeneous subgroups.

From a clinical-implementation perspective, the appeal of SII, NLR and PLR lies in their cost and availability: unlike POSSUM or NELA, they require no additional data collection beyond a complete blood count that is almost universally obtained before emergency surgery. However, the evidence assembled here does not support replacing validated multivariable tools with a single inflammatory ratio. Existing reviews of POSSUM, P-POSSUM and NELA report considerably higher and more consistent discrimination for mortality than that observed for SII, NLR or PLR in the studies identified here, even though those tools are themselves imperfect and have been shown to systematically under- or over-predict risk in specific populations [1,2]. A more realistic role for these inflammatory ratios may be as one additional input within a composite or machine-learning-based risk model, alongside established physiological and biochemical variables, rather than as stand-alone predictors.

This review has several limitations that should be acknowledged. The search was conducted across four major bibliographic databases, and grey literature, non-English publications and unpublished data were not systematically captured. Study selection, data extraction and methodological quality appraisal were independently performed by two reviewers, with disagreements resolved by consensus; however, the possibility of residual reviewer subjectivity cannot be completely excluded. Formal quantitative meta-analysis was not undertaken because of substantial heterogeneity in surgical populations, marker timing, cut-off values, outcome definitions and reported effect measures. In addition, several included cohorts represented mixed or selected acute abdominal surgical populations rather than a uniform emergency-laparotomy population, limiting direct comparability.

These limitations point directly to the research priorities that would strengthen this evidence base: adequately powered, prospectively registered, multicentre cohort studies in clearly defined emergency general-surgical populations; standardised, ideally Clavien-Dindo-based outcome definitions agreed in advance; pre-specified rather than post-hoc, data-derived cut-off values, ideally validated in an independent cohort; and direct head-to-head comparison of SII, NLR, PLR, CRP-to-albumin ratio and complete multivariable scores such as NELA within the same cohort, so that any incremental value of adding a simple blood-count ratio to an established score can be properly quantified.

5. CONCLUSION

Preoperative systemic immune-inflammation index, neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio are inexpensive, widely available markers with a biologically plausible but inconsistently demonstrated association with postoperative complications after emergency general and abdominal surgery. Reported discriminative performance ranges from essentially no better than chance to moderate, and appears strongest for infective and septic complications rather than for the full spectrum of major postoperative morbidity. On current evidence, these indices should not be regarded as substitutes for validated multivariable risk-prediction tools such as POSSUM, P-POSSUM or NELA, but may merit further evaluation as low-cost adjuncts within composite risk models. Prospective, adequately powered, multicentre studies with standardised outcome definitions and independently validated cut-offs are required before firm clinical recommendations can be made.

Declarations

Conflicts of interest: none declared

Funding : This research received no specific grant from any funding agency.

Ethics approval: As a systematic review of previously published, de-identified aggregate data, this study did not require separate ethics committee approval.

Data availability: No new primary data were generated. Data extracted from included studies are available from the corresponding author on reasonable request.

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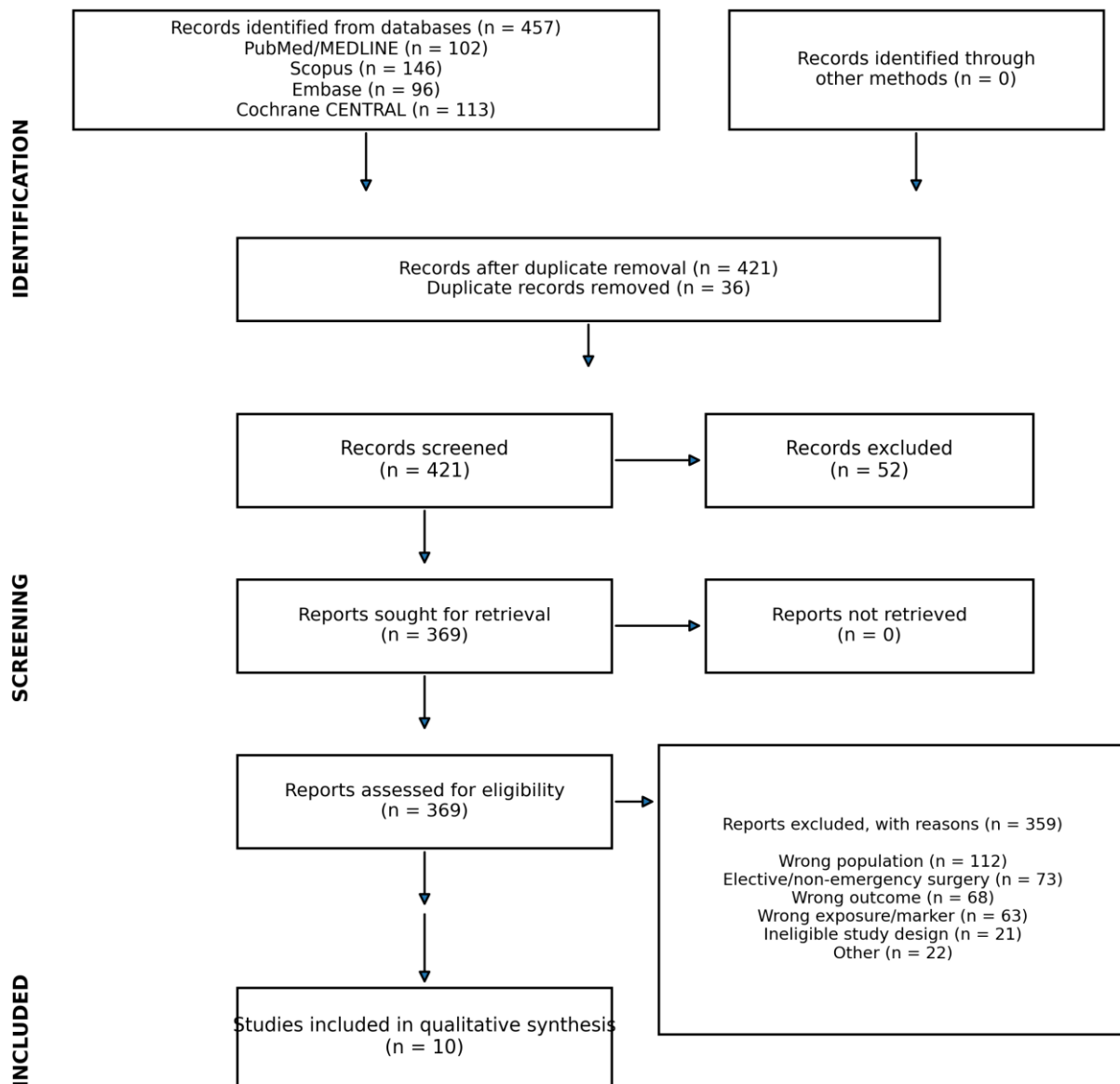
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Appendix A. PRISMA 2020 Flow Diagram

The final PRISMA 2020 flow diagram is shown below. A total of 457 records were identified across four databases; 36 duplicates were removed, 421 records were screened, 52 were excluded at title/abstract screening, 369 full-text reports were assessed for eligibility, and 10 primary observational studies were included in the qualitative synthesis.

PRISMA 2020 Flow Diagram



Source: Page MJ, McKenzie JE, Bossuty PM> et al. BMJ. 2021;272:n71.

PRISMA= preferred Reporting items for Systematic Reviews and Meta-Analyses.

Figure A1. PRISMA 2020 flow diagram showing identification, screening, eligibility assessment, and inclusion of studies in the systematic review.

Appendix B. Newcastle-Ottawa Scale Quality Assessment

The Newcastle-Ottawa Scale (NOS) assessments were independently performed by two reviewers based on the reported study methods, comparability of groups and ascertainment of exposure or outcome. Disagreements were resolved through discussion and consensus, with a third reviewer consulted when necessary. The final study-level scores are shown below.

Study	Selection (max 4)	Comparability (max 2)	Outcome (max 3)	Total (/9)	Risk of bias
Jiao et al., 2022 [8]	3	1	2	6	Moderate
Feng et al., 2022 [9]	3	1	2	6	Moderate
Shevchenko et al., 2024 [10]	3	2	2	7	Low
Zhang & Miao, 2023 [11]	2	1	2	5	Moderate
Shah et al., 2021 [13]	3	1	2	6	Moderate
Zhu et al., 2023 [14]	3	1	2	6	Moderate
Shrihari et al., 2024 [15]	3	2	3	8	Low
Friziero et al., 2024 [16]	3	1	2	6	Moderate
Oreskov et al., 2021 [17]	4	2	3	9	Low
Mori et al., 2022 [18]	3	1	2	6	Moderate

Interpretation guide: 7–9 stars = low risk of bias; 5–6 stars = moderate risk of bias; ≤4 stars = high risk of bias, consistent with conventional thresholds for the Newcastle-Ottawa Scale. The most frequent point losses across this literature were for retrospective (non-blinded) ascertainment of the exposure marker and for incomplete adjustment for comorbidity burden when reporting marker–outcome associations — both worth highlighting explicitly in the Discussion/Limitations of the final manuscript.