JHWCR JOURNAL OF HEALTH, WELLNESS AND COMMUNITY RESEARCH 3007-0570

Vol. 4 Issue 18, 2026
Open Access | DOI: 10.61919/x6q10z84

Review Article

Neutrophil-to-Lymphocyte Ratio in Predicting Severity in Acute Pancreatitis: A Systematic Review and Exploratory Meta-Analysis

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Received: 17 July 2026	Revised: 28 August 2026	Accepted: 17 September 2026	Published: 22 September 2026

HOW TO CITE

Hasan Husain, H.A.A. et al. Neutrophil-to-Lymphocyte Ratio in Predicting Severity in Acute Pancreatitis: A Systematic Review and Exploratory Meta-Analysis. Journal of Health, Wellness and Community Research. DOI:https://doi.org/10.61919/x6q10z84.

ARTICLE INFORMATION

Author Contributions	Concept: HAAHH, HJIAD, RTYK; Design: HAAHH, HJIAD, RTYK; Data Collection: HAAHH, HJIAD, EIEHE, AAO; Analysis: HAAHH, HJIAD, EIEHE, RTYK; Drafting: HAAHH, HJIAD, EIEHE, AAO, RTYK.
Ethical Approval	The study was approved by research ethical board Specialist Gastroenterologist, Bahrain Specialist Hospital, Kingdom of Bahrain
Informed Consent	NA
Conflict of Interest	The authors declare no conflict of interest.
Funding	No external funding.
Data Availability	Available from the corresponding author on reasonable request.
AI Declaration	No generative AI was used for conceptualization, analysis, or content generation. AI use was limited to language refinement, and the authors remain fully responsible for the accuracy, originality, validity, and integrity of the manuscript's content.

ABSTRACT

Background: Early identification of patients at risk of severe acute pancreatitis (AP) remains clinically important. The neutrophil-to-lymphocyte ratio (NLR) is inexpensive, rapidly available, and has been investigated as a prognostic biomarker, but reported thresholds, measurement times, and target outcomes vary substantially. Methods: A systematic review with exploratory quantitative synthesis was conducted using PubMed/MEDLINE, Google Scholar, and Semantic Scholar. Adult studies evaluating admission or early-hospitalization NLR against severe AP, persistent organ failure, intensive care admission, pancreatic complications, mortality, or related adverse outcomes were eligible. Studies were grouped according to NLR timing, target outcome, exposure definition, and effect measure; statistically incompatible estimates were not pooled. Results: Of 149 records screened, 10 primary studies were included in qualitative synthesis and five contributed numerical estimates to graphical quantitative synthesis. Higher NLR was consistently associated with more severe disease. Study-specific AUROCs were 0.760 for admission NLR predicting persistent organ failure, 0.785 for 48-hour NLR predicting severe AP, and 0.998 for day-0 NLR distinguishing mild from combined moderately severe/severe AP. These estimates were not pooled because timing and target outcomes differed. Association estimates also remained separate: NLR ≥11 was associated with persistent organ failure (HR 1.37, 95% CI 1.00–1.89), NLR ≥10 with severe hypertriglyceridemia-induced AP (OR 6.71), and continuous admission NLR with severe AP (OR 3.78, 95% CI 2.83–5.06). Conclusion: NLR is a practical adjunct for early AP risk stratification, but current evidence does not support a universal threshold or single pooled prognostic effect. Prospective validation using standardized timing and outcomes is required. Keywords: Neutrophil, Lymphocyte Ratio, Severity, Acute Pancreatitis

INTRODUCTION

Acute pancreatitis (AP) is a common gastrointestinal emergency with a heterogeneous clinical course. Most patients experience a self-limited illness, whereas a clinically important subgroup develops pancreatic or peripancreatic necrosis, systemic complications, persistent organ failure, prolonged hospitalization, or death.

Under the Revised Atlanta Classification, severe acute pancreatitis is defined by persistent organ failure lasting more than 48 hours, emphasizing the central prognostic importance of early recognition of patients at risk of deterioration (1). Contemporary clinical guidelines similarly emphasize early severity assessment because patients who initially appear stable may subsequently develop organ failure or other complications requiring intensive monitoring and multidisciplinary intervention (2,3).

Early risk stratification remains challenging because the clinical trajectory of AP may evolve substantially during the first 24–48 hours. Several prognostic systems are available, including the Ranson criteria, Acute Physiology and Chronic Health Evaluation II (APACHE II), Bedside Index for Severity in Acute Pancreatitis (BISAP), Glasgow-Imrie score, modified Marshall score, and computed tomography-based severity indices. These approaches provide clinically useful prognostic information but differ in complexity, timing, variable requirements, and dependence on repeat assessment or imaging (2–4). Consequently, there remains interest in simple laboratory-derived markers that can be obtained at presentation and repeated during early hospitalization to complement established clinical assessment.

The neutrophil-to-lymphocyte ratio (NLR), calculated by dividing the absolute neutrophil count by the absolute lymphocyte count, is readily derived from a routine complete blood count without requiring a separate biomarker assay. Its biological rationale reflects the interaction between neutrophil-predominant systemic inflammation and relative lymphopenia accompanying physiological stress and immune dysregulation. Alterations in circulating lymphocyte populations have themselves been associated with AP severity, supporting the potential relevance of leukocyte-derived inflammatory indices in early risk stratification (5). Because NLR is inexpensive, rapidly available, and repeatable, it has particular practical appeal where access to advanced biomarkers, cross-sectional imaging, or complex prognostic tools may be limited.

Clinical studies have repeatedly examined NLR in relation to AP severity and adverse outcomes. Early observational studies reported higher NLR values among patients with severe disease, intensive care requirements, prolonged hospitalization, or organ failure and suggested that both admission values and serial measurements may have prognostic relevance (6,7). A subsequent meta-analysis found that NLR provided useful discrimination for severe AP, although substantial variability existed in thresholds, study populations, and definitions of severity (8). More recent studies have continued to evaluate admission and 24–48-hour NLR in relation to severe AP, persistent organ failure, mortality, and other adverse outcomes (9,10). An updated systematic review and meta-analysis further supports an association between higher NLR and adverse AP outcomes while emphasizing variation in measurement timing, thresholds, and target outcomes across the literature (11).

Despite this accumulating evidence, important methodological heterogeneity remains. Admission NLR and NLR measured after 24–48 hours do not represent identical prognostic time points, and studies have variously defined their target outcome as severe AP, moderately severe/severe AP, persistent organ failure, intensive care admission, pancreatic or infected necrosis, or mortality (8,11). Reported NLR thresholds also vary substantially between cohorts. Combining these clinically different time points, outcome definitions, and exposure thresholds may obscure the specific prognostic question being addressed. Accordingly, interpretation of NLR requires distinction between its association with adverse outcomes, its discriminatory performance for a defined target condition, and its incremental clinical value beyond established prognostic scores.

The principal clinical attraction of NLR is therefore not that it could replace validated severity assessment, but that it may provide an immediately available inflammatory signal that complements clinical examination, biochemical parameters, organ-failure assessment, and established prognostic tools. Current management guidance emphasizes repeated clinical evaluation and early identification of evolving organ dysfunction rather than reliance on any single laboratory marker or severity score (2–4). Within this framework, NLR may be particularly useful as an adjunctive marker during the early phase of AP, provided that its timing, threshold, and predicted outcome are clearly defined.

Accordingly, this systematic review aimed to evaluate the prognostic value of NLR for severity and adverse outcomes in adults with acute pancreatitis. The primary objective was to assess the relationship between admission NLR and severe acute pancreatitis, particularly persistent organ failure. Secondary objectives were to evaluate NLR measured during the first 24–48 hours and its association with clinically relevant outcomes including intensive care admission, pancreatic or infected pancreatic necrosis, prolonged hospitalization, and in-hospital

mortality. Quantitative synthesis was intended for studies with sufficiently comparable NLR timing, outcome definitions, and effect measures, while clinically heterogeneous evidence was evaluated separately.

MATERIALS AND METHODS

Study Design and Reporting Framework

This study was conducted as a systematic review with exploratory quantitative synthesis of the prognostic value of the neutrophil-to-lymphocyte ratio (NLR) in adults with acute pancreatitis. Reporting was structured in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement (12). The review focused on the ability of NLR measured at presentation or during early hospitalization to discriminate or identify patients at increased risk of severe acute pancreatitis and related adverse clinical outcomes.

Information Sources and Literature Search

The literature search included PubMed/MEDLINE, Google Scholar, and Semantic Scholar. Records were screened by title and abstract, followed by more detailed evaluation of potentially relevant reports. The search was directed toward studies evaluating NLR in adult patients with acute pancreatitis in relation to disease severity, persistent organ failure, intensive care requirement, pancreatic or infected pancreatic necrosis, mortality, prolonged hospitalization, or closely related adverse clinical outcomes.

Reference lists and relevant systematic reviews were used to identify potentially pertinent primary studies not captured during the initial screening. Secondary reviews were used for contextual and bibliographic purposes but were not treated as independent primary-study units in the quantitative synthesis.

Eligibility Criteria

Primary clinical studies involving adults with acute pancreatitis were eligible when they evaluated NLR measured at hospital admission or during the early phase of hospitalization and related the measurement to a clinically defined severity or prognostic outcome. Eligible study designs included prospective and retrospective observational cohorts and diagnostic or prognostic accuracy studies.

The primary outcome was severe acute pancreatitis, preferentially defined according to the Revised Atlanta Classification by persistent organ failure lasting more than 48 hours (1). Persistent organ failure was therefore considered the most clinically specific severity endpoint. Studies reporting moderately severe and severe acute pancreatitis as a combined category were retained but classified separately from studies evaluating severe acute pancreatitis alone.

Secondary outcomes included intensive care unit admission, pancreatic necrosis, infected pancreatic necrosis, in-hospital mortality, prolonged hospitalization, and other clearly defined adverse clinical outcomes. Etiology-specific populations, particularly hypertriglyceridemia-induced acute pancreatitis, were retained but analyzed separately from unselected acute pancreatitis populations when clinical differences could affect interpretation.

Studies restricted to post-endoscopic retrograde cholangiopancreatography pancreatitis, non-human studies, and reports not evaluating NLR as a prognostic or discriminatory marker for acute pancreatitis outcomes were excluded.

NLR Measurement and Timing

NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count. Because NLR changes during the inflammatory course of acute pancreatitis, measurements obtained at different stages were not considered directly interchangeable.

- For synthesis, NLR measurements were classified into two clinically distinct time windows:
- Admission NLR, comprising values reported at initial presentation or day 0; and

Early serial NLR, comprising measurements obtained after admission, particularly at approximately 24–48 hours.

Admission and 24–48-hour measurements were evaluated separately wherever possible. Studies reporting serial NLR measurements were retained for qualitative synthesis, but an estimate from a later time point was not combined with an admission estimate merely to increase the number of studies available for pooling.

Data Extraction and Outcome Classification

For each eligible study, the following information was extracted where available: first author, publication year, country, study design, sample size, acute pancreatitis population or etiology, definition of the clinical outcome, NLR measurement time point, NLR threshold or scale, event count, area under the receiver operating characteristic curve (AUROC), corresponding 95% confidence interval, sensitivity, specificity, and association measures such as odds ratios (ORs) or hazard ratios (HRs).

For association studies, whether NLR was modeled as a continuous variable or dichotomized using a study-specific threshold was recorded. Adjusted and unadjusted estimates were distinguished, and adjusted estimates were preferentially considered when the same study reported both. Numerical estimates were obtained from the most complete study report available. An AUROC was classified as an NLR-specific estimate only when the reported receiver operating characteristic analysis explicitly evaluated NLR itself. AUROCs from multivariable models combining NLR with other biomarkers or clinical variables were not treated as NLR-only estimates.

Similarly, effect estimates reconstructed solely from incomplete abstract-level information were not considered equivalent to directly reported estimates when the underlying uncertainty could not be reproduced reliably. Such findings could contribute to the narrative synthesis but were not used to generate a pooled summary effect unless the required numerical information was adequately reported.

Quantitative Synthesis

Quantitative synthesis was organized according to three prespecified dimensions: NLR measurement timing, target clinical outcome, and statistical estimand. Clinical comparability was assessed before statistical pooling. For discrimination analyses, AUROC estimates were considered for pooling only when studies evaluated sufficiently comparable NLR time points and target outcomes. Admission NLR was analyzed separately from 24–48-hour NLR. Likewise, strict severe acute pancreatitis or persistent organ failure was not assumed to be equivalent to a combined moderately severe/severe category, mortality, intensive care admission, or other composite adverse outcomes. AUROC values were analyzed on a transformed scale when quantitative pooling was justified and subsequently back-transformed for presentation. Individual AUROCs and 95% confidence intervals were retained in forest plots even when clinical heterogeneity prevented calculation of a meaningful pooled estimate.

Association analyses were performed separately from discrimination analyses. ORs and HRs were regarded as different effect measures and were not pooled into a single generic ratio estimate. Estimates based on a continuous increase in NLR were also analyzed separately from estimates comparing high versus low NLR according to a threshold. Studies of etiology-specific acute pancreatitis were not combined with general acute pancreatitis populations unless the populations, exposure definitions, and outcomes were sufficiently comparable. A pooled summary estimate was generated only when at least three studies were sufficiently comparable with respect to population, NLR timing and definition, target outcome, and effect measure. When these requirements were not met, results were presented as individual study estimates with narrative synthesis rather than generating an overall pooled effect of uncertain clinical meaning.

Where random-effects pooling was appropriate, between-study heterogeneity was evaluated using the I^2 statistic and between-study variance (τ^2). Statistical heterogeneity was interpreted together with clinical and methodological differences rather than on the basis of I^2 alone. Sensitivity analyses were planned where sufficient comparable studies were available, particularly to examine the influence of markedly extreme estimates or studies with important risk-of-bias concerns.

Risk-of-Bias Assessment

Risk of bias was evaluated according to the methodological role of each included study. Prognostic-factor studies were assessed using the Quality In Prognosis Studies (QUIPS) framework, which evaluates study participation, attrition, prognostic-factor measurement, outcome measurement, confounding, and statistical analysis and reporting (13). Studies primarily reporting test-discrimination or diagnostic-accuracy characteristics were

additionally evaluated using relevant domains of QUADAS-2, including patient selection, index-test assessment, reference standard, and patient flow and timing (14). Particular attention was given to retrospective or single-center recruitment, data-driven selection of NLR thresholds, variation in NLR measurement timing, inconsistent definitions of acute pancreatitis severity, incomplete control of confounding, and possible overoptimism when cut-offs and discriminatory performance were derived and evaluated in the same dataset. Risk-of-bias findings were considered when interpreting both individual-study results and any quantitative synthesis.

RESULTS

Study Selection

A total of 149 records were identified and screened. After title and abstract screening, 111 records were excluded because they did not meet the review criteria, leaving 38 reports for more detailed assessment. Twenty-eight reports were subsequently excluded, and 10 primary studies were retained for qualitative synthesis. Five studies provided sufficiently defined numerical estimates for graphical quantitative presentation. Because the available estimates differed materially in NLR measurement timing, target outcome, exposure definition, or effect measure, quantitative estimates were stratified rather than combined into a single overall meta-analytic estimate.

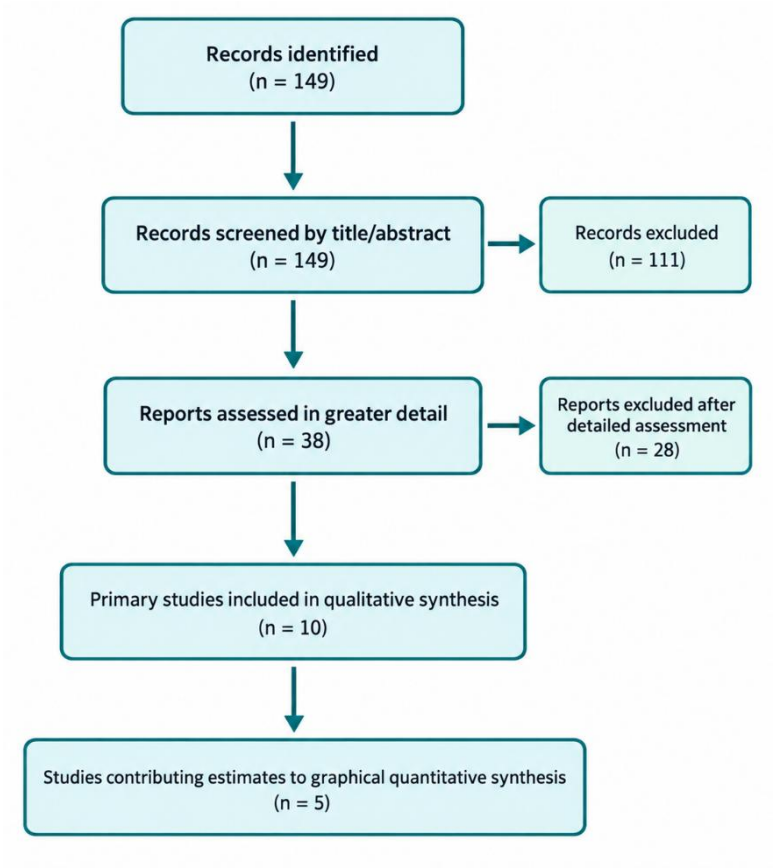

Figure 1 – Study Selection Flow

Characteristics of Included Studies

The 10 included studies were published between 2011 and 2026 and included sample sizes ranging from 110 to 1,639 participants. Most were retrospective or observational single-center studies, although the most recent study by Afridi et al. was a multicenter retrospective cohort. Considerable methodological diversity was present in the definition of severity, timing of NLR measurement, selection of NLR thresholds, and reported outcomes. Early studies evaluated ICU admission, length of stay, severe AP, and serial changes in NLR (6,7). Subsequent investigations assessed persistent organ failure, severe hypertriglyceridemia-induced AP, organ failure, mortality, and serial NLR measurements (15–18). More recent studies evaluated NLR at admission or 48 hours against severe AP, mortality, moderately severe/severe disease, or persistent organ failure (9,10,19,20).

Table 1. Characteristics of Included Primary Studies

Study	Country	Design	N	Primary outcome relevant to this review	NLR timing	Principal NLR finding
Azab et al. (6)	USA	Observational cohort	283	ICU admission/length of stay	Admission	NLR >4.7 and increasing NLR tertiles were associated with adverse outcomes
Suppiah et al. (7)	UK	Observational cohort	146	Severe AP	Days 0, 1, 2	NLR was higher in severe AP; reported cut-offs were 10.6, 8.1, and 4.8
Zhang et al. (15)	China	Retrospective diagnostic/cohort study	974	Persistent organ failure, ICU stay >7 days, mortality	Admission	AUC 0.760 for persistent organ failure; NLR ≥11 was independently associated with adverse outcomes
Wang et al. (16)	China	Retrospective cohort	110	Severe HTG-AP	Admission	NLR ≥10 independently associated with severe HTG-AP
Han et al. (17)	China	Retrospective cohort	1,639	Severe AP	Days 0, 1, 2	Higher serial NLR was associated with severe AP; reported cut-offs were 9.64, 6.66, and 6.50
Jeon and Park (18)	Korea	Retrospective cohort	490	Severe AP/organ failure	Admission to 72 h	Early NLR was associated with severity and organ failure
Cazacu et al. (9)	Romania	Retrospective cross-sectional study	725	Severe AP, mortality, persistent organ failure, ICU admission	Admission and 48 h	NLR48 AUC 0.785 for severe AP and 0.810 for mortality
Salehi et al. (10)	Iran	Retrospective cohort	112	Moderate/severe AP	Admission	NLR cut-off 6.23: sensitivity 77.78%, specificity 62.86%
Kumar et al. (19)	India	Analytical cross-sectional/predictive accuracy study	110	Mild vs combined moderately severe/severe AP	Days 0–3	Day-0 NLR AUC 0.998; discriminatory performance remained high on subsequent days
Afridi et al. (20)	Pakistan	Multicenter retrospective cohort	272	Severe AP defined by persistent organ failure	Admission/first 24 h	Median NLR was higher in severe AP; continuous NLR OR 3.78 for severe disease

Abbreviations: AP, acute pancreatitis; AUC, area under the receiver operating characteristic curve; HTG-AP, hypertriglyceridemia-induced acute pancreatitis; ICU, intensive care unit; NLR, neutrophil-to-lymphocyte ratio.

Qualitative Synthesis

Across the included studies, higher NLR values were generally associated with more severe clinical courses. Azab et al. reported associations between higher admission NLR and ICU admission or prolonged hospitalization, whereas Suppiah et al. demonstrated that NLR measured on days 0, 1, and 2 differed according to disease severity (6,7). Serial measurements were also evaluated by Han et al., who reported higher NLR across the first three measurement points among patients with severe AP (17). Zhang et al. evaluated admission NLR in 974 patients and reported an AUROC of 0.760 for persistent organ failure. With an NLR threshold of 11, elevated NLR was independently associated with persistent organ failure, prolonged ICU stay, and in-hospital mortality (15). In the etiology-specific cohort of Wang et al., an admission NLR threshold of 10 was associated with severe hypertriglyceridemia-induced AP (16).

Later studies continued to demonstrate associations between NLR and AP severity, but the target outcomes and measurement times remained heterogeneous. Cazacu et al. found that NLR measured at 48 hours discriminated severe AP and mortality more strongly than admission NLR (9). Salehi et al. reported a sensitivity of 77.78% and specificity of 62.86% for an admission NLR cut-off of 6.23 in distinguishing moderate/severe from mild AP (10). Kumar et al. reported very high day-0 discriminatory performance, although their severe-disease group combined moderately severe and severe AP rather than restricting the target condition to persistent organ failure (19). Afridi et al. found substantially higher admission NLR values among patients meeting Revised Atlanta criteria for severe AP (20).

Discrimination of Severe Clinical Outcomes

Three studies provided NLR-specific AUROC estimates that could be displayed with sufficiently defined confidence intervals, but their target conditions and measurement time points were not sufficiently homogeneous for a clinically interpretable pooled AUROC. Zhang et al. reported an AUROC of 0.760 (95% CI 0.721–0.799) for admission NLR predicting persistent organ failure (15). Cazacu et al. reported an AUROC of 0.785 (95% CI 0.730–0.840) for NLR measured at 48 hours in relation to severe AP (9). Kumar et al. reported a day-0 AUROC of 0.998 (95% CI 0.989–1.000), but the target group combined moderately severe and severe AP rather than representing strict Revised Atlanta severe AP alone (19). Salehi et al. were not included in the AUROC forest plot because the reported AUROC of approximately 0.74 represented the combined multivariable model incorporating the inflammatory indices rather than a separate NLR-only AUROC. The NLR-specific threshold result was therefore retained descriptively: at an admission NLR cut-off of 6.23, sensitivity was 77.78% and specificity was 62.86% (10).

Table 2. NLR Discrimination Estimates Relevant to Quantitative Synthesis

Study	NLR timing	Target outcome	N	Events	NLR discrimination result	Quantitative treatment
Zhang et al. (15)	Admission	Persistent organ failure	974	223	AUROC 0.760 (95% CI 0.721–0.799)	Displayed individually
Cazacu et al. (9)	48 h	Severe AP/persistent organ failure	725	99	AUROC 0.785 (95% CI 0.730–0.840)	Displayed individually
Salehi et al. (10)	Admission	Moderate/severe AP	112	39	NLR cut-off 6.23; sensitivity 77.78%, specificity 62.86%; no separate NLR-only AUROC	Narrative synthesis
Kumar et al. (19)	Day 0	Moderately severe/severe vs mild AP	110	46	AUROC 0.998 (95% CI 0.989–1.000)	Displayed individually

No overall pooled AUROC, I^2, or τ^2 was calculated because fewer than three estimates represented the same clinically coherent combination of NLR timing and target outcome.

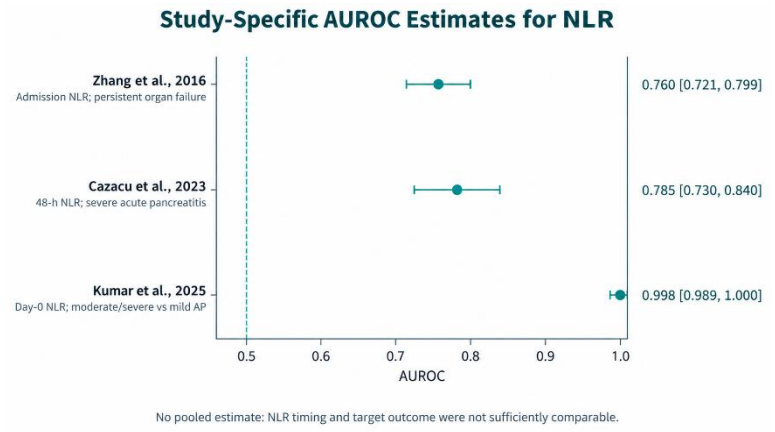

Figure 2 – Study-Specific AUROC Forest Plot

Association Between NLR and Severe Outcomes

Three studies reported ratio-type association estimates, but these estimates represented different statistical measures and different NLR exposure definitions and therefore were not pooled. Zhang et al. treated NLR as a threshold-based exposure and reported that NLR ≥11 was associated with persistent organ failure (HR 1.37, 95% CI 1.00–1.89) after multivariable analysis (15). Wang et al. similarly dichotomized NLR using a threshold of 10 and reported an OR of 6.71 (p=0.019) for severe hypertriglyceridemia-induced AP; an exact 95% confidence interval was not directly reported in the source (16). Afridi et al., in contrast, modeled NLR as a continuous exposure and reported an OR of 3.78 (95% CI 2.83–5.06) per unit increase in NLR for severe AP (20). Because these estimates differed in effect measure (HR versus OR), NLR scale (threshold-based versus continuous), population (general AP versus HTG-AP), and target outcome, calculation of a single pooled "ratio estimate" was not undertaken.

Table 3. Study-Specific Association Estimates for NLR and Severe Clinical Outcomes

Study	Population	NLR exposure	Effect measure	Outcome	Estimate	Quantitative treatment
Zhang et al. (15)	General AP	NLR ≥11	Adjusted HR	Persistent organ failure	1.37 (95% CI 1.00–1.89)	Not pooled
Wang et al. (16)	HTG-AP	NLR ≥10	Adjusted OR	Severe HTG-AP	6.71; p=0.019	Not pooled
Afridi et al. (20)	General AP	Continuous NLR, per unit	Univariable OR	Severe AP	3.78 (95% CI 2.83–5.06)	Not pooled

The vertical reference line represents a ratio estimate of 1.0. Estimates are presented individually rather than as a pooled effect because effect measure, NLR exposure definition, population, and target outcome were not comparable. For Wang et al., the source reported OR 6.71 with p=0.019 but did not directly report the corresponding 95% confidence interval.

Risk of Bias and Applicability

Risk-of-bias concerns were concentrated in study participation and design, prognostic-factor measurement, outcome definition, confounding, threshold selection, and statistical analysis. Most included studies were retrospective or single-center investigations, and many derived an "optimal" NLR cut-off from the same dataset in which discriminatory performance was subsequently evaluated. This creates a risk of optimistic estimates when thresholds are not externally validated.

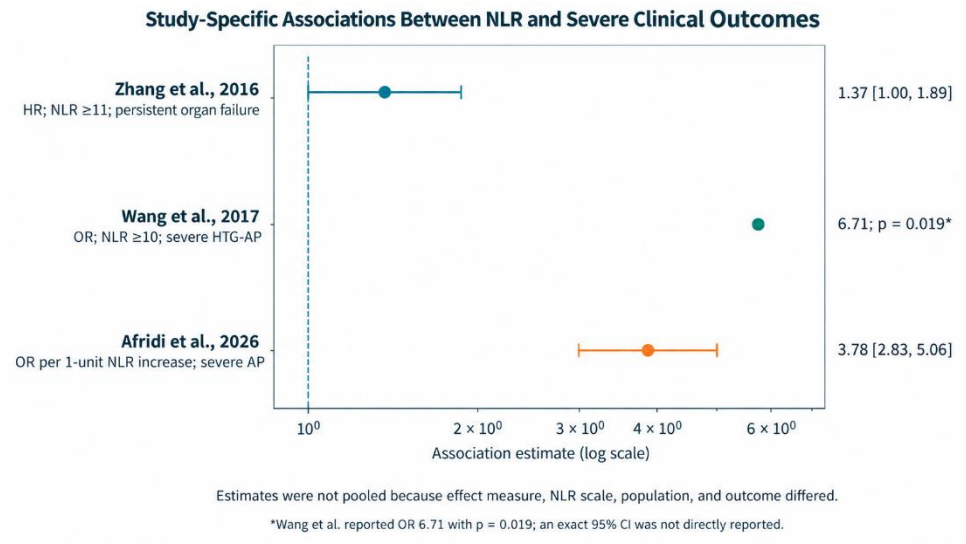

Figure 3 – Study-Specific Association Estimates

Outcome heterogeneity was also important. Some studies used persistent organ failure or Revised Atlanta severe AP, whereas others evaluated ICU admission, hospital stay, moderately severe/severe AP, or etiology-specific severe AP. Measurement timing ranged from admission to 48–72 hours, introducing additional applicability differences. Studies based on later NLR measurements could reflect both underlying disease evolution and treatment received during early hospitalization.

Table 4. Methodological Features Relevant to Risk of Bias and Applicability

Study	Principal methodological considerations
Azab et al. (6)	Observational design; adverse outcomes included ICU admission and length of stay rather than strict Revised Atlanta severe AP
Suppiah et al. (7)	Single-cohort serial assessment; time-specific cut-offs derived within the same dataset
Zhang et al. (15)	Retrospective single-center cohort; data-derived NLR threshold, although adjusted Cox analyses were reported
Wang et al. (16)	Retrospective, relatively small etiology-specific HTG-AP cohort; threshold derived within study population
Han et al. (17)	Large retrospective cohort; serial data-derived cut-offs without external validation
Jeon and Park (18)	Retrospective design; multiple time points and related but non-identical adverse outcomes
Cazacu et al. (9)	Retrospective cross-sectional analysis; 48-hour NLR may reflect early treatment and disease evolution as well as baseline severity
Salehi et al. (10)	Small retrospective cohort; severity classification and combined multivariable ROC analysis limited NLR-specific discrimination assessment
Kumar et al. (19)	Single-center analytical cross-sectional study; moderately severe and severe AP combined; exceptionally high AUROC derived and evaluated within the same sample
Afridi et al. (20)	Retrospective multicenter cohort; continuous NLR effect estimated using univariable logistic regression, leaving potential residual confounding

Overall, the direction of evidence consistently favored higher NLR values among patients with more severe disease or adverse outcomes, but the numerical magnitude of discriminatory and association estimates varied considerably according to NLR timing, severity definition, exposure scale, and study design. Consequently, the evidence supported qualitative consistency but did not support a single pooled AUROC, universal NLR threshold, or overall pooled association estimate.

DISCUSSION

This systematic review found a broadly consistent relationship between higher neutrophil-to-lymphocyte ratio (NLR) and a more severe clinical course of acute pancreatitis (AP), but it also identified substantial clinical and methodological heterogeneity that limits the validity of a single pooled estimate. Across the included studies, higher NLR was associated with severe AP, persistent organ failure, intensive care requirements, mortality, or related adverse outcomes. However, the studies differed in the timing of NLR measurement, definition of disease severity, NLR threshold or scale, AP etiology, and statistical effect measure. Consequently, the most defensible interpretation is that NLR carries prognostic information across several AP outcomes, rather than that one universal NLR threshold or summary effect applies to all patients.

The direction of the findings is consistent with earlier NLR studies and previous evidence syntheses. Azab et al. associated higher NLR with adverse clinical outcomes, while Suppiah et al. demonstrated prognostic differences across serial measurements during the first 48 hours (6,7). Zhang et al. subsequently showed that admission NLR

was associated with persistent organ failure, prolonged ICU stay, and in-hospital mortality, and Han et al. demonstrated that serial NLR remained related to disease severity during early hospitalization (15,17). The 2020 meta-analysis by Kong et al. concluded that NLR had useful discriminatory performance for AP severity, while the more recent systematic review by Chooklin and Chuklin also supported NLR as a potentially useful early risk-stratification marker but emphasized time-specific measurement and variation in clinical endpoints (8,11).

The wider observational literature is similarly directionally consistent. Studies by Gülen et al., Li et al., Cho et al., O'Connell et al., Kokulu et al., Kaplan et al., Kolber et al., and Huang et al. evaluated NLR in relation to mortality, AP severity, organ failure, systemic complications, or etiology-specific disease and generally found higher NLR values among patients with less favorable clinical courses (21–28). Nevertheless, these studies also illustrate why a single threshold is difficult to justify: populations, severity definitions, etiologies, sampling times, and comparator biomarkers differed substantially.

More recent studies reinforce both the potential value and the heterogeneity of NLR. A prospective cohort reported an AUROC of 0.82 for NLR in predicting severe AP, while a study evaluating NLR together with BISAP and C-reactive protein found that combinations of routinely available measures could improve severity discrimination beyond individual markers (29,30). Bengi et al. further reported that the prognostic performance of NLR varied according to sampling time, with 24-hour NLR performing best for severity and 48-hour NLR showing stronger relationships with mortality and organ failure (31). These findings support treating admission NLR and later NLR measurements as related but clinically distinct prognostic variables.

This temporal distinction was important in the present synthesis. Zhang et al. reported an AUROC of 0.760 for admission NLR in predicting persistent organ failure, whereas Cazacu et al. reported an AUROC of 0.785 using NLR measured at 48 hours for severe AP (9,15). Kumar et al. reported a markedly higher day-0 AUROC of 0.998, but their target group combined moderately severe and severe AP rather than restricting the endpoint to persistent organ failure (19). These estimates therefore do not represent interchangeable measurements of the same diagnostic target. The exceptionally high estimate reported by Kumar et al. also warrants cautious interpretation because the cut-off and discrimination were derived within the same relatively small single-center cohort, increasing the potential for optimism in apparent performance. The association analyses demonstrate a related problem. Zhang et al. reported an adjusted hazard ratio of 1.37 for persistent organ failure among patients with NLR ≥11, whereas Wang et al. reported an odds ratio of 6.71 for severe hypertriglyceridemia-induced AP using an NLR threshold of 10 (15,16). Afridi et al. modeled NLR as a continuous exposure and reported an odds ratio of 3.78 per unit increase in NLR for severe AP (20). These estimates differ not only statistically—hazard ratio versus odds ratio—but also biologically and clinically because a continuous increase in NLR is not equivalent to comparing patients above and below a threshold. Combining them into one pooled ratio would therefore produce an effect without a clear clinical interpretation.

The absence of a universal NLR cut-off remains a central limitation to clinical implementation. Thresholds reported across the literature range from approximately 4–6 in some cohorts to approximately 10–11 or higher in others (6,7,15,16,18,21–29). Differences may reflect patient selection, timing from symptom onset, AP etiology, prevalence of severe disease, outcome definitions, analytical methods, and data-driven selection of optimal thresholds. Etiology may be particularly important: Wang et al. and Huang et al. specifically evaluated hypertriglyceridemia-induced AP, whereas other cohorts included mixed etiologies (16,28). A threshold developed in one population should therefore not be assumed to perform equivalently in another. The biological rationale for the observed association is plausible. Acute pancreatitis can produce a marked systemic inflammatory response characterized by innate immune activation, neutrophil recruitment, cytokine signaling, endothelial dysfunction, and, in more severe disease, organ dysfunction. Relative lymphopenia may accompany physiological stress and immune dysregulation, making NLR a composite reflection of neutrophil-predominant inflammation and reduced circulating lymphocyte activity (5). Kolber et al. further demonstrated relationships between early NLR, interleukin-6, soluble urokinase-type plasminogen activator receptor, and subsequent organ failure, providing additional mechanistic support for NLR as a marker of systemic inflammatory activity rather than an isolated hematological observation (27).

NLR should nevertheless be distinguished from a complete prognostic model. Contemporary AP management relies on repeated clinical assessment, physiological deterioration, organ-failure evaluation, biochemical findings, and

established prognostic systems rather than any single laboratory measurement (2–4). Some studies suggest that combining NLR with established scores or other inflammatory markers may improve discrimination (30). This approach is clinically more plausible than replacing BISAP, APACHE II, modified Marshall assessment, or other validated approaches with NLR alone. NLR may be particularly attractive as an early triage adjunct because it is derived from a routine complete blood count, can be recalculated serially, and requires no additional assay. The present review has several strengths. It separates admission from later NLR measurements, distinguishes strict severe AP or persistent organ failure from broader moderate/severe categories, and avoids combining incompatible effect measures. This prevents statistical pooling from obscuring clinically important heterogeneity. It also distinguishes NLR-specific discrimination from multivariable-model performance; accordingly, the approximately 0.74 AUROC reported by Salehi et al. for a combined inflammatory-marker model was not treated as an NLR-only AUROC (10).

Several limitations should also be considered. Most included studies were retrospective or single-center investigations, and some had relatively small samples. NLR thresholds were frequently selected from the same datasets in which performance was evaluated, increasing susceptibility to overoptimistic discrimination. Definitions of severity and adverse outcomes varied, as did the timing of blood sampling. Some studies analyzed admission NLR, whereas others focused on measurements after 24–48 hours, when treatment and evolution of the inflammatory response may already influence the value. Different studies additionally modeled NLR as either a continuous prognostic factor or a dichotomous threshold. The number of sufficiently comparable studies within any one time-outcome-effect-measure stratum was therefore too small to support a statistically and clinically coherent pooled estimate. These limitations also precluded meaningful assessment of small-study effects or publication bias. Future studies should prospectively evaluate NLR using prespecified measurement windows and standardized Revised Atlanta outcomes, particularly persistent organ failure lasting more than 48 hours. Threshold development and validation should occur in separate populations, and studies should report sufficient data to permit reconstruction of sensitivity, specificity, and 2×2 diagnostic tables. External validation across different etiologies and healthcare settings is also required. Of particular interest is whether NLR provides incremental prognostic information beyond established clinical scores and routinely available variables, rather than merely demonstrating statistical association with severity.

CONCLUSION

NLR is a simple, inexpensive, and widely available inflammatory marker that is consistently associated with severe acute pancreatitis and related adverse outcomes. The available evidence supports its use as an adjunct to early clinical risk stratification, but substantial variation in measurement timing, severity definitions, cut-off selection, populations, and statistical estimands prevents specification of a universal threshold or a single pooled prognostic effect. Admission and 24–48-hour NLR should be interpreted as distinct prognostic measurements, and NLR should complement rather than replace established clinical assessment and severity scoring. Prospective multicenter validation using standardized outcomes, prespecified thresholds, and external validation cohorts is required before NLR can be incorporated into a uniform AP risk-stratification algorithm.

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