

Review

The CALLY Index in Critical Illness: Risk Stratification and Its Potential Role in Clinical Monitoring

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Abstract

Background: Critically ill patients frequently exhibit concurrent inflammatory activation, nutritional depletion, and immune dysfunction. Although several laboratory-derived indices exist, there is a growing demand for simple, multi-dimensional prognostic markers in acute settings. The CALLY index integrates inflammatory burden, protein reserve, and immune competence. For intensive care practice, its greatest potential lies in rapid, cost-effective bedside risk stratification and dynamic monitoring. **Methods:** We conducted a systematic narrative review of studies published from January 2021 to February 2026 in PubMed, Web of Science, and Scopus. Eligible studies evaluated the CALLY index in adult populations and reported its association with at least 1 clinical outcome. A total of 56 studies met the inclusion criteria. Given substantial heterogeneity, a structured narrative review was performed rather than meta-analysis, with particular attention to sepsis and critically ill patients. **Results:** Across disease settings, lower CALLY values were generally associated with worse outcomes. The strongest evidence was observed in oncology and in sepsis/critical illness. Among ICU studies, lower CALLY values were associated with higher short-term mortality and greater disease severity. However, current evidence is limited by predominantly retrospective designs, variable cutoff values, and insufficient external validation of incremental value beyond established tools such as SOFA and APACHE II. **Conclusions:** CALLY is a simple, accessible composite biomarker for ICU risk assessment. While useful as an adjunct tool, prospective multicenter studies are required to define its optimal timing and incremental clinical utility in critical care.

Keywords: CALLY index; critical illness; intensive care unit; sepsis; risk stratification



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1. Introduction

Inflammation, nutritional reserve, and immune competence are central determinants of outcome in critical illness [1]. In the intensive care unit (ICU), systemic inflammation, capillary leak, protein depletion, and lymphopenia frequently coexist, shaping short-term prognosis and treatment response. Although routinely available laboratory indices—such as the neutrophil-to-lymphocyte ratio [2], platelet-to-lymphocyte ratio (PLR) [3,4], Glasgow Prognostic Score (GPS) [5], and prognostic nutritional index (PNI) [6]—reflect isolated biological pathways, they often fail to capture the multi-dimensional host response of critically ill patients. Consequently, there is a clinical demand for simple, rapidly obtainable, and integrated biomarkers that can complement established severity scoring systems.

The C-reactive protein–albumin–lymphocyte (CALLY) index has emerged as a composite biomarker that mathematically balances protective host reserves against acute systemic inflammatory stress [7].

$$\text{CALLY} = (\text{Albumin} \times \text{Lymphocyte count}) / (\text{CRP} \times 10^4)$$

By combining these three routinely measured clinical domains into a single score (typically ranging from 0 to 15), the CALLY index tracks the rapid convergence of hyperinflammation, endothelial leakage, and adaptive immune dysfunction [8–10]. Its application in acute settings relies on setting-specific prognostic thresholds that adjust to the underlying pathologies [11–13].

While initially validated in oncology [14], emerging evidence highlights the CALLY index as a promising tool for infection and critical illness, where its constituent domains align closely with the pathophysiology of sepsis. Crucially, the index is not intended to replace multi-organ dysfunction tools like the Sequential Organ Failure Assessment (SOFA) or APACHE II scores. Instead, it serves as a distinct biological axis reflecting immuno-nutritional exhaustion—offering potential value for bedside risk enrichment, patient phenotyping, and exploratory serial monitoring.

This systematic narrative review addresses three core clinical questions: (1) What is the current evidence supporting the CALLY index in sepsis and critically ill populations? (2) What prognostic value does this biomarker add beyond conventional ICU severity scores? (3) What methodological limitations must be addressed before broader clinical adoption can be considered?

2. Materials and Methods

2.1. Literature Search Strategy

A comprehensive literature search was conducted to identify studies evaluating the prognostic and clinical relevance of the CALLY index in critically ill and non-oncologic populations. Three electronic databases, namely PubMed (National Center for Biotechnology Information, National Library of Medicine, Bethesda, MD, USA), Web of Science Core Collection (Clarivate Analytics, Philadelphia, PA, USA), and Scopus (Elsevier B.V., Amsterdam, The Netherlands), were systematically searched for articles published between 1 January 2021 and 28 February 2026.

The search strategy combined terms related to the CALLY index and its individual components with terms related to prognosis and critical illness. Representative search terms included: (“CALLY index” OR “CRP albumin lymphocyte index” OR “C-reactive protein albumin lymphocyte”) AND (prognosis OR mortality OR outcome OR survival OR critical illness OR intensive care OR sepsis).

Additional manual searches of reference lists from relevant articles were performed to identify potentially eligible studies not captured through database searching.

To ensure methodological rigor and high-quality reporting, this review followed established elements of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses PRISMA 2020 Statement (PRISMA Group, Ottawa, ON, Canada) guidelines [15], including a standardized screening workflow. PRISMA checklist can be found in Supplementary Materials. However, the protocol was not formally registered in a public registry (such as PROSPERO) because a qualitative narrative synthesis was deliberately selected instead of a formal quantitative meta-analysis. This decision was dictated by the profound clinical and methodological heterogeneity across the included cohorts regarding baseline disease severity, measurement timing, cutoff thresholds, and clinical endpoints, meaning

the primary objective was to map the available evidence landscape rather than to generate pooled effect estimates.

2.2. Eligibility Criteria

Studies were considered eligible if they met all of the following criteria:

Included adult patients (≥ 18 years);

Evaluated the CALLY index as an exposure variable, prognostic marker, or risk stratification tool;

Reported at least one clinically relevant outcome, including mortality, disease severity, complications, recurrence, functional outcomes, or survival endpoints;

Used an observational cohort, case-control, or cross-sectional study design;

Were published in peer-reviewed journals and are available in English.

Studies were excluded if they: Were review articles, editorials, letters, conference abstracts, or case reports;

Included pediatric populations;

Were animal or in vitro studies;

Did not evaluate clinical outcomes associated with the CALLY index;

Represented duplicate publications derived from overlapping cohorts.

2.3. Study Selection

Study selection was performed independently by two reviewers. After removal of duplicate records, titles and abstracts were screened for potential relevance. Full-text articles were subsequently reviewed to determine final eligibility according to the predefined inclusion and exclusion criteria. Any disagreement regarding study eligibility was resolved through discussion and consensus. When consensus could not be reached, a third senior reviewer adjudicated the decision. The study selection process is summarized in Figure 1.

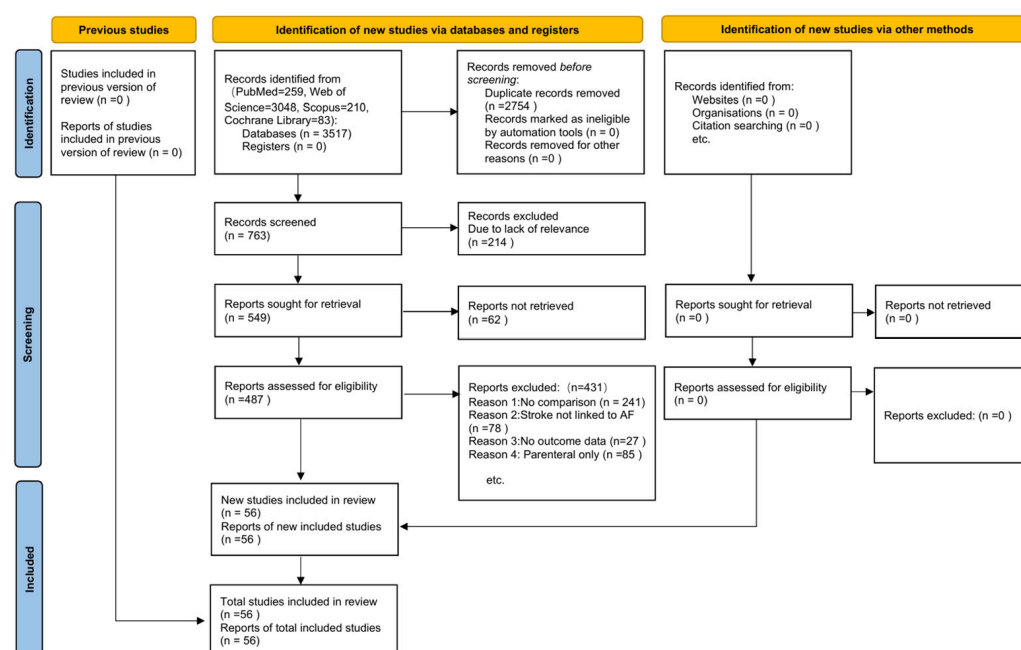


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Flow Diagram of the Study Selection Process. PRISMA Flow Diagram of the Study Selection Process. This flowchart illustrates the multi-stage database screening, retrieval, and exclusion workflow spanning 1 January 2021 to 28 February 2026, culminating in the inclusion of 56 peer-reviewed studies for narrative synthesis.

2.4. Data Extraction

Data extraction was independently performed by two investigators using a standardized extraction form. The following variables were collected from each study: First author; Publication year; Country; Study design; Study setting; Sample size; Patient population; Timing of CALLY assessment; CALLY cutoff value and derivation method; Clinical outcomes evaluated; Follow-up duration; Statistical adjustment variables; Effect estimates (hazard ratios, odds ratios, confidence intervals, AUC values); Main study findings. Discrepancies in extracted data were resolved through joint review and consensus.

2.5. Quality Assessment and Risk of Bias Evaluation

To improve methodological transparency and facilitate interpretation of the evidence base, the methodological quality of included observational studies was assessed using the Newcastle–Ottawa Scale (NOS). The NOS evaluates three major domains: (1) Selection of study participants; (2) Comparability of study groups; (3) Assessment of outcomes. Studies scoring 7–9 points were considered high quality, 5–6 points moderate quality, and <5 points low quality. Quality assessment was performed independently by two reviewers, with disagreements resolved through discussion. Particular attention was paid to studies conducted in sepsis and intensive care populations, given their direct relevance to critical care practice.

2.6. Data Synthesis

Given the substantial heterogeneity among studies with respect to patient populations, disease settings, outcome definitions, timing of CALLY measurement, and cutoff determination methods, a formal quantitative meta-analysis was not performed. Instead, findings were synthesized narratively, with particular emphasis on: Sepsis and septic shock; General ICU populations; Dynamic monitoring applications; Comparisons with established prognostic tools; Evidence from other high-risk clinical settings that support biological plausibility. The strength of evidence was interpreted in the context of study quality, consistency of findings, and relevance to intensive care medicine.

3. Biological Rationale for the CALLY Index in Critical Illness

The biologic relevance of the CALLY index to critical illness stems from the fact that its 3 components [16]—CRP, serum albumin, and lymphocyte count—closely reflect the parallel processes of inflammatory activation, protein depletion, and immune dysregulation driving ICU outcomes. CRP serves as an accessible marker of systemic inflammatory burden. However, because patients with comparable inflammation differ in their physiological reserve, integrating CRP with complementary markers provides a broader clinical perspective. In this context, serum albumin represents a complex interplay of systemic stress, endothelial capillary leakage, and hepatic synthetic function rather than a pure nutritional indicator in acute settings. This pathophysiological complexity is precisely what makes albumin valuable: when interpreted alongside CRP and lymphocyte count, it contributes vital information on a patient's capacity to withstand acute catabolic insult. Concurrently, the absolute lymphocyte count adds an adaptive immune dimension, where persistent lymphopenia signals impaired host defense and stress-induced apoptosis. Together, the C-reactive protein–albumin–lymphocyte score integrates these three fragmented domains into a compact representation of systemic dysregulation, offering a compelling biologic framework [17] for bedside risk enrichment in sepsis and inflammatory critical illness.

4. Evidence for the CALLY Index in Sepsis and Critical Illness

4.1. Sepsis and Septic Shock

Among nononcologic settings, sepsis and septic shock currently provide the most clinically relevant evidence base for evaluating the CALLY index in intensive care medicine. This is biologically plausible because sepsis is characterized by dysregulated inflammation [18], endothelial and microcirculatory dysfunction, capillary leakage, altered protein metabolism, and immune imbalance—precisely the domains captured by CRP, albumin, and lymphocyte count. In this sense, the CALLY index appears particularly well matched to the pathophysiology of septic illness.

Across available sepsis cohorts, lower CALLY values have generally been associated with higher short-term mortality, greater illness severity, and poorer early clinical outcomes [19]. Early investigation of biological thresholds in acute geriatric care [20] provides parallel insights into systemic patterns within acute illness. Studies conducted in emergency department sepsis populations suggest that the index may function as a simple early prognostic marker, whereas ICU-based observational studies indicate that lower CALLY values are linked to worse short-term outcomes in critically ill septic patients. More recently, the index has also been incorporated into composite prognostic models, including work combining the CALLY index with conventional severity assessment frameworks such as SOFA [21], thereby suggesting a possible role beyond simple correlation alone. While some database validations [22] confirm the prognostic value of composite indices in acute syndromes, other recent analyses in intensive care trauma settings suggest its incremental utility may be limited [23]. Collectively, these studies support the idea that the C-reactive protein–albumin–lymphocyte score may capture a clinically meaningful dimension of host vulnerability in sepsis.

From a critical care perspective, the importance of these findings lies not merely in the observation that low CALLY values are associated with mortality, but in what the index may represent biologically. A low score in sepsis corresponds to a phenotype of high inflammatory burden, reduced protein reserve [19], and immune dysfunction. This combination is intuitively aligned with the clinical picture of the high-risk septic patient—one in whom persistent systemic dysregulation may translate into organ failure, poor response to treatment, or delayed recovery. Thus, unlike some biomarkers that capture only 1 aspect of the septic response, the composite framework has potential appeal as a multidimensional signal of biologic instability.

At the same time, the current sepsis literature remains limited by important methodological constraints. Most studies are retrospective, many are single-center, and outcome definitions vary, with a primary focus on short-term mortality rather than broader ICU-relevant endpoints such as duration of organ support, functional recovery, or long-term outcomes. Cutoff values also differ substantially across cohorts, limiting direct comparison. Nevertheless, despite these limitations, sepsis remains the strongest nononcologic clinical setting supporting the translational relevance of the clinical score to intensive care medicine. Taken together, the evidence suggests that sepsis may represent one of the most promising scenarios for risk assessment in ICU practice. As summarized in Table 1, the methodological profiles of representative studies consistently demonstrate that lower CALLY values are associated with poorer clinical outcomes across various sepsis and critical care cohorts.

Table 1. Methodological profiles of representative studies investigating the prognostic performance of the CALLY index in patients with sepsis. The table summarizes the study design, patient population, sample size, timing of CALLY assessment, cutoff determination, outcome measures, covariate adjustment, and principal findings of the included studies. Despite variations in study design and cutoff selection, all studies consistently demonstrated that lower CALLY values were associated with poorer clinical outcomes. Data were synthesized from Sarıdaş et al. (2025) [16], Yılmaz, E.; Ak et al. (2025) [17], Zhang, J.; Zhao et al. (2024) [19], and Lin et al. (2025) [21]. Table 1 Summary Matrix of Methodological Profiles, Operational Cutoffs, and Clinical Endpoints of Core CALLY Index Validation Studies in Sepsis and Critical Care. Methodological Profiles and Parameters of Core CALLY Validation Studies in Sepsis. This matrix cross-references the patient phenotypes, sample sizes, threshold derivation strategies, and primary end points of foundational acute care cohorts.

First Author & Year	Study Design	Patient Population	Sample Size	Timing of CALLY Assessment	Cutoff Value & Derivation	Outcomes Evaluated	Key Adjustment Variables	Principal Findings
Sarıdaş & Çetinkaya (2025) [16]	Retrospective cohort	Emergency Department (ED) patients meeting sepsis criteria	N = 1026	At ICU admission/ED presentation	2.10 (Youden index)	28-day all-cause mortality	Age, comorbidity index, APACHE II, organ dysfunctions	CALLY < 2.10 was an independent risk factor for short-term mortality.
Yılmaz & Ak (2025) [17]	Retrospective cohort	Adult patients with medical/general sepsis	N = 194	Early post-admission or diagnosis	2.50 (ROC-curve maximization)	Mortality and demographic outcomes	Demographics, baseline organ failure, inflammatory biomarkers	Lower CALLY scores robustly predicted worse short-term clinical outcomes.
Zhang et al. (2024) [19]	Retrospective single-center cohort	Critically ill ICU patients with sepsis	N = 134	ICU admission	1.35 (Empirical/ROC analysis)	Short-term/ICU mortality	APACHE II, SOFA, baseline metabolic and immune status	Lower CALLY independently predicted elevated ICU mortality.
Lin et al. (2025) [21]	Retrospective multicenter cohort	ICU adult septic shock populations	N = 111	At diagnosis/early ICU admission	1.10–1.40 (Empirical split/ROC calibration)	Short-term mortality and clinical trajectories	SOFA, mechanical ventilation, lactate, fluid balance	Integration of CALLY into SOFA increased AUC from 0.76 to 0.86 (ΔAUC = 0.10).

4.2. General ICU Populations

Beyond sepsis-specific cohorts, the clinical score may also have broader relevance across heterogeneous ICU populations. Critically ill patients admitted to the ICU for a wide variety of conditions often share overlapping features of systemic inflammation, hypoalbuminemia, protein depletion, and immune suppression. These patterns are not unique to infection, and they may also arise in postoperative critical illness, trauma, acute neurologic injury, and cardiopulmonary instability. From this perspective, the score may have value not only as a sepsis-associated biomarker but also as a more general marker of critical illness severity and host vulnerability.

This broader interpretation is conceptually attractive because ICU populations are often highly heterogeneous in diagnosis yet biologically convergent in the mechanisms that influence short-term prognosis. A composite biomarker derived from routine laboratory tests may therefore help summarize a shared physiologic burden that cuts across diagnostic categories. However, compared with sepsis-focused studies, evidence from mixed ICU cohorts remains less well defined. Direct validation across heterogeneous critical care populations is still limited, and the relative performance of the index may differ according to case mix, timing of laboratory sampling, and treatment intensity. Accordingly, while the general ICU setting remains a plausible field for clinical application, the current evidence is strongest where inflammatory critical illness is most prominent.

4.3. Evaluation of Potential Value Beyond Established ICU Severity Scores

To justify the clinical adoption of the score in intensive care and emergency settings, it is insufficient to demonstrate that it merely retains statistical significance as an independent risk factor in multivariable regressions. Clinicians require precise quantification of its incremental predictive value when partitioned alongside or integrated into validated organ dysfunction scores like SOFA and APACHE II.

Available evidence from early critical care cohorts suggests a potential benefit in discriminative performance when integrating the score into standard multi-variable models. For instance, in a modeling study involving adult septic shock populations [20], the baseline SOFA score achieved a standard area under the receiver operating characteristic curve (AUC) for short-term mortality; when the index was mathematically integrated to form a composite multi-variable model, the discriminative accuracy indicated a potential increase, elevating the AUC from 0.76 to 0.86 ($\Delta\text{AUC} = 0.10$). Similarly, in a retrospective ICU cohort analyzed in previous research [18], adding the score to multivariable models containing both SOFA and APACHE II scores did not cause collinearity, and the index indicated an independent association with ICU mortality. This implies that the score captures aspects of host vulnerability—namely, lymphopenia and capillary-leak-driven hypoalbuminemia—that are mathematically uncaptured by the macro-organ failure cascades quantified by conventional tools.

However, these conclusions must be tempered by significant methodological limitations. The available literature consists almost entirely of retrospective, single-center, observational investigations. Crucially, none of these published critical care studies reported advanced metrics of risk reclassification or calibration, such as Net Reclassification Improvement (NRI), Integrated Discrimination Improvement (IDI), or formal calibration curves for the combined models. Consequently, while these early data indicate potential benefit, they remain insufficient to support the routine clinical use of the score in place of—or at the same level as—established, prospectively validated multi-variable prognostic systems like SOFA or APACHE II. Clinicians should interpret the score not as an autonomous directive, but as an exploratory, complementary tool.

To further contextualize the value of the composite index over traditional scores, evidence from available comparative data must be scrutinized. Although standard inflammation indices like the derived neutrophil-to-lymphocyte ratio (dNLR) have well-established prognostic roles in chronic diseases such as stage II and III colon cancer (where a dNLR > 3 stands as an independent hazard ratio for recurrence 2), their translation into hyper-acute critical care windows requires combination with organ failure metrics. As summarized in Table 1, when the index is added into multivariable models already adjusted for age, comorbidities, and baseline severity, it does not suffer from collinearity with SOFA or APACHE II scores. Instead, the score serves as a distinct biological axis, representing immuno-nutritional exhaustion and endothelial capillary leak—domains that mathematically precede the macro-structural organ damage captured by conventional physiologic checklists.

4.4. Potential Value for Serial Monitoring and Dynamic Assessment

Compared with more stable chronic disease settings, the ICU may provide a uniquely relevant context for serial assessment. In critically ill patients, inflammatory burden, fluid distribution, protein balance, and immune function often change rapidly over time, particularly during resuscitation, infection control, organ support, or recovery from acute physiologic insult. This raises the possibility that dynamic trajectories may offer more clinically informative signals than a single baseline measurement.

Conceptually, a persistently low value or a declining trajectory could reflect unresolved systemic dysregulation, ongoing catabolic stress, or failure to restore immune and inflammatory balance. Conversely, improvement in the index over time might parallel clinical stabilization, improved host response, or recovery of biologic reserve. Unlike static preoperative or baseline measurements in chronic disease, repeated assessment in critical illness is conceptually intriguing for tracking trajectory evolution; its true clinical capacity to capture real-time treatment response remains unproven. Because each component of the index fluctuates due to routine ICU interventions (e.g., fluid resuscitation, hemodilutes, albumin, and corticosteroids drive down lymphocytes), the dynamic interpretation of serial trends is highly confounded by standard intensive care and should currently be regarded strictly as a hypothesis-generating observation rather than an established clinical monitoring practice.

However, this promising concept remains only partially explored. Current studies have largely relied on admission or early single-time-point data, and evidence supporting serial guided monitoring in the ICU remains limited. Furthermore, the clinical interpretation of dynamic changes has not been standardized. Because each component of the index may shift for different reasons—including fluid administration, infection control, hepatic recovery, steroid exposure, or immunomodulatory treatment—the meaning of serial change is unlikely to be straightforward. For this reason, dynamic use of the score should currently be regarded as a hypothesis-generating area rather than an established application. Prospective ICU-focused studies are needed to determine whether serial trajectories can meaningfully track treatment response, persistent physiologic stress, or recovery in critically ill patients.

5. Supporting Evidence from Other High-Risk Clinical Settings

Importantly, the purpose of including these non-ICU studies is not to define clinical practice in critical care, but to support the biological plausibility and cross-context consistency of the CALLY index. To prevent diluting the ICU-centered message, this non-ICU literature must be interpreted hierarchically, distinguishing mature prognostic frameworks from early, non-acute associative data.

5.1. Oncology as the Most Mature Evidence Base

Among all currently studied settings, oncology represents the most mature external evidence base for the index. Multiple studies across digestive malignancies, urologic cancers [24], breast cancer [25], melanoma [26], and other solid tumors have shown that lower values are associated with poorer outcomes, including reduced overall survival, shorter disease-free survival, higher recurrence risk, and worse postoperative outcomes. The consistency of these findings is especially notable in digestive system cancers, where the signal has been observed across multiple cohorts and further supported by systematic synthesis. Pretreatment score serves as a promising novel biomarker in the prediction of surgical and oncological outcomes in esophageal cancer [14]. For intensive care medicine, this robust oncological evidence reinforces the conceptual validity of the score as an immuno-nutritional proxy, though direct clinical translation still requires validation in acutely ill populations rather than extrapolation from malignant cohorts.

5.2. Neurologic and Cardiovascular Conditions

In acute neurologic and cardiovascular conditions, the index acts as a reactive marker of stress and frailty, though its immediate utility in rapid ICU triage remains less defined than in sepsis. In neurologic disease, available reports indicate associations with stroke risk, hemorrhagic transformation, and functional outcome in acute ischemic stroke [27], while associations of neutrophil-percentage-to-albumin ratio with mortality have also been explored in older stroke survivors [8]. Essential amino acid supplementation may attenuate systemic inflammation and improve hypoalbuminemia in subacute hemiplegic stroke patients [9]. Similarly, cardiovascular studies suggest that lower values are often associated with worse outcomes in settings such as acute coronary syndromes [28], post-percutaneous coronary intervention populations [29], heart failure with preserved ejection fraction, and peripheral vascular disease [30–32]. In elderly patients with chronic coronary syndrome, indices predict acute coronary syndrome [33]. However, these cardiovascular and neurological signals are highly context-dependent. They reflect background chronic frailty or systemic secondary injury, and do not establish the same level of acute, short-term translational promise as sepsis-focused investigations.

5.3. Chronic Inflammatory and Metabolic Disorders

In chronic inflammatory, metabolic, rheumatologic, and aging-related conditions, the clinical index functions strictly as an indicator of baseline physiologic vulnerability rather than an acute prognostic instrument. Extrapolating these findings directly to the ICU is inappropriate due to the non-acute nature of the data. Validated associations have been reported with metabolic syndrome, sarcopenia [34–37], depression-related risk [38–41], rheumatoid arthritis activity or mortality [42,43], and frailty-related outcomes in older adults. Specifically, higher index levels indicate lower sarcopenia risk among middle-aged and elderly community residents as well as hospitalized patients [37], while the score exhibits an L-shaped association with all-cause mortality in rheumatoid arthritis patients [42]. Furthermore, persistent depressive symptoms are linked to HPA-axis hyperactivity and inflammation [39], and obesity acts as a linking mechanism for systemic complications [41]. Crucially, because these fields rely predominantly on database-based or retrospective cross-sectional designs, they provide zero insight into dynamic real-time treatment response or acute critical care windows. Their relevance is strictly confined to proving that the index tracks long-term systemic dysregulation. As illustrated in Figure 2, the hierarchical evidence stratification pyramid demonstrates varying degrees of evidence intensity for the CALLY index across diverse clinical contexts, ranging from the strong

evidence zone in malignant tumors and critical care to emerging relevance zones in chronic metabolic disorders.

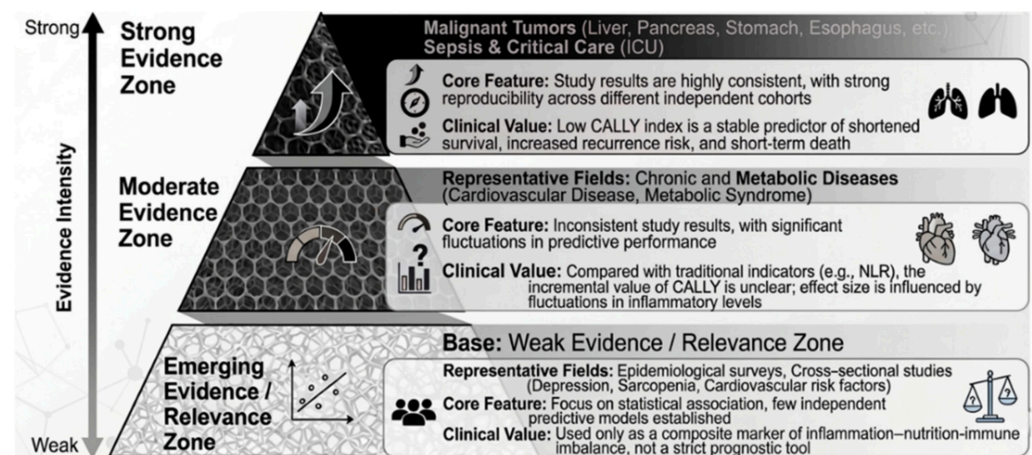


Figure 2. Hierarchical Evidence Stratification Pyramid of the CALLY Index Across Diverse Clinical Contexts.

6. Practical Implications for Intensive Care Medicine

From the perspective of intensive care medicine, the clinical appeal of the CALLY index lies in its simplicity, accessibility, and biologic breadth. All 3 components of the index—CRP, albumin, and lymphocyte count—are routinely available in many critically ill patients, allowing calculation without additional laboratory burden, cost, or delay. In a clinical environment where bedside decisions often must be made rapidly, this practicality is an important advantage. Unlike emerging biomarkers that require specialized assays or have a delayed turnaround, the CALLY index can be incorporated into early assessment using information already embedded in routine ICU care.

Its most plausible role in the ICU is as an adjunctive biomarker rather than a stand-alone prognostic instrument. The CALLY index should not be interpreted as a substitute for established severity scores, such as SOFA or APACHE II, nor should it be viewed as an independent trigger for treatment decisions in isolation. Instead, its potential value lies in adding biologically relevant context to conventional physiologic assessment. Whereas organ failure scores quantify the severity of current dysfunction, the CALLY index may help characterize a related but distinct dimension of host vulnerability—one shaped by inflammatory burden, impaired protein reserve, and immune dysregulation. This distinction may be particularly relevant in critically ill patients whose organ dysfunction severity appears similar by conventional scoring but whose systemic biologic reserve differs substantially.

In practical terms, the index may be most useful during early bedside risk enrichment. At ICU admission or during the initial management of sepsis and other inflammatory critical illness, the CALLY index may help identify patients with a high-risk biologic phenotype in whom systemic dysregulation is already pronounced. This could support prognostic assessment, guide the intensity of early monitoring, and contribute to a more nuanced interpretation of illness severity. Importantly, this proposed value remains complementary: the index may refine clinical judgment, but it cannot replace direct evaluation of hemodynamics, organ dysfunction, treatment response, or trajectory over time.

A second potential application is serial reassessment during the ICU course. Because critical illness evolves dynamically, repeated CALLY assessment may theoretically help clinicians appreciate whether systemic dysregulation is resolving or persisting. For example, a persistently depressed index might raise concern for ongoing inflammatory stress, protein depletion, or impaired immune recovery, whereas improvement over time might parallel

broader physiologic stabilization. However, this application remains preliminary and should be interpreted cautiously. Each component of the index may change for different reasons, and serial values may be influenced by resuscitation strategies, infection source control, hepatic recovery, corticosteroid use, or immunomodulatory therapy. At present, serial monitoring should therefore be viewed as a promising but unvalidated ICU use case rather than an established bedside strategy.

Finally, the CALLY index may have value as a research-oriented enrichment variable in critical care studies. Because it integrates multiple biologic domains relevant to prognosis, it could potentially be incorporated into multivariable models, stratification frameworks, or phenotype-based analyses of critically ill populations. From a translational standpoint, this may prove to be one of its most important immediate applications: not necessarily to direct bedside treatment on its own, but to help identify clinically meaningful subgroups of ICU patients for future prognostic validation and targeted investigation.

7. Sources of Heterogeneity and Current Limitations

7.1. Conceptual Distinction and Transitional Gaps: From Association to Actionable Utility

To avoid overestimating the translational maturity of the index in acute care, it is methodologically essential to explicitly distinguish biological plausibility and prognostic association from true actionable clinical utility. The core pathophysiological alignment of the index is established: the convergence of systemic inflammation (elevated CRP), capillary leak/metabolic stress (hypoalbuminemia), and adaptive immunoparalysis (lymphopenia) closely mirrors the processes driving sepsis progression. Correspondingly, multiple retrospective cohorts [16,19,21] have documented a robust statistical correlation between lower baseline values and short-term mortality. However, statistical correlation at a single early time point does not automatically equate to actionable clinical utility at the bedside. At present, there are zero prospective studies or randomized controlled trials demonstrating that clinical decision-making or patient outcomes are improved when guided by specific thresholds. Until prospective interventional investigations confirm that guided triage can safely alter therapeutic paths or reduce organ failure duration, its bedside application must be restricted to an adjunctive tool for exploratory risk enrichment rather than an actionable clinical directive.

This limitation is highly prominent when considering dynamic monitoring. While tracking serial trajectories to evaluate real-time treatment response is conceptually appealing, the current critical care literature relies almost entirely on static baseline data. Furthermore, because individual components of the index fluctuate rapidly due to routine ICU interventions—such as fluid resuscitation, diluting albumin or exogenous corticosteroid therapy suppressing lymphocyte counts—interpreting dynamic trends remains heavily confounded.

7.2. Methodological Limitations of the Current Review

Beyond the inherent biases within the primary literature, several methodological constraints of this review itself must be explicitly acknowledged. First, our literature search was strictly restricted to peer-reviewed publications available in the English language, potentially omitting relevant localized cohorts or grey literature published in other languages. Second, due to the profound clinical heterogeneity in study environments (ranging from emergency triage to established septic shock), variable cutoff derivation methods, and scattered endpoint definitions across the included 56 studies, a formal quantitative meta-analysis was neither feasible nor statistically appropriate. Third, while the Newcastle–Ottawa Scale was utilized to provide a transparent overview of study quality, a formal systematic risk-of-bias assessment across all endpoints was not conducted. Consequently,

this work should be interpreted strictly as a structured narrative and analytic synthesis aimed at mapping an emerging biomarker field, rather than a definitive meta-analytical framework.. As detailed in Figure 3, the diagnostic mapping of methodological heterogeneity reveals that published CALLY index literature exhibits significant variations spanning disease backgrounds, measurement timepoints, threshold selections, and study endpoints.

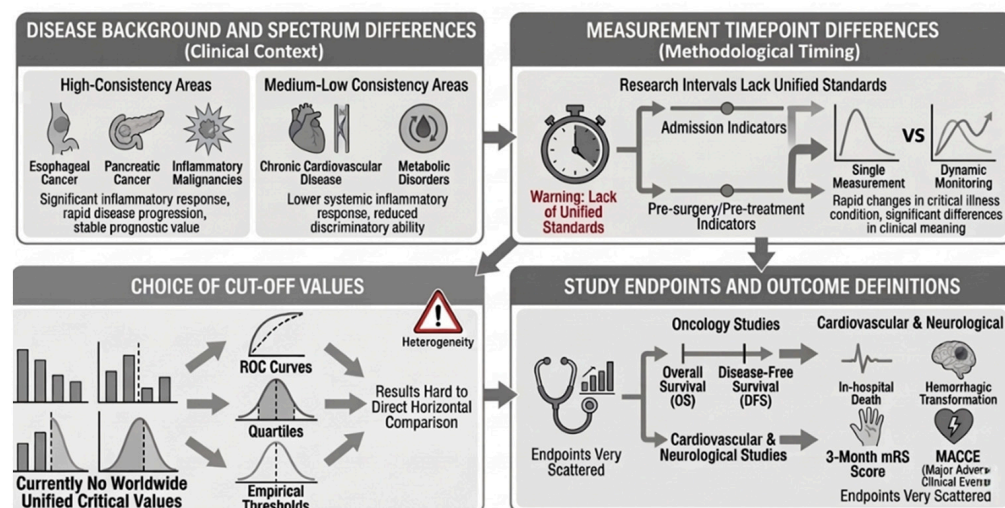


Figure 3. Diagnostic Mapping of Methodological Heterogeneity and Clinical Confounders in Published CALLY Index Literature.

8. Future Directions for ICU-Focused Research

Future investigations should focus on standardizing key methodological aspects of CALLY index research, including the timing of laboratory assessment, derivation of clinically relevant cutoff values, and selection of outcome measures. Harmonized study designs will facilitate comparisons across cohorts and improve the interpretability of future evidence.

Another important priority is the evaluation of longitudinal CALLY trajectories. Prospective studies should determine whether temporal changes in the index reflect treatment response, persistent physiologic stress, or recovery, while accounting for potential confounding effects of fluid resuscitation, corticosteroid therapy, and other common ICU interventions.

Large multicenter cohorts with external validation are also required to evaluate the reproducibility and generalizability of existing findings across different healthcare systems and critically ill populations. Incorporation of modern model evaluation techniques, including calibration and reclassification analyses, would further clarify the incremental value of the index within contemporary ICU prognostic models.

Collectively, these efforts will help define the most appropriate role of the CALLY index in future critical care research and establish a stronger evidence base for its potential clinical application.

9. Discussion

9.1. Clinical Relevance of the CALLY Index in Critical Illness

The present review indicates that the CALLY index is an emerging composite biomarker with particular relevance to critical illness. Across the currently available literature, the strongest nononcologic evidence originates from patients with sepsis and critical illness, where systemic inflammation, hypoalbuminemia, and immune dysfunction frequently coexist. This biological convergence provides a plausible explanation for

the consistent association between lower CALLY values and adverse clinical outcomes observed across multiple cohorts.

Rather than representing a disease-specific marker, the CALLY index may reflect a broader state of host vulnerability characterized by inflammatory activation, impaired protein reserve, and immune dysregulation. This multidimensional framework may explain why the index has demonstrated prognostic associations across diverse clinical settings, including oncology, cardiovascular disease, neurologic disorders, and chronic inflammatory conditions. However, the consistency of these associations should not be interpreted as equivalent levels of clinical evidence. At present, the most clinically relevant data for intensive care practice remain those derived from sepsis and ICU populations, whereas evidence from other disease settings primarily supports the biological plausibility of the index rather than its direct applicability to acute critical care.

9.2. Summary of Current Evidence and Remaining Challenges

Although the available literature consistently demonstrates an association between lower CALLY values and poorer outcomes, the current evidence base remains methodologically limited. Most studies are retrospective and single-center, with substantial heterogeneity in patient populations, measurement timing, cutoff derivation, and outcome definitions. These factors restrict direct comparison across studies and reduce the certainty of pooled interpretation.

Another important limitation is the lack of standardized evaluation of incremental prognostic performance. Few studies have incorporated calibration analysis, reclassification metrics, or external validation. Consequently, future research should emphasize methodological consistency in addition to prospective validation, thereby providing a more robust framework for evaluating the clinical significance of the CALLY index.

9.3. Heterogeneity of Cutoff Values and Prognostic Interpretability in Critical Care

A primary methodological challenge confronting the translational adoption of the index is the substantial cross-study heterogeneity in the selected prognostic thresholds and cutoff values.

In acute and hyper-inflammatory cohorts, the optimal mathematical thresholds vary profoundly based on the baseline severity of the population and the anatomical timing of blood draws. In emergency department (ED) settings involving generalized sepsis populations, previous research [15] derived an optimal cutoff value of 2.10 using standard Receiver Operating Characteristic (ROC) curve maximization via the Youden Index, where scores below 2.10 independently predicted 28-day all-cause mortality. Similarly, related investigations [16] reported a proximal operational baseline cutoff of 2.50 for early risk stratification in general medical wards.

However, when advancing into intensive care unit (ICU) environments populated by critically ill septic shock patients, the threshold dynamics change significantly. In a key retrospective cohort [18], the optimal prognostic cutoff dropped to 1.35, reflecting the severe baseline immune exhaustion and profound capillary leak prevalent in established multi-organ dysfunction syndrome (MODS). Furthermore, multi-variable modeling established that fixing static thresholds yields inferior clinical calibration compared to integrated risk modeling (such as a composite SOFA+CALLY model), because aggressive fluid resuscitation dynamically hemodilutes albumin concentrations, while exogenous corticosteroid administration severely drives down absolute lymphocyte counts.

This variance indicates that the clinical interpretability of a 'low' versus 'high' value cannot be governed by a single universal threshold. Instead, thresholds must be interpreted as approximate operational ranges based on the clinical environment: Available evidence

suggests that cutoff values around 2.0–2.5 have been reported in emergency department cohorts, whereas lower thresholds of approximately 1.1–1.4 have been observed in ICU populations. These values should be interpreted as study-specific operational ranges rather than universally applicable clinical thresholds.

10. Conclusions

The CALLY index is a simple composite biomarker integrating inflammatory activity, protein reserve, and immune status. Current evidence suggests that its greatest potential in critical care lies in identifying biologically vulnerable patients, particularly in sepsis and other inflammatory conditions.

Despite encouraging observational findings, the existing evidence remains insufficient to support routine implementation in clinical decision-making. Standardized prospective multicenter studies are required to determine its incremental prognostic value, optimal timing of assessment, and clinical applicability across diverse ICU populations.

Until such evidence becomes available, the CALLY index should be regarded as a complementary biomarker for risk assessment rather than an independent guide for therapeutic decision-making.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/ecm3030023/s1>, PRISMA 2020 Checklist.

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Abbreviations

The following abbreviations are used in this manuscript:

NLR	neutrophil-to-lymphocyte ratio
PLR	platelet-to-lymphocyte ratio
PNI	prognostic nutritional index
CALLY	C-reactive protein–albumin–lymphocyte
GPS	Glasgow Prognostic Score
CRP	C-reactive protein

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