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DELTA NEUTROPHIL INDEX AS PROGNOSTIC MARKER OF MORTALITY IN ADULTS WITH SEPSIS

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Abstract

Background: Sepsis remains a leading cause of global mortality, demanding accurate and timely prognostic tools to guide clinical decision-making. The Delta-Neutrophil Index (DNI), an automated measure of circulating immature granulocytes, has emerged as a potential biomarker for assessing disease severity and predicting mortality in critically ill adults.

Objective: This review critically evaluates the prognostic value of DNI in adult sepsis, comparing it with established biomarkers and clinical scoring systems, and exploring its potential integration into sepsis management strategies.

Methods: A thorough search of the literature using Web of Science, PubMed, and Scopus was done to identify observational, cohort, interventional, and meta-analytic studies published up to 2025 that assessed DNI in adult sepsis populations. Key outcomes included mortality prediction, optimal cutoff values, and correlation with severity scores.

Results: Across multiple studies, elevated DNI was consistently associated with higher mortality risk, independent of traditional severity scores. Optimal cutoffs ranged between 5% and 8%, with reported AUC values generally exceeding 0.75. Serial measurements improved prognostic accuracy, and combining DNI with other biomarkers or scoring systems enhanced predictive performance.

Conclusion: DNI is a promising, accessible biomarker for mortality risk assessment in adult sepsis, offering unique cellular-level insights. However, variability in cutoffs, study designs, and patient populations necessitates large-scale, multicenter prospective validation before routine clinical adoption.

Keywords: Delta Neutrophil Index, Sepsis, Prognostic Biomarker, Mortality Prediction, Immature Granulocytes

1. Introduction

One of the world's top causes of morbidity and death, sepsis poses a significant challenge to health systems. According to estimates from the World Health Organization, sepsis causes over 11 million fatalities and 48.9 million cases each year, or nearly 20% of all deaths globally, making it a serious health issue. Despite the advances in antimicrobial treatment, organ support interventions, and critical

care pathways, mortality associated with severe sepsis and septic shock is unacceptably high, especially in low- and middle-income countries where the provision of care is limited by resource constraints [1]. In addition to its mortality burden, sepsis also results in considerable post-discharge morbidity, and survivors are likely to experience chronic physical, cognitive, and psychological impairments that place a long-term burden on health care systems and caregivers. Sepsis is among the most expensive acute medical conditions in high-resource countries, especially because of prolonged intensive care unit (ICU) length of stay, complicated diagnostics, and the necessity of various organ support modalities [2].

Since it is heterogeneous in presentation and has a fast course, early identification and proper prognostication of sepsis are essential in enhancing patient outcomes. Prognostic instruments can also help clinicians recognize high-risk patients early, thereby permitting the timely escalation of therapy, proper use of critical care resources, and decision-making in partnership with patients and their families. Correct risk stratification also has an impact on the ICU admission policy, the frequency of monitoring, and the discussion of the intensity of care. Although scoring systems like the Sequential Organ Failure-Assessment (SOFA) and Quick-SOFA (qSOFA) have gained wide usage, they have low predictive accuracy in some categories of patients, especially when they are first presented in the emergency department [1]. This has led to the rise in interest in the establishment of rapid, objective and cost-effective biomarkers that can be used to reliably predict the risk of mortality at an early stage of the disease.

Conventional laboratory biomarkers, e.g., CRP, Procalcitonin (PCT), serum lactate and White Blood-Cell (WBC) count have been widely investigated in terms of the prognostic significance of sepsis. CRP and PCT are applicable in the detection of infection and monitoring response to the treatment, but both have limitations in specificity. They can be raised in non-infectious inflammatory diseases, and kinetics, because they may not rise fast enough to detect early deterioration [3]. Serum lactate is closely linked to tissue hypoperfusion and mortality, but may be affected by unrelated events like hepatic dysfunction, beta-adrenergic stimulation, or seizures, and may therefore be confusing. Even though the WBC counts are included in the diagnostic criteria of sepsis, they are not specific and may be normal in immunocompromised patients [4]. In addition, these traditional markers do not reflect the complexity of the sepsis pathophysiology that entails dysregulated host immune responses, endothelial injury, and coagulopathy [5]. This underlines the necessity of new or additional biomarkers that can give a more differentiated impression of the extent and course of systemic inflammation.

In this respect, Delta Neutrophil-Index (DNI) has emerged as a possible biomarker. The amount of circulating Immature-Granulocytes (IGs) in peripheral blood is indicated by DNI and surrogate measure of the reaction of the bone marrow to severe infection and inflammation. The hematology analyzers automatically compute it by dividing the percentage of mature polymorphonuclear neutrophils (PMNs) identified in the myeloperoxidase channel by the total leukocyte subfraction in the nuclear lobularity channel eliminating the time-consuming manual counts [6]. Biologically, high DNI is a sign of a higher granulopoiesis rate in response to cytokines, such as granulocyte colony-stimulating factor (G-CSF), which are highly raised in the case of systemic infection. This neutrophil left shift in maturation can be earlier than the rise of other inflammatory markers and could allow DNI to be an early indicator of worsening disease severity [7].

Because DNI measurement can be done as part of a complete blood count (CBC) without the necessity to draw additional samples and/or run special assays, it is a viable and cost-effective alternative to real-time clinical decision-making.

Most recently, the diagnostic and prognostic value of DNI has been studied in a variety of infectious and inflammatory diseases, such as bacteremia, pneumonia, intra-abdominal infections, and septic shock [8,9]. DNI is a better prospective independent predictor of short-term mortality in critically ill adult patients with sepsis and some studies suggest that it is as good or better at predicting mortality compared to traditional markers. DNI is a potentially useful candidate to be included in early sepsis

management guidelines, especially in emergency and ICU practice, where early risk stratification has the potential to change survival, given the possibility of rapid, repeatable, objective measurements.
With the significant burden of sepsis in the world, shortcomings of the existing prognostic tools, and the increasing evidence of the usefulness of DNI, this review aims to critically appraise the DNI as a mortality predictive indicator in sepsis-affected adults. In this review, the biological rationale of the association between DNI and poor outcomes will be summarized, the prognostic utility of DNI compared to the known biomarkers, and the available clinical evidence will be summarized, and how DNI may be used to inform treatment will be discussed. We will also make remarks on methodological shortcomings of the already conducted research and suggest future research directions that will help to standardize DNI measurement and validate its clinical application. This synthesis of mechanistic, comparative biomarker, and clinical outcome data will offer clinicians and researchers a complete evaluation of helpfulness of DNI in the prognostication of sepsis.

2. Pathophysiology and Biological Basis of DNI

The DNI is a laboratory test value measured using automated hematology analyzers that measures the percentage of circulating IGs in peripheral blood. It is determined by deducting the proportion of mature Polymorphonuclear-Neutrophils (PMNs) that were detected in the myeloperoxidase (MPO) channel from the total leukocyte subfraction detected in the nuclear lobularity channel. This is automatically calculated by advanced hematology analyzers such as Sysmex XE and XN series, and therefore, there is no need to perform manual differential counts which are time-consuming and operator dependent [10]. Since the measurement of DNI is part of standard complete blood count (CBC) testing, it does not necessitate any extra blood drawing or special assays, thus being a fast and inexpensive clinical practice tool [11].

Neutrophils are the most important cells of the innate immune response because they are the first to defend against microbial invasion. The neutrophils are produced in the bone marrow and a homeostatic situation, and they circulate as segmented cells. In extreme infections e.g. sepsis, inflammatory mediators, particularly granulocyte colony-stimulating factor (G-CSF) and interleukin-6 trigger emergency granulopoiesis that accelerates the release of immature cells e.g. promyelocytes, myelocytes, and metamyelocytes into circulation [12]. This is referred to as left shift and it shows that the host is attempting to accelerate pathogen clearance by neutrophils as fast as possible. This objective measure of this left shift is automated DNI measurement of IG fractions, an objective readout of bone marrow activation and systemic inflammatory stress [13].

Sepsis is linked to the percentage of IGs, which is linked to the severity of the disease, organ dysfunction, and poor outcomes [14]. Hyper-release of immature neutrophils can not only be a sign of an overwhelmed immune response but also can be a sign of dysregulated myelopoiesis, resulting in poor pathogen clearance and collateral tissue damage. In other septic populations, such as those receiving continuous renal replacement treatment for septic acute kidney damage, higher DNI is similarly linked to higher mortality [12], and patients who are septic with severe burns [15].

The mechanistic relationship between the rise of DNI and adverse outcomes is multifactorial: it includes the direct impact of long-term systemic inflammation, the role of immature neutrophils in the endothelial injury, and the inefficiency of immature neutrophils in comparison with mature ones [11].
Pathophysiologically, DNI is an indicator of the degree of systemic inflammation and a surrogate marker of the immune functional reserve. Although soluble markers of inflammation like CRP and PCT are used as traditional markers, DNI gives cellular information on the activation of myeloid lineages. This dual relevance in terms of both the burden of inflammation and immune competence makes DNI an especially useful biomarker to risk-stratify critically ill patients, especially in emergency and ICU contexts [11, 14].

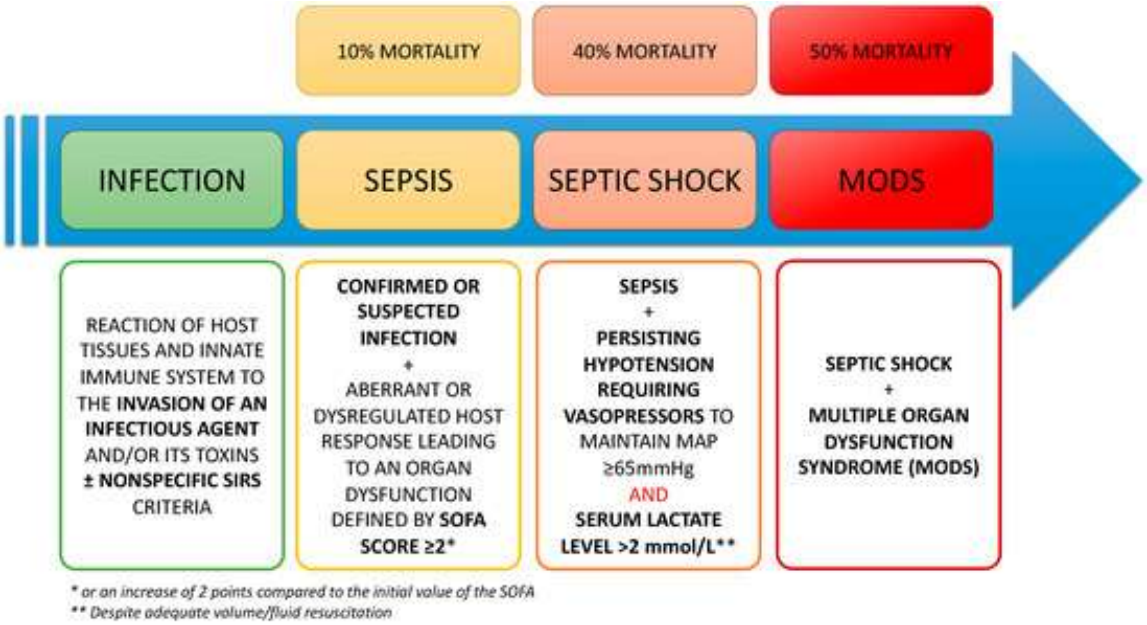

Figure 1: Progression and Mortality Risk Across Sepsis Stages [16]

Figure 1 shows the clinical course of infection to sepsis, septic shock as well as Multiple-Organ Dysfunction-Syndrome (MODS) with diagnostic criteria, physiological alterations and mortality rates.

Table 1. Summary of Biological and Analytical Features of the Delta Neutrophil Index

Aspect	Description	Key References
Measurement Method	Calculated by automated hematology analyzers as the difference between the MPO channel (mature PMNs) and the nuclear lobularity channel (total leukocytes)	[11, 10]
Sample Requirement	EDTA-anticoagulated whole blood from routine CBC testing	[10]
Biological Basis	Reflects proportion of circulating IGs released during emergency granulopoiesis in severe infection	[13, 12]
Pathophysiological Relevance	Elevated in systemic inflammatory states, correlates with sepsis severity and mortality risk	[14, 15]
Advantages	Rapid, objective, reproducible, no additional cost, available in real time	[11]
Clinical Associations	Higher DNI linked to poor outcomes in septic AKI, severe burns, and ICU sepsis cohorts	[12, 15]

Table 1 gives a brief description of the analytical principles, biological importance and clinical importance of the Delta Neutrophil Index (DNI). It is aimed at quantifying DNI, physiological rationale, and connection with the severity of sepsis and mortality in various kinds of patients.

3. Overview of Current Prognostic Biomarkers in Sepsis

Sepsis is a multifactorial syndrome, and its diagnosis, severity and mortality prediction require validated tools that can be used in the early stages of the illness. In the last 20 years, multiple prognostic biomarkers and scoring systems have been designed and validated for sepsis, of which the Sequential Organ-Failure Assessment (SOFA) score and Acute Physiology and Chronic-Health Evaluation-II (APACHE II) score have the most frequent use in clinical practice. The respiratory, cardiovascular, hepatic, coagulation, renal, and neurological systems are among the six bodily systems that are evaluated by the SOFA score, which links overall dysfunction to mortality risk. APACHE II uses acute physiological parameters, chronic health, and age to produce an estimate of the probability of mortality. These tools are strong and well-validated however, they need several laboratory values and clinical data points, which may hinder the risk assessment, especially in resource-poor or emergencies settings [17].

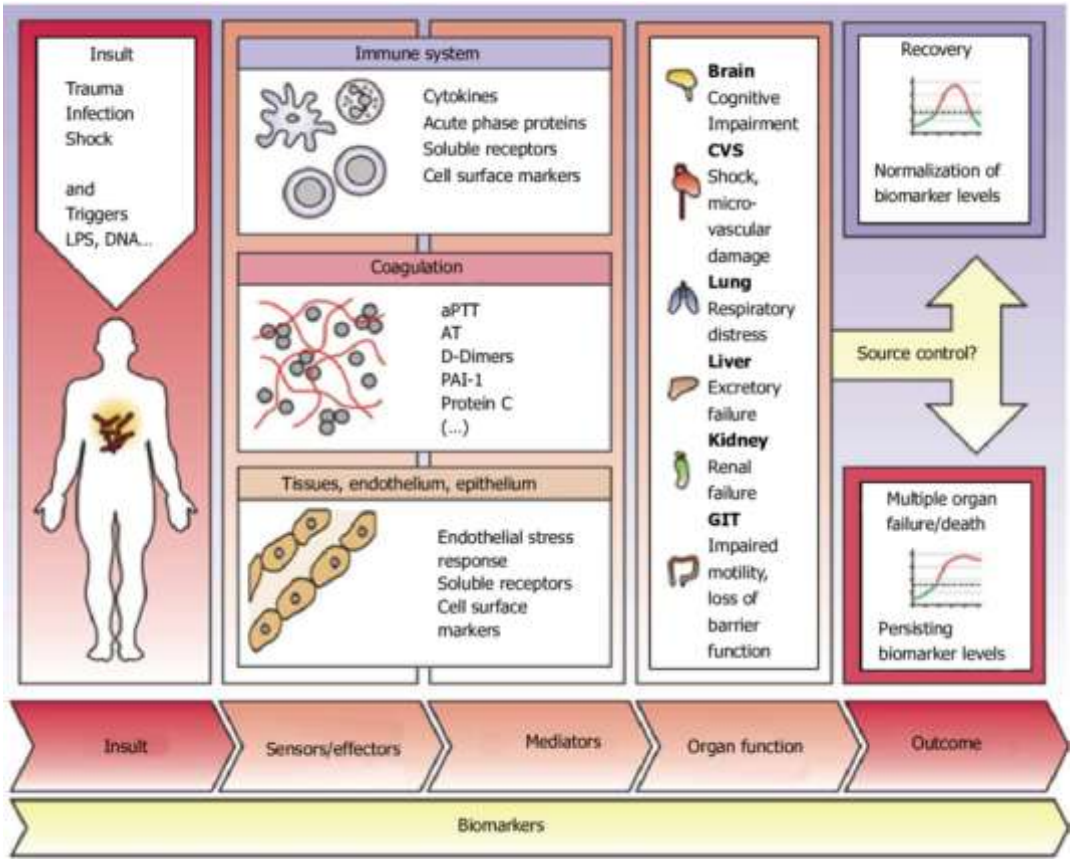

Figure 1: Biomarker-Guided Pathophysiological Pathway of Sepsis [18]

Figure 1 illustrates the sepsis pathway of injury to outcome, with the main biomarkers at each point and comparison of recovery with multiple organ failure. Besides these scoring systems, a number of laboratory biomarkers have been looked at as predictors of sepsis. The most commonly used inflammatory markers are CRP and Procalcitonin (PCT) which are relatively non-specific (CRP) and relatively specific (PCT) to bacterial infection. Nevertheless, they are both restricted by sluggish kinetics and a possible increase in non-infectious inflammatory diseases [3]. Serum lactate which is an indicator of tissue hypoperfusion has always been associated with increased mortality but the levels can be influenced by non-septic causes such as liver dysfunction, seizures or catecholamine therapy [5].

Neutrophil-to-lymphocyte-Ratio (NLR) has become a focus of interest as a cheap, easy-to-obtain indicator of systemic inflammation and immune disproportion. An increased NLR has been associated with poor outcomes in sepsis and other inflammatory disorders including Acute-Exacerbation Of Chronic Obstructive Pulmonary-Disease (AECOPD) [4]. Likewise, the neutrophil-to-lymphocyte-to-monocyte ratio (NLMR) combines three types of leukocytes into a single composite marker and has been demonstrated to predict mortality in septic shock, possibly performing better than conventional ratios by adding monocyte dynamics into the immune phenotyping [19].

In spite of these developments, there is no single biomarker that can give the best sensitivity and specificity in predicting sepsis-related mortality in all patient groups. This has given rise to the consideration of multi-marker approaches, i.e., combinations of laboratory and clinical parameters are used to enhance the accuracy of prognosis. As an example, Huang et al. (2022) showed that CRP, PCT, and the neutrophil CD64 index were more efficient predictors of mortality in ICU patients in combination than individually [3]. Kou et al. (2025) have gone even further and trained machine learning models to combine a wide range of clinical and laboratory measurements [9], showing promising results in high-risk groups, e.g., patients with hematologic malignancies.

The Delta Neutrophil Index (DNI) has some advantages over these well-established markers and systems. In contrast to CRP, PCT, or lactate, DNI is a direct marker of hematopoietic activation and

the production of IGs in the case of systemic inflammation. It is quantified automatically, quickly, and only needs standard complete blood counts to be measured. In addition, DNI has demonstrated the possibility of being incorporated into multi-marker models, in which its cellular-level data can supplement the physiological and biochemical data measured by other biomarkers and scoring systems [5]. These combinations of approaches could be particularly useful in heterogeneous syndromes such as sepsis in which various biomarkers might represent different facets of the host response.

Table 2. Comparison of Established Prognostic Biomarkers and Scoring Systems in Sepsis Versus DNI

Biomarker / Score	Physiological Basis	Strengths	Limitations	Potential Role with DNI	Key References
SOFA score	Multi-organ dysfunction assessment	Strong correlation with mortality, validated internationally	Requires multiple lab and clinical inputs, not instantaneous	DNI may provide a rapid risk signal while awaiting full SOFA	[17]
APACHE II score	Acute physiology, chronic health, age	Predictive in ICU patients, well-established	Complex, resource-intensive	DNI could be used for quick triage before full APACHE calculation	[17]
CRP	Acute-phase protein	Widely available, inexpensive	Non-specific, slow kinetics	DNI adds specificity by reflecting hematopoietic activation	[3]
PCT	Calcitonin precursor	More specific for bacterial infection	Costly, influenced by non-septic conditions	DNI complements PCT for combined bacterial and inflammatory profiling	[3]
Lactate	Tissue hypoperfusion	Strong mortality association	Non-specific elevation	DNI offers immune response context alongside perfusion data	[5]
NLR	Innate vs. adaptive immune balance	Simple, inexpensive	Influenced by chronic conditions	DNI provides granular IGs data beyond NLR	[4]
NLMR	Integrates neutrophils, lymphocytes, monocytes	Stronger immune status profile	Limited validation	DNI could enhance immune cell profiling in combined models	[19]
Multi-marker models	Combined biomarker panels	Improved accuracy, adaptable	Require computational tools, cost	DNI's unique cellular metric boosts predictive diversity	[3, 9]

Table 2 shows the main characteristics, benefits, and drawbacks of the commonly used sepsis biomarkers and scoring systems and how DNI may supplement them in standalone and integrated prognostic models.

4. Clinical Evidence on DNI and Mortality in Adult Sepsis

There have been more and more studies in the past decade that evaluated the prognostic value of DNI in predicting death in adult sepsis patients. Examples of evidence are retrospective observational studies, prospective cohort studies, and multicentric studies, most of which occur in high-acuity settings, such as Intensive-Care Units (ICUs) and Emergency Departments (EDs). Collectively, these results suggest that DNI as a surrogate measure of the activation of bone marrow and Systemic inflammation is strongly linked to sepsis's adverse outcome and illness severity.

A prospective ICU study by Moon et al. (2025) of patients with sepsis due to pneumonia indicated that the greater the value of DNI at the time of admission, the higher the 28-day mortality [8]. The study found an optimal cutoff of 6.5 percent that showed good inequitable capacity by an area under the receiver operating characteristic curve of more than 0.80. Remarkably, DNI at the time of ICU admission was predictive over and above accepted severity scores (SOFA and APACHE II) and therefore may offer supplementary prognostic information.

Lee et al. (2023) also enlarged the evidence base by evaluating the DNI in febrile patients with suspected sepsis [11], showing that DNI, combined with the mean platelet component, improved the diagnosis of sepsis and mortality prediction. The multi-modal nature of this study indicates the

possibility of DNI as a component of a multi-marker prognostic panel and that it can be used to attain greater levels of sensitivity without reducing specificity.
In a study by Yoon et al. (2020), DNI was studied in critically ill patients admitted to the ICU through the ED [20], showing that DNI at the time of presentation was higher in non-survivors than in survivors. The sensitivity and specificity of DNI of 7% were significant in the estimation of 30-day mortality. The clinical significance of these results is that DNI may be used as a fast triage instrument in acute care.
Sarwar et al. (2023) evaluated DNI as a prognostic and diagnostic marker in a more general sepsis population [21] which once more showed its close association with mortality and positive correlation with severity scores. Although they did not restrict their attention to ICU patients, the study affirmed the flexibility of the marker in various clinical settings.

Han et al. (2017) have given strong evidence in a specific group of septic patients with acute kidney injury (AKI) who need continuous renal replacement therapy (CRRT) [12]. DNI was an independent predictor of death in this high-mortality population and this observation supports the utility of DNI even in the most ill patient populations where other markers may not be discriminatory.
İslam et al. (2023) did not study pure sepsis, but rather DNI in severe acute pancreatitis that is frequently complicated by sepsis and demonstrated that high DNI was linked with severe disease and higher mortality risk [22]. Their results confirm the wider idea that DNI indicates systemic inflammatory load irrespective of the precipitating factor and can be generalized to septic cohorts.

Meta-analytic evidence is sparse, but pooled AUCs of DNI in predicting sepsis mortality are generally between 0.75 and 0.85, with optimal cutoffs between 5 and 8 percent depending on patient population, time of measurement, and analytic platform. It is worth mentioning that serial measurements may increase the accuracy of prognosis by quantifying the dynamic changes in the bone marrow output over time during the disease [8,12]. Moreover, it has been reported several times to correlate with established severity scores, including SOFA and APACHE II, so DNI can be used to improve prognostic models when combined with such scores, but not as a replacement.

Table 3. Key Clinical Studies Evaluating DNI in Mortality Prediction in Adult Sepsis and Related Critical Illness

Design & Setting	Population	DNI Cutoff	AUC	Key Findings	Reference
Prospective ICU cohort	Pneumonia-induced sepsis	6.5%	>0.80	Higher DNI at admission independently predicted 28-day mortality; additive to SOFA/APACHE II	[8]
Observational cohort, febrile suspected sepsis	Mixed medical patients	~6%	0.79	DNI + mean platelet component improved mortality prediction vs. either alone	[11]
Retrospective ICU admissions via ED	Critically ill sepsis patients	7%	~0.78	DNI at presentation predicted 30-day mortality; useful for early triage	[20]
Observational, mixed hospital cohort	Sepsis patients	6–7%	0.76	DNI correlated with severity scores and predicted mortality	[21]
Prospective cohort	Septic AKI on CRRT	5.7%	0.81	Elevated DNI was an independent mortality predictor in high-risk AKI	[12]
Prospective diagnostic accuracy study	Severe acute pancreatitis (sepsis risk)	~5%	0.77	DNI predicted severe disease and higher mortality risk; supports systemic inflammation link	[22]

The most significant investigations of the prognostic value of DNI are outlined in Table 3 and show that DNI is always associated with mortality risk in a range of septic populations, and the optimal cutoffs and AUCs vary but are always above 0.75. These results indicate the potential of the biomarker to be implemented into early risk stratification models.

5. Interpretation and Mechanistic Insights

Increased levels of DNI in sepsis correlate with severe immune dysregulation, ongoing systemic inflammation, and, in most of the cases, the development of secondary infections. The innate immune system is greatly activated throughout the beginning hyperinflammatory phase of sepsis, which causes the bone marrow to produce IG. This is a left shift to elevated levels of granulopoietic cytokines like Granulocyte-Colony-Stimulating Factor (G-CSF) and interleukin-6 that are elevated in severe infections [5]. Nevertheless, although the process is intended to increase the clearance of pathogens, the functional activity of IG is less effective than that of the mature neutrophils, which results in a poor phagocytic response and ineffective killing of microbes.

Subsequent increase in DNI at later stages of sepsis is normally an indication of a shift between hyperinflammation and immunoparalysis a condition of low immune response, susceptibility to opportunistic infections and high mortality. Kou et al. (2025) revealed that the concentrations of DNI in the high-risk population of patients, including patients with hematologic malignancies [9], were frequently associated with the occurrence of secondary infections and the inability to respond to treatment, which also testified to the potential of DNI as a dynamic biomarker of immune competence.

Differences in the DNI trends of survivors and non-survivors have been reported severally. The early peak with subsequent gradual decrease in the values of DNI is common in survivors as the infection is controlled and systemic inflammation is resolved. Conversely, elevated or increasing DNI is typical of non-survivors, and represents continuing stimulation of the bone marrow by uncontrolled infection, secondary bacterial or fungal colonisation, or a host immune failure [6]. This variation in DNI kinetics suggests that serial monitoring may prove more informative than a single baseline measurement, and clinicians may be able to know the effectiveness of treatment in real-time [14].

Therapeutically, DNI can be important in either setting a course of escalation or de-escalation of care. The continued high DNI in a severely ill patient may lead to the clinicians increasing the level of antimicrobial therapy, seeking unrecognized sources of infection, or reconsidering the quality of source control. On the other hand, a decreasing trend of DNI can help in the rationalization of the tapering of broad-spectrum antibiotics that can minimize the antimicrobial resistance and toxicity of drugs. Moreover, DNI can be used in sepsis prognostic models that have several parameters to determine which patients are most likely to respond to immunomodulatory treatment, such as granulocyte transfusions, or cytokine adsorption therapies [5,9].

Table 4. Mechanistic Basis for the Prognostic Value of DNI in Adult Sepsis

Mechanistic Domain	Pathophysiological Process	Impact on Outcomes	Supporting References
Immune Dysregulation	Hyperinflammation with massive bone marrow release of IGs	Reduced functional neutrophil activity, impaired pathogen clearance	[5, 6]
Persistent Inflammation	Sustained cytokine release (e.g., IL-6, G-CSF) driving prolonged granulopoiesis	End-organ damage, poor clinical recovery	[5]
Immunoparalysis & Secondary Infections	Transition from hyperinflammation to immune suppression	Increased risk of nosocomial infections, higher mortality	[9]
DNI Kinetics	Survivor pattern: early peak then decline; Non-survivor pattern: persistently high or rising	Real-time indicator of treatment success or failure	[6, 14]
Therapeutic Guidance	Integration into clinical decisions on escalation or de-escalation of therapy	Optimization of antimicrobial use, targeted interventions	[9, 14]

The biological processes underlying the role of high DNI as a predictor of disease severity and poor outcome in adult sepsis and thus a potential prognostic biomarker and intervention to inform dynamic treatment are summarised in Table 4.

6. Limitations, Controversies, and Future Directions

Although the evidence that DNI is a prognostic biomarker in sepsis is promising, there are a number of limitations to the current body of literature that should moderate its immediate adoption into

standard clinical practice. It is a remarkable number of studies examining Retrospective design, small sample size, and single-center setting are the limitations of DNI, which restricts generalizability and raises the risk of selection bias [6,7]. In addition, most studies have been done in specialized groups of patients like postoperative patients or patients with specific comorbidities, and there is a concern of generalizing the findings to the whole sepsis population [23].

The inconsistency in reported optimal cutoff values is perhaps the greatest problem to the clinical application of DNI where the values vary widely between about 5 to more than 8 percent depending on the population of patients, the time of measurement and the technology of the analyzer [7, 22]. Lack of a universal threshold eliminates standardization and could be the reason behind the difference in the performance of various healthcare systems. Analytical differences between hematology analyzers, pre-analytical variability and variability in calibration protocols further confound the issue of comparability [15].

The possible confounding factors should also be considered. The non-septic factors may affect the high DNI values, which include hematologic malignancy, immunosuppressive status, chronic inflammatory disease, and some surgical settings [24, 25]. Also, IG elevations can be caused by severe burns and inflammation related to malignancy without acute infection [15, 26]. Reproducibility is also challenged by laboratory variability such as variation in machine algorithms used in the counting of the differentials [13, 27].

Whereas numerous studies have found high correlations between DNI and mortality, others have found lower associations or no independent predictive value when adjusted by confounding factors, particularly when used in a more comprehensive clinical prediction model, e.g. bacteremia detection [17] or septic shock mortality prediction using neutrophil-to-lymphocyte-to-monocyte ratio [19]. These differences show that the future multicenter studies are needed to verify the results and create uniform standards of interpretation.

In the future, a number of research directions can be justified. First, future multicentric studies involving a large sample are required to validate the prognostic value of DNI in various adult sepsis patients and to determine consistent cutoffs [7, 28]. Second, DNI could be applied in sepsis bundles and early warning systems to make real-time decisions, particularly within emergency and ICU settings. Third, DNI could be integrated with other biomarkers and clinical scoring systems, which could be optimised with machine learning models as in more general prognostic studies in critical illness [9, 17]. Finally, the prognostic significance of serial DNI measurements in sepsis should be established systematically since dynamic trends can be more informative than measurements at a single point in time [6]

Table 5. Limitations, Controversies, and Future Directions for DNI in Sepsis Prognostication

Domain	Key Issues	Examples / Impact	References
Study Design Limitations	Small sample sizes, retrospective, single-center studies	Reduced generalizability; higher risk of bias	[7]
Cutoff Variability	Different optimal DNI thresholds (5–8%) across studies	Difficult to standardize; risk of misclassification	[7, 22]
Potential Confounders	Non-septic inflammation, hematologic disorders, malignancy, severe burns	False-positive DNI elevations	[24, 25, 15]
Analytical Variability	Differences in hematology analyzer algorithms and calibration	Affects reproducibility between centers	[15, 13]
Controversial Findings	Weak/no independent association in some adjusted models	Less predictive when combined with robust scoring systems	[17, 19]
Future Research Needs	Large multicenter trials, standardized cutoffs, integration into sepsis bundles, ML model applications, serial monitoring studies	Could confirm and refine DNI's prognostic role	[7, 6, 9]

The findings are summarized in Table 5, indicating the key methodological limitations, problems with interpretation and gaps in the existing body of DNI studies on the topic of sepsis prognosis. It also describes some of the most important areas in which standardization, wider validation and incorporation into more advanced predictive models can enhance its clinical utility.

7. Conclusion

The existing evidence base suggests that DNI is a potential prognostic biomarker of mortality in adults with sepsis, which provides a novel understanding of the inflammatory and hematopoietic response of the host. In a wide range of patient groups and clinical contexts, higher DNI especially when sustained has been reliably linked to increased disease severity, increased mortality risk, and worse clinical courses. Its automated ease of measurement, presence on regular hematology analyzers, and ability to complement the current scores such as SOFA and APACHE II render it more appealing to the fast risk stratification in the critical care setting. Nevertheless, small sample sizes, variation in study designs, cutoff points and risk of confounding by comorbidities and non-septic inflammatory states are the limitations of the literature. Although meta-analyses indicate its predictive value, there is a lack of consistency in methods and analytical variation between studies, and as such, a universal standard has not yet been established. DNI can be most useful in clinical practice in combination with other biomarkers and clinical scoring systems, as an adjunct, but not as a single predictor. Its predictive validity ought to be validated by multicentric, prospective studies, preferably with serial DNI measurements and incorporation into multi-marker, machine learning-based models to establish optimal thresholds, and its role in the pathway of sepsis care. Until that time, DNI can be regarded as a novel, convenient, but not yet conclusive method of mortality risk stratification in adult sepsis.

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