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Comprehensive Insights into the Neutrophil Percentage to Albumin Ratio (NPAR): An Emerging Integrated Biomarker for Inflammation and Prognosis

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ABSTRACT

Neutrophil Percentage to Albumin Ratio is a new biomarker that measures inflammation severity and prognosis in many inflammatory diseases. **Objectives:** To systematically assess the role of neutrophil percentage to albumin ratio in predicting inflammation and patient prognosis compared to conventional biomarkers C-reactive protein and procalcitonin, in inflammatory diseases. **Methods:** PRISMA guidelines were followed by electronic databases such as PubMed, Science Direct, and Google Scholar using keywords including 'Neutrophil Percentage to Albumin Ratio', 'inflammation', 'biomarkers' and 'prognoses' from 2014 to 2024. Some studies examined the interaction between neutrophil percentage to albumin ratio with systemic inflammation, immune dysfunction and organ injury. Two aspects were analysed comprehensively regarding the comparison of neutrophil percentage to albumin ratio with conventional inflammation biomarkers with consideration of age, baseline characteristics, and comorbidity along with the neutrophil percentage to albumin ratio evaluation in the spectrum of various disorders. A total of 99 studies were taken into consideration for initial screening, finally, 18 studies were taken for in-depth analysis. **Results:** The review showed a significant correlation between higher values of neutrophil percentage to albumin ratio and inflammation, organ, and clinical deterioration. neutrophil percentage to albumin ratio demonstrates higher accuracy in evaluating the severity of inflammation and patient prognosis compared to classical markers, particularly in critical conditions. **Conclusions:** It was concluded that neutrophil percentage to albumin ratio becomes ideal as a stable multiple biomarker to measure inflammation and the overall patient prognosis. Utilization of markers in clinical practice could lead to improved recognition of severe inflammation states.

INTRODUCTION

Inflammatory diseases refer to situations in which the immune system fails to control its response to harm and may lead to acute or chronic conditions affecting the global population. These diseases include several disorders, including autoimmune diseases for instance rheumatoid arthritis, severe infection conditions such as sepsis and cardiovascular disorders. Inflammation plays an important role in the development and course of many diseases, and its role can be considered essential. These diseases are devastating and inflammation is fundamentally involved in several illnesses such as cardiovascular diseases neurological disorders, or chronic obstructive pulmonary diseases. Early detection has been especially emphasized since it enables proper medical management of the condition, so it does not progress and worsens the prognosis [1]. Inflammations have become more common worldwide with certain areas experiencing a higher trend than others. Lupus and rheumatoid arthritis are on the rise in North America and Europe while respiratory and infection-related inflammatory diseases are common in

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Asia and Africa attributable to environmental and infectious causes [2]. Sepsis, an inflammatory response syndrome with comparatively high mortality is still a leading cause of death in sub-Saharan Africa, making access to timely treatment often implausible and yielding mortality ranging from 30-50% [3]. Severe inflammatory disorders such as sepsis, should be identified early for better treatment to help decrease mortality rates occasioned by late detection of the condition. This review is concentrated on the recently introduced marker termed as Neutrophil Percentage to Albumin Ratio, also known as NPAR which indeed holds great promise for identifying and diagnosing inflammation in multiple pathological states, especially those occurring in the intensive care unit. Currently, NPAR has been identified to be a better biomarker than other known markers such as C-reactive protein (CRP), procalcitonin (PCT), and the neutrophil-to-lymphocyte ratio (NLR). As compared to these routine biomarkers, NPAR combines both the neutrophil count and albumin concentrations to provide a better snapshot of the inflammatory state of a patient. This double approach provides more predictive performances, mainly in severe inflammatory disorders such as sepsis for which early and precise identification is of paramount importance [4]. Other biomarkers such as CRP, PCT, and NLR share common restrictions owing to their sensitivity to the patient's condition and other diseases. CRP is used to measure general inflammation but is raised by many other conditions that are not inflammatory and, therefore less specific [5]. Unlike NPAR, Procalcitonin has inherent value in bacterial infection diagnosis but is not as applicable to a wide range of diseases. The ability to include both immune (neutrophil) and nutritional (albumin) observations improves NPAR's usability as a predictor of mortality and the dysfunction of vital organs in a variety of diseases, as indicated in recent studies [6-8]. The originality of this review is its synopsis of NPAR as a biomarker from sepsis to inflammatory liver and cardiovascular diseases. The review gives a comprehensive comparison of NPAR with other biomarkers to show its advantage in critical care cases.

This study aims to include NPAR in the set of standard diagnostic tools and optimize the rates of early diagnosis and management. The future perspective is that NPAR would dramatically solve healthcare costs and human lives in treating inflammatory diseases because patients would receive precise diagnosis and treatment.

METHODS

The current study was carried out in accordance to the guidelines of PRISMA for systematic reviews and meta-analyses. A total of 79 articles were reviewed in this systematic review which were published in English language from 2014 to 2024 in this systematic review that aimed at establishing the Neutrophil Percentage to Albumin Ratio (NPAR) as a biomarker for various inflammatory diseases. For each of the selected manuscripts, data were extracted based on PRISMA inclusion criteria such as: author(s), year of publication, country of study, sample, key factors/variables, study type, and references. Electronic based search was undertaken using web-based databases such as the Pub-Med, Science Direct, Springer Link, Google Scholar. Interestingly, 85% of the articles identified were retrieved from PubMed database. The words used for the search included 'Neutrophil Percentage to Albumin Ratio', 'NPAR', 'inflammatory diseases', 'biomarker', 'sepsis', 'cardiovascular diseases' and 'liver disease'. First, all articles which had both NPAR and inflammatory diseases as keywords were collected and included all types of duplicates and abstracts. These articles were then screened against inclusion and exclusion criteria that had been developed prior to data collection. From the excluded articles, the following were some of the reasons as to why they were excluded: failed to establish relationship between NPAR and inflammatory diseases; duplicate; used wrong methods (non-clinical, observational or experimental); not published in the specified time frame; off topic. This criterion list area was defined as the inclusion criteria and pointed to the role of NPAR in inflammation and prognostic evaluation in the given inflammatory diseases. Consequently, owing to the very specific parameters set, several papers mentioned in the preliminary database search were removed, and only 18 articles qualified for analysis. Of the selected databases, 99 articles were downloaded, but after removing duplicates, 94 articles remained for further review. In the light of the findings that emanated from the full texts review, 43 papers were considered for the systematic review, which were further narrowed down to 18 articles used for in-depth evaluation and analysis of NPAR as a biomarker for inflammatory diseases.

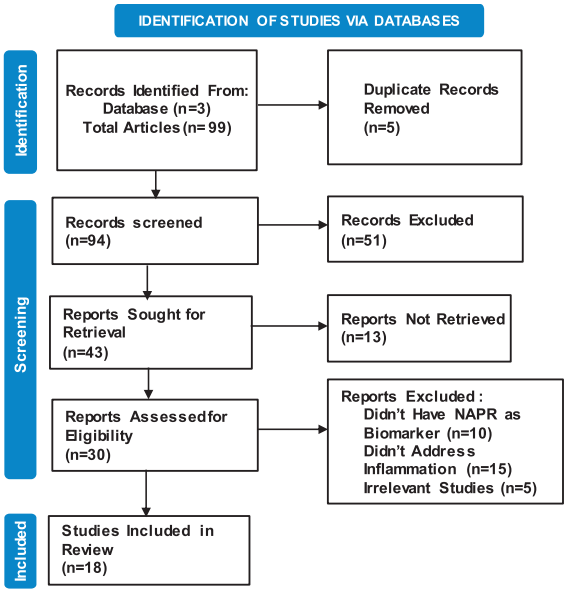

Figure 1: PRISMA Flow Diagram For Systematic Review of NAPR As A Biomarker For Inflammatory Disorders According to Inclusion and Exclusion Criteria

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RESULTS

The studies involved in this review contained multiple disorders because the Neutrophil Percentage to Albumin Ratio (NPAR) can be utilized as biomolecules for a range of inflammatory diseases. Most of the papers targeted clinical studies analysis and evaluated the relation between NPAR levels and outcomes in inflammatory diseases, sepsis, and cardiovascular and liver diseases. Following PRISMA, the sources were identified in databases of scientific articles, 85% of which were found in PubMed, 10% in ScienceDirect, and 5% in SpringerLink. Overall, 14 studies were retrospective, 3 studies used the prospective observational analysis, and 1 used a cross-sectional study design. More importantly, higher NPAR values were positively associated with mortality and higher hospitalization days, organ dysfunction, and inflammation in different inflammatory diseases. The results reported here suggest that NPAR could prove to be a more accurate predictor than inflammation-associated markers, including CRP and PCT. Altogether, the underlying data indicate that NPAR is essential to evaluate the intensity of inflammation and prognosis in patients with a variety of inflammatory disorders, and therefore, it may be important as a biomarker in clinical practice.

Table 1: Systematic Review of Articles Taken Into Consideration for Studying NAPR as a Biomarker Against Various Inflammatory Disorders

Reference	Study Design (Sample size)	Condition Studied (Primary Outcomes),	Key Findings	Confounders	Conclusion
[9]	Retrospective study (n=741)	Sepsis patients, 28-day mortality	High NPAR values associated with significantly higher 28-day mortality (HR for tertile 3 vs 1: 1.35, 95% CI: 1.00-1.82)	Adjusted for age, sex,BMI, APACHE II,SOFA, mechanical ventilation, noradrenaline use, etc.	Elevated NPAR linked to increased 28-day mortality in Chinese patients with sepsis,suggesting its potential as a biomarker.
[10]	Retrospective cohort study (n=2166)	Severe sepsis or septic shock, all-cause mortality	Higher NPAR associated with increased 30-day (HR: 1.29), 90-day (HR: 1.41), and 365-day mortality (HR: 1.44)	SOFA, SAPS II scores, lactate, BUN, WBC, neutrophils, albumin	NPAR was identified as an independent predictor of all-cause mortality in patients with severe sepsis or septic shock.
[11]	Retrospective (n=2364)	Coronary care unit patients, in-hospital and 365-day mortality	NPAR was independently associated with increased in-hospital mortality (OR: 1.83) and 365-day mortality (HR: 1.62)	Compared with PLR,neutrophil count, SOFA, SAPS II scores	NPAR is a moderate predictor of mortality in coronary care patients, suggesting potential utility in inflammatory conditions.
[12]	Retrospective cohort (75 patients)	Sepsis in ICU patients, Mortality in sepsis patients	NPAR was independently associated with increased in-hospital mortality (OR: 1.83) and 365-day mortality (HR: 1.62)	Compared with PLR,neutrophil count, SOFA, SAPS II scores	NPAR is a moderate predictor of mortality in coronary care patients, suggesting potential utility in inflammatory conditions.
[13]	Retrospective observational (5083 patients)	Contrast-associated acute kidney injury (CA-AKI) post-percutaneous coronary intervention, Incidence of CA-AKI and long-term mortality	NPAR >15.7 was a strong predictor of CA-AKI and long-term mortality	Compared with PLR,neutrophil count, SOFA, SAPS II scores	NPAR is a moderate predictor of mortality in coronary care patients, suggesting potential utility in inflammatory conditions.

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[14]	Retrospective (940 patients)	Stroke, 30-day, 90-day, 1-year all-cause mortality	Higher NPAR significantly associated with increased short and long-term mortality	Neutrophil count, albumin, glucose	NPAR is a moderate predictor of mortality in coronary care patients, suggesting potential utility in inflammatory conditions.
[15]	Retrospective cohort (1,599 patients from MIMIC-III and 143 from Wenzhou Medical University)	Cardiac intensive care unit (CICU) patients. Primary outcomes: 30-day, 90-day, and one-year mortality, length of stay, renal replacement therapy (RRT).	Higher NPAR was independently associated with increased mortality, length of stay, and the need for RRT. Positive correlation between NPAR and CRP (inflammatory marker).	Compared with CRP (positive correlation). Also adjusted for factors like age, sex,race, comorbidities, SOFA score, SAPS II score.	Elevated NPAR is a significant predictor of poor outcomes in CICU patients, supporting its potential as a systemic inflammation -based biomarker, including in sepsis cases.
[16]	Cross-sectional (78 patients)	Infectious meningitis. Primary outcomes: NPAR correlation with disease severity.	Higher NPAR was independently associated with increased mortality, length of stay, and the need for RRT. Positive correlation between NPAR and CRP (inflammatory marker).	None specifically compared in this study.	The study indicates that NPAR may serve as a diagnostic marker for systemic infection and inflammation, relevant to sepsis detection.
[17]	Retrospective cohort (87 patients)	Major lower extremity amputation due to diabetic foot infection and PAD. Primary outcome: Early mortality (1-year mortality).	Higher post-op NPAR was significantly associated with early mortality after major amputation. The cut-off for post-op NAR was 0.265 (AUC=0.873).	Compared with NLR, PLR, and CAR. NAR showed higher sensitivity (88%) and specificity (76%) for mortality prediction.	Elevated NPAR can predict early mortality in inflammatory conditions, such as those seen in sepsis, highlighting its potential as a sepsis biomarker.
[18]	Retrospective cohort study (n=475)	Cardiogenic shock (90-day mortality)	NAR>27.86 is associated with higher 90-day mortality (HR 1.93); and higher sensitivity than neutrophils or albumin alone	SOFA, SAPS II scores	NAR was a stronger predictor of mortality than neutrophils or albumin alone, indicating its potential as a biomarker for sepsis prognosis.
[19]	Prospective cohort study (n=918)	Stroke-associated pneumonia in intracerebral hemorrhage (90-day functional outcome)	Higher NPAR independently predicted poor outcomes and pneumonia (aOR 1.72; P=0.04)	Neutrophils, white blood cell count, admission NIHSS score	NPAR emerged as an easily accessible inflammatory biomarker, associated with pneumonia risk and poor outcomes, thus offering potential utility in sepsis.
[20]	Prospective cohort study (n=146 UC patients, 133 controls)	Ulcerative colitis (Inflammatory load, response to infliximab)	NAR increased in UC patients and correlated with disease activity (AUC=0.867), predictive of infliximab response	CRP, ESR, faecal calprotectin, TNF-α, IFN-γ	NAR showed potential to monitor inflammatory activity in UC,suggesting it could have broader pplications, including monitoring sepsis-related inflammatory responses.

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[21]	Retrospective analysis (11,883 patients)	Non-alcoholic fatty liver disease (NAFLD) and liver fibrosis (Prediction of liver fibrosis)	NPAR showed a significant association with NAFLD and liver fibrosis, AUC of 0.795 for NAFLD with fibrosis prediction	Comparison withother inflammatory biomarkers (NLR, PLR, SII)	NPAR is a promising non-invasive predictor for NAFLD and liver fibrosis, useful in assessing liverdisease progression
[22]	Cross-sectional study (51 hemodialysis patients)	Left ventricular hypertrophy (Prediction of cardiovascular risk in ESRD patients)	NPAR was an independent predictor of LVH with OR: 8.83, sensitivity 69%, specificity 72.5%	C-reactive protein (CRP), systemic immune inflammation index (SII)	NPAR may predict cardiovascular inflammation in ESRD patients undergoing dialysis, useful for assessing heartdisease risk
[23]	Retrospective study (618 schizophrenia patients)	Schizophrenia (Inflammatory status in schizophrenia)	NPAR levels are significantly higher in schizophrenia patients compared to controls, AUC for differentiation: 0.741	Comparison with CRP, NLR, PLR	NPAR is a reliable biomarker for systemic inflammation in schizophrenia, suggesting its role in neuroinflammation tracking
[24]	Cross-sectional, NHANES data (n=26,225)	Cardiovascular Disease (CVD prevalence and association with NPAR)	Elevated NPAR levels are significantly associated with increased CVD prevalence.The highest quartile had 46%greater CVD prevalence.	LDL-C, HDL-C, BMI,Smoking status, Hypertension, Diabetes, Hyperlipidemia	NPAR could be a valuable biomarker for assessing systemic inflammation and nutritional status, potentially extending its use to other inflammatory diseases like sepsis.
[25]	Retrospective, cross-sectional (n=161)	Acute appendicitis (AA); Evaluating NAR for diagnosis and predicting perforation	NAR was significantly higher in patients with AA, but no significant correlation was found between NAR and perforation (p=0.697)	CRP, Creatinine, Urea, Neutrophil Count, Albumin Level	NAR is useful for diagnosing AA but insufficient for predicting perforation, indicating limitations in its use as a biomarker for inflammation severity in sepsis.

DISCUSSION

Inflammatory diseases can be defined as a group of disorders, which result from the compromised immune response against the pathogenic agents, toxins or injured cells. They exist in both acute and chronic forms and affect more than half of the world's population. Inflammation is a prominent feature in cardiovascular disease, diabetes, cancer, sepsis, rheumatoid arthritis, and systemic lupus erythematosus and accounts for nearly all deaths in people with chronic rheumatoid arthritis [26]. In the mentioned disorders, there is constant inflammation of tissues which promotes tissue damage, organ impairment and higher death rates. Evaluation of inflammation is important since early detection helps slow down the disease process and enhance patients' prognosis. However, most of the current diagnostic approaches are incapable of delivering timely and precise details on the intensity of inflammatory reactions, mainly due to which patients receive treatments as well as prognoses that are sub-optimal in many instances [26]. Inflammatory biomarkers have developed the potential to diagnose inflammatory diseases. Even if markers like CRP and PCT are applied in common practices properly due to the ambiguity in sensitivity and specificity, the new biomarkers are searched to get a precise and promising approach [27]. The Neutrophil Percentage to Albumin Ratio (NPAR) is one such novel biomarker which is under consideration for better prognosis of the degree of inflammation in various diseases. NPAR is a unique biomarker that integrates two critical indicators of the inflammatory response, the percentage of neutrophils in blood and serum albumin. Neutrophils are multipotent

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leukocytes that are crucial to the body's response to infection and tissue injury, they are the first line of defence in any inflammatory response. At the same time, these cytokines inhibit the synthesis of albumin by the liver, which results in low albumin levels, which in turn impairs nutrition transport and oncotic pressure, hence exacerbating the condition of the patient [28]. Thus, it offers a two-fold perspective in NPAR: the immune neutrophil percent and the metabolic albumin levels. The above makes NPAR to be a very stable measure of the disease severity and the likely prognosis in inflammatory conditions [29]. NPAR has several advantages over other conventional biomarkers such as CRP, PCT and NLR. CRP, which is employed frequently is a rather unspecific indicator of inflammation and can be elevated sometimes due to conditions that are not inflammatory in origin, such as trauma, surgery etc so it wasn't particularly valuable for the assessment of the disease severity. Procalcitonin is broadly positive in bacterial infection but may also be raised in non-infectious conditions such as trauma or shock and therefore not very ideal for general inflammation [30]. NPAR, on the other hand, is a more integrated neutrophil response in combination with the albumin level, which reflects the inflammatory and nutritional status of the body. Furthermore, the results have also illustrated that NPAR is better than numerous biomarkers in the evaluation of outcomes like mortality, development of organ failure, and the duration of hospital stay for patients with inflammation. For instance, critically ill patients with inflammatory diseases indicate that NPAR has better prognosis prediction than both NLR and CRP in possible clinical application [31]. Cross-sectional review of several studies was done to assess the efficacy of NPAR in inflammatory related disease like liver cirrhosis, stroke-associated pneumonia, and cardiovascular disease. The predictors as identified from the studies include findings that showed that values in the NPAR, including LOS, were higher among patients with increased mortality, complicated conditions and longer hospital stays [32]. A recent cohort study of relatively larger sample size of patients with chronic liver disease showed that patients with high NPAR have a significantly higher incidence of complications such as spontaneous bacterial peritonitis and hepatorenal syndrome which has an inflammatory basis [33]. Recent data have demonstrated that NPAR may help define long-term prognosis, including mortality and acute kidney injury after coronary artery bypass graft surgery or percutaneous coronary intervention [34]. Information regarding the interaction between stroke and NPAR showed that stroke related pneumonia was associated with higher NPAR, number of treatments, and influenced worse functional damage and increased risk of mortality [35]. These data confirm NPAR as a pan-inflammatory biomarker for plenty of inflammatory disorders, which will be useful for the clinical conditions of both acute and chronic inflammation. Therefore, this review is useful in pointing out the clinical relevance of NPAR as a more optimal biomarker in the diagnosis and treatment of inflammation. Its capability to provide information about immune and nourishing states gives a better picture of a patient's condition if compared with other biomarkers like CRP or PCT. Through the use of a variety of diseases, this paper also establishes the applicability of NPAR as a forthcoming diagnostic tool in a wide manner in different diseases where early accurate prediction is rather important [36]. However, as it has been seen NPAR has limitations that need to be addressed as follows: Most analyses on NPAR have been performed based on retrospective data, thus confounding the possibility of inferring causality between NPAR values and specific clinical outcomes. Furthermore, even though NPAR has been proven to be superior to other biomarkers in some instances, its effectiveness on different patient populations, such as paediatric or immunocompromised patients, has not been thoroughly investigated [37]. Further prospective studies and well-designed randomized controlled instances have to be conducted to ascertain the clinical efficacy of the NPAR and the recommendations of the identified best-performing cut-off values for several inflammatory syndromes. Further studies should interrogate NPAR into panels of multiple biomarkers that would potentially provide a higher level of diagnostic accuracy via the synergistic effect of several markers of inflammation and immunity. In addition, the obtained data can be useful when developing individualized treatment regimens for patients based on the concept of personalized medicine, according to the inflammatory factors identified in the framework of NPAR. Given the fact that the number of people suffering from chronic inflammatory diseases is on the rise, embracing NPAR as a standard in diagnosis may greatly benefit the patients and also lift the prognosis of these diseases [38].

CONCLUSIONS

It was concluded that NPAR can be considered a relatively new and more accurate biomarker as compared with CRP and PCT utilization for diagnosis and prognosis of inflammatory disorders. While NPAR includes both neutrophil level and albumin status, it is thus possibly a better measure of patients' inflammatory and nutritional conditions than any one of the measures alone, especially for critical care applications. The regular relationship between NPAR and increased mortality, organ

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dysfunction, and the length of stay has important implications for the clinical management of diseases such as sepsis, liver cirrhosis, and cardiovascular disease. Therefore, clinicians are urged to integrate NPAR into clinical practice to build on early detection of patient subgroups and better direction of therapies. In conclusion, this work has potential implications for improved patient health and enhanced healthcare systems in the management of NPARI diseases.

Authors Contribution

Conceptualization: MW, AM, WS
Methodology: MW, AM, WS, NA, MH
Formal analysis: MW, AM, WS
Writing review and editing: AI, FR

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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