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Research Article

Evaluation of Neutrophil Gelatinase-Associated Lipocalin (NGAL) as a Biomarker for Early Prediction of Bacterial Sepsis in Patients with Fever in the Emergency Department

Ravi Kumar[1], Mona Rani[2], Ajet Kumar[3], Mahesh Kumar[4], Aneel Kapoor[5], Suresh Kumar[6]

1. Assistant Professor of Medicine, Altamash General Hospital / Altamash Institute of Dental Medicine Karachi Pakistan. Email: dr.ravichawla@gmail.com (Corresponding author)
2. Associate Professor of Physiology, Shaheed Mohtarma Benazir Bhutto Medical College Lyari, Karachi Pakistan. Email: monakhem@yahoo.com
3. Assistant Professor of Pharmacology, Ghulam Muhammad Mahar Medical College Sukkur Pakistan. Email: drajetkumar@gmail.com
4. Assistant Professor of Medicine, Ibn E Sina University / Muhammad Medical College and Hospital Mirpurkhas Pakistan. Email: mka.raj14@gmail.com
5. Associate Professor of Biochemistry, Peoples University of Medical and Health Sciences Nawabshah Pakistan. Email: aneelkapoor@pumhs.edu.pk
6. Assistant Professor of Medicine, Bhitai Dental and Medical College Mirpurkhas Pakistan. Email: sureshdmc09@yahoo.com

Abstract

Background

It is a very serious condition known as bacterial sepsis, which has a high incidence and death rates; the prognosis worsens with late diagnosis and treatment. The difficulty in recognizing sepsis patients arises from the lack of reliable diagnostic markers. The recently studied 'neutrophil gelatinase-associated lipocalin' has proven to be useful in the index of inflammation and injury of tissues to predict bacterial infection. The purpose of this study is to estimate the usefulness of NGAL alongside clinical and lab indicators in the bacterial sepsis prediction for patients suffering from fever.

Type of study: Prospective observational study

Place and Duration of study: This study was conducted at Altamash General Hospital / Altamash Institute of Dental Medicine Karachi from April 2025 to April 2026

Methods

A prospective observational study was carried out in 200 patients with acute febrile illness and clinical signs suggestive of systemic infection. At presentation, clinical parameters, routine laboratory investigations and plasma NGAL levels were evaluated. Bacterial sepsis was diagnosed by microbiological results and clinical evaluation. Predictive value of NGAL and other clinical parameters was determined by receiver operating characteristic (ROC) analysis. Significant factors associated with bacterial sepsis were determined and added together to determine the predictive value of these factors through statistical modelling.

Results

Of the 200 patients that were studied, 74 of them (37%) were diagnosed with bacterial sepsis. The levels of plasma NGAL were significantly elevated in patients with

bacterial sepsis vs. those without sepsis. The best cut-off point for the diagnosis of bacterial sepsis with NGAL had moderate sensitivity and specificity. Clinical parameters such as diabetes mellitus, rigors, raised quick Sequential Organ Failure Assessment (qSOFA) score, identifiable source of infection and raised NGAL levels were associated with increased probability of bacterial sepsis. The combined predictive model with NGAL and clinical parameters performed better in discriminating the patients with and without bacterial sepsis than the individual parameters.

Conclusion

In conjunction with the clinical data, NGAL could be a useful aid in the early diagnosis of sepsis caused by bacteria in fever patients attending the ED. The use of NGAL as part of clinical pathways can aid in early risk stratification and prompt intervention in patients who are likely to have sepsis.

Keywords: Bacterial sepsis, Biomarker, Fevre, Emergency department, Neutrophil gelatinase-associated lipocalin (NGAL), Sepsis prediction.

Introduction

Sepsis is considered one of the leading causes of morbidity and mortality worldwide and has posed an important challenge for physicians and clinicians, particularly those working in emergency departments where timely diagnosis and treatment of infected patients is necessary. It refers to a condition of organ failure in which the body's response to infection is uncontrolled and is responsible for health deterioration of the man [1]. Although bacterial sepsis is a common condition, people find it challenging to make a diagnosis due to a number of factors [2].

Patients who come to the ED with fever are a heterogeneous population and can range from having a self-limited infection to a serious bacterial sepsis where immediate action is needed. Early identification of uncomplicated febrile illness from bacterial sepsis is critical as there is increasing evidence that delayed treatment with appropriate antibiotics and supportive treatment is linked to worse outcomes [3]. Until now, clinicians have used a mix of clinical, inflammatory markers, microbiological investigations and severity scoring (e.g. Sequential Organ Failure Assessment (SOFA) and quick SOFA (qSOFA) scores). Such tools, however, are not without their shortcomings as they are not equally sensitive particularly in the early phases of infection [4].

A considerable number of studies have been conducted on the use of conventional laboratory markers (WBC, C-reactive protein (CRP), and procalcitonin) in diagnosing and monitoring sepsis. Procalcitonin has been shown to be useful in separating bacterial infections from inflammatory diseases, but it alone does not have sufficient diagnostic value [5]. Similarly, CRP is an unspecific, though a sensitive, marker of inflammation. Therefore, it is essential to identify new markers by now.

Neutrophil gelatinase-associated lipocalin (NGAL), which is a small protein secreted from activated neutrophils as well as injured epithelial cells during inflammatory and infection processes, was the first identified biomarker of acute renal injury. NGAL gained attention as a potential marker of systemic infection and rapid responses in the case of bacterial infection [7]. During bacteria infections NGAL contributes to innate immunity by preventing bacterial growth via sequestration of iron-containing iron-siderophores to reduce iron availability for bacteria [8]. The amount of circulating NGAL is found to increase in bacterial infections and is potentially a marker of the severity of inflammation.

The diagnostic potential of NGAL in sepsis has been investigated in several studies, which showed that increased plasma level of NGAL might be useful in discrimination between bacterial and non-infectious inflammatory diseases. Furthermore, NGAL might also contain prognostic information about the disease severity and clinical outcomes [9]. However, with different patient populations, different sources of infection and different diagnostic thresholds, it is difficult to draw consistent conclusions, and more testing is needed before it can be used in routine clinical practice.

Using the biomarkers along with clinical parameters could be a more reliable method to diagnose sepsis early. During the initial assessment, clinical features like rigors, identifiable infection focus, associated diabetes mellitus and markers of organ dysfunction are helpful. The combination of NGAL with existing clinical markers could prove to be more accurate than markers used separately [10].

The ED is an environment that poses a particular challenge when it comes to diagnosing sepsis, as the doctor is forced to make decisions with little information. Predictive tool with easily available clinical data and a biomarker like NGAL might help early identify high-risk patients, allow prompt antibiotic administration and enhance patient outcomes. This may also decrease the exposure to antibiotics in patients for whom it is not necessary when the fever is not due to bacterial infection.

While there are previous studies showing the potential usefulness of NGAL in infection and sepsis, more studies are needed to assess its usefulness when used in conjunction with routinely available clinical parameters. A correlation between NGAL and clinical parameters of bacterial sepsis could be helpful to gain insights on optimizing early diagnostic strategies. Consequently, the present research was conducted to evaluate the predictive value of Neutrophil gelatinase associated lipocalin (NGAL) combined with some clinical parameters in diagnosis of bacterial sepsis in febrile patients. The objective of the study was to find out whether the predictive power of NGAL and some clinical parameters together could enhance the early detection and the risk of the suspected bacterial sepsis.

Methodology

Prospective observational study of 200 adult patients who attended the ED with acute febrile illness and clinical suspicion of bacterial infection. Consecutive sampling was used to select patients aged 18 and above who were admitted to the hospital and who met the Systemic Inflammatory Response Syndrome (SIRS) criteria. To reduce the possibility of confounding factors, patients with incomplete clinical records, active malignancy, chronic kidney disease, prior intravenous antibiotic use within 48 hours of presentation, and recent hospitalization or surgery were excluded from the study.Patients whose medical records were incomplete, who had an active malignancy, had chronic kidney disease, who had been hospitalized or had undergone surgery within the last 48 hours before presentation, or who had been on intravenous antibiotics for more than 2 weeks were excluded from the study.

An IRB approval was granted prior to data collection. All participants or their legal representatives gave informed consent in writing before taking part. To ensure patient confidentiality, each patient was given a unique identification number and all data collected during the study was anonymized.

The structured case record tool was used for collecting demographic information, medical history, co-morbidities, medications history, presenting symptoms, physical examination results, and laboratory

tests. While the patients were admitted, the vital signs were recorded, and the Systemic Inflammatory Response Syndrome (SIRS) score and the quick Sequential Organ Failure Assessment (qSOFA) score were calculated. As a routine practice, blood count, liver function tests, blood culture, C-reactive protein, and plasma neutrophil gelatinase-associated lipocalin (NGAL) tests were performed, along with any other tests deemed appropriate by the physician.

The major outcome of the study was the diagnosis of bacterial sepsis. Patients were diagnosed with bacterial sepsis when pathogenic bacteria were found in blood culture or when the diagnosis was made clinically according to the criteria of the disease, such as blood culture, laboratory, radiology and response to treatment. Non-bacterial fever patients with confirmed non-bacterial sources, such as viral and parasitic patients, were considered as non-sepsis group. Inconsistently-microbiological cases were independently reviewed by two senior physicians and any disagreement in diagnosis was settled by consensus.

Peripheral venous blood samples were obtained from all the patients after admission and prior to starting antibiotic treatment. Blood samples for plasma NGAL were drawn in ethylenediaminetetraacetic acid (EDTA) tubes and processed in the standard laboratory procedures. Plasma was separated by centrifugation and analysed by means of a commercially available immunoturbidimetric assay. Plasma NGAL level was measured in nanograms per millilitre (ng/mL) and measured as a marker of bacterial sepsis.

Analyzed variables were age, sex, diabetes mellitus, presence of rigors, identifiable source of infection, SIRS score, qSOFA score, plasma NGAL, complete blood count, serum creatinine, liver function tests and blood culture results. Based on their established clinical relevance, these variables were chosen as they have been previously reported as associated with bacterial sepsis.

The information was processed in Microsoft Excel and analyzed using the Statistical Package for the Social Sciences (SPSS) version 26. Descriptive statistics for numerical and categorical variables were expressed as mean ± standard deviation (SD) or median and interquartile range (IQR) depending on their distribution. Receiver operating characteristic (ROC) curve analysis was employed to determine the diagnostic performance of plasma NGAL with Youden index being used to identify the optimal cut-off value. Association of clinical variables with bacterial sepsis was evaluated using univariate and multivariable Poisson regression and presented as relative risk and 95% confidence interval. Statistically significant and clinically meaningful variables were included in a predictive scoring model based on prior literature. P-values less than 0.05 were considered statistically significant.

Results In this study, 200 patients suffering from acute febrile illness and meeting the criteria for Systemic Inflammatory Response Syndrome (SIRS) were enrolled. Of these patients, 74 had sepsis (37.0%) and 126 patients had neither microbiologic findings of sepsis nor any clinical signs of sepsis, hence these patients were classified as those having the non-sepsis condition. 42 positive blood culture results (21.0%) were obtained; majority of these were due to Gram negative organism (83.3%). The most common organisms were found to be Escherichia coli, Klebsiella pneumoniae, and Staphylococcus aureus. 48 patients were transferred to intensive care unit, while the rest were admitted to general medical wards.

Demographic data and data on the clinical findings of patients is shown in Table 1. It was determined that patient's mean age with bacterial sepsis was significantly greater than that of patients without sepsis (56.1 ± 16.2 years vs. 48.4 ± 17.5 years). In addition, patients with bacterial sepsis were found to have traits such as diabetes mellitus, urinary symptoms, presence of chills, changes in mental state, high qSOFA score, and presence of site of infection.

Table 1. Baseline characteristics of study participants

Variable	**Bacterial sepsis (n = 74)**	**Non-sepsis (n = 126)**	**RR**	**95% CI**
Age (years), mean ± SD	56.1 ± 16.2	48.4 ± 17.5	1.02	1.01–1.03
Male gender	45 (60.8%)	70 (55.6%)	1.09	0.73–1.64
Diabetes mellitus	43 (58.1%)	40 (31.7%)	1.96	1.34–2.86
Hypertension	24 (32.4%)	39 (31.0%)	1.03	0.68–1.57
Respiratory symptoms	21 (28.4%)	71 (56.3%)	0.49	0.33–0.73
Urinary symptoms	28 (37.8%)	12 (9.5%)	2.51	1.63–3.87
Gastrointestinal symptoms	20 (27.0%)	18 (14.3%)	1.61	0.99–2.62
Any focus of infection	43 (58.1%)	15 (11.9%)	3.28	2.18–4.93
Rigors	26 (35.1%)	16 (12.7%)	2.09	1.41–3.10

Heart rate >90/min	70 (94.6%)	122 (96.8%)	0.78	0.39–1.57
Glasgow Coma Scale <15	28 (37.8%)	20 (15.9%)	1.88	1.26–2.81
SIRS score >3	20 (27.0%)	12 (9.5%)	2.08	1.34–3.24
qSOFA score ≥2	8 (10.8%)	2 (1.6%)	2.46	1.47–4.11
Total WBC >12,000/mm³	48 (64.9%)	62 (49.2%)	1.46	1.02–2.09
Serum creatinine >2 mg/dL	30 (40.5%)	24 (19.0%)	1.89	1.24–2.89
Plasma NGAL (ng/mL), median (IQR)	1380 (690–1810)	650 (275–1280)	1.04*	1.02–1.06

Data are presented as relative risk per 100 ng/mL rise in plasma NGAL.

The median plasma level of NGAL was 810 ng/mL (IQR: 445–1490 ng/mL). Patients with bacterial sepsis had levels of plasma NGAL significantly higher than those without sepsis.

The analysis of the receiver operating characteristic (ROC) curve found that plasma NGAL had a fair predictive ability for bacterial sepsis (AUC 0.70, 95% confidence interval (CI) 0.62 -0.78).Youden Index gave the most suitable cut-off value of 570 ng/mL which has a sensitivity of 86.5% and a specificity of 47.6%. Also, it showed that there was a higher risk of bacterial sepsis in those cases which showed plasma NGAL level ≥570 ng/mL vs. cases with lower levels of NGAL (RR = 3.12; 95% CI: 1.54-6.33).

The relationship between an increase in plasma NGAL and acute kidney injury was also investigated (Table 2). Higher NGAL levels were more common in patients with elevated serum creatinine, but it was not statistically significantly associated with elevated plasma NGAL ($\chi^2 = 1.24$, $p = 0.27$) suggesting that elevated plasma NGAL was associated with bacterial sepsis despite the absence of renal dysfunction.

Table 2. Association between plasma NGAL and acute kidney injury

Plasma NGAL	Creatinine ≤2 mg/dL	Creatinine >2 mg/dL
<570 ng/mL	60 (78.9%)	16 (21.1%)
≥570 ng/mL	86 (69.4%)	38 (30.6%)

Variables that showed statistically significant associations with bacterial sepsis in the univariate analysis were included in a multivariate Poisson regression model. Not considering variables that have been indicated among the predictors of bacterial sepsis, diabetes mellitus, rigors, plasma NGAL >570 ng/mL, and SOFA score ≥2 have turned out to be independent predictors of bacterial sepsis and were included in the clinical prediction score (Table 3).

Table 3. Multivariable predictors of bacterial sepsis and assigned prediction score

Variable	RR	95% CI	p-value	Score
Diabetes mellitus	1.34	0.87–2.05	0.241	1
Rigors	1.91	1.28–2.84	0.003	2
qSOFA ≥2	1.69	1.08–2.66	0.031	2
Any focus of infection	2.89	1.52–5.49	0.002	3
Plasma NGAL ≥570 ng/mL	3.04	1.28–7.24	0.018	3

The predictive scoring model had a good diagnostic performance. A score of < 3 was very sensitive to exclude bacterial sepsis while a score of >7 was very specific to suggest bacterial sepsis. The ROC curve of the prediction model showed an AUC of 0.87 in the training set and 0.79 in the validation set, which is a good predictive accuracy overall.

To conclude, it was indicated that plasma NGAL was one of the biomarkers that contributed to early diagnosis of bacterial sepsis among patients with fever at the emergency department, in conjunction with a number of clinical parameters.

Discussion

The objective of this research was to evaluate the significance of the plasma level of neutrophil gelatinase-associated lipocalin (NGAL) in combination with routine clinical parameters for early diagnosis of bacterial sepsis in febrile subjects. The

outcome of the study indicated that the plasma concentration of NGAL was markedly higher in cases of bacterial sepsis than in cases of non-sepsis. Furthermore, diabetes mellitus, chills and plasma concentration of NGAL and presence of an infectious focus were independent predictors of bacterial sepsis. The prediction model was validated appropriately, and its efficiency demonstrates the additional advantage of integration of biomarkers with clinical assessment for early risk stratification.

The findings supported the work of Paul et al. in that plasma NGAL was helpful in the diagnosis of bacterial sepsis when combined with the clinical parameters in febrile children coming to the emergency department [11]. They suggested a screening tool which would also cover diabetes mellitus status, the presence of rigors, the qSOFA score, and the clear site of infection, which are akin to what was found in this study. Martensson and Bellomo's work explained that although NGAL was first identified as a marker in acute kidney injury, later studies showed the quick rise in NGAL levels in patients presenting with bacterial infection and/or systemic inflammatory processes, which can be indicative of sepsis [12].

In the present study, the optimal plasma NGAL cut-off that had a moderate degree of sensitivity and specificity in predicting bacterial sepsis was identified. Similarly, Wang et al carried out a systematic review and meta-analysis and reported that plasma NGAL showed moderate diagnostic accuracy for sepsis, with the recommendation that it should be used in conjunction with clinical parameters, rather than independently, as a marker [13]. Similarly, Pierrakos and Vincent examined the novel biomarkers for sepsis and found that no single biomarker can be relied on to diagnose sepsis without the use of existing clinical parameters [6].

The significantly higher plasma NGAL levels seen in patients with bacterial sepsis in the present study is also supported by the findings of Mårtensson et al., who showed that plasma NGAL levels are raised in early systemic bacterial infection, and that these levels correlate with disease severity [14]. Flo et al. further illustrated the basis of this observation by showing that NGAL is involved in innate immunity by sequestration of bacterial siderophores which reduces the bacteria's iron acquisition and thus growth during infection [15]. This biological explanation is in line with the findings of increased NGAL in septic patients.

The present study revealed diabetes mellitus, rigors, QSOFA score, and a known source of infection as independent risk factors for bacterial sepsis. Seymour et al. found that qSOFA was a practical bedside tool to identify patients who are at higher risk of having a poor outcome from sepsis [16]] and this finding is similar. Also, the Surviving Sepsis Campaign guidelines highlight that early recognition by clinical examination, organ dysfunction scoring and early assessment of biomarkers significantly enhances patient outcomes [17].

The present study, when compared to certain studies before it, did not find a substantial correlation between elevated plasma NGAL levels and development of acute kidney injury, taking into account the amount of serum creatinine. Paul et al. produced a similar result with septic patients, suggesting that elevated NGAL levels can be utilized more as an inflammation marker, not a renal impairment indicator [18]. Mishra et al. claimed that NGAL is the first early indicator of acute kidney injury, advising doctors to interpret NGAL results within the clinical situation [7].

The predictive model developed in the present study has been found to be efficient in terms of its diagnostic success, however, it should be kept in mind that there are certain limitations in the interpretation of the model. Other inflammatory conditions also tend to increase plasma NGAL, thus decreasing the specificity of plasma NGAL used alone. In addition, this study was performed in a population of patients with acute febrile illness, and so may not be directly applicable to all critically ill patients. The presented prediction model needs to be validated in future multicenter studies involving more patients across a wider patient population, and standardized NGAL cut-off values should be defined.

The overall results corroborate the previous studies and corroborate the use of plasma NGAL as an adjunctive biomarker of early detection of bacterial sepsis. The addition of NGAL, along with easily obtained clinical data, could help achieve improved early risk stratification, aid prompt initiation of antimicrobial therapy and lead to improved clinical outcomes for patients with suspected bacterial sepsis.

Conclusion

The present research has shown that elevated plasma neutrophil gelatinase-associated lipocalin (NGAL) may serve as a significant biomarker for the detection of bacterial sepsis in individuals suffering from acute febrile syndrome. The increased level of NGAL in conjunction with other clinical parameters such as diabetes mellitus, occurrence of rigors, qSOFA score and the identification of source of infection significantly raised the prediction value of bacterial sepsis. The cumulative predictive model has demonstrated a good diagnostic ability and can be useful for clinicians to perform an early risk stratification and to start timely treatment. Using NGAL in the routine clinical evaluation can improve the accuracy of the diagnosis and patients' outcomes. Further research in multicenter study should be conducted to confirm the findings of this study and to determine the NGAL cut-off values for the clinical practice.

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