OPEN ACCESS

Saudi Journal of Biomedical Research

Abbreviated Key Title: Saudi J Biomed Res
ISSN 2518-3214 (Print) | ISSN 2518-3222 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://saudijournals.com

Original Research Article

NGAL Levels as New Biochemical Marker for the Early Detection and Diagnosis of Osteoporosis in Patients with Meningitis

Noor Ali Gebur[1]*, Makarim Ali Enad[1], Ayat Saeed Awad[2]

[1]Department of Chemistry, College of Science, University of Al-Qadisiyah, Diwaniyah, Iraq
[2]Chemistry and Biochemistry Branch, Faculty of Medicine, Jabir Ibn Hayyan University for Medical and Pharmaceutical Sciences, Iraq

DOI: https://doi.org/10.36348/sjbr.2025.v10i10.004 | **Received:** 05.08.2025 | **Accepted:** 03.10.2025 | **Published:** 14.10.2025

[1]***Corresponding author:** Noor Ali Gebur
Department of Chemistry, College of Science, University of Al-Qadisiyah, Diwaniyah, Iraq

Abstract

Acute inflammation of the meninges the protective membranes enveloping the brain and spinal cord is referred to as meningitis. NGAL, a protein classified as an acute-phase reactant. We aimed to assess serum NGAL levels in individuals with meningitis in this study and to assess potential associations with the evaluated biochemical markers. A case-control study was conducted involving 120 Iraqi participants (60 individuals diagnosed with meningitis, 60 individuals diagnosed as control). Serum levels of NGAL and various markers were measured in all subjects. Statistical evaluation showed increase in hs-CRP, TNF-α, IL-6, CTX and NGAL levels among individuals with meningitis as compared to control group, respectively (10±1 versus 3.5±0.3, P=0.03), (50±4 versus 13±2, P=0.01), (20±1 versus 8±0.5, P=0.03), (0.8±0.1 versus 0.45±0.1, P=0.01) and (165±20 versus 135±10, P=0.04). NGAL exhibited a strong direct positive correlation with hs-CRP, TNF-α, IL-6 and CTX levels. The present study demonstrated individuals with meningitis have significantly elevated serum levels of NGAL as compared to control group, and a strong direct correlation observed between NGAL and hs-CRP, TNF-α, IL-6 and CTX. These findings proposed that NGAL expression may serve as a new biochemical marker for the early detection and diagnosis of osteoporosis in patients with meningitis.

Keywords: Meningitis, Osteoporosis, Lipocalin of Neutrophil – Gelatinase – Associated (NGAL), Factor of Tumor – Necrosis - alpha (TNF-α), Interleukin-6 (IL-6), C-Terminal Telopeptide (CTX).

INTRODUCTION

A broad spectrum of diseases; involving infections of the brain is associated significantly with mortality and morbidity. Meningitis, encephalitis, and brain abscesses are among these conditions. One of the oldest documented infectious diseases is meningitis its clinical features were described as early as the time of Hippocrates. The first recorded epidemic in Europe occurred in 1805, followed by its identification in the United States in 1806, and later in Africa by 1905 [1].

Acute inflammation of the meninges the protective membranes enveloping the brain and spinal cord is referred to as meningitis. This condition often arises as a result of microbial infections. The complications of bacterial meningitis is a high risk of death. In contrast, viral meningitis tends to follow a milder clinical course. Clinically, seizures and purulent cerebrospinal fluid (CSF), particularly in pediatric cases, where are a more common features of meningitis [2].

The clinical symptoms such as severe headache, neck stiffness, nausea, vomiting, high-grade fever, altered consciousness (e.g., drowsiness), and in some cases, seizures are presents with meningitis. Seizures and coma are serious neurological complications of infection with this organism. Outcomes are generally less favorable where the prognosis tends to be particularly poor in elderly patients [3].

Microglia alongside bone marrow derived macrophages, in the initial immune defense that play a role in response to central nervous system (CNS) infections. These immune cells secrete a range of cytokines of pro-inflammatory which is responsible for recruiting neutrophils to the site of inflammation [4]. Appropriate antimicrobial therapy often leads to significant improvement for CNS infections that can result in tissue damage and a variety of clinical manifestations. A well-coordinated immune response by the host is essential for pathogen clearance and symptomatic relief in affected individuals [5].

Lipocalin of Neutrophil – gelatinase - associated (NGAL), a lipocalin protein – superfamily; classified as an acute - phase reactant, is mainly secreted by neutrophils and monocyte-derived macrophages. Additionally, NGAL has emerged as a sensitive biomarker for inflammation-induced tissue injury in organs such as the kidneys, heart, and brain [6]. Recent studies have highlighted its wide range of biological functions, including roles in olfactory signaling and prostaglandin biosynthesis. Obesity and metabolic syndrome have also identified by increased NGAL concentrations [7]. However, to fully understand NGAL connection to diverse inflammatory signaling pathways was more essential in-depth studies in human populations. In addition, the involvement of NGAL in oxidative stress defense and modulating microglial autophagy mechanisms was highlighted by recent research on NGAL's potential neuroprotective properties [8].

NGAL levels in the central nervous system (CNS) under physiological conditions are typically low and being nearly undetectable with its mRNA expression. The specific role of NGAL in promoting the activation of M1-type microglia was suggested by recent findings [9]. However, during CNS-related pathologies or systemic inflammatory responses, microglia are capable of producing NGAL [10]. NGAL levels have been associated with disease of Alzheimer and mild cognitive impairment, characterized by reduced concentrations in the cerebrospinal fluid alongside elevated expression in brain regions affected by pathology. It also enhances microglial sensitivity to apoptotic signals, supports their migration, and contributes to the development of astrocytosis [11]. Additionally, NGAL production mediated by soluble TNF receptor 1 (sTNFR1) has been shown to interfere with the neuroprotective signaling pathway driven by TNF receptor 2 (TNFR2), which is essential for TNF-α-induced neuroprotection. Similarly, research examining NGAL in the context of schizophrenia has produced mixed results, with some studies reporting increased levels in patients, followed by a reduction after therapeutic intervention [12].

Although NGAL is markedly upregulated in numerous inflammatory conditions, it has been reported to exhibit; properties of both-anti-inflammatory and pro-inflammatory. In neutrophils, the secretion of NGAL is tightly regulated in response to inflammatory and infectious stimuli. Interestingly, the gene promoter of NGAL contains sites of binding for two major factors of transcription; highlighting its transcriptional regulation in the context of inflammation [13]. Notably, factor of tumor – necrosis - alpha (TNF-α) and lipopolysaccharide (LPS) are among the most potent inducers of NGAL expression. More recently proposed that NGAL functions as an anti - inflammatory modulator, influencing regulating; the activation of the - NF-κB/STAT3 and polarization of; macrophage signaling - pathway [14]. This was accompanied by increased expression of downstream the target; genes including IL-1β, iNOS, IL-6 and MCP-1, compared to wild type controls reported that stimulation; with lipopolysaccharide (LPS) in NGAL deficient; bone – marrow that derived macrophages (BMDMs), led to enhanced activation of the c-Jun, NF-κB, and STAT3 signaling pathways [15]. Furthermore, pretreatment with recombinant NGAL was found to suppress the genes; expression of pro-inflammatory iNOS and IL-6 in NGAL-deficient BMDMs, as well as attenuate LPS-induced IκBα degradation and STAT3 phosphorylation [16].

The upregulation of expression for NGAL and secretion by glial cells in response to stimuli of inflammatory within the central nervous system was shown by recent studies. In a mouse model of experimental autoimmune encephalomyelitis (EAE) the increase in NGAL expression was observed in the secondary lymphoid organs and spinal cord following disease induction [17]. The expression of NGAL and its receptor 24p3R were predominantly in neutrophils and dendritic cells, respectively in the spleen. Notably, the mice that suffer from NGAL deficient exhibited significantly lower expression of pro-inflammatory mediators compared to wild-type counterparts and reduced inflammatory cell infiltration. Collectively, As a key the progression of EAE and pro-inflammatory factor involved in autoimmune inflammation was highlighted by these findings of NGAL. Additionally, the promotion of NGAL expression in both the spinal cord and peripheral immune tissues by administration of recombinant NGAL protein thereby contributing to EAE pathogenesis [18].

Moreover, several inflammatory has been linked to conditions bone resorption, for instance, the localized bone erosion occurring at the edges of affected joints be characterized by arthritis of rheumatoid (RA). Additionally, The patients suffering from RA, systemic lupus erythematosus (SLE), disease of; inflammatory bowel (IBD), chronic disease of; obstructive of pulmonary (COPD), periodontal disease which involves chronic inflammation of the gums that results in; destruction of; the alveolar - bone that supporting the teeth and other inflammatory illnesses compared to healthy individuals were observed with greater frequency in disorders such as osteoporosis and fragility fractures. The connection between; pro-inflammatory cytokines and osteoclasts—the specialized cells responsible for bone degradation suggested by these observations [19].

However, the pave of the way for novel therapeutic approaches aimed at preventing and managing bone loss in inflammatory patient population by a deeper understanding of the interaction between inflammation and osteoclast activity. Bone loss across various diseases follows a similar pattern: osteoclasts are

the cells of sole that responsible for; osteoporosis – and - bone resorption arises when osteoclast activity surpasses that of osteoblasts [20]. Inflammation influences this bone degradation primarily through two key pathways. The first regulates osteoclast formation (osteoclastogenesis) by modulating the factor of; macrophage colony - stimulating (M-CSF) pathway. The second mechanism involves pro-inflammatory cytokines acting via a central regulator function of osteoclast [21].

This study; aimed to assess NGAL serum levels in individuals with meningitis and to investigate potential associations with the evaluated biochemical markers.

EXPERIMENTAL

Individuals and study design

Ethical clearance for conducting this study was obtained from the University of Al-Qadisiyah / Faculty of Science. The information was secured about participants prior to the commencement of the research. The study involved 120 participants divided into two groups composed of 60 individuals diagnosed with meningitis (30 males, 30 females), matched in age (18–50 years) and 60 individuals as control group to serve as a reference (30 males, 30 females), matched in age (18–50 years), were included to facilitate comparative analysis with the patient group. From April to June 2025, the patients were recruited from Diwaniya Teaching Hospital, located in Al-Qadisiyah, Iraq.

Exclusion criteria

Individuals suffering from different diagnosis such as subarachnoid hemorrhage, brain tumors, brain abscess, or isolated encephalitis. Chronic immune-related diseases such as lupus, sarcoidosis, or multiple sclerosis. Antibiotics before sample collection may affect culture accuracy. Contaminated or insufficient sample (bloody or improperly collected cerebrospinal fluid CSF samples) were excluded from participation in this research.

Collection of samples

Between 8:30 and 10:00 a.m. after an overnight; at fasting <8–12 hours>; from both meningitis patients and healthy control, blood samples were collected, using 23-gauge needles through antecubital venipuncture of venous blood drawn from each participant with <5> milliliters. Then, the collected blood.

Anthropometric evaluation

The assessment for the index of body mass by: BMI=(weight in kg)/ (height in meters).

Biochemical evaluation

The samples of (CSF) were cultured using standard microbiological methods. The performance of inoculation on chocolate agar; blood agar - and mac conkey agar plates (Oxoid, UK), and incubated for 24–48 hours at 37°C under appropriate aerobic or CO_2-enriched conditions. Enrichment was achieved using thioglycolate broth. Identification of bacterial was carried out based on gram staining, colony morphology and conventional biochemical tests. The measuring of serum (TNF-α) levels by using a commercial TBARS-based assay kit supplied by LTA (Italy), following the method of thiobarbituric acid reactive substances (TBARS). To determine the serum (NGAL) levels, assay of enzyme-linked immunosorbent kits from MELSIN (China) were utilized. The (IL-6) content in serum was measured using a kit from LTA (Italy), with readings taken at 585 nm according to spectrophotometric guidelines. The determination of serum (hs-CRP) concentrations by using an ELISA kit from LiNEAR (Spain) based on standard enzyme-linked immunosorbent assay protocols. The serum (CTX) levels was analyzed using a commercial ELISA kit from CORTEZ (USA), in line with the enzyme - linked immunosorbent assay principle. By using spectrophotometric assay kits from MELSIN (China) were utilized, to determine the serum (Na^+); (K^+) and (Ca^{+2}) levels.

Bio-statistical analysis

The analysis of data; by using Microsoft Excel 2010 in conjunction with SPSS software (version 24). Conducted by comparative statistical tests to determine significant differences between the investigated groups. Additionally, employed to examine potential associations between the studied parameters by analysis of correlation coefficient of Pearson.

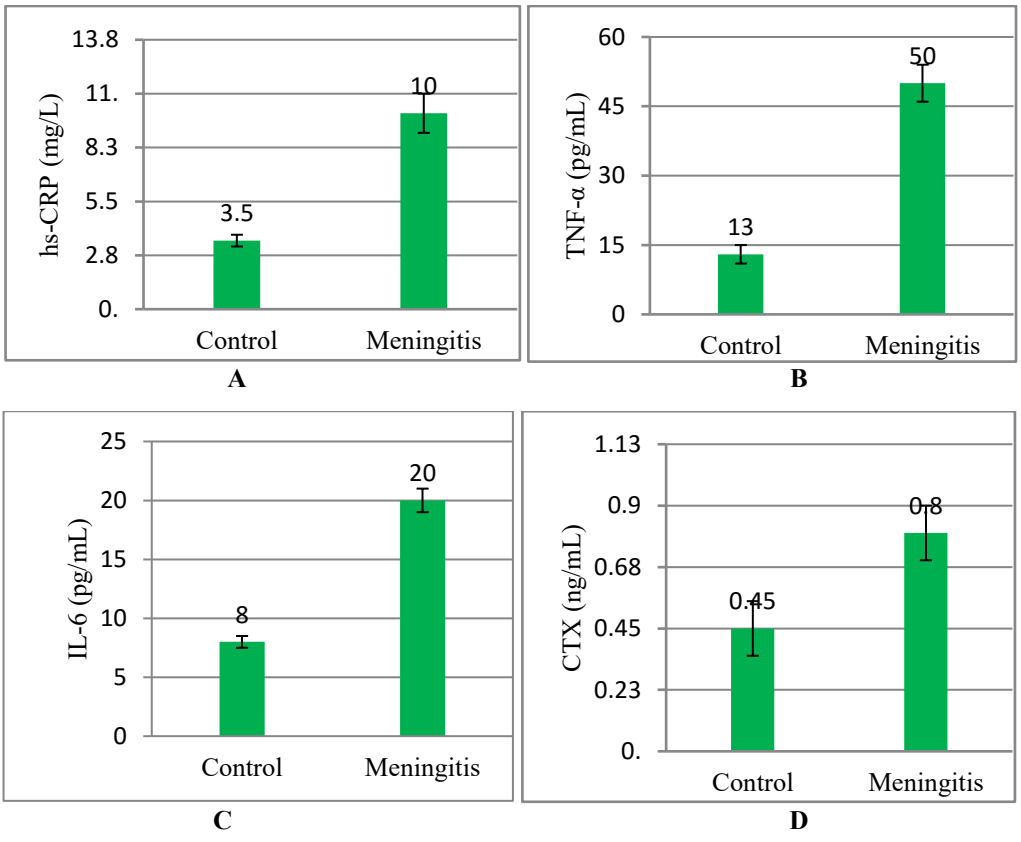
RESULTS AND DISCUSSION

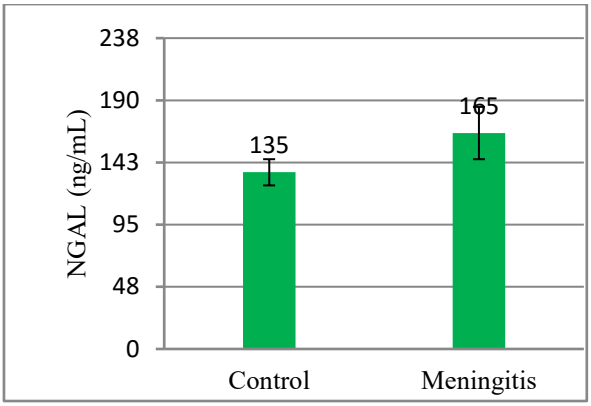
As illustrated in Table 1, the mean of age, gender, BMI, W/H, SBP, DBP, Na^+, K^+ and Ca^{+2} demonstrated no significant variations between the meningitis and the control groups. Nevertheless, in the meningitis group; the mean of hs-CRP, TNF-α, IL-6, CTX and NGAL levels showed a significant increase as compared with the control group. However, the rate of positive CSF culture was significantly higher in meningitis group compared to control group, indicating a greater prevalence of confirmed bacterial meningitis in meningitis group, these findings are depicted in Figure 1 (A, B, C, D, E).

Table 1: Demographic and biochemical data for the meningitis and the control groups

Parameters	Groups		P-value
	Control Mean ±SD (n=60)	Meningitis Mean ±SD (n=60)	
Age (year)	34±5	34±5	0.91
Gender Males/Females	30 (50%)/30 (50%)	30 (50%)/30 (50%)	0.85
BMI (Kg/m2)	23.3±2.0	23.3±2.0	0.94
W/H	0.72±0.1	0.72±0.1	0.87
SBP (mmHg)	120±10	130 ±10	0.79
DBP (mmHg)	75±5	85±2	0.81
CSF Culture	Negative	Positive	0.04
hs-CRP (mg/L)	3.5±0.3	10±1	0.03
TNF-α (pg/mL)	13±2	50±4	0.01
IL-6 (pg/mL)	8±0.5	20±1	0.03
Na^{+} (mmol/L)	140±5	120±2	0.15
K^{+} (mmol/L)	4.25±0.5	2.5±0.1	0.72
Ca^{+2} (mmol/L)	2.35±0.3	1.9±0.1	0.28
CTX (ng/mL)	0.45±0.1	0.8±0.1	0.01
NGAL (ng/mL)	135±10	165±20	0.04

Data represented as - Mean ±SD; n: Number of subjects - SD: <Stander deviation> - P-value of ≤0.05 was considered <significant> - SBP: <Blood Pressure of Systolic> - BMI: <Index of Body Mass> - DBP: <Blood Pressure of Diastolic> - W/H: <Ratio of Waist to Hip> - hs-CRP: <High-Sensitivity C-Reactive Protein> - IL-6: <Interleukin-6> - CTX: <C-Terminal Telopeptide> - TNF-α: <Factor of Tumor - Necrosis – alpha> - NGAL: <Neutrophil Gelatinase-Associated Lipocalin> - Na^{+}: <Sodium> - K^{+}: <Potassium> - Ca^{+2}: <Calcium>.





E

Figure 1: Comparison of serum A: hs-CRP, B: TNF-α, C: IL-6, D: CTX and E: NGAL levels between the meningitis and control groups

As shown in Table 2 that showed the results - of analysis of a linear regression that assessing the relationship between levels of serum NGAL concentrations and selected demographic and biochemical parameters in individuals with meningitis. The findings revealed that no strong significant correlation between NGAL and other studied demographic and biochemical parameters, except that levels of hs-CRP; TNF-α; IL-6 and CTX showed a strong significant positive correlation with NGAL level, as shown in Figure 2 (A, B, C, D).

Table 2: Correlation between serum NGAL levels and others demographic and biochemical parameters in the meningitis group

Parameters	**NGAL (ng/mL)**	
Age (year)	r P-value	0.52 0.83
BMI (Kg/m2)	r P-value	0.45 0.94
W/H	r P-value	0.27 0.81
SBP (mmHg)	r P-value	0.51 0.78
DBP (mmHg)	r P-value	0.37 0.91
hs-CRP (mg/L)	r P-value	0.98 0.02
TNF-α (pg/mL)	r P-value	0.98 0.03
IL-6 (pg/mL)	r P-value	0.96 0.01
Na^{+} (mmol/L)	r P-value	0.12 0.93
K^{+} (mmol/L)	r P-value	0.46 0.79
Ca^{+2} (mmol/L)	r P-value	0.31 0.58
CTX (ng/mL)	r P-value	0.97 0.03

P-value of ≤0.05 was considered <significant> - r: <Correlation Coefficient of Person> - BMI: <Index of Body Mass> - SBP: <Blood Pressure of Systolic> - W/H: <Ratio of Waist to Hip> - DBP: <Blood Pressure of Diastolic> - TNF-α: <Factor of Tumor - Necrosis – alpha> - hs-CRP: <High-Sensitivity C-Reactive Protein> - IL-6: <Interleukin-6> - CTX: <C-Terminal Telopeptide> - NGAL: <Neutrophil Gelatinase-Associated Lipocalin> - Na^{+}: <Sodium> - K^{+}: <Potassium> - Ca^{+2}: <Calcium>.

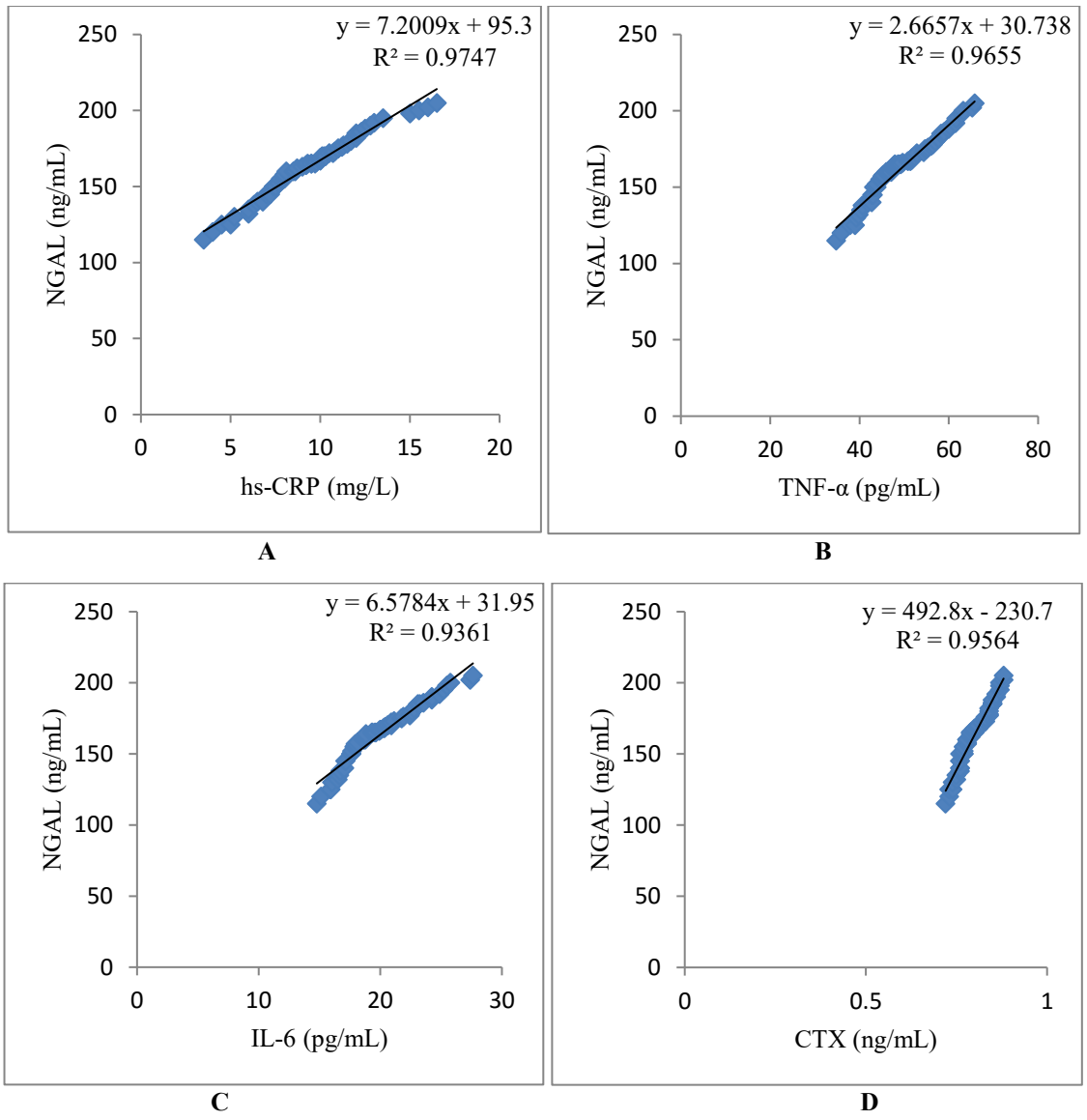


Figure 2: Correlation between serum NGAL levels and A: hs-CRP, B: TNF-α, C: IL-6 and D: CTX in the meningitis group

Table 3 presented the ROC curve analysis for NGAL, revealing a cut-off point of 95% for detecting meningitis. The calculation of; area under the curve (AUC) was at 0.983, reflecting high diagnostic performance. NGAL demonstrated a sensitivity of 95% and a specificity of 100%, as shown in Figure 3.

Table 3: Receiver operating characteristic (ROC) and area under the curve (AUC) analysis of NGAL in diagnosing meningitis patients

Variable	Group	Cut-off concentration %	Sensitivity %	Specificity %	AUC	Std. Error	95% CI of AUC	P-value
NGAL	Meningitis	95	95	100	0.983	0.015	0.953 -1.000	0.001

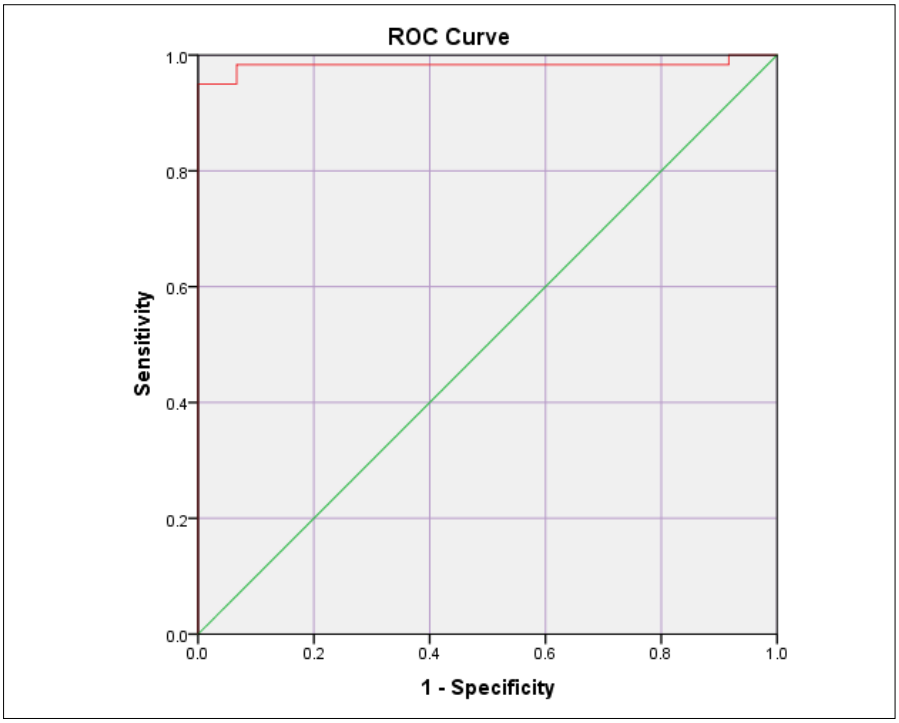


Figure 3: Receiver operating characteristic (ROC) curve analysis of NGAL in diagnosing meningitis patients

The present study revealed a significant increase in serum NGAL levels, alongside a notable increase in the factors hs-CRP, TNF-α, IL-6 and CTX among individuals with meningitis. A strong positive correlation was identified between NGAL and the factors, hs-CRP, TNF-α, IL-6 and CTX in these patients. This pattern can be explained by the fact that in bacterial meningitis, the infection triggers an acute inflammatory response characterized by cytokines of pro-inflammatory elevation levels such as TNF-α and IL-6. This inflammatory environment stimulates immune cells to secrete large amounts of NGAL, both within the peripheral immune tissues - and - central nervous system. Additionally, chronic inflammation influences the balance of bone cells by promoting the activity of osteoclasts, which break down bone, while inhibiting osteoblasts, the cells responsible for bone formation. This shift in cellular activity accelerates the progression of osteoporosis, contributes to increased production of factors that enhance bone resorption, leading to a loss of bone mass. Consequently, elevated NGAL levels could potentially serve as an early biomarker indicating increased risk for osteoporosis in individuals with meningitis.

Numerous research studies have demonstrated that NGAL levels increase in a variety of pathological conditions. The significant source of NGAL is also recognized by adipose tissue, which in turn this protein concentration tends to rise following tissue injury and expressed in multiple tissue types [22]. The stimulating NGAL expression in cells such as neutrophils, epithelial cells, and hepatocytes by the key role of inflammatory cytokines [23]. In individuals with; disease of nonalcoholic fatty liver - and - obesity have been observed elevated levels of NGAL [24]. Furthermore, the risk factor for disturbances in lipid metabolism; hypertension - and insulin resistance - has been identified by elevated NGAL [25]. Several studies suggest that the useful predictor for metabolic complications associated with obesity is measuring NGAL concentrations in the bloodstream [26]. Although the precise role of NGAL in obesity pathogenesis remains unclear, it is thought to be involved in the regulation of a key regulator of adipogenesis and lipogenesis [27]. Additionally; inhibiting the activity; for nuclear factor kappa B (NFκB) by NGAL that may exert anti-inflammatory effects in adipose tissue, thereby counteracting TNF-alpha–mediated inflammation. Previous research found that increased NGAL mRNA expression, which in turn activated PPARγ in obese mice [28]. This process can lead to simultaneously suppressing leptin and adiponectin secretion while; enhanced - production of IL-6 [29-30]. The stimulation role of NGAL is the expression of the factors of inflammatory, whereas NGAL deficiency appears to offer protection against glucose metabolism disorders [31-32]. In patients with insulin resistance; showed that NGAL levels correlated with the expression of TNF-alpha. Moreover, hyperglycemia itself has been found to promote NGAL synthesis [33-34].

The critical role of inflammation in the progression of atherosclerosis, beginning with endothelial dysfunction and advancing through the formation of atherosclerotic plaques. Research has identified activated neutrophils within atherosclerotic lesions [35]. Ultimately, this process may result in plaque rupture; formation of - occlusive thrombus and syndrome of - acute coronary [36]. A key mechanism may involve

the binding of NGAL to matrix metalloproteinase-9 (MMP-9), which amplifies the enzyme's proteolytic function and contributes to plaque vulnerability. Under the influence of TNF-alpha, macrophages derived from bone marrow secrete NGAL, and subsequent exposure to NGAL promotes the expression of markers of macrophage cells, upregulation of; scavenger - receptor, and the transformation of these cells into foam cells [37]. NGAL is thought to enhance proteolytic activity within atherosclerotic plaques, thereby reducing plaque stability and increasing the risk of cardiovascular events. In plaques exhibiting central necrosis or intraplaque hemorrhage; that detected by elevated levels of the complex NGAL/MMP-9 that associated with increased of rupture risk [38]. The activation of MMP-9 has been implicated in both the inflammatory response and the pathogenesis of atherosclerosis [39]. Furthermore, as compared to subjects of asymptomatic; individuals with atherosclerosis of symptomatic; demonstrated significantly elevated levels of plasma NGAL. In human atherosclerotic plaques, the high expression of the complex NGAL/MMP-9 proposed that NGAL as a potential biomarker for identifying high-risk patients [40].

Elevated NGAL concentrations have been observed in atherosclerotic plaques of patients experiencing acute myocardial infarction (MI). Following an infarction, neutrophils infiltrate the damaged myocardial tissue and trigger inflammatory responses. Inflammation is a key component of ischemia-reperfusion injury in the heart [41]. During myocardial infarction, NGAL, a glycoprotein secreted by neutrophils is released in large amounts. While this process may help limit the extent of tissue damage, excessive neutrophil accumulation can hinder proper myocardial repair. Elevated serum NGAL levels in MI patients have been associated with worse clinical outcomes [42]. Its levels in the left ventricular tissue have been found to increase significantly within the first week post-infarction. Moreover, patients with reduced ejection fraction (EF) following MI had elevated NGAL concentrations relative to those with preserved EF [43]. In a patients study involving infarction of myocardial, those who did not survive exhibited significantly higher plasma NGAL levels compared to survivors. Furthermore, an experimental study using anti-NGAL antibodies in mice demonstrated reduced infiltration of neutrophils and macrophages into the ischemic myocardium, along with a decrease in cardiac tissue damage [44]. Echocardiographic assessments indicated better cardiac function post-ischemia in individuals with lower plasma NGAL levels [45].

Inflammation and extracellular matrix degradation are key mechanisms in the development of heart failure (HF). When complexed with matrix metalloproteinase-9 (MMP-9), NGAL enhances the enzymatic activity of MMP-9, thereby exacerbating cardiac remodeling processes. As a contributor to is increasingly recognized as a potential biomarker for heart failure and cardiac remodeling has been identified by NGAL [46]. Following infarction of myocardial; in patients with failure of heart (acute and chronic) that showed elevated serum NGAL levels [47]. In addition, as a function of NGAL by promoting the muscle cells for differentiation by migration of immune cell and growth factors [48]. NGAL could serve as a prognostic indicator in heart failure population by elevated levels of its in serum [49]. The mechanisms of immune - response in the progression of heart failure is the idea that increased plasma NGAL reflected myocardial injury that supported by evidence from clinical and experimental studies. The patients with chronic heart failure as compared to healthy individuals, consistently present with elevated NGAL concentrations, which tend to rise in severity cases of failure of heart [50]. Moreover, in individuals with chronic heart failure, an inverse relationship has been noted between levels of serum NGAL and ejection fraction (EF). The reflecting advanced disease by highest levels of plasma NGAL are typically found in patients classified as NYHA class IV [51].

As a potential biomarker for abdominal – aortic - aneurysms (AAA) progression and pathogenesis has also emerged by NGAL [52]. In experimental mouse models, both NGAL deficiency and treatment with anti-NGAL antibodies were associated with a reduced incidence of AAA formation, suggesting that the suppression of neutrophil activity may play a protective role [53]. Neutrophils isolated from individuals with AAA have been shown to secrete elevated levels of NGAL. Furthermore, research by Ramos-Mozo revealed that the luminal thrombus of AAA released significantly higher amounts of NGAL compared to the abluminal thrombus, the aneurysmal wall, and the media of healthy aortas [54].

CONCLUSIONS

This study results indicated a clear biological positive association between NGAL levels and hs-CRP, TNF-α, IL-6 and CTX in patients with meningitis. These findings suggest that NGAL levels as new biochemical marker for the early detection and diagnosis of osteoporosis in patients with meningitis. Further research was recommended to conduct long-term studies to monitor patients recovering from meningitis in order to track gradual changes in bone mineral density and determine the timeframe in which skeletal effects begin to appear, in addition, analyzing genetic or immunological factors that may predispose certain patients to a higher risk of developing osteoporosis following meningitis compared to others is recommended.

ACKNOWLEDGEMENT

The participants were thanked by the authors for their cooperation, as well as; the authors thanked the medical personnel and laboratory staff at Diwaniya Teaching Hospital in Al Qadisiyah, Iraq, for their

valuable support in sample collection and the execution of essential laboratory analyses.

CONFLICT OF INTERESTS

No conflict among the authors about interest.

FUNDING

Self-funding.

REFERENCES

1. Leimkugel J, Racloz V, Silva A, Gerd P. Global review of meningococcal disease- A shifting etiology. *Journal of bacteriology research* 2009; 12(3): 18-29.
2. Abio A, Neal K and Beck C. An epidemiological review of changes in meningococcal biology during the last 100 years. *Pathogens and Global Health* 2013; 10(5): 20-30.
3. Brandt C. Experimental studies of pneumococcal meningitis. *Danish medical bulletin* 2010; 57(19): 14-25.
4. Houghland J. Seizures in Adults with Bacterial Meningitis. *The Journal of Emergency Medicine* 2008; 35(16): 13-36.
5. Turner M, Nedjai B, Hurst T and Pennington D. Cytokines and chemokines: At the crossroads of cell signalling and inflammatory disease. *Biochimica et Biophysica Acta (BBA) - Molecular Cell Research* 2014; 43(25): 12-32.
6. Katano M. Implication of granulocyte-macrophage colony- stimulating factor induced neutrophil gelatinase-associated lipocalin in pathogenesis of rheumatoid arthritis revealed by proteome analysis. *Arthritis Res Ther* 2009; 11(3): 15-31.
7. Kjeldsen L, Cowland J and Borregaard N. Human neutrophil gelatinase-associated lipocalin and homologous proteins in rat and mouse. *Biochim Biophys Acta* 2009; 82(27): 19-43.
8. Kjeldsen L, Okamoto K and Arito M. Identification of neutrophil gelatinase-associated lipocalin as a novel matrix protein of specific granules in human neutrophils. *Blood* 1994; 33(21): 17-38.
9. Chu S, Lin H, Huang H and Chen Y. The hydrophobic pocket of 24p3 protein from mouse uterine luminal fluid: fatty acid and retinol binding activity and predicted structural similarity to lipocalins. *J Pept Res* 1998; 52(39): 15-22.
10. Bao G, Clifton M and Hoette T. Iron traffics in circulation bound to a siderocalin (Ngal)-catechol complex. *Nat Chem Biol* 2010; 6(2): 23-37.
11. Hvidberg V, Jacobsen C, Strong R. The endocytic receptor megalin binds the iron transporting neutrophil-gelatinase- associated lipocalin with high affinity and mediates its cellular uptake. *FEBS Lett* 2005; 57(37): 13-33.
12. Owen H, Roberts S, Ahmed S and Farquharson C. Dexamethasone- induced expression of the glucocorticoid response gene lipocalin 2 in chondrocytes. *Am J Physiol Endocrinol Metabol* 2008; 29(10): 14-30.
13. Yan Q, Yang Q and Mody N. The adipokine lipocalin 2 is regulated by obesity and promotes insulin resistance. *Diabetes* 2007; 56(25): 10-20.
14. Go´mez R, Scotece M and Conde J. Nitric oxide boosts TLR-4 mediated lipocalin 2 expression in chondrocytes. *J Orthop Res* 2013; 31(10): 12-34.
15. Nairz M, Haschka D and Demetz E. Iron at the interface of immunity and infection. *Front Pharmacol* 2014; 5(3): 18-29.
16. Srinivasan G, Aitken J and Zhang B. Lipocalin 2 deficiency dysregulates iron homeostasis and exacerbates endotoxin-induced sepsis. *J Immunol* 2012; 18(10): 11-40.
17. Devireddy L, Hart D, Goetz D and Green M. A mammalian siderophore synthesized by an enzyme with a bacterial homolog involved in enterobactin production. *Cell* 2010; 14 (6): 17-37.
18. Zhao H, Konishi A and Fujita Y. Lipocalin 2 bolsters innate and adaptive immune responses to blood-stage malaria infection by reinforcing host iron metabolism. *Cell Host Microbe* 2012; 12(7): 16-30.
19. Mundy GR. Osteoporosis and inflammation. *Nutr Rev* 2007; 25(14): 11-35.
20. Romas E, Gillespie M and MartinT. Involvement of receptor activator of NFkappaB ligand and tumor necrosis factor-alpha in bone des- truction in rheumatoid arthritis. *Bone* 2002; 20(6): 14-20.
21. Teitelbaum S. Osteoclasts: what do they do and how do they do it. *Am J Pathol* 2007; 17(12): 15-31.
22. Vijay M, Gentsch J, Kaiser W, Borregaard N, Offermann M, Neish A and Gewirtz A. Protein kinase R mediates intestinal epithelial gene remodeling in response to double-stranded RNA and live rotavirus. *J. Immunol* 2005; 74(22): 13-25.
23. Çelik T, Altekin E, Kenesari Y, Duman M and Arslan N. Evaluationofneutrophilgelatinase-associatedlipocalinin pediatric patients with acute rotavirus gastroenteritis and dehydration. *Ital. J. Pediatr* 2013; 39(22): 21-45.
24. Landrø L, Damås J, Flo T, Heggelund L, Ueland T, Tjønnfjord G, Espevik T, Aukrust P and Frøland S. Decreased serum lipocalin-2 levels in human immunodeficiency virus-infected patients: Increase during highly active anti-retroviral therapy. *Clin. Exp. Immunol* 2008; 15(12): 13-28.
25. Wu G, Li H, Zhou M, Fang Q, Bao Y, Xu A and Jia W. Mechanism and clinical evidence of lipocalin-2 and adipocyte fatty acid-binding protein linking obesity and atherosclerosis. *Diabetes Metab. Res*. Rev 2014; 30(14): 15-28.
26. Wang Y, Lam K, Kraegen E, Sweeney G, Zhang J and Tso A. Lipocalin-2 is an inflammatory marker closely associated with obesity, insulin resistance, and hyperglycemia in humans. *Clin. Chem.* 2007; 53(34): 21-37.
27. Jang Y, Lee J, Wang Y, Sweeney G. Emerging clinical and experimental evidence for the role of lipocalin-2 in metabolic syndrome. *Clin. Exp.*

Pharmacol. Physiol 2012; 39(14): 19-33.
28. Law I, Xu A and Lam K. Lipocalin-2 deficiency attenuates insulin resistance associated with aging and obesity. *Diabetes* 2010; 59(18): 12-47.
29. Liu J, Song E, Xu A, Berger T and Mak T. Lipocalin-2 deficiency prevents endothelial dysfunction associated with dietary obesity: Role of cytochrome P450 2C inhibition. *Br. J. Pharmacol* 2012; 65(20): 21-35.
30. Bhusal A, Rahman M, Lee W and Bae Y. Paradoxical role of lipocalin-2 in metabolic disorders and neurological complications. *Biochem. Pharmacol* 2019; 16(11): 26-38.
31. Yan Q, Yang Q, Mody N and Graham T. The adipokine lipocalin 2 is regulated by obesity and promotes insulin resistance. *Diabetes* 2007; 56(25): 35-40.
32. Zhang J, Wu Y, Zhang Y, and Leroith D. The role of lipocalin 2 in the regulation of inflammation in adipocytes and macrophages. *Mol. Endocrinol* 2008; 22(16): 14-39.
33. Ricote M and Glass C. PPARs and molecular mechanisms of transrepression. Biochim. *Biophys. Acta* 2007; 71(26): 25-46.
34. Lin Y, Rajala M, Berger J and Moller D. Hyperglycemia-induced production of acute phase reactants in adipose tissue. *J. Biol. Chem* 2001; 26(4): 20-32.
35. Libby P, Ridker P and Hansson G. Progress and challenges in translating the biology of atherosclerosis. *Nature* 2011; 43(17): 25-33.
36. Van der Wal A, Becker A, van der Loos C and Das P. Site of intimal rupture or erosion of thrombosed coronary atherosclerotic plaques is characterized by an inflammatory process irrespective of the dominant plaque morphology. *Circulation* 1994; 89(36): 24-50.
37. Oberoi R, Bogalle E, Matthes L and Schuett H. Lipocalin(LCN) 2 Mediates Pro-Atherosclerotic Processes and Is Elevated in Patients with Coronary Artery Disease. *PLoS ONE* 2015; 10(3): 14-42.
38. Hemdahl A, Gabrielsen A, Zhu C and Eriksson P. Expressionofneutrophil gelatinase-associated lipocalin in atherosclerosis and myocardial infarction. *Arterioscler. Thromb. Vasc. Biol* 2006; 26(13): 15-37.
39. Leclercq A, Houard X, Philippe M and Ollivier V. Involvementofintraplaquehemorrhagein atherothrombosis evolution via neutrophil protease enrichment. *J. Leukoc. Biol* 2007; 12(10): 14-33.
40. TeBoekhorst B, Bovens S, HellingsW and vanderKraak P. Molecular MRI of murine atherosclerotic plaque targeting NGAL: A protein associated with unstable human plaque characteristics. *Cardiovasc. Res* 2011; 19(8): 18-45.
41. Cheng L, Xing H and Mao X. Lipocalin-2 promotes m1 macrophages polarization in a mouse cardiac ischaemia-reperfusion injury model. *Scand. J. Immunol* 2015; 21(11): 18-39.
42. Martínez E, Buonafine M, Boukhalfa I, Ibarrola J and Fernández A. Aldosterone Target NGAL (Neutrophil Gelatinase-Associated Lipocalin) Is Involved in Cardiac Remodeling After Myocardial Infarction Through NFκB Pathway. *Hypertension* 2017; 50(11): 11-31.
43. Freitas I, Lima N and Silva G. Novel biomarkers in the prognosis of patients with atherosclerotic coronary artery disease. *Rev. Port. Cardiol* 2020; 39(6): 12-30.
44. Avci A, Ozturk B, Demir K and Akyürek F. The Prognostic Utility of Plasma NGAL Levels in ST Segment Elevation in Myocardial Infarction Patients. *Adv. Prev. Med* 2020; 23(13): 14-23.
45. Yang B, Fan P, Xu A and Lam K. Improvedfunctional recovery to I/R injury in hearts from lipocalin-2 deficiency mice: Restoration of mitochondrial function and phospholipids remodeling. *Am. J. Transl. Res* 2012; 4(2): 11-28.
46. Palazzuoli A, Beltrami M, Pellegrini M, and Nuti R. Natriuretic peptides and NGALinheartfailure: Doesalinkexist. *Clin.Chim. Acta* 2012; 13(8): 18-24.
47. Savic-Radojevic A, Pljesa-Ercegovac M, Matic M and Simic D. Novel Biomarkers of Heart Failure. *Adv. Clin. Chem* 2017; 17(13): 12-27.
48. Han X, Zhang S, Chen Z and Adhikari B. Cardiac biomarkers of heart failure in chronic kidney disease. *Clin. Chim. Acta* 2020; 10(2): 11-24.
49. Yndestad A, Landrø L, Ueland T, Dahl C and Flo T. Increased systemic and myocardial expression of neutrophil gelatinase-associated lipocalin in clinical and experimental heart failure. *Eur. Heart J* 2009; 30(15): 12-27.
50. Bolignano D, Basile G, Parisi P and Coppolino G. Increased plasma neutrophilgelatinase-associated lipocalin levels predict mortality in elderly patients with chronic heart failure. *Rejuvenation Res* 2009; 12(7): 14-27.
51. Oikonomou E, Tsalamandris S and Karlis D. The association among biomarkers of renal and heart function in patients with heart failure: The role of NGAL. *Biomark. Med* 2018; 12(3): 13-25.
52. Karaolanis G, Moris D and Palla V. Neutrophil Gelatinase Associated Lipocalin (NGAL) as a Biomarker- Does It Apply in Abdominal Aortic Aneurysms- A Review of Literature. *Indian J. Surg* 2015; 7(3): 17-29.
53. Tarín C, Fernandez C, Burillo E and Pastor C. Lipocalin-2 deficiency or blockade protects against aortic abdominal aneurysm development in mice. *Cardiovasc. Res* 2016; 11(2): 23-36.
54. Ramos P, Madrigal J and Vegade M. Increased plasma levels of NGAL, a marker of neutrophil activation- in patients with abdominal aortic aneurysm. *Atherosclerosis* 2012; 22(12):16-27.