REVIEW

The Importance of Neutrophil Gelatinase-Associated Lipocalin (NGAL) in Monitoring Patients with Renal Transplantation

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Abstract. Introduction: Neutrophil Gelatinase-associated Lipocalin (NGAL), a glycoprotein, is a promising biomarker for the early detection of acute renal failure (ARF) lesions, with particular relevance in transplant follow-up. **Aim:** This paper reviews clinical analysis's usefulness, limitations and NGAL prospects in monitoring kidney transplant (KT) patients. The work synthesizes, through an analysis of specialized literature, data regarding the role of NGAL as a biomarker of kidney allograft failure. **Discussion:** NGAL (from urinary/plasma samples) predicts delayed graft function (DGF) and long-term prognosis in kidney transplant, with donor urinary NGAL being a relevant pre-transplant factor. **Conclusions:** NGAL is a valuable tool for detecting early ARF in transplantation. The integration of clinical efficiency requires standardization and the establishment of specific background studies that demonstrate the impact of monitoring guided by NGAL on outcomes, thereby maximizing its usefulness in a personalized approach.

Keywords*: NGAL, kidney transplant, acute renal failure.*

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I. INTRODUCTION TO NEUTROPHIL GELATINASE-ASSOCIATED LIPOCALIN (NGAL)

1. Definition, Molecular Characteristics, and Biological Functions

Neutrophil Gelatinase-Associated Lipocalin (NGAL), also known as lipocalin-2 (LCN2) or 24p3 oncogene, is a 25 kDa glycoprotein belonging to the superfamily of lipocalins [1]. Initially identified in mouse kidney cells and later in human neutrophil granules, the human LCN2 gene, which encodes NGAL, is located on chromosome 9 [2]. NGAL exists in several molecular forms, each with distinct potential implications in the body. Thus, the 25 kDa monomer is predominantly released by the renal tubules and is considered particularly relevant for kidney-specific lesions. In contrast, the 45 kDa homodimer is secreted by neutrophils in response to inflammatory processes. A third

important form is a 135 kDa complex composed of NGAL and matrix metalloproteinase-9 (MMP-9). This complex not only protects MMP-9 from degradation but also enhances its activity, thereby contributing to proteolysis, collagen dissolution, and, ultimately, the initiation and progression of fibrotic processes [1].

In addition to neutrophils, NGAL is secreted by a multitude of other tissues and cells, including renal tubular cells, cells from the heart, lung, liver, stomach, colon, various epithelial cells, macrophages, dendritic cells, and adipocytes. This ubiquitous expression of NGAL is a key factor contributing to its limited specificity for renal injury [1].

The biological functions of NGAL are pleiotropic and complex, extending beyond simple damage signaling. In innate immunity, for example, NGAL plays a crucial role by sequestering iron-containing bacterial siderophores, thereby limiting bacterial growth [3]. This protective function is supported by the observation that NGAL-deficient mice are more susceptible to bacterial infections and sepsis [4]. In terms of iron homeostasis, NGAL binds to the mammalian siderophore 2,5-dihydroxybenzoic acid (2,5-DHBA), thereby preventing excessive intracellular iron accumulation and reducing the formation of reactive oxygen species [3]. Furthermore, NGAL transports iron to the proximal tubules, a mechanism that may contribute to its tissue-protective effects [4]. NGAL production is also stimulated by inflammation and is considered an adipokine whose levels are increased in the context of obesity [5]. This protein can induce apoptosis in hematopoietic cells and modulate immune responses, and its expression is induced by proinflammatory cytokines such as IL-1, IL-17, IL-22, and TNF-alpha [4]. NGAL involvement also extends to signal transduction, neutrophil maturation, renal tubular injury and repair processes, cell growth, metabolism, and tissue formation [2]. In addition, NGAL interacts with specific receptors, such as the lipocalin-2 receptor (24p3R), involved in iron regulation and cardiac remodeling, and the megalin receptor, which participates in various cellular processes, including cancer progression [1].

The multifunctionality of NGAL, which encompasses both protective mechanisms (antibacterial defense and iron delivery for tubular repair) and involvement in pathological processes (amplification of MMP-9 activity leading to fibrosis and exacerbation of inflammatory states), complicates its interpretation as a simple marker of "damage". Therefore, increased NGAL levels signal an active repair process, an ongoing lesion process, or both simultaneously. Understanding the specific clinical context and differentiating between the various forms of NGAL (e.g., monomer versus complex with MMP-9) is crucial to distinguishing these varied roles. This complexity also suggests that any therapeutic intervention targeting NGAL should be particular to avoid disrupting its beneficial functions.

2. NGAL as a Biomarker of Kidney Injury

Given its complex functions and involvement in injury and repair processes, NGAL has emerged as an early biomarker for acute kidney injury (AKI), with blood and urinary levels rising significantly earlier than serum creatinine (SCr) within hours of renal insult [3]. This early rise is particularly valuable as it allows for prompt diagnosis and potentially rapid intervention [3]. In contrast to SCr, which is a marker of renal function – particularly glomerular filtration – and whose levels only increase after significant functional loss, NGAL is considered a marker of renal injury, particularly tubular injury [1]. NGAL can be elevated even before a detectable decrease in glomerular filtration rate (GFR) or an increase in serum creatinine (SCr) [6].

The mechanism behind the increase in NGAL in the context of kidney injury is complex. When the proximal tubule is damaged, NGAL is secreted in significant quantities by the loop of Henle and the collecting ducts, subsequently reaching both the urine and the general circulation [4]. Systemic NGAL, in turn, is freely filtered by the glomerulus and reabsorbed by endocytosis in the proximal tubule [4]. Impaired reabsorption due to tubular injury or excessive synthesis exceeding the reabsorptive capacity leads to increased urinary NGAL (uNGAL) [7]. Simultaneously, a decrease in GFR can lead to the accumulation of plasma NGAL (pNGAL) [8]. Although systemic (plasma/serum) and urinary NGAL often exhibit similar sensitivity and specificity for kidney injury, their behavior may differ in

certain patients, suggesting distinct clinical significance [4]. In particular, the 25 kDa monomeric form, released from the renal tubules, is used for the diagnosis of AKI and is described as being "exclusively released from the renal tubules," suggesting that specific assays for this form may offer better renal specificity [3]. Thus, differentiating between forms of NGAL (renal versus inflammatory origin) could improve diagnostic accuracy [3].

It is generally believed that uNGAL primarily reflects local renal production and the degree of tubular reabsorption impairment. In contrast, pNGAL can be influenced by both renal and extrarenal sources, such as systemic inflammation, and is thus inherently less specific to the kidney [4]. It is essential to note that uNGAL can also be influenced by filtered pNGAL, particularly when systemic production is very high [2]. Due to its clinical relevance, lipocalin-2 (NGAL) was approved by the US Food and Drug Administration (FDA) on December 7, 2023, for the detection of lesions that may lead to worsening renal function [3]. Clinicians should evaluate NGAL levels, especially pNGAL, in relation to the patient's overall condition, including the presence of sepsis or systemic inflammation. Choosing between uNGAL and pNGAL helps for accurate diagnosis in complex cases, such as transplantation.

II. NGAL IN MONITORING KIDNEY TRANSPLANT PATIENTS

1. Early Detection of Acute Kidney Injury (AKI) and Delayed Graft Function (DGF)

Delayed graft function (DGF) is a common complication after kidney transplantation from a cadaveric donor, with a reported incidence of 20% to 50%, and is often caused by ischemia-reperfusion injury [9]. This complication is associated with prolonged hospitalization, an increased risk of rejection, and poorer long-term graft survival [7]. Both urinary and plasma NGAL are early predictors of DGF or ARF in renal transplant patients, with their levels often increasing before changes in SCr are observed [4]. For example, on the first postoperative day, uNGAL demonstrated moderate accuracy in predicting the need for dialysis within the first week [10]. Furthermore, studies indicate that uNGAL levels remain significantly higher in patients who develop DGF during the first 14 days post-transplant [11].

One finding is that donor uNGAL (but not donor pNGAL), measured before organ harvest, was associated with prolonged DGF and poorer graft survival at 1 year [12]. This observation suggests that elevated NGAL levels in donor kidneys indicate existing damage, which could impact post-transplant outcomes. This finding highlights the need for closer monitoring of kidneys from donors with high uNGAL levels. Regarding DGF prediction, uNGAL and fractional excretion of NGAL (FE-NGAL) have demonstrated superior performance to other biomarkers in predicting the duration of functional DGF (fDGF) at postoperative day 4, with areas under the ROC curve (AUC) of 0.97 and 0.98, respectively [13].

2. Prognostic Value for Graft Function and Long-term Survival

Beyond predicting DGF, NGAL levels also correlate with the duration of this complication, as well as with the recovery of graft function up to 3 months post-transplant [13]. It has been observed that higher NGAL values in the first week post-transplant predict a longer time required for stabilization of renal function [14].

pNGAL demonstrated the best predictive ability for graft loss, censored for death within 5 years, in stable renal transplant (RT) patients assessed more than 2 months post-transplant (AUC > 0.7) [15]. Although the strong independent association of pNGAL with graft loss was substantially attenuated when estimated GFR (eGFR) was included in the prediction model, pNGAL still contributed to improved risk reclassification [15]. This suggests that NGAL may capture aspects of risk that are not fully captured by eGFR alone.

Urinary NGAL levels in clinically stable RRT patients one-year post-transplant were higher in those with a ≥10% decline in eGFR during follow-up. This suggests that NGAL may be important for monitoring chronic declines in graft function and highlights its evolving prognostic value after transplantation. Initially, NGAL excels in predicting acute events, such as delayed graft function (DGF). Later, in stable patients, elevated NGAL levels appear to signal an increased risk of long-term graft decline or loss, even though their predictive power, independent of eGFR, becomes less

pronounced. This dynamic suggests different roles and potentially different interpretive thresholds for NGAL, depending on the time since transplantation and the clinical context (acute versus chronic monitoring). NGAL reflects ongoing subclinical injury and inflammatory or fibrotic processes that contribute to the development of chronic allograft nephropathy.

3. Urinary versus Plasma NGAL: Clinical Significance in Renal Transplantation

In the specific context of renal transplantation, where ischemia-reperfusion injury primarily affects the renal tubules, uNGAL appears as a logical choice for predicting DGF.

Studies highlight the relevance of uNGAL and FE-NGAL for assessing the duration of DGF, while pNGAL is emphasized for the long-term prediction of graft loss in stable patients [13,15]. Donor uNGAL has also been found to be predictive of graft outcome, in contrast to donor pNGAL [12]. Therefore, the choice of sample type for NGAL measurement may depend on the specific clinical question (early DGF versus long-term risk) and patient stability. It is noteworthy that studies of NGAL mRNA levels in urinary exosomes could not demonstrate a direct predictive capacity for urinary protein levels or early graft function in this context [7].

Therefore, for the prediction of early DGF, where acute tubular injury is a primary concern, uNGAL is highly relevant. In contrast, for long-term monitoring in stable patients, pNGAL could integrate signals from chronic inflammation, systemic NGAL load, and ongoing subtle renal injury, thus providing a broader assessment of risk. As previously mentioned, donor uNGAL is most appropriate for pre-transplant assessment. In conclusion, both research and clinical practice should consider tailoring the choice of NGAL specimen (urinary or plasma) to the specific monitoring objective.

4. Clinical Validation Studies of NGAL after Renal Transplantation

Numerous studies have validated NGAL, both in its urinary and plasma forms, as an early predictor of DGF or ARF after renal transplantation [4]. A multicenter study demonstrated that uNGAL and IL-18, measured on the first postoperative day, were accurate predictors of the need for dialysis and recovery of graft function at 3 months. Another observational study confirmed the accuracy of uNGAL in predicting DGF on days 1 and 3 post-transplant. Furthermore, a meta-analysis supported the value of NGAL in diagnosing and prognosticating ARF, including in the specific context of transplantation [10,11,16].

III. COMPARATIVE UTILITY, LIMITATIONS, AND PRACTICAL CONSIDERATIONS OF NGAL MONITORING

1. Advantages of NGAL over SCr

The main advantage of NGAL is that it can be detected much earlier (within hours) after kidney injury compared to SCr (days) [3]. This early detection provides a crucial window for potential early intervention [3]. Furthermore, NGAL is considered more sensitive to subtle or subclinical kidney injury, which may not immediately result in an increase in SCr or a decrease in eGFR [6]. Unlike SCr, which reflects a decrease in filtration function (a late consequence of injury), NGAL directly reflects structural damage at the tubular level [3]. Another important advantage is the relative independence of NGAL from muscle mass, age, or sex – factors that significantly influence SCr levels – making it potentially more reliable in diverse populations [17]. In addition, uNGAL can help differentiate between prerenal azotemia and intrinsic kidney injury. The absence of NGAL elevation in the presence of transient changes in SCr can help clarify whether these changes reflect real or transient kidney injury [3,15].

Although the clinical efficacy of "NGAL-guided interventions" is still under thorough investigation, the potential for earlier and more targeted action represents the most compelling clinical advantage of NGAL over SCr, particularly in the context of high-risk transplantation [18].

2. Limitations: Specificity Challenges and Factors Affecting NGAL Measurements

Despite these advantages, NGAL is not specific to the kidney. It is also produced by neutrophils and other tissues in response to inflammation,

infection, sepsis, and even some cancers [1]. This extrarenal production may lead to elevated NGAL levels independent of primary renal injury, thus reducing its specificity for renal damage [4]. Transplant patients, in particular, are often in proinflammatory states or are susceptible to infections, which further complicates the interpretation of NGAL levels. Also, common comorbidities such as hypertension, obesity, diabetes mellitus, various metabolic complications, and pre-existing CKD may, in turn, contribute to elevated NGAL levels [1].

A significant challenge is the differentiation between renal and systemic NGAL. Although the 25 kDa monomer is suggested to be more kidney-specific than the 45 kDa dimer derived from neutrophils, assays that quantitatively and reliably differentiate between the two are not yet standardized and widely available in clinical practice [1]. In addition, there is considerable interindividual variability in NGAL levels. The attenuation of the predictive value of pNGAL for long-term graft loss when eGFR was added to the statistical models may partly reflect these non-renal contributions to pNGAL levels, which are less relevant to specific renal outcomes than a functional marker such as eGFR [15].

In transplant patients, there are multiple potential sources of "noise" that can lead to elevated NGAL, including surgical trauma itself, inflammation induced by ischemia-reperfusion injury, the effects of immunosuppression, intercurrent infections, potential rejection episodes, and the patient's underlying comorbidities. In this complex context, the specific "signal" of renal graft injury may be masked by this systemic "noise." Therefore, robust and contextualized interpretation algorithms are needed. This could involve using serial measurements to follow the evolutionary trends of NGAL (rather than interpreting single isolated values), using NGAL in combination with other inflammatory markers to try to distinguish the renal from the systemic component, or focusing on uNGAL (potentially with specific assays for the monomeric form), which could provide a better renal signal-to-noise ratio. Regardless of the approach, detailed contextual clinical information is essential for a correct interpretation of NGAL values.

3. Standardization of NGAL Tests, Threshold Values, and Interpretation

Currently, various tests for measuring NGAL are commercially available (ELISA, immunoassay microparticle chemiluminescent assay, amplified particle turbidimetric immunoassay, and point-of-care assays) for both urine and plasma/serum [3]. However, these assays may have different measurement ranges and performance characteristics. The lack of standardization between different assays and uniform reporting practices (e.g., absolute concentration versus normalization to urinary creatinine) significantly complicates the comparison between studies and consistent clinical implementation [16].

Furthermore, optimal NGAL cutoff values for diagnosing AKI or predicting different clinical outcomes vary significantly between studies and across clinical settings (e.g., cardiac surgery, intensive care, transplant type, pediatric versus adult population). For example, low (200 ng/mL), intermediate (400 ng/mL), and high (800 ng/mL) NGAL levels have been reported overall, as well as a uNGAL cutoff of greater than 50 ng/mL in a specific pediatric study following cardiopulmonary bypass [19]. For example, low (200 ng/mL), medium (400 ng/mL), and high (800 ng/mL) general levels of NGAL, as well as a uNGAL threshold of >50 ng/mL, have been reported in a specific pediatric post-cardiopulmonary bypass study [16].

This lack of universally validated and widely accepted thresholds represents a major barrier to the routine clinical adoption of NGAL. The considerable variability observed in the thresholds proposed in the literature makes it difficult for clinicians to confidently and consistently apply NGAL testing in daily practice. NGAL requires large-scale multicenter validation in adult and pediatric kidney transplant populations before inclusion in clinical guidelines. This will help establish standardized diagnostic and prognostic thresholds for predicting delayed graft function (DGF) and long-term monitoring. Analyzing changes in NGAL values, such as trends and ratios, to a baseline provides a more reliable approach than relying solely on fixed thresholds.

IV. CLINICAL IMPLEMENTATION AND FUTURE DIRECTIONS

1. Current Status in Clinical Guidelines

Currently, KDIGO guidelines for monitoring renal transplant patients are primarily based on SCr, eGFR, and assessment of albuminuria/proteinuria ratio. Renal biopsies are usually performed based on specific clinical or laboratory indications [20]. Currently, KDIGO guidelines for monitoring renal transplant patients are primarily based on SCr, eGFR, and assessment of albuminuria/proteinuria. Renal biopsies are usually performed based on specific clinical or laboratory indications [16,21].

Despite promising research and FDA approval of some NGAL assays, it is not yet a universally adopted routine biomarker in transplant patient monitoring guidelines. Its use is generally more common in research settings or specialized centers with expertise in the field. Thus, a significant gap exists between the promise demonstrated by NGAL in research and its widespread integration into current clinical guidelines and practice. This gap is likely due to unresolved issues, such as the lack of specificity and the absence of universally accepted standardized thresholds, and, perhaps most importantly, the scarcity of large-scale intervention studies that conclusively demonstrate the effectiveness of NGAL-guided management in improving long-term clinical outcomes. For NGAL to move from the status of a " promising biomarker " to that of a "standard of care" tool in monitoring transplant patients, future research must focus not only on confirming its diagnostic or prognostic accuracy but especially on demonstrating its clinical utility—that is, how the use of NGAL can beneficially alter patient management and improve patient-relevant outcomes [22].

2. Perspectives

To overcome current limitations and harness the potential of NGAL, research is moving in several directions. A key direction is to investigate specific NGAL isoforms (e.g., the kidney-specific monomer versus the inflammatory dimer or the NGAL/MMP-9 complex) and develop assays capable of distinguishing between them, which could lead to significant improvements in specificity. Another promising approach is to combine NGAL with other markers of renal injury (such as KIM-1, IL-18 and Cystatin C) or functional markers to obtain a more comprehensive and accurate assessment of renal status [1,17]. Correlating NGAL levels with advanced imaging findings or histopathological data from renal biopsies to better understand the underlying pathology is also an important direction of research.

Relevant to demonstrating the clinical utility of NGAL will be the design and conduct of prospective studies to determine whether early interventions, initiated based on increased NGAL levels, can indeed improve clinical outcomes (e.g., reducing rates of DGF, increasing graft survival, slowing progression of AKI) in transplant recipients [18]. In this context, NGAL could contribute to personalized risk stratification and individualized adaptation of immunosuppressive or nephroprotective strategies [22].

AI-based models that incorporate NGAL levels with clinical data, risk scores, and biomarkers could enhance the accuracy of predicting ARF and long-term graft outcomes [23]. Further research in pediatric transplant populations is essential due to their unique physiology and risks. Finally, defining the role and optimal frequency of NGAL monitoring in stable, long-term transplant recipients for the prediction and management of chronic graft dysfunction remains an important goal [15,23].

The current limitations of NGAL, particularly those related to specificity and the presence of factors influencing NGAL measurements, suggest that its full potential will likely be realized not as a stand-alone "magic bullet" but rather as part of a more sophisticated and integrated diagnostic and prognostic approach. This view is supported by the increasing calls for the use of multi-biomarker panels and the demonstrated potential of AI to synthesize and interpret complex data. Therefore, research should focus on how NGAL data can be intelligently combined with other patient information (clinical, demographic, other biomarkers, genetic data) to create more powerful predictive models and personalized care pathways for transplanted patients.

CONCLUSIONS

NGAL has established itself as an early marker of kidney injury, with demonstrated utility in the context of renal transplantation for predicting DGF and potentially for assessing long-term prognosis, and with emerging utility in HSCT for early detection of AKI in a complex, high-risk clinical setting. Its main advantages over traditional markers, such as serum creatinine (SCr), are its quick detection and sensitivity to early kidney injuries. However, limitations related to the specificity and non-renal factors should be considered when interpreting its values in clinical practice.

Author contributions:

I.M., D.V.S., T.A.T., G.C.N., M.R.B., M.L.O., B.C., A.E.C. and I.C conceived the original draft preparation. I.M., D.V.S., T.A.T., G.C.N., M.R.B., M.L.O., B.C., A.E.C. and I.C was responsible for the data acquisition, collection and assembly of the articles. I.M., D.V.S., T.A.T., G.C.N., M.R.B., M.L.O., B.C., A.E.C. and I.C were responsible for the conception and design. I.C. was responsible with the supervision of the manuscript.

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