ROLE OF PROGNOSTIC NUTRITIONAL INDEX AND INFLAMMATORY INDICES PREDICTION OF AKI IN CRITICALLY ILL PATIENTS

Reda Abdelmoniem Kamel Salem[1*], Amir Mohamed Elokely[2], Walid Mohamed Mohamed Afify[3], Maged Elsayed Elbadawy Mohamed[4], Mohammed Attia Abdel Moneim[5]

Abstract

Background: AKI is a common and serious complication in critically ill patients, affecting up to 30 % of those admitted to the intensive care unit (ICU). AKI is associated with increased mortality, prolonged ICU stay, and higher healthcare costs. A critically ill patient with AKI refers to an individual who is experiencing a severe medical condition or illness that has resulted in sudden kidney dysfunction or damage. The prognostic nutritional index (PNI) and neutrophil-to-lymphocyte ratio (NLR) are composite biomarkers representing patients' immunological nutritional status and systemic inflammation and have the advantages of being simple to use and inexpensive and having improved stability. Previous research has posited that PNI or NLR has prognostic value in numerous illnesses, including sepsis, gastric cancer, hepatocellular carcinoma, and pancreatic cancer. So far, no studies have been conducted to evaluate the predictive value of combined PNI and NLR for S-AKI. Consider that inflammation and immune-nutritional status play a vital role in the physiopathology of S-AKI. The association between inflammation and post-operative AKI or mortality after AKI was examined using serum CRP and albumin levels as markers of inflammation. Lower serum albumin was independently associated with post-operative AKI. Post-operative AKI was associated with higher mortality and this association was at least partially mediated by pre-operative serum CRP and albumin levels. These results suggest that those with underlying inflammation are more likely to develop AKI and rather than AKI itself, but underlying inflammation is associated with higher mortality among those with AKI. Hypoalbuminemia was independently associated with the development of post-operative AKI. Associations between higher CRP or lower albumin and AKI have been reported in contrast-induced nephropathy or post-operative AKI in cardiac surgery. In many of these studies, higher CRP was shown to be associated with AKI.

Keywords: Prognostic Nutritional Index, Inflammatory Indices, Prediction, AKI

[1*,2,3,4,5]Internal Medicine Department, Faculty of Medicine, Zagazig University, Egypt
Email: magedbadwy555@gmail.com

*Corresponding Author : Reda Abdelmoniem Kamel Salem
*Internal Medicine Department, Faculty of Medicine, Zagazig University, Egypt
Email: magedbadwy555@gmail.com

Introduction

Acute kidney injury (AKI) is a common and serious complication in critically ill patients, with a prevalence of up to 57.3%. AKI is associated with increased mortality, prolonged ICU stay, and higher healthcare costs. AKI is a sudden decrease in kidney function that develops within 7 days, as shown by an increase in serum creatinine or a decrease in urine output, or both. AKI is a severe condition commonly encountered in critically ill patients, often leading to significant morbidity and mortality. The management of AKI requires a comprehensive understanding of the patient's underlying disease processes, including the impact of nutritional status and inflammation on clinical outcomes (1).

Nutritional status and inflammation are two important factors that influence outcomes in critically ill patients with AKI. Malnutrition is common in AKI patients and is associated with a higher risk of mortality. Inflammation is also a hallmark of AKI and contributes to its pathogenesis and progression. The prognostic nutritional index (PNI) and inflammatory index are two simple and readily available biomarkers that can be used to assess nutritional status and inflammation, respectively. The PNI is calculated using serum albumin and total lymphocyte count, while the inflammatory index is calculated using neutrophil-to-lymphocyte ratio (NLR) or platelet-to-lymphocyte ratio (PLR) (2).

The Prognostic Nutritional Index (PNI) is a composite score that incorporates both the serum albumin levels and lymphocyte counts, reflecting the nutritional and immune status of the patients. It has been widely used as a prognostic marker in various diseases, including cancer, cardiovascular diseases, and sepsis. Low PNI scores have been associated with increased mortality and poor clinical outcomes in critically ill patients (3).

On the other hand, the Inflammatory Index represents the systemic inflammatory response and is often measured using various biomarkers such as C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α). Elevated levels of inflammatory markers are frequently observed in critically ill patients and have been linked to the development and progression of AKI. The Inflammatory Index serves as an indicator of the magnitude of the inflammatory response and may help in predicting the clinical course and outcomes of AKI (4).

Understanding the impact of PNI and the Inflammatory Index on critically ill patients with AKI is of paramount importance in improving patient management and outcomes. By assessing the nutritional status and inflammatory response, healthcare providers can identify patients who are at high risk of adverse outcomes and develop targeted interventions to optimize their care (5).

A growing body of evidence suggests that the PNI and inflammatory index may be useful for predicting outcomes in critically ill patients with AKI. For example, a low PNI has been shown to be associated with increased mortality in AKI patients. Similarly, a high inflammatory index has also been shown to be associated with increased mortality and other poor outcomes in AKI patients (6).

The aim of this work is to explore the existing literature on the impact of the Prognostic Nutritional Index (PNI) and Inflammatory Index in critically ill patients with acute kidney injury. By synthesizing the available evidence, we aim to provide a comprehensive overview of the relationship between these indices and clinical outcomes in this specific patient population. The findings of this review may have significant implications for risk stratification, treatment decisions, and prognostication in critically ill patients with AKI.

Acute kidney injury (AKI)

Acute kidney injury (AKI), previously called acute renal failure (ARF), denotes a rapid and often reversible reduction in kidney function, as measured by glomerular filtration rate (GFR). Although, immediately after a renal insult, blood urea nitrogen (BUN) or creatinine levels may be within the normal range. The main sign of acute kidney injury may be a decline in urine output. AKI can lead to the accumulation of water, sodium, and other metabolic products. It can also result in several electrolyte disturbances (7).

It is a very common condition, especially among hospitalized patients. It can be seen in up to 7% of hospital admissions and 30% of ICU admissions. Several different criteria have been used in research studies such as RIFLE, AKIN (Acute Kidney Injury Network), and KDIGO (kidney disease: Improving Global Outcomes) criteria. Among these, KDIGO is the most recent and most commonly used tool (8).

Table 1. KDIGO criteria for AKI (9).

Eur. Chem. Bull. **2023**, *12(Special Issue 12), 3517 –3527*

3518

AKI stage	Serum creatinine (SCr)	Uri
1	1.5-1.9 times baseline OR ≥ 0.3 mg/dL increase	< 0. 6-1
2	2.0–2.9 times baseline	< 0. 12
3	3.0 Times baseline OR Increase in SCr to ≥ 4.0 mg/dL OR Initiation of RRT OR Decrease in eGFR to < 35 mL/min/1.73 m² in patients < 18 years	< 0. hou OR Anu

AKI is very commonly seen in patients admitted to the hospital. It is often an important factor in making the decision to hospitalize for other conditions, if not being the sole reason for hospitalization. AKI is one of the most clinically impactful diseases since it affects patient management to a great extent in terms of the treatment options for their primary disease. Most drugs or procedures that use contrast media may need to be delayed due to co-existent AKI. Most of the drugs are renally excreted, and dosages might need to be adjusted on account of the reduced renal function. Sometimes, it may even necessitate frequent monitoring of drug levels, for example, vancomycin. Furthermore, a huge percentage, approximately 95%, of nephrologist consultations are related to AKI. AKI is thus an important contributor to more extended hospital stays and patient morbidity **(10).**

Annually, up to 13.3 million people worldwide are affected by AKI, and approximately 1.7 million dies of AKI. Although renal replacement therapy is widely used in critically ill patients with AKI, these patients still face an increased risk of mortality and irreversible kidney function deterioration, with rapid progression to chronic kidney disease (CKD). Therefore, the identification of effective predictive factors for AKI prevention remains critical **(11).**

Pathophysiology

Glomerular filtration rate (GFR) is a vital measure used to assess kidney function. It refers to the volume of fluid filtered by the glomeruli per unit of time. GFR is influenced by various factors, including blood pressure, renal blood flow, and the integrity of the glomerular filtration barrier. A decrease in GFR can be indicative of impaired kidney function and may be associated with certain kidney diseases or systemic conditions. Nevertheless, whatever the cause of AKI, renal blood flow reduction is a common pathologic pathway for declining glomerular filtration rate. The pathophysiology of AKI has always been traditionally divided into three categories: prerenal, renal, and post-renal. Each of these categories has several different causes associated with it **(12).**

Prerenal Causes:

Prerenal AKI occurs due to factors that reduce blood flow to the kidneys, leading to decreased perfusion and subsequent kidney dysfunction. Common prerenal causes include:

Hypovolemia: Severe dehydration, hemorrhage, or fluid loss from vomiting, diarrhea, or excessive sweating can lead to reduced blood volume.

Hypotension: Conditions such as severe infections (sepsis), heart failure, or shock can result in low blood pressure and inadequate renal perfusion.

Renal artery stenosis: Narrowing of the renal arteries can restrict blood flow to the kidneys, causing prerenal AKI **(13).**

Intrinsic Renal Causes:

Intrinsic renal causes involve damage to the kidney tissue itself, leading to impaired filtration and renal dysfunction. Some intrinsic renal causes of AKI include:

Acute Tubular Necrosis (ATN): ATN is the most common cause of intrinsic AKI. It can result from ischemia (lack of blood flow) or exposure to nephrotoxic substances such as certain medications or contrast agents used in imaging studies.

Acute cortical necrosis (ACN): is characterized by patchy or diffuse ischemic destruction of all the elements of renal cortex resulting from significantly diminished renal arterial perfusion due to vascular spasm and microvascular injury. In addition, direct endothelial injury particularly in setting of sepsis, eclampsia, hemolytic uremic syndrome (HUS) and snake bite may lead to endovascular thrombosis with subsequent renal ischemia. Progression to end stage renal disease is a rule in diffuse cortical necrosis. It is a rare cause of acute kidney injury (AKI) in developed countries with frequency of 1.9%-2% of all patients with AKI **(14).**

Acute Glomerulonephritis: Inflammation of the glomeruli, the filtering units of the kidneys, can cause AKI. Various types of glomerulonephritis, including immune-mediated disorders, can lead to renal impairment.

Acute Interstitial Nephritis: Inflammation of the kidney's interstitial tissue, often caused by allergic

Eur. Chem. Bull. **2023**, *12(Special Issue 12), 3517 –3527*

3519

reactions to medications, infections, or autoimmune disorders, can result in AKI.

Acute Intratubular obstruction: monoclonal gammopathy seen in multiple myeloma, tumor lysis syndrome, toxins such as ethylene glycol **(15).**

Postrenal Causes:

Postrenal AKI occurs when there is an acute complete obstruction that prevents the normal flow of urine from the kidneys. This obstruction can occur at any point along the urinary tract and can be caused by conditions such as:

Kidney stones: Stones in the urinary tract can obstruct the flow of urine and lead to kidney injury.

Enlarged prostate: In men, an enlarged prostate gland can block the urethra and impair urine flow.

Tumors or strictures: Tumors or narrowing in the urinary tract can cause obstruction and subsequent AKI **(1).**

It is important to note that AKI can also result from a combination of these etiologies. Additionally, certain risk factors such as advanced age, pre-existing kidney disease, diabetes, and certain medications can increase the susceptibility to AKI. Prompt identification and management of the underlying etiology are crucial for improving outcomes and preventing further kidney damage in patients with AKI **(16).**

Diagnosis of AKI

A history of urine output is important, which may give clues to the cause of AKI. Following are some associations: Oliguria - favors AKI. Sudden anuria - suggests acute urinary tract obstruction, acute glomerulonephritis, or vascular catastrophe. Gradually diminishing urine output - may be secondary to urethral stricture or bladder outlet obstruction due to causes such as prostate enlargement **(17).**

Performing a detailed examination is imperative as it provides extremely valuable information in establishing the etiology of AKI. A crucial part of the physical exam should be orthostatic vital signs since they are an important clue for hypovolemia and, in an appropriate clinical context, would guide treatment **(18).**

Some AKI patients tend to develop volume overload, which should be corrected as early as possible to avoid pulmonary and cardiac complications. Euvolemic state can be achieved with the help of furosemide, which is a cornerstone in managing such patients. Usually, high doses of IV furosemide are needed to correct volume overload in AKI patients; however, it plays no role

in converting oliguric AKI to non-oliguric AKI **(19).**

Sometimes, AKI may need short-term renal replacement therapy until the kidney function recovers. Dialysis is usually required to manage the complications of AKI, such as severe and nonresponsive hyperkalemia, uremic pericarditis, and pulmonary edema. This is seen especially in the oliguric phase of acute tubular necrosis, where the patient is prone to develop multiple electrolyte and acid-base abnormalities as well as fluid overload. When required, dialysis in this setting is usually performed through a double-lumen central venous catheter. Continuous renal replacement therapy can also be utilized in patients who cannot tolerate hemodialysis due to hypotension. It is a much slower, continuous type of dialysis. Correction of some of the metabolic abnormalities, along with dialysis, may be required **(20).**

Metabolic acidosis is one such instance where systemic administration of citrate or bicarbonate is often required to maintain a suitable blood pH. The requirement for renal replacement therapy should be reevaluated in these patients daily while they are hospitalized and at least weekly thereafter until the kidney function is stable. Renal replacement therapy is usually required for the short-term ranging from a few days to a few weeks in most cases; however, acute tubular necrosis can take up to months to recover and may require intermittent hemodialysis support during that time **(7).**

Certain specific treatments are required for acute kidney injury in specific circumstances, such as administering vasoactive medications and colloids for treatment of hepatorenal syndrome and cautious diuresis in cardiorenal syndrome. Acute kidney injury from various glomerulonephritides may require immunosuppressive medications for treatment. Acute interstitial nephritis, which does not recover with supportive care, may benefit from a trial of steroids. Post renal obstruction may need to be relieved operatively in certain situations. For example, benign prostatic hypertrophy may require surgical relief of bladder outlet obstruction. Urethral calculi may require stenting and lithotripsy. It is also important to note that in certain situations, the risk of acute kidney injury may be decreased by taking some measures. For example, in high-risk patients such as those with compromised renal function at baseline, it may be beneficial to administer peri-procedure intravenous fluids to prevent contrast-induced nephropathy when performing cardiac catheterization **(21).**

Several complications may be associated AKI. Some of these complications are

Eur. Chem. Bull. **2023,** *12(Special Issue 12), 3517 –3527*

3520

directly associated with AKI and can easily be gauged (hyperkalemia, volume overload, metabolic acidosis, hyponatremia); however, the effect of other complications on AKI-related mortality, such as inflammation and infection, is difficult to assess. Most common complications include metabolic derangements such as **(22)**:

1. Cardiovascular - Heart failure secondary to fluid overload is attributable to oliguric AKI, arrhythmias secondary to acidotic state and electrolyte abnormalities, cardiac arrest due to metabolic derangements, and myocardial infarction, and rarely pericarditis **(23)**.

2. Gastrointestinal (GI) - Nausea, vomiting, GI bleeding, and anorexia. A mildly raised level of amylase is commonly found in patients suffering from AKI. Elevation of amylase concentration can make the diagnosis of pancreatitis difficult, therefore measuring lipase, which is not raised in AKI, is necessary to establish AKI diagnosis **(24)**.

3. Neurologic - CNS-related signs of uremic burden are common in AKI, and they include lethargy, somnolence, disturbed sleep-wake cycle, and cognitive impairment **(25)**.

AKI In Critically Ill Patients

AKI is a common and serious complication in critically ill patients, affecting up to 30 % of those admitted to the intensive care unit (ICU). AKI is associated with increased mortality, prolonged ICU stay, and higher healthcare costs. A critically ill patient with AKI refers to an individual who is experiencing a severe medical condition or illness that has resulted in sudden kidney dysfunction or damage **(26)**.

Several factors increase the risk of AKI in critically ill patients such as sepsis, a severe infection that triggers a systemic inflammatory response, is a leading cause of AKI in critically ill patients. Hypovolemia due to dehydration or blood loss, can reduce blood flow to the kidneys, leading to AKI. Nephrotoxic medications such as antibiotics and chemotherapy drugs, can damage the kidneys and contribute to AKI. Patients with pre-existing kidney dysfunction exposed to stress such as critical illness are more susceptible to AKI. Heart failure or other cardiac problems can impair kidney perfusion and increase the risk of AKI. Patients on mechanical ventilation may experience fluid shifts and hemodynamic instability, which can contribute to AKI. Older patients are more vulnerable to AKI due to reduced kidney reserve and higher prevalence of comorbidities **(27)**.

The most common causes of AKI in hospitalized patients are in this order ATN – 45%, Prerenal disease – 21%, Acute superimposed on CKD – 13%, Urinary tract obstruction – 10% (most often due to Benign prostatic hypertrophy in older men), Glomerulonephritis or vasculitis – 4%, AIN – 2% and Atheroemboli – 1% **(28)**.

Management of AKI in critically ill patients involves addressing the underlying cause, optimizing fluid balance, and providing supportive care. Identifying and addressing the root cause of AKI, such as sepsis or hypovolemia, is crucial to prevent further kidney damage. Careful fluid management is essential, ensuring adequate hydration while avoiding fluid overload, which can worsen kidney function. Monitoring and correcting electrolyte imbalances, such as high potassium or low calcium, is important for maintaining organ function. Providing adequate nutrition, often through enteral or parenteral routes, is crucial for recovery and preventing malnutrition. In severe cases of AKI, Renal Replacement Therapy (RRT), such as dialysis, may be necessary to remove waste products and maintain fluid balance **(29)**.

Prevention strategies include:

Identifying patients at high risk for AKI, such as those with sepsis or hypovolemia, allows for early intervention and prevention. Careful medication review and consideration of alternative therapies can minimize kidney damage. Maintaining adequate blood pressure and perfusion to the kidneys is essential for preventing AKI. Close monitoring of fluid status and avoiding both dehydration and fluid overload can reduce AKI risk. Preventing and promptly treating infections, especially sepsis, can lower the incidence of AKI **(30)**.

Outcomes

AKI is associated with a higher risk of death in critically ill patients. The mortality rate can be as high as 60% in patients with severe AKI. Critically ill patients with AKI have longer hospital stays, higher rates of complications, and increased healthcare costs compared to those without AKI. AKI can also have long-term consequences, including an increased risk of chronic kidney disease and end-stage renal disease. The prognosis is generally worse for patients with severe AKI requiring renal replacement therapy (dialysis) **(31)**.

Malnutrition And Inflammation in AKI

Malnutrition is defined as a physical state of imbalanced nutrition that is significantly associated with increased length of stay, complication rates, healthcare costs, and mortality in hospitalized patients. AKI is a common complication of hospitalization and is affected by

undernutrition and metabolic changes. Therefore, malnourished patients may be more prone to progression to AKI **(32).**

There are a number of factors that contribute to malnutrition in AKI patients, including:

Reduced food intake: AKI patients often have a reduced appetite due to factors such as nausea, vomiting, and fluid restrictions.

Increased protein loss: AKI patients often have increased protein loss in the urine. This is due to damage to the glomerular filtration barrier, which allows protein to leak into the urine.

Increased metabolic demands: AKI patients have increased metabolic demands due to the stress of their illness. This can lead to weight loss and muscle waste **(2).**

The possible mechanisms underlying the observed association between malnutrition and an increased risk of AKI are currently unclear, but they can be explained by several factors. Albumin, a popular biomarker of nutritional status in clinically stable conditions, is the most abundant circulating protein and plays an essential role in antioxidant, anti-inflammatory, and antiplatelet aggregation activities. Low albumin levels in malnourished patients may contribute to the development of AKI through the deterioration of endothelial function and oxidative inflammatory pathways **(33).**

In addition, hypercholesterolemia and low high-density lipoprotein levels, which are indicators of underlying malnutrition, have long been regarded as important risk factors for the development and progression of cardiovascular diseases. Previous studies have also demonstrated that a low preoperative high-density lipoprotein cholesterol concentration was associated with an increased risk of AKI after cardiac surgery (**34).**

Malnutrition in AKI patients is associated with a number of adverse outcomes, including increased mortality, prolonged ICU stay, delayed renal recovery and increased risk of complications such as infections and pressure sores **(35).**

Nutritional assessment is an indispensable tool for the evaluation and clinical monitoring of patients with AKI. Acute loss of renal function interferes with the metabolism of all macronutrients, responsible for proinflammatory, pro-oxidative and hypercatabolic situations. The major nutritional disorders in AKI patients are hyper catabolism, hyperglycemia, and hypertriglyceridemia. Those added to the contributions of the underlying disease, complications, and the need for renal replacement therapy can interfere in the nutritional depletion of those patients **(35).**

Biochemical parameters commonly used in clinical practice are influenced by non-nutritional factors like loss of liver function and inflammatory status. Although there are no prospective data about the behavior of nutritional markers, some authors demonstrated associations of some parameters with clinical outcomes. The use of markers like albumin, cholesterol, prealbumin, IGF-1, subjective global assessment, and calculation of the nitrogen balance seem to be useful as screening parameters for worse prognosis and higher mortality in AKI patients.

The management of malnutrition in acute AKI is important for improving outcomes. The goal of nutritional support in AKI patients is to provide adequate calories and protein to meet their metabolic needs while also avoiding complications such as hyperkalemia, hyperphosphatemia, and fluid overload **(36).**

Requirements

In patients with AKI on renal replacement therapy, a caloric intake of 25 to 30 kcal/kg and a minimum amount of 1.5 g/kg/day of protein is recommended to minimize protein catabolism and prevent metabolic complications **(21).**

Enteral nutrition is preferred whenever possible in AKI patients, as it is associated with fewer complications than parenteral nutrition. Enteral nutrition can be provided using a variety of methods, such as nasogastric tubes, orogastric tubes, and gastrostomy tubes **(37).**

Parenteral nutrition may be necessary in AKI patients who are unable to tolerate enteral nutrition or who have high nutrient requirements. Parenteral nutrition is provided through a central venous catheter. The type of nutritional support and the number of calories and protein provided will vary depending on the individual patient's needs. For example, patients with severe AKI may require less protein than patients with mild AKI **(38).**

In addition to nutritional support, there are a number of other things that can be done to manage malnutrition in AKI patients, such as:

Maintaining adequate fluid balance: AKI patients are at risk for dehydration, which can lead to malnutrition. It is important to maintain adequate fluid balance in these patients by providing fluids and electrolytes intravenously.

Avoiding nephrotoxic medications: If possible, nephrotoxic medications should be avoided in AKI patients. However, if these medications are necessary, they should be used at the lowest possible dose and for the shortest possible duration.

Eur. Chem. Bull. **2023,** *12(Special Issue 12), 3517 –3527*

3522

Managing underlying medical conditions: Underlying medical conditions such as diabetes and heart failure can contribute to malnutrition in AKI patients. It is important to manage these underlying conditions effectively.

Providing psychological support: AKI patients may experience anxiety and depression, which can lead to decreased food intake. It is important to provide psychological support to these patients and their families **(39).**

Inflammation in Aki

Inflammation is a complex biologic response that is essential for eliminating microbial pathogens and repairing tissue after diverse forms of injury. AKI is known to be associated with intrarenal and systemic inflammation. Improved understanding of the cellular and molecular mechanisms underlying the inflammatory response is important for identifying effective therapies to prevent or ameliorate AKI **(40).**

Inflammation in AKI can be triggered by various factors, including:

Ischemia-reperfusion injury: In cases where AKI occurs due to reduced blood flow to the kidneys (ischemia) followed by the restoration of blood flow (reperfusion), the reperfusion phase can induce an intense inflammatory response. The restoration of blood flow leads to the release of pro-inflammatory mediators and the activation of immune cells, promoting inflammation within the kidney **(40).**

Immune cell activation: In response to kidney injury, immune cells such as neutrophils, macrophages, and lymphocytes are recruited to the site of injury. These immune cells release inflammatory cytokines, chemokines, and reactive oxygen species, which can cause further tissue damage and perpetuate the inflammatory response **(41).**

Activation of pro-inflammatory pathways: During AKI, various pro-inflammatory pathways, such as nuclear factor kappa B (NF-κB) and toll-like receptor (TLR) signaling, can be activated. These pathways contribute to the production of pro-inflammatory molecules and the recruitment and activation of immune cells, amplifying the inflammatory response **(42).**

Release of damage-associated molecular patterns (DAMPs): DAMPs are molecules released from injured or dying cells that can activate immune cells and trigger an inflammatory response. In AKI, the release of DAMPs, such as high-mobility group box 1 (HMGB1) protein and adenosine triphosphate (ATP), can exacerbate inflammation and contribute to kidney injury **(42).**

Consequences of inflammation: Inflammatory cells migrate to the kidneys, releasing additional inflammatory mediators and potentially causing further damage. Kidney cells and immune cells produce inflammatory mediators like cytokines and chemokines, amplifying the inflammatory response. Inflammation leads to leaky blood vessels, causing fluid accumulation and impaired blood flow in the kidneys. Chronic inflammation can contribute to fibrosis and scarring within the kidneys, leading to permanent damage **(43).**

The inflammatory response in AKI can have both beneficial and detrimental effects. In the early phase, inflammation helps to initiate tissue repair and remove cellular debris. However, excessive and prolonged inflammation can lead to further kidney damage and contribute to the progression of AKI **(43).**

Managing inflammation is an important aspect of AKI treatment. Therapeutic approaches aim to modulate the inflammatory response, prevent further tissue injury, and promote kidney repair. This may involve the use of anti-inflammatory medications, such as corticosteroids or strategies targeting specific inflammatory pathways. Additionally, supportive measures, such as optimizing fluid status, controlling blood pressure, and providing appropriate nutrition, can help mitigate inflammation and support kidney recovery **(44).**

Role Of PNI And Inflammatory Indices Prediction of AKI in Critically Ill Patients

Sepsis is characterized by life-threatening organ dysfunction induced by a dysregulated host response to infection, with a high rate of morbidity and mortality worldwide. The kidneys are highly susceptible to injury in sepsis, and up to 45% of septic patients develop acute kidney injury in intensive care units. Previous studies reported that patients with sepsis-associated acute kidney injury (SA-AKI) have a mortality rate of approximately 45%. In particular, the progression of AKI during sepsis elevated the likelihood of chronic kidney disease as well as other severe organ dysfunction, ultimately resulting in dramatic public health concern. Therefore, it is imperative to identify effective biomarkers for clinicians for the early diagnosis of septic kidney injury and implement appropriate interventions **(45).**

Early treatment with appropriate antibiotics improves the prognosis and survival of severe sepsis and septic shock patients. Procalcitonin (PCT) is the main biomarker used to diagnose sepsis, but its values increase in non-sepsis pathologies as well **(45).**

Eur. Chem. Bull. **2023**, *12(Special Issue 12), 3517 –3527*

3523

The Glasgow Prognostic Score (GPS; based on serum C-reactive protein (CRP) and albumin levels), neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), Prognostic Nutritional Index (PNI; based on albumin and lymphocyte counts), and the Prognostic Index (PI; based on serum CRP and white blood cell counts), are inflammation-based prognostic scores. **(46).**

The pathological processes underlying mechanisms of SAKI are complex and multifaceted. Recent research on S AKI has indicated that inflammation, immunologic dysregulation, and malnutrition together contribute to disease progression. In sepsis, the invading pathogen binds to pattern recognition receptors (PRR) through pathogen associated molecular patterns (PAMPs) to initiate immune responses, resulting in the release of large amounts of inflammatory mediators. There can be direct damage to kidney tissue caused by inflammatory mediators that leads to neutrophils infiltrating the renal interstitial **(47).**

Furthermore, excessive proinflammatory factor release accelerates catabolism, energy and nutritional loss, and the development of fast protein-energy malnutrition (PEM). Inflammatory factors and nutritional indicators may be potential biomarkers to predict the occurrence of S-AKI, while anti-inflammatory and nutritional therapies are vital for the treatment of S-AKI **(47).**

Traditionally, serum creatinine and urine output have been employed to diagnose AKI; nonetheless, these indicators are highly susceptible to extra renal factors and have a significant lag in the detection of renal impairment. In recent years, several novel biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL), urinary tissue inhibitor of metalloproteinase-2 (TIMP-2), soluble thrombomodulin (TM), and kidney injury molecule (KIM-1) have been explored for the diagnosis of AKI. Frustratingly, the majority of those indicators are too costly to apply in clinical practice **(48).**

The prognostic nutritional index (PNI) and neutrophil-to-lymphocyte ratio (NLR) are composite biomarkers representing patients' immunological nutritional status and systemic inflammation and have the advantages of being simple to use and inexpensive and having improved stability. Previous research has posited that PNI or NLR has prognostic value in numerous illnesses, including sepsis, gastric cancer, hepatocellular carcinoma, and pancreatic cancer. So far, no studies have been conducted to evaluate the predictive value of combined PNI and NLR for S-AKI. Consider that inflammation and immune-nutritional status play a vital role in the physiopathology of S-AKI **(49).**

Moreover, the sensitivity of a single inflammatory indicator used in clinical practice is inadequate, and additional confounding factors cannot be completely excluded **(49).**

Malnutrition is highly prevalent in the elderly population with acute kidney injury (AKI), which increases nosocomial mortality. Moreover, patients with malnutrition are proven to have an increased risk of AKI. Nutritional status assessment is critical to identify elderly patients who may easily suffer from AKI and are at risk of mortality. Traditional nutritional screening tools, including weight loss, food intake reduction and laboratory values, are not reliable in AKI patients who cannot provide these details and may have water electrolyte disorders. In addition, elderly patients with AKI in the intensive care unit (ICU) often suffer from volume resuscitation, resulting in rapid weight gain and even tissue edema. Body mass index, skin fold thickness and other data cannot accurately reflect the nutritional status of AKI patients. The association between inflammation and post-operative AKI or mortality after AKI was examined using serum CRP and albumin levels as markers of inflammation. Lower serum albumin was independently associated with post-operative AKI. Post-operative AKI was associated with higher mortality and this association was at least partially mediated by pre-operative serum CRP and albumin levels. These results suggest that those with underlying inflammation are more likely to develop AKI and rather than AKI itself, but underlying inflammation is associated with higher mortality among those with AKI. Hypoalbuminemia was independently associated with the development of post-operative AKI. Associations between higher CRP or lower albumin and AKI have been reported in contrast-induced nephropathy or post-operative AKI in cardiac surgery. In many of these studies, higher CRP was shown to be associated with AKI **(50).**

References

1. Kellum, J. A., Romagnani, P., Ashuntantang, G., Ronco, C., Zarbock, A., & Anders, H. J. (2021). Acute kidney injury. Nature reviews Disease primers, 7(1), 52.
2. Wang, J., Zhao, K., Mao, X., Zhang, Y., Shao, J., Fan, W., & Wang, Y. (2021). Relationship between CRP Albumin Ratio and the Mortality in Critically Ill Patients with AKI: A Retrospective Observational Study. BioMed Research International, 2021, 1-9.

Eur. Chem. Bull. **2023**, *12(Special Issue 12), 3517 –3527*

3524

3. Thongprayoon, C., Cheungpasitporn, W., Radhakrishnan, Y., Petnak, T., Qureshi, F., Mao, M. A., & Kashani, K. B. (2022). Impact of hypoalbuminemia on mortality in critically ill patients requiring continuous renal replacement therapy. Journal of Critical Care, 68, 72-75.

4. Wu, J., Huang, L., He, H., Zhao, Y., Niu, D., & Lyu, J. (2022). Red cell distribution width to platelet ratio is associated with increasing in-hospital mortality in critically ill patients with acute kidney injury. Disease Markers, 2022.

5. Thomas, S., Alexander, C., & Cassady, B. A. (2021). Nutrition risk prevalence and nutrition care recommendations for hospitalized and critically-ill patients with COVID-19. Clinical Nutrition ESPEN, 44, 38-49.

6. Friedman, A. N., Guirguis, J., Kapoor, R., Gupta, S., Leaf, D. E., Timsina, L. R., ... & Sharma, S. (2021). Obesity, inflammatory and thrombotic markers, and major clinical outcomes in critically ill patients with COVID-19 in the US. Obesity, 29(10), 1719-1730.

7. Xu, Z., Tang, Y., Huang, Q., Fu, S., Li, X., Lin, B., ... & Chen, J. (2021). Systematic review and subgroup analysis of the incidence of acute kidney injury (AKI) in patients with COVID-19. BMC nephrology, 22, 1-10.

8. Alfano, G., Ferrari, A., Fontana, F., Mori, G., Magistroni, R., Meschiari, M., ... & Modena Covid-19 Working Group (MoCo19). (2021). Incidence, risk factors and outcome of acute kidney injury (AKI) in patients with COVID-19. Clinical and experimental nephrology, 25(11), 1203-1214.

9. Pandey, V., Kumar, D., Vijayaraghavan, P., Chaturvedi, T., & Raina, R. (2017). Non-dialytic management of acute kidney injury in newborns. Journal of Renal Injury Prevention, 6(1), 1.

10. Dong, J., Feng, T., Thapa-Chhetry, B., Cho, B. G., Shum, T., Inwald, D. P., ... & Vaidya, V. U. (2021). Machine learning model for early prediction of acute kidney injury (AKI) in pediatric critical care. Critical Care, 25(1), 288.

11. Tinti, F., Lai, S., Noce, A., Rotondi, S., Marrone, G., Mazzaferro, S., ... & Mitterhofer, A. P. (2021). Chronic kidney disease as a systemic inflammatory syndrome: update on mechanisms involved and potential treatment. Life, 11(5), 419.

12. Chong, W. H., & Saha, B. K. (2021). Relationship between severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the etiology of acute kidney injury (AKI). The American journal of the medical sciences, 361(3), 287-296.

13. Qian, J. Y., Wang, B., Lv, L. L., & Liu, B. C. (2021). Pathogenesis of acute kidney injury in coronavirus disease 2019. Frontiers in physiology, 12, 586589.

14. Yang, W. A. N. G., Yuchao, Z. H. O. U., Zhiyuan, S. U. N., Zhe, L. I., Shutian, X. U., & Shijun, L. I. (2022). Clinical and prognostic features of acute kidney injury with renal cortical necrosis. Chinese Journal of Nephrology, Dialysis & Transplantation, 31(2), 108.

15. Selmi, Y., Ariba, Y. B., & Labidi, J. (2019). Epidemiology, diagnosis, and etiology of acute kidney injury in the elderly: A retrospective analysis. Saudi Journal of Kidney Diseases and Transplantation, 30(3), 678-685.

16. Ng, J. H., Bijol, V., Sparks, M. A., Sise, M. E., Izzedine, H., & Jhaveri, K. D. (2020). Pathophysiology and pathology of acute kidney injury in patients with COVID-19. Advances in Chronic Kidney Disease, 27(5), 365-376.

17. Scholz, H., Boivin, F. J., Schmidt-Ott, K. M., Bachmann, S., Eckardt, K. U., Scholl, U. I., & Persson, P. B. (2021). Kidney physiology and susceptibility to acute kidney injury: implications for renoprotection. Nature Reviews Nephrology, 17(5), 335-349.

18. Gameiro, J., Fonseca, J. A., Outerelo, C., & Lopes, J. A. (2020). Acute kidney injury: from diagnosis to prevention and treatment strategies. Journal of clinical medicine, 9(6), 1704.

19. Yoon, S. Y., Kim, J. S., Jeong, K. H., & Kim, S. K. (2022). Acute kidney injury: biomarker-guided diagnosis and management. Medicina, 58(3), 340.

20. Vives, M., Hernandez, A., Parramon, F., Estanyol, N., Pardina, B., Muñoz, A., ... & Hernandez, C. (2019). Acute kidney injury after cardiac surgery: prevalence, impact and management challenges. International journal of nephrology and renovascular disease, 153-166.

21. Ostermann, M., Bellomo, R., Burdmann, E. A., Doi, K., Endre, Z. H., Goldstein, S. L., ... & Zarbock, A. (2020). Controversies in acute kidney injury: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Conference. Kidney international, 98(2), 294-309.

22. Advani, A. (2020). Acute kidney injury: a bona fide complication of diabetes. Diabetes, 69(11), 2229-2237.

23. Carlisle, M. A., Soranno, D. E., Basu, R. K., & Gist, K. M. (2019). Acute kidney injury and

Eur. Chem. Bull. **2023**, *12(Special Issue 12), 3517 –3527*

3525

fluid overload in pediatric cardiac surgery. Current treatment options in pediatrics, 5, 326-342.

24. Scarpioni, R., Valsania, T., Albertazzi, V., Blanco, V., DeAmicis, S., Manini, A., ... & Gandolfi, S. (2021). Acute kidney injury, a common and severe complication in hospitalized patients during the COVID-19 pandemic. Journal of Nephrology, 34(4), 1019-1024.

25. Ruetzler, K., Cohen, B., Leung, S., Mascha, E. J., Knotzer, J., Kurz, A., ... & Turan, A. (2020). Supplemental intraoperative oxygen does not promote acute kidney injury or cardiovascular complications after noncardiac surgery: subanalysis of an alternating intervention trial. Anesthesia & Analgesia, 130(4), 933-940.

26. Gabarre, P., Dumas, G., Dupont, T., Darmon, M., Azoulay, E., & Zafrani, L. (2020). Acute kidney injury in critically ill patients with COVID-19. Intensive care medicine, 46, 1339-1348.

27. Xiao, L., Jia, L., Li, R., Zhang, Y., Ji, H., & Faramand, A. (2019). Early versus late initiation of renal replacement therapy for acute kidney injury in critically ill patients: A systematic review and meta-analysis. PLoS One, 14(10), e0223493.

28. Palmisano, A., Gandolfini, I., Delsante, M., Cantarelli, C., Fiaccadori, E., Cravedi, P., & Maggiore, U. (2021). Acute kidney injury (AKI) before and after kidney transplantation: causes, medical approach, and implications for the long-term outcomes. Journal of Clinical Medicine, 10(7), 1484.

29. Gupta, S., Gudsoorkar, P., & Jhaveri, K. D. (2022). Acute kidney injury in critically ill patients with cancer. Clinical Journal of the American Society of Nephrology, 17(9), 1385-1398.

30. Jiang, Y. J., Xi, X. M., Jia, H. M., Zheng, X., Wang, M. P., Li, W., & Li, W. X. (2021). Risk factors, clinical features and outcome of new-onset acute kidney injury among critically ill patients: a database analysis based on prospective cohort study. BMC nephrology, 22(1), 1-11.

31. Shawwa, K., Ghosh, E., Lanius, S., Schwager, E., Eshelman, L., & Kashani, K. B. (2021). Predicting acute kidney injury in critically ill patients using comorbid conditions utilizing machine learning. Clinical Kidney Journal, 14(5), 1428-1435.

32. Li, C., Xu, L., Guan, C., Zhao, L., Luo, C., Zhou, B., ... & Xu, Y. (2020). Malnutrition screening and acute kidney injury in hospitalised patients: a retrospective study over a 5-year period from China. British Journal of Nutrition, 123(3), 337-346.

33. Efe, S. C., Karagöz, A., Doğan, C., Bayram, Z., Cakmak, E. O., Kalkan, S., ... & Ozdemir, N. (2021). Prognostic significance of malnutrition scores in elderly patients for the prediction of contrast-induced acute kidney injury. International Journal of Clinical Practice, 75(7), e14274.

34. Schwartz, E., Hillyer, R., Foley, J., Willcutts, K., & Ziegler, J. (2019). Acute kidney injury masked by malnutrition: a case report and the problem of protein. Nutrition in Clinical Practice, 34(5), 735-750.

35. Ying, M., Yang, J., Huang, Z., Ling, Y., Wang, B., Huang, H., ... & Chen, Z. (2022). Association between malnutrition and contrast-associated acute kidney injury in congestive heart failure patients following coronary angiography. Frontiers in Nutrition, 9, 937237.

36. Yu, J., Li, D., Jia, Y., Li, F., Jiang, Y., Zhang, Q., ... & Wan, Z. (2021). Nutritional Risk Screening 2002 was associated with acute kidney injury and mortality in patients with acute coronary syndrome: Insight from the REACP study. Nutrition, Metabolism and Cardiovascular Diseases, 31(4), 1121-1128.

37. Chen, S., Hu, Y., Liang, J., Zhang, L., Huang, Z., He, Y., ... & Hu, Y. (2023). Background: The relationship between malnutrition and the risk of contrast-associated acute kidney injury (CA-AKI) and the resulting prognosis in patients undergoing percutaneous coronary intervention (PCI) is still not well known. Methods: Patients undergoing PCI were consecutively enrolled in a multicenter study in China (NCT01402232), categorized by nutritional status (non-malnutrition, malnutrition). Nutrition and metabolism in kidney diseases, 16648714.

38. Vega, M. R. W., Cerminara, D., Desloovere, A., Paglialonga, F., Renken-Terhaerdt, J., Walle, J. V., ... & Greenbaum, L. A. (2023). Nutritional management of children with acute kidney injury—clinical practice recommendations from the Pediatric Renal Nutrition Taskforce. Pediatric Nephrology, 1-22.

39. Nielsen, A. J., & Mose, F. H. (2021). Hyponatremia and Acute Kidney Injury as a Consequence of Malnutrition: A Case Report. Case Reports in Clinical Nutrition, 4(1), 1-6.

40. Jin, L., Yu, B., Armando, I., & Han, F. (2021). Mitochondrial DNA-mediated inflammation in acute kidney injury and chronic kidney disease. Oxidative Medicine and Cellular Longevity,

Eur. Chem. Bull. **2023**, *12(Special Issue 12), 3517 –3527*

3526

2021.

41. Zheng, L., Gao, W., Hu, C., Yang, C., & Rong, R. (2019). Immune cells in ischemic acute kidney injury. Current Protein and Peptide Science, 20(8), 770-776.

42. Lee, K., & Jang, H. R. (2022). Role of T cells in ischemic acute kidney injury and repair. The Korean Journal of Internal Medicine, 37(3), 534.

43. Lumlertgul, N., & Ostermann, M. (2023). Dysregulated Immune Response and Kidney Dysfunction. In Management of Dysregulated Immune Response in the Critically Ill (pp. 203-212). Cham: Springer International Publishing.

44. Anders, H. J., Wilkens, L., Schraml, B., & Marschner, J. (2021). One concept does not fit all: the immune system in different forms of acute kidney injury. Nephrology Dialysis Transplantation, 36(1), 29-38.

45. Shimoyama, Y., Umegaki, O., Kadono, N., & Minami, T. (2021). Presepsin and prognostic nutritional index are predictors of septic acute kidney injury, renal replacement therapy initiation in sepsis patients, and prognosis in septic acute kidney injury patients: a pilot study. BMC nephrology, 22(1), 219.

46. Hu, Y., Cao, Q., Wang, H., Yang, Y., Xiong, Y., Li, X., & Zhou, Q. (2021). Prognostic nutritional index predicts acute kidney injury and mortality of patients in the coronary care unit. Experimental and Therapeutic Medicine, 21(2), 1-1.

47. Lu, Y., Ren, C., & Jiang, J. (2021). The relationship between prognostic nutritional index and All-Cause Mortality In Critically ill patients: a retrospective study. International Journal of General Medicine, 3619-3626.

48. Joo, H., Min, S. Y., & Park, M. S. (2021). Association between inflammation-based parameters and prognosis in patients with acute kidney injury. Medicina, 57(9), 936.

49. Gucu, A., Ozluk, O. A., Guvenc, O., Sunbul, S. A., & Engin, M. (2021). The Importance of Prognostic Nutritional Index in Predicting Acute Renal Failure After On-Pump Coronary Artery Bypass Operations in Patients with Insulin-Dependent Diabetes Mellitus. In The Heart Surgery Forum (Vol. 24, No. 4, pp. E651-E655).

50. Huang, Y., Zhang, Q., Li, P., Chen, M., Wang, R., Hu, J., ... & Xu, L. (2023). The prognostic nutritional index predicts all-cause mortality in critically ill patients with acute myocardial infarction. BMC Cardiovascular Disorders, 23(1), 339.

Eur. Chem. Bull. **2023,** *12(Special Issue 12), 3517 –3527*

3527