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Review Article

Biomarkers in acute kidney injury

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Abstract

Acute kidney injury is a common condition associated with high morbidity and short-term mortality. Its pathophysiology varies according to the numerous conditions associated with its genesis. Biomarkers allow detecting changes at the level of kidney function; therefore, they play an important role in the prevention, early diagnosis, therapeutic response and prognosis of acute kidney injury. The search for biomarkers for acute kidney injury began over 15 years ago; initially, only serum creatinine was available for diagnosis. However, throughout history, great advances have been made in research, which have allowed the finding of new biomarkers in order to improve the health and quality of life of patients. A narrative review of the literature is carried out on the basis of available scientific evidence to clarify the role and importance of biomarkers in the context of acute renal injury.

Introduction

In the past 50 years the diagnosis of acute kidney injury (AKI) has been primarily based on the measurement of the serum creatinine (sCr), knowing that a significant reduction in the glomerular filtration rate will increase the sCr [1].

Until the year 2002, there was no standardized definition

of AKI; reason why its definition evolved based on the established criteria for each specific time. Commencing with the RIFLE criteria (risk, injury, failure, loss, end-stage kidney disease), followed by the AKIN (acute kidney injury network) and more recently with a focus on the international guidelines based on KDIGO (kidney disease improving global outcomes), which include changes in serum creatinine, urine output within seven days and the need of renal replacement therapy (RRT). This is concluding that a decrease in serum creatinine, although not defining AKI, should incite healthcare personnel to have a high suspicion for it and could be useful when the baseline creatinine is unknown [3]. Based on this definition, the development of AKI is associated with an increase in morbidity and mortality, with an increase in the length of stay and healthcare costs [4].

The search for AKI biomarkers started more than 15 years ago; it was not until 2006 when the Food and Drug Administration (FDA), the European Medicine Agency (EMA) and the Japanese Agency for Pharmaceutical Devices and Physicians joined several pharmaceutical companies to form the Predictive Security. This focused primarily on the identification of sensitive and specific biomarkers for nephrotoxicity in animal models [5]. In 2008, 7 biomarkers of nephrotoxicity were authorized by the FDA for its use in animals and humans, including urinary KIM–1, beta-2 microglobulin, Cystatin C, Trefoil Factor 3 (TFF3), Clusterin, urinary NGAL (Neutrophil Gelatinase-Associated Lipicalin), albumin, total protein, urinary interleukin-18 and liver fatty acid-binding protein (L-FABP), among others. These biomarkers generally play an essential role in regards to their positive and negative predictive values. These were compared with changes in the serum creatinine levels, given that there were no exact parameters for the detection of AKI. Using serum creatinine measurements as a gold standard for the diagnosis of AKI, these biomarkers have had a fundamental role in regards to their negative predictive value; nevertheless, their positive predictive value has been far less [5].

Only until 2016, the FDA and the National Institute of Health (NIH) in the USA summoned a council to establish the terms that defined AKI's diagnostic biomarkers. Specifically, the council established the BEST (Biomarkers, EndpointS, and other Tools) resources to improve and harmonize the terms utilized in all the pre-existing literature. The council defined "biomarker" as a quantifiable tool that is an indicator of biological and pathological processes, as well as a response to an intervention. Similarly, biomarkers were divided into categories depending on their role in the pathophysiology of AKI [2].

This literature review evaluates the current concepts and the importance of the use of biomarkers in the diagnosis of AKI.

Biomarkers in AKI

AKI is condition currently associated with increased short-term morbidity and mortality [6]. Its incidence has increased exponentially in recent years, given factors such as aging and multiple comorbidities [7].

Given that AKI continues to be a global problem and that its etiology varies, it is fundamental for clinicians to detect it in an early manner and implement preventative and therapeutic strategies. It is there were the biomarkers become essential [8]. The different categories of biomarkers are capable of providing information about diagnosis, prognosis, risk prediction and response to therapy [2].

Early detection of AKI biomarkers can significantly reduce renal damage, improve the results in the long-term and prevent the progression to chronic kidney disease (CKD). These biomarkers could also help identify patients that can benefit from early intervention, even before the AKI becomes clinically detectable [2]. The use of these biomarkers in AKI has been studied thoroughly in recent times. Nevertheless, recent studies have generated some controversy regarding the utility of these [8,9].

Despite its clinical definition, identification and stratification of new AKI biomarkers, it is essential to know the pathophysiological mechanisms of AKI to implement an adequate use of these biomarkers [5].

Pathophysiology of AKI

The pathophysiology of AKI differs depending on the numerous conditions associated with its development [3]. Renal perfusion requires around 20% of the cardiac output, a considerable percentage of the total intravascular volume. Once in the kidney, it is distributed in a particular matter throughout the renal arteries, which will ramify into glomerular arterioles and eventually form a network of capillaries responsible for glomerular filtration, which is in charge of filtering waste substances and other molecules such as proteins [10]. Glomerular filtration is based on the elimination of body residues. One of these molecules is creatinine, a residual product of creatine, which is found in muscle tissues. Creatinine has been a biological biomarker traditionally used to assess renal function, but the latter is affected by age, sex, and muscle mass. This is why its interpretation has to be patient-specific [11,12].

The renal system filters 5000 mg of proteins as an average per day in each individual, 4950 mg of which is reabsorbed in the proximal tubule via endocytosis. Low molecular weight proteins are amongst the reabsorbed proteins; these are freely filtered in the glomerulus, given its weight, and are undetectable in normal physiologic processes. The reason why its detection in urine will only appear once there is tubular epithelial injury. These include, but are not limited

to, beta-2 microglobulin, lysozyme, alpha-1 microglobulin, and retinol-binding protein 4 (RBP4). These molecules serve as biomarkers of kidney injury [13].

In normal conditions, renal blood flow corresponds to 5-6 mls/g/min with a pressure of 60-100 mmHg, which is necessary to maintain normal renal function [10]. Renal blood flow is primarily regulated by multiple factors that involve extrarenal processes such as vascular tone, neuro-hormonal processes and vasodilator/ vasoconstrictor substances, among others. Hence, failure in any of these mechanisms will lead to hypoxia of the organ, which can be spontaneous or not depending on its magnitude. This also depends on the compensatory mechanisms, such as afferent arteriolar dilatation and efferent arteriolar constriction, which can supply the oxygen needs at the time of need. At this time, there is a secretion of pro-inflammatory mediators due to tissue damage, which serve as biomarkers for early kidney injury detection. These include NGAL and KIM-1. IL-8 is secreted by inflammatory cells, such as macrophages are neutrophils that enter the kidneys during the inflammatory phase [13]. These molecules express themselves primarily in distal and proximal epithelial tubular cells, respectively [2,6]. When there is sustained hypoxia, there are changes in renal blood flow, changes in the GFR, and the supply of sodium towards the renal tubules, producing a disequilibrium in between the production and the demand of oxygen nutrients, damaging tubular epithelial cells and leading towards oxidative stress [9,14].

After the renal blood flow reduction, the epithelial cells cannot maintain adequate intracellular ATP for the essential metabolic processes. This ATP depletion leads to cellular damage and, if severe enough, can cause cellular death by necrosis or apoptosis. During an ischemic event, all the segments of the nephrons are potentially affected, but the proximal tubular cells are the most commonly damaged [3]. The damaged endothelium in the small renal arterioles of the vasa recta in the ischemic kidney suffers vasoconstriction due to an increase in endothelin-1, angiotensin II, thromboxane A2, prostaglandin H2, leukotriene C4, and D4, as well an increase in the sympathetic nervous system activity [14].

Consequently, these enzymes are secreted by the tubular epithelial cells and they are excreted in the urine as a response to the AKI; among these, N-Acetyl-b-glucosaminidase (NAG), cytoplasmic protein lactate dehydrogenase and glycoprotein 130 (gp130) [15-17]. The secreted enzymes are the biomarkers themselves, which are classified based on their role in the pathophysiology of AKI [18-21] (Table 1).

Clinical Manifestations and Complications of AKI

Patients with AKI may present with symptoms specific to their underlying condition (e.g heart failure, sepsis, cirrhosis, systemic vasculitis). If there is true involvement of renal function, the dynamic process is as follows: stage 1 (initiation), stage II (oligo-anuria), stage III (polyuria) and stage IV (restitution) [59]. There are numerous complications that can occur if the AKI is left untreated or persists; these include hyperkalemia, uremia, volume overload, metabolic acidosis and progression to chronic kidney disease (CKD). Hyperkalemia, defined as a potassium above 5, is particularly catastrophic in AKI patients and should be treated in an urgent manner to avoid potential life threatening arrhythmias. Management of hyperkalemia includes calcium gluconate to stabilize the cardiac membrane, IV insulin and dextrose, beta-agonists, potassium binding resins and ultimately RRT for refractory hyperkalemia. Persistent metabolic acidosis (defined as a serum bicarbonate level less than 24), volume overload (especially in patients with heart failure and or/ increasing oxygen requirements) and uremia (pruritus, neurological manifestations, nausea, vomiting, diarrhea, anorexia, arrhythmias and insomnia) all are indications for urgent RRT [59]. Patients with AKI are at risk of developing CKD, and those with CKD are at risk for progression to ESKD. A Taiwan study investigated long term renal outcomes in hospitalized patients; it showed that the risk of developing CKD stage 3 was double among patients who developed AKI during hospitalization and recovered renal function, compared to those who did not develop AKI [60].

Low molecular weight molecules that get expressed in AKI

Alpha-1 microglobulin and beta-2 microglobulin: Both molecules rise in serum and urine due to glomerular or tubular lesions, leading to a considerable reduction in the glomerular filtration rate. Their main advantage is their low cost; despite this, it depends on the urinary pH, decreasing its effectiveness if the pH is less than 5.5 [22]. A retrospective

Table 1: Classification and biomarkers of AKI with the highest relevance [18-21]. Each one of them has different properties as a biomarker (e.g., increasing the sensitivity of the diagnoses, predict prognosis, etc.). On the other hand, it has been proposed that the use of a panel of several biomarkers can improve their individual properties [18].

Biomarkers in AKI	
Classification	**Biomarker**
Low molecular weight molecules expressed in AKI	α-1-microglobulin, β-2-microglobulin, RBP4.
Enzymes released by tubular damage	N-Acetyl-b-glucosaminidase (NAG), Alkaline phosphatase, cytoplasmic protein lactate dehydrogenase, TIMP-2, IGFBP-7.
Proteins produced by the kidney in AKI	Urinary NGAL (Neutrophil Gelatinase-Associated Lipocalin), Kidney injury molecule -1 (KIM-1), Interleukin-18 (IL-18)
Structural and functional tubular proteins	F-actin and Na+/H+ exchanger isoforms
Cellular repair indicators	YKL-40
Glomerular filtration markers	Creatinine, Cystatin C.

study of 529 patients showed that patients with AKI had higher serum beta-2 microglobulin and urinary beta-2 microglobulin with an area under the curve (AUC) of 0.84 and 0.83, respectively. In the study, 245 patients developed AKI. Patients had a higher median serum and urinary beta 2-microglobulin with each higher AKI stage; however, neither were associated with renal recovery [65].

Biphosphatase Protein (RBP4): RBP4 is an adipocytokine whose main function is to transport retinol to the circulation; its role on the kidney is unknown. Several studies have demonstrated that levels of RBP4 are elevated in diabetes, obesity, cardiovascular diseases and inflammation. It has been described that RBP4 by itself can be pro-inflammatory by increasing the production of other adipocytokines or inflammatory cytokines. It loses sensitivity to identify changes in tubular function when it is below 10%. Similarly, it has been found that it can serve as a biomarker of bladder tissue degradation, as in neoplastic disease [22,23].

Enzymes released by tubular cell damage

N-acetyl Glucosaminidase (NAG): N-acetyl Glucosaminidase (NAG) is a lysosomal enzyme produced by the proximal and distal tubular cells; it's detected 12 hours after injury [15]. It rises after exposure to several toxic substances such as lead and cadmium, solvents, contrast media, aminoglycosides, nephrotoxic cancer medications, as well as glomerular diseases, including diabetic nephropathy [16].

Alkaline Phosphatase and Gamma-Glumatil Transferase: Alkaline Phosphatase (AP) and Gamma-Glumatil Transferase (GGT) are enzymes in the brush border villi of the proximal tubular cells. They are excreted in the urine when there is significant damage to the microvilli in the brush border membrane [15].

Alkaline phosphatase is an endogenous metalloenzyme found in the serum and multiple organs, including kidneys, liver, bone and intestines. Phase 2 studies in humans have shown efficacy in sepsis-induced AKI with AP [17].

Gamma-Glutamyl Transferase (GGT) is an enzyme located in the cell membrane; it is found in the proximal renal tubules, liver, pancreas and intestines. Urinary GGT is an indicator of tubular damage as it can show changes in renal function before identifying these via conventional methods [24].

Glutathione-S-Transferase: Glutathione-S-Transferase is a soluble cytoplasmic enzyme with two subunits: α y π, expressed in the proximal and distal convoluted tubule, respectively. Epithelial tubular cell damage leads to the accumulation of this enzyme, becoming detectable in urine. It is worth mentioning there are four subtypes; however, α y π are the two most studied ones in AKI [15].

Proteins produced in AKI

NGAL: Neutrophil Gelatinase-Associated Lipocalin (NGAL) is a pro-inflammatory marker of the innate immune system, a useful tool to differentiate between pre-renal and intrinsic AKI. NGAL expression is regulated in the first few hours after ischemic injury in animal models and has been identified as an early biomarker to diagnose AKI. It is a glycoprotein expressed on many cells, including hepatocytes, tubular and endothelial cells [16,17,25].

NGAL is the most studied biomarker in AKI. It was discovered initially in the granules of neutrophils [1]. It is reabsorbed almost totally in the proximal tubule and elevated levels can indicate proximal tubular damage. Production of NGAL can be increased up to 1000 times in Henle's loop and the distal tubule when AKI is present [2]. To summarize, its expression is increased as soon as renal cells detect stress and/or damage [6]. It is also a potential tool to distinguish in between pre-renal azotemia and ATN, as it just elevates mildly in volume depletion, along with L-FABP, with no histologic damage [63].

A meta-analysis of 19 studies in 8 countries involving 2,538 patients showed that the diagnostic OR/AUC of NGAL to predict AKI was 18.6 (95% CI, 9.0-38.1)/0.815 (95%, CI 0.732-0.892), concluding that NGAL has diagnostic and prognostic value in AKI [64]. Another retrospective study of 1,322 patients showed that urinary NGAL had an AUC of 0.75 (95% CI, 0.7-0.8) for persistent AKI, 0.66 (95% CI 0.61 -0.71) for major adverse kidney events (MAKE) at 30 days and 0.64 (95% CI 0.59-0.7) for major adverse kidney events at 1 year.

KIM-1: Biomarkers such as the kidney injury molecule-1 are fundamental for the kidney's response to proximal tubular damage [2]. KIM-1 is a 38.7 kDa transmembrane type 1 glycoprotein with a similar domain as extracellular immunoglobulin, similar to mucin. It is expressed in low levels in the kidney and other organs, but its expression is accentuated in pre-renal kidney injury and after reperfusion [6].

It is found in higher concentrations in people with AKI in comparison to people with CKD without acute injury. A meta-analysis of 11 clinical trials showed that it has a diagnostic sensitivity and specificity of 74% and 86% in AKI [25,28]. Sabisetti, et al. demonstrated significantly elevated plasma KIM-1 levels in serum in patients with AKI compared to patients without AKI, with an AUC of 0.74% (95% CI 0.48-0.91, $p < 0.01$). In 2002, Han et al showed that KIM-1 was specific for ATN; an increase of 1 unit in normalized KIM-1 was associated with an odd's ratio (OR) of 12.4 (95% CI, 1.2–119) for the presence of ATN [61]. This makes it a useful tool in differentiating between pre-renal azotemia and intrinsic injury.

IL-18: Also known as a factor that enhances interferon-gamma, IL-18 is a 24kDa cytokine that belongs to the

superfamily of IL-1. It is initially synthesized as a signal-free inactive precursor and remains in the intracellular space until it is excised by caspase-1. Posteriorly, it gets secreted by monocytes and macrophages [6]. It is an inflammatory mediator produced in response to ischemia of several organs, including the heart, brain, and kidneys [25]. In the kidney, it is produced and excreted in the proximal tubule secondary to ischemia or toxic damage [28].

IL-18 plays a vital role in tubular apoptosis, with high urinary concentrations in the urine of patients with ischemic AKI [29]. It serves as an early diagnostic marker given that it can predict mortality in several clinical settings, including ICU and after cardiovascular surgery [2]. Elevated levels of IL-18 in the urine was shown by Parikh, et al. in 2011 to be an independent predictor of dialysis or death, with an OR of 6.8 [62].

Cysteine 61: Cysteine 61 (Cyr61) is a cysteine-rich secretory protein found in human renal tissue. It promotes cellular proliferation, adhesion, chemotaxis, embryo development and neovascularization. Previous studies have detected low levels of Cyr61 expression in the healthy adult kidney, but increased expression in ischemic renal tissue. It is also elevated in inflammatory states, suggesting it may be a potential biomarker for AKI [30,31]. Xu, et al. found that Cyr 61 could protect tubular epithelial cells from apoptosis; however, its capability to detect AKI and when it is detected is still unknown [32].

Structural and functional tubular proteins

F-actin and Na+/H+ exchanger isoforms: Actin plays a fundamental role in maintaining structural and cellular functions, acting as a barrier between adhesion/union complexes and the cellular matrix [33].

The integrity of the cytoskeleton is essential for proximal tubular cells, given that the amplification of the apical membrane through the microvilli is decisive for healthy cellular function. Loss of actin in the cytoskeleton increases interstitial permeability and an interstitial leak of urine through the tubular basement membrane, causing bidirectional sodium transport between the apical and basolateral portions of the cell. Increased microvascular permeability is seen in AKI, increasing the amount of filtered sodium towards the distal tubule. This mechanism reduces GFR [33].

Biomarkers involved in cellular repair

YKL-40: YKL-40 is a 40 kDa chitinase-like glycoprotein implied in inflammation, cellular protection and repair. It is synthesized by renal macrophages and contributes to tissue remodeling and scarring by limiting cellular apoptosis; it promotes cellular repair after ischemic renal injury, becoming a good option when it comes to predicting AKI recovery [34-37].

GFR biomarkers

Cystatin C: Cystatin C is a low molecular weight protein produced in the nucleated cells. It is freely filtered by the glomeruli and almost completely reabsorbed in the proximal tubule. Its constant production and renal elimination make it an excellent biomarker of glomerular filtration. However, Cystatin C does not estimate GFR in real-time. Serum Cystatin C can be a useful biomarker in AKI prediction; its urinary excretion indicates tubular damage, and it has a moderate diagnostic utility [28,38]. Given this, it has been studied for its use in several clinical settings, especially in patients with a high risk of developing AKI [15, 25]. Its concentrations are elevated in acute and chronic kidney disease, and contrary to creatinine, it does not depend on height, weight, age, sex, nutritional status, and inflammatory processes [16].

In 2017, Deng et al. carried out an observational, multicentric and prospective trial in which Cystatin C was found to be useful when associated with NAG for the early detection and prognosis of AKI, as well as a predictor of mortality [39,40]. Patients with Cystatin C levels below 0.8 mg/L have less chance of developing AKI after kidney injury, while patients with levels superior to 2.04 mg/L have a more significant chance of developing AKI [38]. Another meta-analysis of 19 studies in 11 countries involving 3,336 patients showed that across all settings, the diagnostic OR of serum cystatin C of predicting AKI was 23.5 (95% CI, 14.2-38.9), with sensitivity and specificity of 0.84 and 0.82, respectively [65].

The best evidence-based biomarker in AKI

The list of biomarkers of kidney function and damage has surged in light of the evidence with an uncertain assertive value, with its clinical utility questioned in the context of AKI [41]. Thus, serum creatinine and urine output are very useful tools in the diagnosis of AKI. However, serum creatinine is a late marker of kidney injury [15].

A significant reduction in GFR can be challenging to appreciate given the initial changes in sCr in the acute phase, considering that creatinine excretion decreases during a steady drop in GFR, making the serum creatinine rise with time. Urine output is a result of those mentioned above, conceived as an additional severity marker [39].

Table 2: KDIGO definition of acute kidney injury [44].

Stage	Serum Creatinine	Urine Output
I	Increase in sCr of 1,5-1,9 times baseline or ≥ 0,3 mg/dl (≥ 26,5 µmol/l).	< 0,5 ml/kg/h for 6-12 h
II	Increase in sCr of 2,0-2,9 times baseline	< 0,5 ml/kg/h for ≥12 h
III	Increase of sCr 3 times baseline or increase in sCr of ≥ 4,0 mg/dl (≥ 353,6 µmol/l) OR initiation of RRT OR in patients less than 18 years, a decrease in eFGR < 35 mg/min/1.73m2	< 0,3 ml/kg/h for ≥24 h or anuria for ≥12 h

Consequently, kidney function changes are usually evaluated by monitoring the solutes eliminated by glomerular filtration, such as creatinine [3].

Serum and urinary creatinine act as functional biomarkers, but its utility is limited, given that 400 to 500 milliliters of urine have to be excreted daily to eliminate nitrogen waste products [8]. Serum creatinine and urine output are nor sensitive or specific for AKI detection. Nonetheless, these are the mainstay markers for diagnosis. That is why a decrease in serum creatinine, though not defining AKI, should prompt clinicians to suspect AKI; it can also be useful when the baseline creatinine is unknown [42].

The increase in serum creatinine and the decrease in urine output are not enough for AKI diagnosis, and their sensitivity and specificity are too low to establish a diagnosis. It's also worth to mention that a healthy renal functional reserve can mitigate the rise in serum creatinine [6]. Despite its prognostic value, a rise in serum creatinine typically occurs 24 to 48 hours after the event. Similarly, its levels are affected by independent factors such as muscle mass, sex, diet, and some medications [2]. Even so, the diagnosis and stratification of AKI are made by obtaining serum creatinine levels [43].

However, due to pathophysiological reasons, one can suppose that early intervention is a crucial factor for treatment success, justifying the search for new biomarkers that not only show a decline in kidney function but also permits earlier detection of structural damage [8] (Table 2).

Nephrocheck

AKI is very common in ICU patients, associated with increased short and long term complications; additionally, it is associated with increased morbidity and mortality.

In September 2014, the FDA allowed the commercialization of Nephrocheck, a test made to determine if certain critical patients were at risk of developing AKI [45].

In this sophisticated setting, the idea of introducing a biomarker in clinical practice that is synchronized with renal damage arose, since traditional criteria based on serum creatinine and urine output are not timely in the identification of patients at risk for AKI. This, because clinical manifestations occur when the residual filtration rate cannot compensate [46]. Taking the aforementioned into account, it is necessary to introduce a biomarker capable of identifying high-risk patients to implement preventative strategies even before sCr rises or urine output decreases [46,47].

From that standpoint, in recent years, several studies focused on discovering new biomarkers with the goal of early AKI detection. These include NGAL, IL-18, L-FABP, KIM-1, TIMP-2, and IGFBP-7. Among these, IGFBP-7 and TIMP-2 have shown the most significant utility and have been proposed as a predictive tool in the early detection of AKI in critical care settings [48-50].

TIMP-2 and IGFBP-7 are expressed and secreted in the kidneys as well as other tissues. Some authors postulated that these proteins halt the G1 phase of the cell cycle in response to different factors (for example, oxidative stress, toxins, ischemia, sepsis, and inflammation); their signaling pathways also have an autocrine and paracrine pattern [51,52]. Hence, markers of cellular cycle detention like TIMP-2 and IGFBP-7 act as a warning sign that tubular cells have been a subject of stress and have to shut down their function to preserve energy.

Katani, et al. validated IGFBP-7 and TIMP-2 through a prospective, multicenter clinical trial compared to other biomarkers in AKI. The authors selected a cohort of critical care patients without evidence of AKI on presentation. The primary endpoint was moderate to severe AKI based on the KDIGO guidelines (KDIGO stage 2-3) within the first 12 hours, which occurred in 14% in the patients. [TIMP-2] x According to this trial, [TIMP-2] x [IGFBP-7] were notably superior to other AKI biomarkers ($p < 0.002$), including NGAL and KIM-1, nor of which made an AUC of > 0.27 [53].

Evidence shows that these biomarkers (TIMP-2 and IGFBP-7), identified as Nephrocheck, have a high predictive capacity of identifying patients at risk for AKI. Sapphire investigators and others demonstrated that Nephrocheck predicts stage 2-3 AKI twelve hours before the rise in serum creatinine [53-56]. McCullough et al. evaluate serial Nephrocheck measurements in a retrospective post hoc analysis in the Sapphire ICU cohort and suggest that these can be useful in detecting stage 2-3 AKI in the first seven days of the ICU course [55]. The authors concluded that serial urine Nephrocheck tests [TIMP-2] x [IGFBP-7] at 0, 12, and 24 hours, and even 72 hours are prognostic for AKI development. Three consecutive negative values [< 0.3 (ng/mL) 2/ 1000] are associated with a low incidence (13%) of stage 2-3 AKI in the first seven days. On the contrary, positive results [> 2.0 (ng/mL) 2 /1000) predict a higher incidence (up to 94.4%) of stage 2-3 AKI. Other authors previously suggested that serial measurements of these AKI biomarkers could further characterize patients' risk during their ICU stay [56].

Other studies suggest that these new biomarkers add diagnostic and prognostic certainty, allowing for a better evaluation of patients at risk for AKI. Although they do not differentiate between the type of injury (ischemic, toxins, inflammatory) or the specific site of damage in the nephron, its use today seems to be justified [57,58].

With the routine use of these biomarkers, we can use the data to develop algorithms via artificial intelligence to guide

our practice. We shall see these AKI biomarkers utilized to evaluate AKI risk and diagnosis in the upcoming years.

Conclusion

Nowadays, some biomarkers play an essential role in detecting structural and functional abnormalities in the kidneys. There has not been an established specific biomarker that predicts AKI to its fullest, why it is necessary to introduce clinical biomarkers synchronized with acute kidney injury, like Nephrocheck. With the routine use of these biomarkers, we will have an enormous quantity of useful data to design algorithms for our clinical practice. We will notice an increase in the use of these biomarkers in the upcoming years. Early detection and intervention in AKI decrease the damage caused, reducing the chance of complications and mortality.

References

1. Srisawat N, Kellum JA. The Role of Biomarkers in Acute Kidney Injury. Critical Care Clinics. 2020; 36: 125–140. **PubMed:** https://pubmed.ncbi.nlm.nih.gov/31733675/
2. Menez S, Parikh CR. Assessing the health of the nephron in acute kidney injury: biomarkers of kidney function and injury. Curr Opin Nephrol Hypertens. 2019; 28: 560-566. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/31369422
3. Bellomo R, Kellum JA, Ronco C. Acute kidney injury. Lancet. 2012; 380: 756-766. **PubMed:** https://pubmed.ncbi.nlm.nih.gov/22617274/
4. Joannidis M, Forni LG, Haase M, Koyner J, Shi J, et al. On behalf of the Sapphire Investigators Use of Cell Cycle Arrest Biomarkers in Conjunction With Classical Markers of Acute Kidney Injury. Critical Care Medicine. 2019. 47: e820-e826. **PubMed:** https://pubmed.ncbi.nlm.nih.gov/31343478
5. Zuk A. Bonventre JB. Acute Kidney Injury. Annu Rev Med. 2016; 67: 293-307. **PubMed:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4845743/
6. Schrezenmeier EV, Barasch J, Budde K, Westhoff T, Schmidt-Ott KM. Biomarkers in acute kidney injury – pathophysiological basis and clinical performance. Acta Physiol. 2017; 219: 556-574. **PubMed:** https://pubmed.ncbi.nlm.nih.gov/27474473/
7. Schunk SJ, Zarbock A, Meersch M, et al. Association between urinary dickkopf-3, acute kidney injury, and subsequent loss of kidney function in patients undergoing cardiac surgery: an observational cohort study. Lancet. 2019; 394: 488-496. **PubMed:** https://pubmed.ncbi.nlm.nih.gov/31202596/
8. Tanase DM, Gosav EM, Radu S, Costea CF, Ciocoiu M, et al. The Predictive Role of the Biomarker Kidney Molecule-1 (KIM-1) in Acute Kidney Injury (AKI) Cisplatin-Induced Nephrotoxicity. Int J Mol Sci. 2019; 20: 5238. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/31652595
9. Weiss R, Meersch M, Pavenstädt H, Zarbock A. Acute Kidney Injury, a frequently underestimated problem in perioperative medicine. Dtsch Arztebl Int. 2019; 116: 833-842. **PubMed:** https://www.ncbi.nlm.nih.gov/books/NBK557677/
10. Ostermann M, Liu K. Pathophysiology of AKI. Best Pract Res Clin Anaesthesiol. 2017; 31: 305-314. **PubMed:** https://pubmed.ncbi.nlm.nih.gov/29248138/
11. Menez S, Parikh CR. Assessing the health of the nephron in acute kidney injury: biomarkers of kidney function and injury. Curr Opin Nephrol Hypertens. 2019; 28: 560-566. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/31369422
12. Holditch SJ, Brown CN, Lombardi AM, Nguyen KN, Edelstein CL. Recent Advances in Models, Mechanisms, Biomarkers, and Interventions in Cisplatin-Induced Acute Kidney Injury. Int J Molecu Sci. 2019; 20: 3011. **PubMed:** https://pubmed.ncbi.nlm.nih.gov/31226747/
13. Sriswat N, Kellum J. The Role of Biomarkers in Acute Kidney Injury. Critical Care Clinics. 2020; 36: 125-140. **PubMed:** https://pubmed.ncbi.nlm.nih.gov/31733675/
14. Gonsalez SR, Cortês AL, Silva RCD, Lowe J, Prieto MC, et al. Acute kidney injury overview: From basic findings to new prevention and therapy strategies. Pharmacol Ther. 2019; 200: 1-12. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/30959059
15. Teo SH, Endre ZH. Biomarkers in acute kidney injury (AKI). Best Pract Res Clin Anaesthesiol. 2017; 31: 331-344. **PubMed:** https://pubmed.ncbi.nlm.nih.gov/29248140
16. Benavides-Couto A, Rodríguez-Jiménez Y, González-Borges D, Martinez-Serrano I, et al. Utilización del biomarcador de cistatina C en pacientes con posible fallo renal. Revista Finlay [revista en Internet]. 2019 [citado 2020]; 9: 7. http://www.revfinlay.sld.cu/index.php/finlay/article/view/717
17. Davidson JA, Khailova L, Treece A, Robison J, Soranno DE, et al. Alkaline Phosphatase Treatment of Acute Kidney Injury in an Infant Piglet Model of Cardiopulmonary Bypass with Deep Hypothermic Circulatory Arrest. Sci Rep. 2019; 9:14175. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/31578351
18. Seijas M, Baccino C, Nin N, Lorente JA. Definition and biomarkers of acute renal damage: new perspectives. Med Intensiva. 2014; 38: 376-385. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/24880198
19. Devarajan P. Biomarkers for the early detection of acute kidney injury. Curr Opin Pediatr. 2011; 23: 194-200. **PubMed:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3257513/
20. Alge JL, Arthur JM. Biomarkers of AKI: a review of mechanistic relevance and potential therapeutic implications. Clin J Am Soc Nephrol. 2015; 10: 147-55. **PubMed:** https://pubmed.ncbi.nlm.nih.gov/25092601/
21. Gavrić A, Kališnik JM. Novel biomarkers for early diagnosis of acute kidney injury after cardiac surgery in adults. Kardiochir Torakochirurgia Pol. 2016; 13: 31-38. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/27212976
22. Yu H, Yanagisawa Y, Forbes MA, et al. Alpha-1-microglobulin: an indicator protein for renal tubular function. J Clin Pathol. 1983; 36: 253-259. **PubMed:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC498194/
23. Lombi F, Muryan A, Canzonieri R, Trimarchi H. Biomarkers in acute kidney injury: Evidence or paradigm?. Nefrología (English Edition). 2016; 36: 339-346. **PubMed:** https://pubmed.ncbi.nlm.nih.gov/27207821/
24. Bollick YS, de Carvalho JAM, Tatsch E, Hausen BS, Moresco RN, et al. Reference limits of the urinary gamma- glutamyltransferase in a healthy population and effects of short-term storage on the enzyme activity. Clinica Chimica Acta. 2018.
25. Wajda J, Dumnicka P, Maraj M, Ceranowicz P, Kuźniewski M, et al. Potential Prognostic Markers of Acute Kidney Injury in the Early Phase of Acute Pancreatitis. Int J Mol Sci. 2019; 20: 3714. **PubMed:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6696144/

26. Jouffroy R, Lebreton X, Mansencal N, Anglicheau D. Acute kidney injury during an ultra-distance race. PLoS One. 2019; 14: e0222544. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/31553742

27. Ratnayake I, Mohamed F, Buckley NA, Gawarammana IB, Dissanayake DM, et al. Early identification of acute kidney injury in Russell's viper (Daboia russelii) envenoming using renal biomarkers. PLoS Negl Trop Dis. 2019; 13: e0007486. **PubMed:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6625728/

28. Wallbach M, Tampe B, Dihazi H, Koziolek MJ. Akute Nierenschädigung: von Kreatinin zu KIM-1? [Acute kidney injury: from creatinine to KIM-1?]. Internist (Berl). 2019; 60: 578-586.

29. Antonelli A, Allinovi M, Cocci A, Russo GI, Schiavina R, et al. The Predictive Role of Biomarkers for the Detection of Acute Kidney Injury After Partial or Radical Nephrectomy: A Systematic Review of the Literature. Eur Urol Focus. 2020; 6: 344-353. **PubMed:** https://pubmed.ncbi.nlm.nih.gov/30309817

30. Li C, Zhao L, Wang Y, Che L, Luan H, et al. Cysteine-rich protein 61, a specific ultra-early biomarker in kidney ischemia/reperfusion injury. Nephrology Carlton. 2019; 248: 798-805. **PubMed:** https://pubmed.ncbi.nlm.nih.gov/30328178/

31. Prowle JR. Introduction: Acute Kidney Injury Management in 2019: Somethings Old Somethings New. Semin Nephrol. 2019; 39: 419-420. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/31514905

32. Xu Y, Shen XF, Ma RX, Jiang W, Zhang W. Protection of renal tubular epithelial cells from apoptosis by Cyr61 expression under hypoxia. Cell Biology International Reports. 2014; 2014: 1-4.

33. Diaz MA, Briones JC, Carrillo R, Moreno A, Perez AA. Insuficiencia renal aguda (IRA) clasificación, fisiopatología, histopatología, cuadro clínico diagnóstico y tratamiento una versión lógica. Revista Mexicana de anestesiologia. 2017; 40: 280-287. https://www.medigraphic.com/pdfs/rma/cma-2017/cma174e.pdf

34. Nielsen TL, Plesner LL, Warming PE, Pallisgaard JL, Dalsgaard M, et al. YKL-40 in patients with end-stage renal disease receiving haemodialysis. Biomarkers. 2018; 23: 357-363. **PubMed:** https://pubmed.ncbi.nlm.nih.gov/29357700/

35. Rathcke CN, Vestergaard H. YKL-40--an emerging biomarker in cardiovascular disease and diabetes. Cardiovasc Diabetol. 2009; 8: 61. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/19930630

36. Lorenz G, Schmalenberg M, Kemmner S, Haller B, Steubl D, et al. Mortality prediction in stable hemodialysis patients is refined by YKL-40, a 40-kDa glycoprotein associated with inflammation. Kidney Int. 2018; 93: 221-230. **PubMed:** https://pubmed.ncbi.nlm.nih.gov/28941940/

37. Puthumana J, Hall IE, Reese PP, Schröppel B, Weng F, et al. YKL-40 Associates with Renal Recovery in Deceased Donor Kidney Transplantation. J Am Soc Nephrol. 2017; 28: 661-670. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/27451287

38. Maxwell RA, Bell CM. Acute Kidney Injury in the Critically Ill. Surg Clin North Am. 2017; 97: 1399-1418. **PubMed:** https://pubmed.ncbi.nlm.nih.gov/29132515/

39. Pedroso LA, Nobre V, Carneiro de Almeida CD, da Silva Praxedes MF, Guimarães NS, et al. Acute kidney injury biomarkers in the critically ill, Clinica Chimica Acta. 2020.

40. Deng Y, Chi R, Chen S, Ye J, Yuan J, et al. Evaluation of clinically available renal biomarkers in critically ill adults: a prospective multicenter observational study. Crit Care. 2017; 21: 46. **PubMed:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5339963/

41. Klein SJ, Brandtner AK, Lehner GF, Cooper EH, Crockson RA, et al. Biomarkers for prediction of renal replacement therapy in acute kidney injury: a systematic review and meta-analysis. Intensive Care Med. 2018; 44: 323–336. **PubMed:** https://pubmed.ncbi.nlm.nih.gov/29541790/

42. Kellum JA, Prowle JR. Paradigms of acute kidney injury in the intensive care setting. Nat Rev Nephrol. 2018; 14: 217-230. **PubMed:** https://pubmed.ncbi.nlm.nih.gov/29355173/

43. Jo SK, Yang J, Hwang SM, Lee MS, Park SH. Role of biomarkers as predictors of acute kidney injury and mortality in decompensated cirrhosis. Sci Rep. 2019; 9: 14508. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/31601879

44. Gorostidi M, Santamaría R, Alcázar R, Fernández-Fresnedo G, Galcerán JM, et al. Spanish Society of Nephrology document on KDIGO guidelines for the assessment and treatment of chronic kidney disease. Nefrologia. 2014; 34: 302-316. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/24798565

45. Zuk A, Bonventre J. Acute Kidney Injury. Annu Rev Med. 2016; 67: 293-307. **PubMed:** https://pubmed.ncbi.nlm.nih.gov/26768243

46. Kashani K, Cheungpasitporn W, Ronco C. Biomarkers of acute kidney injury: the pathway from discovery to clinical adoption. Clin Chem Lab Med. 2017; 55: 1074–1089. **PubMed:** https://pubmed.ncbi.nlm.nih.gov/28076311

47. Husain-Syed F, Ferrari F, Sharma A, et al. Preoperative renal functional reserve predicts risk of acute kidney injury after cardiac operation. Ann Thorac Surg. 2018; 105: 1094–1101. **PubMed:** https://pubmed.ncbi.nlm.nih.gov/29382510

48. Mishra J, Dent C, Tarabishi R, Mitsnefes M, Ma Q, et al. Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. Lancet. 2005; 365: 1231–1238. **PubMed:** https://pubmed.ncbi.nlm.nih.gov/15811456/

49. Murray P, Mehta R, Shaw A, Ronco C, Endre Z, et al. Potential use of biomarkers in acute kidney injury: report and summary of recommendations from the 10th Acute Dialysis Quality Initiative consensus conference. Kidney Int. 2020; 180: 513–521. PubMed: https://pubmed.ncbi.nlm.nih.gov/24107851

50. Fan W, Ankawi G, Zhang J, Digvijay K, Giavarina D, et al. Current understanding and future directions in the application of TIMP-2 and IGFBP7 in AKI clinical practice. Clin Chem Lab Med. 2019; 57: 567–576. **PubMed:** https://pubmed.ncbi.nlm.nih.gov/30179848

51. Ortega LM, Heung M. The use of cell cycle arrest biomarkers in the early detection of acute kidney injury. Is this the new renal troponin? Nefrologia. 2018; 38: 361–367. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/29627229

52. Gomez H, Ince C, De Backer D, Pickkers P, Payen D, et al. A unified theory of sepsis-induced acute kidney injury: inflammation, microcirculatory dysfunction, bioenergetics and the tubular cell adaptation to injury. Shock. 2014; 41: 3–11. **PubMed:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3918942/

53. Kashani K, Al-Khafaji A, Ardiles T, Artigas A, Bagshaw S, et al. Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. Crit Care. 2013; 17: R25. **PubMed:**: https://pubmed.ncbi.nlm.nih.gov/23388612/

54. McCullough PA, Bouchard J, Waikar SS, Siew ED, Endre ZH, et al. Implementation of novel biomarkers in the diagnosis, prognosis, and management of acute kidney injury: executive summary from the tenth consensus conference of the Acute Dialysis Quality Initiative (ADQI). Contrib Nephrol. 2013; 182: 5–12. **PubMed:** https://pubmed.ncbi.nlm.nih.gov/23689652

55. Ostermann M, McCullough PA, Forni LG, Bagshaw SM, Joannidis M, et al. Kinetics of Urinary Cell Cycle Arrest Markers for Acute Kidney Injury Following Exposure to Potential Renal Insults. Crit Care Med. 2018; 46: 375–383. **PubMed:** https://pubmed.ncbi.nlm.nih.gov/29189343/

56. Cummings JJ, Shaw AD, Shi J, Lopez MG, O'Neal JB, et al. Intraoperative prediction of cardiac surgery-associated acute

kidney injury using urinary biomarkers of cell cycle arrest. J Thorac Cardiovasc Surg. 2019; 157: 1545–1553.
PubMed: https://pubmed.ncbi.nlm.nih.gov/30389130

57. Di Leo L, Nalesso F, Garzotto F, Xie Y, Yang B, et al. Predicting Acute Kidney Injury in Intensive Care Unit Patients: The Role of Tissue Inhibitor of Metalloproteinases-2 and Insulin-Like Growth Factor-Binding Protein-7 Biomarkers. Blood Purif. 2018; 45: 270–277.
PubMed: https://pubmed.ncbi.nlm.nih.gov/29478052/

58. Bihorac A, Chawla LS, Shaw AD, Al-Khafaji A, Davison DL, et al. Validation of cell-cycle arrest biomarkers for acute kidney injury using clinical adjudication. Am J Respir Crit Care Med. 2014; 189: 932–939.
PubMed: https://pubmed.ncbi.nlm.nih.gov/24559465/

59. Patschan D, Anthon-Muller G. Acute Kidney Injury. J Inj Violence Res. 2015; 7: 19-26.
PubMed: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4288292/

60. Negi S, Kooreda D, Kobayashi S, Yano T, Tatsuta K, et al. Acute kidney injury: Epidemiology, outcomes, complications, and therapeutic strategies. Seminars in Dialysis. 2018, 1-9.
PubMed: https://pubmed.ncbi.nlm.nih.gov/29738093/

61. Han W, Bailly B, Abichandani, R, Tadhani R, Bonventre J. Kidney Injury Molecule-1 (KIM-1): a novel biomarker for human renal proximal tubule injury. Kidney Int. 2002; 62: 237-244.
PubMed: https://pubmed.ncbi.nlm.nih.gov/12081583/

62. Parikh CR, Coca SG, Thiessen-Philbrook H, Shlipak MG et al. Postoperative biomarkers predict acute kidney injury and poor outcomes after adult cardiac surgery. J Am Soc Nephrol. 2011; 22: 1748-1757.
PubMed: https://pubmed.ncbi.nlm.nih.gov/21836143

63. Parikh, CR, Mansour SG. Perspective on Clinical Application of Biomarkers in AKI. J Am Soc Nephrol. 2017; 28: 1677–1685.
PubMed: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5461806/

64. Haase M, Bellomo R, Devarajan P, Schlattman P, Haase-Fielitz A, et al. Accuracy of Neutrophil Gelatinase-Associated Lipocalin (NGAL) in Diagnosis and Prognosis in Acute Kidney Injury: A Systematic Review and Meta-analysis. Am J Kidney Dis. 2009; 54: 1012-1024.
PubMed: https://pubmed.ncbi.nlm.nih.gov/19850388

65. Zhang Z, Lu B, Sheng X, Jin N. Cystatyn C in Prediction of Acute Kidney Injury: A Systematic Review and Meta-analysis. Am J Kidney Dis. 2011; 58: 356-365.
PubMed: https://pubmed.ncbi.nlm.nih.gov/21601330/

66. Barton KT, Kakajiwala A, Dietzen DJ, Goss CW, Gu H, et al. Using the newer Kidney Disease: Improving Global Outcomes criteria, beta-2-microglobulin levels associate with severity of acute kidney injury. Clinical Kidney J. 2018; 11: 797–802.
PubMed: https://www.ncbi.nlm.nih.gov/pubmed/30524714