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Acute Kidney Injury and Early Diagnostic Biomarkers: A Narrative Literature Review

In depth review

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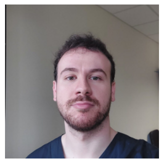

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ABSTRACT

Introduction. Acute kidney injury (AKI) is a serious entity characterized by sudden impairment of renal function in hospitalized patients, particularly in the intensive care unit, resulting in high morbidity and mortality. Current diagnostic methods based on changes in serum creatinine (sCr) and urine output are prone to many confounding variables. The aim of this study is to investigate the role of specific biomarkers, namely NGAL, Cystatin C, IL-18, and KIM-1, in the diagnosis of AKI.

Materials and methods. In this literature review, a thorough search of the PubMed, Scopus and Google Scholar databases was conducted to investigate the early diagnostic potential of NGAL, Cystatin C, IL-18, and KIM-1 in AKI patients.

Biomarkers. Neutrophil Gelatinase-Associated Lipocalin (NGAL), both serum and urinary, was discovered to rise shortly after AKI onset, several hours before sCr elevation, differentiating AKI from chronic kidney disease and prerenal azotemia. Cystatin C (CysC), a protein constantly produced and filtered, was identified as a reliable marker for AKI, although its high cost prohibits its use. Interleukin-18 (IL-18), a pro-inflammatory cytokine, demonstrated potential, particularly in critically ill and post-cardiovascular surgery patients, although results on its predictive ability were inconsistent. Kidney Injury Molecule-1 (KIM-1), a protein released into urine after proximal tubular injury, demonstrated high sensitivity and specificity shortly after AKI onset, while it has been associated with a number of kidney diseases.

Conclusions. Novel biomarkers (NGAL, CysC, IL-18, and KIM-1) provide a faster and more accurate diagnosis of AKI than traditional methods in various clinical settings. Additional research is required to fully incorporate these promising molecules into everyday clinical practice.

KEYWORDS: acute kidney injury, biomarker, NGAL, cystatin-c, IL-18, KIM-1

Introduction

Acute kidney injury (AKI) is a common syndrome affecting up to one third of hospitalized patients with high prevalence among the intensive care unit patients and the older individuals and a high mortality [1, 2]. The term AKI describes a sudden impairment of the renal function and is characterized by increased serum creatinine with or without decreased urine output developing over a period of up to a week [2–4]. Historically, this pathological condition was first mentioned in the early 19th century, while the term acute renal failure was introduced in 1951. For the past two decades, the term acute kidney injury has been used to characterize a wide range of kidney diseases [2]. The first classification system of AKI was the RIFLE system, where R=Risk, I=Injury, F=Failure, L=Loss, E=End-stage disease, using as criteria the respective increase in the levels of serum creatinine and the respective reduction of urine output with or without a decreased GFR (Glomerular Filtration Rate) [5, 6]. As new classifications, AKIN-Acute Kidney Injury Network and KDIGO-Kidney Disease Improving Global Outcomes were developed, GFR was no longer evaluated while the increase of the serum creatinine levels and the decrease of the urine output remained the main criteria for the diagnosis of the acute kidney injury [6–8]. Acute kidney disease is associated with a variety of complications including metabolic abnormalities, pulmonary edema, cardiovascular and long-term renal complications such as the development of chronic kidney disease, while the gastrointestinal, the immune and the nervous systems are also affected [9–12]. Age, chronic kidney disease, diabetes mellitus, hypertension, cardiovascular diseases are not only risk factors for the development of acute kidney injury but also affect the prognosis of these patients along with the duration and severity of the acute kidney disease among others [12].

Pathophysiology of AKI

AKI can result from multiple causes, which are classified according to their pathophysiological mechanism into pre-renal, intra-renal, and post-renal. Among pre-renal causes, the most common are those characterized by reduced renal blood flow or renal ischemia; in intra-renal causes, damage to the renal parenchyma is usually observed; post-renal causes are characterized by an obstruction of the urinary system [3, 9, 13–15] (Table 1).

Pre-renal Decreased renal blood flow	– Sepsis, hypovolemia, shock – Cardiorenal syndrome – Hepatorenal syndrome – Major surgical procedure – Abdominal compartment syndrome – Drugs including antihypertensives, contrast media and NSAIDs – Hypercalcemia
Intra-renal	– Sepsis, systemic infections – Vascular and blood diseases – Autoimmune diseases – Renal diseases including acute interstitial nephritis and rapidly progressive glomerulonephritis – Rhabdomyolysis – Tubular necrosis due to ischemia-prolonged low blood pressure – Acute graft rejection – Drugs including antibiotics, chemotherapy drugs, contrast media and heavy metals – Cancer immunotherapy
Post-renal	– Benign prostatic hyperplasia – Nephrolithiasis, blood clots – Neoplasms of the genitourinary tract – Fibrosis (radiation-induced, retroperitoneal)

Table 1. Common causes of AKI.

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AKI due to surgery, heart diseases or administration of specific medications (Table 1) is more common in populations with a higher income compared to lower income populations, where kidney injury is mainly caused by dehydration, hypotension, infections including sepsis, venomous animal bites and in relatively rare cases as a complication of pregnancy [16].

In cases associated with acute sepsis, the acute kidney injury can be caused by inflammation, hemodynamic, and metabolic alterations [4, 17]. Of note, these factors, as well as mechanical and various other factors including specific medications and neurohormonal alterations, play a significant role in the development of acute kidney injury following a surgical procedure [8, 18, 19]. Neurohormonal alterations are a significant cause of AKI also in patients with hepatorenal syndrome as well as in patients with cardiorenal syndrome, while hemodynamic changes, inflammation and nephrotoxic drugs combined with chronic kidney disease are implicated as well [14].

Prolonged vasoconstriction and direct renal cellular damage due to iodinated contrast media can lead to acute kidney injury especially in patients suffering from diabetes mellitus and chronic kidney disease. These cases are characterized by a prolonged detection and action of the contrast media within the urinary system resulting in an impaired kidney function [20].

Diagnosis of AKI

As mentioned above, the current classifications are based on increased serum creatinine levels and/or a decreased urine output for the diagnosis of acute kidney injury. However, the serum creatinine levels can rise at a slow rate after AKI, and they are also affected by various factors such as diet, age, sex, medication, body muscle volume, hypervolemia, sepsis, rhabdomyolysis, chronic kidney disease, while various technical factors can affect the evaluation of the creatinine levels in the laboratory [6, 13]. Consequently, serum creatinine levels do not always represent accurately the GFR and cannot clarify the cause of the acute kidney injury, while some drugs can affect the prognostic potential of this marker [21].

Specific acute situations, such as surgery, severe pain or hemodynamic instability can result in a decreased urine output which is associated with a lower survival rate, while the duration of this decrease is essential for the prognosis of the patients suffering from acute kidney injury [6, 13, 18].

The management includes fluid administration, vasoactive drugs, withdrawal of the nephrotoxic substances, diuretics, management of the metabolic alterations, while in more severe cases renal replacement therapy may be required [9, 22].

The term biomarker is used to describe a measurable marker that characterizes a biological process as well as a pathological condition or response to treatment [23]. Various biomarkers both in serum and urine have been evaluated to contribute to an earlier diagnosis and as prognostic factors of acute kidney injury [24]. These biomarkers could indicate kidney damage, stress, or an impaired kidney function [22]. In the current literature, the most studied biomarkers for the early diagnosis of AKI are the Neutrophil Gelatinase-associated Lipocalin (NGAL), the Cystatin C, the Interleukin-18 (IL-18), and the Kidney Injury Molecule-1 (KIM-1). To summarize all available data regarding the utilization of the biomarkers mentioned above in early AKI diagnosis, as well as their efficacy compared to conventional biomarkers, we conducted a literature review of all available studies on these molecules. With this report, we aim to draw conclusions from the available literature regarding the use of these biomarkers in early AKI diagnosis.

Materials and methods

Study design

To address the research question, we designed and conducted this literature review to investigate any relationship of selected biomarkers to an early diagnosis of AKI onset. The research question was defined using the PICO (Population/Participants, Intervention/Investigation, Comparison/Comparator, Outcomes) framework:

- Population: All patients diagnosed with Acute Kidney Injury
- Investigation: Use of diagnostic biomarkers (NGAL, Cystatin C, IL-18, KIM-1)
- Comparison: No comparator investigation
- Outcomes: Early diagnosis of Acute Kidney Injury.

Eligibility criteria

For this literature review, original research articles, reviews including meta-analyses, and clinical trials were included. Only articles in English language and with a full text available were selected.

Search strategy

A thorough search of the MEDLINE database via PubMed, Scopus and Google Scholar was conducted, from January 1990 to the last search date, September 16th, 2024, using the algorithms: ((acute kidney injury) OR (aki)) AND ((diagnostic biomarkers) OR (NGAL) OR (cystatin c) OR (IL-18) OR (KIM-1)). Two independent reviewers (GG, AK) performed the title and abstract screening and then assessed the studies for eligibility through full text evaluation of the articles according to the eligibility criteria mentioned above. Disagreements were addressed by a third independent author (AP).

Neutrophil gelatinase-associated lipocalin (NGAL)

Human NGAL, also known as lipocalin-2, is a protein with a specific weight of 25-kDa that is secreted mostly by immune cells such as neutrophils, but it can also be found in numerous human tissues, such as salivary glands, uterus, prostate, trachea, lungs, stomach, colon and kidneys [25, 26].

In the kidneys, NGAL is bound to neutrophil cell gelatinase and is released from the distal tube [27]. The molecule then is filtered through the glomerular membrane and is reabsorbed in the proximal tubule of the kidney while the NGAL quantities observed in urine are caused by proximal tubular damage or originates from their up-regulated synthesis in the distal part of the nephron, especially in the ascending limb and Henle's loop, and in the collecting duct [28].

NGAL is known to be a siderophoric protein that plays a role in regulating iron activity [29]. NGAL quantities that are not bound to iron can interact with the cell surface receptors resulting in extracellular transfer of intracellular iron [30]. Studies have shown that NGAL interferes in binding iron together with a metabolic product called catechol and creates complexes [31] which enhance microbial growth [32] or mediate oxidative damage [33].

Also, NGAL plays a significant role as an acute phase protein and takes part in various antibacterial immune processes. Inflammatory cytokines induce NGAL expression in neutrophils, epithelial cells, or hepatocytes [34]. The injury of epithelial cells in the intestines [35], stomach, liver [36], or lungs during infections results in an increase in serum NGAL (sNGAL) concentration levels. Additionally, sNGAL levels are higher in patients with septic shock and sepsis-related organ failure compared to those with a milder course of sepsis as shown by a study [37]. Research has shown that NGAL is associated with epithelia and in particular its production increases greatly and sharply when epithelial tissues are damaged, a function investigated by many studies in correlation with early diagnosis of AKI. The previous study [38] also reported that while NGAL is expressed normally at very low concentrations in physiologic conditions, its levels increase sharply after tissue damage, thus categorizing the molecule as a defense protein of the host organism. In the same study, it is reported that NGAL rising above a certain level indicates kidney injury about 24-48 hours before serum creatinine (sCr) does [38]. Serum NGAL can be detected within two hours of AKI onset, with a concentration peak after 6 hours while sNGAL levels remained increased for approximately five days after AKI onset [39].

Another study [31] showed that in 30 patients out of 635 who developed AKI, NGAL in urine was elevated much earlier and in higher levels than sCr. In addition, urinary NGAL (uNGAL) appears as a suitable marker to distinguish AKI from chronic renal failure (CKD) and prerenal azotemia given its acute level increase in AKI compared to CKD and prerenal azotemia, in which no increase was observed [31]. An experimental study in animals suggested that sNGAL can predict early diagnosis of cisplatin-induced AKI accurately but is less useful in later stages compared to blood urea nitrogen (BUN) and sCr [40]. Moreover, another study [41] reported that in 45 patients who developed AKI (out of 77 in the study), uNGAL and urine cystatin C (uCysC) increased rapidly in several cases and remained elevated after the acute phase. The utility of sNGAL had also emerged, contributing positively in diagnosing 100% of patients who developed AKI later [41]. The above three indicators increased approximately 6-24 hours before sCr levels exceeded 0.3mg/dl, while uNGAL in some cases immediately increased significantly and within 24 hours of admission and predicted risk of death or the need for hemodialysis [41]. The NGAL seems to have many prospects to be established as an early biomarker of AKI, as it has been reviewed in various applications including a study in children treated with cardiopulmonary bypass (CPB) [42]. Out of the 196 patients who participated in the research and had gone through CPB, 99 later developed AKI. In this study, high levels of creatinine were reported only 2-3 days after CPB, while NGAL increased 15-fold 2 hours and 25-fold 4-6 hours after the surgical procedure [42].

NGAL has been found to be an independent predictor of CKD progression [43], also demonstrating promise as a marker determining the iron status in CKD instead of serum ferritin, including patients who require renal replacement therapy [44].

NGAL performed significantly in a study linking AKI and cardiac failure [45]. Specifically, in 203 patients, of whom 107 already had chronic renal insufficiency and 96 demonstrated normal renal function, 78 developed AKI. In those with AKI (the threshold for sNGAL was 134 ng/ml) sNGAL increased significantly, while on the same metrics cystatin C (CysC) did not perform adequately. Notably, the performance of natriuretic peptide type B (BNP) was remarkable in all cases of AKI. [45]. As a side note, the previous study indicated the potential usefulness of sNGAL in the early diagnosis of AKI in the setting of heart failure, and showed promise as a marker of renal function in the manifestation of cardiorenal syndrome, while CysC did not contribute to the diagnosis of AKI but showed a relevance with CKD and possibly laid the foundations as an indicator of CKD, as well as of decreased kidney function (impaired GFR) [45]. Promising results for NGAL's efficiency for the diagnosis and management of AKI and hepatorenal syndrome have also been shown [46, 47].

In a 2023 study by Gupta et al. in trauma patients in ICU, the cut-off values of sNGAL and uNGAL were determined as 122-125 ng/mL and 16 ng/mL, respectively, with sNGAL demonstrating greater prognostic potential in this study [48]. Similarly, Saha et al. in a 2025 study on the diagnosis of AKI in the setting of acute liver failure (ALF), reported that the cut-off values for sNGAL were 129 ng/mL in AKI without ALF, while in patients with ALF and AKI, sNGAL showed a less significant increase [49]. It is also worth mentioning the prospective study by Katz-Greenberg et al. in 2022, where uNGAL was measured in patients with possible admission to the ICU and a diagnosis of AKI. uNGAL increased up to 24-fold depending on the stage of injury, according to the KDIGO staging, where in stage I a mean value of 1255 ng/ml was measured, while a significant increase was also measured in patients needing RRT [50].

Of note, it should be underlined that studies on NGAL in AKI populations are relatively limited in size and may be affected by a number of conditions, such as pre-existing kidney disease and systemic or urinary tract infections [51].

Of course, there are also elements which show that there is still a long way to go from NGAL's establishment as an indicator for the diagnosis of AKI, such as trials where NGAL had mediocre statistical results and failed at a rate to contribute to diagnosis of AKI [24] or demonstrated limited usefulness, especially when systemic inflammation occurs concurrently with AKI [52].

Cystatin C

Cystatin C (CysC) is a 13-kDa cysteine proteinase inhibitor protein with an important role in the catabolism of intracellular peptides and proteins and is produced by all nucleated cells at a constant rate [53]. As blood is filtered by the kidneys, CysC is freely filtered by the glomerulus and like glucose and other substances, is almost completely reabsorbed and catabolized in the proximal tubule [54]. It is not affected by extrarenal factors such as gender, age, race or muscle mass and thus is considered as an independent marker of renal function, compared to sCr [55]. CysC is considered a reliable biomarker of AKI because it is filtered by 99%, is continuously produced and released into plasma and has been found to be more accurate than serum creatinine in many different patient populations [54]. A study showed that in patients with diagnosed AKI, the levels of cystatin C excreted in urine (uCysC) can be used to predispose the need for possible kidney transplantation [56], while another study by the same research team showed that with the fall of estimated GFR score due to AKI, CysC levels increased quite quickly and earlier than sCr. Specifically, in cases of R, I and F from the classic RIFLE ranking system for AKI, CysC increased to a certain level 1.5 days prior to sCr and thus was characterized as not only more sensitive, but also more specific than sCr [56, 57]. Other potential roles for cystatin C include being an earlier marker for acute kidney injury, a superior marker of kidney transplant function, CVD (cardiovascular disease) risk and transplant failure [58].

CysC has been associated with progression to end stage renal disease and mortality in patients with diabetes [59], acute kidney injury [60], CKD [61, 62], and end-stage CKD on dialysis [63]. CysC has been shown to portray an important role as a biomarker in CKD classification and overall risk and mortality, as shown by a meta-analysis, where a significant difference in GFR estimation using CysC compared with sCr was observed in pre-end-stage CKD [64]. This correlation between CysC and risk and mortality in CKD and end-stage CKD has been shown by many other studies, always compared with sCr [65]. CysC has been found to be more accurate than serum creatinine in many different patient populations [54]. It depicts earlier, more subtle changes in kidney function, while further research and development is needed to improve its cost-effectiveness [66]. This is its most significant limitation, as the cost of CysC, approximately 10-fold of sCr, is considered a significant prohibitive factor for routine use in clinical practice [65] while regarding other restrictions, it can be affected by thyroid disease, obesity, systemic inflammation and steroid use [67]. Lastly, while GFR estimation using CysC can still fall victim to its non-GFR determinants, such as thyroid function and steroid use, its independent association with CVD, end-stage CKD, and all-cause mortality warrants CysC the possibility of becoming a reliable biomarker for these clinical conditions [66].

Interleukin-18

Interleukin 18 (IL-18) is a cytokine promoting inflammation produced by a variety of cells including renal tubular cells [68, 69]. IL-18 has a possible role as a biomarker of AKI as inflammation resulting in parenchymal injury is heavily involved in the pathogenesis of AKI [70], whereas its release is also associated with pre-renal AKI causes such as ischemia, activated by the enzyme caspase-1 and released in urine [71]. IL-18 promotes inflammation and ultimately is a factor that can contribute towards renal fibrosis after AKI, as reported in a renal injury mouse model study in 2022, where possible deficiency of IL-18 in renal tubular cells in mice prevented alterations indicative of further progression of AKI into chronic kidney disease [71]. Also, this pro-inflammatory cytokine is associated with the development and progression of diabetic nephropathy through a wide range of mechanisms [72, 73].

IL-18 levels in urine rise after cardiovascular surgery [74–76] and in critically ill patients, such as septic patients, preceding the diagnosis of AKI [74, 75, 77, 78], while it is reported as both a reliable [69] and a poor [79] prognostic biomarker in these patients. Serum IL-18 levels in critically ill patients with AKI starting hemodialysis predicted the risk of death [80]. Promising results were also reported more in children and adolescents than adults with AKI in the above conditions (cardiovascular surgery, ICU patients), according to a meta-analysis [81]. Higher urinary IL-18 levels after heart surgery are associated with a longer duration of AKI [82], while serum IL-18 also increased within hours [83]. Urinary IL-18 levels were elevated earlier compared to serum creatinine in patients with AKI developing ARDS (acute respiratory distress syndrome) [74, 84, 85], as well as in patients receiving a kidney transplant, where high levels of urinary IL-18 were associated with delayed graft function [75, 84]. Urinary IL-18 in patients with cirrhosis could determine the cause of AKI, specifically for the diagnosis of acute tubular necrosis as well as predict mortality and progression of AKI [86]. The levels of urinary IL-18 were elevated within hours after liver transplantation combined with AKI as shown by a study [87], while another study showed that elevated plasma IL-18 levels post transplantation could also predict AKI [88].

Urinary IL-18 levels were elevated due to AKI in specific situations, such as cardiac catheterization [89], burn injuries [90] and urological interventions.

Serum IL-18 levels are higher in patients under hemodialysis compared to patients with AKI, while its levels rise with age [70]. Urinary IL-18 can also be elevated in autoimmune and inflammatory diseases [68, 84, 91], in various diseases of the urinary system and in diseases of the heart or the lungs [69].

Urinary IL-18 could not only detect AKI earlier compared to elevated serum creatinine levels, with better results in children than adults [68, 69], but also serve as a prognostic marker [92].

Kidney Injury Molecule-1 (KIM-1)

KIM-1 (Kidney Injury Molecule-1) or TIM-1 (T-cell immunoglobulin mucin receptor-1) or HAVCR 1 (Hepatitis A Virus Cellular Receptor 1) is a cellular membrane protein expressed in renal proximal tubular epithelial cells which under normal conditions is found at low levels in urine [93, 94]. Higher levels of this molecule are found after kidney injury as its extracellular portion is released into the urine [93, 94], with the contribution of MAPK (mitogen activated protein kinase) pathways [95]. KIM-1 function is associated with phagocytosis, tissue repair, fibrosis and inflammation, whereas increased levels of this biomarker are detected in the urine in a variety of renal diseases such as acute kidney injury, renal disease due to diabetes, chronic kidney disease, IgA nephropathy, lupus nephritis, polycystic renal disease, renal cell carcinoma as well as in patients with a transplanted kidney suffering from graft loss [93–97]. KIM-1 appears to promote repair of the kidney tubular epithelial cells through the ERK/MAPK signaling pathway [98].

KIM-1 is an FDA approved biomarker of drug induced renal injury, demonstrating encouraging outcomes regarding its use in incidents of cisplatin-induced acute kidney injury [94], as high levels of KIM-1 can be detected prior to creatinine increase [99].

In a meta-analysis by Shao et al in 2014, urinary KIM-1 had a sensitivity of 74% and specificity of 86% for the diagnosis of AKI, demonstrating better results in patients undergoing heart surgery, particularly when urine levels of KIM-1 were measured 2-12 hours post-operatively [100]. Additionally, promising results have been reported in infants and children in the same study compared to adults, while comorbidities and various technical issues regarding the detection methodology could alter the urinary KIM-1 levels [100]. Urinary KIM-1 levels also increased in cases of AKI post heart valve replacement surgery [101]. Furthermore, KIM-1 has been reported to be a promising biomarker of kidney injury associated with chronic heart failure or myocardial infarction [102].

Urinary KIM-1 can predict acute kidney injury 12 hours after coronary angiography, albeit with a lower specificity and sensitivity than NGAL [103].

In renal biopsies, KIM-1 staining was proved to be a valuable marker of acute tubular injury while the KIM-1/serum creatinine ratio appears to be a valuable marker of renal function recovery post injury, respectively [104].

Urinary KIM-1 is a potential early biomarker in instances of acute kidney injury diagnosis due to sepsis, while persistent high levels of this marker could be indicative of a poor prognosis [105].

Significantly increased levels of urinary KIM-1 in type 2 diabetic patients with diabetic nephropathy were associated with a poor prognosis regarding the progression of the renal disease [106]. Also, in patients with type 1 diabetes, increased levels of urinary KIM-1 can precede albuminuria [94]. In renal biopsy specimens of patients with diabetic nephropathy, KIM-1 expression in the renal tubules was found to correlate positively with the associated GFR decline, a correlation that was dependent on the urinary protein-to-creatinine ratio [107].

Urine levels of KIM-1 24 hours post transplantation were reported to be predictive of the recipients' renal graft function [108], while an association between perfusate levels of this biomarker and delayed graft function, as well as an impaired eGFR three years after the transplantation, were also found [109]. KIM-1 staining in specimens received from transplanted kidneys was reported to be a specific and sensitive marker of proximal tubular injury that is negatively associated with the presence of functional epithelial cells of the proximal tubule and eGFR [110, 111] and positively correlated with the serum creatinine and blood urea nitrogen levels [112].

Serum KIM-1 levels correlated positively with the severity of histological features (acute tubular necrosis, interstitial fibrosis-tubular atrophy) and negatively with eGFR in patients suffering from ANCA-associated (antineutrophil cytoplasmic antibodies-associated) vasculitis with glomerulonephritis [113]. KIM-1 is a promising biomarker because it is normally detected in low levels in urine, but after kidney injury, its levels rise rapidly and have been associated with the degree of the injury. Furthermore, the extracellular domain (ectodomain) of KIM-1 that is released into the urine, is stable at room temperature [97]. On the other hand, there are limited data from clinical studies, KIM-1 is frequently measured in combination with other biomarkers to improve its diagnostic utility, its levels in urine may increase hours after the injury, the detection process of this biomarker is expensive, thus rendering it difficult to access, while comorbidities and technical issues regarding the detection methodology could also affect the urinary KIM-1 levels [100, 101, 114].

Future perspectives

Acute kidney injury affects 30-50% of critically ill patients and is associated with increased mortality, longer ICU stay and risk of progression to chronic kidney disease, mainly due to surgical procedures, nephrotoxic drugs, electrolyte imbalances or sepsis [115]. In those patients, a prospective biomarker must possess the ability to detect early and accurately the tubular injury before the decline in renal function becomes clinically apparent, to offer specificity and sensitivity to the various causes of AKI (prerenal, renal, postrenal), to stratify high-risk patients, and to assist in the identification of patients with possible progression to CKD and RRT. Among the biomarkers presented in this review, the most prevalent biomarker performing consistently in the ICU setting, either in sepsis-related [116], trauma-related [48] or post cardiac surgery AKI [117], is the Neutrophil Gelatinase-Associated Lipocalin or NGAL, as mentioned extensively in the corresponding section. Additionally, as already mentioned, sNGAL's threshold values are reported to be in the range of 120-200 ng/ml, as reported by another study [118]. As for uNGAL, cut-off values are not sufficiently defined, however a recent 2025 study by Strander et al. in postoperative patients in the ICU after cardiac surgery reported the threshold value of uNGAL at 150 ng/mL, with satisfactory predictive performance [117].

It is necessary to emphasize again the usefulness of NGAL in predicting the progression of AKI to CKD with the need for RRT [50]. NGAL was found to detect patients with progressively deteriorating AKI, as observed in the ELAIN randomized clinical trial in 2016 [119], while in another study, the STARRT-AKI in 2022, sNGAL ≥ 400 ng/mL along with a two-fold increase in serum creatinine and oliguria was used as guiding criterion predicting the early start of RRT [120]. As already mentioned, NGAL can be affected by various factors, such as systemic or urinary tract inflammation, pre-existing kidney diseases, timing of sampling, and fluid imbalances.

Therefore, considering the multiple applications of NGAL in patients with mild disease, in the ICU, but also in predicting a possible need for RRT, we suggest NGAL as the most mature and clinically applicable biomarker for utilization in critical care of those presented in this study.

Conclusions

Acute kidney injury (AKI) is a common clinical syndrome, primarily diagnosed based on serum creatinine levels and urine output, markers that are affected by various factors such as diet, age, sex, medication and body muscle volume. Current evidence suggests that various novel biomarkers may provide a better alternative, allowing for an earlier and more precise detection of AKI. The most prevalent and clinically applicable biomarker, Neutrophil Gelatinase-Associated Lipocalin or NGAL, has been shown by a large number of studies to be a strong predictor of AKI, mainly in intensive care, showing efficacy in diagnosing AKI of various causes and in predicting the need for RRT. Kidney Injury Molecule-1 appears as a sensitive marker of proximal tubular injury, with significant shifts in concentration occurring hours to days prior to serum creatinine elevation. Cystatin C appears to be a precise marker of deteriorating renal function (eGFR), is produced and filtered at a constant rate, but its high cost prevents it from being utilized frequently in the clinical setting. Lastly, Interleukin-18, a cytokine promoting inflammation, is associated with pre-renal and intra-renal causes of AKI and has demonstrated better results in children rather than adults.

Incorporating these molecules into clinical practice, especially NGAL, offers the clinicians early detection tools, aiding in AKI diagnosis and management. To fully explore their potential in improving clinical results and possibly preventing the progression to chronic kidney disease, future research must focus most importantly on evaluating the accuracy and function of these biomarkers in AKI patients with various existing comorbidities, as well as establishing lab-standardized threshold values.

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