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Biomarkers for early detection and predicting outcomes in acute kidney injury

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Abstract

The current diagnosis of acute kidney injury relies on the measurement of serum creatinine levels and urine output. However, both measures are subject to considerable limitations; for example, change in serum creatinine levels ideally requires a knowledge of baseline function that is often not available. Furthermore, creatinine levels are influenced by many factors including diet, drug therapy, muscle mass, gender and ethnicity, which may lead to underestimation of the extent of renal dysfunction. Similarly, urine output lacks both specificity and sensitivity as a marker of acute kidney injury given that oliguria may be an appropriate physiological response to a multitude of stressors and that output may be maintained until significant renal damage has already occurred.

Given the well-documented consequences of acute kidney injury and the considerable burden associated with its development, much attention has focused on early identification of patients at high risk to try and improve outcomes. Many studies have focused on the identification of candidate molecules that may enable the early detection of individuals at risk of developing acute kidney injury, including constitutive proteins associated with kidney damage, as well as molecules upregulated in response to injury, non-renal products that may be filtered, reabsorbed or secreted by the kidney, and markers of renal stress. Such biomarkers may also aid stratification for adverse events, such as the need for kidney replacement therapy or progression to chronic kidney disease and end-stage kidney disease. This article discusses some of these novel biomarkers and assesses the role they may have in the understanding, management, diagnosis and prognostication of acute kidney injury.

Key words: Acute kidney injury; Biomarkers; Kidney replacement therapy

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Introduction

Acute kidney injury is characterised by an abrupt reduction in kidney function resulting in the accumulation of urea and other renally excreted waste metabolites together with dysregulation of fluid and electrolyte balance. The Kidney Disease Improving Global Outcomes (KDIGO) guidelines define acute kidney injury as an increase in serum creatinine levels by ≥0.3 mg/dl (26.5 µmol/litre) within 48 hours, an increase in serum creatinine levels to ≥1.5x baseline within 7 days or a urine volume <0.5 ml/kg/hour for 6 hours (Khwaja, 2012); this definition evolved from the RIFLE (Risk, Injury, Failure, Loss, End stage kidney disease) criteria and the Acute Kidney Injury Network (AKIN) modification. Acute kidney injury is common, complicating around 20% of hospital admissions worldwide, and is associated with a 21% mortality, which rises to 42% in those with KDIGO stage 3 acute kidney injury and 46% in those requiring renal replacement therapy (Mehta et al, 2015). In the UK, up to 100 000 deaths per year are associated with acute kidney injury, with 30% of these felt to be preventable (National Confidential Enquiry into Patient Outcome and Death, 2009; UK Renal Registry, 2020). The costs to the NHS are estimated at anywhere between £434 million and £1.02 billion annually (Kerr et al, 2014; UK Renal Registry, 2020).

Current definitions and clinical diagnosis of acute kidney injury rely on the measurement of serum creatinine levels and urine output, both of which have significant limitations (Figure 1). Serum creatinine levels are influenced by many factors, including diet, drug therapy, muscle mass, gender and ethnicity, as well as the volume of distribution, which may reduce serum creatinine levels and lead to the underestimation of renal dysfunction in acute illness (Macedo et al, 2010). Serum creatinine level is poorly sensitive when detecting

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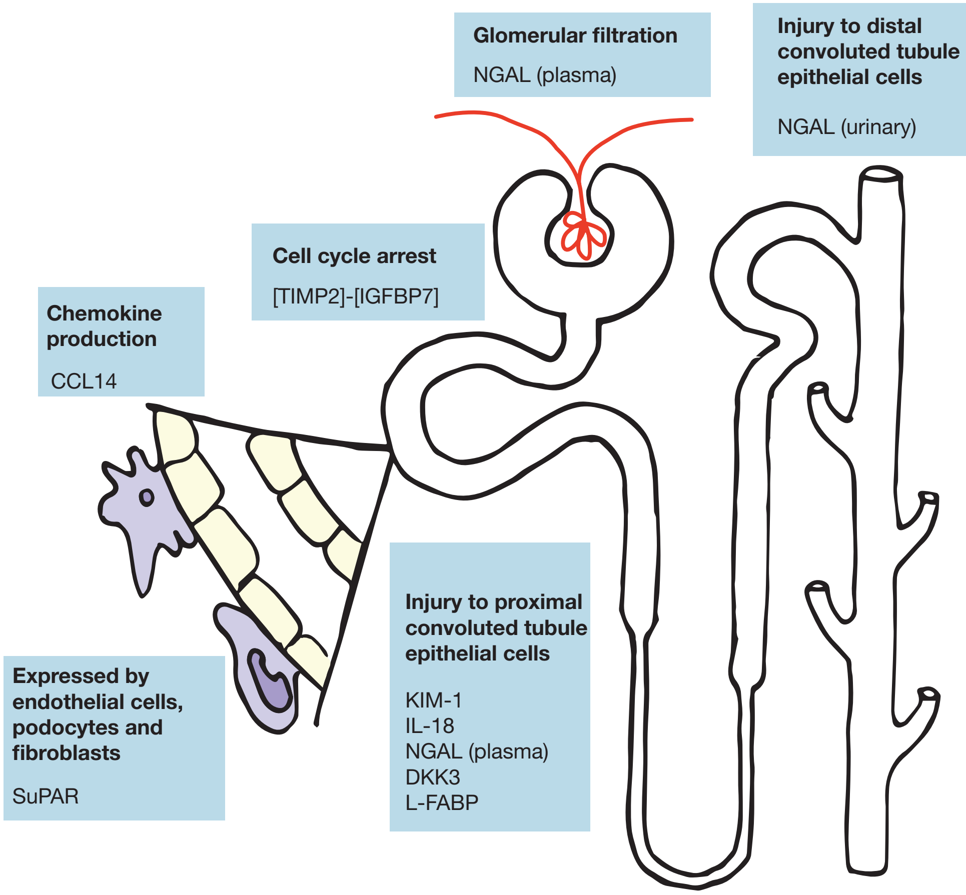

Figure 1. Biomarkers discussed in this article including potential sites of release from the renal tubule. CCL14 = C-C motif chemokine ligand 14; DKK-3 = dickkopf-3; IGFBP-7 = insulin-like growth factor-binding protein 7; IL-18 = interleukin-18; KIM-1 = kidney injury molecule 1; L-FABP = liver-type fatty acid binding protein; NGAL = neutrophil gelatinase-associated lipocalin; SuPAR = soluble urokinase plasminogen activator receptor; TIMP-2 = tissue inhibitor of metalloproteinases-2. .

acute kidney injury – up to 50% of functioning nephrons can be lost before a change in creatinine level is detectable and it may take 24–36 hours from a renal insult for levels to reach a new steady state. Moreover, a significant rise in creatinine levels in a patient with normal baseline kidney function may represent a significant drop in glomerular filtration rate, whereas the same increase in a patient with underlying chronic kidney disease may represent daily variation with non-clinically significant changes in glomerular filtration rate. Urine output also lacks specificity and sensitivity as a marker of acute kidney injury. Urine output may be maintained until significant renal damage has already occurred, while conversely oliguria may be an appropriate physiological response to a multitude of stressors, with increased antidiuretic hormone secretion and the generation of low volume, high concentration urine.

Despite these drawbacks, creatinine has remained a mainstay in the assessment of renal function for the last half century. This is in stark contrast to, for example cardiology, where since the 1960s there has been a stepwise improvement in the performance of biomarkers associated with acute coronary syndrome. Over recent years there has been increasing interest in novel biomarkers associated with the development of acute kidney injury, predominantly focusing on earlier detection and diagnosis. This includes severity prediction and risk stratification for adverse events such as the need for kidney replacement therapy or progression to chronic kidney disease and end-stage kidney disease, as well as differentiating the causes and pathophysiology of acute kidney injury. This article examines the evidence behind some of these biomarkers and assesses the role they may have in furthering the understanding, management, diagnosis and prognostication of acute kidney injury (Table 1).

Table 1. Biomarkers associated with acute kidney injury and potential role		
	Potential role	
Biomarker	Early detection of acute kidney injury	Predicting outcomes of acute kidney injury
Kidney injury molecule 1	✓	✓
Interleukin-18		✓
Liver-type fatty acid binding protein	✓	✓
Soluble urokinase plasminogen activator receptor		✓
Urinary neutrophil gelatinase-associated lipocalin	✓	✓
TIMP-2 IGFBP-7	✓	✓
Urinary C-C motif chemokine ligand 14		✓
Dickkopf-3	✓	✓

IGFBP-7 = insulin-like growth factor-binding protein 7; TIMP-2 = tissue inhibitor of metalloproteinases-2

Kidney injury molecule 1

Description

Kidney injury molecule 1 (KIM-1) is a type 1 transmembrane glycoprotein expressed by the cells of the proximal convoluted tubule. Expression is markedly upregulated in ischaemic injury and acute tubular necrosis, and the ectodomain is shed into the urine and detectable via immunoassay.

Clinical studies

KIM-1 has potential utility in differentiating acute tubular necrosis from other causes of acute kidney injury and from chronic kidney disease, with increased levels associated with a 12-fold increase in risk for the presence of acute tubular necrosis in one study, albeit in only 38 patients (Han et al, 2002). The ability of KIM-1 to predict and diagnose acute kidney injury associated with cardiac surgery has been explored. A case control study of 40 paediatric patients undergoing cardiac surgery showed elevation in KIM-1 levels between 6 and 48 hours post bypass in patients who developed acute kidney injury, with an area under the receiver operating curve of 0.83 at 12 hours and 0.78 at 24 hours (Han et al, 2008). In a further study assessing the ability of urinary biomarkers to predict acute kidney injury progression post cardiac surgery, KIM-1 was a relatively good predictor of progression of acute kidney injury or death. The combination of KIM-1 and interleukin-18 (IL-18) had an area under the receiver operator curve of 0.93 for the prediction of AKIN 3 and death, although KIM-1 correlated poorly with other biomarkers (Arthur et al, 2014). Studies have also suggested a role for KIM-1 as a preoperative predictor of the development of acute kidney injury post-cardiac surgery (Koyner et al, 2010). A 15-minute semi-quantitative rapid dipstick test has been developed for the detection of urinary KIM-1 – its developers demonstrated higher detected levels of KIM-1 in patients with acute kidney injury than in healthy volunteers (Vaidya et al, 2009). KIM-1 may have a role in the prediction, diagnosis and assessment of severity of acute kidney injury, but its clinical utility is likely to be increased via combination with other biomarkers.

Interleukin-18

Description

IL-18 (also known as interferon-gamma inducing factor) is a 24 kDa pro-inflammatory cytokine, part of the IL-1 superfamily. It is produced by monocytes and macrophages, as well as proximal tubular epithelial cells. Following processing by the intracellular cysteine protease caspase-1, the active cytokine is secreted and is detectable in the urine via enzyme-linked immunosorbent assay (ELISA), with elevated levels seen from 6 hours and peaking at 12–18 hours after induction.

Clinical studies

IL-18 has been implicated as a mediator of renal ischaemic reperfusion injury, with elevated urinary levels demonstrated in patients with acute tubular necrosis and delayed cadaveric renal allograft function (Parikh et al, 2004). However, studies in a variety of clinical settings, including critical care, cardiac surgery and post-transplantation, show mixed results. For example, in a study of 1439 critically ill patients, IL-18 only had a poor to moderate ability to predict acute kidney injury, requirement for kidney replacement therapy and 90-day mortality (Nisula et al, 2015), whereas it has demonstrated potential in predicting the progression of acute kidney injury post-cardiac surgery, especially when combined with KIM-1 (Arthur et al, 2014). A systematic review and meta-analysis concluded that IL-18 showed promise as a biomarker for acute kidney injury, but it has only moderate diagnostic value, with conclusions limited by the heterogeneity of included studies (Lin et al, 2015).

The value of IL-18 is likely to increase when combined with other biomarkers. There is also interest in IL-18 as a potential therapeutic target – pre-treatment with IL-18 binding protein before ischaemic reperfusion injury has shown renoprotective effects in animal models (Wu et al, 2008).

Urinary liver-type fatty acid binding protein

Description

Liver-type fatty acid binding protein (L-FABP) is a 14 kDa lipid-binding protein expressed in the liver, intestine, stomach, lung and predominantly proximal convoluted tubule of the kidney. It binds and transports long-chain and very long-chain fatty acids, and also seems to serve a protective role with marked upregulation in response to hypoxia. L-FABP is excreted into the tubular lumen alongside toxic peroxisomal products, with levels correlating with the degree of tubular injury, and is detectable in urine via ELISA.

Clinical studies

A meta-analysis of seven hospital-based cohort studies found that L-FABP could discriminate and diagnose acute kidney injury with an estimated sensitivity and specificity of 74.5% and 77.6% respectively and predict in-hospital mortality with a sensitivity and specificity of 93.2% and 78.8%, but performance in predicting dialysis requirement was poor with only 69.1% and 42.7% sensitivity and specificity (Susantitaphong et al, 2013). It has been proposed to have some utility in predicting the development of acute kidney injury, even before an ischaemic insult, with elevated baseline levels on admission to intensive care (Doi et al, 2011), before administration of intravenous contrast (Nakamura et al, 2006) and before allogenic stem cell transplantation (Shingai et al, 2014), all associated with the development of acute kidney injury. L-FABP has also been investigated as a potential therapeutic target – fibrates act as peroxisome proliferator-activated receptors-α agonists, which leads to the upregulation of L-FABP gene expression. However, in observational studies, use of fibrates appears to be associated with an increased risk of acute kidney injury (Attridge et al, 2013). L-FABP is currently approved for clinical use in Japan.

Soluble urokinase plasminogen activator receptor

Description

This glycosyl-phosphatidylinositol linked protein urokinase is the soluble form of the urokinase-type plasminogen activator receptor. Its membrane-bound form is expressed by cells including endothelial cells, podocytes and fibroblasts, with inducible expression by monocytes and activated T-cells, while its soluble form is detectable in blood, urine and CSF. It has been identified as a marker and driver of injury in podocyte and proximal tubular cells via binding and activation of αvβ3 integrins and triggering of increased mitochondrial metabolism and, therefore, increased oxidative stress.

Clinical studies

Raised levels of soluble urokinase plasminogen activator receptor are predictive of both development and progression of chronic kidney disease in a number of cohorts (Luo et al, 2018; Hayek et al, 2019), as well as those at risk of developing acute kidney injury in the absence of pre-existing chronic kidney disease (Mossanen et al, 2017; Hayek et al, 2020). It has also been studied as both a marker and potential therapeutic target in patients with glomerular disease; for example elevated levels have been found in patients with focal segmental glomerulosclerosis (Wei et al, 2011), with plasmapheresis and reduction of soluble urokinase plasminogen activator receptor levels associated with the stabilisation of recurrent disease.

The utility of soluble urokinase plasminogen activator receptor may be limited by its lack of specificity – levels are also elevated in conditions such as sepsis, malignancy, diabetes and cardiovascular disease. Despite its lack of specificity, it has shown promise as a general prognostic marker in critically unwell patients with sepsis (Backes et al, 2012).

Neutrophil gelatinase-associated lipopcalin

Description

Neutrophil gelatinase-associated lipocalin is a protein that has been identified at low levels in multiple human tissues. It is found at much higher levels in damaged epithelial cells of the kidney and is released into the urine following ischaemic or nephrotoxic insults. It has a known role in iron transport and is thought to have a bacteriostatic effect in infection, as well as a role in upregulating growth hormone that is hypothesised to contribute to renal repair in acute kidney injury. Its use as a biomarker for predicting acute kidney injury has been investigated in multiple different studies, most of which are small single centre studies.

Clinical studies

Mishra et al (2005) focused on cardiac surgery in children and looked at neutrophil gelatinase-associated lipocalin as a predictor of development of acute kidney injury. Promising results showed that urinary neutrophil gelatinase-associated lipocalin levels could predict the development of acute kidney injury, rising just 2 hours after cardiopulmonary bypass, compared to serum creatinine levels rising 24 hours after surgery. Further studies in children have reliably confirmed these findings. Subsequent studies in adults, on both cardiac and general intensive care units, have not been as clear cut, with area under the receiver operator curve curves varying between 0.98 and 0.6 (Makris et al, 2009).

Various hypotheses have been proposed to address the discrepancies between studies, including the presence of chronic kidney disease, differences in storage and timing of samples, the presence of systemic inflammation and, particularly, increasing age. Further evidence pointing to the presence of confounding factors in systemic illness comes from studies in the emergency department (Nickolas et al, 2008) showing that urinary neutrophil gelatinase-associated lipocalin correlated with the presence of sustained acute kidney injury with a specificity of 0.995 and a sensitivity of 0.9. Only 6.1% of these patients were admitted to intensive care. This is in contrast to an emergency department study on neutrophil gelatinase-associated lipocalin predicting acute kidney injury in suspected septic patients that showed a sensitivity of 0.96 but a specificity of only 0.51 (Shapiro et al, 2010). A 2009 meta-analysis of available data showed that neutrophil gelatinase-associated lipocalin appears to be of moderate prognostic value in predicting acute kidney injury post cardiac surgery and in critically ill patients when compared to an increase in serum creatinine level to >50% from baseline, with an overall area under the receiver operator curve value of 0.78 (Haase et al, 2009).

The use of neutrophil gelatinase-associated lipocalin to predict the presence of acute kidney injury has also been investigated in patients with kidney transplants (Hall et al, 2010), liver transplants (Niemann et al, 2009) and as a predictor of contrast-induced nephropathy (Ling et al, 2008). Performance of neutrophil gelatinase-associated lipocalin as a predictive biomarker is improved in patients with predictable onset and cause of acute kidney injury, such as in cardiopulmonary bypass surgery. An observational study in Thailand demonstrated an association between urinary neutrophil gelatinase-associated lipocalin levels and persistence of acute kidney injury, as well as the development of major kidney events at 30 days, such as kidney replacement therapy, persistence of renal dysfunction and death (Lumlertgul et al, 2020). Further studies in intensive care have also demonstrated its usefulness in predicting need for kidney replacement therapy in these patients (Cruz et al, 2010).

To date, the detection of urinary neutrophil gelatinase-associated lipocalin is associated with the development of acute kidney injury, and levels have been shown to correlate with the severity of acute kidney injury. However, its use in isolation is unpredictable because of its low specificity in settings where acute kidney injury is common, such as in the adult intensive care unit and in patients with sepsis.

Tissue inhibitor of metalloproteinases-2 and insulin-like growth factor-binding protein 7

Description

Tissue inhibitor of metalloproteinases-2 (TIMP2) and insulin-like growth factor-binding protein 7 (IGFBP7) are molecules excreted by the renal tubular epithelium during the G_1 cell cycle arrest pathway acting in a paracrine fashion and, as such, are thought to signal ‘renal stress’. This pathway has been implicated in the pathogenesis of acute kidney injury caused by both ischaemic and septic injury to the renal tubules.

Clinical studies

Having been identified as promising biomarkers for the prediction of acute kidney injury, the performance of TIMP2 and IGFBP7 was assessed in the Sapphire study (Kashani et al, 2013). This multicentre trial enrolled critically unwell patients over 21 years of age who were expected to remain in intensive care for at least 48 hours. Paired urine and blood samples were taken at 0 and 18 hours. The primary endpoint was the development of acute kidney injury stage 2 or 3 within 12 hours of sample collection. Secondary endpoints included major adverse kidney events at day 30. [TIMP2]-[IGFBP7] had an area under the receiver operator curve of 0.8 for the development of acute kidney injury stage 2 or 3 within 12 hours, with a clear separation in those who did and did not develop acute kidney injury, unlike urinary neutrophil gelatinase-associated lipocalin and urinary KIM-1, which did not show the same separation. High levels of [TIMP2]-[IGFBP7] were also strongly associated with increased risk of major adverse kidney events at day 30. [TIMP2]-[IGFBP7] also improved prediction of acute kidney injury when added to a 9-parameter clinical model for the prediction of acute kidney injury.

Following the Sapphire study, the Opal (Hoste et al, 2014) and Topaz (Bihorac et al, 2014) study went on to further validate the cut-off value and predictive ability of [TIMP2]-[IGFBP7] in predicting the development of acute kidney injury. In 2014, the Food and Drug Administration approved its use as a commercial biomarker in the form of Nephrocheck.

Further studies have identified that [TIMP2]-[IGFBP7] can be used to accurately predict the development of acute kidney injury in patients undergoing high-risk (Gunnerson et al, 2016) and cardiac surgery (Su et al, 2018), as well as sepsis (Honore et al, 2016). The use of [TIMP2]-[IGFBP7] to predict acute kidney injury in sepsis is particularly important as, compared to urinary neutrophil gelatinase-associated lipocalin and IL-18, its predictive ability was not affected by non-renal organ dysfunction, giving it a more favourable profile in this setting that is prone to confounding factors. Two trials have looked at the use of a biomarker-triggered acute kidney injury care bundle in clinical practice, with reduced rates of acute kidney injury observed (Meersch et al, 2017; Göcze et al, 2018). However, testing is costly compared to serum creatinine testing and not widely available on platform testing. Studies are awaited to demonstrate cost saving that may then translate into widespread adoption (National Institute for Health and Care Excellence, 2020).

Urinary C-C motif chemokine ligand 14

Description

C-C motif chemokine ligand 14 (CCL14) is a chemokine that was originally identified in the haemofiltrate of patients with chronic renal failure. Chemokines have a recognised role in the inflammatory response and act to recruit leucocytes. Their production in the kidney is increased in patients with acute kidney injury. CCL14 primarily recruits monocytes through CCR1, CCR3 and CCR5. Monocytes play a role in both renal injury and renal repair by differentiating into macrophages of different subsets. Kidney biopsies have identified the presence of macrophage infiltration of the glomerulus and the interstitium in varied causes of acute kidney injury. There is evidence that the degree of macrophage infiltration correlates with the severity of acute kidney injury.

Clinical studies

The RUBY study is a multicentre international prospective observational study that evaluated biomarkers associated with the persistence of acute kidney injury stage 3 (>72 hours). It found that urinary CCL14 was the biomarker most predictive of the persistence of acute kidney injury stage 3, which is associated with an increased risk of developing chronic kidney disease (Chawla et al, 2017).

Dickkopf-3

Description

The Wnt/B-catenin pathway is a signalling pathway that was initially identified during embryogenic kidney development. Transient activation of the pathway occurs during the repair and regeneration phase of acute kidney injury, whereas more sustained activity has been implicated in the development of kidney fibrosis and chronic kidney disease. Dickkopf-3 (DKK3) is a glycoprotein that is involved in the modulation of this pathway and has been found in the urine following renal tubular stress and injury.

Clinical studies

Zewinger et al (2018) showed that higher levels of DKK3 are found in patients with chronic kidney disease and albuminuria, as well as being associated with rapid progression of chronic kidney disease. A further study demonstrated that DKK3 levels are higher at baseline in patients who go on to develop acute kidney injury post-cardiac surgery, perhaps indicating that elevated levels of urinary DKK3 can be used to predict the development of acute kidney injury (Schunk et al, 2019). Furthermore, elevated urinary DKK3 levels were associated with persistent renal dysfunction following the development of acute kidney injury post-cardiac surgery.

A smaller study looked at the predictive value of urinary DKK3 levels before coronary angiography in those who developed acute kidney injury. Although only a small number of patients went on to develop acute kidney injury and the results were not as prognostically accurate, urinary DKK3 levels at baseline were raised in those with a very modest rise (AKIN stage 1) in creatinine levels (Seibert et al, 2021).

Early studies of DKK3 as a novel acute kidney injury prediction biomarker are encouraging. The concept of a biomarker that predicts acute kidney injury before the ‘insult’, as well as kidney disease progression, is one that warrants further study.

Clinical implications

Currently, acute kidney injury is defined by the KDIGO consensus criteria that uses a rise in serum creatinine levels and/or a period of oliguria as the parameters by which acute kidney injury is judged to have occurred. These imperfect functional markers may lead to inaccuracies in acute kidney injury estimation for the reasons discussed. Furthermore, the ‘diagnosis’ of acute kidney injury based on markers of function gives no information as to the underlying pathophysiology or cause. In the critically ill patient, acute kidney injury often has multifactorial causes, but the lack of insight into the principal aetiology of the acute kidney injury will no doubt hinder studies directed at prevention or treatment of acute kidney injury given the lack of specificity.

To date, no single biomarker has been proven to be consistently superior across a range of clinical scenarios, although the accrual of evidence may help with this. Alternatively, more diagnostic information may be determined from adoption of a panel of biomarkers that are elevated under different conditions (Figure 1). For example, TIMP-2-IGFBP-7 (markers of renal stress) in combination with markers of persistent acute kidney injury and markers of tubular damage may enable phenotyping of patients with acute kidney injury.

The presence of a predictive biomarker or biomarker panel, suggestive of an underlying cause of acute kidney injury, would allow early identification of acute kidney injury and targetting management to the underlying cause, aimed at preventing acute kidney injury. The addition of biomarkers into the classification of acute kidney injury has been proposed; this is particularly relevant in individuals who demonstrate biomarker positivity without reaching the acute kidney injury thresholds, so called sub-clinical acute kidney injury, who demonstrate worse long-term outcomes than individuals who are biomarker negative. This could prove particularly useful in both community-acquired and hospital-acquired acute kidney injury, allowing timely recognition and targeted intervention before the development of acute kidney injury.

The ability to predict outcomes for patients who develop acute kidney injury secondary to critical illness, such as sepsis or cardiothoracic surgery, would have cost and resource implications, including de-escalation of therapy and treatment. This is particularly relevant in terms of the development of chronic kidney disease and timing, need and dependence of kidney replacement therapy. Table 1 illustrates where the biomarkers described might be incorporated into the diagnostic and prognostic pathway.

The 'liquid renal biopsy' may translate into improved outcomes through targeted prevention and/or directed treatment regimens. Although this is currently limited by both costs and lack of evidence, this may change and be driven by the development of potential therapeutic agents, including the use of cell-based therapies as well as repurposing older drugs to treat acute kidney injury.

Conclusions

Acute kidney injury is a frequently occurring complication of acute illness associated with considerable prognostic implications. Prompt identification and optimisation aims to reduce morbidity and mortality. Current definitions use functional markers but ultimately, acute kidney injury may be defined through more sensitive and specific measures based on biomarkers, which will hopefully translate into improved outcomes for patients with acute kidney injury. Many candidate molecules have been proposed, a few of which have been discussed here, but as yet no one biomarker has proved to be better than others over a range of conditions leading to acute kidney injury. The phenotypical classification of different types of acute kidney injury related to cause may be enhanced by the addition of biomarkers coupled with advanced prediction modelling, which may well be the route to progress in this condition.

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Conflicts of interest

Professor LG Forni has received grant support and honoraria from Baxter and Ortho Clinical Diagnostics, honoraria for lectures from Biomerieux, Exthera, Paion and La Jolla Pharmaceuticals; Drs D Cottam and G Azzopardi declare that they have no conflicts of interest.

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Key points

- Acute kidney injury commonly complicates acute illness and is associated with increased morbidity and mortality, and associated healthcare costs.
- The current definition of acute kidney injury relies on the functional markers of serum creatinine levels and urine output, both of which are subject to considerable confounders in acute illness.
- Much effort has been directed at the identification of biomarkers associated with the development of acute kidney injury, but no single biomarker has been proven to be universally superior.
- Recent proposals for the definition of acute kidney injury include the use of biomarkers and/or a panel of biomarkers, coupled with advanced modelling techniques, to predict patients in the early stage of acute kidney injury, as well as those at highest risk.

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