Advances in the Management of Acute Cardiorenal Syndrome in China: Biomarkers for Predicting Development and Outcomes

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Key Words

Acute cardiorenal syndrome · Acute kidney injury · Angiotensinogen · Biomarker · Prediction

Abstract

Background: Acute cardiorenal syndrome (CRS) is a common clinical condition associated with adverse outcomes. Early identification of acute kidney injury in this setting remains challenging given that serum creatinine level is a marker of renal function and not kidney injury. **Summary:** Several renal injury-related molecules are now available, which may help elucidate the complexities of the organ crosstalk, enabling more accurate risk stratification and effective interventions. **Key Messages:** This review highlights the major studies that have characterized the diagnostic and prognostic predictive power of these biomarkers with reference to acute CRS. Although more research is needed, the current results are very promising.

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Introduction

Renal and cardiac diseases frequently coexist. The clinical entity of the cardiorenal syndrome (CRS), which encompasses patients with heart failure, is the most commonly encountered clinical scenario that exemplifies the interaction between the heart and the kidney. A five-sub-type classification of CRS has been proposed: type 1 = acute heart failure resulting in acute kidney injury (AKI); type 2 = chronic cardiac dysfunction causing progressive chronic kidney disease (CKD); type 3 = an abrupt and primary worsening of kidney function causing acute cardiac dysfunction; type 4 = primary CKD contributing to cardiac dysfunction, and type 5 = acute or chronic systemic disorders that cause both cardiac and renal dysfunction [1].

Patients with acute decompensated heart failure (ADHF) often develop worsening renal function (WRF) in the course of the disease, which is termed ‘acute or type 1 CRS’ [2]. Acute CRS occurs in 25–40% of patients admitted with ADHF in Europe and the United States and in 32–44% of patients in China, depending on the criteria used [3–5].

The relevance of the kidney in heart failure is obvious, as it serves as the regulator of fluid and sodium balance.

For Cardiorenal Syndrome in Western Countries, see Ronco and Di Lullo, Kidney Dis 2016;2:151–163.

Renal dysfunction is central to the development of volume retention, which is a hallmark of the heart failure syndrome [6]. Thus, it is not surprising that AKI or WRF has repeatedly been demonstrated to be one of the strongest predictors of adverse outcomes in ADHF patients [7, 8]. The annual mortality rates for ADHF are 26% in patients without renal injury, 41% in patients with any impairment of renal function, and 51% in those with moderate-to-severe renal dysfunction [9].

Despite widespread recognition of the importance of acute CRS, progress toward an understanding of this syndrome has remained a challenge [3]. The bidirectional interaction between the heart and the kidney is complex with proposed mechanisms ranging from hemodynamic change, endothelial dysfunction, and neurohormonal activation to dysregulation of salt and water balance [1, 10]. Renal dysfunction can result from irreversible nephron loss secondary to preexisting CKD, or it can be induced by heart failure itself. Furthermore, there is evidence that heart failure is associated with structural damage in both organs leading to a worse prognosis [11]. It is, therefore, not surprising in the face of these challenges that the majority of cardiorenal trials have been disappointingly negative [12–15].

However, renal injury biomarkers have the potential to inform some of the intricacies involved in assessing cardiorenal interactions and provide opportunities to overcome these challenges. The novel biomarkers for CRS can help to early detect AKI and predict the prognosis in the setting of ADHF.

Biomarkers for Predicting Development of AKI in Acute CRS

ADHF is one of the major causes of acute CRS. A major barrier to improving the clinical outcomes in such patients is the difficulty in identifying those at high risk of AKI early enough to initiate beneficial interventions. It is well recognized that serum creatinine is not an early marker of renal injury, as AKI heralded by a rise in serum creatinine cannot be diagnosed until 24–48 h after the initial insult. The use of biomarkers to aid in the early detection of AKI or WRF has emerged as an area of increasing scientific interest.

Neutrophil gelatinase-associated lipocalin (NGAL) is a 25-kDa transport protein expressed by neutrophils and epithelial cells, including those in the proximal convoluted tubule [16]. NGAL is detected in human blood and urine at the earliest stage of AKI, 48–72 h before the rise

in creatinine. Although the role of NGAL in detecting AKI early has been shown in adults across all settings [17], only small-scale clinical studies have tested the utility of this biomarker in predicting acute CRS and have gained inconsistent results. In one study, 91 patients with ADHF and serum NGAL >140 ng/ml at hospital admission had a 7.4-times higher likelihood of developing WRF [17]. Another study reported a similar relationship using a cutoff for serum NGAL >170 ng/ml, resulting in an area under the receiver operating characteristic curve (AUC) for WRF of 0.93 [18]. A prospective observational study of ADHF also demonstrated that admission NGAL >89 ng/ml predicted AKI with an AUC of 0.71 [19]. Urinary NGAL was associated with AKI, albeit less powerfully (AUC = 0.78), in our prospective cohort of 317 patients admitted with ADHF [20]. A recent study reported that serial measurements of serum NGAL in ADHF seem to improve its performance for predicting WRF, where the degree of change in NGAL from baseline to peak yields an AUC for WRF of 0.91 as compared to admission NGAL alone (AUC = 0.69) [21]. Results reported to date, however, are by no means conclusive. In a cohort of 207 patients with acute heart failure, although an elevated plasma NGAL level predicted the occurrence of AKI in a univariate analysis, it was not an independent predictor of AKI after controlling for preexisting chronic cardiac or kidney disease in a multivariate analysis [22]. Similar results have been observed in other studies, where NGAL levels were not associated with changes in renal function in the setting of heart failure [23, 24]. Interestingly, a recent study found that the performance of urinary NGAL for predicting AKI was modified by the baseline renal function [25]. The circulating NGAL levels may also be influenced by various extrarenal factors such as infectious disease and anemia [26, 27]. Further research is necessary to understand these findings and to determine whether appropriate stratification based on characteristics of patients would improve the predictive performance of NGAL for acute CRS.

Increasing evidence has revealed that the intrarenal renin-angiotensin system (RAS) plays a vital role in maintaining hemodynamic balance and cardiorenal interaction, which are often disrupted in patients with ADHF [28]. Intrarenal angiotensinogen (AGT), a principal substrate of the local RAS, is mainly formed in proximal tubule cells. The urinary AGT level has been shown to be an indicator of intrarenal RAS activity in both animal and clinical studies [29]. We have recently reported an excellent performance of urinary AGT for the early prediction

of AKI in a prospective, two-stage, multicenter cohort study in 436 patients with ADHF [20]. In patients with the highest quartile of urinary AGT ($>148 \mu\text{g/gCr}$) on admission, the risk for development of AKI increased 50-fold compared to those with the lowest quartile of urinary AGT ($<10 \mu\text{g/gCr}$). For the prediction of AKI, urinary AGT (AUC = 0.84) outperformed urinary NGAL (AUC = 0.78), urinary albumin/creatinine ratio (AUC = 0.71), and the clinical risk model (AUC = 0.77) in this study. Interestingly, urinary AGT levels are associated with incident AKI in patients both with and without pre-existing CKD. In contrast with urinary NGAL, which best identifies AKI in patients with an estimated glomerular filtration rate (eGFR) in the range of 90 to 120 ml/min [25], the predictive performance of urinary AGT is better in individuals with an eGFR <60 ml/min. This unique characteristic of urinary AGT makes it a useful predictor of AKI, in particular among those with acute-on-chronic renal injury, which accounts for 30–45% of WRF in ADHF [4, 30].

Other renal injury biomarkers have been tested in CRS. N-acetyl- β -D-glucosaminidase (NAG), a large lysosomal enzyme originating in proximal tubular cells, is indicative of tubular injury when detected in the urine [31]. Elevated NAG is associated with congestion as tested by brain natriuretic peptide (BNP) and atrial natriuretic peptide and decreases in response to diuretic-induced decongestion [32]. Although baseline NAG was predictive of WRF in the GISSI-HF trial in a univariate analysis, it lost statistical significance after covariates adjustment [33]. Furthermore, although elevated urinary NAG was correlated with tubular injury, it was not specific for CRS, as it also increased in patients with diabetes and hypertension [33].

Interleukin-18 (IL-18) is a cytokine that is produced in mononuclear cells, macrophages, and nonimmune cells. In the kidney, IL-18 is produced and released from the proximal tubule epithelial cells within hours of kidney injury [34]. In heart failure, there have been few studies examining IL-18. In a cohort of 83 patients admitted for ADHF, IL-18 was only modestly correlated with other kidney injury biomarkers and, when adjusted for urine creatinine, showed no correlation with eGFR [35].

Kidney injury molecule-1 (KIM-1) is a type I cell membrane glycoprotein expressed in regenerating proximal tubular cells. Urinary KIM-1 levels are elevated depending on the severity of heart failure [36]. However, KIM-1 levels are only slightly elevated on hospital admission in ADHF and do not predict subsequent AKI [35].

Biomarkers for Predicting Progression of AKI in Acute CRS

Although most patients who develop acute CRS experience a mild form of AKI (e.g. KDIGO/AKIN stage 1 or RIFLE R) and do not progress to more severe AKI (KDIGO/AKIN stage 2/3 or RIFLE F) or do not require dialysis, approximately 29–48% of these patients progress to a higher stage of AKI [37, 38]. Recent studies have demonstrated that the risk of mortality exponentially increases with increasing stages of AKI in ADHF [39]. Early detection of patients at a higher risk for AKI progression would help physicians to plan and initiate the appropriate managements to improve the renal safety of therapies, augment surveillance of cardiac and renal dysfunction, and develop renal-preserving treatments [40, 41].

Unfortunately, predicting which CRS patient will suffer progressive AKI is clinically challenging. In patients with ADHF, fluid retention, low protein intake, and decreased creatinine production secondary to muscle atrophy may dissociate creatinine levels from reflecting the true severity of renal dysfunction. Diagnostic mainstays such as the fractional excretion of sodium and urea have been shown to be suboptimal [42–46]. Assessment of biomarkers for renal tubular injury at the time of creatinine-based diagnosis of AKI offers information on the progression of AKI in multiple settings such as cardiac surgery, intensive care unit, transplantation, and cirrhosis [47–52].

In patients with AKI after cardiac surgery and in the intensive care unit, elevated urinary AGT is associated with progression to higher stages of AKI [49, 53]. In a recent prospective multicenter study of acute CRS, we evaluated the performance of 6 renal injury biomarkers measured at the time of AKI diagnosis for predicting progression of AKI in 213 patients who developed KDIGO stage 1 or 2 AKI [54]. The progression of AKI was defined as worsening of AKI stage. In this study, increase in serum creatinine, the current hallmark for recognizing AKI, was not associated with the risk of AKI progression. However, there was a clear correlation between levels of urinary AGT, NGAL, and IL-18 and the risk of AKI progression after multivariable adjustment. Critically, these renal injury biomarkers, especially urinary AGT, showed a large effect size (category-free net reclassification improvement >0.6) to improve the risk classification for AKI progression and AKI progression with subsequent death beyond the clinical model alone, suggesting that urinary AGT, NGAL, and IL-18 measurement at the time of AKI diagnosis forecasted the progression of AKI in ADHF. This study did not find any benefit of plasma NGAL, uri-

nary KIM-1, and urinary albumin/creatinine ratio measurements for predicting AKI progression in multivariable analysis, although prior reports have shown that these biomarkers may predict worsening of AKI in other clinical settings [47, 48].

Biomarkers for Predicting Outcomes in Acute CRS

In patients with ADHF, the presence of coexistent renal insufficiency portends a grave prognosis. In addition to an increase in the risk of mortality, AKI superimposed on CKD accelerates CKD progression. AKI is associated with an increased risk of end-stage renal disease [55, 56].

The ability of NGAL to predict outcomes has been examined in acute CRS. In a multicenter prospective study of ADHF, elevated plasma NGAL at the time of discharge was a strong prognostic indicator of 30-day outcomes (all-cause mortality and readmissions for acute heart failure) [57]. In a cohort of 231 patients with acute heart failure, admission NGAL >170 ng/ml was associated with increased mortality during a 6-month follow-up period with an AUC of 0.77 [58].

NGAL also may have a role in the chronic aspects of the CRS. A study reported that both serum and urinary NGAL independently predicted CKD progression which was defined by a doubling of serum creatinine or occurrence of end-stage renal disease [55, 56]. These findings suggest that NGAL could be used to identify patients who are at high risk for adverse outcomes and could help in the risk stratification for acute CRS.

Urinary AGT has been recently described as a novel prognostic biomarker of AKI. Increase in urinary AGT is associated with adverse outcomes, such as increased length of hospital stay, requirement for renal replacement therapy, and death [49, 53]. In our recent study of 317 patients with ADHF, a level of urinary AGT ≥ 55 $\mu\text{g/gCr}$ on admission was associated with a significantly increased probability of all-cause mortality (HR 4.7; 95% CI 2.7–8.2) and rehospitalization (HR 3.7; 95% CI 2.2–6.6) over the 1-year follow-up period. Interestingly, we recently found that elevated urinary AGT during acute CRS predicts the transition from acute to chronic renal injury, suggesting that increased intrarenal AGT during AKI may promote the progression of AKI to CKD.

Further studies have examined the role of other biomarkers in predicting outcomes of acute CRS. Although IL-18 does not predict WRF during hospitalization, it is the biomarker significantly associated with persistent renal impairment following discharge; baseline levels >7

pg/gCr were 68% sensitive and 60% specific [35]. KIM-1 is associated with an increased risk of heart failure hospitalization and all-cause mortality in chronic heart failure [11, 36]. In ADHF, however, there is no relationship between the levels of KIM-1 on admission or during hospitalization and 180-day all-cause mortality [35, 59].

Application of Biomarkers to Acute CRS

The natriuretic peptides have aided with the diagnosis and management of ADHF. These classic cardiac markers, as well as the prognostic markers such as mid-regional proadrenomedullin, have demonstrated the potential of a multiple-biomarker approach to ADHF [60]. However, much of the morbidity associated with ADHF comes from the coexistence of AKI not just with the pathophysiological mechanisms but also with the pharmacological treatments. With the combination of renal injury biomarkers and cardiac markers, a multimarker approach to acute CRS that provides insights into both cardiac and renal dysfunction would lead to a more precise risk stratification and more appropriate management. In our cohort of ADHF patients, those with admission levels of urinary AGT ≥ 55 $\mu\text{g/gCr}$ and an NT-proBNP level >5.5 ng/ml had the highest overall mortality and the highest rate of failure of renal recovery at discharge [20].

The application of renal biomarkers to the management of ADHF may provide additional information guiding treatment. For example, diuresis is commonly used for decongestion. Vigorous diuresis may lead to a decline in renal perfusion and even a rise in serum creatinine. The application of renal injury biomarkers may enable precise treatment of this patient group, as it can differentiate between the hemoconcentration-induced reduction in GFR and renal tissue injury (i.e. AKI); in the latter condition, diuretic therapy could be reduced or withheld. Similarly, a role of renal injury biomarkers could be considered when other therapies are used to treat acute CRS. For example, measurement of urinary AGT could play a role in identifying patients with AKI who are likely to progress to CKD and could potentially benefit from RAS blockade.

Conclusion

There is a growing literature of promising and novel renal injury biomarkers for acute CRS. Although research has so far focused on their utility in diagnosis and prognosis, it is likely that through continued study in this area

an understanding of the specific mechanisms involved in cardiorenal dysfunction will allow patient-specific therapeutic approaches in the future.

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Conflict of Interest Statement

All the authors declare no competing interests.

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