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BIOMARKERS OF HEART FAILURE (WH TANG & J GRODIN, SECTION EDITORS)

# Synthesizing Markers of Kidney Injury in Acute Decompensated Heart Failure: Should We Even Keep Looking?

Alexander S. Manguba Jr[1] · Xavier Vela Parada[1] · Steven G. Coca[2] · Anuradha Lala[3]

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## Abstract

**Purpose of Review** This review discusses evidence that has accumulated over the years on the diagnostic and prognostic utility of biomarkers of kidney injury in the setting of acute decompensated heart failure.

**Recent Findings** Despite numerous studies evaluating several different biomarkers both in the serum and urine, the current body of evidence does not support routine use of any of these biomarkers for the purposes of diagnosis of acute kidney injury or for prognosis after hospitalization for acute decompensated heart failure. All studies are observational in nature and, as such, are likely limited by numerous confounders, the most important of which is modification of decongestive therapy in response to worsening renal function. More recent evidence suggests that worsening renal function or kidney injury does not always portend poor outcomes after hospitalization for heart failure.

**Summary** There is currently no conclusive evidence to recommend the routine use of biomarkers of kidney injury in acute decompensated heart failure.

**Keywords** Acute decompensated heart failure · Acute kidney injury · Biomarkers · Cardiorenal syndrome · Worsening renal function

## Introduction

Heart failure is the leading cause of hospitalization in patients over the age of 65 and bears a cost burden of an estimated 40 billion dollars annually in the USA [1]. Despite devoted efforts to reduce associated adverse events, morbidity, and mortality remain unacceptably high for patients who are hospitalized for heart failure. This holds true whether the patient has a reduced or preserved left ventricular ejection fraction. In particular, approximately 30% of patients admitted for acute decompensated heart failure (ADHF) encounter renal impairment [2], variously termed as acute kidney injury (AKI), worsening renal function (WRF), or cardiorenal syndrome (CRS). A number of studies have shown that these patients are at a particularly high risk for poor outcomes and, therefore, need to be readily identified.

Kidney impairment is most commonly recognized by an increase in serum creatinine (SCr), or by a decrease in glomerular filtration rate (GFR). However, SCr is an imperfect marker of AKI for a number of reasons. First, SCr can be higher or lower than expected independent of kidney function or changes in kidney function due to advanced age, increased muscle mass, excessive protein intake, intense exercise, or the effects of tubular handling of creatinine by certain medications. Second, if the SCr is elevated due to kidney dysfunction, an elevation may reflect either decreased glomerular filtration or subsequent kidney tubular injury. This is especially relevant in

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✉ Anuradha Lala
anu.lala@mountsinai.org

Alexander S. Manguba, Jr
alexander.manguba@mountsinai.org

Xavier Vela Parada
xavier.velaparada@mountsinai.org

Steven G. Coca
steven.coca@mssm.edu

[1] Department of Medicine, Icahn School of Medicine at Mount Sinai/St. Luke's-Roosevelt Hospital Center, New York, NY, USA

[2] Division of Nephrology, Icahn School of Medicine at Mount Sinai, New York, NY, USA

[3] The Zena and Michael A. Wiener Cardiovascular Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA

the context of ADHF where patients undergo decongestive therapies causing fluid shifts and hemodynamically mediated elevations in SCr. Elevations in SCr in ADHF, therefore, may reflect a decrease in GFR as a result of hemodynamic changes and not tubular injury. This often leads clinicians to withdraw heart failure therapies, particularly diuretics. Finally, even in the presence of tubular injury, elevation in SCr may be delayed by days due to the effects of various cytokines during acute illness on creatinine kinetics.

The inherent limitations of SCr to fully represent the type or degree of kidney impairment has led to the quest for novel biomarkers collected either in the serum or urine, not only for the purpose of better diagnosing AKI in the setting of ADHF, but also for prognosticating subsequent adverse events. The current review seeks to summarize the work that had been done so far in search for the ideal biomarker of kidney injury in ADHF and to provide insights on where we are today in terms of its clinical utility.

## Definitions of Kidney Impairment

Before embarking on the review of various biomarkers, it is first necessary to review the different definitions of kidney impairment encountered in the literature:

- Acute kidney injury (AKI) refers to a decrease in kidney function without reference to specific etiology. It is most commonly defined using the *Kidney Disease: Improving Global Outcomes* (*KDIGO*) *criteria* [3], which requires *any* of the following:

  1. Increase in SCr by ≥ 0.3 mg/dL within 48 h
  2. Increase in SCr to ≥ 1.5 times the baseline, which is known or presumed to have occurred within the prior 7 days
  3. Urine volume of < 0.5 mL/kg/h for > 6 h

- Cardiorenal syndrome (CRS) refers to a spectrum of interactions between the heart and kidneys and is classified into five types based on the direction of the interaction and whether the disorders are acute or chronic [4]. Pertinent to this review is type 1 CRS, which refers to acute kidney dysfunction resulting from an acute cardiac insult (e.g., myocardial infarction resulting in cardiogenic shock or ADHF).

- Worsening renal function (WRF) is a term that has emerged in heart failure literature used to describe kidney function impairment occurring in the setting of either chronic or acute heart failure. Its definition varies across studies, differing in terms of the marker used (SCr, cystatin C, or GFR) and the magnitude of change [5].

## Biomarkers of Kidney Injury

As previously mentioned, the inadequate sensitivity and specificity of SCr as a measure of kidney injury led to the study of biomarkers to accomplish the following:

(a) Allow for earlier diagnosis of AKI
(b) Distinguish true tubular injury from decreased glomerular filtration
(c) Prognosticate subsequent outcomes for patients with ADHF

In addition, the study of biomarkers has the potential for providing insight into the mechanisms of kidney injury. However, most of these biomarkers are currently limited in terms of availability, cost, and lack of standardization of assays. In the following section, we briefly discuss evidence that has accumulated over the years on the utility of biomarkers of kidney injury, particularly in the setting of ADHF. Details of the major studies are summarized in Table 1 for serum or plasma biomarkers and in Table 2 for urinary biomarkers. Figure 1 provides a schematic of the sources of the different biomarkers.

# Biomarkers of Kidney Injury in Acute Decompensated Heart Failure

## Cystatin C

Cystatin C (CysC) is a low-molecular-weight protein that is produced by all nucleated cells at a constant rate. It is freely filtered by the glomerulus then reabsorbed and catabolized by proximal tubular cells. Therefore, its detection in the serum reflects impaired glomerular filtration, while its presence in urine could indicate proximal tubular injury. Serum CysC as a measure of glomerular filtration has been regarded as being superior to creatinine-based estimates of GFR. However, more recently it has been suggested that in addition to glomerular filtration, other factors could affect the level of CysC in the serum, including age, sex, weight, concomitant medical conditions (e.g., diabetes, thyroid disease, inflammatory states), and drugs (particularly corticosteroids).

### Serum or Plasma CysC

**Diagnostic Utility** Enthusiasm for the measurement of CysC arose from the hypothesis that it would provide earlier detection of AKI compared with SCr. This hypothesis has, however, yet to be proven in the setting of ADHF. A single-center, prospective study found that baseline levels did not predict the occurrence of AKI [6]. On the other hand, another prospective study showed that while baseline levels of CysC may be

**Table 1** Serum or plasma biomarkers of kidney injury in acute decompensated heart failure

| Study | Setting | Design | Number of subjects | Main outcome(s) | Results |
|---|---|---|---|---|---|
| Beta-2 microglobulin (B2M) | | | | | |
| Kawai 2010 [59] | Multicenter | Prospective | 131 | Cardiovascular events (sudden cardiac death or hospital admission at ~2 years) | • Independently associated with cardiovascular events (HR 1.5; 95% CI, 1.2–18) |
| | | | | Cardiac death (~2 years) | • Independently associated with cardiac death (HR 1.8; 95% CI, 1.4–2.4) |
| Beta-Trace protein (BTP) | | | | | |
| Manzano-Fernandez 2011 [61] | Single center | Prospective | 220 | All-cause mortality or HF readmission | • Independently associated with all-cause mortality or HF readmission (HR 3.19; 95% CI, 1.15–8.92) |
| | | | | WRF | • Similar BTP levels among those who developed WRF compared with those who did not |
| Cystatin C (CysC) | | | | | |
| Alvelos 2011 [36] | Single center | Prospective | 119 | Type 1 cardiorenal syndrome within 48 to 72 h | • CysC levels were significantly higher in those who developed type 1 CRS<br>• AUC for predicting type 1 CRS = 0.68 (0.54–0.82, $P = 0.04$) |
| Alvelos 2013 [41] | Single center | Prospective | 120 | All-cause mortality (3 months) | • Not independently associated with all-cause death ($P = 0.771$) |
| | | | | All-cause death or readmission (3 months) | • Not independently associated with death or readmission ($P = 0.621$) |
| Arimoto 2005 [8] | Single center | Prospective | 140 | Cardiac death and rehospitalization for HF | • Increase in CysC by 0.6 ng/mL was associated with outcome (median follow-up 480 days)(HR 1.94; 95% CI, 1.29–6.64) |
| Breidthardt 2017 [7] | Single center (BASEL V) | Prospective | 207 | Early AKI (first 4 days of hospitalization) | • Admission levels were higher in patients who experienced early AKI<br>• However, AUC for prediction of AKI was 0.67, compared with serum creatinine (0.68), and eGFR (0.68) |
| | | | | All-cause mortality (12 months) | • In multivariate analysis, CysC remained independently associated with all-cause mortality at 12 months (adjusted for early AKI, ADHERE risk factors, serum Na, and BNP)(HR 1.41; 95% CI, 1.02–1.95) |
| Campbell 2009 [64] | Single center | Prospective | 240 | Death (1 year) | • Levels in the highest quartile were independently associated with death (HR 2.00, $P = 0.04$) |
| | | | | Death or readmission (1 year) | • Levels in the highest quartile were independently associated with death or readmission (HR 1.94, $P = 0.002$) |
| Carrasco-Sanchez 2011 [65] | Single center | Prospective | 218 | Mortality or readmission (1 year) | • Levels above median were independently associated with all-cause mortality or readmission (3rd quartile, HR 2.54, 95% CI 1.41–4.57; 4th quartile, HR 3.40, 95% CI 1.86–6.21) |
| Carrasco-Sanchez 2014 [66] | Single center | Prospective | 195 | All-cause mortality at 1 year | • Independently associated with all-cause mortality at 1 year(HR 4.87; 95% CI, 1.92–12.36) |
| Demissei 2017 [15] | Multicenter (RELAX-A-HF) | Prospective | 1161 | Cardiovascular mortality at 180 days | • CysC was associated with increased mortality at 180 days<br>• However, did not improve baseline risk model that included clinical and laboratory variables, including BUN (absolute change in C-index <0.01) |
| Flores-Blanco 2015 [67] | Multicenter | Prospective | 613 | All-cause mortality and HF readmission at 1 year | • Combination of NT-proBNP with eGFR using CysC-based CKD-EPI equations better predicts outcomes<br>• However, base model does not include renal function as assessed by creatinine or creatinine-based GFR |
| Inazumi 2016 [68] | Single center | Prospective | 100 | All-cause mortality and rehospitalization at 180 days | • Not associated with death or rehospitalization<br>• Increase in serum CysC from day to day 4 was an independent predictor of decreased risk of primary endpoint |
| Jackson 2016 [16] | Multicenter | Prospective | 648 | All-cause mortality | • Associated with long-term mortality in unadjusted analysis (mean follow-up 3.2 years)<br>• Did not add prognostic value to baseline risk model (includes clinical and laboratory variables) |
| Kim 2015 [12] | Single center | Retrospective | 232 | Composite: cardiac death or recurrent HF hospitalization at 2 years | • CysC was predictive of outcome on multivariate analysis(HR 2.176; 95% CI, 1.208–3.918) |
| Lassus 2007 (FINN-AKVA) [9] | Multicenter | Prospective | 480 | All-cause mortality (12 months) | • Independently predictive of all-cause mortality (HR 3.2; 95% CI, 2.0–5.3) |

**Table 1** (continued)

| Study | Setting | Design | Number of subjects | Main outcome(s) | Results |
|---|---|---|---|---|---|
| Lassus 2010 [69] | Multicenter | Prospective | 292 | All-cause mortality | • Rise in CysC within 48 h from admission was independently predictive of mortality at 90 days but not at 12 months |
| Manzano-Fernandez 2011 [61] | Single center | Prospective | 220 | All-cause mortality or HF readmission | • Independently associated with all-cause mortality or HF readmission (HR 4.20; 95% CI, 1.31–13.3) |
| Naruse 2009 [11] | Single center | Prospective | 328 | Cardiac death | • Associated with outcome in multivariate analysis (median follow-up 915 days) (HR 4.1; 95% CI, 2.12–8.04) |
| Palazzuoli 2015 [6] | Single center | Prospective | 203 | AKI | • No difference in baseline serum CysC between those who developed AKI and those who did not |
| | | | | Cardiac mortality and composite of hospital readmission and cardiovascular death at 6 months | • Not independently associated with outcome (HR 1.00; 95% CI, 0.85–1.37) |
| Perez-Calvo 2012 [70] | Multicenter | Prospective | 596 | All-cause mortality (12 months) | • Independently associated with all-cause mortality (HR 2.86; 95% CI, 1.72–4.77) |
| Rafouli-Stergiou 2015 [13] | Single center | Prospective | 96 | Composite: cardiac death or hospitalization for HF at 60 days | • Rise in CysC ≥ 0.4 mg/L during hospitalization was an independent predictor of the primary endpoint |
| Ruan 2014 [71] | Single center | Prospective | 162 | All-cause mortality (12 months) | • Rise in CysC > 0.3 mg/L was independently associated with outcome (OR 2.72; 95% CI, 1.75–4.16) |
| Selcuk 2018 [72] | Single center | Prospective | 57 | All-cause mortality (36 months) | • CysC was not associated with all-cause mortality on multivariate analysis (adjusted for age, NT-proBNP, sodium, LVEF, and GFR) (HR 0.959; 95% CI, 0.287–3.201 [$P = 0.946$]) |
| Tang 2015 [14] | Multicenter (ASCEND--HF) | Prospective | 811 | All-cause death (180 days) and all-cause death or recurrent hospital stay (30 days) | • Not associated with outcomes in adjusted analysis (model includes BUN, creatinine, and other ASCEND-HF covariates) |
| van Deursen 2014 [42] | Multicenter (COACH) | Retrospective | 562 | 3-year mortality | • Not associated with outcome in adjusted analysis(HR 1.09; 95% CI, 0.96–1.23) |
| Heart-type fatty acid binding protein | | | | | |
| Shirakabe 2015 [31] | Single center | Prospective | 282 (ICU) | AKI on admission | • Independent predictor of AKI on admission (OR 6.709; 95% CI, 3.362 to 13.391) |
| | | | | Mortality (90 days) | • Level ≥ 22.9 ng/mL on admission was an independent predictor of mortality (OR if with AKI, 5.240; 95% CI, 1.980 to 13.867; OR if with no AKI, 3.891; 95% CI, 1.387 to 10.919) |
| Shirakabe 2019 [43] | Single center | Retrospective | 281 (ICU) | "True WRF" (WRF in patients with preexisting AKI) | • Predictive of true WRF (OR 5.472; 95% CI, 2.279 to 10.972) |
| Kidney Injury molecule-1 (KIM-1) | | | | | |
| Grodin 2015 [24] | Multicenter (ASCEND--HF) | Prospective | 874 | Composite: death or hospitalization for recurrent HF at 30 days | • Neither baseline nor 48- to 72-h plasma KIM-1 levels were not associated with death or rehospitalization at 30 days when adjusted for other covariates, including BUN and creatinine (HR for baseline KIM-1: 0.90 [$P = 0.44$]; HR for follow-up KIM-1: 0.88 [$P = 0.34$]) |
| | | | | Death at 180 days | • Neither baseline nor 48- to 72-h plasma KIM-1 levels were not associated with death at 180 days when adjusted for other covariates, including BUN and creatinine (HR for baseline KIM-1: 1.12 [$P = 0.44$]; HR for follow-up KIM-1: 1.23 [$P = 0.21$]) |
| Emmens 2016 [25] | Multicenter (PROTECT) | Prospective | 2033 | All-cause mortality within 180 days | • Baseline plasma KIM-1 levels were not associated with death within 180 days in multivariate analysis (HR 1.03; 95% CI, 0.89-1.21) |
| | | | | HF rehospitalization within 60 days | • Baseline plasma KIM-1 levels were independently associated with HF rehospitalization within 60 days (HR 1.27; 95% CI, 1.03–1.55) |
| | | | | Death or cardiovascular or renal rehospitalization within 60 days | • Baseline plasma KIM-1 levels were not associated with death or cardiovascular or renal hospitalization within 60 days even on univariate analysis (HR 1.05; 95% 0.93–1.19) |
| Neutrophil gelatinase-associated lipocalin (NGAL) | | | | | |
| Aghel 2010 [35] | Single center | Prospective | 91 | WRF | • Admission levels were associated with developing WRF (OR 1.92; 95% CI, 1.23–3.12) |

**Table 1** (continued)

| Study | Setting | Design | Number of subjects | Main outcome(s) | Results |
|---|---|---|---|---|---|
| Alvelos 2011 [36] | Single center | Prospective | 119 | Type 1 cardiorenal syndrome within 48 to 72 h | • Independently associated with type 1 CRS after adjusting for granulocyte count and renal dysfunction at admission (OR 1.47; 95% CI, 1.20–1.80)<br>• AUC for predicting type 1 CRS = 0.93 (0.88–0.98) |
| Alvelos 2013 [41] | Single center | Prospective | 120 | All-cause mortality (3 months)<br>All-cause death or readmission (3 months) | • Independently associated with all-cause mortality (HR 2.696; 95% CI, 1.203–6.041)<br>• Independently associated with death or hospitalization (HR 2.860; 95% CI, 1.593–5.136) |
| Breidthardt 2012 [73] | Multicenter | Prospective | 207 | AKI | • Baseline levels did not predict AKI |
| Chen 2016 [74] | Multicenter | Prospective | 213 | AKI progression (worsening of stage) | • Was not independently associated with AKI progression |
| Damman 2017 [39] | Multicenter (PROTECT) | Prospective | 1447 | WRF<br>Mortality (180 days) | • Did not rise earlier than creatinine in patients with WR<br>• Baseline NGAL was not independently associated with mortality |
| Legrand 2014 [18] | Multicenter | Prospective | 87 | WRF | • Did not predict development of WRF (OR 1.12; 95% CI, 0.93–1.34) |
| Macdonald 2012 [37] | Multicenter | Prospective | 102 | AKI | • Admission NGAL > 89 ng/mL was associated with development of AKI (OR 3.73; 95% CI 1.26–11.01) |
| Maisel 2011 (GALLANT) [40] | Multicenter | Prospective | 186 | Mortality or HF readmission (30 days) | • Was predictive of outcome in model adjusting for BNP and creatinine (HR 19.912; 95% CI, 3.472–114.189) |
| Maisel 2016 (AKINESIS) [38] | Multicenter | Prospective | 927 | WRF | • Was not superior to creatinine for the prediction of WRF (AUCs: Peak NGAL 0.656, first NGAL 0.647, first creatinine 0.652) |
| Mortara 2013 [75] | Single center | Prospective | 30 | WRF | • Baseline levels were not significantly higher in patients who developed WRF |
| Neves 2015 [53] | Single center | Prospective | 201 | AKI | • Baseline levels were not significantly different between those who developed AKI and those who did not |
| Palazzuoli 2015 [6] | Single center | Prospective | 203 | AKI | • Patients who had developed AKI had significantly higher NGAL levels<br>• AUC for predicting AKI = 0.81 |
| | | | | Cardiac mortality and composite of hospital readmission and cardiovascular death at 6 months | • Independently associated with outcome after adjusting for age, sex, LVEF, and any cardiovascular risk factors (HR 1.77; 95% CI 1.24–2.83) |
| Shrestha 2012 [32] | Single center | Prospective | 93 | AKI within 5 days | • Did not independently predict AKI after adjusting for baseline GFR or serum creatinine |
| van Deursen 2014 [42] | Multicenter (COACH) | Retrospective | 562 | 3-year mortality | • NGAL levels higher than the median (84.62 ng/mL) were associated with decreased survival in both CKD and non-CKD patients<br>• NGAL level was an independent predictor for mortality in 3 years on adjusted analysis (HR 1.47; 95% CI 1.27 to 1.69); remained significant even when adjusted for eGFR and CysC |
| Syndecan-1 | | | | | |
| Neves 2015 [53] | Single center | Prospective | 201 | AKI<br>Mortality (6 months) | • Predictive of AKI occurrence (AUC 0.74, up to 0.840 with more severe AKI)<br>• Independent predictor of mortality (HR 1.262; 95% CI, 1.079–1.464) |

*AKI*, acute kidney injury; *BNP*, brain natriuretic peptide; *BUN*, blood urea nitrogen; *CI*, confidence interval; *CRS*, cardiorenal syndrome; *GFR*, glomerular filtration rate; *HF*, heart failure; *HR*, hazard ratio; *LVEF*, left ventricular ejection fraction; *NT-proBNP*, N-terminal prohormone of brain natriuretic peptide

**Table 2** Urinary biomarkers of kidney injury in acute decompensated heart failure

| Study | Setting | Design | Number of subjects | Main Outcome(s) | Results |
|---|---|---|---|---|---|
| Albumin | | | | | |
| Chen 2016 [74] | Multicenter | Prospective | 213 | AKI progression (worsening of stage) | • Was not independently associated with AKI progression |
| Shirakabe 2019 [43] | Single center | Retrospective | 281 (ICU) | "True WRF" (WRF in patients with preexisting AKI) | • Levels were not significantly different between "true" and "pseudo" WRF |
| Yang 2015 [34] | Multicenter | Prospective | 436 | AKI | • Urinary albumin/creatinine ratio predicted AKI with an AUC of 0.71 (0.65–0.77) |
| Angiotensinogen (uAGT) | | | | | |
| Yang 2015 [34] | Multicenter | Prospective | 436 | AKI | • Independent predictor for AKI in multivariable analysis (OR for highest quartile [> 149 μg/g Cr] 50.01; 95% CI, 12.32–203.23)<br>• Performed better (AUC 0.84) at predicting AKI than uNGAL (AUC 0.78) or uACR (AUC 0.71) |
| | | | | All-cause mortality (1 year) | • Level ≥ 55 μg/g Cr associated with higher mortality (OR 4.47; 95% CI, 2.10–9.54) |
| | | | | Rehospitalization (1 year) | • Level ≥ 55 μg/g Cr associated with higher rehospitalization (OR 3.61; 95% CI, 1.63–5.74) |
| | | | | Failure in renal recovery | • Level ≥ 55 μg/g Cr associated with failure in renal recovery (OR 6.59; 95% CI, 2.14–20.30) |
| | | | | Progression to CKD | • Higher incidence of progression to CKD in those with uAGT ≥ 55 μg/g Cr (48%) vs. those who had lower uAGT (16%) |
| Chen 2016 [74] | Multicenter | Prospective | 213 | AKI progression (worsening of stage) | • Highest tertile of uAGT (> 146.4 μg/g Cr) was associated with progression of AKI stage in multivariable analysis (OR 10.8; 95% CI, 3.4–34.7) |
| Beta-2 microglobulin (B2M) | | | | | |
| Hishikari 2017 [49] | Single center | Prospective | 281 (ICU) | AKI | • Did not predict development of AKI ($P = 0.10$) |
| Shirakabe 2019 [43] | Single center | Retrospective | 281 (ICU) | "True WRF" (WRF in patients with preexisting AKI) | • Levels were not significantly different between "true" and "pseudo" WRF |
| Cystatin C (CysC) | | | | | |
| Legrand 2014 [18] | Multicenter | Prospective | 87 | WRF | • Did not predict development of WRF (OR 1.38; 95% CI, 0.53–3.61) |
| Sokolski 2017 [19] | Single center | Prospective | 132 | "True WRF" (WRF associated with deterioration or no improvement in clinical status) | • No difference in urinary CysC levels among patients with or without WRF |
| | | | | All-cause death (12 months) | • Day 2, but not baseline or day 3 levels, was predictive of mortality (HR for day 2 CysC 1.34; 95% CI, 1.08–1.68) |
| Fibrinogen | | | | | |
| Legrand 2014 [18] | Multicenter | Prospective | 87 | WRF | • Did not predict development of WRF (OR 0.53; 95% CI, 0.20–1.41) |
| Interleukin-18 (IL-18) | | | | | |
| Chen 2016 [74] | Multicenter | Prospective | 213 | AKI progression (worsening of stage) | • Levels > 224.4 ng/g Cr was associated with AKI progression (OR 3.6; 95% CI 1.4–9.5) |
| Verbrugge 2013 [22] | Single center | Prospective | 83 | AKI | • Did not predict AKI (AUC 0.643 [0.489–0.798], $P = 0.092$) |
| | | | | All-cause mortality (7 ± 4 months) | • Significantly associated with all-cause mortality (HR 1.48; 95% CI, 1.16–1.87) |
| Kidney injury molecule-1 (KIM-1) | | | | | |
| Ahmad 2018 [23••] | Multicenter (ROSE-A-HF) | Prospective | 283 | WRF | • Similar levels between those who developed WRF and those who did not ($P = 0.54$) |
| | | | | Survival (180 days) | • An increase from baseline to 72-h level was associated with improved survival (adjusted HR 0.88; 95% CI, 0.80–0.98) |
| Chen 2016 [74] | Multicenter | Prospective | 213 | AKI progression (worsening of stage) | • Did not predict AKI progression |
| Legrand 2014 [18] | Multicenter | Prospective | 87 | WRF | • Did not predict development of WRF (OR 1.09; 95% 0.42–2.83) |
| | Single center | Prospective | 201 | AKI | • Baseline levels were not significantly different between those who developed AKI and those who did not |

**Table 2** (continued)

| Study | Setting | Design | Number of subjects | Main Outcome(s) | Results |
|---|---|---|---|---|---|
| Neves 2015 [53] | | | | | |
| Sokolski 2017 [19] | Single center | Prospective | 132 | "True WRF" (WRF associated with deterioration or no improvement in clinical status) | • Day 2, but not baseline or day 3 levels, was predictive of WRF (AUC 0.74) |
| | | | | All-cause death (12 months) | • Did not predict mortality |
| Verbrugge 2013 [22] | Single center | Prospective | 83 | AKI | • Did not predict AKI (AUC 0.658 [0.511–0.805], $P = 0.064$) |
| Liver-type fatty acid binding protein (LFABP) | | | | | |
| Hishikari 2017 [49] | Single center | Prospective | 281 (ICU) | AKI | • Baseline levels were independently associated with AKI (OR 1.08; 95% CI, 1.05–1.12) |
| Okubo 2018 [50] | Single center | Prospective | 138 | WRF | • Urinary L-FABP ≥ 8.4 μg/g Cr was independently associated with occurrence of WRF (HR 1.8; 95% CI, 1.21–2.69) |
| | | | | All-cause mortality (1 year) | • Not associated with all-cause mortality |
| | | | | HF readmission (1 year) | • Not associated with HF readmission |
| Shirakabe 2015 [31] | Single center | Prospective | 282 (ICU) | AKI on admission | • Not an independent predictor of AKI (cutoff ≥ 36.7 ng/mg Cr) on multivariate analysis |
| Shirakabe 2017 [48] | Single center | Prospective | 293 (ICU) | AKI | • Levels ≥ 184 ng/mL Cr were independently associated with AKI during the first 7 days among non-CKD patients (OR 3.85; 95% CI, 1.128–13.140 |
| | | | | Mortality (60 days) | • Levels ≥ 184 ng/mL Cr were independently associated with 60-day mortality among non-CKD patients (HR 13.494, 95% CI 1.512–120.415) |
| Shirakabe 2019 [43] | Single center | Retrospective | 281 (ICU) | "True WRF" (WRF in patients with preexisting AKI) | • Levels were not significantly different between "true" and "pseudo" WRF |
| N-acetyl-beta-D-glucosaminidase (NAG) | | | | | |
| Ahmad 2018 [23••] | Multicenter (ROSE-A-HF) | Prospective | 283 | WRF | • Similar levels between those who developed WRF and those who did not ($P = 0.31$) |
| | | | | Survival (180 days) | • Higher baseline levels were associated with reduced survival (adjusted HR 1.12; 95% CI, 1.0–1.2; $P = 0.026$) |
| | | | | | • An increase from baseline to 72-h level was associated with improved survival (adjusted HR 0.90; 95% CI, 0.81–0.98) |
| Hishikari 2017 [49] | Single center | Prospective | 281 (ICU) | AKI | • Did not predict development of AKI (HR 0.99; 95% CI 0.95–1.02) |
| Legrand 2014 [18] | Multicenter | Prospective | 87 | WRF | • Did not predict development of WRF (OR 1.02; 95% CI, 0.93–1.11) |
| Shirakabe 2015 [31] | Single center | Prospective | 282 (ICU) | AKI on admission | • Was not independently associated with AKI on admission (OR 1.663; 95% CI, 0.817–3.339) |
| Shirakabe 2019 [43] | Single center | Retrospective | 281 (ICU) | "True WRF" (WRF in patients with preexisting AKI) | • Was not associated with "true WRF" (OR 1.474; 95% CI, 0.797–2.724) |
| Neutrophil gelatinase-associated lipocalin (NGAL) | | | | | |
| Ahmad 2018 [23••] | Multicenter (ROSE-A-HF) | Prospective | 283 | WRF | • Similar levels between those who developed WRF and those who did not ($P = 0.69$) |
| | | | | Survival (180 days) | • An increase from baseline to 72-h level was associated with improved survival (adjusted HR 0.88; 95% CI, 0.80–0.98) |
| Chen 2016 [74] | Multicenter | Prospective | 213 | AKI progression (worsening of stage) | • Levels > 185.4 μg/g Cr were independently associated with AKI progression (OR 4.7; 95% CI, 1.7–13.4) |
| Dupont 2012 [28] | Single center | Prospective | 141 | AKI | • Baseline uNGAL/uCr levels were similar between patients who did and did not develop AKI |
| | | | | | • AUC for predicting AKI using day 2 uNGAL/uCr was 0.61 |

**Table 2** (continued)

| Study | Setting | Design | Number of subjects | Main Outcome(s) | Results |
|---|---|---|---|---|---|
| Murray 2019 (AKINESIS) [29] | Multicenter | Prospective | 927 | WRF | • Was not superior to creatinine in predicting WRF or need for RRT (first urinary NGAL AUC 0.61 vs. first creatinine AUC 0.65; peak urinary NGAL AUC 0.51 vs. peak creatinine AUC 0.66) |
| | | | | In-hospital adverse events | • Was not superior to creatinine in predicting in-hospital adverse events (first urinary NGAL AUC 0.65 vs. first creatinine AUC 0.69; peak urinary NGAL AUC 0.56 vs. peak creatinine AUC 0.70) |
| Nakada 2017 [30] | Single center | Prospective | 260 | AKI | • Significantly increased occurrence of AKI during hospitalization in patients with admission urinary NGAL ≥ 32.5 μg/g Cr ($P = 0.0012$) |
| | | | | All-cause death (mean follow-up 18.6 months) | • Admission level ≥ 32.5 μg/g Cr was independently associated with all-cause death (HR 1.60; 95% CI, 1.05–2.46) |
| | | | | Cardiovascular death (mean follow-up 18.6 months) | • Admission level ≥ 32.5 μg/g Cr was not independently associated with cardiovascular death (HR 1.66; 95% CI, 0.89–3.16) |
| | | | | HF admission (mean follow-up 18.6 months) | • Admission level ≥ 32.5 μg/g Cr was independently associated with HF readmission (HR 1.62; 95% CI, 1.07–2.62) |
| Shirakabe 2015 [31] | Single center | Prospective | 282 (ICU) | AKI on admission | • Was independently associated with AKI on admission (OR 5.902; 95% CI, 1.258–27.687) |
| Shirakabe 2019 [43] | Single center | Retrospective | 281 (ICU) | "True WRF" (WRF in patients with preexisting AKI) | • Was independently associated with "true WRF" (OR 2.722; 95% CI, 1.320–5.615) |
| Shrestha 2012 [32] | Single center | Prospective | 93 | AKI | • Baseline urine NGAL levels were not significantly different between those who developed AKI and those who did not<br>• In multivariable analysis, urine NGAL ≥ 64 ng/mL predicted AKI after adjusting for GFR and SCr (OR 2.99; 95% CI, 1.05–8.61) |
| Sokolski 2017 [19] | Single center | Prospective | 132 | "True WRF" (WRF associated with deterioration or no improvement in clinical status) | • Baseline, day 2, and day 3 levels were significantly associated with "true WRF" (OR for baseline urinary NGAL 2.26; 95% CI, 1.41–3.62) |
| | | | | All-cause death (12 months) | • Baseline, day 2, and day 3 levels were significant predictors of mortality (HR for baseline urinary NGAL 1.39; 95% CI, 1.03–1.87) |
| Soyler 2015 [33] | Single center | Prospective | 100 | AKI | • AUC for predicting AKI 0.7789 (0.66–0.90) |
| Verbrugge 2013 [22] | Single center | Prospective | 83 | AKI | • Did not predict AKI (AUC 0.615 [0.434–0.796], $P = 0.177$) |
| Yang 2015 [34] [TIMP2] × [IGFBP7] | Multicenter | Prospective | 436 | AKI | • AUC for predicting AKI 0.78 (0.73–0.83) |
| Schanz 2017 [56] | Single center | Prospective | 40 | AKI | • Levels were significantly higher in patients who developed AKI and discriminated for risk of AKI stages 2–3 (AUC 0.84 [95% CI: 0.72, 0.93]) |

*AKI*, acute kidney injury (definition varies by study); *AUC*, area under the receiver operating curve; *CKD*, chronic kidney disease; *GFR*, glomerular filtration rate; *HF*, heart failure; *ICU*, intensive care unit; *KDIGO*, Kidney Disease Improving Global Outcomes; *SCr*, serum creatinine; *WRF*, worsening renal function (definition varies by study)

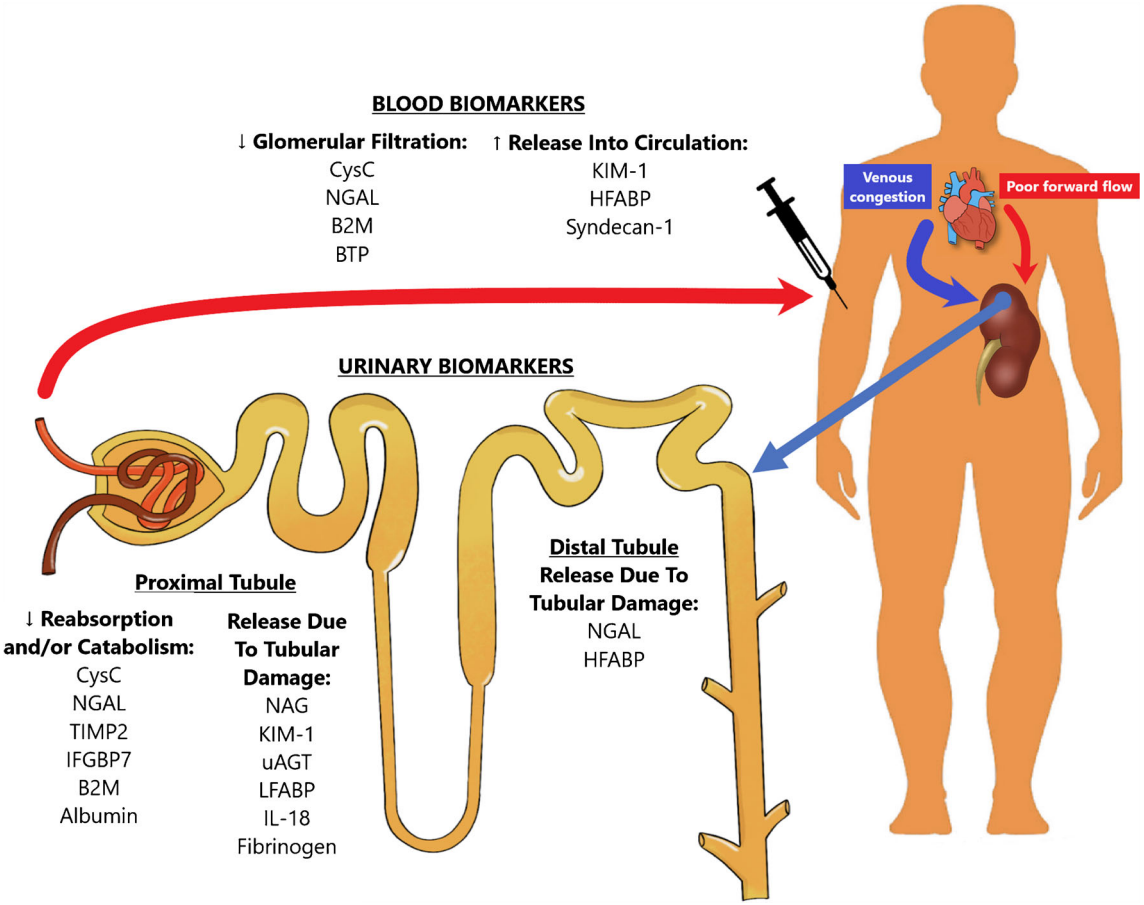


**Fig. 1** Biomarkers of kidney injury in acute decompensated heart failure. CysC, cystatin C; B2M, beta-2 microglobulin; BTP, beta trace protein; IGFBP7, insulin-like growth factor binding-protein 7; IL-18, interleukin 18; HFABP, heart-type fatty acid-binding protein; KIM-1, kidney injury molecule 1; LFABP, liver-type fatty acid-binding protein; NAG, N-acetyl-beta-D-glucosaminidase; NGAL, neutrophil gelatinase-associated lipocalin; TIMP2, tissue inhibitor of metalloproteinase 2; uAGT, urinary angiotensinogen

predictive, its performance was not superior to SCr, as shown by their similar area under the receiver operating characteristic curve (AUC) [7].

**Prognostic Utility** Numerous studies have been conducted on the use of serum or plasma CysC for determining prognosis after hospitalization for ADHF (Table 1), varying in study design and clinical setting, and therefore yielding mixed results. Earlier studies [8–11] suggested that CysC is an independent predictor (after adjustment for baseline SCr and brain natriuretic peptide [BNP]) of long-term outcomes including mortality, further corroborated by more recent single-center experiences [7, 12, 13]. However, large cohort studies that analyzed data from the ASCEND-HF trial [14] and RELAX-AHF trial [15], as well as a prospective multicenter study by Jackson et al. [16] failed to demonstrate incremental value after adjusting for renal function as measured using traditional markers (blood urea nitrogen [BUN], SCr, or GFR).

Higher CysC levels have also been associated with lower diuretic efficiency during treatment for ADHF among patients with CRS, which in turn has been associated with worse outcomes. In a secondary analysis of data from the Heart Failure Network trials ROSE-AHF and CARRESS-HF [17], in 422 patients with ADHF and WRF, CysC was associated with lower diuretic efficiency, defined as the 72-h fluid output per total loop diuretic dose (in 40 mg furosemide equivalent), and in turn, associated with reduced survival at 60 days.

### Urinary CysC

Detection of CysC in the urine reflects decreased reabsorption and catabolism by the proximal tubules, which may indicate tubular injury. In the setting of ADHF, however, data are limited to two single-center studies (Table 2), both of which failed to show that urinary CysC predicts WRF [18, 19].

### Summary: CysC

Based on currently available evidence, serum or plasma CysC levels do not provide incremental value in the prediction of AKI during hospitalization for ADHF over SCr. As such, its

measurement for the purpose of earlier diagnosis of renal dysfunction in this setting lacks substantial evidence. There is also insufficient evidence to recommend routine measurement of CysC for the purposes of prognostication in ADHF. Similarly data on the yield of measuring urine CysC in the setting of ADHF are lacking.

## Kidney Injury Molecule-1

Kidney injury molecule-1 (KIM-1) is a transmembrane glycoprotein expressed by proximal tubular cells in response to kidney injury and serves a role in the clearance of apoptotic cells [20]. In animal models, urinary KIM-1 is an excellent marker for histopathologic kidney injury. While levels of KIM-1 have been more commonly measured in the urine, its levels in plasma could also be indicative of renal tubular injury. The appearance of KIM-1 in plasma is thought to be the result of the loss of tubular cell polarity (which occurs with tubular injury) with the subsequent release of KIM-1 into the interstitium, as well as the back leak of KIM-1 into the circulation secondary to increased transepithelial and microvascular permeability [21].

### Urinary KIM-1

**Diagnostic Utility** The majority of the studies investigating the use of urinary KIM-1 showed that it does not predict the occurrence of kidney dysfunction during hospitalization for ADHF (Table 2). For example, Verbrugge et al. [22] found that baseline urinary KIM-1 levels were not associated with the development of AKI (defined in the study as a decrease in eGFR by ≥ 25% during days 1–5). More recently, Ahmad et al. [23••] conducted a retrospective analysis of the multicenter Heart Failure Network ROSE-AHF trial which sought to determine the utility of low dose dopamine or nesiritide in enhancing decongestion in AHF, and found that neither baseline nor 72-h urinary KIM-1 levels differed between those who developed WRF (defined as a ≥ 20% decrease in eGFR) and those who did not.

**Prognostic Utility** Few studies have examined the utility of urinary KIM-1 for determining prognosis in ADHF. Consistent across these three studies however was the lack of association between urinary KIM-1 and all-cause mortality at various time points, 7 (± 4) months [22], 180 days [23••], and 1 year [19]. Rather, in the analysis of the ROSE-AHF trial, an increase in KIM-1 level from baseline to 72 h was associated with improved survival at 180 days [23••].

### Plasma KIM-1

Two studies have investigated the utility of measuring plasma levels of KIM-1 in ADHF. Grodin et al. analyzed data from 874 subjects in the ASCEND-HF trial of nesiritide versus placebo in ADHF, and found that neither baseline nor 48- to 72-h plasma KIM-1 levels were independently associated with death or rehospitalization for HF at 30 days, or with death at 180 days after adjustment for BUN and SCr [24]. A subsequent study by Emmens and colleagues, which analyzed data from the PROTECT trial, a study that evaluated the efficacy of the selective A1 adenosine receptor antagonist rolofylline in 2033 patients, found that baseline plasma KIM-1 was an independent predictor of heart failure rehospitalization (HR 1.27; 95% CI, 1.03–1.55), but not death (HR 1.03; 95% CI, 0.89–1.21), or with the combined endpoint of death, cardiovascular, or renal rehospitalization within 60 days (HR 1.05; 95% 0.93–1.19) [25].

### Summary: KIM-1

Given currently available evidence, the measurement of either urinary or plasma levels of KIM-1 does not appear to be clinically useful in ADHF. Studies on diagnostic utility failed to show that it predicts WRF or AKI, while studies on prognostic utility found that it was not independently prognostic of outcomes after hospitalization for ADHF.

## Neutrophil Gelatinase-Associated Lipocalin

Neutrophil gelatinase-associated lipocalin (NGAL) is a 25-kD protein found to be maximally induced in ischemic kidney injury [26]. Elevated plasma levels are secondary to decreased glomerular filtration and systemic recirculation of NGAL released from the kidney, while its presence in the urine is due to decreased proximal tubular reabsorption, as well as increased expression in the distal tubules [27].

### Urinary NGAL

**Diagnostic Utility** The role of urinary NGAL in diagnosing AKI or WRF has been examined in a number of studies, yielding discrepant results [22, 23••, 28–34]. The multicenter prospective cohort Acute Kidney Injury Neutrophil Gelatinase-Associated Lipocalin Evaluation of Symptomatic Heart Failure Study (AKINESIS) sought to determine whether NGAL is superior to creatinine for prediction and/or prognosis of WRF in hospitalized patients with ADHF treated with intravenous diuretic agents and included 927 patients [29]. WRF was defined as a sustained increase in SCr of 0.5 mg/dL or ≥ 50% above the baseline or initiation of renal replacement therapy and occurred in 72 subjects (7.8%). Though peak NGAL was more predictive than the first NGAL assessment, neither added incremental diagnostic utility over admission creatinine for prediction of WRF or adverse in-hospital events with lower AUCs at every time point (Table 2).

**Prognostic Utility** In contrast to its diagnostic utility, only a few studies have examined the ability of urinary NGAL to prognosticate outcomes. Two single-center, prospective cohort studies found that urinary NGAL was an independent predictor of all-cause death at ≥ 12 months [19, 30]. Similar to KIM-1 in the analysis of ROSE-AHF by Ahmad and colleagues, an increase from baseline to 72-h level was associated with improved survival at 180 days [23••].

#### Serum or Plasma NGAL

**Diagnostic Utility** While earlier studies showed that serum or plasma NGAL predicted the development of kidney dysfunction in patients hospitalized for ADHF [6, 35–37], more recent studies have yielded opposing findings. The AKINESIS study [38] found that neither baseline nor peak levels of NGAL were better than baseline SCr in predicting WRF. While peak NGAL was an independent predictor in multivariable analysis, it did not significantly improve the accuracy (AUC only increased from 0.707 to 0.711) of a model that included systolic blood pressure, pre-existing chronic kidney disease, admission hemoglobin, and admission BUN. A subsequent study by Damman et al. showed that plasma NGAL levels did not rise sooner than creatinine levels in patients who developed WRF [39].

**Prognostic Utility** While its incremental value over SCr may be limited for diagnostic purposes, measurements of NGAL may have prognostic value in patients with ADHF. The multicenter prospective GALLANT study (NGAL Evaluation Along with B-type Natriuretic Peptide in Acutely Decompensated Heart Failure) was in fact designed to address whether NGAL was an early marker of adverse outcomes alone and in combination with brain natriuretic peptide [40]. Maisel et al. found that plasma NGAL measured prior to discharge is an independent predictor of readmission for heart failure or mortality at 30 days. Subsequent studies have corroborated this finding with longer follow-up times [6, 41, 42]. A more recent study by Damman et al., however, showed that while NGAL was associated with 180-day mortality as well as the composite outcome of death or renal/cardiovascular rehospitalization at 60 days, the association did not persist following multivariable adjustment which included age, creatinine, BUN, systolic blood pressure, edema, previous hospitalization for heart failure, serum albumin, and serum sodium. NGAL was found to confer worse prognosis in patients who developed WRF, but not to those who did not [39].

#### Summary: NGAL

There is no conclusive evidence to support the use of either urinary or serum/plasma NGAL for the purpose of earlier or more accurate diagnosis of AKI/WRF in ADHF. While there is some evidence to support its value for prognostication after hospitalization for ADHF, findings have not been consistently reproducible.

### N-acetyl-beta-D-glucosaminidase

N-acetyl-beta-D-glucosaminidase (NAG) is a lysosomal enzyme found in the brush border of proximal tubular cells and is found in the urine after tubular injury. In the setting of ADHF, studies on the clinical utility of NAG as a biomarker have thus far been mostly negative. Baseline levels of NAG were neither predictive of WRF [18, 23••] nor correlated with AKI on admission [31]. When studied as a marker for predicting "true WRF" (defined as a further increase in SCr of ≥ 0.3 mg/dL in a patient with preexisting AKI on admission) in a cohort of 281 patients admitted to the intensive care unit (ICU) for ADHF, NAG was found to have a modest AUC of only 0.59 [43]. Similar to KIM-1 and NGAL, an increase in NAG levels from baseline to 72 h was paradoxically associated with improved survival at 180 days [23••].

### Urinary Angiotensinogen

Urine angiotensinogen is produced by proximal tubular cells of the kidney and secreted in the tubular lumen [44]. Its presence in the urine is an indicator of intrarenal renin-angiotensin system (RAS) activity [45], which has been implicated in the pathogenesis of AKI reflecting the increased expression of pro-inflammatory and pro-fibrotic cytokines [46].

A multicenter, two-stage prospective cohort (317 subjects across 4 centers and 119 in two additional centers as a validation cohort) study by Yang et al. [34] tested urinary angiotensinogen (uAGT) as a predictor for the development of AKI in patients hospitalized for ADHF. In stage I, 104 (32.8%) patients developed AKI during hospitalization. uAGT levels measured on the first day of admission were significantly higher in patients who subsequently developed AKI, and it was found to peak earlier than SCr. After adjustment for clinical variables (including age, NT-proBNP, SCr, serum albumin, hypertension, diabetes, and treatment with RAS inhibitors), patients who had uAGT levels in the highest quartile (> 148 μg/g Cr) had a 50-fold risk of developing AKI compared with the lowest quartile (OR 50.01, 95% CI 12.32–203.23). The predictive power of uAGT outperformed urinary NGAL and urinary albumin/creatinine ratio (Table 2) and uAGT was also found to be associated with all-cause mortality and rehospitalization at 1 year.

### Fatty Acid-Binding Proteins

Fatty acid-binding proteins (FABPs) are cytoplasmic proteins involved in transport of free fatty acids. Two types of FABPs have been isolated from human kidney [47]. Liver-type fatty

acid-binding protein (LFABP) is found in hepatocytes and renal proximal tubular cells, while heart-type fatty acid-binding protein (HFABP), a marker of myocardial injury, is found in renal distal tubular cells. Both types of FABPs have been studied as biomarkers in ADHF.

Urinary LFABP levels on admission were found to be predictive of AKI within 7 days and of 60-day mortality in patients without chronic kidney disease (CKD) admitted to the intensive care unit for ADHF [48]. Other studies have had different results [31, 43, 49, 50], with some finding no association between LFABP levels and outcomes.

In a single-center, retrospective study of patients admitted to the ICU for ADHF, serum HFABP levels on admission were significantly higher in those with "true WRF," defined as WRF in a patient with pre-existing AKI on admission [43]. A serum HFABP level ≥ 22 ng/mL was found to be independently associated with "true WRF" (OR 5.472; 95% CI, 2.729–10.972). Using this definition, patients under the category of "true WRF" were found to have worse long-term outcomes in this study. A previous study on the same cohort found that a serum HFABP level ≥ 22 ng/mL on admission, with or without AKI, was an independent predictor of 90-day mortality [31]. There are currently no studies evaluating urinary HFABP in ADHF.

### Interleukin-18

Interleukin-18 (IL-18) is a proinflammatory cytokine that can serve as a marker for acute tubular necrosis [51]. As a biomarker, it has been previously studied for early diagnosis of AKI, as well to predict mortality in ICU patients [52]. In patients with ADHF, urinary IL-18 levels were found to be associated with persistent kidney impairment at 6 months and all-cause mortality [22].

### Syndecan-1

Syndecan-1 is a transmembrane proteoglycan found on epithelial and endothelial cells that serves as a marker for endothelial glycocalyx damage. In the only study published thus far on syndecan-1 for ADHF, plasma levels of syndecan-1 were found to be significantly associated with AKI occurrence in ADHF, with higher levels associated with more severe AKI [53]. This association persisted even after adjusting for SCr, BNP, LVEF, diabetes, HTN, hypertension, and serum sodium. In addition, among those who did not develop AKI, syndecan-1 levels were similar regardless of presence or absence of baseline stable CKD. Syndecan-1 levels were also associated with in-hospital and 6-month mortality.

### Tissue Inhibitor of Metalloproteinase 2 and Insulin-Like Growth Factor-Binding Protein 7

Tissue inhibitor of metalloproteinase 2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP7) are cell-cycle arrest markers that are expressed early in response to various kidney tubular insults and were previously found to be predictive of AKI in critically ill patients [54]. The combination of urinary [TIMP-2] × [IGFBP7] is the first FDA-approved biomarker for clinical use to assess the risk of AKI. Urinary [TIMP-2] × [IGFBP7] was subsequently studied in various clinical settings including cardiac surgery, where it was found to be an early predictor of AKI [55]. In ADHF, a small study showed that urinary [TIMP-2] × [IGFBP7] was significantly higher on admission in patients who subsequently developed AKI stage 2-3 and was positively correlated with changes in AKI stage and changes in weight [56].

### Beta-2 Microglobulin

Beta-2 microglobulin (B2M) is an endogenous low molecular weight protein that has been studied as a marker of glomerular filtration [57]. Similar to CysC, it is almost completely reabsorbed and catabolized by the kidney tubules and thus, its detection in the urine may indicate kidney tubular damage [58]. A multicenter, prospective study found that serum levels of B2M in ADHF were associated with cardiac death or cardiovascular events after a follow-up of approximately 2 years [59]. Another study that examined the utility of urinary B2M found that it did not independently predict the development of AKI in ADHF [49].

### Beta-Trace Protein

Beta-Trace protein (BTP), also known as prostaglandin D2 synthetase, is a low molecular weight protein that has been studied as a marker of GFR [60]. In the only published study thus far on the diagnostic and prognostic utility of BTP in ADHF, baseline BTP levels were similar between those who developed WRF and those who did not. However, BTP was found to be independently associated with all-cause mortality or HF readmission after a median follow-up period of 500 days [61].

### Urinary Fibrinogen

Fibrinogen, in addition to its physiologic role in coagulation, is an acute-phase protein that is upregulated in inflammatory states. Its urinary levels have been found to be significantly increased in acute kidney injury [62]. In ADHF, Legrand et al. studied urinary fibrinogen along with other urinary biomarkers for predicting WRF, with negative results [18].

### Urinary Albumin

Increased urinary excretion of albumin is seen in approximately 70% of patients with ADHF and has been found to decrease following decongestive therapies [63]. However, studies on its clinical utility in the setting of ADHF are limited. In the aforementioned study by Yang et al. (see "Urinary Angiotensinogen"), the AUC of the urinary albumin/creatinine ratio for predicting AKI was 0.71, which was lower compared with that of uAGT, urinary NGAL, and a clinical model [34].

## Discussion

The current evidence for the diagnostic and prognostic utility of the various kidney biomarkers in ADHF are mixed and inconclusive, which is partly due to variations in study population, setting, methods, and definitions of kidney impairment used. Most studies used SCr as the standard with which to compare the new biomarkers, and this use of a standard that is neither sensitive nor specific clearly has limitations. Waikar et al. demonstrated that the use of creatinine, an imperfect gold standard, reduces the apparent accuracy of a new biomarker, even if it is 100% sensitive and specific. On the other hand, a biomarker that has a perfect correlation with creatinine indicates that it may have the same limitations as creatinine [76].

Almost all studies on renal biomarkers for ADHF are observational, and no marker has been studied in a randomized controlled trial to examine the effects of a biomarker-guided strategy on hard outcomes. Given the observational nature of these studies, there are numerous potential confounders, including modification of therapy in response to renal dysfunction. In particular, patients with AKI or WRF may have had decongestive therapies withheld, influencing outcomes.

Elevations in creatinine in the context of treatment for ADHF are not always representative of true kidney injury [18, 23••] and, therefore, should not necessarily dictate withdrawing of diuretic agents or neurohormonal antagonists in this setting. In fact, emerging evidence suggests that decongestion is paramount and supersedes the prognostic value of renal impairment during treatment of ADHF [77–79, 80••, 81]. For example, hemoconcentration, a marker of decongestion, has been associated with improved survival despite concomitant worsening renal function [82–85].

Recent evidence also suggests that the presence of true tubular injury does not necessarily portend poor outcomes. Rao et al. [86••] analyzed data from the CARRESS-HF trial and found that in patients with ADHF and preexisting WRF, further intensive volume removal (by diuresis or ultrafiltration) was not consistently associated with an increase in creatinine or tubular injury biomarkers. In fact, patients who did have an increase in markers of tubular injury (urinary NGAL, NAG, and/or KIM-1) paradoxically experienced greater improvement in kidney function at 60 days compared with those without an increase. These findings are consistent with a prior study that analyzed data from the ROSE-AHF trial [23••], which demonstrated that patients who experienced WRF (measured by serum CysC) and had concomitant rise in kidney injury biomarkers had the highest rate of survival at 180 days. Moreover, several promising therapies that could potentially preserve or improve kidney function have previously been investigated in ADHF, but none have been shown to improve outcomes [87–90].

Taken together, these findings suggest that the kidneys are not necessarily the primary driver of poor outcomes in patients with ADHF experiencing WRF. The ubiquitous nature of the SCr in daily hospital care of patients with ADHF may have resulted in a significant amount of bias and confounding of the observational studies, as physicians may de-intensify decongestive therapies when kidney function appears to worsen. However, the studies that examined kidney injury biomarkers and assessed their rise in conjunction with WRF [23] or with decongestion [86••] suggest that employing kidney injury biomarkers in real time would likely cause more harm than benefit, since the treating physicians in these studies were blinded to biomarker concentrations. Thus, similar to elevations in SCr, an increase in biomarker level may lead to unnecessary withdrawal of decongestive treatment. We will never be able to "blind" clinicians to SCr in patients admitted with ADHF; thus, the best that can be done is to focus on the clinical congestive status of these tenuous patients, and encourage physicians to embrace "permissive hypercreatininemia" or "permissive AKI." As Bill Clinton once said in his initial campaign and ascent to the presidency in 1992, "It's the economy, stupid," the tag line in ADHF should be "It's the congestion, stupid." Multiple studies have demonstrated that the number one cause of readmission after AKI is for congestive heart failure and pulmonary edema and not due to recurrent or worsening AKI, or progressive CKD. Thus, the epidemic is fluid overload, and not "over-diuresis."

## Conclusion

Despite numerous studies on markers of kidney injury in ADHF, there is currently no biomarker that can be recommended for routine use for the purposes of earlier diagnosis of AKI or WRF, nor for prognostication following ADHF. The fault likely does not lie inherently with the type of biomarker or its specificity for kidney injury. Rather, it is more likely that the relative importance of kidney dysfunction or injury is trumped by congestion and volume overload.

## Compliance with Ethical Standards

**Conflict of Interest** Dr. Coca reports personal fees and other from RenalytixAI, personal fees from CHF Solutions, personal fees from Quark, personal fees from Takeda, personal fees from Janssen, personal fees and other from pulseData, personal fees from Goldfinch, personal fees from Relypsa, outside the submitted work.

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Dr. Lala has nothing to disclose.

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**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors

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- • Of importance
- •• Of major importance


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