Use of Cell Cycle Arrest Biomarkers in Conjunction With Classical Markers of Acute Kidney Injury

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Objectives: Decreased urine output and/or increased serum creatinine may herald the development of acute kidney injury or reflect normal physiology. In this secondary analysis of the Sapphire study, we examined biomarkers of cell cycle arrest in the settings of oliguria and/or azotemia to improve risk assessment when used with conventional indices in predicting severe acute kidney injury (Kidney Disease: Improving Global Outcomes 3 defined by the need for renal replacement therapy or changes in urine output, serum creatinine or both) or death.

Design: Prospective, international, Sapphire study.

Setting: Academic Medical Center.

Patients: Patients without acute kidney injury Kidney Disease: Improving Global Outcomes stage 2 or 3.

Interventions: None.

Measurements and Main Results: The primary endpoint being development of severe acute kidney injury or death within 1 week. Secondary analysis examined the relationship between tissue inhibitor of metalloproteinases-2 ([TIMP-2]) and insulin growth factor binding protein 7 ([IGFBP7]) and 9-month death or dialysis conditioned on progression to stage 2–3 acute kidney injury within 1 week. Seventy-nine patients reached the primary endpoint and were more likely to be surgical, with higher nonrenal Acute Physiology and Chronic Health Evaluation III scores and more chronic kidney disease. Stage 1 urine output, serum creatinine, and urinary [TIMP-2]•[IGFBP7] greater than 2.0 were all predictive of progression to the primary endpoint independent from nonrenal Acute Physiology and Chronic Health Evaluation III score. Combinations of predictors increased the hazard ratios considerably (from 2.17 to 4.14 to 10.05, respectively). In the presence of acute kidney injury (stage 1), [TIMP-2]•[IGFBP7] greater than 2.0 leads to an increased risk of death or dialysis at 9 months even in the absence of progression of acute kidney injury (stage 2–3) within 7 days.

Conclusions: Cell cycle arrest biomarkers, TIMP-2 and IGFBP7, improve risk stratification for severe outcomes in patients with stage 1 acute kidney injury by urine output, serum creatinine or both, with risk increasing with each acute kidney injury indicator. Longer term outcomes demonstrate that the associated risks of a [TIMP-2]•[IGFBP7] greater than 2.0 is equivalent to acute kidney injury progression even where no progression from stage 1 acute kidney injury is observed. (Crit Care Med 2019; 47:e820–e826)

Key Words: acute kidney injury; biomarkers; cell cycle arrest; oliguria
A
cute kidney injury (AKI) was first described over a
decade ago in order to address limitations in identifying
and categorizing individuals deemed to have acute renal
failure (1, 2). The prior lack of consensus hindered compar-
ative studies and therefore fundamental questions such as out-
comes and the impact of potential interventions were not easily
addressed. The current description of AKI has allowed for more
precision especially in the critically ill (3, 4). AKI is defined and
staged in terms of an increase in serum creatinine (SCR) and/or
a reduction in urine output (UO) (5). Using this definition, the
development of AKI is associated with an increase in both mor-
bidity and mortality together with an increase in the length of
hospital stay and costs (6–8). However, not all stages of AKI are
clearly associated with death or the need for dialysis after con-
trolling for baseline covariates. Furthermore, stage 1 AKI, while
useful in particular clinical settings, is not a clinical endpoint
in the way stage 2 and especially, stage 3 are (9, 10).

Additionally, despite its utility for epidemiology, trial end-
points, and prognosis, the current definition of early stage AKI
has limitations. Although a decrease in UO can be an early sign
of AKI, it is neither sensitive nor specific. Changes in SCR are
more specific but also lack sensitivity and may take up to 48
hours to manifest (11–13). Attempts to improve sensitivity by
using increases in SCR greater than 0.3 mg/dL over 48 hours
may diminish specificity especially in patients with a baseline
SCR greater than 1.5 mg/dL (14). Thus, existing tools are insuf-
cient for determining which patients will progress to stage 3
AKI.

We have previously reported an international, prospective,
observational investigation (the Sapphire study) of tissue in-
hibitor of metalloproteinases-2 (TIMP-2) and insulin growth
factor binding protein 7 (IGFBP7), both markers of G1 cell
cycle arrest (15). These markers appear to increase rapidly after
cell stress, even before injury occurs (16, 17). We have validated
two TIMP-2•IGFBP7 cut-offs for risk assessment for develop-
ment of stage 2–3 AKI (18–20) and have reported an associ-
bation between TIMP-2•IGFBP7 at ICU admission and the
composite endpoint of all-cause mortality and/or the receipt
of renal replacement therapy at 9 months (21).

The clinical assay for urinary TIMP-2•IGFBP7 became
available in Europe in 2012 and the United States in 2014.
Clinicians, therefore, currently use TIMP-2•IGFBP7 in con-
junction with UO and SCR in assessing the risk for stage 2–3
AKI (22, 23). In order to determine whether urinary TIMP-
2•IGFBP7 provides additional information to stage 1 UO
and SCR for development of stage 3 AKI, we analyzed data from
patients without stage 2–3 AKI at enrollment and compared
each criterion along with interactions. Severe AKI (stage 3), dial-
ysis, or death were chosen as endpoints as the prediction of these
outcomes as a function of TIMP-2•IGFBP7, and the other
biomarkers would enable measures to be undertaken to mitigate
the risk of progression. We examined the risk of developing stage
3 AKI, including the need for renal replacement therapy (RRT),
or dying over the first week as well as the composite of dialysis or
death over the course of the first 9 months following enrollment.

MATERIALS AND METHODS

We conducted a secondary analysis of the Sapphire study, an
international, multicenter study of critically ill adults enrolled
within 24 hours of ICU admission and evaluated biomarkers
for AKI risk assessment (15). We analyzed TIMP-2•IGFBP7,
SCR, and UO in patients who did not have AKI stage 2 or 3 at
the time of sample collection. The primary outcome was the
composite of the development of AKI stage 3, dialysis, or death
within 1 week of enrollment. We also examined the 9-month
composite outcome of dialysis or death for patients stratified
by TIMP-2•IGFBP7, the presence of stage 1 AKI, and pro-
gression of AKI (stage 2 or greater) within 1 week.

Urinary samples for measurement of TIMP-2•IGFBP7 were
collected at enrollment and at 12-hour intervals up to 30 hours
after enrollment. The average number of sampling time points
per subject was 2.7. Urinary TIMP-2•IGFBP7 was measured
in units of (ng/mL)^2/1,000 using the NephroCheck Test (Astute
Medical, San Diego, CA) (24). AKI status by UO and SCR were
determined within ±12 hours relative to the time of TIMP-
2•IGFBP7 sample collection according to Kidney Disease:
Improving Global Outcomes (KDIGO) criteria (5).

Cox regression analyses were performed to assess the associ-
ation of AKI status and TIMP-2•IGFBP7 with the primary
outcome. AKI status by UO and SCR and TIMP-2•IGFBP7
(dichotomized around either the 0.3 or 2.0 (ng/mL)^2/1,000 vali-
dated cut-off) (18, 20) were included in the regression models
as time-varying covariates. We performed an additional anal-
ysis including Acute Physiology and Chronic Health Evaluation
(APACHE) III score dichotomized around the median value in
the models. Another Cox regression analysis was performed for
the association of the number of positive risk factors (AKI status
by UO and SCR and TIMP-2•IGFBP7) with the outcome.
Kaplan-Meier curves extended for time-varying covariates were
plotted to illustrate these associations (25).

To assess the association of AKI status and TIMP-
2•IGFBP7 with the outcome of 9-month dialysis or death,
a categorical variable was constructed by whether the max-
imum TIMP-2•IGFBP7 within 30 hours of enrollment was
greater than 2.0 (ng/mL)^2/1,000, whether stage 1 AKI was pre-

tent within ±12 hours of TIMP-2•IGFBP7, and whether
stage 2–3 AKI was reached in a week. Cox regression was then
performed with this categorical variable as a time-indepen-
dent variable. Subjects who died or had dialysis in a week were
excluded from this analysis. Kaplan-Meier curves were gener-
ated to illustrate this association.

All survival analyses were performed with the “survival” pack-
age in R (26). The proportional hazard assumption was checked
with the “cox.zph” function. Overall Goodness-of-fit of Cox
models was assessed by the Grønnesby and Borgan Test using
the “gof” function in R package “survMisc” (27). All analyses
were performed with R Version 3.4.4 (27, 28). Two-sided p values
less than 0.05 were considered statistically significant. The Sapphire
study was approved by investigational review boards/ethics com-
mitees of each of the participating sites. All subjects (or author-
ized representatives) provided written informed consent.
RESULTS

Patient Characteristics

Figure S1 (Supplemental Digital Content 1, http://links.lww.com/CCM/E738; legend, Supplemental Digital Content 5, http://links.lww.com/CCM/E742) shows the consort diagram with 661 patients analyzed from the Sapphire cohort of which 79 (10.9%) reached the primary endpoint (death or stage 3 AKI including RRT, over the first week)—50 patients died, and 41 patients had stage 3 AKI, of which 26 received RRT. Baseline patient characteristics are shown in Supplementary Table 1 (Supplemental Digital Content 2, http://links.lww.com/CCM/E739). Patients who developed stage 3 AKI or died had a higher rate of chronic kidney disease were more likely to be surgical and had higher nonrenal APACHE III scores.

Risk of Death or Stage 3 AKI According to Enrollment UO, SCr or [TIMP-2][IGFBP7]

Table 1 shows hazard ratios (HRs) for [TIMP-2][IGFBP7], stage 1 UO or SCr for death, or AKI stage 3 within 7 days. HRs were stratified for the two established cut-offs for [TIMP-2][IGFBP7] (20). Unadjusted HRs were significant for all three variables, after adjustment [TIMP-2][IGFBP7] greater than 0.3 showed an increased adjusted HR (HR, 2.74; 95% CI, 1.55–4.85) and p value of less than 0.001 with minimal observed decreases in the HRs of UO and SCr (Table 1). Stage 1 SCr showed a similar adjusted HR (3.07; 95% CI, 1.94–4.86) and p value of less than 0.001, and stage 1 UO showed a slightly lower adjusted HR (1.69; 95% CI, 1.05–2.72; p = 0.03). We performed an additional analysis including the nonrenal APACHE III score. [TIMP-2][IGFBP7] greater than 2 showed a strong predictive factor (HR, 2.49; 95% CI, 1.41–4.42; p < 0.002) in the multivariable model with nonrenal APACHE III score. The negative predictive value of [TIMP-2][IGFBP7] in predicting primary endpoint in stage 1 AKI patients was 0.83 (95% CI, 0.78–0.88) for the 2.0 cut-off.

Effects of Predictor Variable Combinations

A single predictor variable was defined by combining AKI status by SCr, AKI status by UO, and tissue inhibitor of metalloproteinases-2 ([TIMP-2]) and insulin growth factor binding protein 7 ([IGFBP7]) level. Reference group is [TIMP-2][IGFBP7] ≤ cutoff and no AKI by serum creatinine and urine output. “1” positive indicates AKI defined by only one of SCr, UO, or [TIMP-2][IGFBP7] > cutoff; “2” positive indicates exactly two of the conditions are met; and “3” positive indicates all three conditions are

TABLE 1. Hazard Ratios for tissue inhibitor of metalloproteinases-2 and [IGFBP7], Urine Output, and Serum Creatinine Unadjusted and Adjusted for the Other Variables

| Variables | Unadjusted | | Adjusted | | |
|-----------|------------|-------------------|----------|-------------------|----------|
|           | HR 95% CI Lower | 95% CI Upper | p        | HR 95% CI Lower | 95% CI Upper |
| A         | [TIMP-2][IGFBP7] > 0.3 | 2.09 | 1.30 | 3.38 | 0.003 | 1.62 | 0.99 | 2.66 | 0.06 |
|           | UO         | 2.57 | 1.65 | 4.00 | < 0.001 | 1.79 | 1.13 | 2.86 | 0.01 |
|           | SCr        | 3.89 | 2.50 | 6.05 | < 0.001 | 3.23 | 2.05 | 5.09 | < 0.001 |
| B         | [TIMP-2][IGFBP7] > 2.0 | 4.33 | 2.53 | 7.41 | < 0.001 | 2.74 | 1.55 | 4.85 | < 0.001 |
|           | UO         | 2.57 | 1.65 | 4.00 | < 0.001 | 1.69 | 1.05 | 2.72 | 0.03 |
|           | SCr        | 3.89 | 2.50 | 6.05 | < 0.001 | 3.07 | 1.94 | 4.86 | < 0.001 |

HR = hazard ratio, SCr = serum creatinine, TIMP-2 = tissue inhibitor of metalloproteinases-2, IGFBP7 = insulin growth factor binding protein 7, UO = urine output. [TIMP-2][IGFBP7] values were stratified by the (A) 0.3 and (B) 2.0 cutoffs. Outcome is stage 3 AKI or death within 7 d.

TABLE 2. Hazard ratios for Stage 3 Acute Kidney Injury or Death by Number of Positive Variables

| Number | 0.3 Cut-off | 2.0 Cut-off |
|--------|-------------|-------------|
|        | HR 95% CI Lower | 95% CI Upper | p | HR 95% CI Lower | 95% CI Upper | p |
| 1      | 2.17 | 1.03 | 4.56 | <0.04 | 2.89 | 1.66 | 5.05 | < 0.001 |
| 2      | 4.14 | 2.00 | 8.55 | <0.001 | 4.91 | 2.62 | 9.21 | < 0.001 |
| 3      | 10.05 | 4.67 | 21.62 | <0.001 | 16.54 | 7.78 | 35.17 | < 0.001 |

HR = hazard ratio.

A single predictor variable was defined by combining acute kidney injury (AKI) status by serum creatinine (SCr), AKI status by urine output (UO), and tissue inhibitor of metalloproteinases-2 ([TIMP-2]) and insulin growth factor binding protein 7 ([IGFBP7]) level. Reference group is [TIMP-2][IGFBP7] ≤ cutoff and no AKI by serum creatinine and urine output. “1” positive indicates only one of AKI by SCr, AKI by UO, or [TIMP-2][IGFBP7] > cutoff; “2” positive indicates exactly two of the conditions are met; and “3” positive indicates all three conditions are met.
Figure 1. Kaplan-Meier curves for Stage 3 acute kidney injury (AKI) or death by AKI status by serum creatinine (SCr) and tissue inhibitor of metalloproteinases-2 ([TIMP-2]) and insulin growth factor binding protein 7 ([IGFBP7]) level relative to the 0.3 (A) and 2.0 (B) cutoffs. Patients are grouped as [TIMP-2][IGFBP7] negative and no AKI by SCr (purple), [TIMP-2][IGFBP7] negative and AKI by SCr (green), [TIMP-2][IGFBP7] positive and no AKI by SCr (blue), [TIMP-2][IGFBP7] positive and AKI by SCr (red). The values below the plots indicate number at risk. Long-rank $p < 0.001$ for both panels.

Figure 2. Kaplan-Meier curves for Stage 3 acute kidney injury (AKI) or death by AKI status by urine output (UO) and tissue inhibitor of metalloproteinases-2 ([TIMP-2]) and insulin growth factor binding protein 7 ([IGFBP7]) level relative to the 0.3 (A) and 2.0 (B) cutoffs. Patients are grouped as [TIMP-2][IGFBP7] negative and no AKI by UO (purple), [TIMP-2][IGFBP7] negative and AKI by UO (green), [TIMP-2][IGFBP7] positive and no AKI by UO (blue), [TIMP-2][IGFBP7] positive and AKI by UO (red). The values below the plots indicate number at risk. Long-rank $p < 0.001$ for both panels.
met (Table 2). Adding each of the single predictor variables, [TIMP-2][IGFBP7] greater than 0.3, UO, SCr, resulted in an incremental HR starting from 2.17 for one variable to 10.05 if all three predictor variables were positive (Table 2). HRs were further increased when the 2.0 cut-off for [TIMP-2][IGFBP7] was applied with an HR of 16.54 observed where all three variables were positive. This was also reflected in the respective Kaplan-Meier curves for Stage 3 AKI or death by the number of positive variables (Fig. S2, Supplemental Digital Content 3, http://links.lww.com/CCM/E740; legend, Supplemental Digital Content 5, http://links.lww.com/CCM/E742).

Figure 1 highlights the predictive ability of different combinations of SCr and [TIMP-2][IGFBP7] at both cut-offs. There was a clear increase in the probability of reaching the endpoint when both [TIMP-2][IGFBP7] and SCr were positive. Applying the 2.0 cut-off of [TIMP-2][IGFBP7], when SCr is positive at stage 1, there is an almost three-fold increase in the probability for reaching the endpoint compared with when SCr is at stage 1 without a positive biomarker. Even when using the lower cut-off of 0.3, the probability of meeting the endpoint was increased compared with SCr alone over the first 48 hours, but by 7 days the difference was more modest—about a third higher.

Where stage 1 UO is positive (Fig. 2A), [TIMP-2][IGFBP7] applied at the lower cut-off approximately doubled the probability of reaching the endpoint. Conversely, when UO is normal, [TIMP-2][IGFBP7] applied at the lower cut-off did not affect risk. However, [TIMP-2][IGFBP7] values greater than 2.0 discriminated for both UO positive and negative patients (Fig. 2B). Finally, we examined the effect of [TIMP-2][IGFBP7] for various combinations of positive or negative UO and SCr (Fig. S3, Supplemental Digital Content 4, http://links.lww.com/CCM/E741; legend, Supplemental Digital Content 5, http://links.lww.com/CCM/E742). Here, we can observe that [TIMP-2][IGFBP7] further discriminated even when both SCr and UO criteria were positive (red curves) but did not discriminate (at either cutoff) when both SCr and UO criteria were negative (purple curves).

**Biomarker Elevations and Long-Term Risk**

Patients may not always manifest kidney injury by changes in functional biomarkers (SCr and UO), and this has been termed “subclinical” AKI (29). The relationship between [TIMP-2][IGFBP7] greater than 2.0 with or without evidence of AKI and 9-month death or dialysis conditional on development/progression of AKI in the first week is shown in Figure 3. In patients without clinical evidence of AKI (stage 1) and no progression, [TIMP-2][IGFBP7] did not discriminate the risk of death or dialysis at 9 months. However, in the presence of AKI, [TIMP-2][IGFBP7] greater than 2.0 led to a roughly two-fold increased risk of death or dialysis even in the absence of progression of AKI within the first week with a [TIMP-2][IGFBP7] greater than 2.0 essentially equivalent to the progression of AKI.

**DISCUSSION**

Our current understanding of AKI dictates that risk assessment is ongoing—not only the risk for developing AKI but also the risk for progression in patients with earlier stages of AKI. This is especially true since most patients developing stage 1 AKI will reverse in the first week (30). Although risk prediction models do exist, they are often limited to specific cohorts and are often poorly generalizable (31–33). Therefore, methods to better assess risk for AKI progression are needed. Our results confirm that patients who develop stage 1 AKI are at significant risk for progression to stage 3 AKI—a level of severity unequivocally associated with
with adverse outcomes. Our results also indicate that urinary [TIMP-2]•[IGFBP7] greater than 2.0 alone poses a risk for subsequent stage 3 AKI or death, similar to stage 1 AKI by either UO or SCr alone. Future staging systems for AKI might well consider this relationship.

Furthermore, our results clearly demonstrate that combining biomarkers with UO or SCr enables substantially enhanced risk prediction by way of a composite risk assessment. This combined approach may well be of direct clinical relevance as previous studies in patients undergoing cardiac surgery demonstrate that SCr alone does not predict AKI progression (34). A previous study has shown that the combination of UO and SCr criteria conveys a substantially increased risk of death over either criterion alone (35). Our results, in this investigation, extend this finding further by demonstrating that when all three variables are positive (stage 1 UO, stage 1 SCr, and biomarkers), the HR for stage 3 AKI or death is 10.05 when using the 0.3 cut-off for [TIMP-2]•[IGFBP7] and 16.54 when using the greater than 2.0 cut-off (Table 2). These represent very large increases in the HR from 4.14 and 4.91 when only two variables are positive. Whether this increase in HR may be considered clinically relevant will depend heavily on the patient’s baseline risk. If, for example, baseline risk is 0.5%, then 1.5–2% might not be considered very different from 5% to 8% because the absolute risk increase is rather small. However, if the baseline is 5%, then the absolute risk increases from 15–20% to 50–80% and likely will be relevant for clinical risk assessment.

In this context, the question is raised whether this may be of clinical relevance because of changing treatment regimens for these patients. Whereas it must be conceded that biomarker-guided management of AKI has not become standard of care in many centers, there are two prospective randomized controlled trials that indicate a clinical benefit when choosing such an approach in specific patients. The prevAKI study showed a reduced rate of AKI including stage 2 and 3, by applying a certain bundle of interventions comprising hemodynamic optimization, avoidance of nephrotoxins and of hyperglycemia in biomarker positive cardiac surgery patients (36). Similar results were obtained in the Biomarker-guided intervention to prevent Acute Kidney injury (BigPAK) study, which included biomarker-positive general surgery patients and used an approach concentrating on optimizing fluid management and nephrology consultation (37).

Interestingly, [TIMP-2]•[IGFBP7] provides additional information as to the risk for stage 3 AKI or death for various combinations of UO and SCr (positive for stage 1, either, or both). Accordingly, assessment of kidney stress using urinary [TIMP-2]•[IGFBP7] represents an additional risk assessment tool whose information cannot be supplanted by SCr or UO. In fact, the 7-day risk of developing AKI stage 3 or death approaches 60% when urinary [TIMP-2]•[IGFBP7] is greater than 2.0 and stage 1 AKI is present using both UO and SCr. Furthermore, even in the absence of meeting this endpoint (or even progression to stage 2), [TIMP-2]•[IGFBP7] greater than 2.0, together with stage 1 AKI, significantly increases the risk of death or dialysis at 9 months. Thus, biomarker positive ([TIMP-2]•[IGFBP7] > 2.0) stage 1 AKI can be viewed on a par with stage 2–3 AKI in terms of the severity of the event. From a practicing clinicians perspective, the use of [TIMP-2]•[IGFBP7] in patients with stage 1 AKI would enable the introduction of measures known to reduce the further progression of AKI (36). Conversely, as we have previously shown (21, 33), an elevation of [TIMP-2]•[IGFBP7] in the absence of AKI does not influence 9-month death or dialysis. This result should be interpreted with caution; however, since it has been recently shown that in cardiac surgery patients, an increase in [TIMP-2]•[IGFBP7] confers a risk for the loss of functional renal reserve even in patients without clinical AKI (38) which supports the concept of early identification of subclinical AKI (29).

Our study is not without limitations. As a post hoc analysis of the Sapphire study, there are known risks of bias inherent to post hoc analyses like unrecognized confounding. Although we performed several multivariate analyses to control for confounding, the use of [TIMP-2]•[IGFBP7] levels in combination with SCr and/or UO in risk prediction still needs to be confirmed prospectively.

CONCLUSIONS

We have shown in a heterogeneous cohort of patients that cell cycle arrest biomarkers, TIMP-2 and IGFBP7, can improve risk stratification for severe outcomes (stage 3 AKI or death) even in patients with stage 1 AKI by UO, SCr, or both. We also found that risk for this outcome increases with each indicator of AKI, UO, SCr, and biomarkers. Finally, longer term outcomes (9 months) are also influenced by the elevated biomarkers in stage 1 AKI, even when they do not appear to progress. This analysis reflects the reality of clinical practice where multiple sources of information are integrated into medical decision-making.

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