Common Chronic Comorbid Conditions Do Not Affect Performance of Cell Cycle Arrest Biomarkers for Risk Stratification of Acute Kidney Injury

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BACKGROUND

- Identification of acute kidney injury (AKI) can be challenging in patients with underlying chronic disease, and previous studies have suggested that biomarkers often perform poorly in this population.
- Diabetes mellitus (DM) and chronic kidney disease (CKD) are both risk factors for AKI and possible confounders for biomarkers.
- We recently reported data from two multi-center studies of 728 (Sapphire) and 408 (Topaz) critically ill patients where a panel of urinary tissue inhibitor of metalloproteinases-2 (TIMP2) and insulin-like growth factor-binding protein 7 (IGFBP7), both markers of cell cycle arrest, were validated for risk stratification for moderate to severe AKI (KDIGO stages 2 and 3).
- Here we report performance characteristics of this novel biomarker panel ([TIMP2]•[IGFBP7]) in patients with a variety of comorbidities, including DM, CKD, or both.

METHODS

- The Sapphire and Topaz studies were prospective, multi-center trials of patients admitted to an intensive care unit who were considered at clinical risk for development of AKI. Additional details of both trials have been previously published.(1,2)
- We conducted subgroup analyses of patients with DM and CKD with or without AKI from the Sapphire and Topaz studies.
- Receiver operating characteristic (ROC) curves were constructed using urinary [TIMP2]•[IGFBP7] for prediction of moderate to severe AKI within 12 hours. We also examined the relative risk (RR) for AKI using a pre-specified cutoff for [TIMP2]•[IGFBP7] of 0.3. Biomarker concentrations were also measured in 378 apparently healthy subjects.

RESULTS

- In the overall cohort, 139 patients (12.3%) developed moderate to severe AKI within 12 hours.
- There were 326 patients with DM, 97 patients with CKD, and 50 patients with both. Patient demographics between the Sapphire and Topaz studies were similar.
- The area under the ROC curve was 0.83 (95%CI 0.77-0.89), 0.91 (95%CI 0.85-0.97), and 0.89 (95%CI 0.80-0.99), respectively, for patients with DM, CKD, and both DM and CKD.
- The RR for AKI above the 0.3 cutoff was 13 (95%CI 4-40), 32 (95%CI 2-530), and 22 (95%CI 1-361), respectively, for patients with DM, CKD, and both DM and CKD.

Table 1: Patient characteristics, stratified by AKI group

	No AKI or Stage 1	AKI Stage 2 or 3	P-value
All patients	992	139	
Male	589 (59%)	74 (53%)	0.169
Age, Years	62 (16)	65 (15)	0.081
Body Mass Index, kg/m²	27 (24-32)	31 (26-38)	<0.001
Race			0.948
Black	127 (13%)	16 (12%)	
White	794 (80%)	113 (81%)	
Other/Unknown	70 (7%)	10 (7%)	
Medical History			
Chronic Kidney Disease	84 (8%)	13 (9%)	0.746
Diabetes Mellitus	274 (28%)	52 (37%)	0.021
Congestive Heart Failure	174 (18%)	32 (23%)	0.127
Coronary Artery Disease	296 (30%)	40 (29%)	0.843
Hypertension	599 (60%)	101 (73%)	0.005
Chronic Obstructive Pulmonary Disease	213 (21%)	23 (17%)	0.220
Admitted to ICU from			0.244
ED	380 (38%)	62 (45%)	
Floor	175 (18%)	18 (13%)	
OR	275 (28%)	30 (22%)	
Other Hospital	140 (14%)	25 (18%)	
Other ICU	10 (1%)	1 (1%)	
Unknown	12 (1%)	3 (2%)	
Time from ICU admission to biomarker sample collection, Hours	16 (7-20)	16 (11-20)	0.427
Non-Renal Apache III	57 (43-78)	69 (50-87)	<0.001
Enrollment serum creatinine, mg/dL	0.9 (0.7-1.2)	1.3 (0.9-1.8)	<0.001

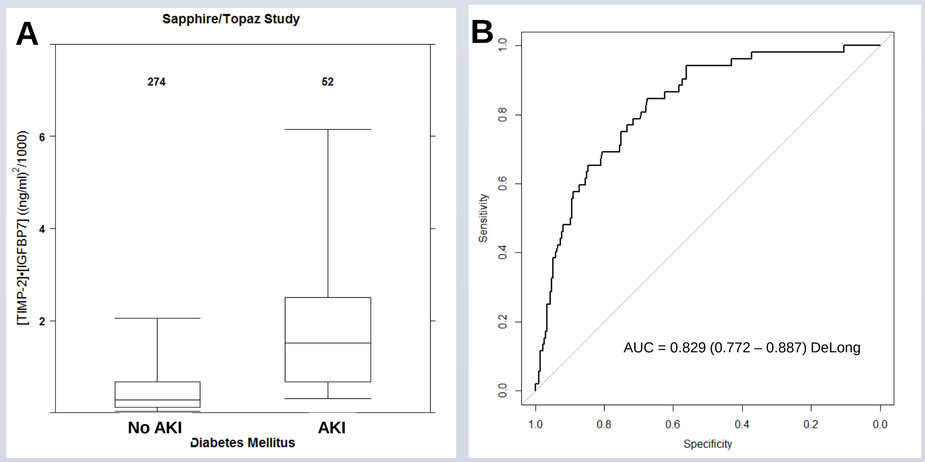


Figure 1: Diabetes cohort.
A) [TIMP2]•[IGFBP7] levels in diabetic patients with and without AKI.
B) ROC curve for AKI risk.

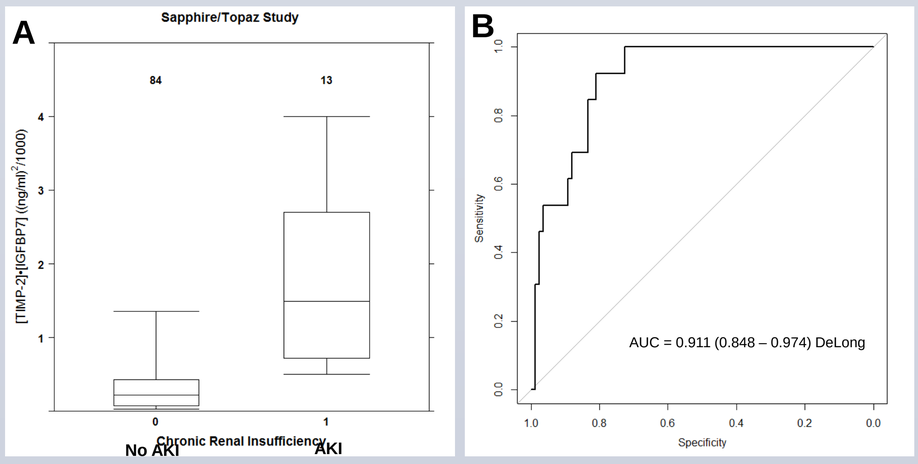
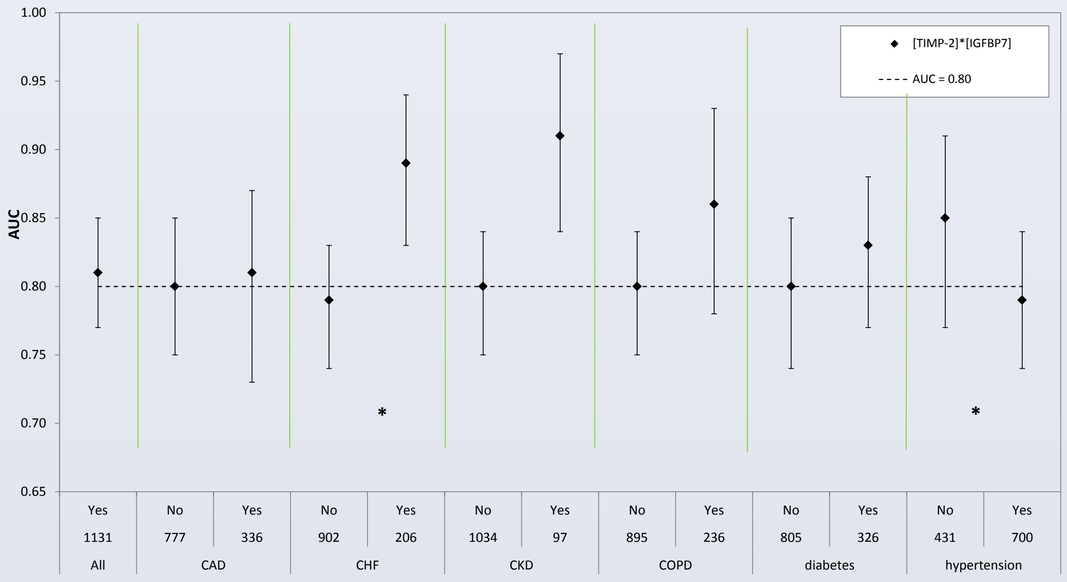


Figure 2: Chronic kidney disease cohort.
A) [TIMP2]•[IGFBP7] levels in CKD patients with and without AKI.
B) ROC curve for AKI risk.

RESULTS (con't)

Figure 3: [TIMP-2]•[IGFBP7] AUC values for AKI risk in various clinical subgroups



*Statistically significant interaction with [TIMP-2]•[IGFBP7] in logistic regression model

DISCUSSION

- Cell cycle arrest markers have emerged as important tools in the prediction of moderate to severe AKI. Because a variety of stress states can contribute to cell cycle arrest, it is important to examine the influence of comorbidities on the test characteristics of these markers.
- Urinary [TIMP2]•[IGFBP7] levels remained similar to levels in healthy subjects (mean<0.3) in all comorbidity subgroups among patients who did not develop AKI.
- The performance of urinary [TIMP2]•[IGFBP7] levels for AKI risk remained high in both the DM (Figure 1) and CKD (Figure 2) subgroups as demonstrated by AUC values above 0.80. These findings are consistent with test characteristics in the overall population and are similar to or better than the test characteristics reported for other AKI biomarkers.
- Of particular note, in the CKD group urinary [TIMP2]•[IGFBP7] performed better than the general population, with AUC exceeding 0.90 (Figure 3). This is important because CKD patients are at higher risk for developing AKI, yet other AKI biomarkers are noted to perform poorly in this population.

CONCLUSIONS

- For patients with underlying comorbidities such as DM, CKD, or both, urinary [TIMP2]•[IGFBP7] levels are not elevated in the absence of AKI and the test accurately identifies patients at risk for developing AKI within 12 hours in these populations.

REFERENCES

1. Kashani K, Al-Khafaji A, Ardiles T, et al. Discovery and validation of cell cycle arrest biomarkers in human acute kidney injury. Crit Care 2013;17(1):R25.
2. Bihorac A, Chawla LS, Shaw AD, et al. Validation of cell-cycle arrest biomarkers for acute kidney injury using clinical adjudication. Am J Resp Crit Care Med 2014;189(8):932-9.

This study was supported by Astute Medical, San Diego, CA