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:R25. doi: 10.1186/cc12503.

INTRODUCTION

Acute kidney injury (AKI) can evolve quickly and clinical measures of function often fail to detect AKI at a time when interventions are likely to provide benefit. Identifying early markers of kidney damage has been difficult due to the heterogeneous nature of human AKI, in which multiple etiologies exist. This paper reports the results of a prospective, multicenter investigation in which two novel biomarkers for AKI were identified in a discovery cohort of critically ill adult patients and subsequently validated using a clinical assay and compared to existing makers of AKI in an independent validation cohort of heterogeneous critically ill patients.

OVERVIEW

Blood and urine samples from three distinct cohorts (Discovery study) were collected to identify novel protein biomarkers for AKI. These single-center studies were used to identify the best biomarkers among 340 proteins, including novel candidates and previously described biomarkers. A fourth cohort (Sapphire study) was assembled from 35 clinical sites in North America and Europe and used to validate the performance of the best biomarkers from the Discovery study. AKI status was classified using the RIFLE or AKIN criteria together as described in the recent KDIGO international guideline based on the serum creatinine (sCR) and urine output (UO) available in the hospital record. The primary endpoint for the Sapphire study was the development of moderate or severe AKI (KDIGO stage 2 or 3) within 12 hours of sample collection.

RESULTS

The Sapphire study enrolled 744 subjects of which moderate-severe AKI occurred in 14% of subjects. The two top biomarkers from the Discovery study were insulin-like growth factor-binding protein 7 (IGFBP7) and tissue inhibitor of metalloproteinases-2 (TIMP-2), both inducers of G1 cell cycle arrest, a key mechanism implicated in AKI, and together demonstrated an AUC of 0.80 (0.76 and 0.79 alone). [TIMP-2]•[IGFBP7] was significantly superior to all existing markers of AKI, none of which achieved an AUC > 0.72, and unlike existing markers, showed clear separation between AKI and non-AKI conditions. Furthermore, [TIMP-2]•[IGFBP7] improved risk stratification when added to a 9-variable clinical model. Finally, sensitivity analysis for the method of determining the sCR reference value and for exclusion of samples after the first occurrence of KDIGO stage 2 or 3 did not change the [TIMP-2]•[IGFBP7] AUC from the primary analysis and was higher than the AUC of all existing biomarkers.

CONCLUSION

Two novel markers for AKI have been identified and validated in independent multicenter cohorts. Both markers performed better than any other biomarker reported to date, showed significant enhancement over clinical variables, are mechanistically relevant, and can be easily measured with existing technology. The introduction of this new test should significantly improve the ability of physicians caring for critically ill patients to identify risk of impending AKI; and also facilitate future AKI research by permitting more accurate identification of high-risk patients for enrollment into intervention trials.

LEARNING POINTS

- Over 340 proteins were analyzed in blood and urine samples in the Discovery study to identify the top two performing markers.
- Top performing markers were insulin-like growth factor-binding protein 7 (IGFBP7) and tissue inhibitor of metalloproteinases-2 (TIMP-2), both inducers of G1 cell-cycle arrest, a key mechanism implicated in AKI.
- Markers were validated in a large multicenter study assembled from 35 sites in North America and Europe.
- The AUC for [TIMP-2]•[IGFBP7] was 0.80 as compared to existing markers, none of which achieved an AUC >0.72.
- [TIMP-2]•[IGFBP7] showed clear separation between AKI and non-AKI conditions, unlike existing markers.
- [TIMP-2]•[IGFBP7] significantly improved risk stratification when added to a nine variable clinical model when analyzed using Cox proportional hazards model, generalized estimating equation, integrated discrimination improvement or net reclassification improvement.
- Risk for major adverse kidney events (death, dialysis or persistent renal dysfunction) within 30 days (MAKE30) elevated sharply for [TIMP-2]•[IGFBP7] above 0.3 and doubled when values were >2.0.

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