

Clinical Applications of Biomarker [TIMP2]×[IGFBP7] in Acute Kidney Injury

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Abstract:

Acute kidney injury (AKI) is one of the most prevalent clinical syndromes characterized by renal functional and structural abnormalities. Serum creatinine (SCr) levels increase, or urine output (UO) decrease dramatically within a specific period of time, which is considered the criteria for diagnosing AKI. Novel biomarkers that accurately predict AKI are being employed to detect renal dysfunction at an early stage. Cell cycle block is one of the mechanisms of AKI, with increasing levels of tissue inhibitor of metalloproteinases 2 (TIMP2) and IGF-binding protein 7 (IGFBP7). Thus, [TIMP2]×[IGFBP7] can be an important novel biomarker for predicting AKI in urine, which has not been widely explored. Research reveals the bright side of [TIMP2]×[IGFBP7] as a biomarker-protective effect on DNA during cell division, as well as the dark side-cellular senescence and fibrosis phenotypes. This review describes the positive predictive value of [TIMP2]×[IGFBP7] for AKI after cardiac surgery, AKI in pediatrics, and sepsis-related AKI. This review aims to stimulate relevant studies targeting the predictive role of [TIMP2]×[IGFBP7] for AKI, to facilitate the exploration of predicting AKI in different fields.

Keywords: Acute kidney injury; biomarkers; [TIMP2]×[IGFBP7]; cell-cycle arrest.

1. Introduction

A common clinical disease known as acute kidney injury (AKI) is characterized by anomalies in the structure and function of the kidneys, occurring in 5.0-7.5% of hospitalized patients and 50-60% of critically ill patients. Currently, a sharp decline in glomerular filtration rate (GFR) as demonstrated by an abrupt rise in serum creatinine (SCr) levels or a sharp decline in urine output (UO) during a predetermined period of time is the diagnostic criteria for AKI [1]. Additionally, new and more precise biomarkers to predict AKI are being implemented to prompt the identification of renal dysfunction. In line with ADQICC's suggestions, some new biomarkers were found to be more sensitive than urinary volume and serum creatinine in detecting AKI, and it is meaningful to use a set of biomarkers to identify and diagnose patients with AKI in an early and accurate way.

Overall, a myriad of biomarkers is present in the urine of patients with AKI, reflecting different pathophysiological pathways, including constitutively expressed proximal tubular proteins (e.g., lysosomal n-acetylamino glucosidase (NAG), cytoplasmic proteins lactate dehydrogenase, etc.), tubular "stress molecules", and low molecular mass plasma proteins [2]. Among these biomarkers, consisting of

the arithmetic product of two separate biomarker proteins - TIMP2 and IGFBP7 can be seen as a biomarker of renal "cell cycle block" as TIMP2 and IGFBP7 can promote AKI-induced suppression of the cell cycle. [TIMP2]×[IGFBP7] as a set of biomarkers showed performed predominantly. Several clinical trials have validated the usefulness of [TIMP2]×[IGFBP7]. In 2014, the US FDA authorized the use of urine TIMP2 and [IGFBP7] (marketed as NephroCheck™) as a means of diagnosis for AKI [3].

This review summarizes the biomarkers of AKI, introduces cell cycle block, and addresses the applications of [TIMP2]×[IGFBP7] in AKI after cardiac surgery, AKI in pediatric, and sepsis-related AKI.

2. Cell-cycle arrest and AKI

It is uncertain whether TIMP-2 and IGFBP-7 can be utilized to prevent AKI, but it is clear that the cell cycle block biomarkers TIMP-2 and IGFBP-7 serve as indicators on both sides of this intricate physiology (Figure 1).

On the one hand, the cell cycle block acts as a protective mechanism designed to prevent 196 DNA-damaged cells from division, thus allowing for adequate repair. It has a "bright side". IGFBP7 and TIMP-2 are able to initiate G1 cell cycle block in tubular cells when they are damaged DNA or other possible forms of damage to initial tubular

cells. IGFBP7 can increase p53 and p21 transcription substantially, while TIMP2 promotes p27 expression. IGFBP7 and TIMP-2 receptors are the means by which these actions are mediated through both paracrine and autonomous pathways. CyclD-CDK4 and CycleE-CDK2 complexes (CyclD-CDK2) have the ability to block the cell cycle-promoting effects of P proteins, which can cause a brief duration of G1 cell cycle block [4]. When cells are injured, or under stress, they are protected against the catastrophic consequences of beginning cytokinesis with defective DNA or inadequate bioenergetic resources. On the

other hand, there is a “dark side” to cell cycle arrest, contributing to the emergence of ongoing kidney disease. A fibrotic phenotype can be formed if the cells fail to initiate the cell cycle and remain locked up at G1 or G2 (or possibly other stages of the cell cycle). Quickly reversing the process is crucial to avoid negative consequences, such as cellular senescence and fibrosis. Future therapeutic interventions can be targeted for targeting cell cycle arrest activation as well as inactivation during crucial clinical intervals in patients [5].

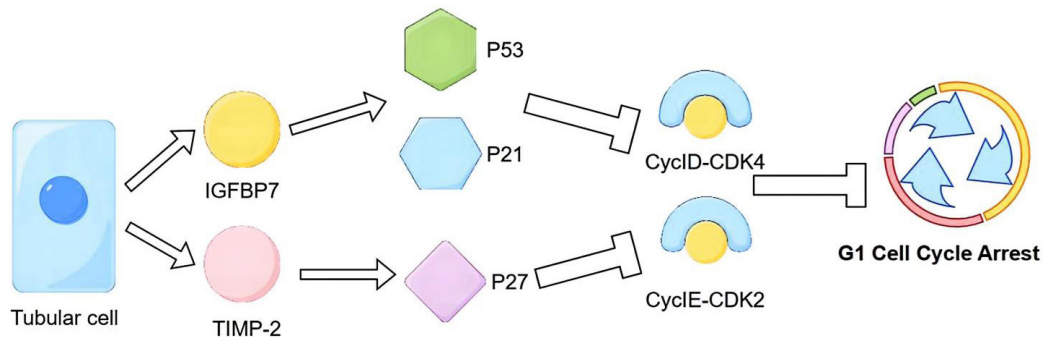


Fig. 1 The suggested mechanistic participation of the [TIMP2]×[IGFBP7] in AKI. Figure credit: original. Made from Figdraw.

3. Clinical Applications

[TIMP2]×[IGFBP7], as an AKI biomarker, has been widely tested in different scenarios, including cardiac-associated AKI, sepsis-associated AKI, pediatric AKI, etc. (Table 1).

3.1 Cardiac-Associated AKI

Over two million heart operations are carried out annually worldwide, and a portion of these patients require renal replacement medication [6]. The prognosis of the patient is affected by cardiac surgery-associated AKI, which can result in an elevated threat of death and development of chronic kidney disease (CKD), or a longer hospitalization duration.

A single-center study using urinary [TIMP2]×[IGFBP7] to evaluate its effectiveness in preventing AKI compared the incidence of AKI in two groups with elective cardiac surgery before and after measurements of urinary [TIMP-2]×[IGFBP7]. The findings indicated a substantial decrease in AKI incidence in the patients that had [TIMP-2]×[IGFBP7] (38/185 [21%] versus 59/197 [30%]), particularly in the patients with mild to moderate AKI [7]. Additionally, the net reclassification improvement (NRI) analysis uncovered a new model utilizing [TIMP2] ×[IGFBP7] enhanced AKI prediction by 0.280 (IC 95% 0.489-0.515). The frequency of AKI following heart surgery was reduced by renal support care that relied

on urinary [TIMP2]×[IGFBP7] AKI risk stratification. The ERASS recommends the use of [TIMP-2] ×[IGFBP7] in preoperative care for cardiac surgery [7]. It is utilized for early detection of high-risk patients and guidance on intervention strategies to reduce AKI.

3.2 Sepsis-Associated AKI

One significant predictor of the emergence of AKI is sepsis. More than 30% of sepsis patients and more than 50% of septic shock individuals have AKI. Specific organs as well as the entire body are affected by the bacteria that cause sepsis and their toxins. High amounts of damaging chemicals can enter proximal tubular cells and cause renal injury, oxidative stress, inflammation, and ultimately cellular destruction. Individuals admitted from the emergency room to the ICU staying shorter than 48 hours were included in prospective observational research. Before ICU admission, the [TIMP2]×[IGFBP7] index was examined twice in the 12 hours prior. The findings demonstrated that in critically sick patients who were both septic and non-septic, [TIMP2]×[IGFBP7] predicted AKI as opposed to other renal biomarkers. These biomarkers are very helpful in quickly identifying patients who do not have AKI from those who are extremely probable to getting AKI. The [TIMP2]×[IGFBP7] index is also capable of excluding patients in our research group who needed renal replacement therapy (RRT) below a threshold value of 0.8

((ng/mL)²/1000) [8].

Additionally, a second cohort study recruited patients who had AKI while in septic shock using the Protocol for the Care of Early Infectious Shock (ProCESS), which included critically ill patients with infectious shock between 2008 and 2013. The study discovered that patients with functional AKI who would have a worse 30-day survival rate could be identified by an increase in urinary [TIMP2]×[IGFBP7] levels [9]. Furthermore, monitoring changes in urine [TIMP2]×[IGFBP7] following first fluid resuscitation in the first six hours of sepsis revealed patients at varying risks of unfavorable outcomes, according to a similar protocol-based trial of early septic shock therapy [10].

3.3 Pediatric AKI

AKI is a common independent risk factor for morbidity and mortality in children in addition to being a serious health issue in adults. About 10% of children in pediatric intensive care units (PICUs) emerge from AKI. As the severity of the illness worsens, this percentage rises to almost 80%. It is still estimated that up to 60% of seriously ill children die from AKI. Furthermore, the etiology of AKI varies in juvenile and adult patients in terms of both frequency and severity. Therefore, research on AKI in children is essential. In an upcoming cohort investigation, 133 participants between the ages of 0 and 18 had their

urinary [TIMP2]×[IGFBP7] concentrations measured using a commercially available immunoassay (NephroCheck™). Of these, 46 patients had AKI diagnosed based on the RIFLE criteria, 27 patients did not have AKI, and 60 neonates and children who appeared to be in good health. According to the findings, patients in the “failure” phase had a median urine [TIMP2]×[IGFBP7] that was 3.7 times higher than that of non-AKI patients (P<0.001). Elevated [TIMP2]×[IGFBP7] values related to the degree of renal impairment according to the RIFLE classification, and merely a single measurement of [TIMP2]×[IGFBP7] exhibited strong diagnostic performance in predicting death in the combined neonatal and pediatric AKI sample [11].

Furthermore, 94 infants (age of 154.2±85.7 days) were included in multicenter prospective research of infants undergoing cardiac surgery with extracorporeal circulation (CPB). The study discovered that patients with AKI had a significantly higher concentration of [TIMP2]×[IGFBP7] 12 hours after CPB initiation than at baseline (p=0.006). Patients with [TIMP2]×[IGFBP7] concentrations≥0.78 had a threefold increased risk of developing AKI in comparison to those with concentrations <0.78. Thus, concentrations of [TIMP2]×[IGFBP7] can be utilized to forecast AKI defined by serum creatinine in newborns upon CPB [12].

Table 1. Clinical applications of [TIMP2]×[IGFBP7] in AKI after cardiac surgery, AKI in pediatric, and sepsis-related AKI.

Authors	Design	Subjects	Tests	Results	References
Couturier et al. 2021	Single-center study	382 patients undergoing cardiac surgery	Implementation of urinary [TIMP-2]×[IGFBP7]	A significant reduction in AKI incidence	[7]
Cuartero et al. 2017	Prospective observational study	98 patients in ICU	[TIMP2]×[IGFBP7] index was analyzed	[TIMP2]×[IGFBP7] predicted AKI in septic	[8]
Molinari et al. 2022	Cohort study	999 patients	AKI stage after enrollment was evaluated.	Biomarker-positive patients had lower survival and higher mortality	[9]
Fiorentino et al. 2020	Protocol-based trial	688 patients with septic shock	[TIMP-2]×[IGFBP7] before and after resuscitation was measured.	[TIMP-2]×[IGFBP7] changes identify sepsis patients in different AKI stages	[10]
Westhoff et al. 2015	Prospective cohort study	133 patients	[TIMP-2]×[IGFBP7] was accessed by NephroCheck™.	[TIMP-2]×[IGFBP7] has a good diagnostic performance in AKI	[11]

Gist et al. 2017	Multicenter prospective study	94 infants	[TIMP-2]×[IGFBP7] was measured using the Astute 140®.	In newborns, the concentration of [TIMP-2]×[IGFBP7] can be utilized to predict the eventual serum creatinine-defined AKI.	[12]
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4. Conclusion

In summary, this article describes the biomarkers of AKI, introduces cell cycle block, and accounts for [TIMP2]×[IGFBP7] in AKI in three areas: pediatrics, post-cardiac surgery, and sepsis. Renal cell stress is largely caused by cell cycle block, and the cell cycle block biomarkers TIMP-2 and IGFBP-7 are markers of both facets of this intricate physiology. In terms of practical use, the incidence of AKI following heart surgery is decreased by renal supportive therapy predicated on urine [TIMP2]×[IGFBP7] AKI risk classification. Monitoring for changes in urinary [TIMP2]×[IGFBP7] identifies patients at different risk for adverse sepsis outcomes. [TIMP2]×[IGFBP7] also has good diagnostic performance in predicting AKI mortality in children. Future studies should focus more on enhancing the understanding of [TIMP2]×[IGFBP7] itself and exploring their use for detection in more diseases.

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