TIMP2 and IGFBP-7 as Biomarkers For The Diagnosis of Acute Kidney Injury (AKI) in Post-operative Patients: An Evidence-based Case Report

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ABSTRACT

Background: *Acute kidney injury (AKI) is defined as a sudden reduction in kidney function which commonly occurs as a complication of major surgeries. It is traditionally diagnosed using serum creatinine elevation. AKI has relatively slow kinetics that makes it unable to diagnose at an earlier more reversible stage. Furthermore, previous research has shown that TIMP-2 and IGFBP7 were urinary biomarkers to use as a diagnostic tool for AKI. We aimed to compare the accuracy of TIMP2 and IGFBP-7 to the gold standard (serum creatinine) in diagnosing AKI in postoperative patients.* ***Methods:*** *A thorough search was performed using a search strategy on EMBASE, PubMed, and Medline (Ovid) using keywords according to the objective. The collected articles were critically appraised using CEEBM critical appraisal tool.* ***Results:*** *5 studies that fulfilled the inclusion criteria were selected and evaluated. They all stated that the use of TIMP2 and IGFBP7 could not detect AKI better than the gold standard as shown in the sensitivity and specificity of the biomarkers. Furthermore, the examination of AKI using both biomarkers showed a sensitivity of 60-100% and specificity of 58-91%.* ***Conclusion:*** *TIMP2 and IGFBP7 are promising diagnostic tools for AKI. However, due to the wide variation in results amongst the different studies, further research is required to ensure the credibility of this result.*

Keywords: *Postoperative AKI, Diagnosis, TIMP2, IGFBP7, Serum Creatinine Level*

INTRODUCTION

Acute kidney injury (AKI) is defined as a sudden reduction in kidney function. It is a common complication of major surgeries resulting in a significant increase in mortality and morbidity.[1] The diagnosis of AKI has remained unchanged over the years and is based on the acute rise of SCr and/or a decline in urine output over time. SCr elevation, however, has proven to be an imperfect gold standard due to its relatively slow rise[2], disabling it from detecting AKI early on, during a potentially reversible stage.[3] This prompts the search for potential biomarkers with comparable accuracy to SCr that are able to detect AKI at an earlier stage. An example is the urinary cell-cycle arrest markers, namely TIMP-2 and IGFBP7, whose levels were found to increase following a kidney injury.[4] Both TIMP-2 and IGFBP7 are urinary cell-cycle arrest markers that are secreted by the tubule cells of the kidney. They are capable of inducing G1 cell cycle arrest and differential in secretion localization can predict kidney damage. Research stated that the used of both the markers simultaneously added the predictive value in diagnosing AKI. Nephrocheck is the brand used to diagnose both these markers simultaneously.[4] The clinical and economic

benefits of these biomarkers in diagnosing AKI have been previously evaluated in the US hospital system settings by Berdugo MA, et al. Currently, they have not been evaluated in the Indonesian hospital setting. Furthermore, studies investigating the potential use of TIMP-2 and IGFBP7 in the diagnosis of AKI compared to SCr were collected and analyzed. They were also evaluated to know whether these biomarkers have enough potential to be implemented in Indonesia.

CASE ILLUSTRATION

A 63-year-old male underwent cardio-pulmonary bypass without abnormalities in a tertiary hospital in Indonesia. The patient was then transferred to the general ward and monitored. Laboratory tests (blood and urine) were performed, and the results did not indicate any abnormalities (serum creatinine level 1.1 mg/dL and he was hemodynamically stable) and thus he was treated in the general ward. Suspicion was made after his surgery and Nephrocheck (TIMP2*IGFBP7) was used and found that there were increasing amounts of the biomarkers. He was then admitted to intensive care unit (ICU) due to suspected AKI for early treatment. In ICU, his blood pressure kept increasing from 140/90 to 180/110 mmHg and his SCr increased to 4.7 mg/dL during 3 days after the surgery. He was then diagnosed with Acute Kidney Injury (AKI) and severe hypertension related to the surgery.

CLINICAL QUESTION

Do TIMP-2 and IGFBP7 (Nephrocheck) provide a good accuracy in diagnosing AKI as a postoperative complication, considering its capability of early detection?

METHODS

Search Strategy

A thorough search was performed in three databases, namely EMBASE, Medline(Ovid), and Pubmed, utilizing MesH terms and keywords (**Table 2**). This made it possible to obtain studies investigating the accuracy of TIMP2 and IGFBP7 compared to SCr in diagnosing postoperative AKI. Furthermore, these searches were performed on October 29, 2021 as shown in **Figure 1**.

Eligibility Criteria

Studies were screened based on the following criteria, namely to investigate AKI, which is defined by either an increase in SCr by 0.3 mg/dl (or 26.5 lmol/l) within 48 hours or by 1.5 times baseline, which is presumed to have occurred within the prior 7 days or Urine volume < 0.5 ml/kg/h for 6 hours. Based on KDIGO[5], this involved patients in a postoperative setting older than 18 years old, whereby TIMP2 and IGFBP7 alongside SCr were measured. Scr was used as the compactor because we believe that SCr is still the gold standard in diagnosing AKI. However, we are trying to investigate the diagnosis accuracy of TIMP2 and IGFBP7 in diagnosing AKI in early stages. Studies that investigated pregnant and pediatric patients, and also did not provide full texts or utilize other languages other than English and Bahasa Indonesia, were excluded.

Study Selection

This was performed simultaneously by about four people carried out this process which involved passing the studies through independent screening. The titles, abstracts, and the ones that passed this phase were screened

Tabel 1. PICO Framework.

Patient/Problem (P)	Intervention (I)	Comparison (C)	Outcome (O)
Patients who underwent surgery suspected of AKI as a postoperative complication	Combination of TIMP-2 and IGFBP7 (Nephrocheck)	Serum Creatinine	Diagnosis of postoperative AKI
Type of Clinical Question	Diagnosis		
Study Design	Evidence Based Case Report		

Table 2. Search Terms Per Database.

Database	Search strategy	Hits	Selected articles
PubMed	((((TIMP2[Title/Abstract]) OR (TIMP-2[Title/Abstract])) AND ((IGFBP-7[Title/Abstract]) OR (IGFBP7[Title/Abstract]) OR (Nephrocheck[Title/Abstract])) AND ((acute kidney injur*[Title/Abstract]) OR (AKI[Title/Abstract]) OR (acute renal injur*[Title/Abstract])) AND ((diagnos*[Title/Abstract]) OR (detect*[Title/Abstract])) AND ((creatinine) OR (scr) OR (gold standard)) AND (sensitiv*) AND (specific*) AND ((surger*) OR (postoperative) OR (post-operative) OR (post-op)))	2	5
EMBASE	((timp2 OR 'timp 2') AND ('igfbp 7' OR igfbp7) OR nephrocheck) AND (acute AND kidney AND injur* OR aki OR (acute AND renal AND injur*)) AND (diagnos* OR detect*) AND (creatinine OR scr OR (gold AND standard)) AND sensitiv* AND specific* AND (surger* OR (post AND operative) OR 'post operative' OR 'postoperative complication'/exp OR 'postoperative complication')	21	
MEDLINE	((timp2 OR 'timp 2') AND ('igfbp 7' OR igfbp7) OR nephrocheck) AND (acute AND kidney AND injur* OR aki OR (acute AND renal AND injur*)) AND (diagnos* OR detect*) AND (creatinine OR scr OR (gold AND standard)) AND sensitiv* AND specific* AND (surger* OR (post AND operative) OR 'post operative' OR 'postoperative complication'/exp OR 'postoperative complication')	24	

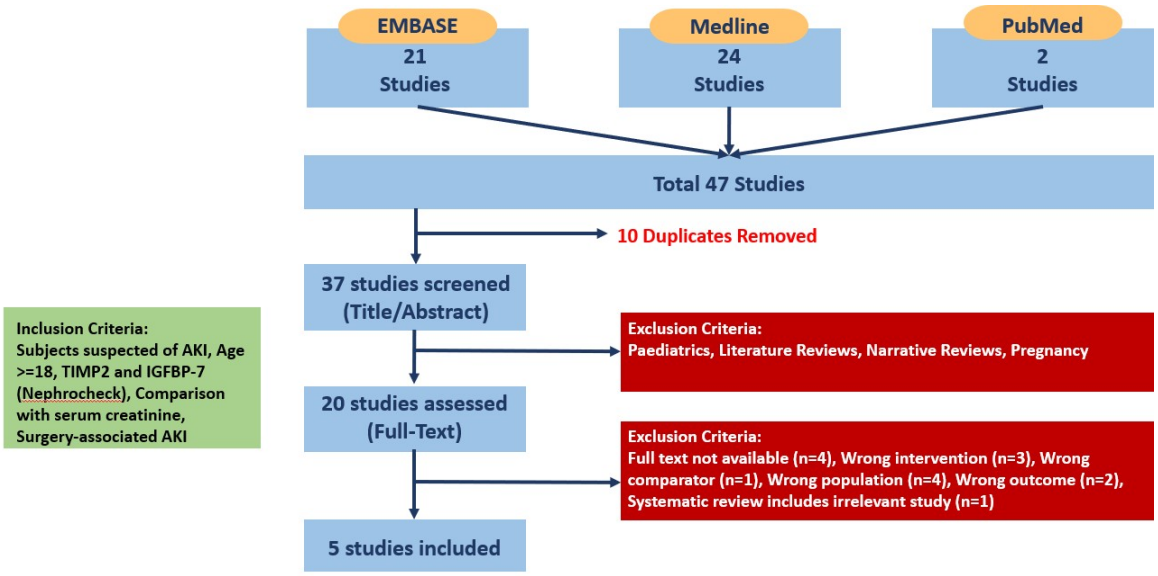

Figure 1. Study Selection Flow Chart.

thoroughly in each of their full texts against the eligibility criteria. A discussion between the two conflicting reviewers was also held in order to reach a consensus in cases of conflicting decisions during the study selection. However, in a situation whereby a consensus was not reached, a third reviewer would provide a final decision. Covidence© was used to perform this selection in order to ensure the accuracy of the selected study.

Critical Appraisal

Critical appraisal was performed using Oxford CEBM diagnostics critical appraisal sheet.

RESULTS

Search Results

Based on the search from the three databases, 47 studies were retrieved consisting of 10 duplicates (**Figure 1**). The remaining had their title and abstract, and later the full text screened against the eligibility criteria. In the full-text screening phase, 15 studies were excluded due to the following reasons namely, 4 studies did not have a full-text version, 3 assessed different biomarkers in combination with Nephrocheck, one study did not include gold standard comparison (SCr), and 4 studies were excluded as it assessed pediatric population. Furthermore, one study used Nephrocheck as a predictor of renal recovery instead of a diagnosis of AKI, another measured the incidence of AKI instead of the accuracy of the diagnostic tools and one systematic review included irrelevant studies. The full-text screening phase resulted in 5 studies which were later critically appraised.

Critical Appraisal

This was performed on the selected studies and the result are summarized in **Table 3**. It was concluded that they were valid and important for the patients. However, about three studies[6–8] did not perform blinding. Based on the applicability test, it was inferred that some were not applicable because the diagnostic test was not available in Indonesia. In addition, 4 out of the 5 studies showed a low percentage of post-test probability. The ones that were selected aimed to determine the level of TIMP2, IGFBP7, and SCr in specific time points and compare the concentration between the biomarkers and SCr as summarized in **Table 4**.

24 hour TIMP2 and IGFBP7 level in detecting AKI

All studies, except for Meersch et al, measured the urinary biomarkers after 24 hours timepoint. There were different cutoff values of

Table 3. Summary of Critical Appraisal Results Performed on the Five Remaining Studies.

			Validity			Importance			Applicability				
Study	Sample Size	Study Design	Representative Patient Spectrum	Compared to Gold Standard	Independent/ Blind Comparison	Sensitivity	Specificity	Likelihood Ratio	Diagnostic test is available, affordable, accurate	Clinical Estimate of Prevalence	Affect Patient Management	Consequences help patients	LOE#
Meersch, et al (2014)	50	Cohort	✓	✓	✓/-	73%	58%	1.74*	-	✓	-	✓	2b
Dusse, et al (2016)	40	Cohort	✓	✓	✓/✓	100%	91%	11.11*	-	✓	✓	✓	2b
Oezkur, et al. (2017)	148	Cohort	✓	✓	✓/-	60%	69%	1.94*	-	✓	-	✓	2b
Mayer, et al. (2017)	110	Cohort	✓	✓	✓/-	77.8%	64.1%	2.17*	-	✓	-	✓	2b
Pilarcyzk, et al. (2015)	60	Cohort	✓	✓	✓/✓	89%	81%	4.68*	-	✓	-	✓	2b

Table 4. Summary of Findings in the Selected Studies.

Author	Patient group	Outcome	Key results	Comments
Dusse, et al.	40 patients with	[TIMP2]*[IGFB	In KDIGO AKI 0/1:	In patients underwent TAVI, [TIMP
(2016), BMC	severe symptomatic	P7] urine	- No significant rise of [TIMP2]*[IGFBP7] urine concentration at	2]*[IGFBP7] concentrations within
Anesthesiology	aortic stenosis who underwent transapical or transaortic	concentration compared to serum creatinine	all times - Serum creatinine and eGFR remained stable at all times;	24 h after surgery is associated with the onset of AKI within the next 72 h.
Cohort study (2b)	Transcatheter Aortic Valve Implantation (TAVI) were included	(sCr)	In KDIGO AKI 2/3: - [TIMP2]*[IGFBP7] increased significantly on 1st postoperative day (POD) (4.62 ± 3.14 (ng/ml)2/1000) - sCr elevated on POD 2 with a maximum of 1.64 ± 0.99 mg/dl [TIMP2]*[IGFBP7] elevated as early as 24h after TAVI	[TIMP 2]*[IGFBP7] urine concentrations show an excellent diagnostic accuracy for the prediction of severe AKI requiring RRT. .
		Sensitivity and specificity of [TIMP2]*[IGFB P7] (Diagnostic accuracy)	Diagnostic accuracy for [TIMP2]*[IGFBP7] 4h after intervention was better than using serum creatinine concentration with sensitivity of 75% and specificity of 55.6% (AUC 0.646). One day after TAVI, [TIMP2]*[IGFBP7] showed sensitivity of 100% and specificity for KDIGO 2 / 3 (AUC 0.971). Within 24 hours after TAVI, [TIMP2]*[IGFBP7] showed sensitivity of 87.5% and specificity of 82.8% (AUC 0.869) compared to serum creatinine concentration.	
Oezkur, et al. (2017), Kidney Blood Press Res **Cohort study (2b)**	148 patients undergoing elective cardiac surgery	Value of [TIMP-2*IGFBP7] compared to serum creatinine (sCr) 24 hours post surgery	24h post surgery measurement of [TIMP2]*[IGFBP7] had significant result.(OR 2.11, p=0.06, sensitivity 60%, specificity 69%). PPV= 57.1%, NPV= 89.9%	It was concluded that early detection of elevated [TIMP-2*IGFBP7] at ICU admission was more likely to predict postoperative AKI compared to subsequent measurements
Meersch et al (2014), PLOS one Cohort Study (2b	50 patients undergoing cardiac surgery	Biochemical value and performance of [TIMP-2*IGFBP7] for early diagnosis of AKI	The first 24 h after surgery urine [TIMP-2]*[IGFBP7] using cutoff 0.3 yielded sensitivity of 73% and specificity 58% (AUC: 0.90, CI:0.79–1.00) PPV=0.66 NPV=0.67, when compared to serum creatinine Maximum [TIMP2]*[IGFBP7] value was achieved at 24h 24 patients who did not develop AKI showed no statistically significant increase in [TIMP2]*[IGFBP7	Urinary [TIMP-2]*[IGFBP7] serves as a sensitive and specific biomarker to diagnose AKI early after cardiac surgery and to predict renal recovery.

Pilarczyk, et al. (2015), Ann Intensive Care	60 patients (>18 y.o.) undergoing CABG	Post-operative course of [TIMP-2]*[IGFBP7] and serum creatinine	In patients with AKI 0/1: - No significant rise of urinary [TIMP-2]*[IGFBP7] was observed at all times - sCr remains stable at all times	Urinary [TIMP-2]*[IGFBP7] (G2 cell cycle arrest iomarkers) allow earlier diagnosis of AKI compared to creatinine-based definition of AKI
Cohort study (2b)		Diagnosis of AKI with [TIMP-2]*[IGFBP7] on the 1st postoperative day	In patients with AKI 2/3: - [TIMP-2]*{IGFBP7] increased significantly 4 hrs post surgery; reached maximum level on 3rd day - sCr elevation observed at POD 2 - POD 4, reached maximum at POD 3 & 4 Accuracy of [TIMP-2]*[IGFBP7] at AKI diagnosis: - sensitivity 0.80, specificity 0.81 (cut-off value 0.89); CI 0.696-1.0, $p = 0.04$	
Mayer et al (2017), Journal of Cardiothoracic and vascular anesthesia	110 patients (>18 y.o.) underwent cardiac surgery	Urine levels of [TIMP-2]*[IGFBP7] at an early time point after surgery for prediction of AKI	1 hour after the start of CPB, the levels of TIMP-2*IGFBP7 were measured to predict postoperative AKI. Sensitivity and specificity were found to be 0.778 and 0.641, respectively. Positive and negative predictive values were also calculated (0.156 and 0.972, respectively).	Urine levels of TIMP-2 IGFBP7 are able to diagnose AKI at 1 hour afe CPB. TIMP-2 and IGFBP7 may be recommended for supplementary criteria of AKI prediction.

[TIMP2]*[IGFBP7], three studies[6,8,9] utilized 0.3, while Pilarcyzk et al., and Mayer et al., utilized 0.817 and 0.41 respectively. Dusse et al., reported the best sensitivity and specificity (100% and 91%) while others[6–8,10] reported different values ranging from 60% - 89% and 58% - 81% respectively. As for the likelihood ratio, it was manually calculated and it was found that only Dusse et al., (11.1) reported a significantly favorable likelihood ratio. However, Meersch et al., and Oezkur et al., reported an unfavorable likelihood ratio, namely 1.74 and 1.94 respectively.

DISCUSSION

The diagnosis of AKI is usually performed by following the diagnostic criteria of Kidney Disease, such as Improving Global Outcome (KDIGO) of AKI [5] using creatinine elevation as the focus of the measurement. However, this diagnosis method poses limitations because of its incapability in diagnosing AKI at its earliest point before the disease becomes irreversible.[3] TIMP-2 and IGFBP7 are stress markers that are rapidly secreted during kidney injuries.[4] These biomarkers were used as detection methods of AKI at its earliest development.[9] Furthermore, all studies assessed within this case report presented similar findings such as increased levels of TIMP-2 and IGFBP7 within 24 hours of surgery. This is in line with previous findings that [TIMP2]*[IGFBP7] accurately identified patients with increased risk of AKI in an earlier time frame postoperatively.[3,11,12]

Dusse, et al.,[9] and Pilarczyk, et al.,[10] examined the diagnostic accuracy of [TIMP-2]*[IGFBP7] in diagnosing AKI by comparing it to the concentration of SCr level in several time points. Different from the other cohort studies, this study performs blinding on the investigators, which reduces information bias. However, Dusse, et al., and Pilarczyk et al., had a low sample size with 40 and 60 samples respectively, which was justified by their sample size calculator but risked a less representative result. In summary, both studies reported high diagnostic accuracy of [TIMP-2]*[IGFBP7] and were the only ones whose likelihood ratio indicated that [TIMP-2]*[IGFBP7] provided benefits in diagnosing AKI.

Mayer et al.,[7] employed a larger sample size of 110 subjects to examine the diagnostic capability of [TIMP-2]*[IGFBP7] in diagnosing AKI. The samples were consecutive patients which reduced selection bias. The measurement of urinary biomarkers was performed one hour after the surgery unlike other studies (within 24 hours), which tested their early capability in diagnosing AKI. However, this study poses limitations, such as being a single-center cohort and having low number of AKI events which lead to limited evidence for the obtained results.

In the study by Meersch, et al.[8] the samples were heterogeneous and had comorbidities associated with AKI, and the result showed TIMP2 and IGFBP7 performed well in predicting AKI. Both biomarkers had significantly higher specificity and sensitivity in diagnosing AKI. However, this study had a relatively small sample size of 50 from a single center. As a result, a larger population is required to validate the result despite the statistical and clinical significance.

Oezkur, et al.[6] had the largest sample when compared to other prospective cohort studies exploring AKI diagnosis in post-cardiac surgery patients. They excluded patients with chronic kidney diseases from their sample. Therefore, the use of TIMP2 and IGFBP7 as AKI diagnostic tools in these groups of patients is unknown.

In summary, the sensitivity and specificity results of Nephrocheck reported by the studies seemed to vary by quite a wide margin ranging from 60-100% for sensitivity and 58-91% for specificity. This indicates that the probability of a patient with AKI and being tested positive was 60-100% and those without AKI and tested negative was 58-91%. This variation may have occurred because the studies employed different [TIMP-2]*[IGFBP7] cut-off values. Therefore, further studies need to be carried out in order to assess the value of [TIMP- 2]*[IGFBP7] in diagnosing postoperative AKI, especially in determining a standardized cut- off value.

The highest likelihood ratio of 11.11 was reported by Dusse, et al., and this indicates that when Nephrocheck was used to detect AKI, the result was 11.11 times more suitable for patients suffering from this disease. Furthermore, they had positive results than those that were not suffering from AKI. This result is significantly higher than the LR from the other four studies included. There is a possibility of different methods and factors, including blinding, surrounding the population leading to this peculiarity. Therefore, there needs to be standardized and controlled study methods to ensure the credibility of this finding.

This case report posed several strengths which include the utilization of 3 renowned scientific databases to search for relevant studies. This was carried out using an independent screening process in order to ensure objectivity in the study selection process. On the other hand, the limitation of this case report was a language barrier that caused several studies to be excluded. Besides this case report also did not standardize the methodology of the appraised studies.

CONCLUSION

The [TIMP-2]*[IGFBP7] value was reported to be a promising AKI diagnostic tool that was able to diagnose postoperative AKI earlier. However, it seemed to be significantly influenced by the degree of severity, favouring moderate-to-severe AKI leading to a variety of results, and

more studies are required to ensure its credibility. Though [TIMP-2]*[IGFBP7] value is a promising diagnostic tool, it is not still recommended in diagnosing postoperative AKI.

ACKNOWLEDGMENTS AND AFFILIATIONS

The authors are grateful to the Faculty of Medicine, Universitas Indonesia for the opportunity to conduct this report under professional guidance.

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