The Association Between Urine TIMP2*IGFBP7 and Successful Discontinuation of Renal Replacement Therapy in Patients with Acute Kidney Injury: A Prospective Observational Study

Teeraporn Suttayamook, Pongsathorn Gojaseni

Division of Nephrology, Department of medicine, Bhumibol Adulyadej Hospital, Royal Thai Air Force

Abstract

Background: Currently, there are no recommendations in terms of timing for discontinuation of intermittent kidney replacement therapy (IKRT) in acute kidney injury (AKI). Cell cycle arrest biomarkers including urine tissue inhibitor of metalloproteinase-2 (TIMP2) and urine insulin-like growth factor binding protein-7 (IGFBP7) have been shown to have good performance in predicting AKI in different groups of patients. Recent evidence also suggests the ability of urine cell cycle arrest biomarkers in predicting renal recovery. The present study evaluated the association between urine TIMP2*IGFBP7 levels and successful discontinuation of intermittent hemodialysis in patients with AKI.

Methods: We prospectively enrolled medical and surgical patients who were diagnosed with AKI based on KDIGO 2012 criteria and required intermittent hemodialysis from July 2021 to January 2022. Urine volume, serum creatinine, and urine TIMP2*IGFBP7 were measured before every session of hemodialysis that was likely to be the last session. The primary outcome was the successful discontinuation of IKRT for 14 days.

Results: Thirty-nine sessions of hemodialysis from 17 patients were included. Successful termination of IKRT for 14 days followed 8 (20.51%) of the 39 sessions. There was no association between urine TIMP2*IGFBP7 and the outcome with the area under the receiver operating characteristic curve (AUC) of 0.55 [95% confidential interval (CI) 0.32-0.77, P=0.66]. On the other hand, 24-hour urine volume prior to hemodialysis session had a fair performance in predicting successful discontinuation of IKRT with the AUC of 0.76 [95% CI 0.56-0.96, P=0.023]. The optimal cut-point of urine volume was >1,478 ml/day (Youden's index 0.49)

Conclusion: There was no association between urine TIMP2*IGFBP7 levels and successful discontinuation of IKRT in patients with AKI. 24-hour urine volume prior to hemodialysis session showed a fair predictive performance of renal recovery.

Keywords: acute renal failure; urine biomarkers; renal recovery; TIMP2; IGFBP7

Corresponding author: *Teeraporn Suttayamook*
Email: *teerasu107@gmail.com*

Received: 24 February 2023; Revised: 14 April 2023; Accepted: 1 May 2023

All material is licensed under terms of the Creative Commons Attribution 4.0 International (CC-BY-NC-ND 4.0) license unless otherwise stated.

ความสัมพันธ์ระหว่างระดับของ TIMP2*IGFBP7 ในปัสสาวะกับการหยุดการบำบัดทดแทนไตได้สำเร็จในผู้ป่วยภาวะไตวายเฉียบพลัน: การศึกษาเชิงสังเกตแบบไปข้างหน้า

ธีราภรณ์ สัตยมุข, พงศธร คชเสนี

หน่วยโรคไต ภาควิชาอายุรศาสตร์ โรงพยาบาลภูมิพลอดุลยเดช กรมแพทย์ทหารอากาศ

บทคัดย่อ

บทนำ: ปัจจุบันยังไม่มีแนวทางปฏิบัติที่ชัดเจนในการหยุดการบำบัดทดแทนไตในผู้ป่วยไตวายเฉียบพลัน ข้อมูลในปัจจุบันพบว่าระดับ tissue metalloprotease inhibitor 2 (TIMP2) และ insulin like growth factor binding protein 7 (IGFBP7) ในปัสสาวะมีความสามารถในการพยากรณ์การเกิดไตวายเฉียบพลันได้ค่อนข้างดีในผู้ป่วยหลายกลุ่ม และเริ่มมีข้อมูลที่แสดงความสัมพันธ์ระหว่างระดับ TIMP2*IGFBP7 ในปัสสาวะกับการฟื้นตัวจากไตวายเฉียบพลัน งานวิจัยนี้เป็นการศึกษาความสัมพันธ์ของระดับ TIMP2*IGFBP7 ในปัสสาวะกับความสำเร็จในการหยุดการบำบัดทดแทนไตด้วยการฟอกเลือดด้วยเครื่องไตเทียมในผู้ป่วยไตวายเฉียบพลัน

วิธีการศึกษา: การศึกษาแบบไปข้างหน้าในกลุ่มผู้ป่วยอายุรกรรมและศัลยกรรมที่ได้รับการวินิจฉัยภาวะไตวายเฉียบพลันตามเกณฑ์ของ KDIGO 2012 และได้รับการบำบัดทดแทนไตด้วยการฟอกเลือดระหว่างเดือนกรกฎาคม 2564 - มกราคม 2565 การศึกษามีการบันทึกข้อมูลปริมาณปัสสาวะ ระดับคริอะตินีนในเลือดและระดับ TIMP2*IGFBP7 ในปัสสาวะก่อนการฟอกเลือดในแต่ละครั้งที่น่าจะเป็นการฟอกเลือดครั้งสุดท้าย โดยจะศึกษาความสัมพันธ์ของปัจจัยดังกล่าวกับการสามารถหยุดฟอกเลือดได้สำเร็จเป็นระยะเวลานาน 14 วัน

ผลการศึกษา: ผู้ป่วยที่เข้าร่วมวิจัยมีจำนวนทั้งสิ้น 17 ราย และได้รับการเก็บข้อมูลของปริมาณปัสสาวะ ระดับคริอะตินีนในเลือดและระดับ TIMP2*IGFBP7 ในปัสสาวะก่อนการฟอกเลือดทั้งหมด 39 ครั้ง จากจำนวนการฟอกเลือดที่น่าจะเป็นครั้งสุดท้ายทั้งหมด 39 ครั้ง มี 8 ครั้ง (ร้อยละ 20.5) ที่ตามมาด้วยการสามารถหยุดการฟอกเลือดได้สำเร็จนาน 14 วัน จากการวิเคราะห์ข้อมูลไม่พบความสัมพันธ์อย่างมีนัยสำคัญทางสถิติระหว่างระดับ TIMP2*IGFBP7 ในปัสสาวะก่อนการฟอกเลือดกับความสำเร็จในการหยุดการบำบัดทดแทนไต โดยมีค่า area under the receiver operating characteristic curve (AUC) เท่ากับ 0.55 [95% confidential interval (CI) 0.32-0.77, P 0.66] ในขณะที่พบว่าปริมาณปัสสาวะ 24 ชั่วโมงก่อนการฟอกเลือดสามารถพยากรณ์ความสำเร็จในการหยุดการฟอกเลือดได้ [AUC of 0.76; 95% CI 0.56-0.96, P 0.023] โดยพบความสัมพันธ์มากที่สุดที่ระดับปัสสาวะ >1,478 มิลลิลิตรต่อวัน (Youden's index 0.49)

สรุป: การศึกษานี้ไม่พบความสัมพันธ์ระหว่างระดับ TIMP2*IGFBP7 ในปัสสาวะก่อนการฟอกเลือดกับความสำเร็จในการหยุดการบำบัดทดแทนไต แต่ปริมาณปัสสาวะ 24 ชั่วโมงก่อนการฟอกเลือดสามารถพยากรณ์ความสำเร็จใจการหยุดการบำบัดทดแทนไตได้

คำสำคัญ: ฟอกเลือด; ไตวาย; ไตบาดเจ็บ; พยากรณ์โรค; ทำนาย

Introduction

Acute kidney injury (AKI) is common in critically ill patients. Patients who require kidney replacement therapy (KRT) showed increased risk of mortality and development of chronic kidney disease (CKD). Approximately 10-30% of patients with AKI who require KRT remain on dialysis at discharge from the hospital.[1-3] The Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice

ผู้ประพันธ์บรรณกิจ: *ธีราภรณ์ สัตยมุข*
อีเมล์: *teerasu107@gmail.com*

รับบทความ: 24 กุมภาพันธ์ 2566; ปรับปรุงแก้ไข: 14 เมษายน 2566; รับตีพิมพ์: 1 พฤษภาคม 2566

All material is licensed under terms of the Creative Commons Attribution 4.0 International (CC-BY-NC-ND 4.0) license unless otherwise stated.

Guideline 2012 for AKI suggests discontinuing KRT when it is no longer required or not consistent with the goals of care. However, there are no data on timing or parameters that may predict successful discontinuation of intermittent kidney replacement therapy (IKRT) in AKI.[4] The decision to discontinue KRT largely depends on the perspective and experience of primary nephrologist. Tissue inhibitor metalloprotease 2 (TIMP2) and Insulin-like growth factor binding protein 7 (IGFBP7) produced and secreted from renal tubular cells during early stress exposure, are involved in the G1 phase of cell cycle arrest and play role in cell recovery. TIMP2*IGFBP7 have good performance in predicting the risk for AKI in many populations. Recent evidence also suggests TIMP2*IGFBP7 may be able to predict renal recovery. This study evaluated the association between pre-IKRT urinary TIMP2*IGFBP7 level and successful discontinuation of IKRT in critically ill patients.

Methods

This is a prospective observational study that was conducted at Bhumibol Adulyadej Hospital, Bangkok, Thailand. This study was approved by the Human Ethics Committee of Bhumibol Adulyadej Hospital, Royal Thai Air Force (Bangkok, Thailand) with the institutional board review number 67/64. Due to COVID-19 pandemic, informed consents were obtained by signature or verbally from all patients.

Study population

We prospectively enrolled medical and surgical patients who were admitted between July 2021 to January 2022. Sessions of IKRT from the enrolled patients were included in the analysis. The inclusion criteria were as follows: (1) age ≥18 years; (2) diagnosed with AKI according to KDIGO guidelines 2012; (3) required at least 2 sessions of IKRT (including those who were switched from continuous kidney replacement therapy (CKRT); (4) had the potential last IKRT session (causes of AKI were managed, urine output ≥ 200 ml/day, had none of the following metabolic abnormalities including serum potassium >6 mEq/L, ECG abnormalities, serum magnesium >3 mEq/L, arterial pH <7.15 or venous pH <7.12), had no signs or symptoms of volume overload and received any vasopressors at a dosage <0.1 mcg/kg/min. We excluded patients with chronic kidney disease stage G5 (CKD G5), kidney transplantation, glomerular diseases, thrombotic microangiopathy (TMA), obstructive uropathy, and the decision to forgo life-sustaining treatment.

Data collection

Baseline parameters including age, gender, weight, height, cause of AKI, underlying diseases, and 24-hour urine output before IKRT sessions were recorded. Sequential organ failure assessment (SOFA) score, acute physiology and chronic health evaluation (APACHE) II score and blood parameters including complete blood count, blood urea nitrogen, creatinine, albumin and electrolyte levels were measured before each IKRT session. Urine volume, 24-hour urine creatinine and serum creatinine were collected until the next IKRT session or for a maximum of 3 days post-IKRT session. Urinary TIMP2*IGFBP7 levels were measured before IKRT session. The primary outcome was the successful discontinuation of IKRT for 14 days. The secondary outcome was the successful discontinuation of IKRT for 28 days.

Biomarker measurements

Urine samples were collected prior to the IKRT session. Immediately after collection, 5 milliliters of urine were centrifuged at 3000 RPM for 10 minutes and stored at – 20 degrees Celsius. TIMP-2 and IGFBP7 were measured with the VITROS 5600 Integrated System (Astute Medical, San Diego, CA, USA). The VITROS 5600 Integrated System reports the product value of the two protein concentrations ([TIMP-2]*[IGFBP7]) in units of (ng/mL)2/1000.

Statistical analysis

Stata MP 13.0 (StataCorp LP, TX, USA) was used for statistical analyses. The Shapiro-Wilk normality test was used to identify the distribution of the data. Categorical data were reported as numbers and

percentages. Continuous data were reported as mean ± standard deviation (SD) or median (25th and 75th percentiles). Continuous data were compared using Mann–Whitney U and Student's T-test. Categorical data were compared using the Chi-square test. The causative association was tested by Poisson regression. The predictive ability was tested with the receiver operating characteristic (ROC) curve and the optimal cut-off value was determined by the Youden index. Statistical significance was indicated by a two-sided $p < 0.05$ for all analyses.

Results

During the study period, 17 patients with 51 sessions of IKRT were enrolled in the study. Twelve sessions were excluded because 7 sessions were from the patients who had CKD G5, and 5 sessions had protocol violation. Of 39 sessions included in the analysis, 8 sessions were followed by successful discontinuation of IKRT. The study diagram is shown in **Figure 1**. The mean age for all patients was 68.35 ± 17.60 years. Seven out of 8 successful IKRT discontinuation were sustained for 28 days. Most patients were female. The common underlying diseases were diabetes mellitus, hypertension and dyslipidemia. There was no significant difference in baseline characteristics between the two groups except for urine output. The level of pre-IKRT urine TIMP2*IGFBP7 was lower in the successful IKRT discontinuation group but the difference did not reach statistical significance [0.58 (0.20,1.26) and 0.88 (0.18,0.64); p=0.67] (**Table 1 and Figure 2a**). The group with successful IKRT discontinuation showed significantly higher 24-hour urine output prior to IKRT compared to unsuccessful discontinuation group (1,755 (683) milliliters vs. 1131.35 (566) milliliters, p= 0.04) (**Table 1 and Figure 2b**). The causative association analyzed by Poisson regression model showed no association between pre-IKRT urine TIMP2*IGFBP7 level and successful IKRT discontinuation at 14 days. (**Table 1**) On the other hand, we found that 24-hour pre-IKRT urine output ≥1,500 ml/day was associated with a higher rate of successful discontinuation of IKRT at 14 days. (estimated incidence rate ration (IRR) 5.36; 95% CI 1.24-23.08, P=0.01). From ROC curve analysis, we found an association between 24-hour pre-IKRT urine output and successful discontinuation of IKRT [AUC 0.76 (95% CI 0.56-0.96, P=0.023)]. The AUC of pre-IKRT urine TIMP2*IGFBP7 level for successful discontinuation of IKRT was 0.55 (95% CI 0.32-0.77, P=0.66). The combination of pre-IKRT urine output and urine TIMP2*IGFBP7 level did not improve the AUC (data not shown). However, the cutoff of 24-hour pre-IKRT urine output at 1,478 ml/day yielded good sensitivity and specificity in predicting successful discontinuation of IKRT (Youden's index 0.49). (**Figure 3**)

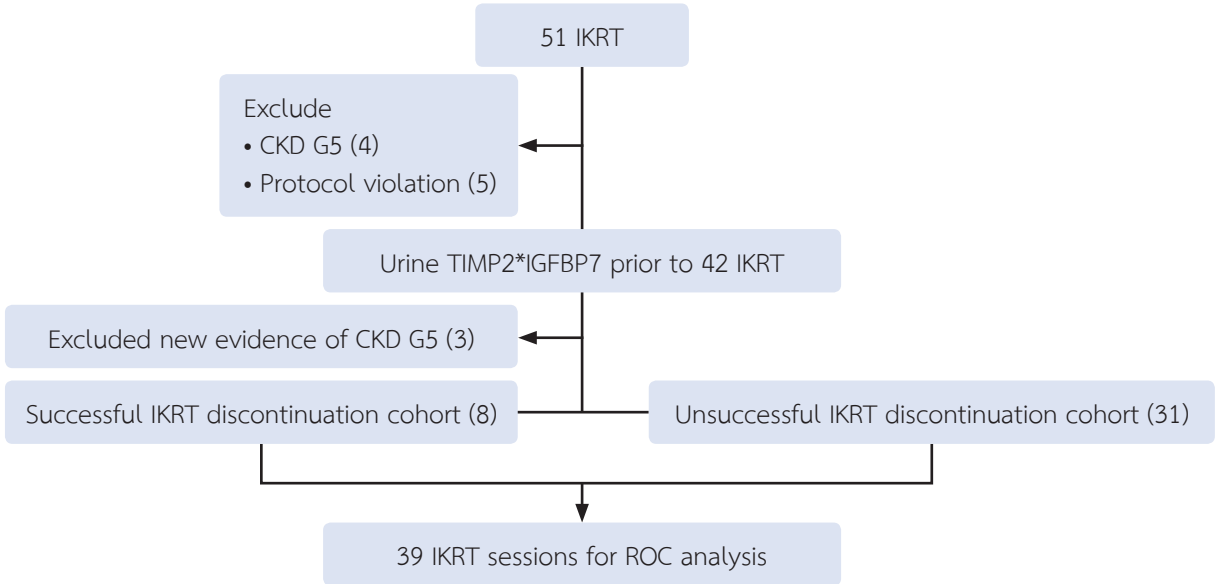

Figure 1 Study flow diagram

Table 1 Baseline characteristics of successful and unsuccessful discontinuation of kidney replacement therapy

Parameters	Successful discontinuation (n=8)	Unsuccessful discontinuation (n=30)	P-value
Age, years	62.87 (20.60)	69.77 (16.83)	0.55
Male, n (%)	3 (37.50)	11 (35.48)	0.92
Comorbidity, n (%)			
Diabetes mellitus	4 (50.00)	19 (61.29)	0.56
Hypertension	3 (37.50)	10 (32.26)	0.77
Dyslipidemia	2 (25.00)	11 (35.48)	0.57
Coronary artery disease	1 (12.5)	4 (12.9)	0.97
Cerebrovascular disease	1 (12.5)	4 (12.9)	0.97
CKD G3b	1 (12.5)	1 (3.23)	0.28
CKD G4	0 (0)	5 (16.13)	0.22
BMI, median in kg/m^2	22.42 (21.47,23.87)	24.52 (20.44,26.29)	0.43
Admission type, n (%)			
Medical	6 (83.87)	26 (65.00)	0.56
Surgical	2 (25.00)	5 (16.13)	0.56
KRT initiation, n (%)			
Intermittent KRT	5 (62.50)	24 (77.42)	0.38
Continuous KRT	3 (37.50)	7 (22.58)	0.38
Cause of AKI			
Septic	4 (50.00)	14 (45.16)	0.80
Ischemic	4 (50.00)	21 (61.74)	0.35
Covid-19 infection	1 (12.5)	5 (16.3)	0.80
SOFA score, Median	7.5 (6.5,8)	8 (6,9)	0.96
APACHE II score, Median	23 (20,28.5)	23 (18,28)	0.97
MAP, mmHg	101.12 (12.8)	94.36 (22.26)	0.79
Vasopressor usage, n (%)	1 (12.5)	1 (3.23)	0.28
Glasgow coma score	12.50 (1.97)	11.51 (1.92)	0.37
Urine output, ml/day	1,755 (68)	1131.35 (566)	0.04*
Laboratory data			
BUN, mg/dL	88.62 (48.02)	90.38 (26.70)	0.37
Creatinine, mg/dL	5.68 (3.67,8.21)	6.76 (4.92,6.76)	0.51
Hemoglobin, g/dL	9 (8.35,9.55)	9.3 (8.7,10.5)	0.76
Platelet, $/m^3$	310,375 (212,078)	210,774 (105,080)	0.42
Total bilirubin, mg/dL	1.20 (1.29)	3.24 (6.34)	0.33
pH	7.38 (7.36,7.42)	7.34 (7.32,7.4)	0.34
Sodium, mEq/L	136.5 (134.5,141.5)	137 (134,141)	0.64
Potassium, mEq/L	4 (3.9,4.7)	4.4 (3.9,4.8)	0.87
HCO_3, mEq/L	19 (17,22)	19 (16,23)	0.70
Urine TIMP2*IGFBP7	0.58 (0.20,1.26)	0.88 (0.18,0.64)	0.67

CKD, chronic kidney disease; BMI, body mass index; IKRT, intermittent kidney replacement therapy; AKI, acute kidney injury; MAP, mean arterial pressure

Table 2 Poisson regression models for factors associated with successful disontinuation of kidney replacement therapy

Parameters	IRR*	95% Confidence Interval	P-value
Urine TIMP2*IGFBP7 <0.21+	1.28	0.19-8.569	0.80
Urine TIMP2*IGFBP7 <0.3+	1.07	0.30-3.83	0.92
Urine TIMP2*IGFBP7 <0.975+	2.32	0.53-10.09	0.23
Urine TIMP2*IGFBP7 <2+	1.53	0.22-10.54	0.65
Pre- IKRT urine output ≥1,000 ml/day	1.68	0.39-7.24	0.47
Pre- IKRT urine output ≥1,500 ml/day	5.36	1.24-23.08	0.01
Pre- IKRT urine output ≥2,000 ml/day	4.08	1.38-12.02	0.02
APACHE II score <19	0.85	0.20-3.58	0.82
Lactate ≥ 2 mmol/L	0.79	0.122-5.29	0.80
BUN <50 mg/dL	1.71	0.30-9.92	0.55
Creatinine <4 mg/dL	1.52	0.39-6.14	0.55

*Estimated incidence rate ratio; +ln unit of (ng/mL)2/1000; IKRT, intermittent kidney replacement therapy

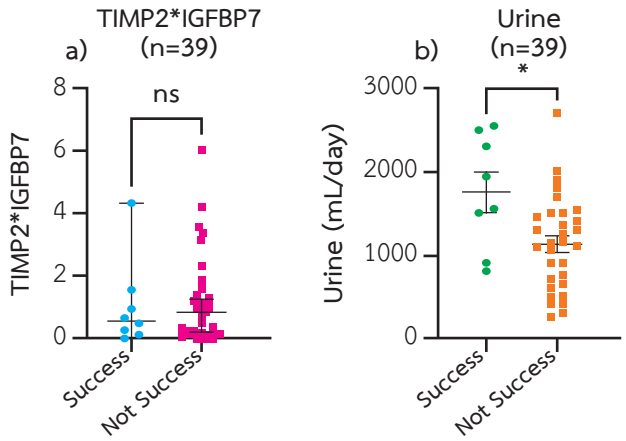

Figure 2 Differences in parameters associated with successful and unsuccessful discontinuation of intermittent kidney replacement therapy. a) urine TIMP2*IGFBP7 and b) 24-hour pre-IKRT urine output
IKRT, intermittent kidney replacement therapy

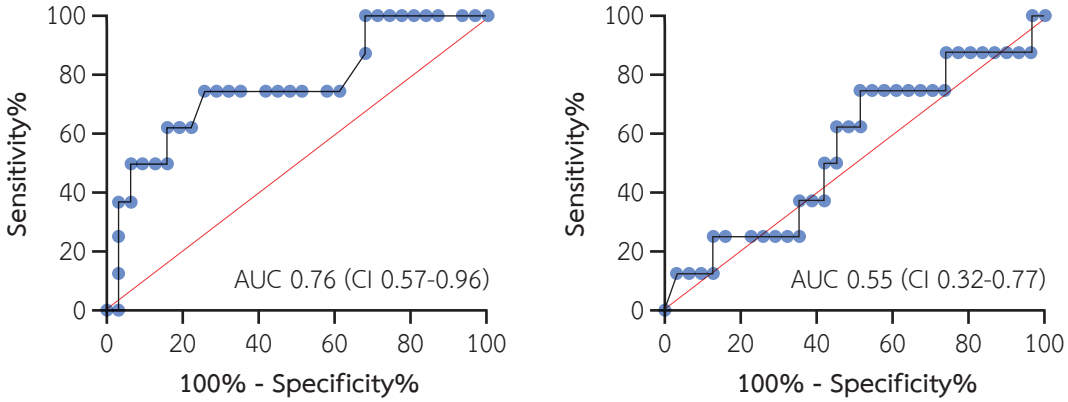

Figure. 3. Receiver Operating characteristic curve for successful discontinuation of intermittent kidney replacement therapy. a) 24-hour pre-IKRT urine output and b) pre-IKRT urine TIMP2*IGFBP7
IKRT, intermittent kidney replacement therapy; AUC, area under the curve

Discussion

Despite the suggestion by KDIGO guidelines 2012 to discontinue KRT when it is no longer required, there are no clear recommendations in terms of useful parameters or optimal timing for IKRT discontinuation in AKI. Most studies were conducted in CKRT population, and the parameter values varied depending on the timing (before or after IKRT) of data collection.[4] According to the systematic review, several variables have been identified as predictors for successful discontinuation of KRT but there was heterogenicity in the timing of measurement and threshold values, the pooled analysis was not possible. Despite this limitation, urine output before discontinuation of KRT was the most studied variable and seemed to be the most robust variable for prediction of IKRT discontinuation. However, the reported optimal cut-offs for pre-IKRT urine output varied between 191 ml/day to 2,330 ml/day.[5-7] Due to this wide range of pre-IKRT urine output, using urine output as the only parameter to predict KRT discontinuation may be unreliable.

Cell cycle arrest biomarkers, urinary TIMP2*IGFBP7 has been approved by FDA in 2014 for risk prediction of moderate to severe AKI in critically ill patients. These biomarkers are expressed and secreted from renal tubular cells after early renal stress. Urinary TIMP2*IGFBP7 are involved in G1 cell cycle arrest during the early phase of cellular stress and play a role in cell recovery. In theory, KRT may be discontinued when intrinsic renal function recovers. Unfortunately, there is no reliable parameter to predict the recovery of renal function. The ability of urinary TIMP2*IGFBP7 in predicting AKI is helpful in risk assessment.[8-12] The decline in urinary TIMP2*IGFBP7 after recovery of AKI has also been suggested in patients receiving cardiac surgery.[13-14]

In this study, we did not find a causative association between pre-IKRT urinary TIMP2*IGFBP7 level and successful discontinuation of IKRT at 14 days. On the other hand, 24-hour pre-IKRT urine output was associated with a higher rate of successful discontinuation of IKRT at 14 days. With the cut-off value of ≥1,478 ml/day, 24-hour pre-IKRT urine output showed a fair predictive ability. Our data agrees with the previous systematic review on the importance of urine output as a clinical marker to help guiding IKRT discontinuation.[5] To our knowledge, the present study was the first prospective study that evaluated the ability of urinary TIMP-2*IGFBP7 level in predicting successful discontinuation of IKRT. Limitations of this study include small number patients and the criteria for the last potential IKRT session were subjective. A larger study will be necessary to confirm the usefulness of urine TIMP-2*IGFBP7 in predicting successful discontinuation of IKRT.

In conclusion, pre-IKRT urinary TIMP2*IGFBP7 level did not show predictive performance for successful discontinuation of IKRT in AKI. Pre-IKRT urine output had a fair predictive ability for successful discontinuation of IKRT at 14 days.

Acknowledgements

This study was supported by The Kidney Foundation of Thailand. We would like to thank Wariya Sanrattana, B.Pharm, MSc., Ph.D from the Ministry of Public Health for her assistance in analyzing the data and preparing the figures.

References

1. Viallet N, Brunot V, Kuster N, et al. Daily urinary creatinine predicts the weaning of renal replacement therapy in ICU acute kidney injury patients. Ann Intensive Care. 2016;6(1):71.
2. Bellomo R, Kellum JA, Ronco C. Acute kidney injury. Lancet. 2012;380(9843):756-66.
3. Coca SG, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. Kidney Int. 2012;81:442–8.
4. The 2012 kidney disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for AKI Kidney International Supplement. 2012;1:2.
5. Katulka, R.J., Al Saadon, A., Sebastianski, M. et al. Determining the optimal time for liberation from renal replacement therapy in critically ill patients: a systematic review and meta-analysis (DOnE RRT). Crit Care. 2020;24(1):50.
6. Jeon J, Kim DH, Baeg SI, et al. Association between diuretics and successful discontinuation of continuous

renal replacement therapy in critically ill patients with acute kidney injury. Crit Care. 2018;22(1):255.

7. Uchino S, Bellomo R, Morimatsu H, et al. Discontinuation of continuous renal replacement therapy: a post hoc analysis of a prospective multicenter observational study. Crit Care Med. 2009;37(9):2576–82.
8. Liu C, Lu X, Mao Z, et al. The diagnostic accuracy of urinary [TIMP-2]·[IGFBP7] for acute kidney injury in adults: A PRISMA-compliant meta-analysis. Medicine (Baltimore). 2017;96(27):e7484.
9. Guzzi, L.M., Bergler, T., Binnall, B. et al. Clinical use of [TIMP-2]•[IGFBP7] biomarker testing to assess risk of acute kidney injury in critical care: guidance from an expert panel. Crit Care 2019 ;23(1):225.
10. Schanz M, Shi J, Wasser C, Alscher MD, Kimmel M. Urinary [TIMP-2] × [IGFBP7] for risk prediction of acute kidney injury in decompensated heart failure. Clin Cardiol. 2017;40(7): 485-91.
11. Wang, Y., Zou, Z., Jin, J. et al. Urinary TIMP-2 and IGFBP7 for the prediction of acute kidney injury following cardiac surgery. BMC Nephrol. 2017;18(1):177.
12. Yang QH, Liu DW, Long Y, et al. (2009) Acute renal failure during sepsis: potential role of cell cycle regulation. J Infect. 2009;58(6):459-64.
13. Jia, HM., Cheng, L., Weng, YB. et al. Cell cycle arrest biomarkers for predicting renal recovery from acute kidney injury: a prospective validation study. Ann. Intensive Care 2022; 12(1):14.
14. Meersch M, Schmidt C, Van Aken H, et al. Urinary TIMP-2 and IGFBP7 as early biomarkers of acute kidney injury and renal recovery following cardiac surgery. PLoS One. 2014;9(3): e93460.