Evaluation of the Diagnostic Utility of Urine Biomarkers Tissue Inhibitor of Metalloproteinases-2 (TIMP-2) and Insulin-like Growth Factor Binding Protein-7 (IGFBP-7) in Predicting Acute Kidney Injury and Short-term Outcomes among High-risk, Critically Ill Patients in a Tertiary Government Hospital in the Philippines

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ABSTRACT

Background and Objectives. Acute kidney injury (AKI) is a common complication of critical illness that often leads to increased mortality and morbidity. Biomarkers detect AKI earlier, providing a window of opportunity for timely intervention. Of the recent biomarkers in literature, the cell cycle arrest biomarkers tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor binding protein-7 (IGFBP-7) were found to be superior in predicting AKI. Our study aimed to evaluate the diagnostic performance of urine TIMP-2/IGFBP-7 in its ability to predict AKI and major adverse kidney events within 30 days (MAKE30) among high-risk patients for AKI. MAKE30 is a composite outcome comprised of all-cause mortality, use of renal replacement therapy (RRT), or persistent renal dysfunction at hospital discharge truncated at 30 days.

Methods. We conducted a prospective, cross-sectional study which included 135 adult, non-COVID ICU patients. Baseline urine TIMP-2/IGFBP-7 results were used to dichotomize the population into low risk (<0.3 ng/mL) or high risk (≥0.3 ng/mL) for AKI. Participants were then observed for 30 days and monitored for MAKE30 outcomes. ROC curves were created to calculate the sensitivity, specificity, NPV, PPV, and the AUC of the 0.3 ng/mL cut-off to predict the AKI and MAKE30.

Results. Urine TIMP-2/IGFBP-7 cutoff of 0.3 ng/mL predicted AKI with a sensitivity of 82.4%, specificity of 79.2%, PPV of 57.1%, NPV of 93% and AUC of 0.81. MAKE30 was detected with a sensitivity of 62.8%, specificity of 76.1%, PPV of 55.1%, NPV of 81.4% and AUC of 0.69. Elevated levels of urine TIMP-2/IGFBP-7 were found to be associated with AKI (p<0.01), MAKE30 (p<0.01) and all of its subcomponents. Survival or discharge after 30 days were found to be associated with lower urine TIMP-2/IGFBP-7 levels (p<0.01).

Conclusions. Urine TIMP-2/IGFBP-7, at its current cut-off at 0.3 ng/mL, can predict the likelihood of developing AKI and major adverse kidney events among high-risk patients for AKI. It can serve as a useful adjunct to existing methods, such as serum creatinine, in the early diagnosis and prognosis of acute kidney injury and expanding the therapeutic window to prevent disease progression and improve outcomes.

Keywords: acute kidney injury, biomarkers, urine TIMP-2/IGFBP-7

eISSN 2094-9278 (Online)

Published: September 13, 2024
https://doi.org/10.47895/amp.v58i16.7066

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INTRODUCTION

Acute kidney injury (AKI) is a common complication of critical illness that often leads to increased mortality, prolonged hospital stay, and a significant risk of cardiovascular and chronic kidney disease.[1] AKI also increases the need for renal replacement therapy (RRT) and its related complications.[2,3]

The current consensus definition of AKI is based on the 2012 Kidney Disease Improving Global Outcomes (KDIGO) – Clinical Practice Guidelines for AKI which relies on serum creatinine and urine output.[4] However, these two measures are already considered late markers of kidney damage. Not only is serum creatinine affected by multiple factors such as age, sex, and drug interactions, its levels only increase 48-72 hours after injury.[5] Urine output is far less specific as severe AKI may present as either oliguric or non-oliguric renal failure.[6]

Biomarkers provide a window of opportunity for earlier diagnosis and intervention to prevent disease progression. Of the recent renal biomarkers, the cell cycle arrest proteins, tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor binding protein-7 (IGFBP-7), were found to be superior in predicting AKI.[7] TIMP-2 and IGFBP-7, functioning as cell-cycle arrest proteins, actively participate in the regulation of cell growth and proliferation. In AKI, G1 cell-cycle arrest is frequently observed, and this arrest can be facilitated by the induction of p27KIP1 through TIMP-2 and p21 through IGFBP-7. Thus, the elevated concentrations of TIMP-2 and IGFBP-7 in urine hold potential as indicators for assessing both the existence and severity of AKI.[8] Available data on TIMP-2 and IGFBP-7 in chronic kidney disease is limited, however, the discovery and validation trials investigating urine TIMP-2 and IGFBP-7 did not report any specific effects of chronic kidney disease on the diagnostic capability of urine TIMP-2 and IGFBP-7 in detecting AKI.[7,9]

The currently available test kit for urine TIMP-2/IGFBP-7 in the Philippines is the Nephrocheck® system (distributed by Ortho Clinical Diagnostics Philippines). The test produces a single numerical AKI Risk® Score in a reportable range of 0.04 to 10.0. A cut-off value of <0.3 ng/mL is considered "Low risk" for developing acute kidney injury while values ≥0.3 ng/mL are "High risk".[10] Appropriate populations for testing include: ICU patients ≥21 years of age with one other risk factor for AKI such as cardiac or other major high-risk surgeries and sepsis. Urine TIMP-2/IGFBP-7 is not approved for patients under the age of 21, in the ambulatory setting, after minor surgeries, and patients with established AKI KDIGO stage II and stage III. It is also not applicable for daily serial measurement and cannot be used as a substitute for serum creatinine.[8,11]

Although several researches have assessed urine TIMP-2/IGFBP-7 in predicting acute kidney injury in different clinical scenarios, studies that explore its association with endpoints such as need for RRT, mortality, and persistent renal dysfunction are lacking. Moreover, none have been conducted locally or investigated its applicability to our local setting. Our study aimed to evaluate the diagnostic performance of urine TIMP-2/IGFBP-7 in its ability to predict acute kidney injury and short-term outcomes, specifically major adverse kidney events within 30 days of hospitalization, among our critically ill Filipino patients who are high risk for AKI.

METHODS

Study Design and Subjects

The study protocol was approved by the University of the Philippines Manila Research Ethics Board (UPMREB). Informed, written consent was obtained for each study participant or their legally authorized representative.

This prospective, cross-sectional study was conducted at the Philippine General Hospital from January 12, 2022 to April 1, 2022. Patients eligible for the study included those 21 years old and above, admitted at a non-COVID-19 intensive care unit (ICU), or non-COVID-19 wards but with indication for ICU care (e.g., need for mechanical ventilation or inotropic support), at least one serum creatinine determination prior to enrollment, and at least one of the following: 1) age ≥75 years old; 2) pre-existing chronic kidney disease (estimated glomerular filtration rate or eGFR 30-59 mL/min/1.73 m^2) as computed using CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration); 3) use of intravenous or arterial contrast agent within the last 48 hours; 4) underwent cardiovascular surgery or other major high-risk surgeries (emergent procedures, intraperitoneal, intrathoracic, surgeries with large fluid shifts or blood loss); 5) sepsis or septic shock; 6) acute myocardial infarction. Our study opted to classify contrast administration as either arterial or venous as current literature suggest a difference in risk for contrast-induced nephropathy, with the arterial route being more nephrotoxic.[12]

Participants were excluded if: 1) age < 21 years old; 2) with preexisting AKI KDIGO stage II-III (moderate-severe AKI) as defined by 2012 KDIGO Clinical Practice Guidelines for AKI; 3) already receiving renal replacement therapy (peritoneal dialysis or hemodialysis) during the time of eligibility; 4) pregnant. We also excluded patients with SARS-CoV-2 (COVID-19) confirmed infections, either via real time polymerase chain reaction (RT-PCR) or antigen testing due to the lack of studies on COVID-19-associated AKI prediction using urine TIMP-2/IGFBP-7.

Data Collection

Clinical and demographic data were collected for all eligible participants. Baseline serum creatinine was defined as the nadir value from seven days prior to hospital admission to enrollment. If more than one value is available, the value closest to enrollment was utilized. A pregnancy test was done for female patients within the child-bearing age (up to 51 years old) to rule out pregnancy.

Urine TIMP-2/IGFBP-7 levels were measured upon study inclusion using NephroCheck™ test (Ortho Clinical Diagnostics, Philippines). A 10 mL fresh, urine sample was collected from each participant and was sent to the laboratory within one hour of collection. The sample was mixed thoroughly in the urine container and then centrifuged for 10 minutes at 1000 x g at 4°C. The NephroCheck™ test simultaneously measured the urinary concentrations of TIMP-2 and IGFBP-7 on 100 µL of urine mixed with 100 µL of test buffer solution via the Astute140 meter. A single numerical risk result was then produced which corresponds to the product of the TIMP-2 and IGFBP-7 concentrations, divided by 1000. A cut-off level of ≥0.3 ng/mL was considered "High risk" for AKI while "Low risk" for AKI was set at <0.3 ng/mL. A blood extraction for serum creatinine was performed 24 hours after collection of the urine TIMP-2/IGFBP-7 sample together with documentation of the urine output (mL/kg/hr) in order to determine occurrence or progression of AKI.

Participants were followed up on a 30-day observation period or until discharge or mortality, whichever came first, to measure major adverse kidney events at 30 days or MAKE30. This composite outcome is achieved if at least one or more of the following criteria are met: all-cause mortality, use of renal replacement therapy (RRT), or persistent renal dysfunction. The following definitions were used for the subcomponents of MAKE30: All-cause mortality was defined as death from any cause prior to hospital discharge truncated at 30 days after ICU admission; Use of RRT was defined as receipt of any modality of RRT between ICU admission and 30 days in a patient not known to have received RRT prior to ICU admission; Persistent renal dysfunction was defined as doubling of the baseline serum creatinine value on the final serum creatinine value before hospital discharge or mortality.

All available measurements for serum creatinine (as basis for persistent renal dysfunction), renal replacement therapy (hemodialysis or peritoneal dialysis), and clinical outcome (all-cause mortality or discharge/survival at 30 days) were recorded. Figure 1 demonstrates the flow during the conduct of the study.

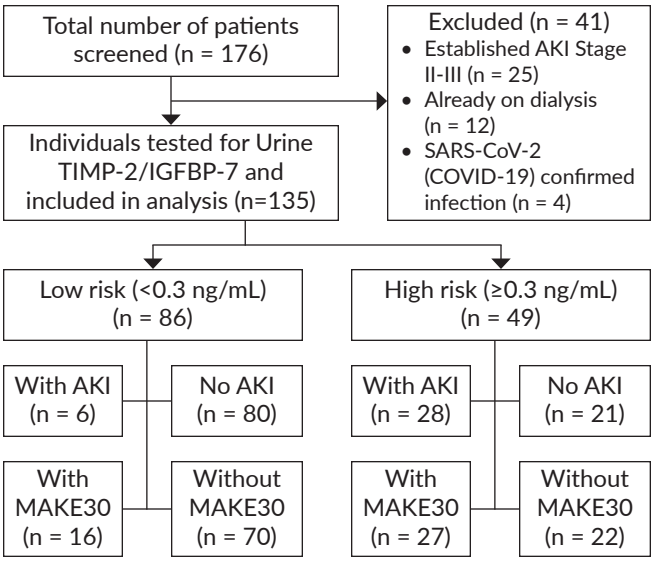

Figure 1. Flow diagram of study.

Statistical Analysis

At least one hundred thirty-five patients were needed given the following conditions: a two-sided level of confidence and power set at 95% and 80%, respectively, an area under the curve of 0.82 for detecting the presence of AKI based on the article by Vijayan et al. in 2016,[8] with 10% adjustment for incomplete information and precision of the estimates between 15%.

The recruited population was dichotomized into "Low" (<0.3) or "High" risk (≥0.3) based on the levels of urine TIMP-2/IGFBP-7 during the recruitment. The clinico-demographic characteristics were presented using median and interquartile range for age and serum levels of creatinine, and frequency and percentage for the remaining categorical variables such as sex, presence of co-morbid conditions, etiology and severity of AKI, and clinical outcomes. In addition, t-test, Wilcoxon rank-sum test and chi-square test were also performed to determine the possibility of an association between the pre-specified cut-off of the urine TIMP-2/IGFBP-7 across these clinico-demographic characteristics, clinical outcome of acute kidney injury, and MAKE30 (including its components: all-cause mortality, use of renal replacement therapy, persistent renal dysfunction).

The proportion of patients developing AKI and the presence of at least one MAKE30 component were also estimated, together with their interval estimates. Receiver operating characteristic (ROC) curves were created to calculate the sensitivity, specificity, positive and negative predictive values, and the areas under the curve of <0.3 ng/mL and ≥0.3 ng/mL cut-off to predict the occurrence of acute kidney injury and MAKE30. The level of significance for all sets of analysis was set at a p-value less than 0.05 using two-tailed comparisons.

Data processing and analysis was carried out using Stata version 13.

Ethical Considerations

The study and informed consent procedures were approved by the University of the Philippines Manila Research Ethics Board (UPM-REB, 2021-0605-01). All methods described in this manuscript were carried out in accordance with relevant guidelines and regulations, including the Declaration of Helsinki for research involving human participants, human material, or human data. Informed consent was obtained from all participants. They were provided with a clear explanation of the study's purpose, procedures, potential risks, benefits, and voluntary nature. Participants were assured of the confidentiality of their personal information, and that their

data would be anonymized for scientific purposes. They were given the opportunity to ask questions and received satisfactory answers. Consent was documented through signed consent forms.

RESULTS

Baseline Characteristics

The clinical and demographic data of the study are presented in Table 1. One hundred and seventy-six individuals were screened at the onset of the study. Overall, forty-one patients were excluded due to the presence of at least one exclusion criteria: twenty-five patients presented with established AKI KDIGO stage II-III, twelve patients were already on hemodialysis and four patients had a confirmed SARS-CoV-2 (COVID-19) infection via RT-PCR.

One hundred thirty-five (135) patients were included into the study proper. Eighty-six patients (63.7%) were classified as low risk while forty-nine (36.3%) were identified as high risk for AKI. The study population consisted of seventy-seven males (57%) and fifty-eight females (43%), with a median age of 50.2 ± 15.6 years old. Patients with hypertension (n = 69, 51.1%) comprised the majority of comorbidities followed by cardiovascular disease (n=41, 30.4%) and diabetes mellitus (n=29, 21.5%). Sepsis (n=97, 71.9%), arterial contrast (n = 46, 34.1%), and preexisting CKD (n = 23, 17%) were the more prevalent risk factors for AKI.

Autoimmune disease was associated with a high urine TIMP-2/IGFBP-7 (p = 0.02), while those with diabetes mellitus (p <0.01) or exposure to arterial contrast media (p = 0.01) had lower urine TIMP-2/IGFBP-7 levels. There was also an observed trend towards elevated urine TIMP-2/IGFBP-7 levels among patients with sepsis (p = 0.06).

High-risk patients for AKI had lower median baseline urine output 0.92 mL/kg/hr (95% CI 0.80, 1.06, p <0.01), lower median 24-hour post collection urine output 0.73 mL/kg/hr (95% CI 0.51, 1, p <0.01) and a higher median 24-hour post collection serum creatinine level of 1.2 mg/dL (95% CI 0.89, 1.78, p <0.01), as compared to low-risk patients.

Diagnostic Characteristics of urine TIMP-2/IGFBP-7 for the prediction of AKI and MAKE30

Table 2 shows the diagnostic performance of urine TIMP-2/IGFBP-7. A cutoff of 0.3 ng/mL predicted AKI with a sensitivity of 82.4% (95% CI 65.5 - 93.2), specificity of 79.2% (95% CI 70 - 88.6), positive predictive value (PPV) of 57.1% (95% CI 42.2 - 71.2%) and a negative predictive value (NPV) of 93% (95% CI 85.4 - 97.4%). The composite outcome MAKE30 was detected with a sensitivity of 62.8% (95% CI 46.7 - 77%), specificity of 76.1% (95% CI 66.1 -

Table 1. Characteristics of the Study Population across Urine TIMP-2/IGFBP-7 Levels

Characteristics	Overall	Urine TIMP-2/IGFBP-7 Level		*p*-value
		Low risk (<0.3 ng/mL)	High risk (≥0.3 ng/mL)	
Number of patients (%)	135 (100%)	86 (63.7%)	49 (36.3%)	-
Age in years ± SD	50.2 ± 15.6	50.3 ± 13.3	50.1 ± 19.2	0.94
Sex, n (%)				0.15
Female	58 (43%)	33 (38.4%)	25 (51%)	
Male	77 (57%)	53 (61.6%)	24 (49%)	
Co-morbidities, n (%)				
Hypertension	69 (51.1%)	46 (53.5%)	23 (46.9%)	0.46
Diabetes mellitus	29 (21.5%)	25 (29.1%)	4 (8.2%)	<0.01*
Autoimmune disease	8 (5.9%)	2 (2.3%)	6 (12.2%)	0.02*
Cardiovascular disease	41 (30.4%)	29 (33.7%)	12 (24.5%)	0.26
Risk Factor for AKI, n (%)				
>75 years old	6 (4.44%)	2 (2.33%)	4 (8.2%)	0.11
Pre-existing Chronic Kidney Disease	23 (17%)	15 (17.4%)	8 (16.3%)	0.87
Post-Arterial Contrast	46 (34.1%)	36 (41.9%)	10 (20.4%)	0.01*
Post-Intravenous Contrast	17 (12.6%)	11 (12.8%)	6 (12.2%)	0.93
Cardiac Surgery	2 (1.5%)	2 (2.3%)	-	0.28
Major Non-Cardiac Surgery	19 (14.1%)	11 (12.8%)	8 (16.3%)	0.57
Sepsis	97 (71.9%)	57 (66.3%)	40 (81.6%)	0.06
Myocardial Infarction	22 (16.3%)	17 (19.8%)	5 (10.2%)	0.15
Levels of serum creatinine in mg/dL (95%CI)				
Baseline	0.78 (0.61, 1.13)	0.77 (0.61, 1.14)	0.8 (0.61, 1.12)	0.81
24-hour post collection	0.89 (0.62, 1.32)	0.77 (0.59, 0.97)	1.2 (0.89, 1.78)	<0.01*
Urine output in mL/kg/hr (95%CI)				
Baseline	1.05 (0.87, 1.35)	1.17 (0.89, 1.44)	0.92 (0.80, 1.06)	<0.01*
24-hour post collection	1.05 (0.76, 1.37)	1.21 (0.96, 1.46)	0.73 (0.51, 1.00)	<0.01*

TIMP-2 – tissue inhibitor of metalloproteinases-2; IGFBP-7 – insulin-like growth factor binding protein-7

Table 2. Diagnostic Performance of Urine TIMP-2/IGFBP-7 Levels across AKI and MAKE30

Characteristics	AKI	MAKE30
Sensitivity	82.4%	62.8%
n/N	28/34	27/43
95% CI	65.5-93.2%	46.7-77%
Specificity	79.2%	76.1%
n/N	80/101	70/92
95% CI	70-88.6%	66.1-84.4%
Positive Predictive Value	57.1%	55.1%
n/N	28/49	27/49
95% CI	42.2-71.2%	40.2-69.3%
Negative Predictive Value	93%	81.4%
n/N	80/86	70/86
95% CI	85.4-97.4%	71.6-89%
Area under the Curve	0.81	0.69
95% CI	0.73-0.88	0.61-0.78

MAKE30 – major adverse kidney events at 30 days; AKI – acute kidney injury; TIMP-2 – tissue inhibitor of metalloproteinases-2; IGFBP-7 – insulin-like growth factor binding protein-7

84.4%), PPV of 55.1% (95% CI 40.2 - 69.3%) and an NPV of 81.4% (95% CI 71.6 - 89%).

Area under the curve measurements for AKI was noted at 0.81 (95% CI 0.73 - 0.88) and 0.69 (95% CI 0.61 - 0.78) for MAKE30 (Table 2, Figures 2 and 3).

Association of urine TIMP-2/IGFBP-7 to clinical outcomes

Table 3 describes urine TIMP-2/IGFBP-7 levels in relation to clinical outcomes. Overall, thirty-four participants reached AKI (25.2%) and forty-three patients met the MAKE30 endpoint (31.9%). Elevated levels of urine TIMP-2/IGFBP-7 (≥0.3 ng/mL) were associated with the development of AKI (n = 28, p <0.01). All three components of MAKE30 (mortality n = 23 p <0.01, new renal replacement therapy n = 8 p = 0.01 and persistent renal dysfunction n = 17 p <0.01) were also associated with higher levels of urine TIMP-2/IGFBP-7. Conversely, survival or discharge after 30 days were found to be associated with lower urine TIMP-2/IGFBP-7 levels <0.3 ng/mL (p <0.01).

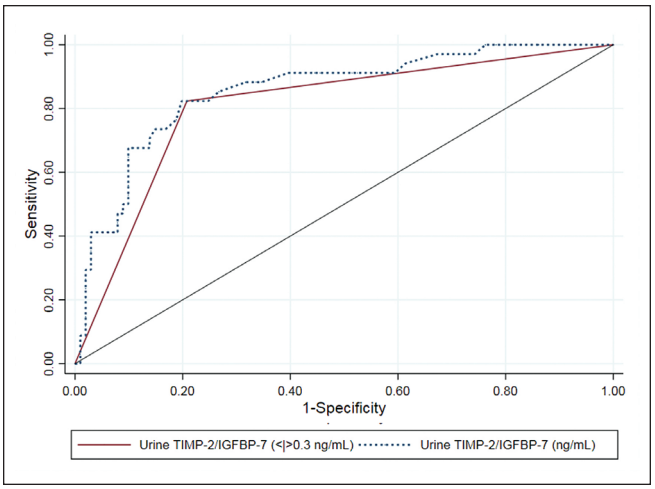

Figure 2. Receiver operating characteristic (ROC) curves for predicting AKI across urine TIMP-2/IGFBP-7 levels.

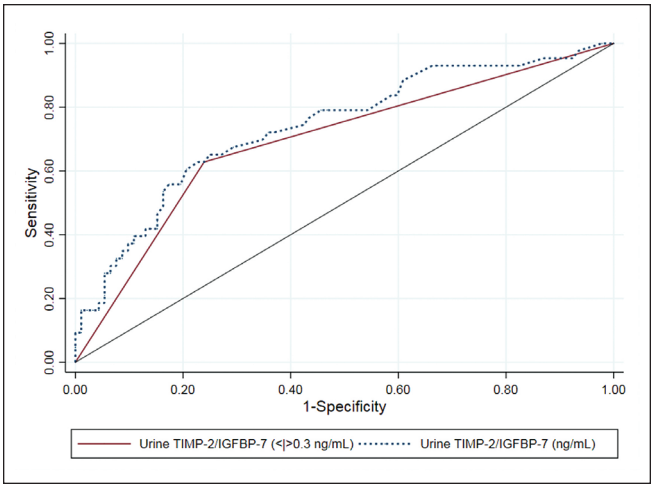

Figure 3. Receiver operating characteristic (ROC) curves for predicting MAKE30 across urine TIMP-2/IGFBP-7 levels.

Table 3. Clinical Outcomes of the Study Population across Urine TIMP-2/IGFBP-7 Levels

Characteristics	Overall	Urine TIMP-2/IGFBP-7 Level		*p*-value
		Low risk (<0.3 ng/mL)	High risk (≥0.3 ng/mL)	
Number (%)	135 (100%)	86 (63.7%)	49 (36.3%)	-
Presence of AKI	34 (25.2%)	6 (7%)	28 (57.1%)	<0.01*
MAKE30	43 (31.9%)	16 (18.6%)	27 (55.1%)	<0.01*
Mortality	39 (28.9%)	16 (18.6%)	23 (46.9%)	<0.01*
New renal replacement therapy	11 (8.2%)	3 (3.5%)	8 (16.3%)	0.01*
Persistence of renal dysfunction	20 (14.8%)	3 (3.5%)	17 (34.7%)	<0.01*
Discharged from the hospital or survived	97 (71.9%)	71 (82.6%)	26 (53.1%)	<0.01*

MAKE30 – major adverse kidney events at 30 days; AKI – acute kidney injury; TIMP-2 – tissue inhibitor of metalloproteinases-2; IGFBP-7 – insulin-like growth factor binding protein-7

DISCUSSION

The present study demonstrated the diagnostic performance of urine TIMP-2/IGFBP-7 in predicting acute kidney injury and major adverse kidney events in 30 days or MAKE30, among high-risk patients.

Sepsis was the most prevalent risk factor for AKI, consisting of 71% of the study population. It also trended towards elevated levels of urine TIMP-2/IGFBP-7 but did not reach statistical significance (p = 0.06). This is in contrast with existing literature that found high levels of urine TIMP-2/IGFBP-7 was significantly associated with sepsis-induced AKI.[13-17] A higher biomarker cutoff level (>3 ng/mL up to 2 ng/mL) or a larger study population may produce the robust association demonstrated in these studies.

Among the comorbidities, only autoimmune disease was noted to have a significant association with elevated levels of urine TIMP-2/IGFBP-7. This may be due to its pathophysiology leading to renal injury. TIMP-2 and IGFBP-7 are proteins expressed in renal tubular cells during periods of cellular injury. Both are hypothesized to alter the cellular response to inflammatory mediators, mark injured tubular epithelium, send signals in case of septic or ischemic insults, and induce G1 cell cycle arrest to prevent injury aggravation.[6,8] Autoimmune disease may trigger local complement activation, cytokine and chemokine secretion, leading to increased cell-cycle arrest protein release and higher urine TIMP-2/IGFBP-7.[18,19] On the other hand, diabetes mellitus was found to be associated with low urine TIMP-2/IGFBP-7 levels and low AKI risk. This finding is contradictory with multiple studies linking an increased risk for AKI with diabetes mellitus[19-21] while others such as Bell et al., have noted its effect and association with elevated urine TIMP-2/IGFBP-7.[22] Our result may be explained by albuminuria, which has been demonstrated (>125 mg/dL) to affect results.[8,11,23] Given that diabetic nephropathy produces variable amounts of albuminuria, we cannot fully discount the possibility of result interference without accounting for urine albumin excretion.

Our study did not identify any association between intravenous contrast infusion and urine TIMP-2/IGFBP-7, while arterial contrast administration was found to be associated with low risk for AKI (urine TIMP-2/IGFBP-7 <0.3 ng/mL, p=0.01). Current literature surrounding the risk for contrast-associated AKI of either arterial or venous route are still conflicting as some authors support the hypothesis of a clinically negligible toxicity of iodinated contrast and do not credit the existence of true renal risk with contrast exposure.[24-27] While dedicated studies on arterial contrast and urine TIMP-2/IGFBP-7 are presently lacking, our findings of a low-risk association may be suggestive of an exaggerated renal risk placed on arterial contrast-induced nephropathy. The lack of association in our intravenous contrast population mirrors the results of an observational cohort study by Rouve et al. on urine TIMP-2/IGFBP-7 and contrast-associated AKI which failed to find any significant changes in urine TIMP-2/IGFBP-7 levels with intravenous contrast media.[28]

Our measures of validity regarding biomarker accuracy among high-risk individuals are consistent with existing literature.[6,15,23,29-32] Against the standard cutoff of 0.3 ng/mL, urine TIMP-2/IGFBP-7 exhibited efficient prediction of early AKI (within 24 hours) with a sensitivity of 82.4%, specificity of 79.2%, PPV of 57.1% and an NPV of 93%. This is further evidenced by a high area under the curve value (AUC 0.81, Figure 2) suggesting a good degree of accuracy and balance with sensitivity and specificity.[33] Our study also affirms the capability of urine TIMP-2/IGFBP-7 of being an excellent screening test for early (within 24 hours) AKI given its high NPV.[6,8,32]

Even in mild AKI, elevated urine TIMP-2/IGFBP-7 is a signal for poor prognosis.[34] It has been shown that an increase in urine TIMP-2/IGFBP-7 confers a risk for renal functional and reserve loss in subclinical AKI.[35] Thus, we sought to explore other potential uses of this biomarker. We identified an association between elevated levels of urine TIMP-2/IGFBP-7 and MAKE30 (p<0.01). Conversely, short term survival and/or discharge was associated with lower levels (p<0.01).

There have been several investigations evaluating short and long-term outcomes and urine TIMP-2/IGFBP-7. In the SAPPHIRE validation study, there was a markedly increased risk for MAKE30 with urine TIMP-2/IGFBP-7 levels above 0.3 ng/mL, which continued to increase with levels up to 2 ng/mL.[7] Subsequent studies by Koyner et al. demonstrated that in the presence of AKI, urine TIMP-2/IGFBP-7 is associated with all-cause mortality and need of RRT. Additionally, the authors showed that the link between the biomarker and the composite end point is specific to subjects who develop AKI within 72 hours of measurement.[36,37] Xie et al. also reached the same findings, noting that AKI patients with values of >0.3 ng/mL had a significantly increased risk of death or need for continuous renal replace-ment therapy as compared to patients with values of <0.3 ng/mL. The authors also found urine TIMP-2/IGFBP-7 on ICU admission had good performance in predicting the probability AKI free days in the first four days in the ICU.[34]

In our study, further analysis of the urine biomarker's ability to predict MAKE30 occurrence at the standard cut-off of 0.3 ng/mL yielded a sensitivity of 62.8%, specificity of 76.1%, PPV of 55.1%, NPV of 81.4% and an AUC of 0.69. It appears that the current cut-off may be useful in predicting the likelihood of a MAKE30 outcome. While no direct MAKE30 comparisons can be made with existing literature, measures of validity have been made to the components of MAKE30. Gocze et al. identified an AUC of 0.83 for the early use of RRT and 0.77 for 28-day mortality among post-surgical patients[38], a finding shared by Esmeijer et al. who noted post cardiac surgery values of TIMP-2 and IGFBP-7

adequately predicted RRT (C statistic 0.80) and 30-day mortality (C statistic 0.74 for TIMP-2 and C statistic of 0.80 for IGFBP-7)[39] emphasizing the potential of urine TIMP-2/IGFBP-7 for the prediction of renal outcomes.

Strengths, Limitations and Recommendations

To our knowledge, this is the first local study that evaluated urine TIMP-2/IGFBP-7 in predicting AKI among high-risk Filipino patients and one of the few that explored its association with outcomes. However, our study has several limitations. A more representative sampling of patients at risk for AKI could have been done. An example of which are cardiac surgery patients who only accounted for less than 2% of the entire study group. Considering that cardiovascular surgery is a risk factor for AKI that was proven to be associated with urine TIMP-2/IGFBP-7,[29,39-41] our findings may have led to an underestimation of the biomarker's diagnostic capability. Since our study site, the Philippine General Hospital, was converted to a COVID-19 referral center, our recruitment was also limited due to our exclusion of COVID-19 confirmed patients. A larger study population may enable several complementary subgroup analyses such as long-term CKD risk. Although the present cut-off value may be useful for detecting occurrence of MAKE30, we would recommend a study exploring different cut-off values for urine TIMP-2/IGFBP-7 to better predict mortality, need for renal replacement therapy, and persistent renal dysfunction. As mentioned previously, our study did not account for the proteinuria that may have been present during the analysis of patients presenting with diabetic nephropathy, thus, future studies should also control for this confounder.

CONCLUSIONS

We have demonstrated that urine TIMP-2/IGFBP-7 with its cut-off value at ≥0.3 ng/mL, can be useful in predicting the likelihood of developing AKI and at least one major adverse kidney event among high-risk Filipino patients for AKI. It serves as a useful adjunct to existing methods, such as serum creatinine, in the early diagnosis and prognosis of acute kidney injury and expanding the therapeutic window to prevent disease progression and improve outcomes.

Acknowledgments

The authors thank Alvin Duke Sy, RN, MSPH for his contributions to the statistical analysis of the study.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Statement of Authorship

All authors certified fulfillment of ICMJE authorship criteria.

Author Disclosure

All authors declared no conflicts of interest.

Funding Source

The research described in this manuscript was supported by the Expanded Health Research Office, University of the Philippines-Philippine General Hospital Research Council, Fellow Research Grant 2022. The funding received was instrumental in conducting various aspects of this study, including data collection, analysis, interpretation, and the eventual completion of this research.

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