Reversibility of Acute Kidney Injury in Medical ICU Patients

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Reversibility of Acute Kidney Injury in Medical ICU Patients: Predictability Performance of Urinary Tissue Inhibitor of Metalloproteinase-2 x Insulin-Like Growth Factor-Binding Protein 7 and Renal Resistive Index

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Objectives: Urinary biomarkers and renal Doppler sonography remain considered as promising tools to distinguish transient from persistent acute kidney injury. The performance of the urinary biomarker, tissue inhibitor of metalloproteinase-2 x insulin-like growth factor-binding protein 7 and of renal resistive index to predict persistent acute kidney injury showed contradictory results. Our aim was to evaluate the performance of tissue inhibitor of metalloproteinase-2 x insulin-like growth factor-binding protein 7 and renal resistive index in predicting reversibility of acute kidney injury in critically ill patients.

Design: Prospective observational study.

Setting: Twenty-bed medical ICU in an university hospital.

Patients: Consecutive patients with acute kidney injury.

Intervention: None.

Measurements and Main Results: Renal resistive index was measured within 12 hours after admission, and urinary tissue inhibitor of metalloproteinase-2 and insulin-like growth factor-binding protein 7 was measured at H0, H6, H12, and H24. Renal dysfunction reversibility was evaluated at day 3. Receiver operating characteristic curves were plotted to evaluate diagnostic performance of renal resistive index and tissue inhibitor of metalloproteinase-2 x insulin-like growth factor-binding protein 7 to predict a persistent acute kidney injury. Overall, 100 patients were included in whom 50 with persistent acute kidney injury. Renal resistive index was higher in persistent acute kidney injury group. Urinary tissue inhibitor of metalloproteinase-2 x insulin-like growth factor-binding protein 7 was not significantly different at each time between both groups. The performance of tissue inhibitor of metalloproteinase-2 x insulin-like growth factor-binding protein 7 was poor with respectively an area under the receiver operating characteristic curves of 0.57 (95% CI, 0.45–0.68), 0.58 (95% CI, 0.47–0.69), 0.61 (95% CI, 0.50–0.72), and 0.57 (95% CI, 0.46–0.68) at H0, H6, H12, and H24. The area under the receiver operating characteristic curve for renal resistive index was 0.93 (95% CI, 0.89–0.98). A renal resistive index greater than or equal to 0.685 predicting persistent acute kidney injury with 78% (95% CI, 64–88%) sensitivity and 90% (95% CI, 78–97%) specificity.

Conclusions: Renal resistive index had a good performance for predicting the reversibility of acute kidney injury in critically ill patients. Urinary tissue inhibitor of metalloproteinase-2 x insulin-like growth factor-binding protein 7 was unable to differentiate transient from persistent acute kidney injury. (*Crit Care Med* 2019; XX:00–00)

Key Words: acute kidney injury; insulin-like growth factor-binding protein 7; intensive care unit; renal recovery; renal resistive index; tissue inhibitor of metalloproteinase-2

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Acute kidney injury (AKI) is a common complication in critically ill patients and is associated with short-term morbidity and an increase in mortality (1, 2). Early recognition of severe AKI with no short-term renal recovery or persistent AKI is mandatory to improve outcome (3).

Routinely, diagnosis of AKI is based on oliguria and serum creatinine (sCr) (4) but these markers are unspecific and the elevation of sCr is delayed (5, 6). Furthermore, AKI reversibility

is still hard to predict at early stage. Urinary indices have indeed demonstrated limited diagnostic performance (7, 8). Recently, new tools including urinary biomarkers and renal Doppler sonography have been evaluated to detect AKI at the early stage, assess its reversibility and evaluate its prognosis.

The product of the urinary concentration of two markers, tissue inhibitor of metalloproteinase-2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP7) which are both cell-cycle arrest proteins showed promising results in AKI diagnosis and scoring. TIMP-2 and IGFBP7 have been implicated in the G_1 cell-cycle arrest phase noted to occur during the very early phases of cellular stress (9). It has also been demonstrated that renal tubular cells go through this G_1 cell-cycle arrest phase after stress due to several injuries (10). Therefore, TIMP-2 and IGFBP7 are released in the urine by renal tubular cells in response to injury. In several studies, [TIMP-2] × [IGFBP7] appears to be an effective biomarker to predict AKI in ICU within 12–24 hours (11–13). However, only few studies have assessed the capacity of [TIMP-2] × [IGFBP7] to predict the reversibility of AKI and the results were disappointing and conflicting (14, 15).

Beyond these biomarkers, renal resistive index (RI) measurement is a noninvasive and rapid tool that was evaluated to predict AKI (16–19) and to differentiate transient from persistent AKI in ICU (18, 20). Several studies have shown its efficiency to predict a persistent AKI (17, 18, 21). Nevertheless, these preliminary studies were performed in expert centers on a limited number of patients. A meta-analysis has highlighted the good performance of RI to predict a persistent AKI, yet also shown a great heterogeneity between the studies (22).

Therefore, this study was conducted to evaluate the ability of urinary [TIMP-2] × [IGFBP7] and RI to predict persistent AKI in unselected critically ill patients.

PATIENTS AND METHODS

Patients

This prospective, observational study has been conducted in the medical ICU at the University Hospital of Montpellier, France. It was approved by our institutional review board. A printed information sheet was given to each patient and their relatives. None of them refused to participate. From July 2015 to July 2017, all consecutive patient admitted to the ICU with an AKI were included. Exclusion criteria were an age under 18, pregnancy, legally protected adults, anuria, renal transplant, chronic kidney disease stage IV–V. Cardiac arrhythmia, obstructive renal disease, AKI of glomerular etiology, stage C cirrhosis were also exclusion criteria because of their impact on the RI. Patients staying less than 72 hours were secondarily excluded because of the inability to assess AKI reversibility. According to the French law, this collection was registered to the "Ministère de l'Enseignement supérieur et de la Recherche" (number DC-2008-417).

Definitions

AKI was defined and staged according to the Kidney Disease: Improving Global Outcomes (KDIGO) scoring system (4). AKI was diagnosed by either an increase in sCr greater than or equal to 26.4 µmol/L or a sCr greater than 1.5 times from baseline or a urine output less than 0.5 mL/kg/hr for 6–12 hours (4). For each patient, baseline sCr was defined according to the sCr measured the year prior admission in ICU. When baseline sCr level was unknown, this variable was estimated according to the Modification of Diet Renal Disease formula back-calculation (4).

AKI improving within 72 hours after inclusion was considered as transient AKI (18, 23). AKI improvement was defined as decrease of at least one stage in AKI severity according to KDIGO criteria (i.e., decrease of sCr, reversal of oliguria in the absence of diuretic therapy, and absence of renal replacement therapy [RRT]) (18). Persistent AKI was defined as persistent oliguria and/or as a steady or higher AKI KDIGO stage.

Sepsis and septic shock were diagnosed according to the criteria developed by the European Society of Intensive Care Medicine and the Society of Critical Care Medicine (24).

Hemodynamic stabilization was considered when mean arterial pressure (MAP) was at least at 65 mm Hg without need of a bolus fluid and/or the initiation or the increase of vasopressors dose within the last 6 hours.

Data Collection and Study Protocol

Baseline patient characteristics were collected. The following variables were recorded at H0, H6, H12, H24 then daily until ICU discharge: systolic, mean and diastolic blood pressure, heart rate, urine output, arterial saturation of oxygen, nephrotoxic treatment, type and quantity of fluid, vasoactive drugs, mechanical ventilation, inspired fraction of oxygen in ventilated patients and RRT. The severity of illness was determined using Simplified Acute Physiology Score (SAPS) II and Sequential Organ Failure Assessment (SOFA) score at inclusion. The nature—transient or persistent—of AKI was assessed at 72 hours after inclusion.

Blood and urines samples were collected at H0, H6, H12, H24 then daily for blood and urine determination of urea, creatinine, and electrolytes. Fresh urines samples were analyzed at H0, H6, H12, and H24 for [TIMP-2] and [IGFBP7] by technicians blinded to clinical data. A clinical immunoassay (NephroCheck Test and Astute 140 Meter; Astute Medical, San Diego, CA) was used. The NephroCheck Test measure the product of TIMP-2 and IGFBP7 on 100 µL of urine mixes with 100 µL of buffer. Samples were either immediately processed or delayed with sample storage and freezing at –20°C. [TIMP-2] × [IGFBP7] were expressed in units of ([ng/mL]²/1,000). Investigators were blinded to urinary [TIMP-2] × [IGFBP7] concentration. We evaluated herein the performance of NephroCheck Test to detect AKI reversibility which is an off-label use of its regulated diagnostic tool.

RI were measured within 12 hours after admission and after hemodynamic stabilization by two investigators who were not involved in patient management. A Vivid S70 ultrasound machine with a 4-MHz curved-array multifrequency transducer was used (GE Healthcare, Buckinghamshire, United Kingdom). On ultrasound, after visualization of both kidney in gray-scale

and color-Doppler modes, the absence of signs of chronic renal disease and obstruction were checked. RI were measured in the right kidney by selecting an interlobar or arcuate artery and using pulse-wave Doppler. An optimal Doppler spectrum was defined as visualization of at least three similar consecutive waveforms. The peak systolic velocity (V_{max}) and the minimal diastolic velocity (V_{min}) were recorded and the RI was calculated with the following formula $(V_{max}–V_{min})/V_{max}$. The results from three to five consecutive RI values were averaged and were used for the study. The investigators who performed RI measurement attended a half-day course on renal Doppler and RI calculation.

Statistical Analysis

Data were described as median and interquartile range or mean and SD. Qualitative values were compared using chi-square test. Quantitative variables were compared using the Student *t* test or the nonparametric Wilcoxon test or Mann-Whitney *U* test. Correlation tests were performed by using the Spearman correlation coefficient. Receiver operating characteristic (ROC) curves were plotted to evaluate diagnostic performance of RI, [TIMP-2] × [IGFBP7], fractional excretion of sodium (FeNa), and sCr to diagnose a persistent AKI. Area under the curves (AUCs) values were compared using the DeLong's nonparametric approach (25). Optimal cutoff was defined using Youden's J statistic (26).

Based on previous study (18), the sample size was calculated as follow. Assuming a RI of 0.69 in patients with transient AKI and a SD of 0.08, using a two-sided test with an α-risk (type I error) of 5% and a statistical power of 80%, we needed 42 patients per group to detect a 15% absolute difference in RI between patients with transient AKI and those with persistent AKI. Taking into account a rate of failure to obtain RI of 10% and a rate of failure to measure urinary biomarker of 10%, we would be needed 100 patients.

We performed logistic regression to identify variables significantly associated with persistent AKI. Given the number of events (50 patients with persistent AKI), we selected five variables according to their clinical relevance and statistical significance in univariate analysis (27). Selected variables were "Vasoactive drugs," "Renal resistive index," "SOFA," "Diagnosis," and "Lactate." Then, a conditional stepwise regression was used to select the most informative variables. A p value of less than 0.05 was considered statistically significant. Statistical analysis was performed using R Software Version 3.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study Population

Among the 185 consecutive patients admitted with AKI, 85 were excluded mainly because of missing [TIMP-2] × [IGFBP7] dosages and cardiac arrhythmia (**Fig. 1**). The characteristics of the 100 analyzed patients are shown in **Table 1**. The most frequent diagnosis was septic shock (51%). Seventy-one patients were treated with vasoactive drugs and 62 were intubated and ventilated. Overall, 14 patients needed RRT during hospitalization. The median of ICU stay was 5 days (3–11 d) and ICU mortality rate was 22%.

Comparison of Transient and Persistent AKI Patients

Fifty patients had a transient AKI and 50 a persistent AKI. Their characteristics and management are displayed in Table 1. At inclusion, sCr, arterial lactate, fluid loading, and severity assessed by SAPS II and SOFA scores were associated with persistent AKI in univariate analysis (Table 1). In patients with persistent AKI, RRT was initiated in 28% of them, ICU stay duration was significantly increased (5 d [4–13 d] vs 4 d [3–7 d]; $p = 0.03$) but ICU mortality did not differ significantly between groups (28% vs 16%; $p = 0.22$).

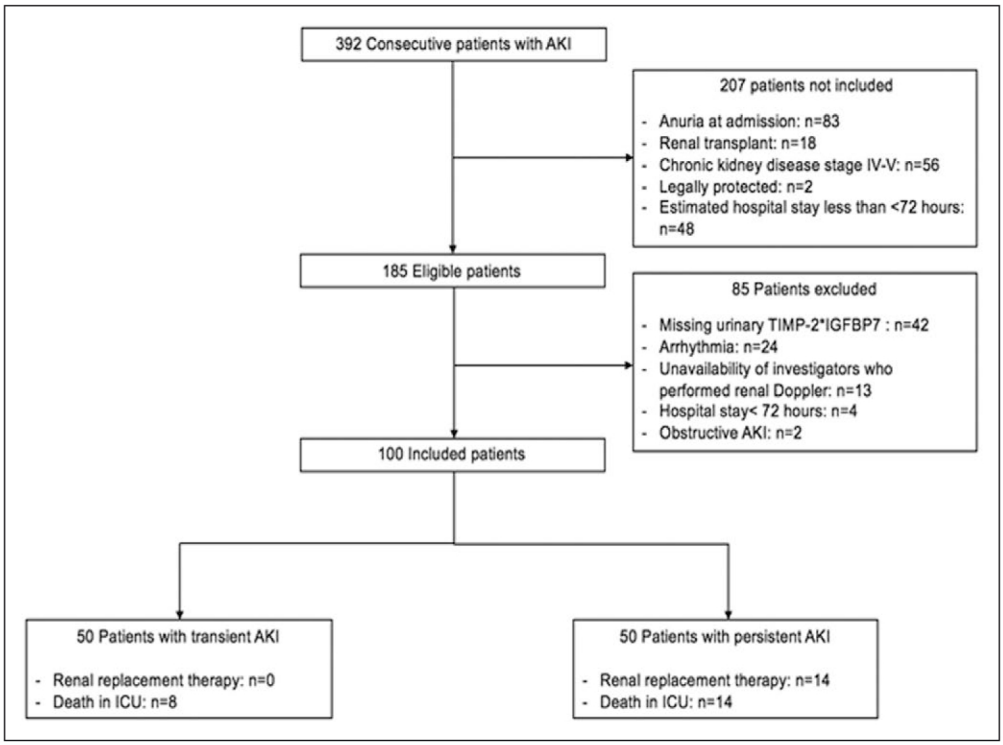

Figure 1. Flowchart. AKI = acute kidney injury, TIMP-2 × IGFBP7 = tissue inhibitor of metalloproteinase-2 and insulin-like growth factor-binding protein 7.

Performance of [TIMP-2] × [IGFBP7], Serum Creatinine, Diuresis, and Urinary Indices to Predict Persistent AKI

Urinary [TIMP-2] × [IGFBP7] did not differ significantly between the two groups at every time measurements (Table 1; **Table S3**, Supplemental Digital

TABLE 1. Characteristics of the Studied Population and Differences According to Acute Kidney Injury Reversibility

Variables	All Patients, *n* = 100	Transient AKI, *n* = 50	Persistent AKI, *n* = 50	*p* (Univariate Analysis)
Patient characteristics				
Sex, male, *n* (%)	66 (66)	34 (68)	32 (64)	0.83
Age, yr, mean ± SD	65.7 ± 14.7	65.1 ± 14.2	66.4 ± 15.3	0.67
Risk factors for AKI				
History of hypertension	35 (35)	19 (38)	16 (32)	0.67
Diabetes	28 (28)	14 (28)	14 (28)	1.00
Moderate chronic kidney diseases[a]	8 (8)	4 (8)	4 (8)	1.00
Diuretics	3 (23)	12 (24)	11 (22)	1.00
Angiotensin II converting enzyme inhibitor or angiotensin receptor blockers	36 (36)	23 (46)	13 (26)	0.06
Characteristics at inclusion				
Mean arterial pressure, mm Hg, mean ± SD	80.9 ± 20.8	80.0 ± 15.9	81.8 ± 24.9	0.68
Arterial oxygen saturation (%), median (IQR)	97 (95–99)	97 (95–99)	96 (95–99)	0.79
Lactate (mmol/L), median(IQR)	1.8 (1.3–3.2)	1.6 (1.1–2.2)	2.6 (1.4–3.9)	0.01
Simplified Acute Physiology Score II, mean ± SD	60 ± 20	55 ± 19	64 ± 21	0.02
Sequential Organ Failure Assessment, median (IQR)	10 (6–11)	8 (6–10)	11 (8–12)	0.002
KDIGO ≤ 2, *n* (%)	81 (81)	42 (84)	39 (78)	0.65
KDIGO = 3, *n* (%)	19 (19)	8 (16)	11 (22)	
Diagnosis				
Septic shock, *n* (%)	51 (51)	25 (50)	26 (52)	
Cardiogenic shock, *n* (%)	10 (10)	8 (16)	2 (4)	
Respiratory distress, *n* (%)	19 (19)	8 (16)	11 (22)	0.14
Cardiac arrest, *n* (%)	18 (18)	7 (14)	11 (22)	
Other, *n* (%)	2 (2)	2 (4)	0 (0)	
Renal function at inclusion				
Diuresis (mL/kg/hr), median (IQR)	1.7 (0.9–3.5)	1.8 (0.9–3.8)	1.6 (0.9–2.9)	0.53
Serum creatinine (μmol/L), median (IQR)	135.5 (112.8–197.0)	129.0 (109.0–166.0)	148.0 (117.2–204.0)	0.50
Plasma urea (mmol/L), mean ± SD	14.6 ± 8.2	14.4 ± 7.6	14.8 ± 8.8	0.81
Organ support and treatment at inclusion				
Quantity of fluid (mL/kg), median (IQR)	11.6 (6.9–17.3)	14.0 (8.3–18.7)	7.9 (5.9–16.0)	0.049
Vasoactive drugs, *n* (%)	71 (71)	31 (62)	40 (80)	0.08
Mechanical ventilation, *n* (%)	62 (62)	28 (56)	34 (68)	0.37
TIMP-2 × IGFBP7 and renal resistive index				
TIMP-2 × IGFBP7 H0, median (IQR)	0.60 (0.11–1.75)	0.31 (0.10–1.30)	0.97 (0.12–2.00)	0.24
TIMP-2 × IGFBP7 H6, median (IQR)	0.23 (0.07–0.79)	0.18 (0.05–0.51)	0.24 (0.10–0.87)	0.16
TIMP-2 × IGFBP7 H12, median (IQR)	0.20 (0.06–0.67)	0.12 (0.04–0.61)	0.25 (0.10–1.03)	0.05
TIMP-2 × IGFBP7 H24, median (IQR)	0.23 (0.09–0.69)	0.18 (0.07–0.63)	0.28 (0.11–0.73)	0.28
Renal resistive index H12, mean ± SD	0.67 ± 0.07	0.61 ± 0.05	0.72 ± 0.05	< 0.001
Prognosis				
RRT during hospitalization, *n* (%)	14 (28)	0 (0)	14 (28)	< 0.001
Length of ICU stay (d), median (IQR)	5 (3–11)	4 (3–7)	5 (4–13)	0.03
Death in ICU, *n* (%)	22 (22)	8 (16)	14 (28)	0.22

AKI = acute kidney injury, IQR = interquartile range, KDIGO = Kidney Disease: Improving Global Outcomes, RRT = renal replacement therapy, TIMP-2 × IGFBP7 = tissue inhibitor of metalloproteinase-2 and insulin-like growth factor-binding protein 7.

[a]Chronic kidney disease was defined as a creatinine clearance before ICU admission of 30–60 mL · min^{-1}.

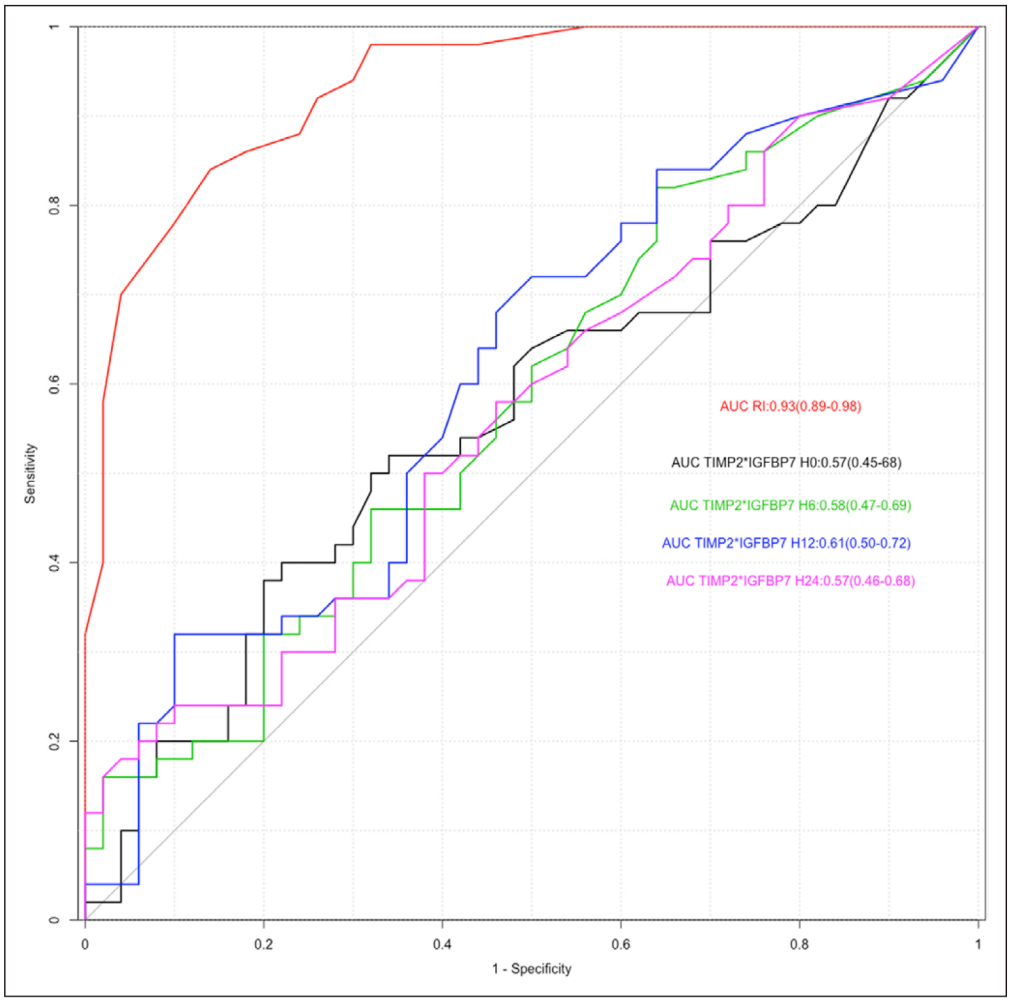

Figure 2. Receiver operating characteristic (ROC) curve of renal resistive index (RI) (*red*) and tissue inhibitor of metalloproteinase-2 and insulin-like growth factor-binding protein 7 ([TIMP-2 × IGFBP7]) at H0 (*black*), H6 (*green*), H12 (*blue*), and H24 (*pink*) to predict persistent acute kidney injury in the overall population. The ROC curve represents the proportion of true positives (sensitivity) against the proportion of false positives (1–specificity). AUC = area under the ROC curve.

Performance of the Renal Resistive Index to Predict Persistent AKI

RI was significantly higher in persistent AKI than transient AKI patients (0.72 ± 0.05 vs 0.61 ± 0.05; $p < 0.001$) (Table 1; and Fig. S1, Supplemental Digital Content 2, http://links.lww.com/CCM/F307). RI was not correlated either with age ($\rho = 0.12$, $p = 0.23$) with a MAP ($\rho = -0.14$, $p = 0.16$) or with amount of fluid at admission ($\rho = 0.07$; $p = 0.49$). Also, mechanical ventilation did not alter RI (0.67 ± 0.06 vs 0.67 ± 0.08; $p = 0.89$) in patients with and without mechanical ventilation.

The AUC ROC of RI to predict persistent AKI was 0.93 (95% CI, 0.89–0.98) (Fig. 2). A RI greater than or equal to 0.685 predict a persistent AKI with 78% (95% CI, 64–88%) sensitivity and 90% (95% CI, 78–97%) specificity (Table 2). The AUC ROC of RI was significantly better than that of the urinary TIMP-2 × IGFBP7 ($p < 0.001$).

A stepwise logistic regression revealed that the factors predicting persistent AKI were RI and SOFA score (**Table 3**).

Content 1, http://links.lww.com/CCM/F306; and **Fig. S1**, Supplemental Digital Content 2, http://links.lww.com/CCM/F307). The performance of [TIMP-2] × [IGFBP7] to predict persistent AKI was poor with respectively an area under the ROC curve (AUC ROC) of 0.57 (95% CI, 0.45–0.68), 0.58 (95% CI, 0.47–0.69), 0.61 (95% CI, 0.50–0.72), and 0.57 (95% CI, 0.46–0.68) at H0, H6, H12, and H24 (**Fig. 2** and **Table 2**). Sensitivity and specificity were of 52% (95% CI, 37–66%) and 66% (95% CI, 52–79%) for an optimal cutoff equal to 0.885 for [TIMP-2] × [IGFBP7] at H0 (Table 2).

Comparison of diuresis, sCr, and urinary indices (FeNa and fractional excretion of urea [FeUrea]) at the different time measurements between patients with transient and persistent AKI are shown in **Table S1** (Supplemental Digital Content 1, http://links.lww.com/CCM/F306). The performance of sCr to predict persistent AKI was fair with an AUC ROC at 0.82 (95% CI, 0.74–0.90) at H24 (**Table S2**, Supplemental Digital Content 1, http://links.lww.com/CCM/F306). Nonetheless, the performance of FeNa to predict renal reversibility was poor (Table S2, Supplemental Digital Content 1, http://links.lww.com/CCM/F306).

DISCUSSION

In this study, we evaluated urinary biomarkers, [TIMP-2] × [IGFBP7], and RI to predict a persistent AKI in unselected critically ill patients. Urinary [TIMP-2] × [IGFBP7] was unable to distinguish transient from persistent AKI at different time measurements in the first ICU 24 hours. By contrast, evaluation of RI within the first ICU 12 hours was better than any other variable to predict a persistent AKI and showed an excellent performance.

An early differentiation between transient and persistent AKI is challenging but crucial in ICU settings. Transient AKI may be characterized by a rapidly reversible increase in sCr while a more prolonged AKI may reflect more severity. Persistent AKI and AKI of longer duration are associated with an increasingly poor outcome (23). The distinction between transient and persistent AKI might be, therefore, a clinically relevant surrogate outcome and may help to optimize treatment, like promptly restoring renal perfusion, limiting fluids, avoiding nephrotoxic agents, or facing RRT (23). Of note, almost one-third of our patients with persistent AKI underwent RRT and none of those with transient AKI.

TABLE 2. Performance of Renal Resistive Index and Tissue Inhibitor of Metalloproteinase-2 and Insulin-Like Growth Factor-Binding Protein 7 for Predicting Persistent Acute Kidney Injury in the Overall Population

Performance	Renal Resistive Index ≥ 0.685	TIMP2 × IGFBP7 H0 ≥ 0.885	TIMP2 × IGFBP7 H6 ≥ 0.085	TIMP2 × IGFBP7 H12 ≥ 0.145	TIMP2 × IGFBP7 H24 ≥ 0.205
Overall population, prevalence of persistent acute kidney injury = 50%					
Sensitivity (%)	78	52	82	68	58
Specificity (%)	90	66	36	54	54
Positive predictive value (%)	89	60	56	59	56
Negative predictive value (%)	80	58	67	63	56
Positive likelihood ratio	7.8	1.53	1.28	1.48	1.26
Negative likelihood ratio	0.24	0.73	0.50	0.59	0.78
Youden's index	1.68	1.18	1.14	1.22	1.12
Area under the receiver operating characteristic curve[a]	0.93 (0.89–0.98)	0.57 (0.45–68)	0.58 (0.47–0.69)	0.61 (0.50–0.72)	0.57 (0.46–0.68)

TIMP-2 × IGFBP7 = tissue inhibitor of metalloproteinase-2 and insulin-like growth factor-binding protein 7.
[a]Values are given with 95% CI.

TABLE 3. Multivariate Conditional Stepwise Regression to Predict Persistent Acute Kidney Injury in ICU

Variables	Coefficient Beta	Adjusted OR (95% CI)	*p*
Sequential Organ Failure Assessment	0.41	1.51 (1.12–2.03)	< 0.01
Renal resistive index (0.1 unit step)[a]	4.42	83.29 (14.91–465.14)	< 0.001
Vasoactive drugs	1.51	4.54 (0.96–21.57)	0.06

OR = odds ratio.
[a]An increase of 0.1 of renal resistive index multiplies the risk of persistent acute kidney injury by 83.29.

Clinical and biological evidences (FeNa, FeUrea, urinary/plasma urea) are widely used to differentiate transient from persistent AKI, but several studies have unveiled their lack of reliability especially in ICU (7, 8, 28). In our cohort, urinary indices were not performing and results again disappointed. This emphasizes the value of identification and validation of new performing urinary biomarkers. In a Sapphire's ancillary study, IGFBP7 was identified as an early marker of the AKI's severity, duration, and associated mortality (29). Also, Yamashita et al (30) showed that TIMP-2 was performing in severe AKI detection and was predictive of poor prognosis. More interestingly, Dewitte et al (15) investigated NephroCheck (NC) ([TIMP-2] × [IGFBP7]) score's kinetics and reported that NC score was significantly higher at H0 and H24 in persistent AKI patients. The authors concluded to a good predictability of the NC score's kinetics over the first 24 hours in the recovery of the renal function after the second day. In these studies, the cause of AKI was fairly uniform and the clinical population homogenous. By contrast, we previously reported a higher absolute values of [TIMP-2] × [IGFBP7] in transient AKI as compared with persistent AKI in medical ICU patients (14). We hypothesized then that [TIMP-2] × [IGFBP7] are released as an alarm signal of aggression with a greater response in case of hemodynamic changes like in functional AKI. In the present study, [TIMP-2] × [IGFBP7] values were not different at every time measurements between both groups and were unable to predict persistent AKI. Our population was exclusively medical with many comorbidities and AKI was mostly multifactorial. The type and the exact timing of the renal insult were rarely precisely identified conversely to postoperative AKI. In ICU patients exposed to various identified renal insults, it has been demonstrated that urinary [TIMP-2] × [IGFBP7] concentrations increased on the day of exposure but exhibited a characteristic secondary fall the day after especially in those who develop AKI (31). Most of our patients exhibited an established AKI soon at ICU admission meaning that renal injury would occurred several hours or days before and that urinary markers have already fallen. One should keep in mind that AKI is not a single disease but a heterogeneous clinical syndrome of mixed causes and various evolution especially in medical ICUs. [TIMP-2] × [IGFBP7], unlike sCr, may not therefore fit to all kidney injuries leading to AKI. A recent meta-analysis on

diagnostic accuracy of urinary [TIMP-2] × [IGFBP7] for AKI prevented clinicians about utility and limitations of this biomarker in clinical practice (32). However, we must acknowledged that measurements of urinary [TIMP-2] × [IGFBP7 were primarily developed and used for both detection of AKI risk and early AKI diagnosis and not to differentiate transient from persistent AKI.

The use of Doppler ultrasonography is increasing in the ICU because it is simple, rapid, easy to apply and noninvasive. It permits to measure RI which may be a repeatable marker of renal blood flow and renal vascular resistance (RVR) (33). Several studies have shown that RI could help to early AKI detection in ICU patients (16–19). In preliminary studies conducted in ICU, RI measured at admission was higher in patients with persistent AKI. These studies have suggested the good capacity of RI to differentiate transient from persistent AKI (17, 18, 34). Similar results were reported in a meta-analysis (22). However, most of these studies were conducted in expert center and on a limited number of patients. Also, a great heterogeneity between studies has been underlined exposing to a high risk of bias. Furthermore, a recent multicenter study included 233 AKI patients who reported contradictory results with a poor performance of RI to predict a persistent AKI (35). Consequently, the aim of the current study was to reassess the capability of RI to early detect a persistent AKI in unselected critically ill patients. RI was the variable with the highest value of AUC ROC for predicting persistent AKI. In multivariate logistic regression, RI and SOFA score were the two variables associated with persistent AKI. A resistive index equal or above 0.69 best detect persistent AKI in our cohort while optimal cutoff points varied across studies from 0.71 to 0.80. These results are in the opposite of those of the multicentric study (35) and may be explained by the fact that our population included medical ICU patients and was investigated by two physicians with similar Doppler ultrasonography skill (35). Numerous confounding factors could however influence RI values including vascular compliance, MAP, age, mechanical ventilation, heart rate, and oxygen level (16, 20, 21, 36). The study of 321 renal-allograft recipients demonstrated that intrarenal RI was principally related to recipient age and central hemodynamic factors (37). The relationship between RI and RVR seems to be linear only when vascular compliance is normal and progressively disappeared when arterial stiffness increases like in the elderly (38, 39). Additionally, an acute change in renal or intra-abdominal pressure may lead to a decrease in renal vascular compliance and an increase in RI (40).

Our study has several strengths. It was the largest study to evaluate concomitantly RI and urinary [TIMP-2] × [IGFBP7] for predicting reversibility of AKI. Additionally, consecutive inclusion of unselected critically ill patients may limit selection bias. To reduce a possible bias, investigators who performed Doppler was not in charge of patients and were blinding of [TIMP-2] × [IGFBP7] results. Also, the differentiation between transient and persistent AKI, based on predefined criteria, was assessed at day 3 while measuring RI and [TIMP-2] × [IGFBP7] were carried out before. Last, we tried to control for any confounding factors through multivariate logistic regression, and we found that RI remained an independent factor of persistent AKI. This study has also several limitations. First, it is a monocentric study conducted exclusively on medical patients. In addition, arrhythmia and other factors precluded RI and [TIMP-2] × [IGFBP7 measurements in 85 of 185 eligible patients. This may limit the generalization of the present findings to all critical care settings particularly the surgical one. Second, our definition of transient and persistent AKI differs from that suggested by Acute Disease Quality Initiative group (41). Indeed, this definition appeared after the beginning of our study. Third, we measured [TIMP-2] × [IGFBP7] in urinary spots at different time measurements. Whether biomarkers should be normalized for urinary creatinine remains questionable (42). Last, identification and measurement of RI by Doppler sonography are obviously operator dependent. To limit inter-observer variability, only two investigators performed renal Doppler but potential variations of RI across operators were not assessed in this study. The previous study has shown however that a brief training in renal Doppler sonography of clinicians not familiarized with this technique leaded to feasible and reliable results (34).

CONCLUSIONS

RI measured early after hemodynamic stabilization was the better tool to differentiate transient from persistent AKI in unselected medical critically ill patients. In multivariate logistic regression, RI and severity score were the two parameters that associated with persistent AKI. Also, urinary [TIMP-2] × [IGFBP7] demonstrated a poor performance for distinguishing transient from persistent AKI. Further studies are needed to confirm these findings and to determine factors influencing RI.

This work was performed at Lapeyronie University Hospital, 371 Av du Doyen Gaston Giraud 34090 Montpellier, France.

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