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Clinical paper

The urine biomarkers TIMP2 and IGFBP7 can identify patients who will experience severe acute kidney injury following a cardiac arrest: A prospective multicentre study

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Abstract

Aim: To determine whether the urine biomarkers tissue inhibitor of metalloproteinases-2 (TIMP-2) and insulin-like growth factor-binding protein 7 (IGFBP7) can identify patients who will develop severe acute kidney injury (AKI) soon after cardiac arrest.

Methods: We performed a prospective, multicentre study in three French ICUs. The performance of [TIMP-2]*[IGFBP7] was assessed for urine samples collected a median [IQR] of 240 [169–315] minutes post-collapse. The primary end-point was severe AKI (KDIGO stage 3), within 48 h of admission.

Results: Of the 115 patients analyzed, 32 (28%) developed severe AKI. Eleven of these required renal replacement therapy. The median [IQR] baseline [TIMP-2]*[IGFBP7] level was higher in patients who developed severe AKI (1.57 [0.80–6.62] $(ng/ml)^2/1000$) than in those who did not (0.17 [0.05–0.59] $(ng/ml)^2/1000$; $p < 0.001$). The baseline [TIMP2]*[IGFBP7] predicted–severe AKI with an area under the curve [95% confidence interval (CI)] of 0.91 [0.84–0.95], an optimal cut-off value of 0.39 $(ng/ml)^2/1000$, a sensitivity [95%CI] of 97% [84–100], and a specificity of 72% [61–82]. A cut-off of 2.0 $(ng/ml)^2/1000$ yielded a specificity of 98% [92–100]. For predicting severe AKI, baseline [TIMP-2]*[IGFBP7] was significantly more discriminant than baseline SCr (AUC [95%CI]: 0.73 [0.63–0.84]; $p = 0.005$), and slightly but not significantly more discriminant than baseline UO (AUC [95%CI]: 0.86 [0.78–0.94], $p = 0.08$) Combining the baseline [TIMP2]*[IGFBP7] with baseline SCr and UO significantly improved the latter markers' predictive performance.

Conclusion: Urine [TIMP-2]*[IGFBP7] effectively identify patients with a risk of severe AKI. Below a cut-off of 0.39 $(ng/ml)^2/1000$, the risk of severe AKI is low.

Keywords: Acute kidney injury, Cardiac arrest, Biomarker

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Introduction

Although most cardiac arrest (CA) patients admitted to the intensive care unit (ICU) will die as a result of brain injury, about one third of deaths are related to early-onset multi-organ failure syndrome caused by the so-called "post cardiac-arrest syndrome".[1,2] Acute kidney injury (AKI) commonly occurs in this setting,[3–7] and severe AKI has been identified as an independent risk factor for death.[8] Any intervention that may limit the worsening of renal function might therefore reduce mortality in the ICU. For example, some researchers suggest that an invasive fluid management strategy can help to reduce the incidence of AKI in this population.[9] It is difficult to distinguish between mild-to-moderate AKI and severe AKI immediately after CA, given that the serum creatinine (SCr) level and urine output (UO) are late markers of renal dysfunction. It has been shown that the product of the concentrations of two urine cell-cycle arrest biomarkers (tissue inhibitor of metalloproteinases-2 and insulin-like growth factor-binding protein 7 ([TIMP-2]*[IGFBP7], which increase in a patient's urine in response to early kidney cell stress) predicts AKI in critically ill patients.[10–12] However, it remains to be seen whether these biomarkers could help to early identify severe AKI in patients after CA. The objective of the present study was to determine whether urine [TIMP-2]*[IGFBP7] can identify CA patients who will develop early-onset, severe AKI (defined as stage 3 in the Kidney Disease Improving Global Outcome (KDIGO) classification.[13]

Methods

Patients and setting

We performed a prospective, multicentre study in three French ICUs. The study protocol was approved by the local independent ethics committee (*CPP Nord Ouest II*, Amiens, France; reference: 2016/53). Each patient's next of kin were informed, and were free to refuse the patient's inclusion.

Between July 2016 and November 2017, adult patients admitted within 6 h of a resuscitated CA were included in the study. The exclusion criteria were severe chronic kidney disease (CKD, defined as a glomerular filtration rate < 30 mL/min/1.73 m^2), severe AKI on admission (SCr 3.0 times greater than baseline, anuria or another indication of mandatory renal replacement therapy (RRT)), an AKI with an obstructive, glomerular or vascular aetiology, pregnancy, tutorship, and guardianship. The patients were managed in accordance with the current European guidelines on post-resuscitation care.[14]

Study endpoint

The study's primary objective was to determine whether the urine [TIMP-2]*[IGFBP7] on admission to the ICU (within six h of CA) predicted the occurrence of severe AKI (KDIGO stage 3) within 48 h of admission.

Data collection

Demographic data (age, gender, height, and bodyweight) and any history of hypertension, diabetes mellitus, chronic kidney disease or cardiovascular disease were recorded. Concerning the circumstances of the CA, the following variables were recorded for each patient: in-hospital or out-of-hospital CA, bystander basic life support, initial type of cardiac rhythm, estimated no-flow time (the time interval between collapse and the provision of basic life support), estimated low-flow time (the time interval between basic life support and the return of spontaneous circulation), the epinephrine dose, the number of defibrillation shocks, and the cause of the CA. During treatment, we recorded contrast injections (for CT scans or coronary angiography), fluid therapy received within 48 h of admission to the ICU, the dose of vasopressor, the need for RRT, the Simplified Acute Physiology Score (SAPS II), and the Sequential Organ Failure Assessment (SOFA) score assessed on admission to the ICU and then on days 1, 2 and 3. Clinical biochemistry data included the arterial blood pH and lactate and SCr levels. Data on mortality and the neurological outcome were recorded.

The urine TIMP-2 and IGFBP7 assays, and AKI staging

Fresh urine samples were collected from a bladder catheter on admission to the ICU and then 6 h and 24 h after admission. The urine was centrifuged, and the supernatant was frozen and stored at $-80\,^{\circ}$C prior to analysis. The [TIMP-2]*[IGFBP7] value was calculated for a 100 μl sample of thawed urine, using the NephroCheck® Test (Astute Medical Inc., San Diego, CA, USA). The product of the two biomarker concentrations was divided by 1000, in order to give a result in (ng/ml)^2/1000.

The patient's long-term baseline SCr level was determined from all available laboratory test data acquired in the preceding 12 months. The SCr level was back-estimated using the Modification of Diet in Renal Disease equation for 64 patients whose historical data were unavailable.[15,16] Urine output was measured at the bladder catheter, and the baseline UO was defined as the total volume over the first 6 h post-admission. The SCr was measured on admission, 24 h after admission, and then daily. The AKI severity stages 24, 48 and 72 post-admission were determined from the change in SCr and the change in UO, according to the KDIGO guidelines. Severe AKI was defined as follows: a SCr 3.0 times greater than the baseline or a SCr value >354 μmol/l; UO < 0.3 ml/kg/h for 24 h; or the initiation of renal replacement therapy. Transient AKI was defined as a return to the KDIGO 0 level within the first 72 h. Persistent AKI was defined as KDIGO ≥ 1 at 72 h or at the time of death, whichever occurred first.

Statistical analysis

Qualitative variables were expressed as the median [interquartile range (IQR)], and categorical variables were expressed as the frequency (n) percentage (%). Intergroup comparisons were performed using the Mann-Whitney U test, Fisher's exact test, or the chi-squared test, as appropriate. Discriminative power was evaluated in a receiver operating characteristic (ROC) curve analysis. The area under the curve (AUC) was quoted with its 95% confidence interval (CI), and AUCs were compared using DeLong's test. We used the Youden index to find the optimal cut-off for [TIMP-2]*[IGFBP7]. Multivariable analysis was performed by using a logistic regression model. The threshold for statistical significance was set to $p < 0.05$. All statistical analyses were performed using MedCalc® software (version 17.9.7, MedCalc Software, Ostend, Belgium) and RStudio® software (version 1.0.143, RStudio Inc., Boston, MA, USA).

Results

Of the 122 patients included, 7 were excluded, due variously to severe AKI on admission (n = 3), death within 24 h of admission (n = 3) and a protocol deviation for sample processing (n = 1) (Fig. 1). The 115 definitively included patients were predominantly males, 96 (84%) presented an out-of-hospital CA (OHCA). The most common cause of CA was a cardiac event (in 63 patients, including 30 myocardial infarctions and 18 cases of primary arrhythmia), followed by a respiratory cause (in 32 patients). Fifty-nine patients were in shock on admission, and 89 (79%) had received targeted temperature management. The main characteristics of the study population are summarized in Table 1.

Twenty-three (20%) patients developed mild AKI, 27 (23%) developed moderate AKI, and 32 (28%) developed severe AKI within 48 h of admission to the ICU. The diagnosis of severe AKI was based on a low UO in 22 patients, an elevated SCr in five patients, both criteria in four patients, and the requirement for RRT in one patient. Twenty patients reached stage 3 within the first 24 h, and 11 patients required RRT during their stay on the ICU. When compared with patients who did not reach stage 3 AKI, patients with stage 3 AKI were older, and had more comorbidities (such as CKD and congestive heart disease). The median dose of epinephrine delivered during resuscitation, vasopressor dose, and volume of fluid administered during the first day of the ICU stay were significantly greater in the stage 3 AKI group. In-hospital mortality in general and death related to multiple organ failure in particular were significantly higher in the stage 3 AKI group. Five of the 32 patients who developed severe AKI survived during their hospital stay, and were discharged with normal kidney function.

The ability of the [TIMP-2][IGFBP7] metric to predict severe AKI*

The first urine sample was collected a median [IQR] of 240 [169–315] minutes post-collapse. The median baseline [TIMP-2]*[IGFBP7] value was significantly higher in the stage 3 AKI group (1.57 [0.80–6.62]) than in the group of patients who did not reach stage 3 (0.17 [0.05–0.59] $p < 0.001$) (Fig. 2). Compared with the 6 h and 24 h samples, the baseline [TIMP-2]*[IGFBP7] was significantly more discriminant for the detection of stage 3 AKI, with an AUC [95%CI] of 0.91 [0.84–0.95] (Supplemental Fig. 1). The highest Youden index was obtained for a baseline [TIMP-2]*[IGFBP7] level above 0.39 $(ng/ml)^2/1000$; this gave a sensitivity of 97% [84–100] and a specificity of 72% [61–82] (Table 2). Twenty-four patients were misclassified using the cut-off of 0.39 $(ng/ml)^2/1000$; these included 23 patients who did not develop severe AKI (9 without AKI, 10 with mild AKI, and 4 with moderate AKI) and one patient who developed severe AKI with a baseline [TIMP-2]*[IGFBP7] of 0.31 $(ng/ml)^2/1000$. A baseline [TIMP-2]*[IGFBP7] level above 2 $(ng/ml)^2/1000$ yielded a specificity of 98% [92–100] and sensitivity of 45 [29–65] for the detection of severe AKI.

The baseline [TIMP-2]*[IGFBP7] value was significantly more discriminant than the baseline SCr level (AUC [95%CI] of 0.73 [0.63–0.84]; p for comparison = 0.005) for prediction of severe AKI, and slightly but not significantly more discriminant than the baseline UO (AUC [95%CI] of 0.86 [0.78–0.94]; p for comparison = 0.08). The combination of these three parameters in a multivariable model gave

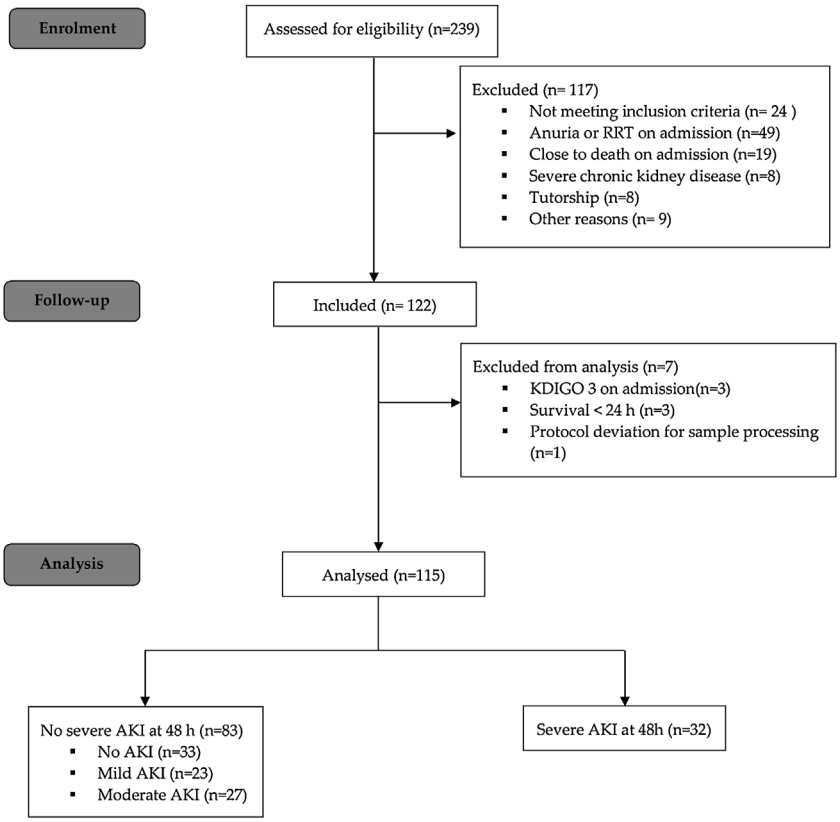

Fig. 1 – Study flow chart.
RRT: renal replacement therapy; KDIGO: Kidney Disease Improving Global Outcomes; AKI: acute kidney injury.

Table 1 – Characteristics of the study population.

	All patients (n = 115)	KDIGO ≤2 (n = 83)	KDIGO 3 (n = 32)	p-value
Demographic data				
Age (years)	64 [52–75]	62 [49–72]	72 [60–82]	0.006
Male gender	75 (65)	50 (60)	25 (78)	0.072
Chronic kidney disease	10 (9)	2 (2.4)	8 (25)	<0.001
Congestive heart failure	13 (11)	5 (6)	8 (25)	0.004
Diabetes mellitus	19 (17)	11 (13)	8 (25)	0.14
Cardiac arrest characteristics				
Out-of-hospital cardiac arrest	96 (84)	68 (82)	28 (88)	0.47
Witnessed cardiac arrest	102 (89)	76 (92)	26 (81)	0.12
Bystander basic life support	78 (68)	57 (69)	21 (66)	0.75
Cardiac cause	63 (55)	46 (55)	17 (53)	0.99
Respiratory cause	32 (28)	22 (27)	10 (31)	0.93
Other or unknown cause	20 (17)	15 (18)	5 (16)	1
Shockable rhythm	46 (40)	33 (41)	13 (42)	0.93
Dose of epinephrine delivered (mg)	2 [0.3–4.4]	2 [0.0–4.0]	3.5 [2.0–5.0]	0.015
Number of shocks delivered	1 [0–2]	1 [0–2]	1.0 [0–2]	0.69
Time to ROSC (min)[a]	20 [12–30]	20 [10–30]	25 [15–32]	0.23
Percutaneous coronary intervention	54 (47)	40 (48)	14 (44)	0.67
Contrast-enhanced computed tomography	33 (29)	25 (30)	8 (25)	0.65
ICU management				
Time from collapse to inclusion (min)	240 [169–315]	255 [180–315]	228 [160–325]	0.55
Baseline SOFA	10 [6–11]	6 [6–11]	10 [8–15]	0.024
Shock at admission	59 (51)	38 (46)	21 (66)	0.06
Baseline lactate (mmol/l)	4.3 [2.1–7.0]	3.9 [1.8–6.5]	6.4 [2.6–8.7]	0.026
Baseline SCr (μmol/l)	99 [76–129]	91 [69–110]	131 [99–173]	<0.001
Baseline [TIMP-2]*[IGFBP7]	0.36 [0.07–1.14]	0.17 [0.05–0.59]	1.57 [0.80–6.62]	<0.001
Baseline urine output (ml/kg/h)	0.82 [0.43–1.41]	1.08 [0.66–1.53]	0.35 [0.15–0.61]	<0.001
[TIMP-2]*[IGFBP7] at 6 h	0.14 [0.05–0.61]	0.10 [0.05–0.32]	0.59 [0.21–2.75]	<0.001
SCr at 24 h (μmol/l)	81 [57–125]	74 [53–96]	175 [109–241]	<0.001
[TIMP-2]*[IGFBP7] at 24 h	0.34 [0.10–0.75]	0.32 [0.08–0.59]	0.57 [0.26–1.87]	0.005
Urine output at 24 h (ml/kg/h)	0.67 [0.46–1.01]	0.74 [0.57–1.11]	0.29 [0.14–0.57]	<0.001
Perfusion fluid at 24 h (l)	2.0 [1.3–2.5]	1.7 [1.0–2.5]	2.3 [1.8–3.1]	0.017
Vasopressor therapy at 24 h (μg/kg/min)	0.11 [0.00–0.29]	0.06 [0.00–0.24]	0.18 [0.06–0.44]	0.008
SOFA at 24 h	8 [6–11]	7 [5–9]	12 [9–15]	<0.001
SAPS II	71 [57–86]	68 [55–85]	80 [71–91]	0.003
Targeted temperature management	89 (79)	61 (74)	28 (88)	0.023
Renal replacement therapy	11 (10)	0	11 (34)	<0.001
Outcome				
In-hospital mortality	73 (64)	46 (55)	27 (84)	0.004
Death related to brain injury	62/73 (84)	45/46 (98)	17/27 (63)	<0.001
Death related to multi-organ failure	10/73 (14)	1/46 (2)	9/27 (33)	<0.001

Median and interquartile range, n (%). PCI: percutaneous coronary intervention; ROSC: return of spontaneous circulation; SCr: serum creatinine; SOFA: sequential organ failure assessment; SAPS II: simplified acute physiology score; RRT: renal replacement therapy.
[a] Not calculated for the 13 patients with unwitnessed cardiac arrest.

an AUC [95%CI] of 0.94 [0.89–0.98] for the prediction of severe AKI. This model was significantly more predictive than the baseline SCr (p for comparison<0.001) or UO (p for comparison = 0.005) values but was not significantly more predictive than the baseline [TIMP-2]*[IGFBP7] value (p for comparison = 0.23) (Fig. 3).

Among the 82 patients who developed AKI within the first 48 h, 45 patients had persistent AKI and 37 patients had transient AKI. The median baseline [TIMP-2]*[IGFBP7] was significantly higher in patients with persistent AKI (0.91 [0.27–3.68]) than in patients with transient AKI (0.24 [0.08–0.87] p = 0.002), although this variable was poorly discriminant for the detection of persistent AKI (AUC [95%CI] of 0.70 [0.59–0.79]). From baseline to 6 h, the [TIMP-2]*[IGFBP7] level dropped in both groups, and the transient and persistent AKI groups did not different with regard to the 6 h and 24 h [TIMP-2]*[IGFBP7] levels (Supplemental Fig. 2). The change in [TIMP-2]*[IGFBP7] from baseline to 6 h was significantly greater in the persistent AKI subgroup, reflecting the higher baseline level. However, this change was also poorly discriminant (AUC [95%CI] of 0.69 [0.58–0.79]).

Discussion

Our present results show that the urine [TIMP-2]*[IGFBP7] value measured on admission can efficiently predict the early development of severe AKI in CA patients admitted to the ICU. With one false-negative result, the cut-off value of 0.39 $(ng/ml)^2/1000$ gave a negative predictive value [95%CI] of 98% [91–100] - suggesting that severe AKI is unlikely below this level. When combined with the baseline SCr and

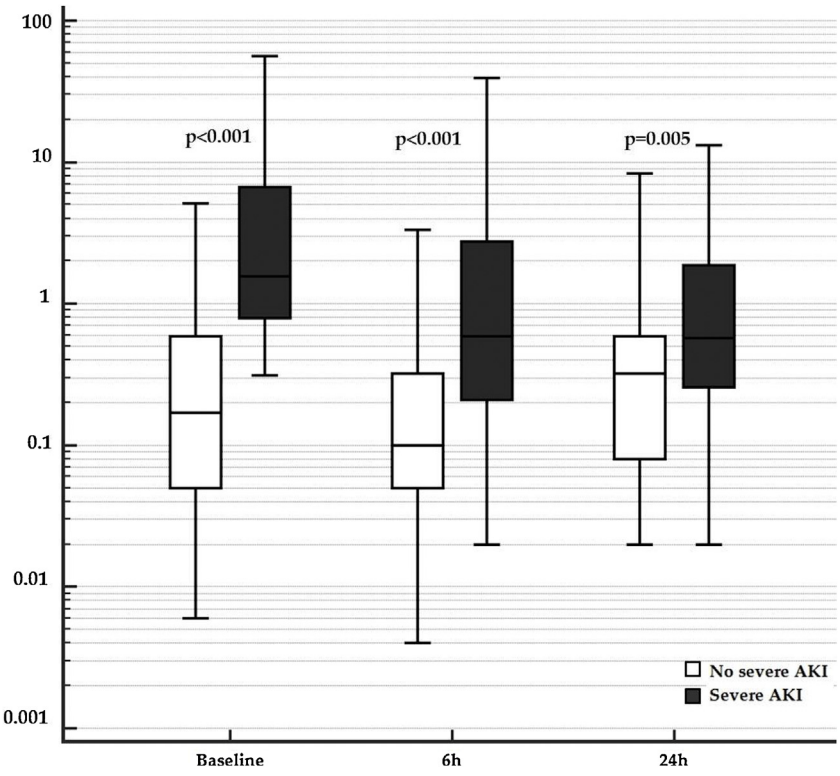

Fig. 2 – Box plots of baseline, 6 h and 24 h urine [TIMP-2][IGFBP7] values.
The data presented had been log-transformed. The boxes and whiskers correspond to interquartile ranges and total ranges, respectively. The urine [TIMP-2]*[IGFBP7] value was significantly higher in patients with severe AKI than in those without severe AKI (Mann-Whitney U test: $p < 0.001$ at baseline and 6 h, and $p = 0.005$ at 24 h). Sample size: n = 115 at baseline, n = 108 at 6 h, n = 95 at 24 h. TIMP-2: tissue inhibitor of metalloproteinases-2; IGFBP-7: insulin-like growth factor-binding protein 7; AKI: acute kidney injury.

Table 2 – Estimated predictive performance of the baseline urine [TIMP-2]*[IGFBP7] value at different cut-offs.

Cut-off value	Sensitivity [95%CI]	Specificity [95%CI]	Youden index	PPV [95%CI]	NPV [95%CI]
>0.20	100 [89–100]	58 [47–69]	0.58	48 [35–60]	100 [93–100]
>0.31	97 [84–100]	66 [55–76]	0.63	53 [36–66]	98 [90–100]
>0.39	97 [84–100]	72 [61–82]	0.69	57 [43–71]	98 [92–100]
>0.59	84 [67–95]	76 [65–85]	0.60	57 [42–72]	93 [84–98]
>0.81	75 [57–89]	83 [73–91]	0.58	63 [46–78]	90 [81–95]
>1.1	69 [50–84]	90 [82–96]	0.59	73 [54–88]	88 [79–94]
>1.3	66 [47–81]	93 [85–97]	0.59	78 [58–91]	88 [79–94]
>1.5	50 [32–68]	93 [85–97]	0.43	73 [50–89]	83 [74–90]
>1.8	47 [29–65]	95 [88–99]	0.42	79 [54–94]	82 [73–89]
>2.0	45 [29–65]	98 [92–100]	0.43	88 [64–99]	83 [74–90]

PPV: positive predictive value; NPV: negative predictive values.

UO, the urine [TIMP-2]*[IGFBP7] value considerably improved the specific predictive performance of these two conventional markers. The specific performance of the urine [TIMP-2]*[IGFBP7] value did not differ significantly from that of the baseline UO. One advantage of [TIMP-2]*[IGFBP7] is its availability within 30 min of admission (rather than 6 h later); it therefore constitutes an early marker of kidney dysfunction—an advantage that may counterbalance the cost of this test. A health economics study is now required to establish the test's likely cost-benefit ratio in routine practice.

All the patients who developed severe AKI in the present study had a [TIMP-2]*[IGFBP7] value above the highly sensitive cut-off of 0.3 $(ng/ml)^2/1000$—a value that has been validated for moderate-to-severe AKI in the large Sapphire and Opal cohorts.[11,12] As in the latter studies, the specificity of the urine [TIMP-2]*[IGFBP7] value was relatively low at the best cut-off of 0.39 $(ng/ml)^2/1000$ but increased to 98% [92–100] at a cut-off of 2.0. More specifically, Beitland et al. assessed the predictive performance of the urine [TIMP-2]*[IGFBP7] value measured within 6 h of collapse in a population of 195 OHCA

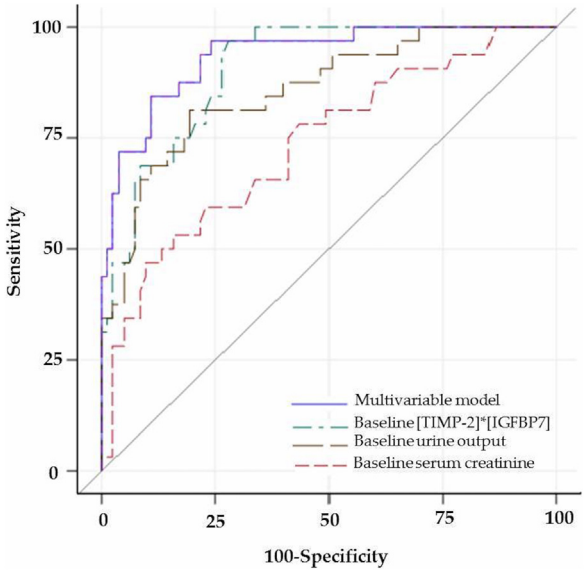

Fig. 3 – Comparison of ROC curves for the prediction of severe AKI.
Comparison of ROC curves for the baseline SCr (red line), the baseline UO (brown line), the baseline urine [TIMP-2]*[IGFBP7] (green line), and the multivariable model containing each of the preceding variables (purple line) for predicting severe AKI. The multivariable model was significantly more predictive than baseline SCr ($p < 0.001$) and UO ($p = 0.005$) but was not significantly better than the baseline urine [TIMP-2]*[IGFBP7] value ($p = 0.23$). TIMP-2: tissue inhibitor of metalloproteinases-2; IGFBP-7: insulin-like growth factor-binding protein 7.

survivors. Of the 88 patients who developed AKI, 52 had mild AKI, and only 13 (7%) developed severe AKI. The researchers found an urine [TIMP-2]*[IGFBP7] value $\geq$0.36 (ng/ml)2/1000 on admission to be predictive of AKI, regardless of the degree of severity.[17] In the latter study, 66% of the patients had an initial shockable rhythm, 88% received bystander CPR, and patients with CKD were excluded from the analysis. These differences might explain (at least in part) the smaller number of cases of severe AKI, relative to our study. Adler et al. found that a level >0.24 $(ng/ml)^2$/1000 at 3 h post-collapse was highly predictive of AKI in a population of 48 OHCA survivors,[18] of whom 21 developed mild-to-moderate AKI and 10 (21%) developed severe AKI. Our study focused on severe AKI; this level of severity is associated with a poor prognosis after CA, and is typically the stage at which the initiation of RRT is first considered. A large French database analysis showed that stage III AKI (i) occurred in almost half the patients admitted to the ICU after OHCA, and (ii) was independently associated with elevated mortality (odds ratio [95%CI]: 1.60 [1.05, 2.43]).[8] Considering patients who presented with anuria or an indication for RRT, the proportion of cases of severe AKI in the present study was about 35%.

One could hold that early prediction of severe AKI is futile in this setting, given that an independent association between AKI and neurologic outcome has not been observed in recent studies.[4,5,8] Nevertheless, it has been well established that severe AKI is associated with elevated mortality and constitutes a major risk factor for CKD in critical ill patients.[19,20] A therapy that limits the degree of renal injury could therefore improve the long-term prognosis of hospital survivors. A future Phase II study (ClinicalTrials.gov identifier: NCT03369275) will test the potential benefit of cellular immunotherapy in septic shock[21] (notably with regard to kidney function) by using the [TIMP-2]*[IGFBP7] metric as a kidney injury marker. Other therapies (such as nicotinamide) have shown promising results in cardiac surgery patients with a high risk of AKI.[22] In this regard, the ability to distinguish the most at-risk patients by using the urine [TIMP-2]*[IGFBP7] value might help to stratify post-CA participants in trials of potentially nephroprotective therapies.

Our study had a number of limitations. The relatively small sample size might limit the validity of the results. The diagnosis of severe AKI was considered only within 48 h of admission; however, no additional cases of severe AKI were observed between 48 and 72 h. The relatively great variations in the urine sampling time post-collapse might have affected the urine [TIMP-2]*[IGFBP7] concentration, although this time was similar in the severe and mild-to-moderate AKI groups. Targeted temperature management was used less frequently in the group of patient who did not develop severe AKI; this probably reflects differences in the attending physicians' practices. However, we did not observe significant differences in the urine [TIMP-2]*[IGFBP7] level between patients who were cooled and those who were not. Lastly, the estimation of the historical baseline creatinine level for patients lacking laboratory test data might have overestimated the number of AKIs. However, this method of estimation is considered to be reliable for the diagnosis of severe AKI.[15,16]

Conclusions

The urine [TIMP-2]*[IGFBP7] value measured within 6 h of collapse can efficiently identify CA patients with a risk of severe AKI. Below a cut-off of 0.39 $(ng/ml)^2$/1000, the risk of severe AKI is low. However, urine [TIMP-2]*[IGFBP7] was not significantly more discriminant than baseline UO for severe AKI.

Conflicts of interest

None.

Acknowledgments

The ASTUTE company provided the NephroCheck® Test free-of-charge but did not have access to the analysis or the manuscript.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2019.06.008.

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