BIOMARKERS [TIMP-2]*[IGFBP7]: APPLICATION IN CLINICAL PRACTICE FOR ACUTE KIDNEY INJURY PREVENTION

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ABSTRACT

Introduction*: Acute kidney injury is a widespread problem mainly among critical area patients, therefore it has been necessary to address research towards the identification of biomarkers able to foresee its development and gravity.*

Materials and methods*: This study, prospective observational unicentric, carried out at the multispecialty Department of Anesthesia and Intensive Care of the "G.Rodolico" Polyclinic Hospital of Catania. , aims to evaluate the utility of biomarkers [TIMP-2]*[IGFBP7]. Urinary measurements were performed using the NephroCheck,ASTUTE 140™ , which from the measurement of the two markers directly elaborates the AKI RISK INDEX. The subjects enrolled, 37 adults patients, were subjected to non-cardiac major surgery. A first withdrawal was carried out before the surgery (T0) and a second one 4 hours (T4) after it. Furthermore, a telephonic interview was carried out one month after the surgery, in order to investigate the general health conditions of the patients and any possible return to hospital.*

Results*: Among the 37 patients, 34 (92%) have not developed acute kidney injury and 3 (8%) manifested KDIGO 1 stage AKI. In 5/37 (13.5%) in which the AKI Risk Index was negative at T0 and became positive at T4 was analyzed the course of pre-operative creatinine, at 24 hours and at 48 hours. The same measurements have been correlated even in patients who had developed acute kidney injury with positive AKI Risk Index both at T0 and T4.*

Conclusions*: Currently, according to literature data, TIMP-2 and IGFBP7 markers appear to be the most promising in the identification of acute kidney injury at subclinical level. The results we obtained are in line with the literature data, with all the limitations set by the exiguity of the analyzed sample. For this reason, we claim the usefulness of further studies that confirm the effectiveness of biological markers in the early identification of patients at risk of AKI.*

Keywords: *biomarkers, AKI, intensive care, early diagnosis.*

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Introduction

Acute kidney injury is a widespread problem, particularly among hospitalized patients in critical conditions and in those subjected to major surgery[(1)]. This increase might be partially attributable to a greater recognition of AKI and to a greater sensibility of diagnostic and classification schemes. AKI associated mortality is decreasing, but it remains unacceptably high: it is estimated that, in patients subjected to major surgery with serious IRA that requires CRRT, it could reach 44%[(2)].

Currently, diagnosis and staging of AKI are mainly based on serum creatinine increases and/or on diuresis contraction. Both indices are however lacking specificity, because the first one increases only after 48-72 hours, and the second one may be influenced by a great multiplicity of factors[(3-4)]. Therefore, it has been necessary to direct the research towards the identification of biomarkers able to foresee development and gravity of AKI in a critically ill patient. A new test measures two AKI biomarkers, the biotextile inhibitor of metalloproteinase 2 (TIMP-2) and the insulin-like growth factor binding

protein 7 (IGFBP7) in human urine. This innovative urinary biological markers are rapidly hyper-expressed from kidney tubules cells after a stress, like an early alarm signal, before the insurgence of acute kidney injury. IGFBP7 and TIMP-2 are both involved in cell cycle arrest in G1 during the initial phase of cell injury[5-6]; this arrest can prevent the division of cells with damaged DNA until the DNA damage isn't repaired[7-8]. In the Sapphire study it has been demonstrated that the AUC valor to foresee AKI development (AKIN stage 2 or 3) in critically ill patients within 12 hours was 0,76 for IGFBP7 and 0,79 for TIMP-2. The multiplication of the two markers [(TIMP-2]*[IGFBP7)/1000] determined an even higher AUC (0,80) and was noticeably higher than every AKI marker previously described[7]). The test to measure the multiplication of the two markers is called NephroCheck,ASTUTE 140™. The Nephrocheck® is a quantitative test, with results expressed as AKIRisk score.

· Negative AKIRisk score (≤ 0,3): low risk of developing moderate or serious AKI within 12h from the patients evaluation.

· Positive AKIRisk score (>0,3): high risk of developing moderate or serious AKI within 12h from the patients evaluation.

This study's purpose was to test the two markers variations, evaluating the AKI risk index in the pre-operative period and in the immediate post-operative period in order to early predict a kidney injury, in line with literature data.

Materials and methods

This study, prospective observational unicentric, was carried out at at multispecialty Department of Anesthesia and Intensive Care of the "G.Rodolico" Polyclinic Hospital of Catania.

In the study were enrolled 42 adult patients subjected to non-cardiac major surgery lasting more than two hours and with a mean arterial pressure (MAP) ≥ 65 mmHg. Among these, 5/42 were excluded due to a lack of follow-up data. The recruitment period has been extended from January 2019 to January 2020.

Inclusion criteria:

· Informed consent

· Age ≥ 18

· Elective noncardiac surgery with expected duration not less than 2 hours

· General anesthesia

· Arterial access necessity during surgery

· Required MAP during surgery ≥ 65 mmHg

Exclusion criteria:

· Patient refusal to participate to the study

· Age under 18

· Necessity to maintain MAP < 65 mmHg

· Chronic kidney disease that needs CRRT

· Acute kidney injury from moderate to serious (KDIGO 2 and 3) already present at the entrance

The following biometric and comorbid conditions characteristics were examined:

· Sex

· Age

· ASA

· Surgery

· Hypertensive heart disease

· Chronic obstructive pulmonary disease (COPD)

· Insulin-dependent diabetes mellitus (IDDM)

· Pre-operative serum creatinine concentration at 24 and at 48 hours

Biomarkers urinary measurements were performed using a test available on the market, the NephroCheck ASTUTE 140™. The measurements were performed in two stages:

· T0 (before the surgery and immediately after the introduction of anesthesia and urinary catheterization)

· T4 (4 hours after the end of the surgery)

The urine samples were withdrawn from the urinary catheter in sterile conditions and treated immediately after the collection. To perform the test 100 μl of tampon solution of the NEPHROCHECK® test were pipetted in the vial of conjugate, 100 μl of centrifuged urine were added, then 100 μl of sample/conjugate mixed solution were pipetted on the NEPHROCHECK® test cartridge. The test was completed using the Astute140 measurer and after 20 minutes we obtained the result of the concentration of the product of the two biomarkers [(TIMP-2) × (IDFBP-7)/1000].

Furthermore, the kidney function was monitored with routine blood tests such as serum creatinine at 24 and at 48 hours from the surgery. The perioperative treatment of the patient wasn't influenced in any way by the dosing of biological markers, but performed according to the needs of individual cases, through: control ABG, volume optimization, pharmacological therapy etc.

Furthermore, a telephonic interview was carried out one month after the surgery, in order to investigate the general health conditions of the patients and any possible return to hospital.

Results

In a twelve months period, 42 patients were enrolled. 5 of them were excluded due to a lack of follow-up data. Of the 37/42 included in our study, 20 were men (54,1%) and 17 were women (45,9%) with an average age of 68,4. 34/37 (92%) patients have not developed acute kidney injury and 3/37 (8%) manifested KDIGO 1 stage AKI; of the latter, two were subjected to left hemicolectomy and one to gastrectomy. The 37 patients urinary samples analysis was then carried out, withdrawn at T0 and at T4 (Table 1).

PATIENTS	AKI Risk index T0	AKI Risk Index T4
P01	0.06	0.41
P03	0.04	0.38
P04	0	0.03
P05	0.05	0.03
P06	0.08	0.19
P07	0	0.44
P09	1.6	0
P10	0.02	0.04
P11	0	0.04
P12	0.32	1.3
P13	0.28	0.02
P14	3.2	0.04
P15	3.29	0
P16	0.22	0.28
P17	3.22	0
P18	0.89	0.27
P20	0.09	0.10
p21	0.74	0
p22	0.06	0
p23	3.01	0.33
p24	1.43	0
p25	0.50	0.10
p27	0.06	0.04
p28	1.27	0.02
p29	0.09	0
p30	0.56	0.83
p31	0.30	0.05
p33	0.22	0.71
p34	1.00	0.07
p35	0.17	0
p36	3.03	0.03
p37	0.17	0.06
p38	0.26	0.03
p39	0.58	0.16
p40	0.25	0.35
p41	1.61	0.15
p42	2.32	0.02

Table 1: AKI risk index at T0 and at T4.

The correlation between the AKI risk index measured at T0 and at T4 was subsequently evaluated (Figure 1).

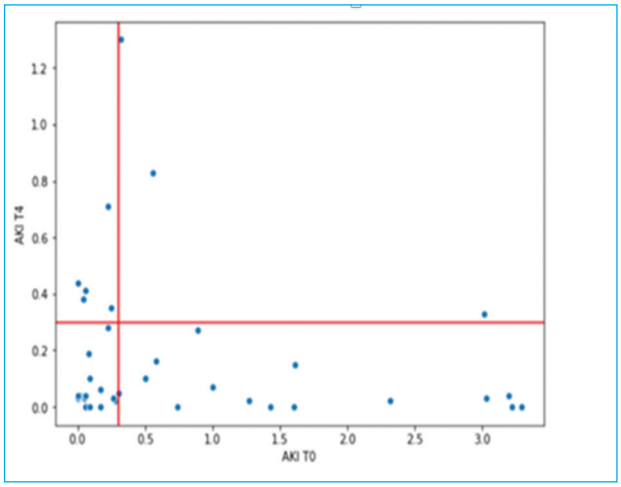

Figure 1: The correlation between the AKI risk indexmeasure at T0 and at T4.

In detail:

· I group:

15/37 (40.5%) AKI Risk Index T0 and T4 ≤0,3

· II group:

14/37 (37.8%) AKI Risk Index T0>0,3T4 ≤0,3

3/37 (8.1%) AKI Risk Index T0 and T4 >0,3

· III group:

5/37 (13.5%) Aki Risk Index T0 ≤0,3T4>0,3

The course of pre-operative creatinine was analyzed at 24 and at 48 hours from the surgery in the 5 patients in which the AKI Risk Index was negative at T0 and became positive at T4. (Table 2).

PATIENTS	pre-operative creatinine	Creatinine at 24 h	Creatinine at 48 h	ASA
P01	0.73	0.60	0.63	II
P03	0.93	0.84	0.84	III
P07	1.03	1.04	1.05	III
P33	0.83	0.85	0.66	II
P40	0.73	0.67	0.63	III

Table 2: Pre-operative creatinine at 24h and 48h in patients with Aki risk index negative at T0 and positive at T4.

There was no significant increase in creatinine in any of the five patients, in which the AKI Risk Index was negative at T0 and was positive at T4, at 24 and at 48 hours from the surgery. Eventually the pre-operative creatinine data have been correlated at 24 and at 48 hours from the surgery in the patients who had developed an acute kidney injury with AKI Risk Index at T0 and T4. (Table 3).

Patients	AKIT0	AKI T4	pre-operative creatinine	24h creatinine	48h creatinine
P09	1.6	0	0.43	1.21	1.22
P12	0.32	1.3	1.13	1.50	1.61
P28	1.27	0.02	2.14	2.53	2.85

Table 3: Correlation between pre-operative creatinine at 24h and 48h after surgery in the patients who had developed an acute kidney injury with AKI index at T0 an T4.

Table 3 shows that two patients (P09-P28) were positive at T0 time and become negative at T4 time, while a patient (P12) was positive both at T0 and T4.

A telephonic interview was carried out one month after the surgery, in which it emerged that 89% (33/37) of the patients had developed no post-operative complications and had no other access to emergency room, 3% (1/37) was hospitalized again

for the onset of an episode of atrial fibrillation and 8% (3/37) deceased for the occurrence of medical and/or surgical complications in the post-operative period.

Discussion

According to literature data, patients with an AKI Risk Index <0,3 should not develop kidney damage and this data has been confirmed even in our study. In the first patients group (T0 and T4 ≤0,3), no one manifested acute kidney damage. In the second group of patients (14/37 with T0 >0,3 T4 ≤ 0,3; 3/37 with T0 and T4 >0,3) only in 3 subjects a mild degree acute kidney injury occurred. In all these three patients the AKI Risk Index was at T0>0,3; this data might be correlated to the execution of radiological instrumental examinations with iodized contrast agent performed in the 24 hours prior to surgery. In the third group of patients (5/37 with T0 ≤0,3 T4 >0,3) kidney injury didn't develop, and this appears to be in contrast with what was found in literature. Probably this data could be correlated to an adequate post-operative medical management, in fact these 5 patients haven't been subjected to radiological instrumental examinations with iodized contrast agent in the following 48 hours, they have not received antibiotic therapy with nephrotoxic drugs and were managed with correct fluid therapy and hemodynamic monitoring protocols. This adequate management allowed high-risk patients not to evolve towards full-blown kidney injury. Finally, a telephone interview was conducted one month after surgery, from which it is clear that, excluding the three patients who died because of perioperative complications, the rest of the patients (34/37) had no postoperative complications or new access to the emergency room for kidney problems, in line with our results, including the three patients who had developed mild renal damage in the perioperative period.

Given the importance of AKI as an independent risk factor for mortality in critically ill patients, the costs associated with it and its consequences also in the long term, recognizing and treating this pathological condition early is a crucial point in the care of the critically ill patient. However, the identification of "renal troponin", or a biomarker that may be early, sensitive and specific to acute kidney injury is not easy, as it is generally multifactorial (hypoperfusion, inflammation, oxidative stress, toxins, etc.). The cost-effectiveness of the Nephrocheck® test is still to be evaluated. In a 2015 analysis, the cost attributable to postoperative acute kidney injury using the RIFLE criteria was $ 10,700 in the Risk class, $ 21,400 in the Injury class and $ 38,200 in the Failure[9] class. Therefore, recognizing and treating AKI early allows to limit its evolution in terms of severity, and so it is possible to hypothesize a favorable cost-effectiveness ratio. Currently, from the data in the literature, the TIMP-2 and IGFBP7 markers appear to be the most promising, in our experience. Despite the encouraging results, the exiguity of numbers did not allow us to include them in clinical practice; on the other hand, some centers, having a larger number of cases, take them into consideration in routine diagnostics. In conclusion, it is reaffirmed the usefulness of further studies confirming the efficacy of biological markers in order to identify patients at risk of kidney injury early and to allow their inclusion in clinical management protocols.

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