ORIGINAL RESEARCH

Robert L., et al.

Community-acquired acute kidney injury induced by drugs in older patients: a multifactorial event

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Table S1: Criteria used to define AKI according to KDIGO criteria

Stage	***Serum creatinine****
1	*1.5-1.9 times baseline* *OR* *≥ 0.3 mg/dl (≥ 26.5 µmol/l) increase* **
2	*2.0-2.9 times baseline*
3	*3.0 times baseline* *OR* *Increase in serum creatinine to ≥ 0.4 mg/dl (≥ 353.6µmol/l)* *OR* *Initiation of renal replacement therapy* *OR* *In patients < 18 years, decrease in eGFR to < 35 ml/min per 1.73m^2*

* Data on urine output was not available and therefore we did not take this parameter into account in the diagnosis of AKI

** This criterion was used only if serum creatinine was < 1.2 mg/dl

Table S2: ATC code of drugs known to be involved in AKI and extracted in the study

Drugs classes	***ATC code***
ACEi	*C09AA* *C09BA* *C09BB* *C09BX*
ARB	*C09CA* *C09DA* *C09DB* *C09DX*
Loop diuretics	*C03CA* *C03CB* *C03EB*
Thiazide diuretics	*C03AA* *C03AX* *C03BA* *C03BX* *C03EA*
K-sparing diuretics	*C03DA* *C03DB* *C03EA* *C03EB*
Chemotherapy	*L01AA01* *L01AA06* *L01BA01* *L04AX03* *L01XA01* *L01XA02*
NSAIDs	*M01A*
Aminoglycoside	*J01GA* *J01GB*

Abbreviation: ATC: anatomical, therapeutic and chemical classification system; ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin II receptor blocker; K: potassium; NSAIDs: non-steroidal anti-inflammatory drugs

Table S3: Characteristics of drugs involved in the occurrence of the 713 CA-AKI events

Drugs	Causality assessment [a] (N =713)	Inappropriate [b] **	Avoidability of the event [c]	
			Definitely **	Possibly **
ACEi and ARB	330 (46.3%)	44 (13.3%)	14 (4.2%)	202 (61.2%)
Diuretics *	327 (45.9%)	20 (6.1%)	15 (4.6%)	191 (58.4%)
NSAIDs	8 (1.1%)	2 (25.0%)	1 (12.5%)	5 (62.5%)
Aminoglycoside	1 (0.1%)	0	0	0

Abbreviations: ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin II receptor blocker; NSAIDs: non-steroidal anti-inflammatory drugs

[a] Causality assessment was evaluated by the Naranjo scale with a score ≥ 1

[b] Inappropriateness was evaluated by the STOPP criteria

[c] Avoidability was evaluated by the Hallas criteria

** divided by the number of medications with a Naranjo score ≥ 1 in each drug category (e.g. 330 for ACEi and ARB, 327 for diuretics…)

*** Avoidability of the events was assessed by the Hallas criteria

[a]: Diuretics include loop diuretic, thiazide diuretic and potassium-sparing diuretic

Table S4: Criteria of Naranjo scale for causality assessment

	Yes	No	Do not know
1. Are there previous conclusive reports on this reaction?	+1	0	0
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0
4. Did the adverse reaction reappear when the drug was re-administered?	+2	-1	0
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0
6. Did the reaction appear when a placebo was given?	-1	+1	0
7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0
8. Was the reactions more severe when the dose was increased, or less severe when dose decreased?	+1	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0

Results of Naranjo score:

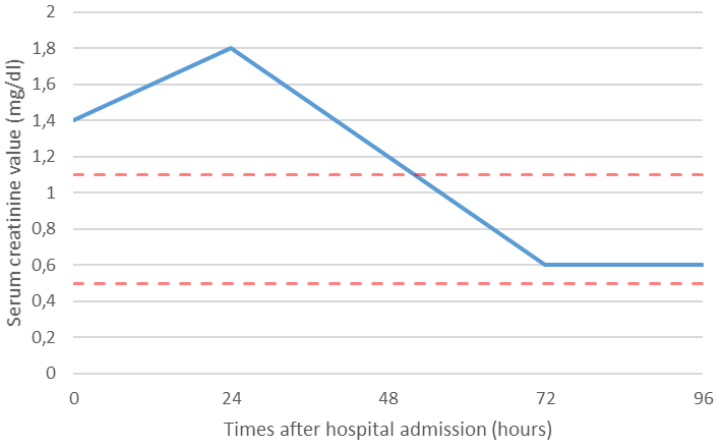
- Definite: score ≥ 9
- Probable: 5-8
- Possible: 1-4
- Doubtful: ≤ 0

Table S5: Details of the Hallas criteria (avoidability of the event)

	Explanations
Definitely avoidable:	The drug event was due to a drug treatment inconsistent with present-day knowledge of good medical practice or was clearly unrealistic, taking the known circumstances into account.
Possibly avoidable:	The prescription was not erroneous, but the drug event could have been avoided by an effort exceeding the obligatory demands.
Not avoidable:	The drug event could not have been avoided by any reasonable means or it was an unpredictable event in the course of a treatment fully in accordance with good medical practice.
Unevaluable:	The data for rating could not be obtained or the evidence was conflicting.

Figure S1: Example CA-AKI of inclusion and non-inclusion scenario

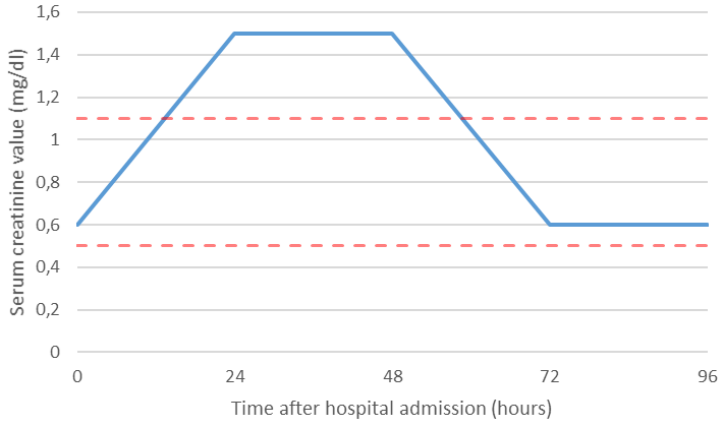
Cases n°1: significant increase in serum creatinine according to KDIGO criteria during the first 48 hours after hospital admission



Creatinine at admission = 1.4 mg/dl

Highest creatinine value (1.8 mg/dl) = 3 times the baseline creatinine value (0.6 mg/dl)
=> Stage 3 according to KDIGO criteria

Double expert review confirmed the CA-AKI

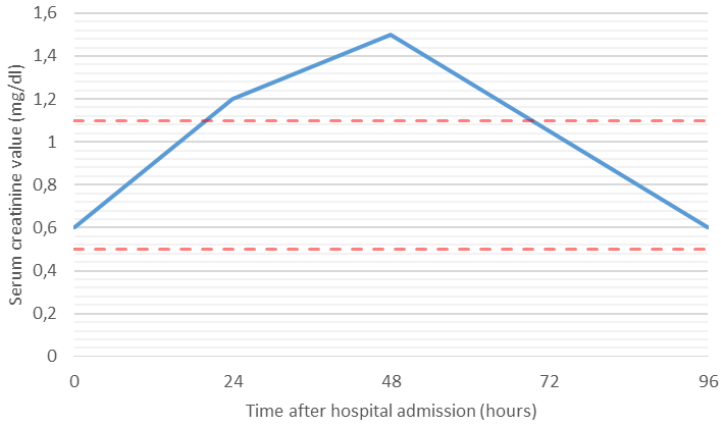


Creatinine at admission = 0.6 mg/dl

Increase of serum creatinine during the first 48 hours after the hospital admission

Highest creatinine value (1.5 mg/dl) = 2.5 times the baseline creatinine value (0.6 mg/dl)
=> Stage 2 according to KDIGO criteria

=> Expert review confirmed the CA-AKI

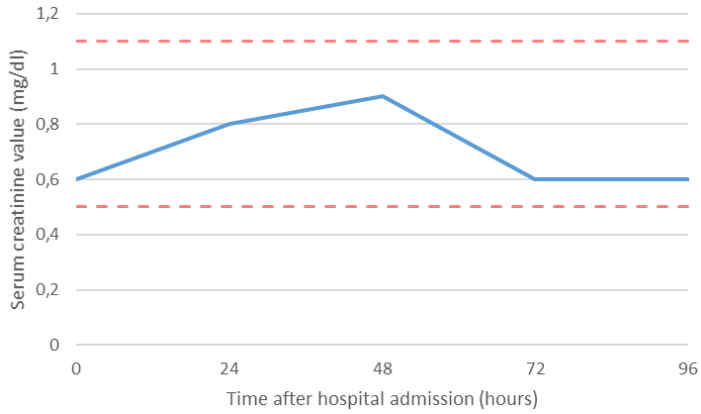


Creatinine at admission = 0.6 mg/dl

Increase of serum creatinine during the first 48 hours after the hospital admission

Highest creatinine value (1.5 mg/dl) = 2.5 times the baseline creatinine value (0.6 mg/dl)
=> Stage 2 according to KDIGO criteria

=> Expert review confirmed the CA-AKI



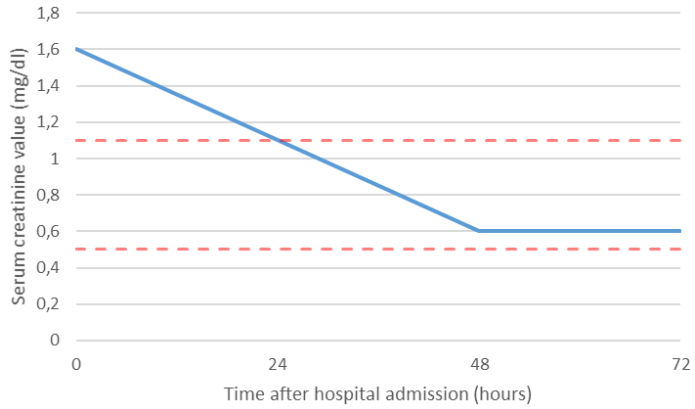
Creatinine at admission = 0.6 mg/dl

Increase of serum creatinine during the first 48 hours after the hospital admission

Highest creatinine value (0.9mg/dl) = increase of 0.3 mg/dl compared to baseline => Stage 1 according to KDIGO criteria

=> Expert review confirmed the CA-AKI

Cases n°2: significant decrease of serum creatinine according to KDIGO criteria during the inpatient stay with serum creatinine value at admission time significantly higher than the lowest value during inpatient stay

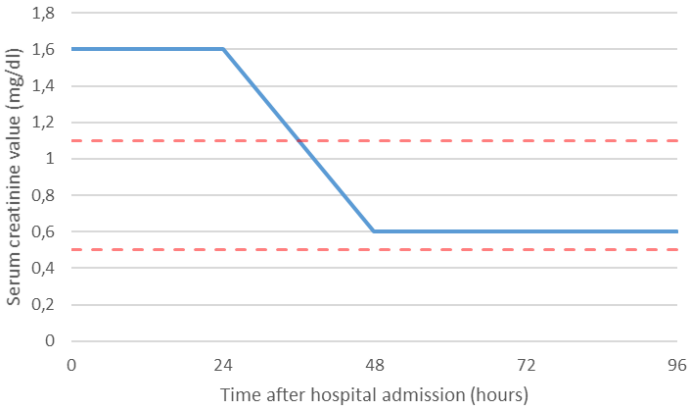


Creatinine at admission = 1.6 mg/dl

Decrease of serum creatinine value during the inpatient stay

Highest serum creatinine (1.6 mg/dl) = 2.6 times the baseline creatinine value (0.6 mg/dl) => Stage 2 according to KDIGO criteria

=> Expert review confirmed the retrospective CA-AKI



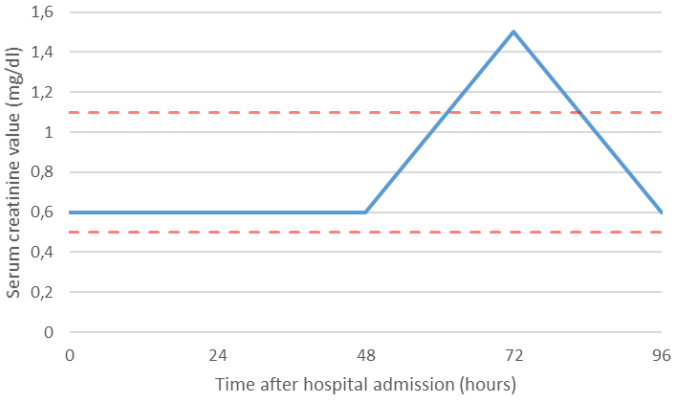
Creatinine at admission = 1.6 mg/dl

Decrease of serum creatinine value during the inpatient stay

Highest serum creatinine (1.6 mg/dl) = 2.6 times the baseline creatinine value (0.6 mg/dl) => Stage 2 according to KDIGO criteria

=> Expert review confirmed the retrospective CA-AKI

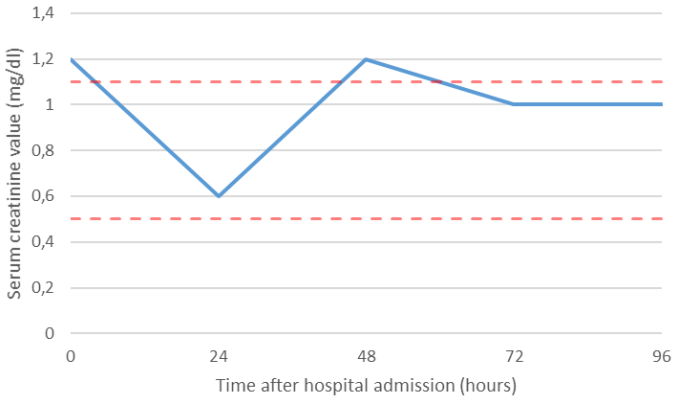
Cases n°3: exclusion criteria of CA-AKI



Creatinine value at admission = 0.6 mg/dl

Highest creatinine value is during the inpatient stay (i.e. after 48 hours of the hospital admission)

=> Expert review did not confirm the CA-AKI

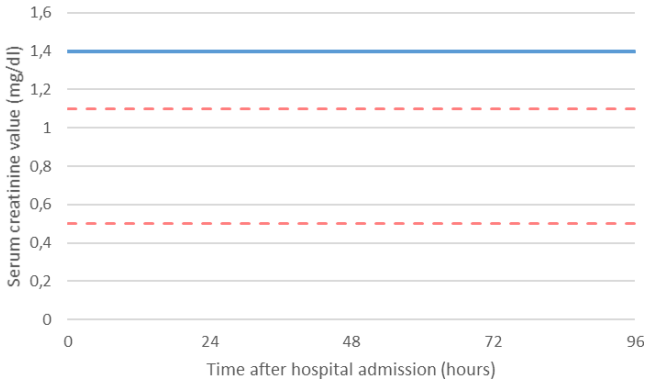


Creatinine value at admission = 1.2 mg/dl

Decrease of serum creatinine to 0.6 mg/dl
But the baseline creatinine value is in fact at 1 mg/dl

Highest creatinine value (1.2 mg/dl) = 1.2 times the baseline creatinine
=> Not a stage according to KDIGO

=> Expert review did not confirm the CA-AKI



Creatinine value at admission = 1.4 mg/dl

Constant serum creatinine value during the hospitalization without any improvement of the serum creatinine value.

=> Case deemed to be a chronic kidney disease

=> Expert review did not confirm the CA-AKI