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Clinical paper

Long term renal recovery in survivors after OHCA

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Abstract

Backgrounds: In survivors of out-of-hospital cardiac arrest (OHCA), acute kidney injury (AKI) is frequent and is associated with numerous factors of definitive renal injury. We made the hypothesis that AKI after OHCA was a strong risk factor of long-term chronic kidney disease (CKD). We aimed to evaluate long-term renal outcome of OHCA survivors according the occurrence of AKI in ICU.

Methods: We used prospectively collected data from consecutive OHCA patients admitted between 2007 and 2012 in a tertiary medical ICU. AKI was defined by the Kidney Disease Improving Global Outcomes (KDIGO) criteria. Long-term creatinine level was the last blood creatinine assessment we were able to retrieve. The main outcome was the occurrence of CKD, defined by an estimated glomerular filtration rate (eGFR) lower than 60 mL/min/1.73m^2 according to the MDRD equation. Long-term mortality was evaluated as well. Factors associated with CKD occurrence were evaluated by competing risk survival analysis (Fine Gray and Cox cause specific models).

Results: Among the 246 OHCA patients who were discharged alive, outcome of 133 patients was available (median age 55 [iqr 46, 68], 75.2% of male). During a median follow-up time of 1.8 [0.8–2.5] years, CKD occurred in 17 (12.7%) patients and 24 (18%) patients died. A previous history of arterial hypertension (sHR = 3.28[1.15;9.39], p = 0.027; CSH = 4.83 [1.57;14.9], p = 0.006), AKI during ICU stay (sHR = 3.72[1.40;9.84], p = 0.008; CSH = 5.41 [1.79;16.3], p = 0.003) and an age higher than 55 (sHR = 6.13[1.55;24.3], p = 0.009; CSH = 2.16[1.72;43.8], p = 0.006) were independently associated with CKD occurrence. AKI was not associated with long-term mortality (sHR = 0.73 [0.27;1.99], p = 0.55; CSH = 0.75 [0.28;2.01], p = 0.57).

Conclusion: In OHCA survivors, CKD was a frequent long-term complication. AKI during ICU stay was a strong determinant of long-term CKD occurrence.

Keywords: Acute kidney injury, Out-of-hospital cardiac arrest, Chronic kidney disease, Outcome

Introduction

Severe acute kidney injury (AKI) frequently occurs in successfully resuscitated out-of-hospital cardiac arrest (OHCA) patients and is strongly associated with intensive care unit (ICU) and day-30 mortality.[1,2] However, most of OHCA survivors who suffered severe AKI recover a normal glomerular filtration rate at day-30 and the vast majority of them is independent of renal replacement therapy after hospital discharge.[1] The mechanism of AKI in these patients is related to complex and intense ischemia-reperfusion phenomena. Acute tubular necrosis is the assumed histological pattern that could explain the apparent full-recovery of renal function.

However, an increased risk of long-term chronic kidney disease (CKD) in patients who suffered AKI has been recently raised, especially in severe AKI patients.[3–5] This risk seems to exist even if the glomerular filtration rate is measured in "normal range" at hospital discharge, leading to the "*de novo*" CKD concept.[6] Similar data have

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been reported in critically ill patients,[7] but no data have been published so far in successfully resuscitated OHCA patients. This is all the more so important that such patients may be at increased risk of endothelial maladaptative recovery regarding the huge ischemia-reperfusion syndrome observed after restoration of spontaneous circulation (ROSC) leading to major endothelial dysfunction.[8]

The present study is the first evaluating long-term recovery after AKI in OHCA patients. This may help to identify a subgroup of OHCA survivors who are at risk of chronic kidney disease and who could benefit of secondary prophylactic treatments and/or a tight nephrologist follow-up.

Patients and methods

Study population

Inclusion and exclusion criteria have been described earlier.[1] Briefly, all consecutive non-trauma OHCA patients survivors admitted in our ICU between January 2007 and December 2012 were included if they had at least one weight determination and one serum creatinine level available at ICU admission. Because the kidney disease improving global outcomes (KDIGO) guidelines defined CKD as abnormalities of kidney function or structure present for more than 3 month,[9] only patients discharged alive from hospital and with a 3-month minimal follow-up were analyzed. Patients with history of chronic kidney disease before OHCA were not included in the analysis.

Early management

As previously described,[10] our local practices include an early imaging diagnosis strategy (including coronary angiography and/or brain and chest CT scan) performed within the first 24 h after an immediate assessment of the feasibility of further investigations by the Emergency Medical Services (EMS) and ICU physician. Renal replacement therapy is initiated at ICU admission in case of severe metabolic acidosis (defined by a pH lower than 7.20 and an admission bicarbonate level lower than 20 mmol/L) and/or in case of life-threatening hyperkalaemia (defined by blood potassium level higher than 6 mmol/L with electrocardiographic findings suggestive of hyperkaliemia). Therapeutic hypothermia was performed using forced cold air method until 2012 and is performed using a temperature feedback control device since 2012 (Arctic Sun, Medivance Corp., Louisville, CO).

Data collection

Cardiac arrest characteristics, inhospital management and outcome data were prospectively collected according to Utstein style.[11] The following information were prospectively recorded for each patient: demographic data, comorbidities, clinical parameters, cardiac arrest location, time from collapse to ROSC, initial rhythm, pre-hospital management and ICU management. Post-resuscitation shock was defined as the need for vasopressors (epinephrine or norepinephrine) lasting more than 6 h despite adequate fluid loading or the need for ventricular assistance.[12]

Laboratory values were computed from medical files and extracted from the patient data management system (Clinisoft, GE Healthcare). We specifically collected arterial blood lactate and blood creatinine at ICU admission. Creatinine level was also collected at ICU discharge and hospital discharge.

During follow-up, recorded information were: latest serum creatinine level, latest proteinuria, nephrology referral, use of angiotensin converting enzyme inhibitors or angiotensin 2 receptors antagonists treatment and cardiovascular risk factors (diabetes mellitus, arterial hypertension and current smoking). To collect these data, patient's family doctor was first contacted by mail. If the name of the family doctor was not recorded in the patient's chart, or if the family doctors was either no more in charge or did not have any required information, we directly contacted the patient by mail. This study was approved by our local ethic committee (IRB number CE SLRF 16–31).

Outcomes and main exposure

The main outcome was the occurrence of CKD during follow-up. CKD was defined by an eGFR below than 60 mL/min/1.73 m^2 according the MDRD equation[13] (stage 3a to 5 of the KDIGO classification). Secondary outcomes included death and event-free survival.

The main exposure was AKI. As previously described, AKI was defined by the occurrence of stage 3 of the KDIGO definition within the first 48 h.[14] Since premorbid creatinine was often unavailable, we used admission serum creatinine (SCr) level as baseline. The KDIGO urine output criteria for stage 3 (less than 0.3 mL/kg/h for 24 h or anuria for at least 12 h) was used only during the first 24 h. Finally, patients who received RRT within the first 48 h were considered to have met the criteria for KDIGO stage 3 irrespective of other criteria.

Statistical analysis

Descriptive statistics were presented as median [interquartile] and counts (percentages) for continuous and categorical variables, respectively. Baseline characteristics were compared according to the three final status (CKD, death and event-free survival) using Kruskall–Wallis test, and Pearson Chi-square test or the Fisher's exact test, as appropriate, for continuous and categorical variables, respectively.

Because three competing events were observed during follow up (CKD, death and event-free survival), we performed a cause-specific proportional hazard model and a Fine Gray model regression.[15] The multivariate models were built by including all risk factors for death that met the 0.20 significance threshold in univariate analysis. Backward stepwise regression for both regression models were performed using Akaïke as selection criteria. The results were given as sub-distribution hazard ratio (sHR) and 95% confidence interval (CI) and cause-specific hazard (CSH) and 95% CI for Fine Gray model regression and cause-specific hazard model, respectively.

All statistical tests will be two-sided using a type I error of 0.05 unless otherwise mentioned. Analyses will be performed using R® software (R foundation for Statistical Computing Vienna, Austria).

Results

899 patients were admitted for OHCA during the study period. 319 were excluded from the princeps study (247 patients died before 48 h, 22 patients had CKD at ICU admission, 48 patient were not treated by therapeutic hypothermia and 2 patients had missing weight

information at admission). Among these 580 patients, 339 patients died within the first 3 months, and 133 patients were finally included in the analysis (Supplementary Fig. 1).

Baseline characteristics

Baseline characteristic are described in Table 1. Patients were mostly male [n = 100 (75.2%)] of median age 55 [46–68] years. A history of arterial hypertension was reported in 44 (33.1%) patients. Cardiac arrest occurred in public place in 60 (45.1%) cases and was related to an initial shockable rhythm in 101 (75.9%) cases. Post-resuscitation shock was observed in 55 (41.3%) patients and AKI KDIGO 3 occurred in 44 (33.1%) patients. Renal replacement therapy was used in 32 (24.1%) patients at day-1 and in 8 (6%) patients at day-3. Median ICU and hospital lengths of stay were 6^{4-10} and 17^{11-25} days, respectively. At hospital discharge, the median blood SCr level was 75 [64–85] μmol/L.

Occurrence of CKD and death in OHCA survivors

In the analysis cohort, CKD occurred in 17 (12.8%) patients, 24 (18%) patients died during the follow-up while 92 (69.2%) patients remained free of event (Fig. 1). The latest SCr were available at 3.1 [0.7–5.4] years after OHCA.

Overall, patients who suffered CKD were older and had more frequently cardiovascular diseases. Median SCr level at ICU admission was 106, 108 and 82 μmol/L in CKD patients, in patients who died and those event-free, respectively ($p < 0.001$). At ICU discharge, median SCr level was higher in CKD patients while it did not differ at hospital discharge (91 [61–134] μmol/L vs 67 [58–78] μmol/L, $p = 0.005$ and 80 [75–91] μmol/L vs 73 [63–84] μmol/L, $p = 0.11$, respectively) (Supplementary Fig. 2). Acute kidney injury was more frequently observed and was more severe in CKD patients (Table 1 and Fig. 2).

Table 1 – Characteristics according to competing event.

	All patients n = 133	CKD n = 17	Death n = 24	EFS n = 92	p Value
Demographics					
Male gender	100 (75.2%)	9 (52.9%)	20 (83.3%)	71 (77.2%)	0.07
Age, y	55 [46–68]	71 [65–82]	68 [54–76]	53 [43–61]	<0.001
Body mass index, kg/m^2	22 [20–24]	22 [20–24]	21 [18–23]	22 [20–23]	0.76
Past medical history					
Arterial hypertension	44 (33.1%)	11 (64.7%)	10 (41.7%)	23 (25%)	0.002
Diabetes mellitus	17 (12.8%)	5 (29.4%)	2 (8.3%)	10 (10.9%)	0.12
Dyslipidemia	48 (36.1%)	7 (41.2%)	10 (41.7%)	31 (33.7%)	0.66
Current smoking	62 (46.6%)	1 (5.9%)	10 (41.7%)	51 (55.4%)	<0.001
OHCA characteristics					
Public setting	60 (45.1%)	9 (52.9%)	8 (33.3%)	43 (46.7%)	0.41
Witnessed cardiac arrest	118 (88.7%)	14 (82.3%)	21 (87.5%)	83 (90.2%)	0.49
Bystander CPR	75(56.4%)	12 (70.6%)	13 (54.2%)	50 (54.3%)	0.40
Initial shockable rhythm	101 (75.9%)	12 (70.6%)	10 (41.7%)	79 (85.9%)	<0.001
Collapse to ROSC, min	18 [12–25]	15 [11–21]	15 [7–20]	19 [12–25]	0.25
N. of electric shock	1 [1,2]	1 [0–2]	0 [0–1]	1 [1–3]	0.57
Ephedrine total dose, mg	1 [0–2]	2 [1,2]	1 [0–3]	1 [0–2]	0.08
Biological characteristics at ICU admission					
Creatinine level, μmol/L	87 [74–106]	106 [86–129]	108 [81–132]	82 [72–102]	<0.001
Lactate level, mmol/L	3 [1.8–5]	3.7 [2.4–5.8]	3.3 [1.8–5.6]	2.7 [1.7–4.9]	0.31
In-hospital characteristics					
Cardiac cause related cardiac arrest	102 (76.7%)	13 (76.5%)	14 (81.1]	75 (81.1]	0.05
Post resuscitation shock	55 (41.3%)	7 (41.2%]	12 (50%)	36 (39.1%)	0.66
Acute kidney injury					0.003
No AKI	68 (51.1%)	4 (23.5%)	11 (45.8%)	53 (57.6%)	
KDIGO 1	8 (6%)	0 (0%)	4 (16.7%)	4 (4.3%)	
KDIGO 2	11 (8.2%)	2 (11.7%)	4 (16.7%)	5 (5.4%)	
KDIGO 3	44 (33.1%)	11 (64.7%)	4 (16.7%)	29 (31.5%)	
Coronary angiography	110 (82.7%)	15 (88.2%)	13 (54.2%)	81 (88%)	0.004
RRT at day-1	32 (24.1%)	7 (41.2%)	3 (12.5%)	22 (23.9%)	0.11
RRT at day-3	8 (6%)	1 (5.8%)	1 (4.2%)	6 (6.5%)	>0.9
Follow up					
Creatinine level at ICU discharge, μmol/L	69 [59–82]	91 [61–134]	103 [95–140]	66 [57–75]	<0.001
Creatinine level at hospital discharge, μmol/L	75 [64–85]	82 [75–94]	111 [100–124]	73 [62–84]	0.008
ICU length of stay, d	6 [4–10]	10 [6–22]	9 [8–10]	6 [3–8]	0.003
Last creatinine level, μmol/L	82 [72–100]	120 [112–145]	73 [60–95]	80 [72–95]	<0.001
Last eGFR, mL/1.73 m^2	85 [70–106]	47 [42–52]	96 [75–129]	88 [76–106]	<0.001
Follow up delay, years	3.1 [0.7–5.4]	2.7 [1.6–5.3]	1.8 [0.8–2.5]	3.7 [1.2–5.9]	<0.001

Categorical variables are shown as n(%) and compared using χ^2 test.
Continuous variables are shown as median [iqr] and compared using a Kruskal–Wallis test.
OHCA = out of hospital cardiac arrest; CPR = cardiopulmonary resuscitation; ROSC = return of spontaneous systemic circulation; AKI = acute kidney injury; RRT = renal replacement therapy; ICU = intensive care unit; eGFR = estimated glomerular filtration rate; EFS: event free survival.

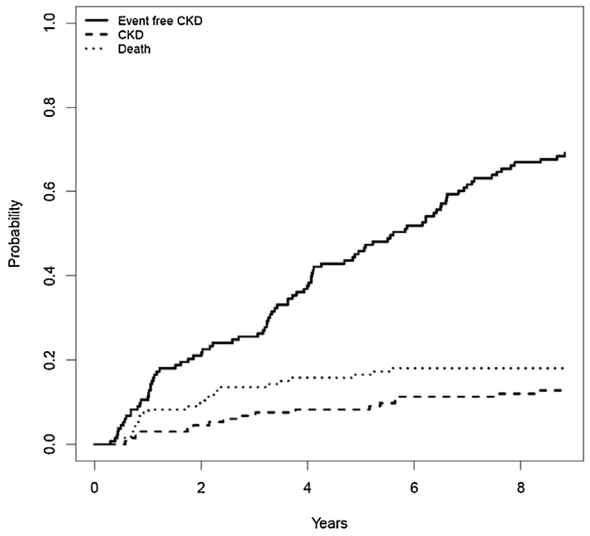

Fig. 1 – Cumulative incidence of competing events.

Factors associated with CKD

In univariate analysis, patients with CKD were older (sHR = 1.08 [1.03;1.13] per one year increasing, $p < 0.001$; CSH = 1.10 [1.05;1.14] per one year increasing, $p < 0.001$). A history of arterial hypertension (sHR = 4.81 [1.68;13.8], p = 0.003 ; CSH = 4.89 [1.68;14.2], p = 0.003) and of diabetes mellitus (sHR = 2.90 [1.06;7.89], p = 0.04 ; CSH = 1.88 [0.66;5.38], p = 0.24) were more frequently reported. No difference was observed in terms of OHCA characteristics and management according to the occurrence of CKD. Conversely, AKI occurred more frequently in the CKD group (sHR = 2.66 [1.04;6.82], p = 0.04 ; CSH = 2.51 [0.97;6.55], p = 0.06) (Fig. 3). SCr at hospital discharge was not associated with the occurrence of CKD during follow up (sHR = 1 [0.98;1.01] per μmol/L increasing, p = 0.37 ; CSH = 1.03 [0.99;1.05] per μmol/L increasing, p = 0.06) (Supplementary Table 1).

In multivariable analysis, both regression models evidenced an association between a history of arterial hypertension (sHR = 3.28 [1.15;9.39], p = 0.027 and CSH = 4.83 [1.57;14.9], p = 0.006), AKI during ICU (sHR = 3.72[1.40;9.84], p = 0.008 and CSH = 5.41 [1.79;16.3], p = 0.003) and an age older than 55 years (sHR = 6.13 [1.55;24.3], p = 0.009 and CSH = 2.16[1.72;43.8], p = 0.006) and CKD occurrence (Table 2).

Relation between AKI with death and event free survival

AKI was not associated with death (sHR = 0.74 [0.27;1.99], p = 0.55; CSH = 0.75 [0.28;2.02], p = 0.57) and event free survival (sHR = 0.83 [0.51;1.34], p = 0.44; CSH = 0.97 [0.59;1.58], p = 0.90) (Supplementary Table 2 and Fig. 3).

Factors associated with death included eGFR at hospital discharge (SHR = 0.96 [0.94;0.98], p = 0.013 ; CSH = 0.94 [0.88;0.98], p = 0.01), an non shockable initial rhythm (SHR = 0.17 [0.08;0.39], $p < 0.001$; CSH = 0.17 [0.07;0.38], $p < 0.001$), an older age (SHR = 1.03 [1–1.05], p = 0.03; CSH = 1.03 [1.01–1.06], p = 0.02) and a non cardiac cause related cardiac arrest (SHR = 0.34 [0.15–0.78], p = 0.001 ; CSH = 0.31 [0.13–0.72], p = 0.006). Event free survival was observed in younger patients (SHR = 0.96 [0.95–0.98], p = 0.001 ; CSH = 0.97 [0.95–0.99], p = 0.001), with higher time of collapse to ROSC (SHR = 1.03 [1.01–1.05], p = 0.01 ; CSH = 1.02 [1.01–1.05], p = 0.02) and an higher eGFR at hospital discharge (SHR = 1.01 [1–1.02], p = 0.005; CSH = 1.01 [1–1.02], p = 0.04).

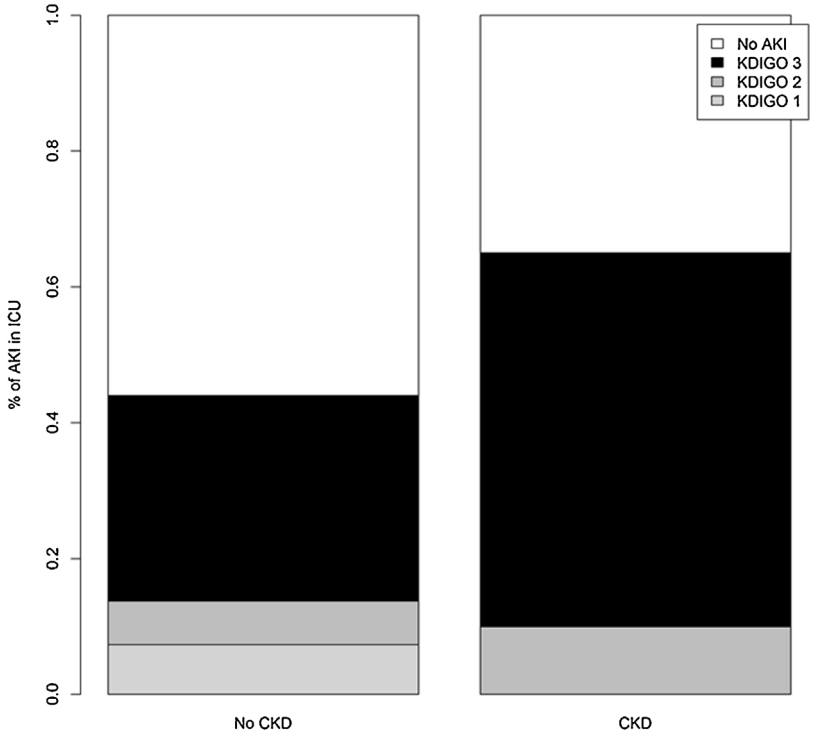

Fig. 2 – Severity of AKI during the ICU stay according to CKD occurrence.

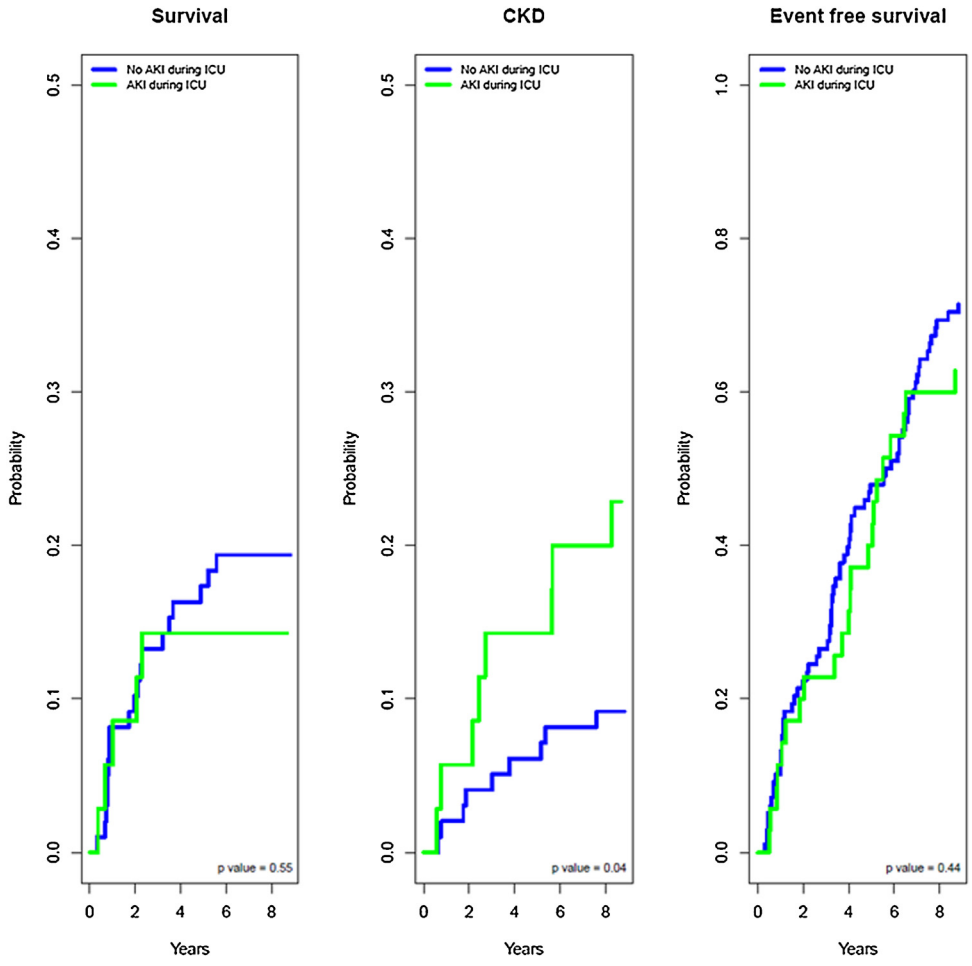

Fig. 3 – Probability of CKD occurrence (left panel), mortality (middle panel) and event free survival (right panel) according to AKI during the ICU stay.

Table 2 – Factors associated with CKD in multivariate competing risk analyses.

	Fine Gray model regression			Cox cause specific model regression		
	SHRs	95%CI	p Value	CSH	95%CI	p Value
Arterial hypertension	3.28	1.15–9.39	0.027	4.83	1.57–14.9	0.006
AKI	3.72	1.40–9.84	0.008	5.41	1.79–16.3	0.003
Age ≥55 years old	6.13	1.55–24.3	0.009	2.16	1.72–43.8	0.006

SHRs = sub distribution hazard ratios. 95C%I = 95% confidence interval; CSH = cause specific hazard ratio; AKI = acute kidney injury.
Adjustment for Age ≥55 years old, AKI, Arterial hypertension, diabete mellitus, current smoking, creatinine level at ICU discharge, bystander resuscitation and first temperature for both models.

Discussion

In the present study, we followed-up 133 out-of-hospital cardiac arrest survivors and evaluated long-term renal function. We observed that CKD was frequently observed in these patients (almost 15% of patients discharged alive from ICU) and that patient's characteristics (i.e. past cardiovascular medical history, age) and acute kidney injury during the ICU stay were associated with CKD occurrence more than cardiac arrest's characteristics.

The risk of CKD occurrence after AKI has been highlighted for a few years, essentially in nephrology ward patients without other organ failure.[6,16] This risk exists even if the creatinine level has returned in normal ranges, defining the concept of de novo CKD. Its incidence has been evaluated at 1.7/1000 patient-year in the general population.[17] In the ICU setting, several studies have underlined the increased risk of developing an end-stage renal disease after severe AKI (i.e. requiring renal replacement therapy). Wald et al. recently reported an incidence rate up to 25/1000 patient years of *de novo* end stage renal disease in patients who suffered AKI stage 3 during their ICU stay.[4]

This result has been recently confirmed.[16,18,19] Interestingly, our results are similar to those recently reported by Wald et al. through a 3-years follow-up retrospective study of patients treated by RRT in ICU.[20] Even if the risk of CKD seems proportional to AKI severity, the early stages of AKI, often neglected by clinicians, may be associated with a substantial increased risk of CKD occurrence. Again, the prevalence of CKD in OHCA survivors which had not experimented AKI during ICU is more than 5% corresponding to twice the prevalence of a same age general population.[21]

In the present study, we observed that age and past history of arterial hypertension were independently associated with CKD occurrence. Age has already been reported as risk factor of non-recovery after AKI in several retrospective cohort and/or registry analysis[7,18,22] especially in patients with pre-existing altered glomerular filtration rate.[23,24] This finding might be intuitive as an older age may be associated with a decreased potential of adaptative repair.[25] Accordingly, arterial hypertension may alter the capacity of the kidney to adjust after acute injury, especially when injuries are repeated leading to a substantial loss of the renal reserve. Arterial hypertension has already been identified as risk factor of non renal recovery at short[26] and long term[22] from AKI episode. This may be related to different mechanisms: insufficient renal blood flow in OHCA patients with known arterial hypertension and who suffer a post-resuscitation hemodynamic failure and/or an additional renal injury in patients with sub-clinical hypertensive nephropathy. These mechanisms might often be associated but even if there is no specific treatment for nephrangiosclerosis in ICU patients, optimal hemodynamic target could be revisited in these specific patients. Indeed, international guidelines recommend a 65 mmHg-mean arterial pressure target in successfully resuscitated OHCA patients with hemodynamic failure while no data can support such a recommendation. Only one study suggested to increase this hemodynamic target but the main outcome was the neurological status and no data regards to the renal function was provided.[27] In line with studies performed in septic shock,[28] it might be interesting to evaluate the impact of a higher hemodynamic target in this patients on the rate of CKD occurrence.

Besides these factors inherent to the patient, we observed no association between CKD occurrence and cardiac arrest characteristics or inhospital management characteristics. This result may be very important as it confirms the already known lack of impact of most of the cardiac arrest characteristics on long-term outcome. Such a result has already been observed in one of our group's study evaluating the relationship between early predictors and long-term health-related quality of life.[29] This might be explained by the huge impact of these early prognostic factors on short-term survival, leading to dramatically select patients discharged alive from ICU. This finding reinforces the necessity to better understand the impact of inhospital procedures on such long-term outcomes.

We acknowledge several limitations in the present study. First, due to the retrospective design, we were not able to confirm the causality of the association we observed. Second, we were not able to collect additional information on nephrotoxic exposure or renal protection measure after cardiac arrest. Third, biomarker like proteinuria during follow-up, because not routinely assessed, could not be analyzed because a too important missing data proportion. Fourth, we are not able to provide renal follow-up data from non-cardiac arrest ICU patients. A control group of ICU patients who did not suffer cardiac arrest would be of particular interest to confirm and compare the trends of CKD during follow-up. Our study has also several strengths. To the best of our knowledge, this is the first study that evaluated chronic kidney disease occurrence after AKI in the specific OHCA setting. The three risk factors associated to CKD occurrence might allow an easier identification of high-risk OHCA survivors that could potentially benefit from early and specialized follow-up. Finally, we used survival competing analysis with both Fine Gray and Cox cause specific regression models. This choice is more fitted to assess the occurrence of complication or event during follow-up.

Conclusion

In OHCA survivors resuscitated from an OHCA, CKD was a frequent long-term complication. AKI during ICU stay, older age and a history of arterial hypertension were strong determinants of long-term CKD occurrence. Larger prospective studies are necessary to confirm our results and could identify high-risk patients to initiate monitoring of renal function in the months following episode and/or to improve the design of interventional trials which aim at reducing the long-term consequences of AKI on renal function.

Conflict of interest statement

No conflicts of interest to disclose.

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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.2019.06.284.

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