Renal Function and Outcome of Out-of-Hospital Cardiac Arrest
— Multicenter Prospective Study (SOS-KANTO 2012 Study) —

Tomoyoshi Tamura, MD; Masaru Suzuki, MD; Kei Hayashida, MD; Junichi Sasaki, MD; Naohiro Yonemoto, PhD; Atsushi Sakurai, MD; Yoshio Tahara, MD; Ken Nagao, MD; Arino Yaguchi, MD; Naoto Morimura, MD on behalf of the SOS-KANTO 2012 Study Group

Background: Renal dysfunction is associated with increased cardiovascular-related mortality, but its impact on outcome of out-of-hospital cardiac arrest (OHCA) remains unclear. We assessed whether post-OHCA outcome correlated with renal function early after OHCA.

Methods and Results: Of the 16,452 registered patients in the SOS-KANTO 2012 Study, 5,112 cardiogenic OHCA adults with creatinine measurement (mean age, 72 years; male, 64%) were examined. First-obtained creatinine was used to assess eGFR. Associations between eGFR groups, ≥60 (n=997), 45–59 (n=1,311), 30–44 (n=1,441), and <30 mL/min/1.73 m² (n=1,363), and 3-month survival and neurological outcomes were examined. Favorable neurological outcome was defined as cerebral performance categories 1 or 2. Survival rate (15.1%, 9.7%, 3.9%, and 2.9%; P<0.001) and proportion of favorable neurological outcome (12.3%, 7.4%, 2.6%, and 2.2%; P<0.001) were determined for eGFR groups ≥60, 45–59, 30–44, and <30 mL/min/1.73 m², respectively. The survival rate decreased with eGFR (<60 mL/min/1.73 m²), and survival adjusted OR were 0.74 (95% CI: 0.54–1.03), 0.42 (95% CI: 0.25–0.64), and 0.48 (95% CI: 0.29–0.81), respectively.

Conclusions: An independent and graded association was observed between decreased eGFR and 3-month survival and proportion of favorable neurological outcome in cardiogenic OHCA patients.

Key Words: Cardiovascular disease; Neurological outcome; Out-of-hospital cardiac arrest; Renal function; Survival

Renal dysfunction, both chronic and acute, is a major comorbidity in a number of diseases and conditions. In particular, renal dysfunction is associated with increased incidence of cardiovascular diseases (CVD) such as myocardial infarction, heart failure, and peripheral artery disease. In several epidemiological studies, renal dysfunction was further associated with increased mortality from cardiovascular causes even after adjusting for coexisting risk factors. Moreover, even a moderate decrease in renal function was associated with increased rates of death. Through bidirectional interactions, dysfunction in either the heart or kidney initiates and perpetuates disease in the other organ.

Out-of-hospital cardiac arrest (OHCA) is a major health problem in developed countries. The annual number of OHCA events in North America, Europe, and Japan has traditionally been reported to be approximately 350,000, 275,000, and 100,000, respectively. In adult OHCA, cardiac causes, predominantly acute myocardial infarction and ventricular arrhythmia, are the most common etiology of cardiac arrest (CA). The survival and neurological outcome after OHCA remains unsatisfactory, despite vigorously attempted resuscitation and post-CA care. Although chronic kidney disease (CKD) is a risk factor in the development of acute kidney injury (AKI), patients with pre-existing renal dysfunction were excluded in studies...
Patient Selection

We examined adult OHCA patients (aged ≥18 years) with presumed cardiac etiology whose serum creatinine was initially measured immediately after arriving at the hospital. Patients with do-not-attempt resuscitation (DNAR) order and those with missing information on the implementation of advanced life support were excluded.

Definitions and Data Collection

The diagnosis of CA of presumed cardiac etiology was made, unless an obvious non-cardiac etiology was observed (i.e., cerebrovascular disease, respiratory disease, obvious trauma, drowning, asphyxiation, or drug intoxication). Pre- and in-hospital treatment information were prospectively collected. The pre-hospital information collected by emergency medical service (EMS) providers in the standardized Utstein style included age, sex, and initial cardiac rhythm. Additional information included pre-arrest functional status, witness status, presence of bystander resuscitation (cardiopulmonary resuscitation [CPR]), location of CA, and ROSC prior to hospital arrival. In-hospital information, serum creatinine, and hemoglobin immediately after hospital arrival, survival status at 3 months after CA, and the neurological outcome at 3 months after CA were collected by researchers at each institution. Researchers were not blinded to any of the clinical data. Researchers used the phone survey to collect the survival and neurological outcome information if the patients were discharged from hospital or transferred to another hospital. Neurologic outcomes were reported using the cerebral performance category (CPC) scale.28 The CPC scale range from 1 to 5 as follows: CPC 1, good cerebral performance: conscious,
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Renal Function Classification

We modified this classification considering the number of patients in each category by dividing further into 4 eGFR categories as follows: eGFR ≥60 mL/min/1.73 m², normal renal function; 45–59 mL/min/1.73 m², mildly-moderately decreased renal function; 30–44 mL/min/1.73 m², moderately-severely decreased renal function; 15–29 mL/min/1.73 m², severely decreased renal function; and <15 mL/min/1.73 m², severely decreased to end-stage kidney failure.

Outcome Measures

The primary and secondary outcome measures were 3-month survival and favorable neurological outcome, respectively.

Statistical Analysis

Descriptive statistics are reported as mean±SD, and as n (%) for continuous and categorical variables, respectively, unless otherwise specified. The chi-squared test was used for comparisons of binary variables and the analysis of variance for comparing distributions of continuous variables. Pearson correlation coefficient was calculated to determine the correlation between first obtained serum alert, able to work, might have mild neurologic or psychological deficit; CPC 2, moderate disability: conscious, sufficient cerebral function for independent activities of daily life, and able to work in sheltered environment; CPC 3, severe disability: conscious, dependent on others for daily support because of impaired brain function; CPC 4, comatose or persistent vegetative status; and CPC 5, brain death or death. CPC 1 and 2 were further categorized as favorable neurological outcome; and CPC 3, 4, or 5 as poor neurological outcome.

Classification of Renal Function

Estimated glomerular filtration rate (eGFR) was calculated using the standard formula for Japanese subjects using serum creatinine obtained immediately after hospital arrival at the emergency department (ED). Thus, serum creatinine was obtained either during CA for those transferred to ED without ROSC, or after CA for patients with pre-hospital ROSC. The modified National Kidney Foundation classification of CKD classifies renal function according to eGFR as follows: eGFR ≥60 mL/min/1.73 m², normal renal function; 45–59 mL/min/1.73 m², mildly-moderately decreased renal function; 30–44 mL/min/1.73 m², moderately-severely decreased renal function; 15–29 mL/min/1.73 m², severely decreased renal function; and <15 mL/min/1.73 m², severely decreased to end-stage kidney failure. We modified this classification considering the number of patients in each category by dividing further into 4 eGFR categories as follows: eGFR ≥60, 45–59, 30–44, and <30 mL/min/1.73 m².

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### Table 1. OHCA Patient Characteristics vs. eGFR

<table>
<thead>
<tr>
<th>eGFR (mL/min/1.73 m²)</th>
<th>≥60 (n=997)</th>
<th>45–59 (n=1,311)</th>
<th>30–44 (n=1,441)</th>
<th>&lt;30 (n=1,363)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male</td>
<td>66.0±16.8</td>
<td>69.0±14.2</td>
<td>75.0±13.1</td>
<td>76.5±12.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pre-CA functional status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.45</td>
</tr>
<tr>
<td>No disability</td>
<td>651 (65.3)</td>
<td>864 (65.9)</td>
<td>901 (62.5)</td>
<td>894 (65.5)</td>
<td></td>
</tr>
<tr>
<td>Mild disability</td>
<td>131 (13.1)</td>
<td>185 (14.1)</td>
<td>196 (14.1)</td>
<td>163 (12.0)</td>
<td></td>
</tr>
<tr>
<td>Severe disability</td>
<td>61 (6.1)</td>
<td>50 (3.8)</td>
<td>63 (3.8)</td>
<td>71 (5.2)</td>
<td></td>
</tr>
<tr>
<td>Data missing</td>
<td>154 (15.4)</td>
<td>212 (16.2)</td>
<td>281 (16.2)</td>
<td>235 (17.2)</td>
<td></td>
</tr>
<tr>
<td>Witness status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Witnessed</td>
<td>540 (54.2)</td>
<td>707 (53.9)</td>
<td>735 (51.0)</td>
<td>649 (47.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Not witnessed</td>
<td>456 (45.7)</td>
<td>603 (46.0)</td>
<td>706 (49.0)</td>
<td>714 (52.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pre-hospital ROSC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Yes</td>
<td>255 (25.6)</td>
<td>269 (20.5)</td>
<td>252 (17.5)</td>
<td>280 (20.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>739 (74.1)</td>
<td>1,039 (79.3)</td>
<td>1,185 (82.2)</td>
<td>1,079 (79.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>12.4±2.8</td>
<td>12.6±2.5</td>
<td>11.9±2.6</td>
<td>10.9±2.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR (mL/min/1.73 m²)</td>
<td>82.7±25.2</td>
<td>51.8±4.3</td>
<td>37.9±4.2</td>
<td>17.6±8.0</td>
<td>–</td>
</tr>
</tbody>
</table>

Data given as mean±SD or n (%). Percentages may not total 100 because of rounding. CA, cardiac arrest; CPR, cardiopulmonary resuscitation; eGFR, estimated glomerular filtration rate; EMS, emergency medical service; Hb, hemoglobin; OHCA, out-of-hospital cardiac arrest; PEA, pulseless electrical activity; ROSC, return of spontaneous circulation; VF, ventricular fibrillation; VT, ventricular tachycardia.
creatinine and that after a time interval following emergency call to hospital arrival (this parallels the time from CA to initial blood sampling). A trend between outcome variables with eGFR categories was determined using the Cochran-Armitage test. To improve the quality of comparisons, multiple imputation and multivariable analyses were performed as previously described. Briefly, we performed multiple imputation to impute incomplete variables 1 at a time using the filled-in variable, from 1 step, as a predictor for all subsequent steps; known as the Markov chain Monte Carlo algorithm. Linear regression was used to impute continuous variables, and logistic regression was used for categorical variables. A multivariable logistic regression model was used with adjustment for known potential covariates to analyze the associations between eGFR categories and primary and secondary outcomes. Independent variables selected for adjustment were age, sex, witness status, bystander CPR, initial shockable rhythm, location of CA, ROSC prior to hospital arrival, and hemoglobin. Sensitivity analysis with the generalized estimating equation model was used to account for within-institution clustering. P<0.05 was considered statistically significant. All analyses were conducted using IBM SPSS version 24.0 (IBM, Armonk, NY, USA).

Results

Baseline Characteristics
A total of 16,452 CA patients were identified during the study period. Of the 7,330 adult OHCA patients, 5,221 had serum creatinine measured immediately after arrival at hospital. After excluding patients with DNAR order and those lacking information on the implementation of advanced life support, data on 5,112 patients were included in the analyses (Figure 1). The eGFR groups (≥60, 45–59, 30–44, and <30 mL/min/1.73 m²) consisted of 997 (19.5%), 1,311 (25.6%), 1,441 (28.2%), and 1,363 patients (26.7%), respectively. There were significant differences in age, sex, witness status, bystander CPR, location of CA, initial cardiac rhythm, and ROSC prior to hospital arrival between the eGFR groups (Table 1). There were significant differences in initial rhythm documented by EMS across eGFR groups. Further, the overwhelming majority of cases across all renal function groups involved either pulseless electrical activity or asystole (79% in preserved and 86% in the advanced renal function group). Renal dysfunction (defined as eGFR <60 mL/min/1.73 m²), was observed in 4,115 patients (80.5%); while 2,804 (54.3%) had a moderate decrease in renal function (<45 mL/min/1.73 m²). There were no statistically significant differences in baseline characteristics with or without missing data (Table S1). Regardless of ROSC status on hospital arrival, first obtained serum creatinine did not show significant correlation with the time interval; Pearson correlation coefficient for patients who achieved or did not achieve pre-hospital ROSC was 0.06 (P=0.17) and 0.01 (P=0.44), respectively. Mean eGFR differed between survivors and non-survivors (56.7±25.3 vs. 42.8±24.3 mL/min/1.73 m², respectively; P<0.001); and between 3-month favorable and poor neurological outcome (57.5±24.8 vs. 43.0±24.4 mL/min/1.73 m², respectively; P<0.001; Figure 2).

Outcome Measures
Graded association between 3-month survival rate and eGFR categories was observed as follows: 15.1%, 9.7%, 3.9%, and 2.9% for eGFR ≥60, 45–59, 30–44, and <30 mL/min/1.73 m², respectively (Cochrane-Armitage trend test, P<0.001; Figure 3A). Multivariable logistic regression analysis showed a decrease in odds of survival as eGFR decreased: 45–59 mL/min/1.73 m², adjusted OR, 0.74; 95% CI: 0.54–1.03 (P=0.07); 30–44 mL/min/1.73 m², adjusted OR, 0.42; 95% CI: 0.28–0.62 (P<0.001); and <30 mL/min/1.73 m², adjusted OR, 0.43; 95% CI: 0.28–0.68 (P<0.001; Table 2).

Also, a graded association was observed between proportion of favorable neurological outcome and eGFR category as follows: 12.3%, 7.4%, 2.6%, and 2.2% with eGFR ≥60, 45–59, 30–44, and <30 mL/min/1.73 m², respectively (Cochrane-Armitage trend test, P<0.001; Figure 3B). Moreover, on multivariable logistic regression analysis the adjusted OR for 3-month favorable neurological outcome also decreased as eGFR decreased, as follows: 45–59 mL/min/1.73 m², adjusted OR, 0.74; 95% CI: 0.52–1.06 (P=0.10); 30–44 mL/min/1.73 m², adjusted OR, 0.40; 95% CI: 0.25–0.64 (P<0.001); and <30 mL/min/1.73 m², adjusted OR, 0.48; 95% CI: 0.29–0.81 (P=0.006; Table 3). We performed
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CI: 0.25–0.64 (P<0.001); and <30 mL/min/1.73 m², adjusted OR, 0.48; 95% CI: 0.31–0.76 (P=0.002), respectively (Tables S2,S3).

**Discussion**

In the present study, renal dysfunction was associated with survival and neurological outcome after OHCA caused by presumed cardiac etiology. A graded association was
observed between renal function and both the survival and neurological outcomes in post-CA patients. Moreover, eGFR <45 mL/min/1.73 m² was an independent predictor of 3-month mortality and poor neurological outcome. To the best of our knowledge, this is the first study to indicate a graded association between first obtained renal function after CA and the outcome of CA using a large prospective cohort.

The present findings are concordant with those of previous studies. Go et al reported a graded association between renal function and CVD events and mortality using a large population-based cohort. The increased CVD risk was seen not only in patients with end-stage renal disease (ESRD) but also in those with moderately decreased renal dysfunction. Thus, both the clinical and public health importance of renal dysfunction that does not require hemodialysis have been emphasized. Similar results were also obtained in a Japanese community-dwelling population cohort. The present study further extends on the association between renal function and outcome in previously reported population-based cohorts of cardiogenic post-CA patients (a population that has experienced a cardiovascular event).

Cardiac dysfunction is frequently found in patients with renal dysfunction due to the bidirectional interaction between the heart and kidney. Furthermore, myocardial dysfunction contributes to the high mortality rate after OHCA. Therefore, it is understandable that renal function would have a graded association with survival rate in post-CA patients.

Several possible explanations exist for the graded association between renal dysfunction and neurological outcome. The brain is vulnerable to hemodynamic perturbations after ROSC due to the loss of normal cerebral autoregulation and the disruption of microvascular perfusion. Kilgannon et al investigated the association between blood pressure and outcome after OHCA and found a strong association between hypotension and poor neurological outcome, as opposed to an association between intrinsic hypertension and better neurological outcome. In their subgroup analysis, they also found that patients who were able to maintain blood pressure without vasopressors had a higher proportion of good neurological outcome compared with patients who required vasopressors. From this observation, it was suggested that the cardiovascular function rather than blood pressure itself can be a predictor of neurological outcome. Renal dysfunction, as reported, is associated with both vascular and cardiac dysfunction. Hence cerebral perfusion may be further impaired in post-CA patients with renal dysfunction due to the impaired cardiovascular function, eventually leading to the observed graded association between renal function and neurological outcome in post-CA patients.

While creatinine obtained immediately after hospital arrival reflects the chronic status of renal function before CA in some patients, in others the renal function may be influenced by AKI prior to and/or after CA. AKI is a known risk factor of short-term mortality after cardiovascular events. Mechanisms by which AKI leads to early mortality is multifactorial, including acute elevation in inflammatory cytokines, endothelial dysfunction, and worsened cardiac ischemia. Given that creatinine did not have a significant correlation with time interval, it is possible that creatinine obtained immediately after hospital arrival represents the renal function at the time of CA and is not affected by AKI after CA, which occurs in a time dependent manner. Moreover, given the sudden onset of cardiogenic OHCA, the majority of the observed renal dysfunction was presumed to be CKD.

CKD and CVD share many cardiovascular risk factors, but the frequency and severity of cardiovascular events in CKD are proportional to the underlying traditional cardiovascular risk factor profiles. This is explained by other CKD-related risk factors, which have an additive effect and accelerate atherosclerosis and progression of CKD. For these reasons, cardiovascular mortality is exponentially increased in severely decreased renal function and ESRD group. In contrast to these previous studies, in the present study the OR for 3-month survival and for favorable neurological outcome were similar in the <45-mL/min/1.73 m² eGFR group in post-CA patients. This is an important finding because the outcome after cardiogenic OHCA worsens with moderately decreased renal function and the odds are comparable with the severely decreased renal function group (Tables 2, 3).

The significance of AKI in post-CA patients has been recently reported. Although it is well known that the risk of developing AKI increases as CKD progresses, patients with pre-arrest renal dysfunction were excluded from those studies. Given that emergency coronary angiography is now commonly performed in post-CA patients, pre-existing renal dysfunction may be further exacerbated with the use of contrast medium, and outcomes may ultimately be affected. For these reasons, renal dysfunction at the time of CA is deserving of attention, and warrants further research.

The fact that more than half of the present OHCA cohort had moderate to severe decrease in renal function, which was found to be an independent poor prognostic factor, is noteworthy. Efforts implemented after OHCA have contributed to improved the outcome to some extent, but they are still inadequate. Therefore, intervention prior to CA is being recognized as important for improving the outcome of OHCA. The importance of maintaining good renal function has been discussed elsewhere. Interventions to preserve renal function might play an important role in improving the outcome of CA.

The association between eGFR estimated with the first obtained serum creatinine (either obtained during CA or after ROSC), and CA outcome provides clinically useful information. Given that most of the OHCA patients transferred to ED lack a baseline serum creatinine, it is of greater clinical importance that the determination of the predictor of CA outcomes, be based on the first obtained eGFR.

Study Limitations
We acknowledge that the current study has important limitations. Most notably, this was a post-hoc analysis of a prospective observational study. Given that the treating physicians were not blinded to the renal function results, this may have influenced the selection of subsequent treatment. As opposed to important covariates for predicting outcome after CA, cardiovascular and CKD-related risk factors were not available for adjustment in the logistic regression model because this study was not specifically designed to collect these data. Longitudinal data on renal function are lacking and therefore the association between renal function at the time of CA and the chronic state was not clear. Given that the patients we examined were adults.
with OHCA of presumed cardiac etiology, most of the in-hospital data obtained after ROSC were unavailable in patients who did not achieve ROSC in the ED. Thus, several in-hospital variables could not have been considered for adjustment in the present study. Last, although the eGFR at the time of CA was an independent predictor of outcome in post-CA patients, the adjusting for other biomarkers or the making of comparisons with other known prognostic factors were not possible due to considerable missing data. Despite several limitations, the current study provides a new insight: that decreased renal function at the time of OHCA is associated with poor outcome in post-CA patients, and this warrants further research.

Conclusions

There was an independent and graded association between decreased eGFR and 3-month survival and proportion of favorable neurological outcome in OHCA patients. These risks were evident at eGFR <45 mL/min/1.73 m² after adjusting for known confounding factors.

Acknowledgments

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Disclosures

T.T. received travel expenses unrelated to research from Taiyo Nippon Sanso. The other authors declare no conflicts of interest.

Name of Grants

Kanto Chapter of the Japanese Association for Acute Medicine Research Grant.

References


Supplementary Files

Supplementary File 1

Table S1. Patient characteristics with or without missing data
Table S2. Odds ratio of eGFR categories for 3-month survival with inter-institutional heterogeneity adjustment
Table S3. Odds ratio of eGFR categories for favorable neurologic outcome at 3 months with inter-institutional heterogeneity adjustment
Appendix S1. SOS-KANTO 2012 Study Group

Please find supplementary file(s):