Journal of the American Heart Association

ORIGINAL RESEARCH

Shrunken Pore Syndrome: A New and More Powerful Phenotype of Renal Dysfunction Than Chronic Kidney Disease for Predicting Contrast-Associated Acute Kidney Injury

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BACKGROUND: Shrunken pore syndrome (SPS) as a novel phenotype of renal dysfunction is characterized by a difference in renal filtration between cystatin C and creatinine. The manifestation of SPS was defined as a cystatin C–based estimated glomerular filtration rate (eGFR) <60% of the creatinine-based eGFR. SPS has been shown to be associated with the progression and adverse prognosis of various cardiovascular and renal diseases. However, the predictive value of SPS for contrast-associated acute kidney injury (CA-AKI) and long-term outcomes in patients undergoing percutaneous coronary intervention remains unclear.

METHODS AND RESULTS: We retrospectively observed 5050 consenting patients from January 2012 to December 2018. Serum cystatin C and creatinine were measured and applied to corresponding 2012 and 2021 Chronic Kidney Disease Epidemiology Collaboration equations, respectively, to calculate the eGFR. Chronic kidney disease (CKD) was defined as a creatinine-based eGFR <60 mL/min per 1.73 m^2 without dialysis. CA-AKI was defined as an increase in serum creatinine ≥50% or 0.3 mg/dL within 48 hours after contrast medium exposure. Overall, 649 (12.85%) patients had SPS, and 324 (6.42%) patients developed CA-AKI. Multivariate logistic regression analysis indicated that SPS was significantly associated with CA-AKI after adjusting for potential confounding factors (odds ratio [OR], 4.17 [95% CI, 3.17–5.46]; *P*<0.001). Receiver operating characteristic analysis indicated that the cystatin C–based eGFR:creatinine-based eGFR ratio had a better performance and stronger predictive power for CA-AKI than creatinine-based eGFR (area under the curve: 0.707 versus 0.562; *P*<0.001). Multivariate logistic analysis revealed that compared with those without CKD and SPS simultaneously, patients with CKD and non-SPS (OR, 1.70 [95% CI, 1.11–2.55]; *P*=0.012), non-CKD and SPS (OR, 4.02 [95% CI, 2.98–5.39]; *P*<0.001), and CKD and SPS (OR, 8.62 [95% CI, 4.67–15.7]; *P*<0.001) had an increased risk of CA-AKI. Patients with both SPS and CKD presented the highest risk of long-term mortality compared with those without both (hazard ratio, 2.30 [95% CI, 1.38–3.86]; *P*=0.002).

CONCLUSIONS: SPS is a new and more powerful phenotype of renal dysfunction for predicting CA-AKI than CKD and will bring new insights for an accurate clinical assessment of the risk of CA-AKI.

Key Words: contrast-associated acute kidney injury ■ outcome ■ percutaneous coronary intervention ■ shrunken pore syndrome

Contrast-associated acute kidney injury (CA-AKI) is the third major pathogenic factor of acute kidney injury and 1 of the most common complications after percutaneous coronary intervention.[1] It is associated with longer hospital stays, more medical costs, and higher risks of developing end-stage renal disease.[2] Early identification of relevant risk factors and appropriate intervention are effective approaches against CA-AKI.[3]

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Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.122.027980

For Sources of Funding and Disclosures, see page 8.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Shrunken pore syndrome is a new and more powerful phenotype of renal dysfunction for predicting contrast-associated acute kidney injury than chronic kidney disease and increased all-cause mortality.
- Patients with both shrunken pore syndrome and chronic kidney disease presented the highest risk of contrast-associated acute kidney injury and long-term poor prognosis compared with those without.

What Are the Clinical Implications?

- Shrunken pore syndrome is helpful to identify the risk population earlier and can be used in future studies of risk stratification during clinical practice.
- We suggest that optimal risk stratification of contrast-associated acute kidney injury requires not only an analysis of the creatinine-based estimated glomerular filtration rate and the urine albumin:creatinine ratio but also the cystatin C–based estimated glomerular filtration rate:creatinine-based estimated glomerular filtration rate ratio to determine the presence of shrunken pore syndrome.

Nonstandard Abbreviations and Acronyms

CA-AKI	contrast-associated acute kidney injury
eGFRcr	creatinine-based estimated glomerular filtration rate
eGFRcys	cystatin C–based estimated glomerular filtration rate
SCr	serum creatinine
SPS	shrunken pore syndrome

Glomerular filtration dysfunction associated with a poor prognosis of CA-AKI is considered as an independent risk factor of that. However, as injury factors are diverse, the changes of glomerular filtration function are extraordinarily complex.

Shrunken pore syndrome (SPS) is another phenotype of glomerular filtration dysfunction mainly manifested by the impairment of moderate-sized molecular filtration.[4] A previous study showed that the glomerular filtration rate (GFR) was normal in patients with early diabetic nephropathy, for the clearance of some medium-sized molecules such as cystatin C might be reduced by the narrowing pore size between endothelial cells.[5] Accordingly, a new hypothesis called SPS presented by Grubb et al sum up this phenomenon and defined it as a cystatin C–based estimated GFR (eGFRcysC):creatinine-based estimated GFR (eGFRcr) ratio <0.6.[6] In recent years, the relationship between SPS and cardiovascular disease has attracted much attention. Clinical studies have proved that SPS is related to atherosclerosis progress,[7] myocardial infarction occurrence,[8] and heart failure prognosis.[9]

As SPS is closely related to kidney disease, which is an important risk factor of CA-AKI, it is essential to investigate the unknown relationship between SPS and CA-AKI. This study aimed to explore the predictive value of SPS for the incidence of CA-AKI and long-term mortality in patients undergoing elective percutaneous coronary intervention. Furthermore, by comparing the capacity and value of SPS and chronic kidney disease (CKD) in CA-AKI, we determined their different significance in clinical application.

METHODS

The retrospective study was approved by the Institutional Review Board of Fujian Provincial Hospital (K2019-07-011), and informed consent was waived. The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Study Population

We conducted a retrospective and observational study that included consenting patients undergoing elective percutaneous coronary intervention at the Fujian Provincial Hospital cardiac catheterization laboratory between January 2012 and December 2018. The exclusion criteria were the following: (1) pregnancy, lactation, or malignant tumor with an expectation of life <1 year (n=30); (2) died within 24 hours after admission (n=3); (3) end-stage renal disease (eGFRcr <15 mL/min per 1.73 m^2) or long-term dialysis (n=17); (4) intravascular administration of iodic contrast medium for 7 days before or 3 days after the procedure (n=6); (5) used nephrotoxic drugs during hospitalization (n=9); (6) lacked cystatin C data (n=987); (7) lacked serum creatinine (SCr) level data of before or after procedure (n=119); (8) treatment with high doses of corticosteroids (n=3); and (9) thyroid disease (n=13). Consequently, 5050 eligible patients were selected in the final analysis.

Study Protocol

For all visits, cystatin C was detected at admission, and SCr was measured at admission and at least the next 3 consecutive days after contrast exposure by using the COBAS automatic biochemical analyzer (Roche Diagnostics, Basel, Switzerland). Biochemical

parameters such as serum glucose, fasting lipid profiles, routine blood tests, and glycated hemoglobin were also measured on admission or following 8 to 12 hours of overnight fasting. Data including baseline demographic, comorbidities, clinical risk factors, clinical treatment, angiographic characteristics, and laboratory results were gathered from medical records.

Percutaneous Coronary Intervention

Elective percutaneous coronary intervention procedures were conducted by experienced interventional cardiologists, and the prescription was determined by clinicians according to American Heart Association/American College of Cardiology Foundation guidelines. The nonionic, low-osmolarity contrast medium (either Iopamiron or Ultravist, both 370 mg I/mL) was administered during all procedures. In addition, all patients received 0.9% normal saline (at a rate of 1 mL/kg per hour) for 12 hours throughout the perioperative period (or 0.5 mL/kg per hour for those who were intolerant) according to the guidelines.

Definitions and Follow-Up

According to the Acute Kidney Injury Network, CA-AKI was defined as either a relative increase in SCr ≥50% or an absolute SCr increase ≥0.3 mg/dL within 48 hours after contrast medium exposure. Serum cystatin C and SCr were measured and applied to corresponding 2012 and 2021 Chronic Kidney Disease Epidemiology Collaboration equations, respectively, to calculate the eGFR.[10] SPS was defined as eGFRcys <60% of eGFRcr. CKD was defined as eGFRcr <60 mL/min per 1.73 m^2 but without dialysis. The further additional end point was long-term mortality. Survival time was calculated from discharge until death or censoring time. Follow-up data were obtained by trained specialists (relevant doctors and research nurses) through outpatient consultation or telephone interviews following hospital discharge.

Statistical Analysis

We compared the baseline characteristics between the SPS group and the non-SPS group. Categorical variables were presented as numbers and percentages and analyzed with the χ^2 test or Fisher's exact test. Continuous variables were expressed as mean±SD (normally distributed) or median and interquartile range (nonnormally distributed). The Student *t*-test or Wilcoxon rank-sum test was performed to determine the differences between groups. The predictive values of the eGFRcys:eGFRcr ratio, eGFRcr, and a combination for CA-AKI were analyzed by receiver operating characteristic (ROC) curve, and time-dependent ROC was used for prognosis. Restricted cubic splines were constructed for better visualization of the predictive value of the eGFRcys:eGFRcr ratio on CA-AKI. Univariate and multivariate logistic regression analyses were performed to identify risk factors of CA-AKI. Variables that were found to be statistically significant ($P<0.05$) in the univariate analysis and of great clinical significance were included in the multiple logistic regression analysis. For adjusted models, model 1 adjusted for demographic characteristics (age >75 years, sex); model 2 adjusted for covariables in model 1 plus smoking, diabetes, hypertension, atrial fibrillation, congestive heart failure, and eGFRcr <60 mL/min per 1.73 m^2; and model 3 adjusted for variables incorporated in model 2 plus acute myocardial infraction, anemia, and contrast volume >150 mL. The interaction and subgroup analyses were performed to determine if there were any interaction effects across various subgroups, and the results are presented in the form of forest plots.

Unadjusted Cox proportional hazards regression analysis found significant variables for further multivariable Cox regression analysis. A Kaplan–Meier curve was used to assess the survival time between SPS and non-SPS. To determine the relationship between SPS and CKD in predicting CA-AKI, patients were categorized into 4 subgroups according to with or without SPS and CKD. Differences in the risks of CA-AKI and prognosis between groups were calculated using multivariate logistic regression and Cox regression analysis. Statistical analyses were performed by R (version 4.1.2; R Foundation, Vienna, Austria) and SPSS (version 25.0; IBM, Armonk, NY). A value of $P<0.05$ (2-tailed) was considered statistically significant.

RESULTS

Baseline Characteristics of Study Population

Of 5050 eligible patients, 649 (12.9%) patients had SPS, and 324 (6.62%) patients developed CA-AKI. Baseline and procedural clinical characteristics are listed in Table 1, including known risk factors for SPS. Cystatin C levels were higher in patients with SPS than those without SPS, which resulted in a lower eGFRcys, whereas the baseline SCr levels were similar between the 2 groups. This is typical in patients with SPS. Patients with SPS were older and tended to have higher cystatin C, cholesterol, D-dimer, and NT-proBNP (N-terminal pro–brain natriuretic peptide) and lower hemoglobin, albumin, and left ventricular ejection fraction. They presented with a higher rate of congestive heart failure incidence (7.09% versus 3.95%) and were more frequently treated with diuretics. Baseline characteristics between patients excluded because of cystatin or creatinine deficiency and those selected in this study are shown in Table S1. Baseline

Table 1. Baseline Variables Between the Non-SPS and SPS Groups

	Non-SPS group, n=4401	SPS group, n=649	*P* value
Demographics			
Age, median (IQR), y	66.0 (58.0–73.0)	69.0 (61.0–76.0)	<0.001
Male sex, n (%)	3472 (78.9)	487 (75.0)	0.03
Weight, median (IQR), kg	66.0 (60.0–74.3)	65.0 (58.0–72.0)	0.013
Body mass index, median (IQR), kg/m^2	24.2 (22.4–26.4)	23.9 (21.8–25.9)	0.024
Systolic blood pressure, mean±SD, mm Hg	133±20.1	136±23.4	0.024
Diastolic blood pressure, mean±SD, mm Hg	75.3±11.7	75.6±12.3	0.703
Smoking, n (%)	1830 (48.2)	298 (49.5)	0.589
Comorbidities, n (%)			
Diabetes	1572 (35.7)	229 (35.3)	0.864
Hypertension	2970 (67.5)	454 (70.0)	0.226
Atrial fibrillation	278 (6.32)	57 (8.78)	0.023
Congestive heart failure	174 (3.95)	46 (7.09)	<0.001
Acute myocardial infarction	1303 (29.6)	228 (35.1)	<0.001
Laboratory measurements, median (IQR)			
WBC, 10^9/L	6.96 (5.80–8.34)	7.05 (5.84–8.63)	0.14
Hemoglobin, g/L	139 (128–149)	134 (122–145)	<0.001
Platelets, 10^9/L	213 (181–253)	208 (174–252)	0.117
Cholesterol, mmol/L	4.05 (3.41–4.88)	4.14 (3.49–5.00)	0.037
HDL-C, mmol/L	1.00 (0.84–1.20)	1.02 (0.86–1.19)	0.378
LDL-C, mmol/L	2.56 (2.00–3.27)	2.65 (2.05–3.35)	0.031
Cystatin C, mg/L	0.94 (0.82–1.10)	1.51 (1.34–1.89)	<0.001
Serum creatinine, mg/dL	0.88 (0.76–1.02)	0.87 (0.75–1.01)	0.268
NT-proBNP, pg/mL	181 (65.2–668)	405 (104–1566)	<0.001
D-dimer, mg/L FEU	0.31 (0.18–0.60)	0.47 (0.30–0.87)	<0.001
HbA1c, %	6.20 (5.80–7.00)	6.20 (5.80–7.00)	0.783
LVEF, %	59.0 (56.4–62.0)	58.2 (55.0–61.0)	<0.001
Medical therapy use during hospitalization, n (%)			
Antiplatelet agent	4395 (99.9)	648 (99.8)	1.000
Statin	4366 (99.2)	643 (99.1)	0.914
ACEI/ARB	3663 (83.2)	539 (83.1)	0.953
β-blocker	3675 (83.5)	536 (82.6)	0.597
CCB	1549 (35.2)	245 (37.8)	0.221
Diuretic	985 (22.4)	250 (38.5)	<0.001

ACEI/ARB indicates angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; CCB, calcium channel blocker; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro–brain natriuretic peptide; SPS, shrunken pore syndrome; and WBC, white blood cell.

characteristics of patients with and without CA-AKI are shown in Table S2.

Predictive Value of the SPS on CA-AKI

ROC analysis showed an area under the curve of 0.707 (95% CI, 0.605–0.667; *P*<0.001) for SPS in predicting CA-AKI (Figure 1). Restricted cubic spline in logistics regression analysis revealed that the nonlinear relationship between the eGFRcys:eGFRcr ratio and CA-AKI risk (*P* for nonlinearity<0.001) (Figure S1).

To further examine the predictive value of SPS on CA-AKI, univariate and multivariate logistic regression analyses were conducted (Table S3). In model 1, after adjusting for demographic characteristics, the SPS was strongly correlated with CA-AKI compared with non-SPS (odds ratio [OR], 4.68 [95% CI, 3.66–5.96]; *P*<0.001). In model 2, the association between SPS and CA-AKI remained significant (OR, 4.32 [95% CI, 3.32–5.61]; *P*<0.001). A similar result was observed in model 3 after additional adjusting of clinical factors that were found to be significantly associated with CI-AKI in the univariate analysis (OR, 4.17 [95% CI, 3.17–5.46]; *P*<0.001) (Table 2). Subgroup analysis revealed that there were no significant interaction effects observed among the various subgroups (Figure S2). SPS was

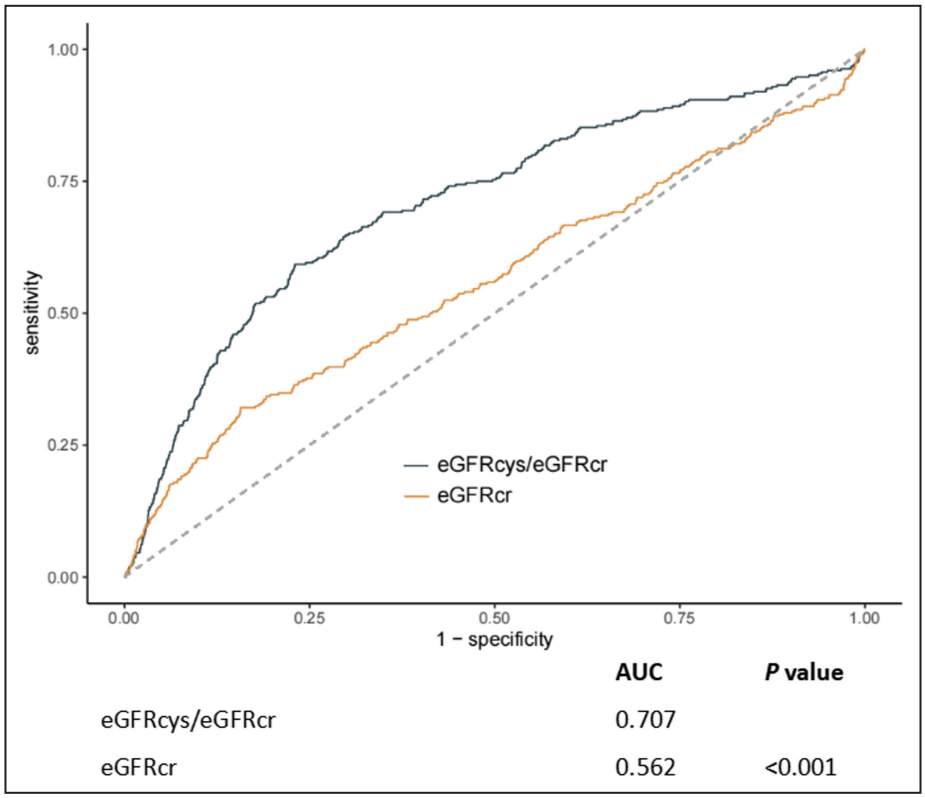

Figure 1. Receiver operating characteristic curves of the eGFRcys:eGFRcr ratio and eGFRcr for contrast-associated acute kidney injury.
AUC indicates area under the curve; eGFRcr, creatinine-based estimated glomerular filtration rate; and eGFRcys, cystatin C–based estimated glomerular filtration rate.

associated with an increased CA-AKI risk irrespective of CKD status (*P* for interaction=0.532).

Follow-Up

There were 324 (6.42%) deaths during the median follow-up period of 2.8 years. A total of 213 patients (4.2%) were lost to follow-up at the beginning of the study. After adjusting for potential confounding factors, multivariate Cox regression analysis showed that SPS was associated with an increased risk of long-term mortality (hazard ratio [HR], 1.37 [95% CI, 1.08–1.74]; *P*=0.011).

The Kaplan–Meier curve demonstrated that the SPS group had a higher rate of all-cause mortality compared with the non-SPS group (log-rank *P*<0.001) (Figure 2).

Comparison of SPS and CKD

ROC curves were generated to compare the predictive ability of the eGFRcys:eGFRcr ratio and eGFRcr for CA-AKI. The area under the curve for the eGFRcys:eGFRcr ratio was significantly higher than that of eGFRcr (area under the curve: 0.707 versus 0.562; *P*<0.001) (Figure 1). To examine the effects of SPS and

Table 2. Subgroup Analysis for Relationship of SPS With CA-AKI and Prognosis

	Relationship Between SPS and CA-AKI				Relationship Between SPS and Prognosis			
		95% CI				95% CI		
Models	Odds ratio	Lower	Upper	*P* value	Hazard ratio	Lower	Upper	*P* value
Unadjusted	4.96	3.89	6.31	<0.001	1.56	1.41	1.72	<0.001
Model 1	4.68	3.66	5.96	<0.001	1.53	1.22	1.92	<0.001
Model 2	4.32	3.32	5.61	<0.001	1.42	1.12	1.81	0.004
Model 3	4.17	3.17	5.46	<0.001	1.37	1.08	1.74	0.011

Model 1: adjusted age >75 years and sex. Model 2: model 1+smoking, diabetes, hypertension, atrial fibrillation, congestive heart failure, and creatinine-based estimated glomerular filtration rate <60 mL/min per 1.73 m^2. Model 3: model 2+acute myocardial infarction, anemia, and contrast volume >150 mL. CA-AKI indicates contrast-associated acute kidney injury; and SPS, shrunken pore syndrome.

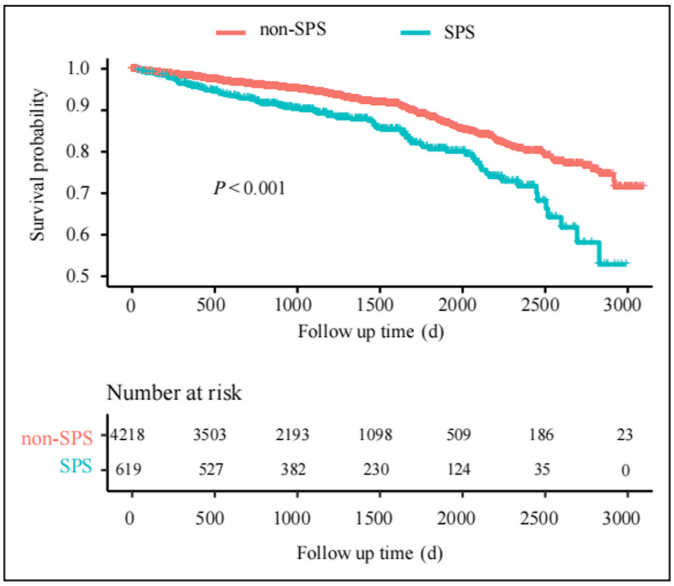

Figure 2. Mortality between patients with and without SPS.
SPS indicates shrunken pore syndrome.

CKD in predicting CA-AKI, patients were categorized into 4 groups according to with or without SPS and CKD (Figure 3). Multivariate logistic analysis indicated that compared with those without CKD and SPS simultaneously, patients with CKD and non-SPS (OR, 1.70 [95% CI, 1.11–2.55]; *P*=0.012), non-CKD and SPS (OR, 4.02 [95% CI, 2.98–5.39]; *P*<0.001), and CKD and SPS (OR, 8.62 [95% CI, 4.67–15.70]; *P*<0.001) had an increased risk of CA-AKI. Notably, patients with both SPS and CKD appeared to present the highest risk of long-term mortality compared with those without both S(HR, 2.30 [95% CI, 1.38–3.86]; *P*=0.002).

Sensitivity Analysis

An optimal cutoff point derived from ROC analysis was 0.7 for the eGFRcys:eGFRcr ratio, which has also been adopted for diagnosing SPS in a few studies. Therefore, we conducted a series of sensitivity analyses, and the overall results aligned with the main findings. SPS maintained a strong association with CA-AKI and prognosis regardless of taking 0.6 or 0.7 as the cutoff point (Table S4, Figure S3). In addition, we also used eGFRcys instead of eGFRcr as the covariate. The results still showed a strong statistical difference (Table S5).

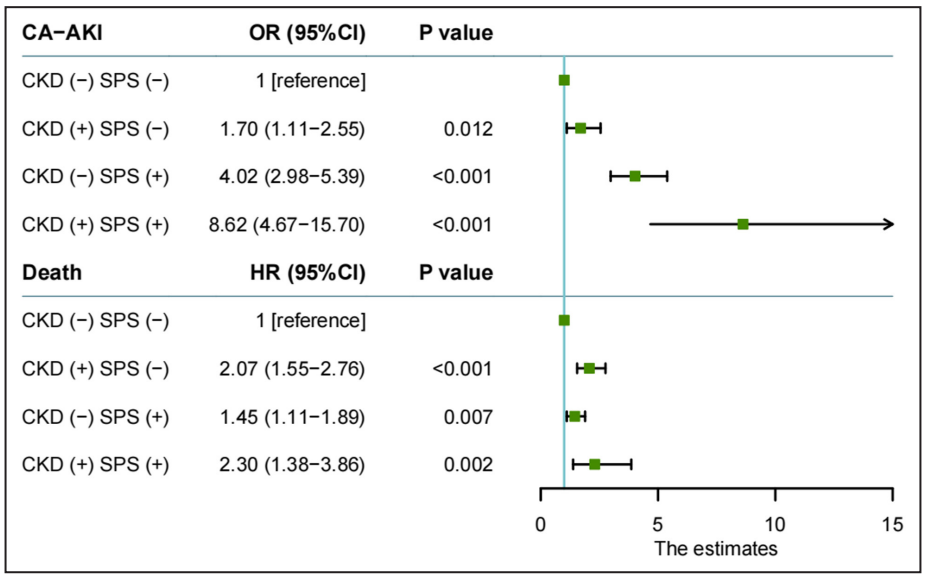

Figure 3. Subgroup analysis stratified by with or without SPS and CKD.
CKD indicates chronic kidney disease; HR, hazard ratio; OR, odds ratio; and SPS, shrunken pore syndrome.

DISCUSSION

To the best of our knowledge, this is the first study revealing the association between SPS and CA-AKI incidence. Consistent with our hypothesis, the results showed that even after adjusting potential confounding risk factors, SPS was significantly associated with CA-AKI and long-term mortality. Further ROC and subgroup analysis revealed that SPS was a more valuable phenotype of renal dysfunction for predicting CA-AKI than CKD. Patients with both SPS and CKD presented the highest risk of CA-AKI and long-term poor prognosis compared with those without.

In previous studies, it was observed that >20 additional proteins with sizes similar to cystatin C in patients with SPS also showed corresponding high protein:creatinine ratios.[7] Scholars have proposed several hypotheses to explain this difference, and the most widely accepted explanation is the shrunken size and density of the glomerular endothelial cell pore. SPS may be an early manifestation or compensatory change of kidney injury with significant swelling of glomerular endothelial cells, eventually decreasing the size and density of the endothelial cell pore.[5] These ultrastructural changes will lead to deranged renal filtration of middle molecules. However, these early pathological changes are reversible. With the improvement of the condition and the reappearance of the pore, the glomerular filtration function recovers.[11] Also, the thickening glomerular basement membrane leads to an increased diffusion distance for mid-sized molecules, failed filtration exacerbation, and plasma concentration elevation. In addition, an experiment has proved that there was a negative linear correlation between the eGFRcys:eGFRcr ratio and glomerular basement membrane thickness.[12]

In addition to the pathophysiological susceptibility, the changes in the internal environment and health conditions of patients with SPS also partially explain the relationship between SPS and CA-AKI. A series of recent literature suggested that SPS displayed a specific proteome feature that is independent of the GFR level. Some of these proteins associate with or accelerate atherosclerosis,[7] such as interleukin-6,[13] monocyte chemotactic protein-3,[14] tumor necrosis factor receptor,[15] and osteoprotegerin.[15,16] These protein accumulations are supposed to link to atherosclerosis occurrence and increase in vascular disease morbidity increase, which are important risk factors for CA-AKI.[7] In addition, studies have shown that patients with SPS with heart failure are at risk of having right ventricular systolic dysfunction, whereas women with SPS are associated with a higher risk of coronary artery disease progression. These findings may build the pathophysiological bridge between kidney and heart diseases.[8,17]

Abnormal renal function, known as a risk factor for CA-AKI, has been included in the Mehran risk score.[18] In our study, SPS is associated with a 4-fold risk of CA-AKI even in patients without CKD. It indicates that a significant part of patients with a great risk of CA-AKI might be neglected under conventional risk stratification. As an independent risk factor of CA-AKI, SPS is helpful to identify the risk population earlier and can be used in future studies of risk stratification during clinical practice. The capacity and value of SPS are superior to CKD in CA-AKI prediction; however, the latter is more reflective in prognosis. Therefore, we suggest that optimal risk stratification of CA-AKI requires not only analysis of eGFRcr and the urine albumin:creatinine ratio but also the eGFRcys:eGFRcr ratio to determine the presence of SPS.

Another distinct significance of this study is that we first propose SPS to use in CA-AKI prediction. As a reversible change compared with other risk factors, it is more meaningful because the treatment for SPS before exposure to a contrast medium may reduce the risk of CA-AKI. Thus, it is necessary to conduct more SPS-related studies. Some theories have been put forward. Recent research has found that NO bioavailability is decreased in patients with SPS. Supplementation with arginine or NO donor drugs to antagonize impairment of NO metabolism is a potential therapeutic target.[19] In addition, experiments demonstrated that disruption structures of endothelial cell glycocalyx lead to glomerular filtration dysfunction. Glycocalyx can be used as an important therapeutic direction to restore glomerular filtration function.[20] At present, there is no drug to prevent CA-AKI. Therefore, drugs targeting SPS may be a breakthrough for the prevention and treatment of CA-AKI in the future.

There are several limitations in our study. First, our study was a single-center observational study that only included Chinese people, thus the results cannot be extrapolated to other ethnic groups. Our findings, therefore, need to be confirmed in a prospective, multicenter trial. Second, owing to the lack of data on other traditional risk factors for CA-AKI, there were still some potential confounders that cannot be adjusted. Third, measuring GFR by administration of iohexol or CrEDTA (chromium ethylenediamine-tetraacetic acid) was not available, so we used the 2021 Chronic Kidney Disease Epidemiology Collaboration creatinine equations to estimate GFR. This may not be a disadvantage, as eGFR is more consistent with the clinical environment. Fourth, renal-related death was missing from our follow-up information and could not be analyzed. Finally, muscopenia leads to a decrease in creatinine production and lower eGFRcr, which is a common interference factor of SPS. Our research lacks objective measures of muscle mass, such as dual-energy x-ray absorptiometry, which might influence the creatinine plasma levels.

CONCLUSIONS

Our study demonstrated that SPS, the manifestation of early renal function impairment, can independently and markedly predict the occurrence and poor long-term prognosis of CA-AKI. SPS is a new and more powerful phenotype of renal dysfunction than CKD for predicting CA-AKI. Moreover, the eGFRcys:eGFRcr ratio may provide more information on the risk stratification of CA-AKI. Hopefully, drugs for SPS might be applied to patients undergoing an elective interventional operation to protect patients from developing CA-AKI in the future.

ARTICLE INFORMATION

Received August 28, 2022; accepted October 19, 2022.

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Sources of Funding

This study was funded by grants from the National Natural Science Foundation of China General Program (81873495, 82171569), the Heart Failure Center Research Foundation of Fujian Provincial Hospital (supported by the Fujian Provincial Department of Finance), and the National Key Clinical Specialty Construction Project of China (Cardiovascular Medicine 2021). The grants played a role in the design of the study, collection of data, follow-up of the patients, interpretation of data, and manuscript writing.

Disclosures

None.

Supplemental Material

Tables S1–S5
Figures S1–S3

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SUPPLEMENTAL MATERIAL

Table S1. Baseline Variables between excluded group due to cystatin or creatinine deficiency and study group

	Excluded n=1106	**Included n=5050**	***P* value**
Demographics			
Age, median (IQR), years	64.0 (57.0-71.0)	66.0 (59.0-73.0)	<0.001
Sex, male, n (%)	866 (78.3%)	3959 (78.4%)	0.976
Smoking, n (%)	528 (51.4%)	2128 (48.4%)	0.093
Weight, mean ± SD, kg	67.9 ± 13.4	67.2 ±11.7	0.378
BMI, mean ± SD, kg/m2	24.9 ± 4.9	24.4 ± 3.59	0.125
Comorbidities			
diabetes, n (%)	379 (34.3%)	1801 (35.7%)	0.398
hypertension, n (%)	733 (66.3%)	3424 (67.8%)	0.344
Atrial fibrillation, n (%)	61 (5.52%)	335 (6.63%)	0.192
CHF, n (%)	452 (95.6%)	4830 (95.6%)	1.000
Laboratory measurements			
WBC, median (IQR), 10^9/L	7.20 (5.93-8.80)	6.96 (5.80-8.39)	<0.001
HGB, median (IQR), g/L	138 (128-148)	138 (127-148)	0.927
PLT, median (IQR), 10^9/L	215 (181-262)	213 (180-253)	0.043
Cholesterol, median (IQR), mmol/L	4.12 (3.49-4.93)	4.06 (3.42-4.90)	0.102
HDL-C, median (IQR), mmol/L	0.99 (0.83-1.16)	1.00 (0.84-1.20)	0.012
LDL-C, median (IQR), mmol/L	2.66 (2.07-3.31)	2.57 (2.00-3.28)	0.033
Serum creatinine, median (IQR), mg/dL	77.0 (66.0-88.0)	78.0 (67.0-90.0)	0.038
HbA1c, median (IQR), %	6.20 (5.80-7.00)	6.20 (5.80-7.00)	0.664
LVEF, median (IQR), %	59.0 (56.0-62.0)	59.0 (56.0-62.0)	0.119

Abbreviations: BMI, body mass index; CHF, congestive heart failure; WBC, white blood cell; HGB, hemoglobin; PLT, platelet; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; HbA1c, glycated haemoglobin; LVEF, left Ventricular ejection fraction.

Table S2. Baseline Variables between non-CA-AKI group and CA-AKI group

	non-CA-AKI n=4726	**CA-AKI n=324**	***P* value**
Demographics			
Age, median [IQR], years	66.0 (59.0-73.0)	69.0 (62.0-77.0)	<0.001
Sex, male, n (%)	3721 (78.7%)	238 (73.5%)	0.031
Weight, median [IQR], kg	66.0 (60.0-74.0)	65.0 (58.5-72.0)	0.079
Body mass index, median [IQR], kg/m^2	24.2 (22.4-26.3)	23.9 (22.1-25.7)	0.139
Smoking, n (%)	2005 (48.9%)	123 (41.7%)	0.020
Comorbidities			
diabetes, n (%)	1657 (35.1%)	144 (44.4%)	0.001
hypertension, n (%)	3175 (67.2%)	249 (76.9%)	<0.001
Atrial fibrillation, n (%)	290 (6.14%)	45 (13.9%)	<0.001
Acute myocardial infarction, n (%)	1345 (28.5%)	186 (57.4%)	<0.001
Laboratory measurements			
WBC, median [IQR], $10^9/L$	6.94 (5.80-8.33)	7.38 (6.08-9.32)	<0.001
HGB, median [IQR], g/L	138 (128-148)	131 (118-144)	<0.001
PLT, median [IQR], $10^9/L$	213 (180-253)	210 (177-252)	0.644
Cholesterol, median [IQR], mmol/L	4.05 (3.42-4.89)	4.15 (3.49-5.08)	0.13
HDL-C, median [IQR], mmol/L	1.00 (0.85-1.20)	0.95 (0.82-1.14)	0.005
LDL-C, median [IQR], mmol/L	2.56 (2.00-3.28)	2.68 (2.06-3.33)	0.076
LVEF, median [IQR], %	59.0 (57.0-62.0)	57.0 (48.0-60.0)	<0.001
Cystatin C, median [IQR], mg/L	0.97 (0.83-1.18)	1.23 (0.99-1.58)	<0.001
Serum creatinine, median [IQR], mg/dL	0.88 (0.76-1.02)	0.88 (0.73-1.11)	0.458
NT-proBNP, median [IQR], pg/mL	177 (65.2-645)	1158 (324-3139)	<0.001
Medical therapy during hospitalization			

	non-CA-AKI n=4726	CA-AKI n=324	*P* value
Antiplatelet agents use, n (%)	4721 (99.9%)	322 (99.4%)	0.07
Statin, n (%)	4688 (99.2%)	321 (99.1%)	0.745
ACEI/ARB, n (%)	3921 (83.0%)	281 (86.7%)	0.094
β-blocker, n (%)	3931 (83.2%)	280 (86.4%)	0.150
CCB, n (%)	1667 (35.3%)	127 (39.2%)	0.171
Diuretic, n (%)	1033 (21.9%)	202 (62.3%)	<0.001
Procedure performed			
Contrast volume, mean (SD), mL	196 (64.1)	198 (64.4)	0.598
Number of stents, mean (SD), n	1.65 (0.86)	1.73 (0.93)	0.143
Stent length, mean (SD), mm	44.8 (26.6)	47.9 (27.8)	0.052

Abbreviations: WBC, white blood cell; HGB, hemoglobin; PLT, platelet; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; NT-proBNP, N-terminal pro-brain natriuretic peptide; HbA1c, glycated haemoglobin; LVEF, left Ventricular ejection fraction; ACEI/ARB, angiotensin-converting enzyme inhibitor / angiotensin receptor blocker; CCB, calcium channel blockers.

Table S3. The effect size and *P* value of covariates for CA-AKI

	Model 1		Model 2		Model 3	
	OR (95%CI)	***P* value**	**OR (95%CI)**	***P* value**	**OR (95%CI)**	***P* value**
SPS	4.68 (3.66-5.96)	<0.001	4.32 (3.32-5.61)	<0.001	4.17 (3.17-5.46)	<0.001
Age >75 years	1.62 (1.24-2.11)	<0.001	1.16 (0.85-1.55)	0.349	1.04 (0.76-1.42)	0.802
Male	1.22 (0.93-1.58)	0.140	1.08 (0.78-1.47)	0.652	1.10 (0.79-1.52)	0.563
Smoking			0.87 (0.66-1.16)	0.335	0.83 (0.62-1.11)	0.204
Diabetes			1.37 (1.06-1.76)	0.015	1.39 (1.07-1.80)	0.012
Hypertension			1.30 (0.97-1.75)	0.082	1.33 (0.99-1.80)	0.059
Atrial fibrillation			1.81 (1.21-2.65)	0.003	1.85 (1.22-2.75)	0.003
CHF			2.68 (1.75-4.01)	<0.001	2.41 (1.55-3.65)	<0.001
CKD			2.18 (1.55-3.04)	<0.001	1.82 (1.27-2.58)	<0.001
AMI					3.31 (2.57-4.27)	<0.001
Anemia					1.65 (1.26-2.16)	<0.001
CV > 150mL					0.91 (0.69-1.20)	0.495

Abbreviations: SPS, shrunken pore syndrome; CHF, congestive heart failure; CKD, eGFRcr<60 mL/min/1.73m2; AMI, acute myocardial infarction; CV, contrast volume.

Table S4. Subgroup analysis for relationship of SPS (eGFRcys/eGFRcr < 0.7) with CA-AKI and prognosis

Models	Relationship between SPS and CA-AKI				Relationship between SPS and Prognosis			
	Odds ratio	95% CI		*P* value	Hazard ratio	95% CI		*P* value
		Lower	Upper			Lower	Upper	
Unadjusted	4.34	3.45	5.46	< 0.001	1.66	1.36	2.02	< 0.001
Model 1	4.11	3.26	5.18	< 0.001	1.44	1.18	1.76	< 0.001
Model 2	3.64	2.84	4.67	< 0.001	1.33	1.07	1.64	0.008
Model 3	3.58	2.78	4.62	< 0.001	1.27	1.03	1.57	0.027

Model 1: adjusted age > 75 years and sex.

Model 2: Model 1 +smoking, diabetes, hypertension, atrial fibrillation, congestive heart failure and eGFRcr < 60 mL/min/1.73m2.

Model 3: Model 2 +acute myocardial infarction, anemia and contrast volume > 150mL.

Table S5. Subgroup analysis for relationship of SPS with CA-AKI (adjusted for eGFRcys)

Models	Relationship between SPS and CA-AKI			
	Odds ratio	95% CI		*P* value
		Lower	Upper	
Unadjusted	4.96	3.89	6.31	< 0.001
Model 1	4.68	3.66	5.96	< 0.001
Model 2	3.51	2.45	5.07	< 0.001
Model 3	3.64	2.53	5.29	< 0.001

Model 1: adjusted age > 75 years and sex.

Model 2: Model 1 + smoking, diabetes, hypertension, atrial fibrillation, congestive heart failure and eGFRcys < 60 mL/min/1.73m^2.

Model 3: Model 2 + acute myocardial infarction, anemia and contrast volume > 150 mL.

Figure S1. Restricted cubic spline of the association between eGFRcys/eGFRcr and the risk of CA-AKI

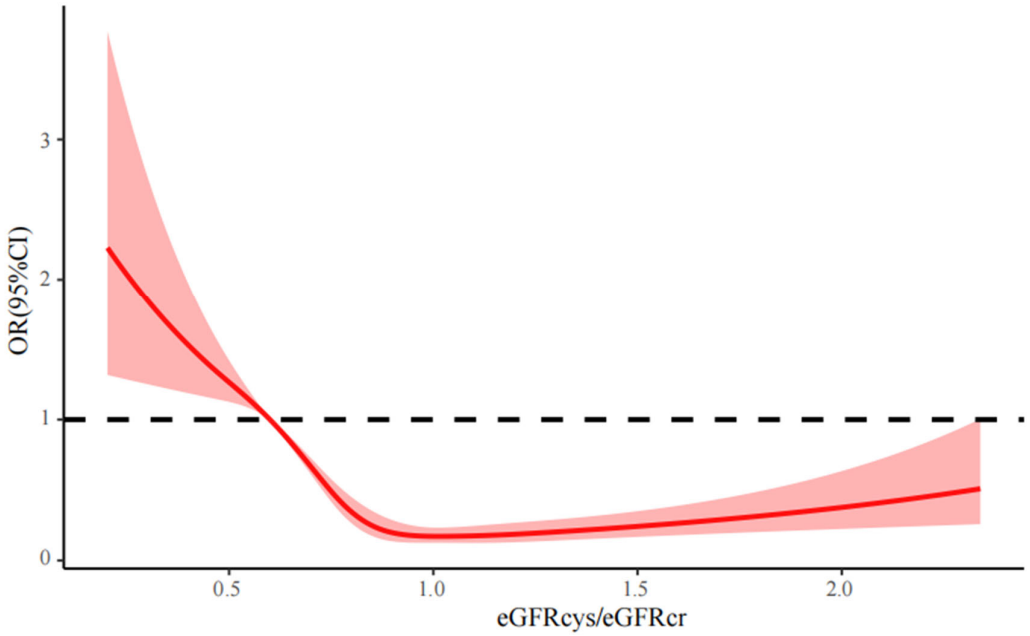
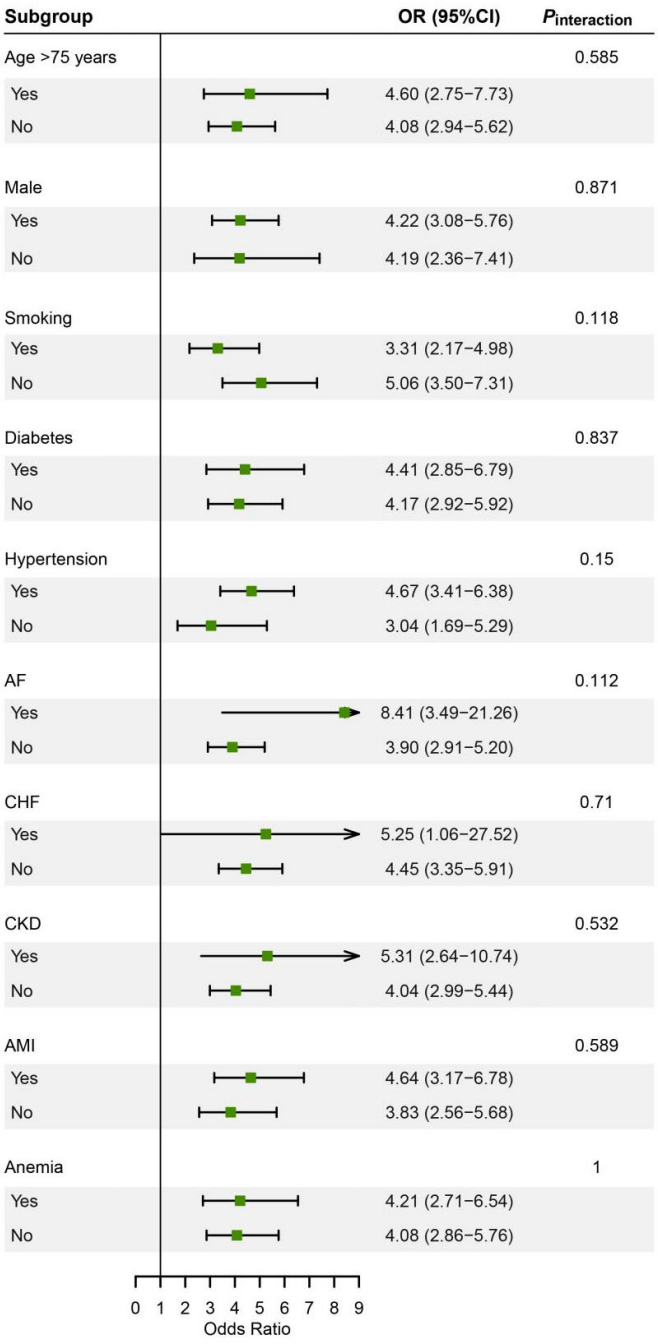


Figure S2. Subgroup analysis stratified by CA-AKI risk factors



Abbreviations: AF, atrial fibrillation; CHF, congestive heart failure; CKD, Chronic kidney disease; AMI, acute myocardial infarction.

Figure S3. Mortality between patients with and without SPS (eGFRcys/eGFRcr < 0.7)